Terms and Conditions of Use of Digitised Theses from Trinity College Library Dublin

Copyright statement

All material supplied by Trinity College Library is protected by copyright (under the Copyright and Related Rights Act, 2000 as amended) and other relevant Intellectual Property Rights. By accessing and using a Digitised Thesis from Trinity College Library you acknowledge that all Intellectual Property Rights in any Works supplied are the sole and exclusive property of the copyright and/or other IPR holder. Specific copyright holders may not be explicitly identified. Use of materials from other sources within a thesis should not be construed as a claim over them.

A non-exclusive, non-transferable licence is hereby granted to those using or reproducing, in whole or in part, the material for valid purposes, providing the copyright owners are acknowledged using the normal conventions. Where specific permission to use material is required, this is identified and such permission must be sought from the copyright holder or agency cited.

Liability statement

By using a Digitised Thesis, I accept that Trinity College Dublin bears no legal responsibility for the accuracy, legality or comprehensiveness of materials contained within the thesis, and that Trinity College Dublin accepts no liability for indirect, consequential, or incidental, damages or losses arising from use of the thesis for whatever reason. Information located in a thesis may be subject to specific use constraints, details of which may not be explicitly described. It is the responsibility of potential and actual users to be aware of such constraints and to abide by them. By making use of material from a digitised thesis, you accept these copyright and disclaimer provisions. Where it is brought to the attention of Trinity College Library that there may be a breach of copyright or other restraint, it is the policy to withdraw or take down access to a thesis while the issue is being resolved.

Access Agreement

By using a Digitised Thesis from Trinity College Library you are bound by the following Terms & Conditions. Please read them carefully.

I have read and I understand the following statement: All material supplied via a Digitised Thesis from Trinity College Library is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of a thesis is not permitted, except that material may be duplicated by you for your research use or for educational purposes in electronic or print form providing the copyright owners are acknowledged using the normal conventions. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.

Prescription Refill Models of Medication Taking Behaviour

A thesis submitted to the University of Dublin, Trinity College
in fulfilment of the requirements for the degree of
Doctor of Philosophy (Pharmacology & Therapeutics)

T. Ian Barron

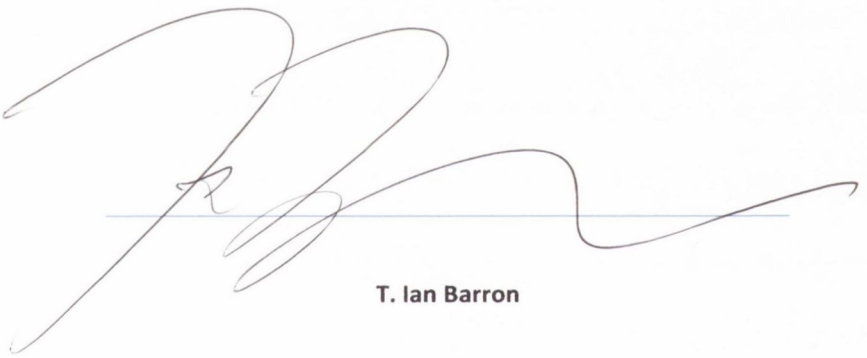
September 2008

DECLARATION

I the undersigned declare that this thesis is entirely my own work and

has not previously been submitted as an exercise for a degree at this or any other University.

The Library of Trinity College, Dublin may lend or copy this thesis on request.



T. Ian Barron

September 2008

ACKNOWLEDGEMENTS

First and foremost my thanks go to my supervisor Professor John Feely. The door to his office was never closed and our discussions there helped shape my enthusiasm for the little details into an appreciation of the bigger picture. His knowledge, experience and patience were invaluable to me throughout this project. I must also thank Dr. Kathleen Bennett without whom I could not have overcome the many difficulties encountered along the way. I am grateful for the hours of statistical support, the critical eye and the friendship she has given me. I am fortunate to have had the opportunity to work with both Professor John Feely and Dr. Kathleen Bennett and I look forward to continuing that work in the future.

Of the many people who shared their time with me in the Department of Pharmacology & Therapeutics I would like to give special thanks to Dr Corina Naughton. I wish her every luck in the future and hope that our paths may cross again. I would also like to thank Dr. Cara Usher, Dr. Ifanyi Okechukwu, Dr Zubair Kabir, Dr Tom O'Hara, Bernie McGowan and Teresa Mulroy. My work was made all the more enjoyable by those I had the privilege to work with.

To my Mother and Father, you have offered me only encouragement in everything I have done. Having your support makes anything possible. I hope that thank you is enough. To my brother Peter, you have always led the way. Where to now?

To my amazing wife Róisín, we have known each other for ten years. Ten years full of adventures. This is the end of another, and we have already started the next. Your support, your love and your belief in me makes this thesis as much yours as it is mine. I love you.

Lastly and most importantly to my wonderful Owen, you are 217 days old today. You began life sleeping peacefully on the desk beside me and now you play patiently on the floor beneath. Your giggles and mischief have carried me through.

SUMMARY

Medication taking can be defined in terms of two separate and distinct behaviours; adherence and persistence. These behaviours represent the ways in which a patient may take a treatment correctly; namely, acting in accordance with the prescribed interval and dosage of the treatment (adherence) and continuing the treatment for the prescribed duration of time (persistence).

Prescription refill records are an invaluable resource for the efficient and objective assessment of medication taking behaviours in large numbers of patients, over extended periods of time. They can provide otherwise unobtainable information about the pattern and timing of drug exposure and the determinants and consequences of non-adherence and non-persistence. The use and validity of prescription refill records for the measurement of adherence has however been the subject of a number of recent criticisms. The most significant of these is the contention that; while prescription refill records are suitable for the measurement of treatment duration (persistence) they are unsuitable for the measurement of treatment execution (adherence), because they are unable to provide an adequate distinction between non-adherent and non-persistent behaviours.

These criticisms are based upon the fact that the majority of prescription refill adherence models proposed to date permit the inclusion of a "*terminal gap*" – the time between treatment discontinuation and the end of follow-up – in adherence calculations. If adherence and persistence are considered separate and distinct behaviours, the measurement of adherence beyond the time that a patient has discontinued treatment underestimates adherence rates and biases estimates of non-adherence risk for covariates that are associated with non-persistence. The appropriate analysis of adherence and persistence as separate behaviours requires the use of an adherence measure that provides an unambiguous distinction between non-adherent and non-persistent behaviours. Adherence measures based upon the length of a patient's treatment episode have the potential to provide this distinction, by excluding the time between treatment discontinuation and the end of follow-up from adherence calculations. Unfortunately the use of observation periods based on the length of a patient's treatment episode raises considerable methodological difficulties

when applied to prescription refill data. The first of these is the inability of prescription refills to provide accurate adherence estimates in patients who receive a single prescription or no more than a few prescriptions. The second is the non-random or informative nature of non-persistence and the systematic variation in lengths of patient follow-up this produces.

The ability of adherence models based on prescription refill records to distinguish between non-adherent and non-persistent behaviours was assessed in this thesis. The first objective of this research was to model adherence behaviours using pre-existing standard models of adherence and to assess the ability of these models to allow the exclusion of non-persistent behaviour from adherence analyses, with or without further adaptation. The second objective was to develop a novel adherence measure model using prescription refill data that allows the distinction between non-adherent and non-persistent behaviours to be made. All models of adherence behaviour in this research were undertaken using a common patient cohort selected from the Irish Health Services Executive Primary Care Reimbursement Services prescription refill database. This cohort consisted of 79,364 general medical services patients over the age of 16 years who commenced a statin as initial anti-hyperlipidaemic treatment between January 2004 and the January 2006.

Three general types of adherence measure model were identified from the literature; these were the single measure model of adherence, the repeated measure model of adherence and the time to non-adherence model. The first of these, the single measure model, uses a single measure of adherence calculated over a specified observation period to describe adherence behaviour. The second, the repeated measure model, calculates multiple estimates of a patient's adherence over a number of consecutive intervals of a defined length. This data is then modelled using appropriate techniques for repeated measures. The third, the time to non-adherence model, identifies the time at which a patient's adherence drops below a defined level. This provides an estimation of the length of time a patient can be expected to take a therapy at or above a specific intensity. None of these pre-existing models were capable of addressing the methodological difficulties introduced by the assessment of adherence exclusive of non-persistence.

To overcome these difficulties a novel competing risks model of time to non-adherence and time to non-persistence was proposed. In this model the non-random follow-up times produced by non-persistence are appropriately accounted for in the measurement and analysis of adherence This is achieved by changing the

focus of analysis away from making inferences about the probability of non-adherence in patients who are adherent, towards making inferences about the probability of non-adherence occurring in patients who are both adherent and persistent. The use of the competing risks methodology also allows the inaccurate adherence estimates obtained for patients receiving very few prescriptions to be disregarded. The competing risks adherence model provides a clearer understanding of the way in which non-adherence contributes to poor medication taking behaviour by specifically estimating the probability of non-adherence in patients who are persistent with treatment. This also allows a more appropriate comparison of non-adherence risk between treatments or covariates that have different baseline non-persistence rates.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

TABLE OF EQUATIONS

TABLE OF DEFINITIONS

TABLE OF ABBREVIATIONS

ATC.....Anatomical therapeutic classification

CI.....Confidence interval

CRM .....Competing risks model of adherence and persistence

CRM-A180.....

Competing risks model of time to non-adherence defined as a PDC of <80% for at least 180 consecutive days

CRM-A180P180.....

Competing risks model of time to non-adherence defined as a PDC of <80% for at least 180 consecutive days or time to non-persistence defined as a permissible gap of ≥180 days

CRM-A180P360.....

Competing risks model of time to non-adherence defined as a PDC of <80% for at least 180 consecutive days or time to non-persistence defined as a permissible gap of ≥360 days

CRM-P180.....

Competing risks model of time to non-persistence defined as a permissible gap of ≥180 days

CRM-P360.....

Competing risks model of time to non-persistence defined as a permissible gap of ≥360 days

DPS..... Drug payments scheme

GEE.....Generalised estimating equations

GMS .....General medical services scheme

GMS-PB.....General medical services payments board

HR ..... Hazard ratio

HSE..... Health services executive

HTD .....High technology drugs scheme

IHD .....Ischaemic heart disease

IQR ..... Inter-quartile range

ISPOR ..... International society for pharmacoeconomics and outcomes research

LTI ..... Long term illness scheme

OR ..... Odds ratio

PCRS ..... Primary care reimbursement services

PDC ..... Proportion of days covered

PER-G ..... Permissible gap model of non-persistence

PER-G180 ..... Permissible gap model of non-persistence with a permissible gap of ≥180 days

PER-G270 ..... Permissible gap model of non-persistence with a permissible gap of ≥270 days

PER-G360 ..... Permissible gap model of non-persistence with a permissible gap of ≥360 days

PER-G90 ..... Permissible gap model of non-persistence with a permissible gap of ≥90 days

RMM ..... Repeated measure model of adherence

RMM-180 .....

Repeated measure model of adherence over consecutive 180 day adherence calculation intervals

RMM-30 .....

Repeated measure model of adherence over consecutive 30 day adherence calculation intervals

RMM-60 .....

Repeated measure model of adherence over consecutive 60 day adherence calculation intervals

RMM-90 .....

Repeated measure model of adherence over consecutive 90 day adherence calculation intervals

SAS ..... Statistical analysis software

SD ..... Standard deviation

S-HR ..... Sub-distribution hazard ratio

SMM ..... Single measure model of adherence

SMM-720 .....

Single measure model of adherence at 720 days follow-up in patients with at least 720 days follow-up

SMM-EFU ..... Single measure model of adherence at 720 days follow-up or end of follow-up

SMM-LastRx ..... Single measure model of adherence at 720 days follow-up or last statin prescription

SMM-NonPer ..... Single measure model of adherence at 720 days follow-up or non-persistence

TNA ..... Time to non-adherence model of adherence

TNA-80/1 ..... Time to non-adherence model defined as a PDC of <80% for at least 1 day

TNA-80/180 ..... Time to non-adherence model defined as a PDC of <80% for at least 180 days

TNA-80/360 ..... Time to non-adherence model defined as a PDC of <80% for at least 360 days

TNA-80/90 ..... Time to non-adherence model defined as a PDC of <80% for at least 90 days

WHO ..... World health organisation

CHAPTER ONE

1 INTRODUCTION

The way in which patients take their prescribed medications has been the focus of research for many years.[1] The assessment of medication taking behaviours is important to not only understand the factors related to inadequate treatment execution and early treatment discontinuation but also to evaluate the clinical and economic consequences of these behaviours. The quality and duration of a patient's treatment execution have the potential to significantly influence both the benefits and the cost effectiveness of therapy. Numerous studies have demonstrated that suboptimal medication taking behaviours result in increased morbidity and mortality as well as increased health care costs, for a wide variety of illnesses.[2-8] For example; statins are prescribed for the reduction of cholesterol and their use is associated with significant reductions in cardiovascular morbidity and mortality for patients with and without a history of cardiovascular disease.[9-14] Studies examining the impact of medication taking behaviours on the effectiveness of statins have shown that the benefits of therapy are significantly reduced by both poor treatment execution and early treatment discontinuation.[2-5, 8, 15, 16] There is also evidence that the cost effectiveness of statin medications for patients who are 100% adherent versus 0% adherent varies from US$[i] 4500 per life year saved to over US$ 250,000 per life year saved.[6]

An examination of the number of articles classified as relating to *"patient compliance"*[ii] in the PubMed index over the past 30 years shows that there has been an almost exponential rise in the number of publications relating to medication taking behaviours since the late 1990's (see Figure 1.1 below). By 2007 approximately 1 out of every 300 PubMed citations were classified as relating to patient compliance. The increasing availability of electronic prescription refill records has played an important role in the growth of this research. Pharmacy databases from a variety of sources are increasingly being used to quantify, characterise and assess the impact of medication taking behaviours[17]

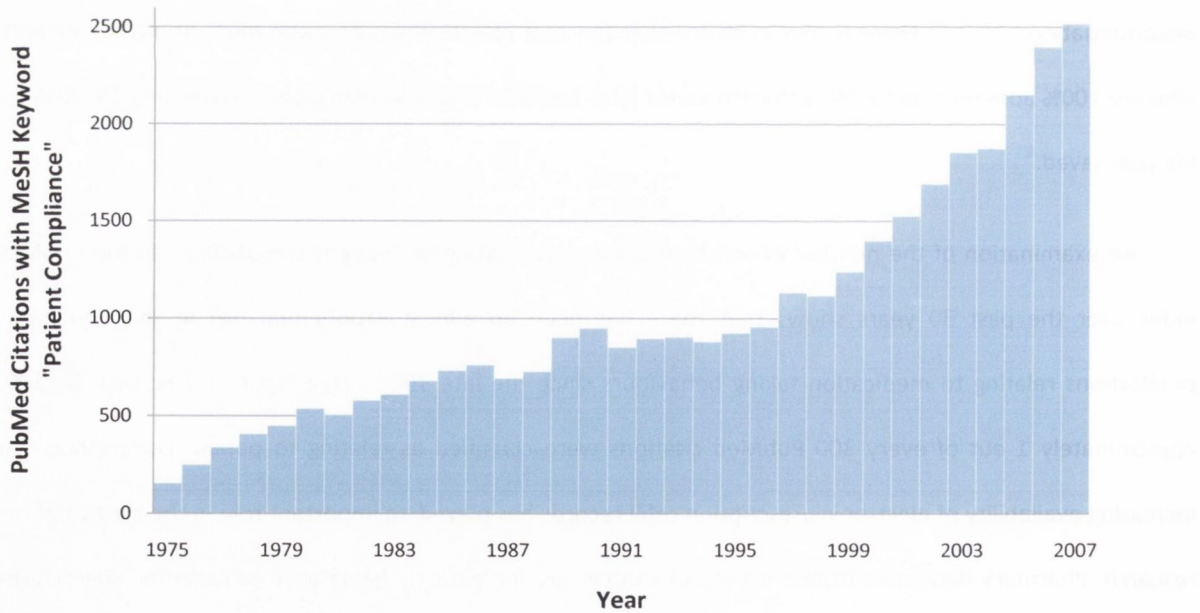
[i] The mean United States Dollar (US$) to European Union Euro (€) exchange rate in 2005 was 0.657.

[ii] Identified by the medical subject heading (MeSH) keyword *"patient compliance"*. This keyword was introduced to the PubMed index in 1975.

Pharmacy databases provide objective information about prescription refills and can be considered an invaluable resource for the assessment of medication-taking behaviour in large numbers of patients, over extended periods of time. The challenge for researchers using these databases has been to develop measures that capture the complexities of patients' medication-taking behaviours in a concise way. This has resulted in a proliferation of proposed methodologies for the measurement of adherence and persistence using prescription refill data.[17-21]

The use and validity of prescription refill records for the measurement of adherence has however been subject to a number of recent criticisms.[22, 23] The most significant of these is the contention that while prescription refill records are suitable for the analysis of treatment duration (persistence) they are unsuitable for the analysis of treatment execution (adherence) because they are unable to provide an adequate distinction between non-adherent and non-persistent behaviours. This thesis will seek to characterise and if possible address this limitation.

FIGURE 1.1: NUMBER OF PUBMED CITATIONS BY YEAR WITH MESH KEYWORD "PATIENT COMPLIANCE" BETWEEN 1975 AND 2007



1.1 Medication-Taking Behaviours – Adherence & Persistence Defined

There have been numerous attempts to define and refine the terminology used to describe medication taking behaviours.[24] This is, in some part, due to concern regarding the semantics of the language used;[25] the possibility that it may be in some way derogatory or unacceptable to patients, or that it may lack the complexity necessary to fully describe the underlying processes that contribute to the observed medication-taking behaviours. Irrespective of the terminology used, it is generally accepted that medication-taking behaviours can be defined in terms of two distinct variables, adherence (synonym: compliance[24]) and persistence.[26, 27] These two behaviours represent the two ways in which a patient may take a treatment correctly; namely, acting in accordance with the prescribed interval and dosage of the treatment (adherence) and continuing the treatment for the prescribed duration of time (persistence).

The definitions of adherence and persistence developed by the International Society for Pharmacoeconomics and Outcome Research (ISPOR) Medication Compliance and Persistence Working Group[24] were selected for use in this thesis (see Definition 1.1 & Definition 1.2 below). Adherence is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen. This refers to the act of conforming to the recommendations of the prescriber with respect to the timing, dosage and frequency of medication taking. Persistence is defined as the duration of time from initiation to discontinuation of therapy. Continuing to take any amount of medication is considered consistent with this definition of persistence.

DEFINITION 1.1: ADHERENCE

Adherence is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen [24]

DEFINITION 1.2: PERSISTENCE

Persistence is defined as the duration of time from initiation to discontinuation of therapy.[24]

These two definitions classify adherence and persistence as distinctly separate constructs or behaviours. The authors of the definitions suggest that as the clinical outcomes of treatment are affected not only by how well a patient takes their medication (adherence) but also by the length of time they take their medication for (persistence); these two behaviours should be defined and measured separately to characterise medication-taking behaviour comprehensively. The importance of the distinction between non-adherent and non-persistent behaviour is also discussed in an editorial by Steiner.[28] In this, it is suggested that a differentiation between treatment adherence and persistence could be significant; patients who stop taking their medication entirely may no longer be convinced that a treatment's advantages outweigh the disadvantages, while those who continue to refill their prescription, even at less than the recommended supply, at least appear to subscribe to the need for ongoing treatment. The assumption that adherence and persistence are separate and distinct behaviours makes it reasonable to also assume that the risk factors associated with non-adherent and non-persistent behaviour may also differ. This has been demonstrated in studies of self reported (see Section 1.2 below) non-adherence and non-persistence.[29] There is also evidence to suggest that interventions to improve medication taking behaviour have a differential effect on non-adherence and non-persistence.[30]

It is important to note that the general adherence and persistence definitions proposed by the ISPOR Medication Compliance and Persistence Work Group[24] cannot be directly employed in the measurement and analysis of medication taking behaviours. They first require translation into working definitions that can then be applied to the available medication usage data. It is essential that these working definitions continue to provide an unambiguous distinction between non-adherent and non-persistent behaviours.

1.2 Adherence Measurement Techniques

The various techniques available for measuring medication taking behaviour have been reviewed in detail previously.[26, 27, 31] These techniques can, in general, be divided into direct and indirect methods of measurement. Direct measurement usually involves either the measurement of the actual drug intake (directly observed therapy) or the detection in a bodily fluid (blood, urine) of the drug, its metabolite or a biologic marker added to the drug formulation. These approaches to medication taking behaviour measurement are expensive, invasive, time consuming and, with the exception of directly observed therapy, susceptible to distortion by the patient.

Indirect techniques of medication taking behaviour measurement include the assessment of clinical response, patient self reported behaviour, pill counts, electronic medication event monitoring and prescription refill records. The use of clinical response may be confounded by the many other factors other than medication taking behaviour that can contribute to a clinical outcome. A patient can have a clinical response for reasons other than good medication taking behaviour and a patient's condition can deteriorate or remain stable even when medications are taken as prescribed. Patient self reported medication taking behaviour is susceptible to both recall bias and the overestimation of adherence rates due to self presentational bias. Patients can have difficulty accurately recalling their dosing histories, and even with use of contemporaneous medication taking behaviour diaries there is a general tendency to overestimate the quality of medication taking behaviour. Pill counts are also subject to self presentational bias by patients who may discard medication prior to a scheduled appointment in order to appear to be following the prescribed treatment regimen. It is also possible that patients may switch medications between containers.

Electronic medication event monitors allow the recording of both the frequency and the time of the medication container opening. This information provides a detailed insight into the daily use of medications by patients, and has allowed the identification of specific medication taking behaviours such as the *"drug holiday"*[i] and *"white coat compliance"*[ii]. The use of electronic medication event monitors is however limited by their expense, and the possibility that patients may open the container and not take a dose, take the wrong dose, remove more than one dose at a time or switch the medication to another container. There is also the possibility that the use of electronic medication event monitors may enhance patients' medication taking behaviour if they are aware it is being measured. Despite these limitations, the overall accuracy and richness of the data provided by electronic medication event monitors means that they can be considered the gold standard for medication behaviour measurement.[26, 31]

Prescription refill records have the ability to provide objective, *"real life"* data, on medication taking behaviour in large populations, over long periods of time.[26] They are however subject to a number of

[i] A drug holiday is defined as a gap in medication taking of greater than or equal to three days.

[ii] White coat compliance is defined as an increase in medication taking timed to coincide with a scheduled appointment with a health care provider.

limitations. The use of prescription refill records for the measurement and analysis of medication taking behaviours is the focus of this thesis and a review of this technique is presented in Section 1.3 (see below).

1.3 Measuring Adherence with Prescription Refill Records

Prescription refill records have been used with growing frequency for the assessment of medication taking behaviours.[17, 19] Their popularity stems, most likely, from their relative efficiency in comparison to other medication taking behaviour assessment techniques and the increasing availability of centralised electronic prescription refill records. Prescription refill records can provide otherwise unobtainable information about the pattern and timing of drug exposure, and the determinants and consequences of non-adherence and non-persistence. There is however a number of specific criteria that must be fulfilled for the results from prescription refill records of medication taking behaviour to be considered valid (see Section 1.3.1 below).

1.3.1 Prerequisites for Prescription Refill Records

1.3.1.1 Closed Pharmacy Systems

A pharmacy system is defined as *"closed"* if patients are unable or extremely unlikely to obtain medication from an unrecorded source (see Definition 1.3 below).[19] The requirement for a pharmacy system to be closed is key to the accurate measurement of medication taking behaviours using prescription refill data. The validity of medication taking behaviour measurements derived from prescription refill data is dependent on the assumption that the pharmacy claims database captures a patient's complete prescription refill history over the period of medication taking behaviour analysis.[19] This is because adherence rates are underestimated for patients who are receiving medication from unrecorded sources outside of the pharmacy claims system. For a pharmacy system to be considered closed, the incentives to obtain medications within the pharmacy system (i.e. cost) must be sufficient to discourage patients from obtaining medication supplies from other unrecorded sources.

DEFINITION 1.3: CLOSED PHARMACY SYSTEM

A pharmacy system is defined as closed if patients are unable or extremely unlikely to obtain a medication supplies from a source other than the pharmacy system under study.

1.3.1.2 Upper Limits of Adherence

Prescription refill data is limited by the fact that the refilling of a prescription by a patient does not provide any information on when the medication was taken – other than after the date of refill – or indeed if the medication was taken by the patient. There is of course evidence that the very act of refilling a prescription is associated with positive treatment outcomes.[32-34] Nevertheless, exactly how patterns of prescription refills relate to the precise underlying adherence behaviour of a patient is difficult to determine from prescription refill data alone. It is therefore not possible to ascertain what a patient's true adherence rate is from prescription refill data, it is only possible to determine how adherent a patient could have been had they taken all of their prescription refills as prescribed. For example; if over a 200 day period from treatment initiation a patient refills prescriptions for 90 days of medication supply, all that can be concluded from the available prescription refill data is that this patient could have had a maximum adherence rate of 45% by day 200. This patient's adherence rate may have been less than 45% on day 200, as they may not have consumed all of their received medication by that time. However, it could not have been greater than 45% (assuming that the prescription refill data was obtained from a closed pharmacy system, and no medication supplies were received from another source, see Section 1.3.1 above).

For this reason the concept of an upper limit of adherence was devised (see Definition 1.4 below).[19] Using prescription refill data it is possible to calculate the maximum adherence rate a patient could have achieved at any time from treatment initiation onwards had they displayed perfect adherence with each prescription refill they received. The general equation for the calculation of an upper limit of adherence at any point in a patient's follow-up is shown in Equation 1.1 (see below). In this equation only the value of β, the day upon which adherence is to be calculated, is allowed to vary and the maximum value for this is specified by the adherence measure definition selected for use in the analysis (see Section 1.3.2 below). The values for α (the first day of a patient's treatment episode) and δ (the number of day's supply assigned to each day, see explanation below) do not vary, irrespective of the selected adherence measure.

DEFINITION 1.4: UPPER LIMIT OF ADHERENCE

The upper limit of adherence is defined as the maximum adherence rate a patient could have achieved had they displayed perfect adherence with each prescription refill they received.

EQUATION 1.1: UPPER LIMIT OF ADHERENCE

$$Upper\ Limit\ of\ Adherence\ (\%) = \left[\sum_{\delta=\alpha}^{\beta} \delta \Big/ \beta\right] \times 100$$

Where α denotes the first day of a patient's treatment episode, β denotes the day on which adherence is to be calculated and δ denotes the number of day's supply (1 or 0) assigned to each day in a patient's follow-up.

For a measure of adherence to be considered an upper limit of adherence a number of criteria must be fulfilled. Firstly, the maximum quantity of medication that is available to a patient over the period of adherence calculation must be accurately defined. Patients must be unable or extremely unlikely to obtain medication from an unrecorded source; either from outside the pharmacy system (closed pharmacy system, see Section 1.3.1 above), or from medication carried over from any previous treatment episodes (this is usually achieved by specifying a run in period over which no prescriptions for the study medication can be filled). Secondly, it is assumed that patients' display perfect adherence with the supply of medication that is available to them. In other words, a single days' supply of the medication received by a patient must be assigned to each consecutive treatment day from the date of the prescription refill. Where there is an overlap in days' supply from successive prescription refills the new supply is appended to the last assigned treatment day of the previous prescription. Any gaps in medication taking are therefore assumed to occur immediately after the exhaustion of the available medication supply and prior to the refilling of a subsequent prescription. Thirdly, over supplies of medication cannot be used to retrospectively 'fill' gaps that occurred between prescription refills prior to the time that the medication was received by the patient.

The limitations of prescription refill data; namely the inability to ascertain if and when the medication received by a patient was taken, means that an upper limit of adherence can be considered the only consistent measures of adherence that can be derived from prescription refill data. Upper limits of adherence should be interpreted in the light that they represent a hypothetical situation of perfect adherence to the treatment received. They represent the absolute best a patient could do with the medication available to them, not necessarily what the patient actually did with the medication available to them. Upper limits of adherence are therefore a specific but insensitive measure of non-adherence and they will generally overestimate the true rate of adherence. Nevertheless, the high specificity of upper limits of adherence allows the accurate

identification of a subset of individuals who cannot be taking enough medication to attain a treatment goal, because they have not obtained enough prescription refills

1.3.2 Methods of Adherence Calculation – Adherence Measures

Numerous methods have been described in the literature for calculating adherence values using prescription refill data.[17-19] These measures generally express adherence as a proportion of the days' supply obtained by a patient over a specified observation period.[17] In most cases these adherence measures differ subtly in their definition of the number of days' supply received by a patient, or the length of the observation period to be included in calculations, or in the manner that days' supply of medication are assigned to treatment days (see Section 1.3.1.2 above). It is important to note that a number of the proposed adherence measures do not fulfil the criteria for an upper limit of adherence because they either do not assume perfect adherence to the medication received or they allow gaps between prescription refills to be filled retrospectively (see Section 1.3.1.2 above). A comprehensive description of adherence measures can be found in the reviews by Andrade,[17] Hess[18] and Steiner[19].

Inconsistencies in the definition and application of adherence measures are commonplace[17] and there can be considerable variation in the estimates of adherence obtained by them.[18] This has led to calls for caution in the interpretation of adherence results from studies of prescription refills, as well as a need for greater attention to the standardisation and consistency of both terminology and methodology.[17] While methods are focusing on a few general approaches there is still little consensus on recommendations for a standard adherence measure.[17-19, 24, 35] It has been suggested that the selection of an adherence measure should be determined by criteria such as biological rationale, the overall goals of the study, and the advantages and limitations of the individual measures.[17] However, with respect to the fact that upper limits of adherence can be considered the only consistent measure of adherence that can be derived from prescription refill data, it is of primary importance that adherence measures fulfil the criteria for an upper limit of adherence (see Section 1.3.1.2 above).

1.3.3 Methods of Adherence Measure Analysis – Adherence Measure Models

There have been numerous reviews of prescription refill methodologies, all of which have focussed on the way in which adherence is calculated and the relative appropriateness of these adherence measures (see

Section 1.3.2 above).[17-19, 35] There has been considerably less attention paid to the way in which the results from these adherence measures are subsequently analysed or modelled to provide information about either the risk of non-adherence or the way in which this risk is divided across patient populations and covariates.

A number of adherence measure models have been suggested for use with prescription refill data. A review of the available literature identified three general types of model that have been commonly applied. In addition to these three models, other models that were identified included the less commonly applied Markov adherence model[36] and a number of models that have not been applied to prescription refill data beyond their initial proposal.[37] There has been no published taxonomy of these model types; therefore, they are classified here according to their specific properties.

Single Measure Models (SMM): Medication-taking behaviour analyses based upon a single measure of adherence at a defined point in time are the most commonly utilized models for the assessment of adherence using prescription refill data.[17] Their widespread use stems from their straightforward implementation and relative simplicity: these models calculate a single measure of adherence at the end of a specified observation period (e.g. 2 years) and utilise the results to construct predictive models of non-adherent behaviour. A number of variations of the single measure model methodology have been implemented; these usually involved the use of alternative definitions for the length of the observation period over which adherence is calculated.

Repeated Measure Models (RMM): Repeated measure models of adherence are based upon the periodic calculation of a patient's adherence over a number of consecutive intervals of a defined length (e.g. 90 days).[38] These models calculate multiple repeated measures of adherence for each patient and have been applied to prescription refill data in an attempt to overcome some of the limitations of single measure models; in particular, their failure to take account of the dynamic nature of adherence behaviour and the longitudinal data available in prescription databases.

Time to Non-Adherence Models (TNA): Time to non-adherence models of medication-taking behaviour are based upon the identification of the time at which a patient's upper limit of adherence drops below a specified level. They provide an estimation of the length of time a patient can be expected to take a therapy at or above a specific intensity; where the intensity can be defined in terms of both the level of non-adherence and the length of non-adherent episodes. As with

repeated measure models of adherence, time to non-adherence models take account of the longitudinal nature of medication-taking behaviour.

The relative merits and appropriate application of these models have not been reviewed or objectively compared. There is therefore little information available to aid the selection of a suitable adherence measure model in prescription refill studies. The few recommendations that have been made relate to statistical generalities and offer little specific guidance.[17, 35, 39] For example; Andrade et al[17] suggest that the length of observation time in these models should be specified and consistent for all individuals in the study cohort or failing this, methods should be used to account for differing lengths of follow-up, e.g. survival analysis techniques. Also, Halpern et al[35] and Peterson et al[39] suggest that, where possible, the adherence measure should be included as a continuous variable in regression analyses.

1.3.4 Limitations of Prescription Refill Records for Medication-Taking Behaviour Analysis

The use of prescription refill records for the measurement of medication taking behaviours is subject to a number of well recognised limitations.[19] First, the validity of adherence measures derived from prescription refill data is dependent on the assumption that patients only obtain prescription refills from the pharmacy system under study (closed pharmacy system, see Section 1.3.1 above). This is an assumption that is rarely rigorously tested and may not be true where the financial incentives to obtain drugs within the system are weak or patients are affluent. Second, prescription refill records may not explicitly record the number of days' supply represented by each prescription refill (i.e. units per dose & doses per day) and this information will have to be imputed from the available data.

Third, prescription refill records are in general only of use for the measurement of medication taking behaviours with treatments prescribed for long-term non-discretionary use. They are of limited use in assessing medication taking behaviours with short-term treatments, or treatments prescribed on an as-required basis, or treatments with frequent dose changes between prescription refills. Fourth, prescription refill data cannot provide information about the timing of doses and the appropriateness of these in relation to the duration of drug action. This is because prescription refill data is considerably less detailed than the data available from techniques such as electronic medication event monitors. Although in general prescription refill studies model and present their results in terms of the number of days' supply obtained by a patient, in reality

the unit of analysis in these studies is the individual prescription refill (≈ 30 days' supply). In comparison to electronic medication event monitors, where the unit of analysis is the opening of a medication container (≈ 1 dose), this is a relatively blunt instrument for the detailed measurement of adherence behaviours.

Fifth, prescription refill records cannot account for patients who are prescribed a treatment but never fill a prescription for this treatment. The exclusion of patients who fail to initiate treatment from prescription refill records may result in an overestimation of the quality of medication taking behaviour. Sixth, measures of adherence derived from prescription refill data can only be interpreted as upper limits of adherence (see Section 1.3.1.2 above). These can be considered a highly specific but relatively insensitive measure of non-adherence. Seventh, it is difficult to establish the reasons for poor medication taking behaviour from prescription refill records alone. Factors that may affect a patient's medication taking behaviour such as perceptions or beliefs about the severity of their illness and the efficacy of their treatment are beyond the scope of data normally available in prescription refill records.

1.3.5 Criticisms of Prescription Refill Models of Adherence

In addition to the inherent limitations of prescription refill records listed in Section 1.3.4 (see above) the use of prescription refill records for the measurement of adherence has been the subject of a number of recent criticisms.[22, 23] The most significant of these is the contention that while prescription refill records are suitable for the analysis of treatment duration (persistence) they are unsuitable for the analysis of treatment adherence because they are unable to provide an adequate distinction between non-adherent and non-persistent behaviours.

1.3.5.1 Distinguishing Between Non-Adherent & Non-Persistent Behaviours

The criticisms of adherence measures derived from prescription refill records are based upon the fact that the majority of adherence measure models proposed to date permit inclusion of a "*terminal gap*"[19] – the time between treatment discontinuation and the end of follow-up – in adherence calculations. The measurement of adherence beyond the time that a patient has discontinued treatment introduces a number of significant problems to medication taking behaviour analysis.

Firstly, the inclusion of time after treatment discontinuation in adherence calculations produces adherence rates that are underestimated for non-persistent patients. For example; consider a patient with 200

days of follow-up who is 90% adherent for the first 100 days of treatment but subsequently discontinues treatment. This patient will be assigned an adherence rate of 45% at day 200 despite having an adherence rate of 90% for the duration of time that they persisted with treatment. A more appropriate description of this patient's medication taking behaviour would be that they were 90% adherent to treatment but non-persistent after 100 days. The distinction between adherent and persistent behaviour definitions (see Section 1.1 above) implies that the quality of a patient's treatment execution can only be evaluated with respect to the length of time that they are taking treatment. The degree to which a patient acts in accordance with the prescribed interval and dosage of a treatment cannot be measured after treatment has been discontinued. The time after treatment discontinuation should not, therefore, be considered part of a patient's adherence behaviour. Secondly, as the adherence rates in these models are underestimated specifically for non-persistent patients, predictive models of non-adherence risk will be biased for covariates associated with non-persistence. This is because non-adherence risk is incorrectly assigned to covariates that are associated with an increased risk of non-persistence.

Adherence rates calculated from prescription refill data without accounting for treatment discontinuation cannot, therefore, distinguish between non-adherent and non-persistent behaviours. Instead these adherence measures can be thought of as representing both non-adherent and non-persistent behaviours in a single hybrid or composite estimate of medication taking behaviour; with the risk assigned to covariates in predictive models reflecting the combined risk for either of these behaviours. This fact has been acknowledged by the authors of previous adherence studies.[35, 40] It must be noted, however, that adherence measures taken over the length of a patient's follow-up can only be interpreted as a crude estimate of the combined non-adherence, non-persistence risk. This is because they rely on adherence calculations as a surrogate measure for treatment discontinuation.

A composite approach to medication-taking behaviour analysis such as this may be acceptable if non-adherence and non-persistence can be considered synonymous behaviours or where the research interest lies solely in the combined estimation and analysis of adherence and persistence. It is, however, doubtful that non-adherence and non-persistence are the same behaviour (see Section 1.1 above) and there is evidence from studies of patient self-reported adherence and persistence to suggest that the risk factors for these two behaviours differ considerably.[29] In addition, the use of a composite measure for the analysis of non-

adherence and non-persistence is likely to be too limited to address many relevant questions about medication taking behaviours. For example; as the relative contributions of non-adherence and non-persistence to the composite estimate are unknown and may vary according to population or treatment characteristics, it is difficult to draw any meaningful conclusions from models that compare the composite outcome risk between covariate values. It is also difficult to accurately compare the results from these composite measures with those obtained from studies using measurement techniques that provide estimates of adherence that are exclusive of persistence behaviour, e.g. electronic medication event monitors. For this reason; the need to measure adherence and persistence as separate and distinct behaviours in order to characterise medication taking behaviour comprehensively has been expressed by the authors of a number of reviews and editorials.[28, 35, 41] In situations where the research interest does include the composite estimation and analysis of non-adherence and non-persistence, the inclusion of the time after treatment discontinuation in adherence rate calculations may not be the most accurate or appropriate method of combining the effects of these two behaviours. It would be preferable to consider any composite analyses of medication-taking behaviour in conjunction with the individual estimates and analyses of their component parts.

The exclusion of the time between treatment discontinuation and the end of follow-up from adherence calculations would allow a distinction between adherent and persistent behaviours to be made. A number of adherence measure models based upon this premise have been proposed.[17, 35, 39, 42] Unfortunately the validity of the results obtained from these models is questionable. This is because the use of observation periods based on the length of a patient's treatment episode raises considerable methodological difficulties that are not addressed adequately by these proposed methods. The first of these difficulties relates to the inability of prescription refill data to provide accurate adherence estimates in patients who receive no more than a single prescription in an individual treatment episode.[17] The second concerns the non-random or informative nature of non-persistence and the systematic variation in lengths of patient follow-up this produces. A detailed discussion of both of these methodological difficulties will be undertaken in later chapters.

CHAPTER TWO

2 OUTLINE OF RESEARCH

2.1 RESEARCH HYPOTHESIS

The inability of currently available adherence measure models to provide a distinction between non-adherent and non-persistent behaviours using robust methodology limits the utility of prescription refill records for the measurement and analysis of adherence behaviour (see Section 1.3.5 above). The appropriate analysis of adherence and persistence as separate behaviours using prescription refill data requires an adherence measure model that can provide an unambiguous distinction between non-adherent and non-persistent behaviours.

This research is based upon the hypothesis that the exclusion of non-persistent behaviour from adherence analyses, using suitable methodology, will allow the appropriate partitioning of their individual contributions to poor medication taking and the differential assignment of risk estimates to covariates for both behaviours.

A medication taking behaviour model such as this will yield adherence and persistence estimates that are capable of simultaneously addressing the questions: How long has the patient continued to take the medication in an effort to treat the disease? Has the patient taken enough medication during that time period to treat the disease? In addition, a distinction between non-adherent and non-persistent behaviours and knowledge of the risk factors for each will provide important guidance for the tailoring of effective interventions to tackle poor medication-taking behaviours.

2.2 RESEARCH AIM & OBJECTIVES

The aim of this research is to develop a method of adherence analysis using prescription refill data that allows the distinction between non-adherent and non-persistent behaviours to be made in both the estimation of the risk of these behaviours and the assignment of this risk to covariates in predictive models of non-adherence and non-persistence.

The first objective of this research is to model adherence behaviours using pre-existing standard models of adherence and to assess the ability of these standard models to allow the exclusion of non-persistent behaviour from adherence analyses. Should the exclusion of non-persistent behaviour from these pre-existing models not be possible the second objective of this research will be to develop a novel adherence measure model that allows the distinction between non-adherent and non-persistent behaviours to be made in both the estimation of the risk of these behaviours and the assignment of this risk to various covariates in predictive models.

2.3 Outline of Research Methodology

Using prescription refill data from a national prescribing database the adherence behaviour of a defined cohort of patients prescribed a treatment intended for long term non-discretionary use will be assessed using a variety of pre-existing adherence measure models. The general suitability of these adherence measure models for the analysis of adherence behaviour using prescription refill records will be assessed. As part of this assessment the capacity of these models to distinguish between non-adherent and non-persistent behaviours, with or without further adaptation, will be considered. If the use or adaptation of these pre-existing models for the exclusive measurement and analysis of adherence is not possible the methodological difficulties preventing the appropriate exclusion of non-persistent behaviour from these models will be identified. Novel methodology to overcome these difficulties will be proposed and implemented.

CHAPTER THREE

3 STUDY COHORT & COVARIATES

All analyses of medication-taking behaviour in this thesis were undertaken using a single patient cohort and a common set of covariates to facilitate the straightforward comparison of methodologies and results. The source, definition, assembly and characteristics of this patient cohort, and the associated patient covariates, are described here.

3.1 SOURCE OF DATA

3.1.1 THE HSE-PCRS PHARMACY CLAIMS DATABASE

The Irish Health Services Executive (HSE) Primary Care Reimbursement Services (PCRS) pharmacy claims database was the primary source for all data in this study. The HSE-PCRS, formerly known as the General Medical Services Payments Board (GMS-PB), provides financial reimbursement to primary care contractors (General Practitioners, Pharmacists, Dentists etc.) for the provision of primary healthcare services in Ireland. Payments are made by the PCRS under a number of schemes for the supply of healthcare services and medicines.

General Medical Services (GMS) Scheme. The GMS scheme provides free healthcare services, including the provision of medicines, to patients over the age of 70 and patients who are unable without undue hardship to arrange primary healthcare services for themselves and their dependents. There were 1.22 million patients registered for this scheme by December 2006. The number of prescription forms and items dispensed under the GMS scheme in 2006 was 13.9 million and 40.5 million respectively.[43]

Drug Payments Scheme (DPS). Patients without eligibility for the GMS scheme can avail of the DPS scheme. This scheme ensures that an individual or family has to pay no more than a monthly threshold amount (≈ €85, as of 1st January 2006) for approved medicines in a calendar month. There were 1.53 million patients registered for this scheme by December 2006.[43]

Long Term Illness (LTI) Scheme. The LTI scheme allows all patients without GMS eligibility who suffer from one or more of a schedule of illnesses (e.g. diabetes) to obtain, without charge, necessary medicines for treatment. There were 0.11 million patients registered for this scheme by December 2006.[43]

High Tech Drugs (HTD) Scheme. The HTD scheme facilitates the dispensing of "*High Technology*" drugs through community pharmacies. These include, for example, anti-rejection medicines for transplant patients, and medicines used for oncological purposes in conjunction with chemotherapy.

Claims for all medicines dispensed by community pharmacists under each of these schemes are submitted on a monthly basis to the HSE-PCRS Pharmacy Claims Database. The database is considered to have a high degree of accuracy and completeness because of its use for claims and because the greater part of data is submitted electronically. Monthly files of prescription claims data and a selection of additional data fields are provided by the HSE-PCRS to the Department of Pharmacology & Therapeutics, Trinity College Dublin for research purposes. Complete nationwide prescribing data was available for the GMS scheme from 1st January 2000 onwards.

The study cohort was selected from patients participating in the GMS scheme only, as this is a closed pharmacy system (see Section 1.3.1 on page 32) and medication histories are deemed complete. While patients registered with the GMS scheme may obtain medications from other sources, the incentive for patients to obtain their medicines within the scheme, i.e. no cost, is considered sufficient to discourage this. Prescription refill data from the DPS scheme is not suitable for medication-taking behaviour analysis because the DPS is not a closed pharmacy system. Patients are not obliged to obtain all of their medications through this scheme and therefore medication histories may be incomplete.

3.1.2 The General Medical Services Scheme (GMS)

Eligibility for the GMS scheme is assessed under three categories; means test, undue hardship and age, with patients over 70 years of age automatically qualifying for entry since the 1st July 2001. Medical cards are initially issued for a one year period with eligibility reviewed on a yearly basis thereafter. The eligible population and activity statistics for the GMS scheme between the years 2002 – 2006 are presented in Table

3.1 (see below).[43] Due to the dynamic nature of the GMS population, with patients gaining and losing eligibility for the scheme over the course of the study period, the number of individual patient records available for analyses in a longitudinal study is greater than the eligible population values in Table 3.1 indicate. The HSE-PCRS database records full details of every drug dispensed within the GMS scheme including the date of dispensing, the exact product dispensed (brand, strength & pack size), the quantity dispensed and cost data for the item. Each prescription record also includes a unique patient identifier, basic demographic data (age & sex) and unique identifiers for the patient's registered doctor, the doctor prescribing the item and the pharmacy dispensing the item. The World Health Organisation (WHO) Anatomical Therapeutic Classification (ATC) code for the dispensed item is also recorded.[44]

TABLE 3.1: SUMMARY OF STATISTICAL INFORMATION FOR THE HSE-PCRS GMS SCHEME (NATIONAL DATA 2002 – 2006)[43]

Year ended December	2002	2003	2004	2005	2006
Number of eligible persons in December	1,168,000	1,158,000	1,148,000	1,155,000	1,221,000
Number of prescription forms	11,551,000	12,243,000	12,794,000	13,227,000	13,932,000
Number of prescription items	29,500,000	32,241,000	35,030,000	37,428,000	40,569,000
Number of prescription items per form	2.55	2.63	2.74	2.83	2.91

3.1.2.1 The Hospital Emergency Scheme

In addition to recording primary care prescribing, the HSE-PCRS database also holds information on hospital discharge prescriptions dispensed under a separate scheme known as the hospital emergency scheme. This scheme allows GMS patients to present hospital discharge prescriptions directly to a community pharmacy to obtain a seven day supply of medication when it is not possible or convenient for them to attend their general practitioners to have the hospital prescription transcribed onto a GMS prescription form. Prescriptions dispensed under the hospital emergency scheme can be identified on the HSE-PCRS database and provide information on prescribing for GMS patients by hospital prescribers. It should be noted that patients are not obliged to avail of the hospital emergency scheme and the scheme does not therefore capture all hospital discharge prescribing.

3.1.3 Limitations of the HSE-PCRS Pharmacy Claims Database & the GMS Scheme

There are of course a number of limitations to the GMS data available in the HSE-PCRS database. The lack of diagnostic and morbidity/mortality data is the most significant of these. The presence of certain co-morbidities must therefore be inferred from the prescribing of specific drug therapies. The eligibility criteria for the GMS scheme also produces bias in the population available for analysis, with an over-representation of the elderly and lower socioeconomic categories in younger age groups. Importantly this socioeconomic bias is not present in patients over the age of 70 where eligibility for the GMS scheme is universal; this can however further complicate the interpretation of comparisons between age categories.

3.2 Study Treatment – Statins

The medication taking behaviours of patients prescribed statin therapy[i] were chosen for analysis in this study. This selection was made for a number of reasons. First, statins are prescribed for long term non-discretionary use and are therefore suitable for medication-taking behaviour analyses using prescription refill records (see Section 1.3.4 on page 37). Second, statin therapy is extensively prescribed in the GMS population for both males and females across a wide range of ages. This will provide a large cohort of patients with varied demographic features for analysis. Third, there have been a considerable number of prescription refill studies of statin adherence, using a variety of adherence measure models, published to date.[17] The results from these studies will aid in the comparison and validation of statin adherence results from the GMS cohort. Fourth, there is a well defined link between statin non-adherence and reduced clinical outcomes with reasonable evidence to support the use of an adherence rate less than 80% to dichotomously define non-adherence.[2, 3, 5, 45] The ability to define adherence behaviour as a dichotomous endpoint is necessary for a number of adherence measure models.

3.3 Identification of the Number of Days' Supply

The number of days' supply received by a patient at each prescription refill is not explicitly stated in the HSE-PCRS prescription refill database. However, the regulations for the GMS scheme state that no more than a

[i] Non-statin anti-hyperlipidaemic treatments were not included in the medication taking behaviour analyses, except where they were prescribed as part of a single combination product with a statin (i.e. combined simvastatin/ezetimibe; Inegy®)

single month's supply of treatment may be dispensed on a single prescription form.[i] This makes it possible to infer the number days supply received by a patient from the number of dosage units dispensed by making a number of reasonable assumptions. The first of these assumptions is that, because of the wide variety of dosage strengths available, the splitting of statin dosage units by patients is unlikely. Second, the wide variety of dosage strengths will also mean that the majority of patients will be taking a single dosage unit per day. Third, where patients are taking more than one dosage unit per day the quantity received by them will correspond to multiples of the number of days in a standard month's supply, i.e. one dosage unit daily – 28, 30, 31; two dosage units daily – 56, 60, 62; three dosage units daily – 84, 90, 93; four dosage units daily – 112, 120, 124.

The second and third of these assumptions are supported by an examination of the distribution of statin dosage unit quantities dispensed through the GMS scheme during the year 2005. Of the 1,146,457 statin prescriptions dispensed in this year 97.8% were for 28, 30 or 31 dosage units, and a further 0.9% were for quantities of 56, 60 or 62; 84, 90 or 93; 112, 120 or 124 dosage units. Of the 1.3% remaining prescriptions, 1.1% were for less than 28 dosage units.

Based on these assumptions the number of days' supply received by a patient was determined thus; prescriptions for less than 35 dosage units were assumed to correspond to one dosage unit per day and the number of days supply was taken to be the same as the quantity of medication dispensed. Prescriptions for 35 to 69 dosage units were assumed to correspond to two dosage units per day and the number of days' supply was taken to be half of the quantity of medication dispensed. Prescriptions for 70 to 104 dosage units were assumed to correspond to three dosage units per day and the number of days' supply was taken to be a third of the quantity of medication dispensed. Prescriptions for 105 or greater dosage units were assumed to correspond to four dosage units per day and the number of days' supply was taken to be a quarter of the quantity of medication dispensed. Similar criteria were used to define cut offs for dosage unit quantities in hospital emergency prescriptions; patients receiving <9, 9-19, 20-25 or >26 dosage units on a hospital emergency prescription were assumed to be taking one, two, three or four dosage units per day respectively. In situations where a patient received two strengths of the same statin on the same prescription form the

[i] The maximum number of days' supply that can be dispensed on a hospital emergency prescription is seven days (see Section 3.1.2.1 above).

statin strength corresponding to the highest number of days was used to define the number of days' supply. The identification of the number of days' supply received by a patient also allows the subsequent calculation of their daily dose using the equation $(quantity\ of\ dosage\ unit \times strength\ of\ dosage\ unit)/days'supply$.

3.4 Statin Prescription Refill Longitudinal Dataset Assembly

A longitudinal dataset of statin prescription refills was assembled for all patients in the study cohort by assigning the supply from each prescription to sequential days from the date of dispensing. Prescription overlaps (i.e. a prescription refilled prior to the assigned daily supply from previous prescriptions being exhausted) were handled in the following way: where an overlapping prescription was for the same statin type and dose as the previous prescription, the days' supply was appended to the last assigned day of the previous prescription; where the overlapping prescription was for the same statin but a different dose, or for a different statin, the days' supply remaining from previous prescriptions was discarded as this indicated a switch in statin type and/or dose.

3.5 Study Cohort Definition

The study cohort included all patients over the age of 16 who commenced a statin (simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, combined simvastatin/ezetimibe; Inegy®) as initial anti-hyperlipidaemic treatment between the 1st January 2004 and the 2nd January 2006 (733 days) on the GMS database. The date of the first prescription for a statin during this period was identified as the index date for each patient. Commencing statin treatment was defined as having no statin prescribed in the 365 days prior to the index date. Initial treatment with a statin was defined as having no other anti-hyperlipidaemic treatment (e.g. fibrate, niacin, ezetimibe) prescribed in the 365 days prior to the index date. In addition to these criteria for inclusion, all patients were required to have received at least one prescription for any item in the 365 days prior to the index date. This excluded patients with a pre-existing prescription for a statin who had become newly eligible for inclusion in the HSE-PCRS scheme. All patients were followed up to the 30th June 2006, giving a total follow-up time of between 180 and 912 days from the index date. For this study national GMS prescribing data was available for the dates 1st January 2003 to 30th June 2007.

3.5.1 Lost to Follow-Up

Patients were considered lost to follow-up from the date they received their last prescription for any item on the HSE-PCRS database. Loss to follow-up may be accounted for by death or loss of eligibility for the GMS scheme, but can also include patients who have ceased receiving any medication.

3.6 Study Covariate Definitions

The common set of covariates for inclusion in analyses was selected with reference to previous studies of statin adherence and persistence. Although some covariates may remain constant over the course of a patient's follow-up (e.g. gender), others do not. Covariates such as age, the type of treatment received and co-morbidities have the potential to change in value over time. Where the appropriate statistical methodologies exist these time-varying covariates are incorporated into analyses. Otherwise covariates are treated as static, if suitable, and baseline values at treatment initiation are used.

3.6.1 Demographic Covariates

The HSE-PCRS database records basic demographic data such as gender and age, with patients assigned to one of ten age categories (<5, 5-11, 12-15, 16-24, 25-34, 35-44, 45-54, 55-64, 65-69, 70-74, ≥75). For this analysis patients under the age of 16 years were excluded from the study cohort, due to the low number of statin prescriptions, and the remaining age categories were condensed into six groups.

Age. 16-34 years; 35-44 years; 45-54 years; 55-64 years; 65-74 years; ≥75 years: time-varying covariate.

Gender. Male; female: static covariate.

3.6.2 Statin Treatment Covariates

Statin treatment covariates were identified from the HSE-PCRS database. These included the type of statin, the initial prescriber of the current statin (e.g. General Practitioner or Hospital Doctor), the statin dose (simvastatin, pravastatin, atorvastatin, rosuvastatin: Low < 20mg/day, Intermediate 20-40mg/day, High > 40mg/day; fluvastatin: Low < 40mg/day, Intermediate 40-60mg/day, High > 60mg/day) and whether the statin dose had changed and in what way (increase, decrease).

Current Statin Type. Simvastatin; pravastatin; fluvastatin; atorvastatin; rosuvastatin; simvastatin/ezetimibe: time-varying covariate.

Current Statin Initiator. General practitioner; hospital doctor: time-varying covariate.

Current Statin Dose. Low; intermediate; high: time-varying covariate.

Statin Dose Change. Decrease; static; increase: time-varying covariate.

3.6.3 Clinical Covariates

The presence of certain co-morbidities was identified using the prescription of specific drugs as a surrogate marker for disease. Ischaemic heart disease was identified by the use of a nitrate[46] (ATC: C01DA) or potassium channel activator (nicorandil, ATC: C01DX16). Diabetes was identified by the presence of a prescription for an oral anti-diabetic medication (ATC: A10B) or insulin (ATC: A10A). A diagnosis of depression was identified by the presence of a prescription for an antidepressant (ATC: N06A). Patients identified as commencing an antidepressant within the past 180 days were classified as having a recent diagnosis of depression. Parkinson's disease and Alzheimer's disease were identified by the presence of a prescription for anti-Parkinson (ATC: N04) or anti-Alzheimer medications (ATC: N06D). The number of individual non-cardiovascular pharmacological agents (all ATC codes excluding cardiovascular agents, ATC: C) and the number of individual cardiovascular pharmacological agents (ATC: C, excluding statins) received by a patient over the preceding 365 days was recorded. The cumulative number of prescription items dispensed (excluding statins) was also recorded. These three variables were stratified into four categories according to their median and inter-quartile ranges

Ischaemic Heart Disease. Present; not present: time-varying covariate.

Diabetes. Present; not present: time-varying covariate.

Depression. Present; not present: time-varying covariate.

Recent Diagnosis of Depression (Preceding 180 days). Present; not present: time-varying covariate.

Parkinson's Disease. Present; not present: time-varying covariate.

Alzheimer's Disease. Present; not present: time-varying covariate.

Number of Non-Cardiovascular Pharmacological Agents (Preceding 365 Days). Categorical variable, time-varying covariate

Number of Cardiovascular Pharmacological Agents (Excluding Statins, Preceding 365 Days). Categorical variable, time-varying covariate.

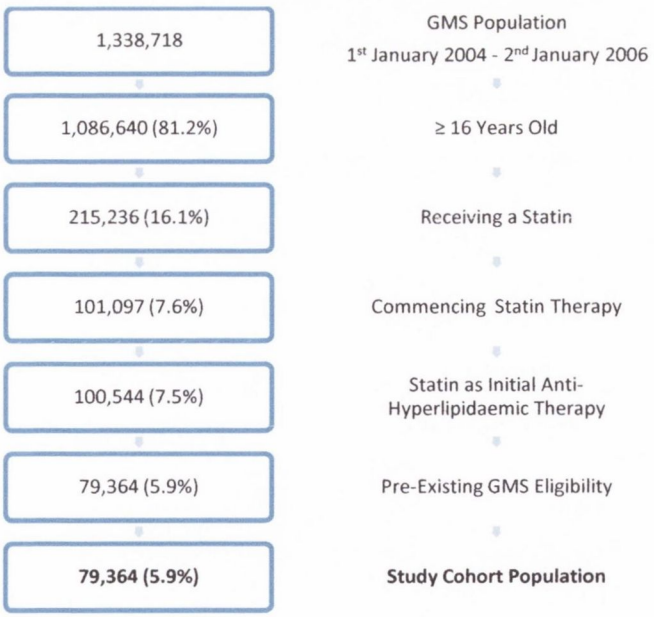
Number of Dispensed Prescription Items (Excluding Statins, Preceding 365 Days). Categorical variable, time-varying covariate.

3.7 Study Cohort & Covariate Characteristics

3.7.1 Study Cohort

A total of 79,364 patients aged 16 years or older were identified commencing a statin as initial anti-hyperlipidaemic treatment between the 1st January 2004 and the 2nd January 2006 (see Figure 3.1 below). These patients were identified from an available GMS population of 1.34 million patients. This total GMS population figure is estimated from those patients who received any treatment on the HSE-PCRS pharmacy claims database during the period of interest. Of these patients 1.09 million were over the age of 16 and 0.22 million received at least one prescription for a statin. In total 79,364 of these patients commenced a statin as initial anti-hyperlipidaemic therapy and had evidence of pre-existing GMS eligibility.

FIGURE 3.1: STUDY COHORT SELECTION FROM THE HSE-PCRS PHARMACY CLAIMS DATABASE (% OF ORIGINAL GMS POPULATION)



3.7.2 Study Covariates

The demographic, treatment and clinical characteristics of the study cohort are presented in Table 3.2 (see below). Females accounted for 55.6% of the study population and 62.5% of patients were 65 years of age or over at treatment initiation. This reflects the over-representation of elderly patients in the GMS population. Atorvastatin represented 60.3% of initial prescriptions, with 14.2% of patients receiving two different statins during the course of follow-up and 1.8% of patients receiving three or more different statins. Statin therapy was prescribed by a general practitioner in 90.5% of patients. 57.0%, 41.1% and 1.9% of patients initiated treatment at a low, intermediate and high dose respectively. Evidence of ischaemic heart disease was present in 9.3% of patients at baseline rising to 18.2% over the course of follow-up. Diabetes was present in 10.8% of patients at baseline and 16.8% by the end of follow-up. Depression was identified in 21.6% of patients at any time prior to statin therapy initiation and in 31.1% by the end of follow-up. The number of patients with a recent diagnosis of depression (prior 180 days) at treatment initiation was 3.5%. The neuro-degenerative diseases, Parkinson's and Alzheimer's, were present in 3.4% of patients at baseline and 6.2% of patients at the end of follow-up. The median number of non-cardiovascular and cardiovascular pharmacological agents received by a patient in the 365 days prior to statin initiation was 6 (inter-quartile range 3, 11) and 1 (inter-quartile range 0, 2) respectively. In total patients received a median of 52 (inter-quartile range 14, 110) prescription items in the 365 days prior to treatment initiation.

TABLE 3.2: DEMOGRAPHIC, TREATMENT AND CLINICAL CHARACTERISTICS FOR THE SOURCE STUDY COHORT

Characteristic		Population	(%)
N		79,364	-
Gender			
	Male	35,265	(44.4)
	Female	44,099	(55.6)
Age*			
	16-34	2,666	(3.4)
	35-44	3,676	(4.6)
	45-54	8,576	(10.8)
	55-64	14,864	(18.7)
	65-74	25,382	(32.0)
	≥75	24,200	(30.5)
Statin Type*			
	Simvastatin	4,553	(5.7)
	Pravastatin	17,085	(21.5)
	Fluvastatin	1,375	(1.7)
	Atorvastatin	47,881	(60.3)
	Rosuvastatin	8,145	(10.3)
	Simvastatin/Ezetimibe	325	(0.4)
Statin Initiator*			
	General Practitioner	71,841	(90.5)
	Hospital Prescriber	7,523	(9.5)
Statin Dose*			
	Low	45,204	(57.0)
	Intermediate	32,676	(41.1)
	High	1,484	(1.9)
Baseline Co-morbidities*			
	IHD	7,413	(9.3)
	Diabetes	8,852	(10.8)
	Depression	17,159	(21.6)
	Depression (Recent)	2,779	(3.5)
	Parkinson's Disease	1,613	(2.0)
	Alzheimer's Disease	1,117	(1.4)
Total Co-morbidities†			
	IHD	14,430	(18.2)
	Diabetes	13,341	(16.8)
	Depression	24,701	(31.1)
	Parkinson's Disease	2,387	(3.0)

Characteristic	Population	(%)
Alzheimer's Disease	2,533	(3.2)
Prescribing History		
Number of Pharmacological Agents‡ Median & IQR	6	3, 11
Number of Cardiovascular Agents‡ Median & IQR	1	0, 2
Number of Prescription Items‡ Median & IQR	52	14, 110

*Baseline values at treatment initiation. †Prevalence over complete patient follow-up. ‡ In 365 days prior to treatment initiation. ***IHD***, ischaemic heart disease. ***IQR***, inter-quartile range. ***N***, number of patients in cohort.

CHAPTER FOUR

4 STATIN ADHERENCE – SINGLE MEASURE MODEL

4.1 INTRODUCTION

Medication-taking behaviour analyses based on a single measure of adherence at a defined point in time are the most commonly utilized models for the assessment of adherence using prescription refill data.[17] Their widespread use stems from their straightforward implementation and relative simplicity – These models calculate a single measure of adherence over a specified observation period (e.g. 2 years) and utilise the results to construct predictive models of non-adherent behaviour. The application of a single measure model for statin adherence in the GMS population is described here. Adherence was calculated using four observation period definitions and the results of these analyses are compared with previous similar studies of statin adherence. The advantages and limitations of these observation period definitions and of single measure models of adherence in general are discussed.

4.2 METHODS

4.2.1 SELECTION OF AN ADHERENCE MEASURE

Of the available adherence calculation methods, the proportion of days covered (PDC) adherence measure proposed by Avorn et al[38, 47] was selected as the most appropriate for this analysis. This selection was based primarily on the consideration that the PDC adherence measure fulfils all of the criteria for an upper limit of adherence (see Section 1.3.1.2 on page 33). Also, the PDC adherence measure is flexible enough to be adapted to a number of adherence models. Variations in PDC methodology will be used in each of the subsequent models of medication-taking behaviour (see Chapters 5 & 6 on pages 83 & 115) and its consistent use across these models will aid the comparison of results.

4.2.2 CALCULATION OF PROPORTION OF DAYS COVERED

The proportion of days covered was calculated using Equation 4.1[47] (see below) with the length of observation period (γ) defined in four separate ways. Firstly, the observation period was defined as a uniform

720 days (≈ 2 years) for every patient (SMM-720[i]). All patients were required to have an observation period of at least 720 days; patients commencing a statin on or after the 31st July 2004 were therefore excluded from the analysis. In addition to this patients who become lost to follow-up (see Section 3.5.1 on page 49) before the end of 720 days in the PDC observation period were also excluded from the analysis. Secondly, the observation period was defined as 720 days or up to the end of a patient's follow-up whichever occurred first (SMM-EFU[ii]). All patients in the source study cohort (see Chapter 3 on page 43) were therefore included in the analysis. Thirdly, the observation period was defined as 720 days or up to the date a patient received their last statin prescription (SMM-LastRx[iii]). Patients receiving less than two prescriptions were excluded from the analysis as there was insufficient information to calculate an adherence rate for them. Finally, the observation period was defined as 720 days or up to the date a patient became non-persistent with treatment, where non-persistence was defined as a permissible gap in treatment of 180 days (SMM-NonPer[iv], see Chapter 7 on page 139). The number of assigned doses in an observation period was determined from the constructed longitudinal database of medication supply (see Section 3.3 on page 46). The calculated proportion of days covered measures in each of the models have a maximum value of 100% and may be interpreted as an upper limit of adherence (see Section 1.3.1.2 on page 33). Non-adherence was defined as a PDC of less than 80% (see Section 3.2 on page 46).

EQUATION 4.1: PROPORTION OF DAYS COVERED FOR THE SINGLE MEASURE MODEL[47]

$$Proportion\ of\ Days\ Covered\ (Single\ Measure\ Model, \%) = \left[\sum_{\delta=\alpha}^{\gamma} \delta \Big/ \gamma\right] \times 100$$

Where α denotes the first day of a patient's treatment episode, γ denotes the last day of a patient's adherence calculation observation period and δ denotes the days supply (1 or 0) assigned to each day (see Section 1.3.1.2 on page 33 & Section 3.3 on page 46).

4.2.3 Statistical Analysis

The proportion of days covered results were dichotomized into adherent (PDC ≥ 80%) and non-adherent (PDC < 80%). Logistic regression analyses (SAS® PROC LOGISTIC) were used to estimate the univariate and

[i] Single measure model of adherence at 720 days follow-up in patients with at least 720 days follow-up.
[ii] Single measure model of adherence at 720 days follow-up or up to end of follow-up.
[iii] Single measure model of adherence at 720 days follow-up or up to last statin prescription.
[iv] Single measure model of adherence at 720 days follow-up or up to non-persistence.

multivariate odds ratios for non-adherence for each of the defined observation periods (SMM-720, SMM-EFU, SMM-LastRx & SMM-NonPer). The multivariate analyses were adjusted for all included covariates. Crude and adjusted odds ratios with 95% confidence intervals are presented for independent covariates. Covariates with the potential to change over the course of a patient's follow-up were only included where baseline covariate values could be appropriately substituted. Significance at $p < 0.05$ was assumed. SAS® version 9.1[i] was used for all analyses.

4.2.4 Covariates Included in the Single Measure Model

Baseline covariate values at statin treatment initiation were included for the following time-varying covariates; age, statin type, statin dose, statin prescriber, all co-morbidities and the number of non-cardiovascular pharmacological agents, cardiovascular pharmacological agents and prescription items received by a patient in the 365 days prior to statin initiation. The time-varying covariate 'statin dose change' was not included in the model as a decrease or increase in statin dose could not be recorded at baseline. Patient gender was also included. A full description of these covariates can be found in Section 3.6 (see page 49).

4.3 Results

4.3.1 Single Measure Model – Study Cohort Subsets

23,184 (29.2%) patients from the source study cohort (see Table 3.2 on page 53,) commenced a statin prior to the 1st July 2004 and consequently have a possible follow-up time of at least 720 days. However, 15.9% (3,690) of these patients became lost to follow-up prior to the end of the 720 days observation period and were therefore excluded from the SMM-720 cohort. In total the number of patients with sufficient follow-up time for inclusion in the SMM-720 cohort was 19,494 (24.6%). The number of patients in the source study cohort who received no more than one statin prescription during the course of follow-up was 9,013 (11.4%). These patients were excluded from the SMM-LastRx study cohort; leaving 70,351 (88.6%) patients eligible for inclusion in the analysis. The characteristics of these abridged cohorts are presented in Table 4.1 (see below). The definition of the SMM-EFU observation period and the SMM-NonPer observation period permitted the inclusion of all patients from the source study cohort (n=79,364).

[i] SAS Institute, Cary, NC, USA.

TABLE 4.1: CHARACTERISTICS OF THE SMM-720, SMM-EFU, SMM-LASTRX & SMM-NONPER STATIN ADHERENCE COHORT SUBSETS

Characteristic	SMM-720 (%)		SMM-EFU (%)‡		SMM-LastRx (%)		SMM-NonPer (%)‡	
N	19,494	-	79,364	-	70,351	-	79,364	-
Gender								
Male	8,622	(44.2)	35,265	(44.4)	31,137	(44.3)	35,265	(44.4)
Female	10,872	(55.8)	44,099	(55.6)	39,214	(55.8)	44,099	(55.6)
Age								
16-34*	384	(2.0)	2,666	(3.4)	1,260	(1.8)	2,666	(3.4)
35-44*	751	(3.9)	3,676	(4.6)	2,776	(3.9)	3,676	(4.6)
45-54*	1,965	(10.1)	8,576	(10.8)	7,459	(10.6)	8,576	(10.8)
55-64*	3,637	(18.7)	14,864	(18.7)	13,615	(19.4)	14,864	(18.7)
65-74*	6,780	(34.8)	25,382	(32.0)	23,580	(33.5)	25,382	(32.0)
≥75*	5,977	(30.7)	24,200	(30.5)	21,661	(30.8)	24,200	(30.5)
Statin Type								
Simvastatin*	1,308	(6.7)	4,553	(5.7)	3,954	(5.6)	4,553	(5.7)
Pravastatin*	4,742	(24.3)	17,085	(21.5)	14,687	(20.9)	17,085	(21.5)
Fluvastatin*	331	(1.7)	1,375	(1.7)	1,128	(1.6)	1,375	(1.7)
Atorvastatin*	10,441	(53.6)	47,881	(60.3)	42,952	(61.1)	47,881	(60.3)
Rosuvastatin*	2,672	(13.7)	8,145	(10.3)	7,344	(10.4)	8,145	(10.3)
Simvastatin/Ezetimibe*	0	(0.0)	325	(0.4)	286	(0.4)	325	(0.4)
Prescriber								
General Practitioner*	18,215	(93.4)	71,841	(90.5)	63,307	(90.0)	71,841	(90.5)
Hospital Prescriber*	1,279	(6.6)	7,523	(9.5)	7,044	(10.0)	7,523	(9.5)
Dose								
Low Dose*	11,698	(60.0)	45,204	(57.0)	40,823	(58.1)	45,204	(57.0)
Intermediate Dose*	7,575	(38.9)	32,676	(41.1)	28,281	(40.2)	32,676	(41.1)
High Dose*	221	(1.1)	1,484	(1.9)	1,247	(1.8)	1,484	(1.9)
Co-morbidities								
IHD*	1,872	(9.6)	7,413	(9.3)	6,901	(9.8)	7,413	(9.3)
Diabetes*	2,172	(11.1)	8,852	(10.8)	8,043	(11.4)	8,852	(10.8)
Depression*	3,856	(19.8)	17,159	(21.6)	15,152	(21.5)	17,159	(21.6)
Depression (Recent)*	678	(3.5)	2,779	(3.5)	2,466	(3.5)	2,779	(3.5)
Parkinson's Disease*	354	(1.8)	1,613	(2.0)	1,360	(1.9)	1,613	(2.0)
Alzheimer's Disease*	196	(1.0)	1,117	(1.4)	963	(1.4)	1,117	(1.4)
Prescribing History								
Pharmacological Agents†	6	3, 11	6	3, 11	6	3, 11	6	3, 11
Cardiovascular Agents†	1	0, 2	1	0, 2	1	0, 2	1	0, 2
Prescription Items†	61	20, 117	52	14, 110	55	15, 112	52	14, 110

*Baseline values at treatment initiation. † Number in 12 months prior to treatment initiation with median & inter-quartile range. ‡ Same as source study cohort (see Table 3.2 on page 53). ***SMM-720***, proportion of days covered at 720 days

follow-up. ***SMM-EFU***, proportion of days covered at 720 days follow-up or end of follow-up. ***SMM-LastRx***, proportion of days covered at 720 days follow-up or last statin prescription. ***SMM-NonPer***, proportion of days covered at 720 days follow-up or non-persistence. ***IHD***, ischaemic heart disease. ***N***, number of patients in cohort.

4.3.2 Single Measure Model – Proportion of Days Covered Results

The number of patients identified as non-adherent, with a PDC of less than 80%, for each of the four observation period definitions, SMM-720, SMM-EFU, SMM-LastRx and SMM-NonPer was 47.1%, 47.3%, 37.6% and 27.4% respectively (see Table 4.2 below). The median PDC for these observation periods were 82.0%, 82.1%, 86.8% and 91.3%. The mean PDC was 66.0%, 67.1%, 76.8% and 85.0%. The distributions of PDC values for the four observation periods are shown in Figure 4.1, Figure 4.2, Figure 4.3 and Figure 4.4 (see below).

TABLE 4.2: DESCRIPTIVE MEASURES FOR THE SMM-720, SMM-EFU, SMM-LASTRX & SMM-NONPER STATIN ADHERENCE COHORTS

	SMM-720		SMM-EFU		SMM-LastRx		SMM-NonPer	
N	19,494	-	79,364	-	70,351	-	79,364	-
PDC < 80% (%)	9,174	(47.1)	37,528	(47.3)	26,480	(37.6)	21,797	(27.4)
Mean (SD)	66.0	(33.1)	67.1	(32.9)	76.8	(25.3)	85.0	(18.1)
Median & IQR	82.0	39.7, 92.5	82.1	40.7, 93.9	86.8	66.9, 95.3	91.3	78.0, 99.6

N, number of patients in cohort. ***SD***, standard deviation. ***IQR***, inter-quartile range. ***SMM-720***, proportion of days covered at 720 days follow-up. ***SMM-EFU***, proportion of days covered at 720 days follow-up or end of follow-up. ***SMM-LastRx***, proportion of days covered at 720 days follow-up or last statin prescription. ***SMM-NonPer***, proportion of days covered at 720 days follow-up or non-persistence. ***Non-adherence*** = PDC < 80%.

FIGURE 4.1: DISTRIBUTION OF PROPORTION OF DAYS COVERED BY STATIN SUPPLY AT 720 DAYS FOLLOW-UP (SMM-720)

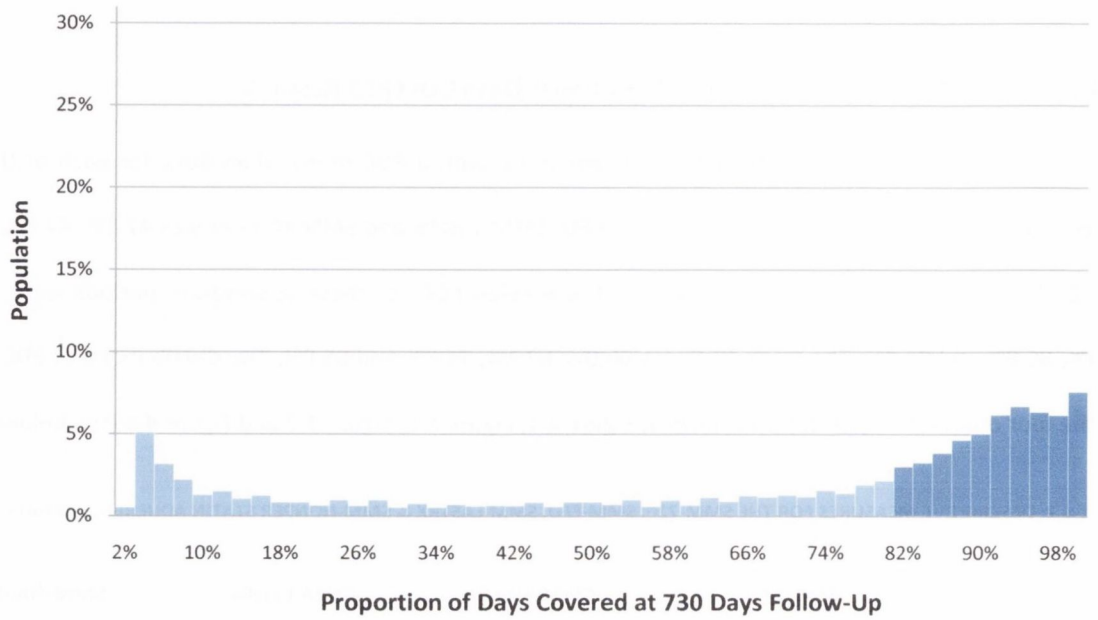


FIGURE 4.2: DISTRIBUTION OF PROPORTION OF DAYS COVERED BY STATIN SUPPLY AT 720 DAYS FOLLOW-UP OR END OF FOLLOW-UP (SMM-EFU)

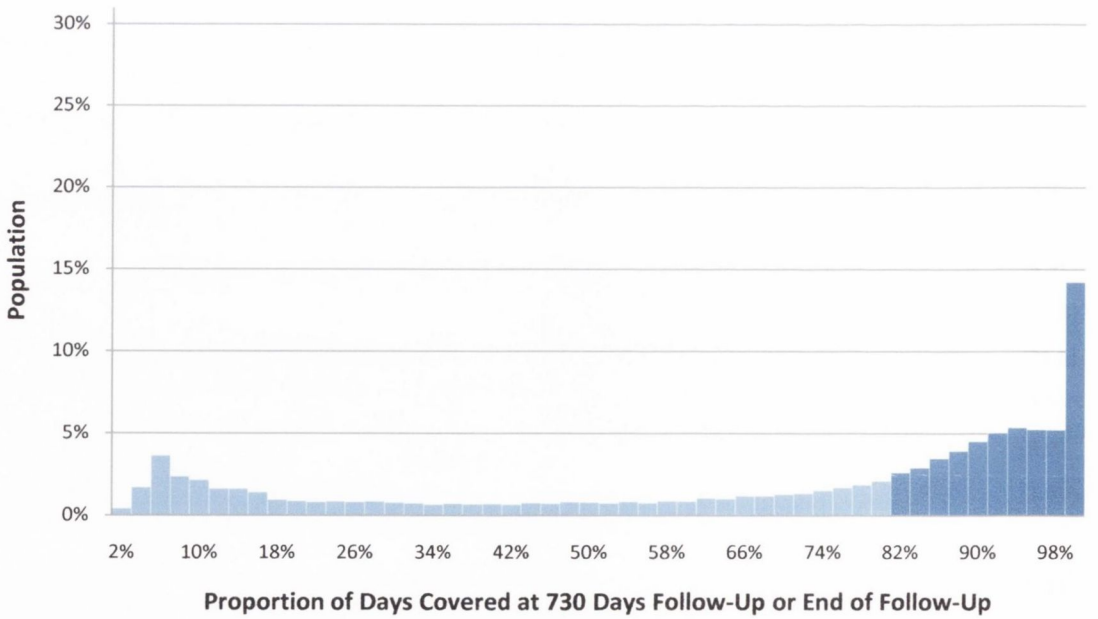


FIGURE 4.3: DISTRIBUTION OF PROPORTION OF DAYS COVERED BY STATIN SUPPLY AT 720 DAYS FOLLOW-UP OR LAST STATIN PRESCRIPTION (SMM-LASTRX)

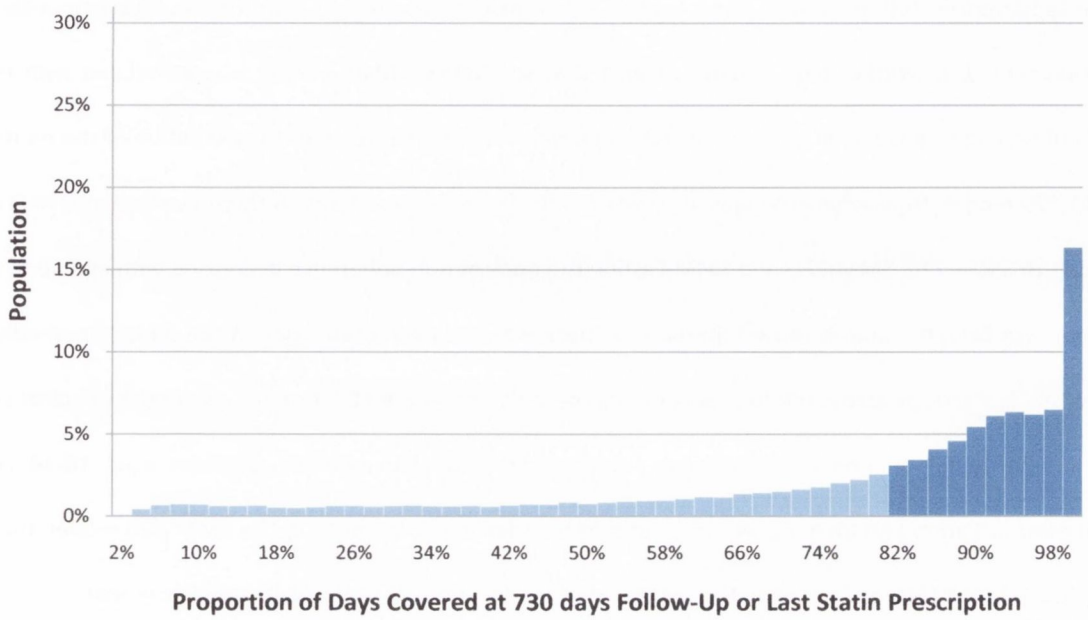
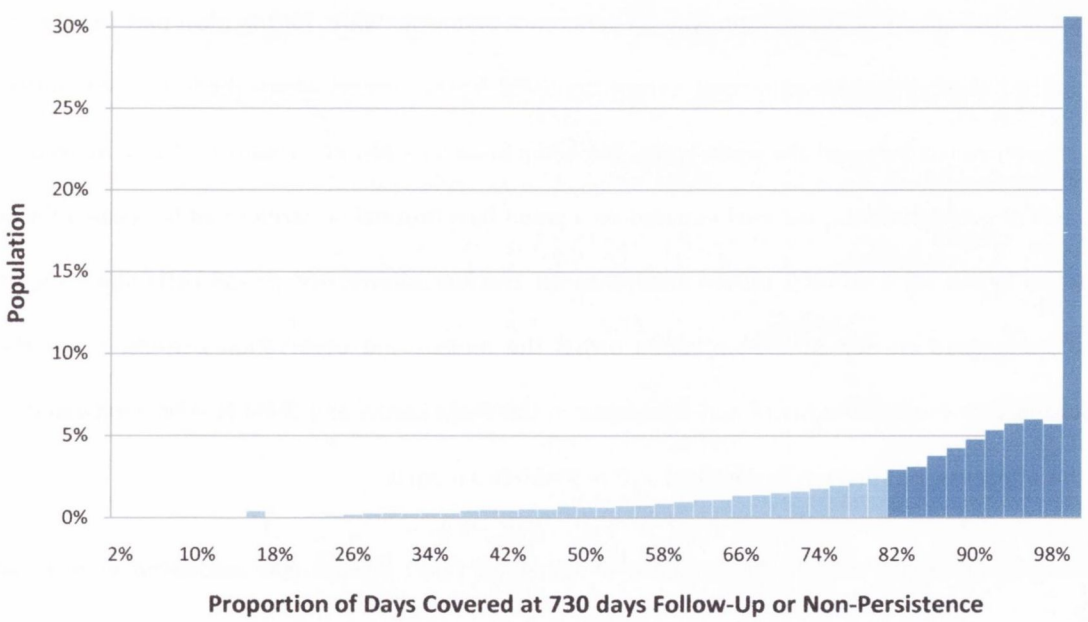


FIGURE 4.4: DISTRIBUTION OF PROPORTION OF DAYS COVERED BY STATIN SUPPLY AT 720 DAYS FOLLOW-UP OR NON-PERSISTENCE (SMM-NONPER)



4.3.3 Logistic Regression Analyses – Univariate & Multivariate Models

The results from the univariate and multivariate models of non-adherence for the four observation periods are presented in Table 4.3 and Table 4.4 (see below). The results from the multivariate analyses are also presented in whisker plot format in Figure 4.5 (see below). Male gender was associated with reduced odds of non-adherence in all of the univariate and multivariate analyses with the exception of the multivariate SMM-720 model. Non-adherence was associated with the extremes of age in the univariate and multivariate models of SMM-720, SMM-EFU and SMM-LastRx; the odds of non-adherence decreased with age up to the 65-74 year age category and increased thereafter. There was however a reduction in the odds of non-adherence in certain age groups across the four observation periods and in the PDC-NonPer model the effect of younger age (16-34 years) on non-adherence risk reversed direction. For example; patients aged 16-34 years at treatment initiation had an adjusted odds ratio of 5.60 for non-adherence in the SMM-720 model, this fell to 2.40 in the SMM-EFU model 0.69 in the SMM-LastRx model and 0.71 in the SMM-NonPer model.

In comparison to pravastatin, patients initiated on atorvastatin had reduced odds of non-adherence in all analyses except the SMM-NonPer model. Patients prescribed rosuvastatin as initial therapy had reduced odds of non-adherence in the SMM-720 models and patients prescribed fluvastatin were least likely to adhere to treatment. The effects of initial statin type on adherence behaviour were, for the most part, consistent across the defined observation period models except the SMM-NonPer model where there was little difference in non-adherence risk between the statin types. The initial prescriber of statin treatment had a marked effect on the odds of non-adherence; patients initiated on a statin by a hospital prescriber had between a 6% and 22% reduction in the adjusted odds of non-adherence for the four observation period definitions. The effect of initial statin dose on non-adherence varied across the models and observation periods. A low dose was associated with increased odds of non-adherence in the SMM-LastRx and SMM-NonPer multivariate models but this effect was not present in the SMM-720 or SMM-EFU models.

In the univariate models the presence of ischaemic heart disease was associated with a significant reduction in the odds of non-adherence across all observation periods. However, in the multivariate model the effect of ischaemic heart disease was absent for patients in the SMM-720 and SMM-EFU cohorts and reversed for patients in the SMM-LastRx and SMM-NonPer cohorts. A diagnosis of depression or recent depression was not associated with an increased or a decreased risk of non-adherence in the multivariate models. Parkinson's

disease and Alzheimer's disease were respectively associated with a decreased and an increased risk of non-adherence in the multivariate model of SMM-NonPer. Diabetes was the only co-morbidity to have a significant effect on the odds of non-adherence across all models and observation periods, except for the multivariate model of SMM-NonPer.

Increasing numbers of non-cardiovascular agents were associated with an increase in the adjusted odds of non-adherence across the four observation periods. The opposite trend was observed for cardiovascular pharmacological agents, with increasing numbers associated with a reduction in the odds of non-adherence. There was also a reduction in the odds of non-adherence as the number of prescription items filled by a patient in the 365 days prior to statin initiation increased.

TABLE 4.3: RESULTS FROM THE UNIVARIATE LOGISTIC REGRESSION ANALYSES OF STATIN NON-ADHERENCE FOR THE SMM-720, SMM-EFU, SMM-LASTRX & SMM-NONPER STUDY COHORTS

Univariate Model Covariates	SMM-720		SMM-EFU		SMM-LastRx		SMM-NonPer	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Gender								
Male	0.94	(0.89, 0.99)	0.94	(0.91, 0.96)	0.96	(0.93, 0.99)	0.94	(0.91, 0.97)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	7.61	(5.76, 10.1)	3.18	(2.92, 3.46)	2.49	(2.22, 2.79)	0.84	(0.76, 0.92)
35-44*	3.18	(2.70, 3.73)	2.65	(2.46, 2.84)	2.28	(2.10, 2.46)	1.47	(1.37, 1.59)
45-54*	2.02	(1.83, 2.24)	1.88	(1.79, 1.98)	1.83	(1.73, 1.93)	1.56	(1.48, 1.65)
55-64*	1.25	(1.15, 1.35)	1.25	(1.20, 1.30)	1.25	(1.20, 1.31)	1.23	(1.18, 1.29)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.12	(1.05, 1.21)	1.11	(1.07, 1.15)	0.96	(0.92, 1.00)	0.95	(0.91, 0.99)
Statin Type								
Simvastatin*	1.01	(0.89, 1.14)	1.00	(0.94, 1.07)	1.03	(0.96, 1.11)	1.03	(0.96, 1.11)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.33	(1.06, 1.66)	1.26	(1.12, 1.40)	1.22	(1.08, 1.38)	1.01	(0.90, 1.14)
Atorvastatin*	0.85	(0.80, 0.91)	0.85	(0.82, 0.88)	0.87	(0.84, 0.90)	0.99	(0.95, 1.03)
Rosuvastatin*	0.90	(0.82, 0.99)	0.95	(0.90, 1.00)	1.01	(0.96, 1.07)	1.05	(0.99, 1.12)
Simvastatin/Ezetimibe*	-	-	1.02	(0.82, 1.27)	1.03	(0.81, 1.31)	1.39	(1.11, 1.76)
Prescriber								
General Practitioner*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.74	(0.66, 0.83)	0.72	(0.69, 0.76)	0.71	(0.68, 0.75)	0.87	(0.82, 0.92)
Dose								
Low Dose*	0.91	(0.86, 0.96)	0.96	(0.93, 0.98)	1.02	(0.99, 1.06)	1.08	(1.04, 1.11)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	0.96	(0.74, 1.26)	0.97	(0.87, 1.08)	0.94	(0.83, 1.05)	0.94	(0.83, 1.06)
Co-morbidities								
IHD*	0.71	(0.65, 0.79)	0.73	(0.70, 0.77)	0.74	(0.70, 0.78)	0.85	(0.80, 0.89)
Diabetes*	0.65	(0.60, 0.72)	0.72	(0.68, 0.75)	0.79	(0.75, 0.83)	0.90	(0.85, 0.95)
Depression*	1.12	(1.05, 1.21)	1.07	(1.03, 1.10)	1.00	(0.97, 1.04)	1.02	(0.98, 1.06)
Depression (Recent) *	1.42	(1.22, 1.65)	1.27	(1.18, 1.37)	1.27	(1.17, 1.38)	1.28	(1.18, 1.39)
Parkinson's Disease*	0.86	(0.69, 1.06)	0.91	(0.83, 1.01)	0.78	(0.69, 0.87)	0.72	(0.64, 0.82)
Alzheimer's Disease*	0.88	(0.66, 1.17)	0.95	(0.85, 1.07)	0.91	(0.80, 1.04)	1.01	(0.88, 1.15)
Prescribing History								
Non-Cardio PAs† ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	0.94	(0.87, 1.03)	0.99	(0.95, 1.03)	0.91	(0.87, 0.95)	1.00	(0.96, 1.05)
6 - 11	0.93	(0.85, 1.00)	0.96	(0.92, 1.00)	0.84	(0.81, 0.88)	0.39	(0.90, 0.98)

Univariate Model Covariates	SMM-720		SMM-EFU		SMM-LastRx		SMM-NonPer	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
≥ 11	1.10	(1.01, 1.20)	1.08	(1.03, 1.12)	0.89	(0.85, 0.93)	0.98	(0.93, 1.02)
Cardio PAs† ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.62	(0.58, 0.67)	0.67	(0.64, 0.69)	0.67	(0.64, 0.69)	0.83	(0.80, 0.87)
2	0.47	(0.43, 0.51)	0.55	(0.53, 0.57)	0.55	(0.52, 0.57)	0.71	(0.68, 0.75)
≥ 3	0.48	(0.45, 0.52)	0.52	(0.50, 0.54)	0.50	(0.48, 0.52)	0.67	(0.64, 0.70)
Rxs† ≤ 13	Ref	-	Ref	-	Ref	-	Ref	-
14-51	0.99	(0.91, 1.07)	0.99	(0.96, 1.03)	0.89	(0.86, 0.93)	0.96	(0.92, 1.00)
52-109	0.64	(0.59, 0.70)	0.65	(0.62, 0.67)	0.59	(0.56, 0.62)	0.73	(0.70, 0.77)
≥ 110	0.50	(0.46, 0.55)	0.54	(0.52, 0.56)	0.45	(0.43, 0.47)	0.57	(0.55, 0.60)

*Baseline values at treatment initiation. † Number in 12 months prior to treatment initiation. ***SMM-720***, proportion of days covered at 720 days follow-up. ***SMM-EFU***, proportion of days covered at 720 days follow-up or end of follow-up. ***SMM-LastRx***, proportion of days covered at 720 days follow-up or last statin prescription. ***SMM-NonPer***, proportion of days covered at 720 days follow-up or non-persistence. ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***Rxs***, number of prescription items. ***IHD***, ischaemic heart disease. ***OR***, odds ratio. ***CI***, confidence interval. ***Non-adherence*** = PDC < 80%. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

TABLE 4.4: RESULTS FROM THE MULTIVARIATE LOGISTIC REGRESSION ANALYSES OF STATIN NON-ADHERENCE FOR THE SMM-720, SMM-EFU, SMM-LASTRX & SMM-NONPER STUDY COHORTS

Multivariate Model Covariates	SMM-720		SMM-EFU		SMM-LastRx		SMM-NonPer	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Gender								
Male	0.96	(0.90, 1.02)	0.95	(0.92, 0.98)	0.95	(0.92, 0.98)	0.93	(0.90, 0.96)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	5.60	(4.22, 7.43)	2.40	(2.20, 2.62)	1.94	(1.73, 2.18)	0.69	(0.62, 0.76)
35-44*	2.51	(2.12, 2.96)	2.15	(2.00, 2.32)	1.89	(1.75, 2.05)	1.27	(1.18, 1.37)
45-54*	1.75	(1.58, 1.95)	1.63	(1.55, 1.71)	1.60	(1.52, 1.69)	1.42	(1.34, 1.49)
55-64*	1.18	(1.09, 1.28)	1.17	(1.12, 1.22)	1.18	(1.13, 1.24)	1.18	(1.13, 1.24)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.29	(1.20, 1.39)	1.26	(1.22, 1.31)	1.13	(1.08, 1.17)	1.05	(1.01, 1.10)
Statin Type								
Simvastatin*	1.05	(0.92, 1.19)	1.00	(0.93, 1.07)	1.02	(0.95, 1.10)	1.02	(0.95, 1.10)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.33	(1.04, 1.70)	1.27	(1.13, 1.44)	1.24	(1.09, 1.42)	1.04	(0.91, 1.18)
Atorvastatin*	0.88	(0.82, 0.95)	0.88	(0.85, 0.92)	0.89	(0.85, 0.92)	0.98	(0.94, 1.02)
Rosuvastatin*	0.91	(0.82, 1,02)	0.95	(0.89, 1.00)	0.96	(0.90, 1.02)	0.99	(0.93, 1.05)
Simvastatin/Ezetimibe*	-	-	0.93	(0.74, 1.16)	0.96	(0.75, 1.23)	1.38	(1.09, 1.74)
Prescriber								
General Practitioner*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.78	(0.69, 0.88)	0.79	(0.75, 0.83)	0.80	(0.76, 0.85)	0.94	(0.89, 1.00)
Dose								
Low Dose*	0.99	(0.93, 1.06)	1.01	(0.97, 1.04)	1.07	(1.03, 1.11)	1.10	(1.06, 1.14)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	0.87	(0.64, 1.17)	0.92	(0.82, 1.03)	0.90	(0.79, 1.02)	0.93	(0.82, 1.06)
Co-morbidities								
IHD*	0.99	(0.89, 1.11)	1.01	(0.96, 1.07)	1.07	(1.01, 1.13)	1.07	(1.01, 1.14)
Diabetes*	0.74	(0.68, 0.82)	0.81	(0.77, 0.85)	0.92	(0.87, 0.97)	1.02	(0.96, 1.07)
Depression*	1.07	(0.98, 1.17)	1.04	(0.99, 1.08)	1.04	(0.99, 1.08)	1.05	(1.00, 1.10)
Depression (Recent) *	1.04	(0.87, 1.24)	0.97	(0.89, 1.06)	0.96	(0.88, 1.06)	1.03	(0.94, 1.12)
Parkinson's Disease*	0.89	(0.71, 1.11)	0.99	(0.89, 1.09)	0.89	(0.79, 1.00)	0.82	(0.73, 0.93)
Alzheimer's Disease*	0.96	(0.72, 1.29)	1.06	(0.94, 1.20)	1.09	(0.95, 1.24)	1.15	(1.01, 1.32)
Prescribing History								
Non-Cardio PAs† ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	1.20	(1.09, 1.31)	1.24	(1.19, 1.30)	1.15	(1.09, 1.20)	1.18	(1.12, 1.24)
6 - 11	1.59	(1.43, 1.76)	1.60	(1.52, 1.68)	1.43	(1.36, 1.51)	1.37	(1.30, 1.45)

Multivariate Model Covariates	SMM-720		SMM-EFU		SMM-LastRx		SMM-NonPer	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
≥ 11	2.57	(2.26, 2.91)	2.41	(2.27, 2.56)	2.07	(1.94, 2.21)	1.84	(1.72, 1.96)
Cardio PAs† ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.78	(0.72, 0.84)	0.80	(0.77, 0.83)	0.81	(0.77, 0.84)	0.94	(0.90, 0.98)
2	0.67	(0.61, 0.74)	0.75	(0.71, 0.78)	0.76	(0.73, 0.80)	0.90	(0.86, 0.95)
≥ 3	0.78	(0.71, 0.86)	0.78	(0.74, 0.82)	0.80	(0.75, 0.84)	0.94	(0.89, 0.99)
Rxs† ≤ 13	Ref	-	Ref	-	Ref	-	Ref	
14-51	0.86	(0.78, 0.95)	0.87	(0.83, 0.91)	0.80	(0.76, 0.84)	0.82	(0.78, 0.86)
52-109	0.54	(0.49, 0.61)	0.55	(0.52, 0.58)	0.51	(0.48, 0.54)	0.58	(0.55, 0.62)
≥ 110	0.35	(0.31, 0.40)	0.39	(0.37, 0.42)	0.34	(0.32, 0.37)	0.39	(0.37, 0.42)

*Baseline values at treatment initiation. † Number in 12 months prior to treatment initiation. ***SMM-720***, proportion of days covered at 720 days follow-up. ***SMM-EFU***, proportion of days covered at 720 days follow-up or end of follow-up. ***SMM-LastRx***, proportion of days covered at 720 days follow-up or last statin prescription. ***SMM-NonPer***, proportion of days covered at 720 days follow-up or non-persistence. ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***Rxs***, number of prescription items. ***IHD***, ischaemic heart disease. ***OR***, odds ratio. ***CI***, confidence interval. ***Non-adherence*** = PDC < 80%. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

FIGURE 4.5: WHISKER PLOT OF ODDS RATIOS WITH 95% CI FROM THE MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF STATIN NON-ADHERENCE FOR PDC-720 ■, PDC-EFU ■, PDC-LASTRX ■ & PDC-NONPER ■.

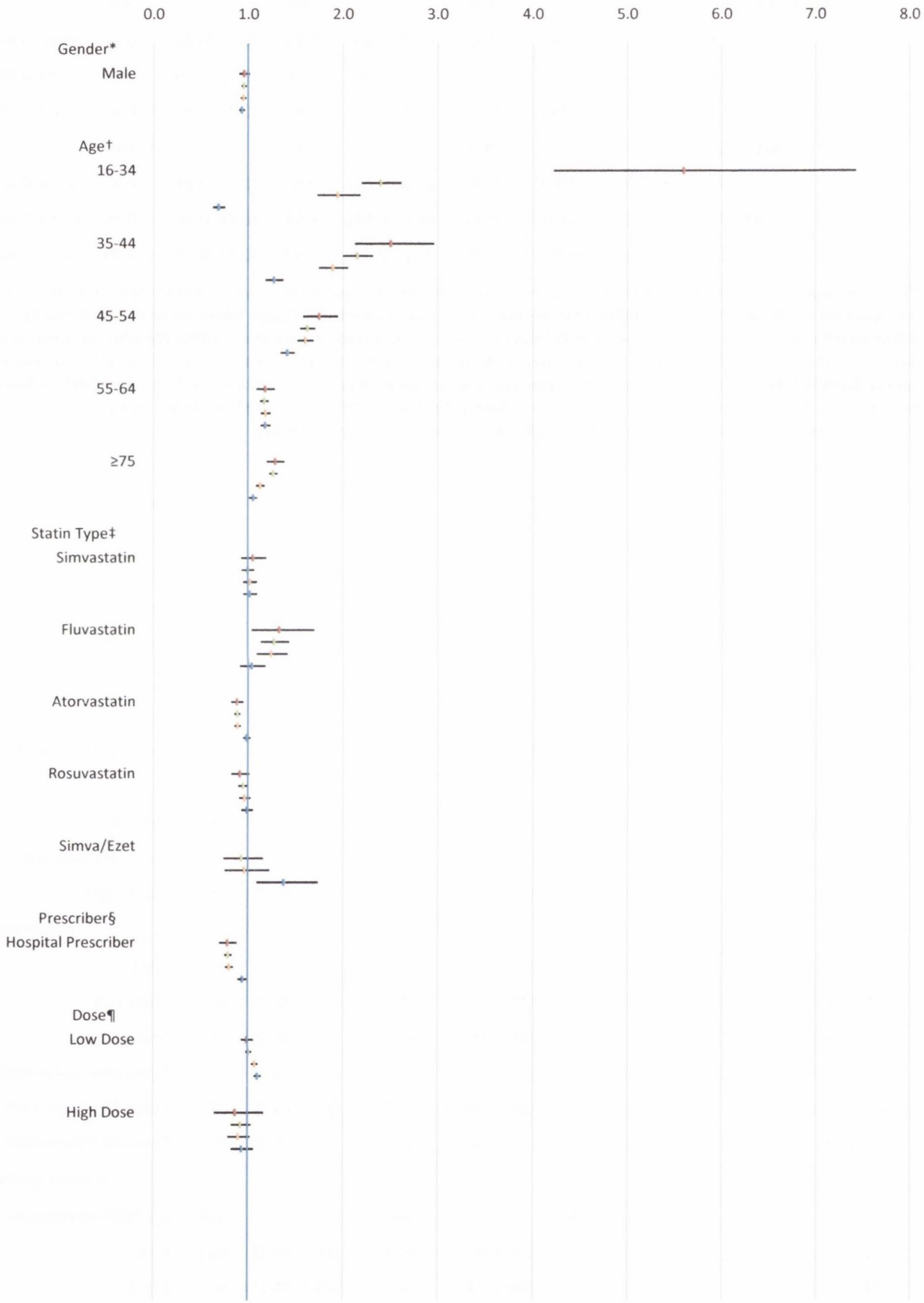
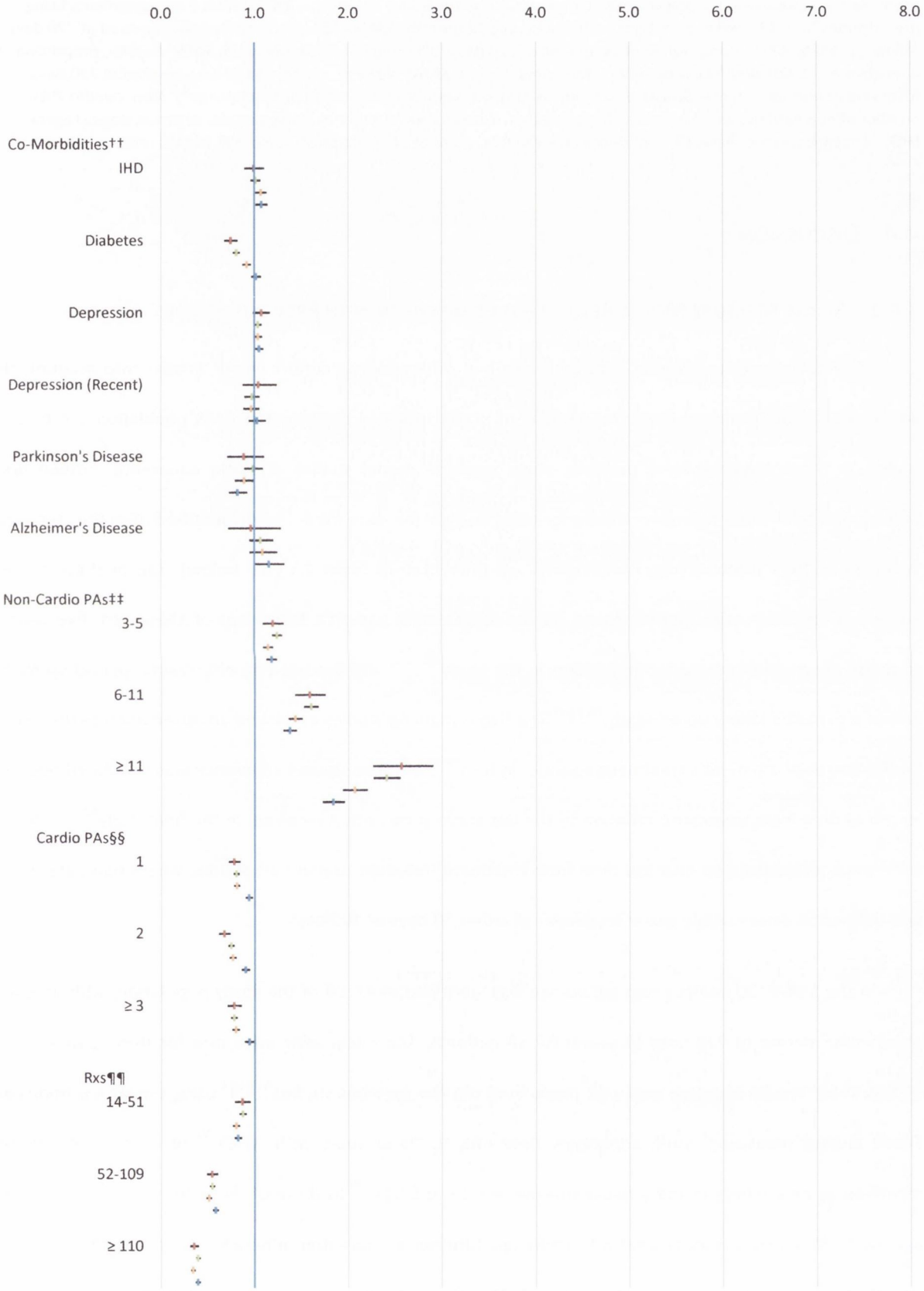


FIGURE 4.5 (CONTINUED): WHISKER PLOT OF ODDS RATIOS WITH 95% CI FROM THE MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF STATIN NON-ADHERENCE FOR PDC-720 ■, PDC-EFU ■, PDC-LASTRX ■ & PDC-NONPER ■.



■ = PDC-720. ■ = PDC-EFU. ■ = PDC-LastRx. ■ = PDC-NonPer* Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. ***SMM-720***, proportion of days covered at 720 days follow-up. ***SMM-EFU***, proportion of days covered at 720 days follow-up or end of follow-up. ***SMM-LastRx***, proportion of days covered at 720 days follow-up or last statin prescription. ***SMM-NonPer***, proportion of days covered at 720 days follow-up or non-persistence. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio.

4.4 Discussion

4.4.1 Single Measure Model Results – A Comparison with Previous Studies

After taking methodological considerations and differences in cohort characteristics into account, the adherence results obtained from the analysis of statin usage in the selected GMS population are broadly similar to those obtained from previous single measure model studies of statin adherence. Fifteen prior prescription refill studies of statin adherence using a single measure model were identified from the literature. Synopses of their methodologies and results are presented in Table 4.5 (see below). Ten of these studies employed an observation period based on the length of a patient's follow-up; of these ten, five used a common observation period for all patients in the study[40, 48-51] and five used an observation period up to the end of a patient's follow-up or death.[47, 52-55] The five remaining studies employed an observation period based on the length of a patient's treatment episode. In four[56-59] of these studies adherence was calculated over the length of time from treatment initiation to the last statin prescription received. In the final study[42] a patient's adherence was calculated over the time from treatment initiation to non-persistence, where non-persistence was defined as a permissible gap in treatment of either 30 days or 120 days.

In the SMM-720 analysis non-adherence was identified in 47.1% of the study population, with an equal observation period of 720 days (2 years) for all patients. The mean adherence rate for these patients was 66.0%. These results compare well with those from the five previous studies[40, 48-51] using similar methodology. These studies measured statin adherence over one to three years with 37.6%[50] to 72.0%[48] of patients identified as non-adherent and a mean adherence rate of 62.1%.[49] In three of these studies[40, 48, 49] increasing age, up to 65 years, was associated with improved adherence, thereafter adherence subsequently declined.[48] This is in agreement with results from the SMM-720 cohort analysis. Reduced statin adherence was also

identified in females,[40, 48, 49] but while a similar effect was observed in the univariate analysis of the SMM-720 cohort it was not present in the multivariate analysis. The effect of cardiovascular co-morbidities on statin adherence was assessed by Gibson[48] and Schultz,[40] interestingly patients in these two studies who had undergone a cardiovascular procedure (PTCA[i], CABG[ii]) or patients who had experienced a myocardial infarction had significantly higher odds of adherence; a diagnosis of ischaemic heart disease was however not associated with an effect on statin adherence. This may explain the results from the SMM-720 cohort analysis where a diagnosis of ischaemic heart disease did not influence a patient's odds of non-adherence. Initiation of a statin by a hospital prescriber was associated with reduced odds of non-adherence in the SMM-720 cohort. No other studies examined the effect of statin prescriber on adherence; however, in one study[40] an increasing number of hospitalizations was associated with improved adherence.

In the SMM-EFU analysis non-adherence was identified in 47.3% of patients with an observation period up to 720 days (2 years) or the end of follow-up. The mean adherence rate for patients in the SMM-EFU cohort was 67.1%. These adherence rates are comparable with those from the five statin adherence studies using similar methodology.[47, 52-55] These studies measured statin adherence over one to five year observation periods or up to a patient's death or end of follow-up, whichever occurred first. The proportion of patients identified as non-adherent in these studies was 34.0%[55] to 45.0%[52] and the mean adherence rate was 64.3%[47] to 83.9%.[54] The high mean adherence rate (83.9%) observed in the study by Campione[54] reflects the exclusion from the study cohort of patients under 50 years of age and patients in whom statin treatment was discontinued at the direction of a prescriber. Covariate analyses from these studies are in accordance with the higher rates of non-adherence observed in the SMM-EFU cohort for patients over and under the age of 65 years[47, 53, 54] and with the reduction in non-adherence associated with a diagnosis of diabetes.[47, 53, 54]

In the SMM-LastRx analysis non-adherence was identified in 37.6% of patients with an observation length of up to 720 days (2 years) or the date of the last statin prescription. The mean adherence rate for these patients was 76.8%. Four prior studies calculating adherence using a similarly defined observation period were identified from the literature.[56-59] These studies calculated adherence to treatment over two[57, 59] and three[56, 58] years or up to either the date a patient received their last statin prescription[56, 58, 59] or the last day's supply of a

[i] Percutaneous Transluminal Coronary Angioplasty.
[ii] Coronary Artery By-pass Graft.

patient's last statin prescription.[57] Two of these studies[58, 59] did not study adherence in new statin users and their results cannot therefore be easily compared with those from the SMM-LastRx analysis. In the two remaining studies non-adherence was identified in 36.1% of patients[57] and a mean adherence rate of 81%[57] to 82.1%[56] was observed. These mean adherence rates are marginally higher than those observed in the SMM-LastRx cohort; this may be explained by some minor methodological differences between the studies. In the analysis by LaFleur,[57] the observation period was defined up to the last day's supply of the last statin prescription. The addition of the number of days supply in the last prescription to both the assigned statin supply (numerator) and the observation period (denominator) will produce an increase in the calculated adherence rate compared to observation periods that exclude the last statin prescription. In the study by Grant[56] the length of time used to define an initial statin user was shorter (90 days) than that used in the SMM-LastRx cohort. There may therefore have been a higher proportion of existing statin users in the study cohort selected by Grant; these patients are known to have higher adherence rates than initial statin users.[47, 54, 55] Covariate analyses from these two studies show no effect on the risk of non-adherence for gender, or the presence of diabetes. As with the SMM-LastRx cohort analysis, increasing age, the number of co-prescribed cardiovascular medications and the presence of ischaemic heart disease were associated with a reduced risk of non-adherence.

Non adherence was identified in 27.4% of patients in the SMM-NonPer analysis and the mean adherence rate for these patients was 85.0%. The single study[42] identified from the literature using a similar observation period definition recorded 12.7% of patients as non-adherent at a follow-up of 5 years. The discrepancy between these two results may be related to the different definitions of non-persistence used. In the study by Larsen[42] a permissible gap of 30 days or 120 days was used to define non-persistence. A permissible gap of 180 days was used in the SMM-NonPer analysis. In the study by Larsen, results from the covariate analysis show a reduced odds ratio of non-adherence for patients aged between 0-44 years compared to patients 45-74 years of age (OR 0.46 95% CI 0.27, 0.78). This is in agreement with the covariate analysis results from the SMM-NonPer model where younger age was also associated with improved adherence to statin treatment.

TABLE 4.5: SYNOPSES OF SINGLE MEASURE MODEL STUDIES OF STATIN ADHERENCE USING PRESCRIPTION REFILL DATA

Study	Observation	Population	N	Adh <80%	Mean
Shrank[49] 2006	1 year follow-up for all patients†	Health insurance database, males & females, any age, initial user (6 months)	1,641	-	62.1%
Thiebaud[50] 2005	1 year follow-up for all patients†	Health insurance database, males & females, 18-65 years old, initial user (1 year)	38,866	37.6%	-
Schultz[40] 2005	1 year follow-up for all patients†	Health insurance database, males & females, > 18 years old, initial user (1 year)	21,239	57.3%	-
Gibson[48] 2006	1.5 years follow-up for all patients†	Medicare & health insurance databases, males & females, > 18 years old, initial user (1 year)	93,253	72.0%	-
Larsen[51] 2000	3 years follow-up for all patients†	Pharmacy claims database, males & females, any age, initial user (1 year)	-	*55.0%	-
Avorn[47] 1998	1 year or death‡	Medicare, PAAD & Quebec RAMQ databases, males & females, > 65 years old, initial user (1 year) & current user	1,938	35.2%	64.3%
Kopjar[55] 2003	1.5 years or death‡	Veterans administration database, males only, coronary heart disease, any age, initial user (1 year)	8,768	34.0%	-
Campione[54] 2005	2 years or end of follow-up‡ **Note** – patients required to have a minimum of 90 days follow-up	Veterans administration database, males & females, > 50 years old, initial user (6 months)	4,707	-	83.9%
Lachaine[53] 2006	2 years or treatment switch or end of follow-up‡	Quebec RAMQ database, any age, initial user (1 year)	14,076	40.2%	-
Wei[52] 2007	5 years or end of follow-up‡	Tayside MEMO database, > 20 years old, initial user (5 years)	16,363	45.0%	-
LaFleur[57] 2006	2 years or last day of last statin prescription§	Health insurance database, males & females, any age, initial user (6 months) **Note** – patients with only 1 statin prescription were excluded from the analysis	2,173	36.1%	81.0%
Grant[56] 2004	3months to 3 years or last statin prescription§	Health insurance database, males & females, any age, initial user (> 90 days) **Note** – patients with only 1 statin prescription were excluded from the analysis	4,518	-	82.1%
Sung[59] 1998	2 years or last statin prescription§ **Note** – patients required to have a minimum of 3 months follow-up	Health insurance database, males & females, any age, current user **Note** – patients with only 1 statin prescription were excluded from the analysis	772	**36.7%	74.0%

Study	Observation	Population	N	Adh <80%	Mean
Ellis[58] 2004	3 years or last statin prescription§	Health insurance database, males & females, ≥ 18 years old, current user **Note** – patients with only 1 statin prescription were excluded from the analysis	4,802	38.3%	79.0%
Larsen[42] 2002	5 years or non-persistence§ **Note** – non-persistence defined as a permissible gap of either 30 or 120 days in treatment	Odense OPED database, males & females, any age, initial user (> 1 year)	3,623	12.7%	-

*Non-adherence defined as < 82%. **Non-adherence defined as < 90%. † Total Time: Equal observation period for all patients in study. ‡Patient Time: Observation period to end of patient follow-up or death or treatment switch. §Treatment Time: Observation period to last statin prescription or non-persistence. ***Observation***, length of time over which single adherence measure calculated. ***Population***, Characteristics of study cohort. ***N***, number of patients in the study. ***Adh < 80%***, proportion of the study population with an adherence rate less than 80% if reported. ***Mean***, the mean adherence rate for the study population if reported.

4.4.2 Single Measure Model Results – A Comparison of Observation Period Definitions

The choice of observation period definition for the calculation of adherence at 720 days follow-up in this study produced a broad range of results. The proportion of patients classified as non-adherent varied from 27.4% to 47.3% and the mean adherence rate was between 66.0% and 85.0% (see Table 4.2 above). There was little difference in adherence results between the observation periods used in the SMM-720 and SMM-EFU analyses, however the mean adherence rate increased and the number of patients identified as non-adherent decreased for the SMM-LastRx analysis and for the SMM-NonPer analysis. The covariate analyses results also differed considerably between the defined observation periods, most notably with age where there was a large reduction in the adjusted odds of non-adherence for most age categories and in some cases even a reversal of effect. For example the odds ratio for non-adherence dropped from 5.60 to 0.69 in patients aged 16-34, from 2.51 to 1.27 in patients aged 35-44 and from 1.29 to 1.05 for patients aged ≥ 75 years (see Table 4.4 above). The effect of statin type and co-morbidity also varied across the observation period definitions, with each having little influence on non-adherent behaviour in the SMM-NonPer analysis.

The considerable variation in the adherence rate and covariate analysis results obtained from these four methods is similar to the variation in results obtained from the thirteen prior single measure model studies of statin non-adherence (see Table 4.5 above).[40, 42, 47-59] This variation prompts the question; which observation period is most appropriate for adherence calculation and analysis with single measure models?

4.4.3 Which Observation Period is Appropriate for Adherence Calculation & Analysis?

The four observation period definitions used in this study can be classified into two groups; observation periods based on the length of a patient's follow-up (SMM-720 & SMM-EFU) and observation periods based on the length of a patient's treatment episode (SMM-LastRx & SMM-NonPer). In the first set, adherence is measured over the time that a patient remains in the study, irrespective of whether the patient continues with the treatment of interest. In the second set, adherence is measured over the time that a patient can reasonably be assumed to be continuing with treatment.

There is conflicting opinion in the published literature as to which observation period is the most appropriate choice for adherence calculation and analysis. In reviews of adherence methodologies by Andrade,[17] Peterson[39] and Steiner[19] the authors suggest that the motivation for the use of one method in preference to the other should be determined by the goals of the individual study. However, in reviews by Cramer[41] and Halpern[35] the length of time from treatment initiation to treatment discontinuation is recommended; whereas Hess[18] recommends that the length of time from treatment initiation to the end of a patient's follow-up be used. Despite the conflicting opinions of various reviewers, there are in fact compelling methodological and analytical reasons for selecting observation periods based on the length of a patient's treatment episode rather than the length of a patient's follow-up. These are discussed in detail in Section 1.3.5.1 (see page 38) and relate to the need to provide a distinction between non-adherent and non-persistent behaviours.

The accurate measurement of non-adherence risk and the assignment of this risk to covariates requires the use of an adherence measure that provides an unambiguous distinction between non-adherent and non-persistent behaviours. Adherence measures based on the length of a patient's follow-up (SMM-720, SMM-EFU) do not allow this distinction to be made. This is because the observation periods used in these measures permit inclusion of a *"terminal gap"*[19] – the time between treatment discontinuation and the end of follow-up – in adherence calculations. This can result in adherent patients, who become non-persistent, being miss-classified as non-adherent. The rationale for continuing to measure a patient's adherence after treatment has been discontinued is unclear and this issue has been acknowledged by the authors of previous statin adherence studies.[54, 57] The misclassification as non-adherent, in these analyses, of adherent patients who become non-persistent has a number of consequences. Firstly, adherence rates for non-persistent patients are

underestimated. Secondly, as adherence rates are underestimated specifically for non-persistent patients, predictive covariate models of non-adherence risk will be biased for covariates associated with non-persistence. This is because non-adherence risk is incorrectly assigned to covariates that are associated with an increased risk of non-persistence resulting in an overestimation of the magnitude of non-adherence risk for these covariates.

Adherence measures based on the length of a patient's treatment episode (SMM-LastRx, SMM-NonPer) exclude the *"terminal gap"*[19] – the time between treatment discontinuation and the end of follow-up – from adherence calculations. This allows the calculation and analysis of adherence over the time that a patient can reasonably be expected to be taking treatment.[17] Adherence and persistence are treated as separate behaviours and the influence of treatment discontinuation is therefore excluded from adherence rate estimates and predictive covariate models of non-adherence. This approach may be considered more suitable for adherence calculation and analysis as it avoids the potential overestimation of non-adherence rates and biasing of non-adherence risk observed in models using the length of a patient's follow-up.

The use of observation periods based on the length of a patient's treatment episode raises considerable methodological difficulties when applied to single measure models of adherence. The most significant of these is the inability of prescription refill data to provide accurate estimates of adherence in patients who receive no more than a single prescription in a treatment episode. This is best illustrated with an example; consider a patient who fills an initial prescription for 30 days' supply and then discontinues treatment. In the SMM-NonPer analysis this patient will be assigned an adherence rate of 100% (100 x 30/30). It is however not possible with the available data to conclude with any certainty how adherent this patient was, or would have been if they had continued with treatment. It is only possible to state that this patient became non-persistent after receiving a prescription for 30 days treatment. Non-persistence can be thought of as preventing the development or accurate identification of a patient's underlying adherence behaviour. The inclusion of this patient in adherence analyses will therefore overestimate adherence rates, underestimate the number of non-adherent patients and produce a bias in the risk of non-adherence for covariates associated with early non-persistence. The SMM-LastRx model attempts to overcome this limitation by excluding patients with a single prescription from the analysis. This approach can, however, only be considered valid if there is no correlation between the risk of filling a single prescription and the risk of non-adherence; this is improbable and the

exclusion of patients discontinuing treatment is likely to introduce bias to both the estimates of adherence and the covariate analysis of non-adherence risk.

In addition to the difficulties raised by patients receiving a single prescription, both the SMM-LastRx and the SMM-NonPer models assume that the filling of even a small number of prescriptions prior to treatment discontinuation provides enough information to accurately estimate a patient's adherence. This may not be the case and there has been caution expressed in the literature regarding the ability of prescription refill data to provide meaningful estimations of adherence over short periods of time.[17, 54, 59, 60] Finally, the accurate calculation of adherence rates in models based on the length of a patient's treatment episode requires the development of a consistent definition of treatment episode. This issue is discussed in detail in Chapter 7 (see page 139).

4.4.4 Single Measure Model – Adherence Rate Distributions

An inspection of the adherence rate distributions for the four observation periods employed in this study (see Figure 4.1, Figure 4.2, Figure 4.3 & Figure 4.4 above) illustrates many of the differences previously discussed between these methods (see Section 4.4.3 above). Specifically, there are two features to note about the distributions. Firstly there is a peak in adherence rates between 0% – 10% for SMM-720 and SMM-EFU analyses. This peak represents the considerable number of patients who normally discontinue treatment soon after initiation (see Chapter 7 on page 139) but continue to have an adherence rate calculated for the length of time in their follow-up. This peak is not present in the SMM-LastRx and SMM-NonPer adherence rate distributions because adherence rates are not calculated beyond the point of treatment discontinuation in these methods. Very low adherence rates are uncommon in the SMM-LastRx and SMM-NonPer analyses. Secondly there is a peak in the number of patients identified in the 98% – 100% adherent category and this peak increases across the four observation period definitions (SMM-720, 7.6% < SMM-EFU, 14.2% < SMM-LastRx, 16.36% < SMM-NonPer, 30.7%). There are a number of reasons for this. A proportion of the peak can be accounted for by the capping of adherence rates at 100% in the PDC adherence calculations (see Section 4.2.2 above). An assigned adherence rate of 100% therefore includes patients who filled prescriptions for exactly the right amount of medication as well as the patients who filled prescriptions for more medication than was required to cover the number of days in their observation period. In the three analyses where the length of observation period was allowed to vary (SMM-EFU, SMM-LastRx, SMM-NonPer), patients with very

short observation periods – due to either the end of a patient's follow-up or the end of a patient's treatment episode – were more likely to have high rates of adherence due to the limitations of prescription refill data in providing accurate estimates of adherence over short periods of time.[17, 54, 59, 60] The largest rise, however, occurs in the SMM-NonPer analysis where all patients receiving a single prescription (11.4% of the total cohort) were assigned an adherence rate of 100%.

4.4.5 Limitations of Single Measure Models of Adherence

In addition to the specific advantages and disadvantages of the various observation period definitions for the calculation and analysis of adherence there are a number of notable general limitations to the use of single measure models of adherence. Most importantly single measure models of adherence fail to recognise the longitudinal nature of medication-taking behaviour. Factors such as the length of time patients remain non-adherent and variations in patients' medication-taking behaviour from adherent to non-adherent or vice-versa are not considered in either the calculation of adherence rates for these single measure models or in the analysis of their results

4.4.5.1 Definition of Non-Adherence

The accurate identification of adherent and non-adherent patients using the results from single measure models of adherence is limited by the fact that patients' calculated adherence rates can rise as well as fall over the course of treatment. Patients may develop non-adherence at different times after treatment initiation and those who become non-adherent may not remain so. Patients may also experience more than one episode of non-adherence and the length of non-adherent episodes may vary within and between patients. Therefore, while non-adherent patients have customarily been defined by an adherence rate of less than a specified permissible level (e.g. < 80%), in practice the degree of non-adherence experienced by a patient is also dependent on the length of a non-adherent episode (e.g. ≥ 365 days) and the time after treatment initiation at which non-adherence occurs. Although single measure models of adherence can provide accurate estimates of patients' treatment adherence at a defined point in time and can therefore be used to identify patients who are non-adherent at this point, they cannot classify the severity of non-adherence in terms of the length of the non-adherent episode or the time at which non-adherence developed. For example, while medication possession ratios for the sample statin cohort show that 27.4% – 47.3% of patients had a PDC of less than 80%

at a follow-up time of 720 days (or end of follow-up, last statin prescription, non-persistence); this result gives no indication of adherence rates prior to or after this point, or of the length of time patients have remained non-adherent, or at what time after treatment initiation non-adherence developed. Non-adherence should therefore be thought of in two dimensions, with the time at which non-adherence occurs and the length of the non-adherent episode being as important in analyses as the degree of non-adherence.

4.4.5.2 Timing of Non-Adherence

One of the aims of medication-taking behaviour research, other than documenting the incidence and prevalence of non-adherent behaviour, is to develop predictive models in which the risk of non-adherence is dependent on covariates. The use of single measure adherence results in these models is limited by the fact that they overlook important information on the timing of events, the censoring of observations and the time dependent nature of covariates. It is reasonable to expect that patients who become non-adherent one month after treatment initiation have, on average, a higher propensity to be non-adherent than patients who become non-adherent after one year or later. By disregarding the timing of non-adherence behaviour, single measure models of adherence imply that all patients identified as non-adherent at a specific time point follow the same path to non-adherence. This approach eliminates meaningful variation in non-adherence times from analyses, ignores the temporal profile of non-adherence risk and may reduce the precision of any estimates from predictive models. It should also be noted that in most studies the time selected for measurement of adherence in single measure models (e.g. 720 days) is arbitrary and contradictory results may arise due to nothing more than a difference in the time at which adherence was measured.

4.4.5.3 Variable Follow-Up Time

Single measure models of adherence have difficulty handling patients with variable follow up times and in general the appropriate analysis of their results require that observation times are consistent for all patients.[17] This is because, patients with longer follow up times have a greater risk of experiencing non-adherence than those followed for shorter periods and any observed differences in non-adherence risk may be attributable to this. Therefore, of the four observation period definitions employed in this study only the SMM-720 analysis is appropriate for use in a single measure model. In the SMM-720 analysis all patients with insufficient follow up times (<720 days) are excluded from the study cohort, thus ensuring all patients have

equivalent risk periods. While this approach may be acceptable when the proportion of discarded patients is small; in the calculation of SMM-720 for this study 15.9% of patients with potential eligibility for inclusion in the study cohort (720 days follow-up) were excluded from the analysis because of loss to follow-up at 720 days. The consequent loss of potentially important information may result in bias.

4.4.5.4 Time-varying Covariates

Although some covariates (e.g. gender) remain fixed over a patient's entire follow-up, others do not. Covariates such as the type of treatment received, co-morbidities and numerous other potential influences on adherence behaviour may change over the time that adherence is calculated. There are few mechanisms available for incorporating these time dependent covariates into predictive models of medication-taking behaviour and determining their individual effect on adherence is complex. As single measure models of adherence do not identify the exact time of non-adherence, there is the possibility that co-variate values measured after treatment initiation may relate to a time after non-adherence has occurred and may even be a consequence of non-adherence rather than a cause. To avoid this problem the four single measure models in this study ignored the time dependent nature of covariates by only including baseline covariate values in analyses, where appropriate (see Section 4.2.4 above). This approach is subject to the limitation that estimated risk may be incorrectly attributed to a baseline covariate that has changed in value over the course of a patient's follow up.

4.5 Summary

Statin adherence was measured in a cohort of GMS patients using prescription refill data from the HSE-PCRS pharmacy claims database. A single measure model of adherence was employed for the analysis and four definitions of observation length were used for adherence rate calculations. The adherence rate and predictive covariate analysis results for the four observation periods were broadly similar to those obtained in the fifteen previous single measure model studies of statin adherence identified from the literature.[40, 42, 47-59] Adherence rates and covariate analysis results did however differ considerably across the observation definitions.

The four observation periods used in this study can be classified into two categories based on either the length of a patient's follow-up (SMM-720 & SMM-EFU) or the length of a patient's treatment episode (SMM-LastRx & SMM-NonPer). The rationale behind the selection of one of these methods over the other is based on

a consideration of what, if any, distinction there is between adherence and persistence. If non-adherence and non-persistence are considered separate and distinct behaviours each with their own unique risk factors, the accurate calculation of adherence rates and assignment of non-adherence risk to covariate values therefore requires the use of an adherence measure that provides an unambiguous distinction between non-adherent and non-persistent behaviour. Adherence measures based on the length of a patient's follow-up (SMM-720, SMM-EFU) do not allow this distinction to be made as they continue to measure a patient's adherence after treatment has been discontinued. Observation periods based on the length of a patient's treatment episode are theoretically preferable for the calculation of adherence as they only measure adherence over the time that a patient can reasonably be expected to be continuing with treatment. Unfortunately their application to prescription refill data presents a number of significant methodological difficulties.

In addition to the limitations and advantages of the various observation period definitions, Single measure models also have a number of limitations which make their use in the analysis of adherence questionable. These include their inability to appropriately measure non-adherence in terms of both the degree of non-adherence and the length of any non-adherent episode; their inability to identify the timing of non-adherence and their inability to appropriately handle variable follow-up times and time-varying covariates in analyses.

4.6 Conclusion

The exclusion of non-persistent behaviour from adherence estimation and analysis using single measure models of adherence is not possible. Single measure models are unable to appropriately account for the variable patient follow-up times or the inaccurate adherence estimates obtained for patients receiving only a single prescription refill. In addition to this single measure models of adherence do not provide the necessary analytical detail for adherence analysis. This is principally because they lack the ability to take account of the longitudinal nature of medication-taking behaviour. Proposed methods for addressing some of the limitations of single measure adherence models will be explored in Chapter 5 and Chapter 6 (see pages 83 & 115).

CHAPTER FIVE

5 STATIN ADHERENCE – REPEATED MEASURES MODEL

5.1 INTRODUCTION

Repeated measure models of adherence are based upon the periodic calculation of a patient's adherence over a number of consecutive intervals of a defined length (e.g. 90 days). These models calculate multiple measures of adherence for each patient and have been applied to prescription refill data in an attempt to overcome some of the limitations of single measure models (see Section 4.4.5 on page 78); in particular, their failure to take account of the dynamic nature of adherence behaviour and the longitudinal data available in prescription databases. The application of a repeated measures model to statin adherence in the GMS population is described here. The results of these analyses are compared with results from previously published repeated measure models of statin adherence.[38, 61-65] The advantages and disadvantages of this method are also discussed with respect to the measurement of adherence, the identification of adherence risk factors and the distinction between non-adherent and non-persistent behaviours.

5.2 METHODS

5.2.1 SELECTION OF AN ADHERENCE CALCULATION METHOD

Four repeated measure models of statin adherence were constructed from adherence measures calculated using proportion of days covered methodology (See Section 4.2.1 on page 55) and a selection of repeated adherence calculation intervals; 30 days, 60 days, 90 days and 180 days. This choice of methodology was based primarily on a consideration of what interval lengths had been used in previously published studies and what the most common adherence calculation method was in these studies. Nine prescription refill studies of adherence using repeated measures methodology were identified from the literature. Six of these studies observed adherence behaviour in patients prescribed statin therapy,[38, 61-65] with or without the concurrent use of other cardiovascular agents, and the remaining three studies examined the use of

medications for osteoporosis[66], HIV[i] infection[67] and COPD[ii][68]. Of these nine studies, eight used a proportion of days covered methodology to calculate adherence rates.[38, 61-66, 68] In these eight studies the number of days covered by medication supply in consecutive intervals of a defined length was expressed as a proportion of the number of days in each interval. Although the majority of these studies employed similar adherence calculation methods, there was considerable variation, from one[65] to twelve[67] months, in the length of interval chosen to calculate adherence. In the studies of statin adherence interval lengths ranged from one[65] to six[38, 63] months with a modal length of three months.[38, 61, 62, 64] None of the identified studies provided or referenced objective evidence to support their selection of interval length and in all but one of the studies the rationale for the choice of adherence calculation interval is not discussed. In their study of adherence to osteoporosis medications Solomon et al. [66] suggest that the reasoning for their choice of a 60 day interval is dictated by the standard number of days' supply in a single prescription refill; between 30 and 60 days in their study. This study was also the only one to carry out sensitivity analyses to determine the effect of varying the length of adherence calculation interval. The authors concluded that there were no important differences between a 60 day and a 120 day interval. The results of these sensitivity analyses were not presented.

5.2.2 Calculation of Proportion of Days Covered

The proportion of days covered was calculated for each consecutive interval in a patient's follow-up using Equation 5.1[38] (see below) and each of the four interval lengths, 30 days (RMM-30[iii]), 60 days (RMM-60[iv]), 90 days (RMM-90[v]) and 180 days (RMM-180[vi]). Adherence calculations were repeated for each complete interval over the length of a patient's follow-up. Therefore, patients with less than a single interval's follow-up were excluded from the analyses. The number of assigned doses in an adherence calculation interval was determined from the constructed longitudinal database of medication supply (see Section 3.3 on page 46). The calculated proportion of days covered measures have a maximum value of 100% but are not interpretable as an upper limit of adherence (see Section 1.3.1.2 on page 33 & Section 5.4.3.1 below). Non-adherence in any interval was defined as a PDC of less than 80% (see Section 3.2 on page 46).

---

[i] Human Immunodeficiency Virus.
[ii] Chronic Obstructive Pulmonary Disease.
[iii] Repeated measure model of adherence over consecutive 30 day adherence calculation intervals.
[iv] Repeated measure model of adherence over consecutive 60 day adherence calculation intervals.
[v] Repeated measure model of adherence over consecutive 90 day adherence calculation intervals.
[vi] Repeated measure model of adherence over consecutive 180 day adherence calculation intervals.

EQUATION 5.1: PROPORTION OF DAYS COVERED FOR THE REPEATED MEASURE MODEL[38]

$$Proportion\ of\ Days\ Covered\ (Repeated\ Measure\ Model, \%) = \left[\sum_{\delta=\alpha}^{\alpha+(\mu-1)} \delta \Big/ (\mu) \right] \times 100$$

Where α denotes the first day of each consecutive interval, δ denotes the days supply (1 or 0) assigned to each day (see Section 1.3.1.2 on page 33 & Section 3.3 on page 46) and μ denotes the number of days in the adherence calculation interval (e.g. 30, 60, 90 or 180).

5.2.3 Statistical Analysis

The assumption of independence between outcomes, required for traditional regression models, is not fulfilled by the calculated adherence rates in repeated measure models. This is because repeated adherence measurements derived from the same patient are more likely to be similar than those obtained from different patients. Analysis of these results using standard regression models may result in a biasing of standard errors for covariates; or more precisely the pooling of these repeated measures without accounting for their increased correlation may result in an underestimation and overestimation of standard errors for time-invariant and time-varying covariates respectively.[69, 70] The application of standard regression techniques to these adherence calculations is therefore not appropriate. The modelling of repeated measure adherence data requires the use of analytic techniques that do not assume the correlation between adherence measurements to be zero. The method of generalised estimating equations (GEE) has been used for this purpose by each of the nine identified repeated measure adherence studies.[38, 61-68]

5.2.3.1 Generalised Estimating Equations

Generalised estimating equations represent an extension of generalised linear models to accommodate correlated data.[71] They estimate regression coefficients and standard errors with sampling distributions that are asymptotically normal, they can be used to evaluate categorical or continuous independent variables and they can be applied to both covariate effects and their interactions. GEE estimates are the same as those from ordinary least squares regression when the dependent variable is normally distributed and no correlation within response is assumed. The focus in GEEs is on estimating a population-averaged or marginal model, rather than the regression parameters that would enable prediction of the effect of changing one or more covariate values on a given individual. Marginal models give an average response for observations sharing the same covariates as a function of the covariates; in other words, for every one-unit increase in a covariate

across the population GEEs estimate how much the average population response would change.[72] Reviews of their application to clustered or repeated measure longitudinal data can be found in the articles by Zorn,[72] Ballinger[73] and Ghisletta.[69]

The fitting of a GEE model requires the prior specification of three parameters; the dependent variable distribution, the link function to be used in the transformation of the dependent variable and the correlation structure of the dependent variable. GEEs permit the specification of dependent variable distributions from the exponential family. These include normal, inverse normal, binomial, Poisson, negative binomial and Gamma distributions. Generally, if the dependent variable responses are binary data, as is the case with the dichotomised adherence rates in this study, a binomial distribution should be specified. The choices available for the link function are limited by the selection of dependent variable distribution. For example, the logit link is the standard linking function for binary dependent variables. This link fits a logistic regression model by allowing the regression equation to map the interval between the binary variables. Alternatively a probit, power or reciprocal link could be specified.[73] Finally, the specification of the form of the correlation of dependent variables within subjects is required.

There are several options to select from in specifying the working correlation and the specific choice will differ depending on the nature of the dependent variable. While GEE models are, in general, robust to miss-specification of the correlation structure, empirical factors are often differentially influential across different working correlations and the incorrect specification of the correlation matrix can affect the efficiency of β estimates. Therefore, wherever possible the choice of working correlation matrix should be based on substantive reasons and sensitivity analyses of the different specifications of the correlation structures are recommended to test the robustness of inferences about the regression coefficients.[72] A selection of available correlation structures and considerations for their selection are listed below.

Independent. Assumes the non-existence of dependency (i.e. zero intra-patient correlation between measurements), so that all off diagonal elements of the working correlation matrix are zero. This structure is appropriate when there is no correlation between measurements.

Exchangeable. Assumes a constant dependency so that all off diagonal elements of the working correlation matrix are equal. This structure is appropriate when there is no logical ordering of the dependent variable observations (i.e. not collected over time).

Autoregressive. Assumes correlations to be an exponential function of the time between them. This structure is appropriate for longitudinal repeated measure data.

Unstructured. Assumes a saturated, free specification of correlation coefficients with no constraints. This structure is appropriate for longitudinal repeated measure data.

5.2.3.2 Selection of a Working Correlation Structure

There are two assumptions about the nature of the dependence between repeated adherence measurements that may be taken into account when choosing which of the correlation structures to use in a final analysis. The first of these is the assumption that the dependence between adherence measurements may be expected to decrease as the length of time between the measurements increases. This implies that, for example, the correlation between adherence measures in the first and second intervals will be greater than the correlation between adherence measures in the first and tenth intervals. The second assumption is that the dependence between adherence measurements the same length of time apart may be expected to increase as the length of time from treatment initiation increases. This implies that, for example, the correlation between the ninth and tenth interval will be greater than the correlation between the first and second interval; or in other words as the length of time from treatment initiation increases, adherent patients are more likely to remain adherent and non-adherent patients are more likely to remain non-adherent.

An examination of the available correlation matrices indicates that the first assumption – that there is a reduction in dependence between adherence calculation intervals that are successively further apart – can be accounted for in both the autoregressive and unstructured correlation matrices. The second assumption – that there is an increase in correlation between adherence calculation intervals that are the same distance apart as the length of time from treatment initiation increases – can only be accounted for in the unstructured matrix. For this reason the unstructured correlation matrix was selected as the most appropriate for the analyses in this study.

5.2.3.3 Statistical Analysis of the Repeated Measure Adherence Models

The proportion of days covered results were dichotomized into adherent (PDC ≥ 80%) and non-adherent (PDC < 80%). Univariate and multivariate generalised estimating equation models were specified with a binomial variance distribution a common logit link function and an unstructured correlation matrix for the RMM-30, RMM-60, RMM-90 and RMM-180 adherence outcomes. A sensitivity analysis to test the robustness of inferences about the β regression coefficients was performed by specifying a second model with an autoregressive correlation structure for the RMM-90 adherence outcome; the results of this analysis are presented in Appendix 1 (see page 213). Crude and adjusted odds ratios with 95% confidence intervals are presented for independent categorical variables. While GEEs can be used to calculate relative risks for covariates (by specifying a log link function in place of a logistic link function[74]) odds ratios were calculated instead to allow comparability with results from the single measure model in Chapter 4 (see Table 4.3 & Table 4.4 on pages 63 & 66). β regression coefficients are presented in place of odds ratios for continuous variables. Odds ratios may be calculated for any two continuous covariate values by exponential $(\beta_1-\beta_2)$; where β_1 and β_2 are the products of the chosen covariate values and the β regression coefficient for that covariate.[73, 74] Multivariate analyses were adjusted for all included covariates. Significance at $p < 0.05$ was assumed. SAS® version 9.1[i] was used for all analyses.

5.2.4 Covariates Included in the Repeated Measures Model

Patient gender and the following time-varying covariates were included in the model; age, current statin type, current statin dose, current statin prescriber, statin dose change, all identified co-morbidities and the number of non-cardiovascular pharmacological agents, cardiovascular pharmacological agents and prescription items received by a patient in the prior 365 days. Values for the time-varying covariates were taken from the first day in each adherence calculation interval. A full description of these covariates can be found in Section 3.6 (see page 49). The decline in adherence over time was assumed to be linear on the natural logarithmic scale. Log normal time was also included in the GEE model to allow a determination of the effect of time on non-adherence risk.

[i] SAS Institute, Cary, NC, USA.

5.3 Results

5.3.1 Repeated Measure Model – Study Cohort Subsets

The number of patients from the source study cohort (n = 79,364, see Chapter 3 on page 43) with sufficient follow-up time to enable the calculation of adherence over at least one interval was 77,325 (97.4%) for the RMM-30 analysis, 76,696 (96.6%) for the RMM-60 analysis, 76,119 (95.9%) for the RMM-90 analysis and 74,519 (93.9%) for the RMM-180 analysis. The number of patients with sufficient follow-up to allow adherence calculation declined over time, with only 1,768 patients contributing to the final adherence calculation interval up to 900 days in each of the four analyses. The characteristics of the four study cohort subsets at treatment initiation are presented in Table 5.1 below.

In comparison to baseline covariate values in the RMM-30, RMM-60, RMM-90 and RMM-180 cohorts a change in age category occurred in 14.6%, 12.7%, 10.7% and 7.0% of patients respectively over the course of the study; 10.9%, 9.9%, 8.8% and 6.1% of patients switched statin type; 16.2%, 15.1%, 13.8% and 10.0% of patient had a dose change; 4.1%, 3.9%, 3.6% and 2.6% of patients developed ischaemic heart disease after statin initiation; 2.2%, 2.1%, 1.9% and 1.3% developed diabetes; 6.3%, 5.8%, 5.3% and 3.7% had a new diagnosis of depression; between 0.7% to 0.4% of patients had a new diagnosis of Parkinson's disease and 1.1% to 0.6% of patients had a new diagnosis of Alzheimer's disease.

TABLE 5.1: CHARACTERISTICS OF THE RMM-30, RMM-60 RMM-90 & RMM-180 STATIN ADHERENCE STUDY COHORT SUBSETS IN THE FIRST ADHERENCE CALCULATION INTERVALS

Characteristic	RMM-30 (%) Days 1 – 30		RMM-60 (%) Days 1 – 60		RMM-90 (%) Days 1 – 90		RMM-180 (%) Days 1 – 180	
N	77,325	-	76,696	-	76,119	-	74,519	-
Gender								
Male	34,228	(44.3)	33,921	(44.2)	33,646	(44.2)	32,857	(44.1)
Female	43,097	(55.7)	42,775	(55.8)	42,473	(55.8)	41,662	(55.9)
Age								
16-34*	2,210	(2.9)	2,154	(2.8)	2,118	(2.8)	1,995	(2.7)
35-44*	3,472	(4.5)	3,431	(4.5)	3,384	(4.4)	3,269	(4.4)
45-54*	8,342	(10.8)	8,273	(10.8)	8,199	(10.8)	7,971	(10.7)
55-64*	14,624	(18.9)	14,525	(18.9)	14,424	(18.9)	14,162	(19.0)
65-74*	25,053	(32.4)	24,910	(32.5)	24,821	(32.6)	24,510	(32.9)
≥75*	23,624	(30.6)	23,385	(30.5)	23,173	(30.4)	22,612	(30.3)
Statin Type								
Simvastatin*	4,408	(5.7)	4,371	(5.7)	4,336	(5.7)	4,239	(5.7)
Pravastatin*	16,556	(21.4)	16,410	(21.4)	16,284	(21.4)	15,923	(21.4)
Fluvastatin*	1,322	(1.7)	1,315	(1.7)	1,307	(1.7)	1,281	(1.7)
Atorvastatin*	46,725	(60.4)	46,340	(60.4)	45,988	(60.4)	45,014	(60.4)
Rosuvastatin*	7,995	(10.3)	7,943	(10.4)	7,891	(10.4)	7,756	(10.4)
Simvastatin/Ezetimibe*	319	(0.4)	317	(0.4)	313	(0.4)	306	(0.4)
Prescriber								
General Practitioner*	70,076	(90.6)	69,540	(90.7)	69,030	(90.7)	67,646	(90.8)
Hospital Prescriber*	7,249	(9.4)	7,156	(9.3)	7,089	(9.3)	6,873	(9.2)
Dose								
Low Dose*	44,235	(57.2)	43,943	(57.3)	43,658	(57.4)	42,866	(57.5)
Intermediate Dose*	31,656	(40.9)	31,333	(40.9)	31,054	(40.8)	30,282	(40.6)
High Dose*	1,434	(1.9)	1,420	(1.9)	1,407	(1.8)	1,371	(1.8)
Dose Change								
No Dose Change*	77,325	(100.0)	76,696	(100.0)	76,119	(100.0)	74,519	(100.0)
Dose Decrease*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dose Increase*	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Co-morbidities								
IHD*	10,696	(24.3)	10,602	(24.2)	10,514	(13.8)	10,258	(13.8)
Diabetes*	11,226	(14.5)	11,122	(14.5)	11,038	(14.5)	10,801	(14.5)
Depression*	18,762	(24.3)	18,536	(24.2)	18,371	(24.1)	17,917	(24.0)
Depression (Recent)*	4,674	(6.0)	4,614	(6.0)	4,554	(6.0)	4,416	(5.9)
Parkinson's Disease*	1,748	(2.3)	1,722	(2.2)	1,705	(2.2)	1,657	(2.2)

Characteristic	RMM-30 (%) Days 1 – 30		RMM-60 (%) Days 1 – 60		RMM-90 (%) Days 1 – 90		RMM-180 (%) Days 1 – 180	
Alzheimer's Disease*	1,536	(2.0)	1,501	(2.0)	1,476	(1.9)	1,418	(1.9)
Prescribing History								
Pharmacological Agents†‡	6	3, 11	6	3, 11	6	3, 11	6	3, 11
Cardiovascular Agents†‡	2	1, 3	2	1, 3	2	1, 3	2	1, 3
Prescription Items†‡	53	15, 110	53	15, 110	53	15, 110	53	15, 110

*Time-varying covariates, value taken from the first day of adherence calculation interval. † Time-varying covariates, number in 12 months prior to the first day of adherence calculation interval. ‡ Median & inter-quartile range. ***RMM-30***, proportion of days covered in consecutive 30 day adherence calculation intervals. ***RMM-60***, proportion of days covered in consecutive 60 day adherence calculation intervals. ***RMM-90***, proportion of days covered in consecutive 90 day adherence calculation intervals. ***RMM-180***, proportion of days covered in consecutive 180 day adherence calculation intervals. ***IHD***, ischaemic heart disease. ***N***, number of patients in cohort.

5.3.2 Repeated Measure Model – Proportion of Days Covered Results

The number of patients identified as non-adherent, with a PDC of less than 80%, at each of the adherence calculation intervals for the four repeated measure models are presented in Figure 5.1, Figure 5.2, Figure 5.3 and Figure 5.4 (see below). Selected adherence values and descriptive statistics from each of these models are presented in Table 5.2, Table 5.3, Table 5.4 and Table 5.5 (see below). The proportion of patients identified as non-adherent in the first adherence calculation interval was 3.3%, 36.1%, 44.0% and 47.6% respectively for the RMM-30, RMM-60, RMM90 and RMM-180 models. These proportions increased to a maximum of 44.2%, 47.4%, 49.3% and 48.5% respectively. In general the proportion of patients identified as non-adherent increased as the length of the adherence calculation interval was increased up to 90 days; whereafter it stabilised or decreased. It is also of note that, while the mean adherence rates were similar across the four models and across the adherence calculation intervals in each of the models, the median and inter-quartile ranges for each of the adherence calculation intervals indicate that the distribution of calculated adherence values changed considerably.

FIGURE 5.1: PROPORTION OF PATIENTS CLASSIFIED AS ADHERENT (RMM-30 ≥ 80%) OR NON-ADHERENT (RMM-30 < 80%) AT EACH STATIN ADHERENCE CALCULATION INTERVAL IN THE RMM-30 ANALYSIS

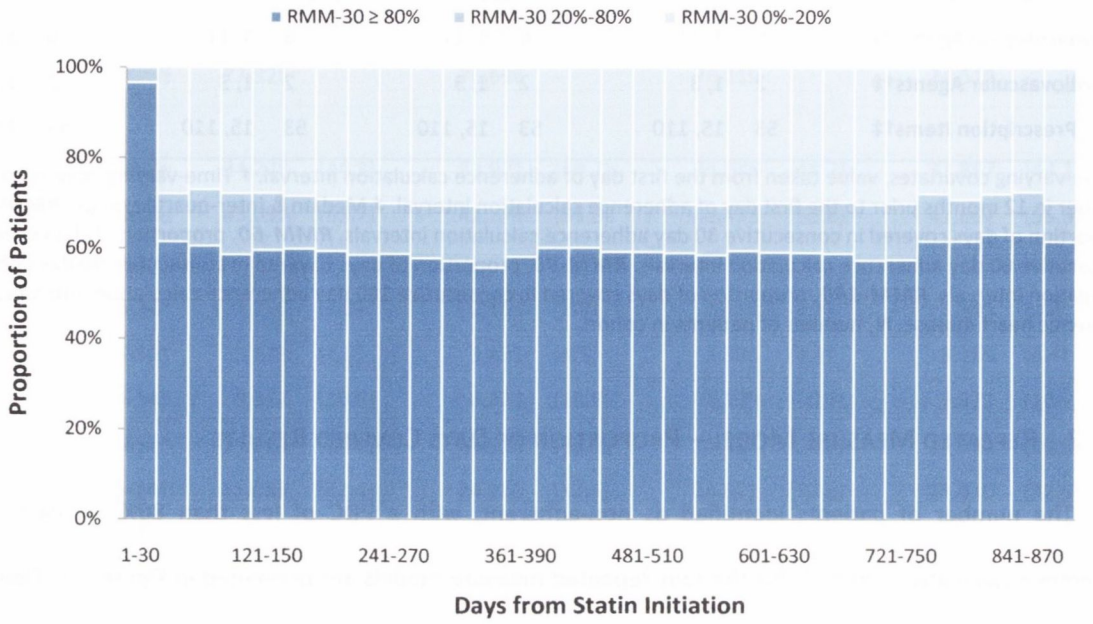


TABLE 5.2: DESCRIPTIVE MEASURES AND PROPORTIONS OF PATIENTS CLASSIFIED AS ADHERENT (RMM-30 ≥ 80%) OR NON-ADHERENT (RMM-30 < 80%) AT SELECTED STATIN ADHERENCE CALCULATION INTERVALS IN THE RMM-30 ANALYSIS

	Days from Statin Initiation					
	1-30	151-180	331-360	511-540	691-720	871-900
N	77,325	74,519	54,743	36,018	20,118	1,768
RMM-30 ≥ 80% (%)	96.7	59.9	55.8	59.0	57.3	61.5
RMM-30 < 80% (%)	3.3	40.1	44.2	41.0	42.7	38.5
60% - 80% (%)	0.5	5.7	6.0	5.1	5.6	4.2
40% - 60% (%)	0.7	3.2	4.0	3.4	3.7	2.7
20% - 40% (%)	2.1	2.7	3.4	2.3	3.1	1.7
0% - 20% (%)	0.1	28.4	30.9	30.2	30.3	29.9
Mean (%)	95.4	64.8	61.6	63.6	62.7	65.1
SD (%)	12.0	43.2	43.9	44.1	44.0	44.4
Median (%)	100.0	93.3	90.0	93.3	93.3	96.7
75% IQR (%)	100.0	100.0	100.0	100.0	100.0	100.0
25% IQR (%)	93.3	0.0	0.0	0.0	0.0	0.0

RMM-30, proportion of days covered in consecutive 30 day adherence calculation intervals. ***N***, number of eligible patients at each adherence interval. ***SD***, standard deviation. ***IQR***, inter-quartile range. ***Adherence*** = RMM-30 ≥ 80%. ***Non-adherence*** = RMM-30 < 80%.

FIGURE 5.2: PROPORTION OF PATIENTS CLASSIFIED AS ADHERENT (RMM-60 ≥ 80%) OR NON-ADHERENT (RMM-60 < 80%) AT EACH STATIN ADHERENCE CALCULATION INTERVAL IN THE RMM-60 ANALYSIS

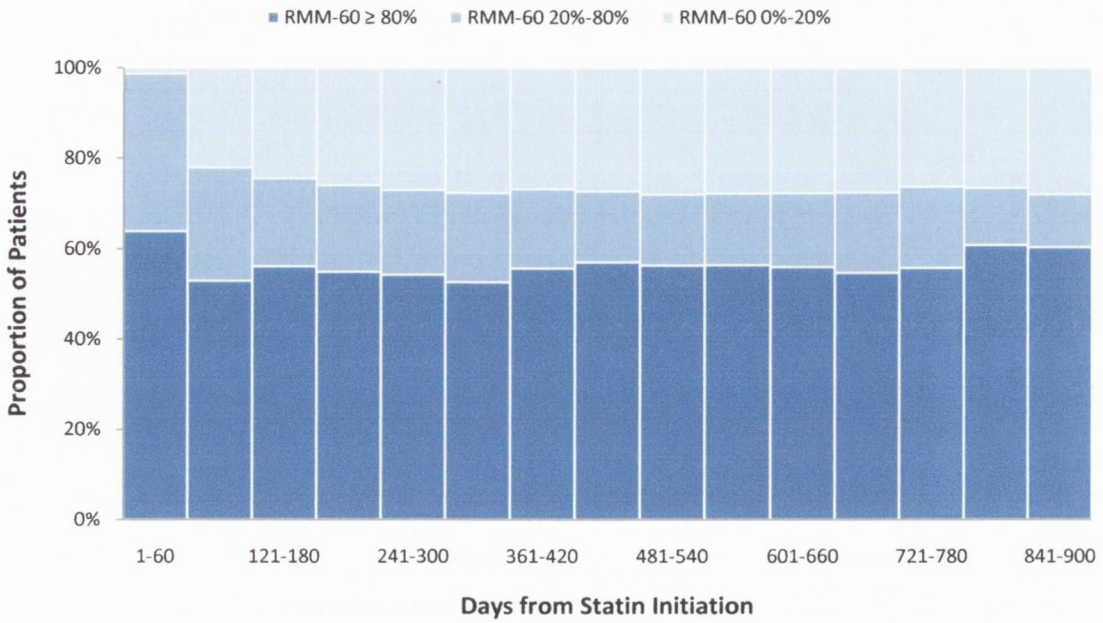


TABLE 5.3: DESCRIPTIVE MEASURES AND PROPORTIONS OF PATIENTS CLASSIFIED AS ADHERENT (RMM-60 ≥ 80%) OR NON-ADHERENT (RMM-60 < 80%) AT SELECTED STATIN ADHERENCE CALCULATION INTERVALS IN THE RMM-60 ANALYSIS

	Days from Statin Initiation					
	1-60	**121-180**	**301-360**	**481-540**	**661-720**	**841-900**
N	76,696	74,519	54,743	36,018	20,118	1,768
RMM-60 ≥ 80% (%)	63.9	56.2	52.6	56.3	54.7	60.4
RMM-60 < 80% (%)	36.1	43.8	47.4	43.7	45.3	39.6
60% - 80% (%)	7.0	7.1	8.4	6.8	8.1	5.3
40% - 60% (%)	27.3	9.6	8.6	6.6	7.1	4.4
20% - 40% (%)	0.5	2.7	2.7	2.2	2.4	2.0
0% - 20% (%)	1.3	24.4	27.6	28.0	27.6	28.0
Mean (%)	80.1	64.9	62.1	63.6	63.2	65.3
SD (%)	23.3	40.6	41.7	42.5	42.1	43.1
Median (%)	93.3	88.3	83.3	90.0	86.7	93.3
75% IQR (%)	100.0	100.0	100.0	100.0	100.0	100.0
25% IQR (%)	50.0	23.3	0.0	0.0	0.0	0.0

RMM-60, proportion of days covered in consecutive 60 day adherence calculation intervals. ***N***, number of eligible patients at each adherence interval. ***SD***, standard deviation. ***IQR***, inter-quartile range. ***Adherence*** = RMM-60 ≥ 80%. ***Non-adherence*** = RMM-60 < 80%.

FIGURE 5.3: PROPORTION OF PATIENTS CLASSIFIED AS ADHERENT (RMM-90 ≥ 80%) OR NON-ADHERENT (RMM-90 < 80%) AT EACH STATIN ADHERENCE CALCULATION INTERVAL IN THE RMM-90 ANALYSIS

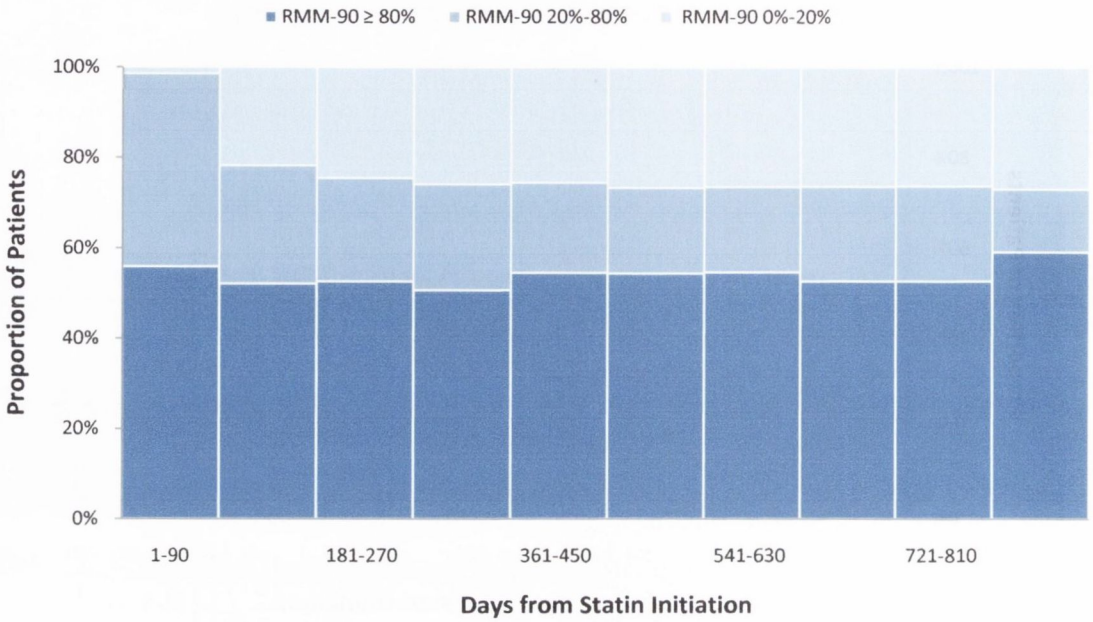


TABLE 5.4: DESCRIPTIVE MEASURES AND PROPORTIONS OF PATIENTS CLASSIFIED AS ADHERENT (RMM-90 ≥ 80%) OR NON-ADHERENT (RMM-90 < 80%) AT SELECTED STATIN ADHERENCE CALCULATION INTERVALS IN THE RMM-90 ANALYSIS

	Days from Statin Initiation					
	1-90	91-180	271-360	451-540	631-720	811-900
N	76,119	74,519	54,743	36,018	20,118	1,768
RMM-90 ≥ 80% (%)	56.0	52.2	50.7	54.4	52.7	59.2
RMM-90 < 80% (%)	44.0	47.8	49.3	45.6	47.3	40.8
60% - 80% (%)	19.8	14.3	13.3	10.8	12.6	7.5
40% - 60% (%)	3.5	5.3	5.0	4.2	4.4	2.7
20% - 40% (%)	19.4	6.5	5.1	4.0	3.9	3.7
0% - 20% (%)	1.4	21.7	25.9	26.7	26.3	27.0
Mean (%)	75.1	64.8	62.3	63.6	63.3	65.3
SD (%)	26.7	38.8	40.6	41.5	41.1	42.4
Median (%)	87.8	83.3	80.0	86.7	83.3	92.2
75% IQR (%)	98.9	98.9	100.0	100.0	100.0	100.0
25% IQR (%)	62.2	31.1	11.1	2.2	4.4	0.0

RMM-90, proportion of days covered in consecutive 90 day adherence calculation intervals. ***N***, number of eligible patients at each adherence interval. ***SD***, standard deviation. ***IQR***, inter-quartile range. ***Adherence*** = RMM-90 ≥ 80%. ***Non-adherence*** = RMM-90 < 80%.

FIGURE 5.4: PROPORTION OF PATIENTS CLASSIFIED AS ADHERENT (RMM-180 ≥ 80%) OR NON-ADHERENT (RMM-180 < 80%) AT EACH STATIN ADHERENCE CALCULATION INTERVAL IN THE RMM-180 ANALYSIS

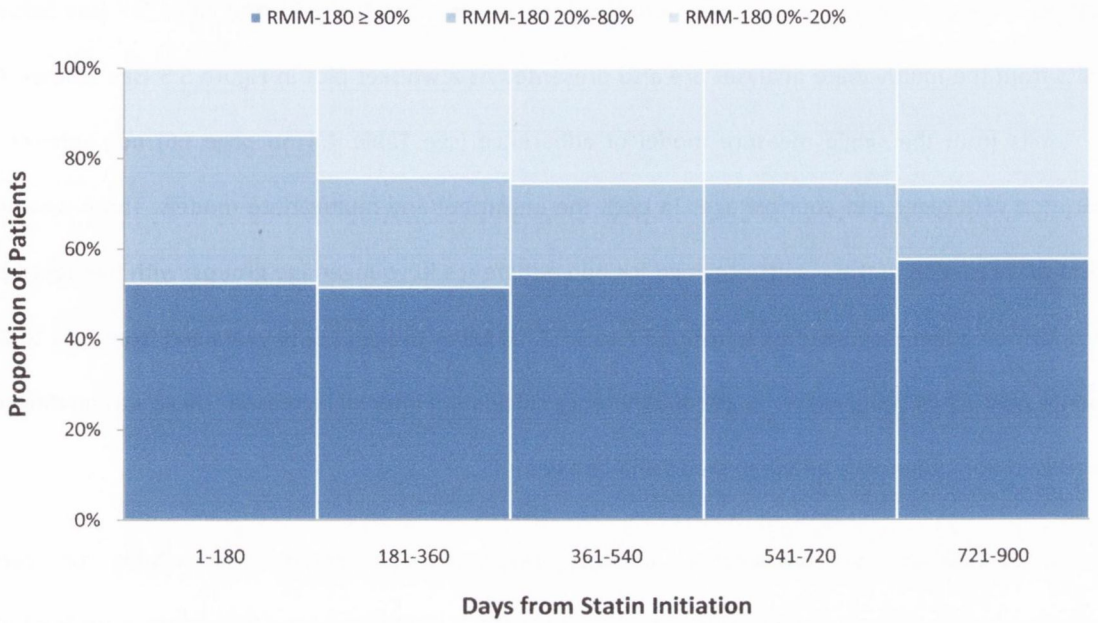


TABLE 5.5: DESCRIPTIVE MEASURES AND PROPORTIONS OF PATIENTS CLASSIFIED AS ADHERENT (RMM-180 ≥ 80%) OR NON-ADHERENT (RMM-180 < 80%) AT EACH STATIN ADHERENCE CALCULATION INTERVALS IN THE RMM-180 ANALYSIS

	Days from Statin Initiation				
	1-180	181-360	361-540	541-720	721-900
N	74,519	54,743	36,018	20,118	1,768
RMM-180 ≥ 80% (%)	52.4	51.5	54.4	54.9	57.6
RMM-180 < 80% (%)	47.6	48.5	45.6	45.1	42.4
60% - 80% (%)	17.6	13.6	11.0	11.2	8.7
40% - 60% (%)	8.6	6.3	5.4	5.1	4.2
20% - 40% (%)	6.4	4.2	3.6	3.3	3.1
0% - 20% (%)	14.9	24.3	25.5	25.4	26.4
Mean (%)	70.0	63.1	63.8	64.0	65.0
SD (%)	30.0	38.6	39.8	39.9	41.2
Median (%)	81.7	81.1	83.3	83.3	88.3
75% IQR (%)	95.6	96.7	98.3	98.9	100.0
25% IQR (%)	47.8	24.4	16.7	16.7	15.6

RMM-180, proportion of days covered in consecutive 180 day adherence calculation intervals. ***N***, number of eligible patients at each adherence interval. ***SD***, standard deviation. ***IQR***, inter-quartile range. ***Adherence*** = RMM-180 ≥ 80%. ***Non-adherence*** = RMM-180 < 80%.

5.3.3 Generalised Estimating Equation Analyses – Univariate & Multivariate Models

The results from the univariate and multivariate GEE analyses of adherence for the RMM-30, RMM-60, RMM-90 and RMM-180 repeated measure models are presented in Table 5.6 and Table 5.7 (see below). The results from the multivariate analyses are also presented as a whisker plot in Figure 5.5 (see below). As with the results from the single measure model of adherence (see Table 4.4 on page 66) non-adherence was associated with older and younger ages in both the univariate and multivariate models. There was however substantial variation in the results obtained for non-adherence in younger age groups; with the adjusted odds ratios for non-adherence increasing from 2.57 to 3.92 for patients aged 16-34 years and from 1.81 to 2.11 for patients aged 35-44 years as the length of adherence calculation interval increased. There was no difference in the odds of non-adherence between males and females.

In comparison to pravastatin, patients receiving atorvastatin, rosuvastatin or combined simvastatin/ezetimibe had reduced odds of non-adherence. Patients receiving fluvastatin were least likely to adhere to treatment in all four models. In the multivariate analysis patients receiving a statin at a low dose had reduced odds of non-adherence and patients receiving a high dose had increased odds of non-adherence. The effect of a dose change on adherence behaviour was also significant. There was however considerable variation in the results obtained; with patients who received a dose decrease or increase having a reduction of 42% to 22% and 41% to 21% in the odds of non-adherence respectively. The effect of initial prescriber on the odds of non-adherence also varied considerably across the four adherence calculation intervals; reversing direction as the length of the adherence calculation interval was increased. Patients who had a statin treatment initiated by a hospital prescriber had a 31% increase in the adjusted odds of non-adherence in the RMM-30 analysis and a 21% reduction in the adjusted odds of non-adherence in the RMM-180 analysis.

A diagnosis of Parkinson's disease or depression was associated with an increase in the adjusted odds of non-adherence. A recent diagnosis of depression was, however, associated with a modest reduction in the adjusted odds of non-adherence. Patients receiving treatments for ischaemic heart disease or diabetes were less likely to be non-adherent to statin treatment. As the number of non-cardiovascular pharmacological agents received by a patient in the prior twelve months increased the adjusted odds ratio of non-adherence also increased. The opposite trend was observed for cardiovascular pharmacological agents, where the odds ratio of non-adherence decreased as the number of agents received by a patient in the prior twelve months

increased. A similar, although more marked trend was observed for the number of prescription items filled by a patient in the prior twelve months with patients receiving 110 prescription items or more having a 55% (RMM-60) to 62% (RMM-180) reduction in the odds of non-adherence.

TABLE 5.6: RESULTS FROM THE UNIVARIATE GENERALISED ESTIMATING EQUATION REGRESSION ANALYSES OF STATIN NON-ADHERENCE FOR THE RMM-30, RMM-60, RMM-90 & RMM-180 STUDY COHORTS WITH A BINOMIAL VARIANCE DISTRIBUTION, A COMMON LOGIT LINK FUNCTION AND AN UNSTRUCTURED WORKING CORRELATION MATRIX

Univariate Model Covariates	RMM-30		RMM-60		RMM-90		RMM-180	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Gender								
Male	0.99	(0.98, 1.01)	0.99	(0.97, 1.01)	0.98	(0.96, 1.00)	0.97	(0.95, 1.00)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	2.38	(2.26, 2.51)	3.66	(3.36, 4.00)	4.04	(3.66, 4.46)	4.85	(4.29, 5.47)
35-44*	1.77	(1.70, 1.83)	2.21	(2.10, 2.33)	2.30	(2.18, 2.43)	2.54	(2.38, 2.72)
45-54*	1.35	(1.31, 1.38)	1.52	(1.47, 1.57)	1.56	(1.50, 1.61)	1.70	(1.63, 1.78)
55-64*	1.07	(1.05, 1.10)	1.11	(1.08, 1.14)	1.12	(1.09, 1.16)	1.16	(1.13, 1.05)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.03	(1.01, 1.05)	1.01	(0.99, 1.03)	1.02	(1.00, 1.05)	1.02	(0.99, 1.05)
Statin Type								
Simvastatin*	0.98	(0.93, 1.03)	0.98	(0.93, 1.03)	1.00	(0.95, 1.05)	0.96	(0.91, 1.02)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.15	(1.06, 1.24)	1.21	(1.11, 1.31)	1.23	(1.13, 1.34)	1.30	(1.18, 1.43)
Atorvastatin*	0.88	(0.85, 0.90)	0.85	(0.82, 0.87)	0.86	(0.84, 0.88)	0.84	(0.81, 0.87)
Rosuvastatin*	0.89	(0.85, 0.92)	0.90	(0.86, 0.93)	0.93	(0.89, 0.97)	0.93	(0.89, 0.98)
Simva/Ezet*	0.65	(0.57, 0.75)	0.70	(0.61, 0.79)	0.73	(0.64, 0.85)	0.82	(0.68, 0.99)
Prescriber								
GP Prescriber*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	1.18	(1.13, 1.22)	0.81	(0.78, 0.84)	0.79	(0.76, 0.82)	0.71	(0.68, 0.74)
Dose								
Low Dose*	0.96	(0.94, 0.98)	0.97	(0.96, 0.99)	0.98	(0.96, 1.00)	0.98	(0.96, 1.01)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	1.10	(1.03, 1.17)	1.06	(1.00, 1.14)	1.06	(0.99, 1.14)	1.04	(0.96, 1.13)
Dose Change								
No Dose Change*	Ref	-	Ref	-	Ref	-	Ref	-
Dose Decrease*	0.69	(0.66, 0.73)	0.76	(0.73, 0.79)	0.79	(0.75, 0.82)	0.73	(0.69, 0.78)
Dose Increase*	0.77	(0.74, 0.81)	0.80	(0.78, 0.83)	0.81	(0.78, 0.83)	0.79	(0.75, 0.83)
Co-morbidities								
IHD*	0.85	(0.83, 0.87)	0.78	(0.76, 0.80)	0.76	(0.74, 0.79)	0.73	(0.70, 0.75)
Diabetes*	0.85	(0.83, 0.87)	0.81	(0.79, 0.83)	0.79	(0.76, 0.81)	0.76	(0.74, 0.79)
Depression*	1.10	(1.08, 1.12)	1.09	(1.06, 1.11)	1.08	(1.06, 1.11)	1.08	(1.05, 1.11)
Depression(Recent)*	0.99	(0.96, 1.01)	1.00	(0.98, 1.03)	1.03	(1.00, 1.06)	1.09	(1.05, 1.13)
Parkinson's Disease*	1.07	(1.01, 1.13)	1.07	(1.00, 1.14)	1.04	(0.97, 1.11)	1.01	(0.93, 1.09)

Univariate Model Covariates	RMM-30		RMM-60		RMM-90		RMM-180	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Alzheimer's Disease*	1.03	(0.97, 1.09)	1.02	(0.96, 1.08)	0.99	(0.93, 1.06)	0.94	(0.87, 1.02)
Prescribing History								
Non-Cardio PAs† ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	1.02	(1.00, 1.04)	0.99	(0.97, 1.00)	0.95	(0.93, 0.97)	0.90	(0.88, 0.93)
6 - 11	1.04	(1.02, 1.06)	0.99	(0.97, 1.01)	0.93	(0.91, 0.96)	0.88	(0.85, 0.90)
≥ 11	1.08	(1.06, 1.10)	1.01	(0.99, 1.03)	0.95	(0.93, 0.98)	0.90	(0.87, 0.92)
Cardio PAs† ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.92	(0.91, 0.94)	0.85	(0.84, 0.87)	0.80	(0.78, 0.81)	0.73	(0.71, 0.75)
2	0.86	(0.85, 0.88)	0.77	(0.76, 0.76)	0.71	(0.70, 0.73)	0.64	(0.62, 0.65)
≥ 3	0.82	(0.81, 0.84)	0.71	(0.70, 0.70)	0.64	(0.63, 0.66)	0.58	(0.56, 0.59)
Rxs† ≤ 13	Ref	-	Ref	-	Ref	-	Ref	-
14-51	0.92	(0.90, 0.94)	0.86	(0.84, 0.88)	0.82	(0.80, 0.84)	0.84	(0.81, 0.86)
52-109	0.77	(0.75, 0.78)	0.67	(0.65, 0.68)	0.61	(0.60, 0.63)	0.58	(0.56, 0.60)
≥ 110	0.68	(0.67, 0.70)	0.56	(0.55, 0.58)	0.50	(0.49, 0.52)	0.46	(0.44, 0.48)
Time (Ln)*§	0.3129	(0.3098, 0.3160)	0.0680	(0.0654, 0.0705)	0.0248	(0.0223, 0.0273)	-0.0051	(-0.0077, -0.0025)

***** Time-varying covariates, value taken from the first day of each adherence calculation interval. **†** Time-varying covariates, number in 12 months prior to the first day of each adherence calculation interval. **§** Beta (β) coefficients are presented for continuous variables instead of odds ratios. Odds ratios may be calculated from these β coefficients for any two covariate values by exponential $(\beta_1\text{-}\beta_2)$; where β_1 and β_2 are the products of the chosen covariate values and the β coefficient. ***RMM-30***, proportion of days covered in consecutive 30 day adherence calculation intervals. ***RMM-60***, proportion of days covered in consecutive 60 day adherence calculation intervals. ***RMM-90***, proportion of days covered in consecutive 90 day adherence calculation intervals. ***RMM-180***, proportion of days covered in consecutive 180 day adherence calculation intervals. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***Ln***, natural logarithmic scale. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***OR***, odds ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

TABLE 5.7: RESULTS FROM THE MULTIVARIATE GENERALISED ESTIMATING EQUATION REGRESSION ANALYSES OF STATIN NON-ADHERENCE FOR THE RMM-30, RMM-60, RMM-90 & RMM-180 STUDY COHORTS WITH A BINOMIAL VARIANCE DISTRIBUTION, A COMMON LOGIT LINK FUNCTION AND AN UNSTRUCTURED WORKING CORRELATION MATRIX

Multivariate Model Covariates ‡	RMM-30		RMM-60		RMM-90		RMM-180	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Gender								
Male	0.98	(0.96, 1.00)	0.99	(0.97, 1.02)	0.99	(0.97, 1.01)	0.99	(0.96, 1.01)
Female	Ref		Ref	-	Ref	-	Ref	-
Age								
16-34*	2.57	(2.43, 2.73)	3.17	(2.90, 3.46)	3.37	(3.06, 3.71)	3.92	(3.47, 4.42)
35-44*	1.81	(1.71, 1.88)	1.94	(1.84, 2.04)	1.95	(1.85, 2.07)	2.11	(1.97, 2.25)
45-54*	1.34	(1.30, 1.38)	1.39	(1.35, 1.44)	1.39	(1.35, 1.44)	1.50	(1.44, 1.57)
55-64*	1.06	(1.03, 1.08)	1.06	(1.04, 1.09)	1.07	(1.04, 1.10)	1.10	(1.06, 1.14)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.08	(1.05, 1.10)	1.10	(1.08, 1.13)	1.14	(1.11, 1.17)	1.18	(1.15, 1.22)
Statin Type								
Simvastatin*	0.97	(0.93, 1.02)	0.97	(0.92, 1.02)	0.99	(0.94, 1.04)	0.95	(0.90, 1.01)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.12	(1.03, 1.22)	1.15	(1.06, 1.26)	1.18	(1.07, 1.29)	1.25	(1.13, 1.39)
Atorvastatin*	0.89	(0.87, 0.91)	0.88	(0.85, 0.90)	0.89	(0.87, 0.91)	0.87	(0.84, 0.90)
Rosuvastatin*	0.91	(0.87, 0.95)	0.91	(0.87, 0.95)	0.94	(0.90, 0.98)	0.93	(0.89, 0.98)
Simva/Ezet*	0.68	(0.60, 0.76)	0.72	(0.63, 0.81)	0.75	(0.65, 0.86)	0.84	(0.69, 1.01)
Prescriber								
GP Prescriber*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	1.31	(1.26, 1.37)	0.91	(0.87, 0.94)	0.89	(0.86, 0.93)	0.79	(0.76, 0.83)
Dose								
Low Dose*	0.94	(0.92, 0.96)	0.95	(0.93, 0.97)	0.95	(0.93, 0.97)	0.99	(0.96, 1.02)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	1.15	(1.07, 1.23)	1.11	(1.03, 1.19)	1.10	(1.02, 1.18)	1.04	(0.94, 1.14)
Dose Change								
No Dose Change*	Ref	-	Ref	-	Ref	-	Ref	-
Dose Decrease*	0.58	(0.55, 0.60)	0.72	(0.69, 0.75)	0.78	(0.74, 0.81)	0.76	(0.71, 0.81)
Dose Increase*	0.59	(0.57, 0.61)	0.70	(0.67, 0.73)	0.74	(0.71, 0.77)	0.79	(0.75, 0.83)
Co-morbidities								
IHD*	0.88	(0.86, 0.90)	0.92	(0.89, 0.94)	0.92	(0.89, 0.95)	0.91	(0.87, 0.94)
Diabetes*	0.84	(0.82, 0.86)	0.85	(0.82, 0.87)	0.84	(0.82, 0.87)	0.82	(0.79, 0.85)
Depression*	1.09	(1.07, 1.11)	1.11	(1.09, 1.14)	1.12	(1.09, 1.15)	1.13	(1.10, 1.17)
Depression(Recent)*	0.99	(0.96, 1.01)	0.94	(0.92, 0.97)	0.93	(0.90, 0.96)	0.94	(0.90, 0.98)
Parkinson's Disease*	1.11	(1.04, 1.17)	1.11	(1.04, 1.18)	1.10	(1.02, 1.17)	1.09	(1.01, 1.19)

Multivariate Model Covariates ‡	RMM-30		RMM-60		RMM-90		RMM-180	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Alzheimer's Disease*	0.99	(0.94, 1.06)	1.04	(0.98, 1.11)	1.03	(0.97, 1.10)	1.01	(0.93, 1.10)
Prescribing History								
Non-Cardio PAs† ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	1.07	(1.05, 1.09)	1.06	(1.04, 1.08)	1.08	(1.05, 1.10)	1.09	(1.05, 1.12)
6 - 11	1.17	(1.15, 1.19)	1.17	(1.14, 1.19)	1.20	(1.17, 1.23)	1.26	(1.22, 1.31)
≥ 11	1.28	(1.26, 1.31)	1.31	(1.28, 1.34)	1.40	(1.36, 1.44)	1.58	(1.52, 1.64)
Cardio PAs† ≤ 0	Ref		Ref	-	Ref	-	Ref	-
1	0.93	(0.91, 0.95)	0.88	(0.87, 0.90)	0.86	(0.85, 0.88)	0.83	(0.81, 0.86)
2	0.89	(0.87, 0.91)	0.84	(0.82, 0.85)	0.82	(0.80, 0.84)	0.80	(0.77, 0.82)
≥ 3	0.87	(0.85, 0.89)	0.80	(0.79, 0.82)	0.79	(0.77, 0.81)	0.79	(0.77, 0.82)
Rxs† ≤ 13	Ref		Ref	-	Ref	-	Ref	-
14-51	0.71	(0.69, 0.72)	0.74	(0.72, 0.76)	0.74	(0.72, 0.76)	0.77	(0.74, 0.79)
52-109	0.52	(0.51, 0.53)	0.55	(0.53, 0.57)	0.53	(0.51, 0.55)	0.51	(0.49, 0.53)
≥ 110	0.43	(0.42, 0.44)	0.45	(0.44, 0.47)	0.42	(0.41, 0.44)	0.38	(0.37, 0.40)
Time (Ln)*§	0.3704	(0.3669, 0.3739)	0.0972	(0.0943, 0.1000)	0.0506	(0.0478, 0.0534)	0.0187	(0.0157, 0.0218)

***** Time-varying covariates, value taken from the first day of each adherence calculation interval. **†** Time-varying covariates, number in 12 months prior to the first day of each adherence calculation interval. **§** Beta (β) coefficients are presented for continuous variables instead of odds ratios. Odds ratios may be calculated from these β coefficients for any two covariate values by exponential $(\beta_1\text{-}\beta_2)$; where β_1 and β_2 are the products of the chosen covariate values and the β coefficient. **‡** Adjusted for all included covariates. ***RMM-30***, proportion of days covered in consecutive 30 day adherence calculation intervals. ***RMM-60***, proportion of days covered in consecutive 60 day adherence calculation intervals. ***RMM-90***, proportion of days covered in consecutive 90 day adherence calculation intervals. ***RMM-180***, proportion of days covered in consecutive 180 day adherence calculation intervals. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***Ln***, natural logarithmic scale. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***OR***, odds ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

FIGURE 5.5: WHISKER PLOT OF ODDS RATIOS WITH 95% CI FROM THE MULTIVARIATE GEE REGRESSION ANALYSIS OF REPEATED MEASURE STATIN NON-ADHERENCE (PDC < 80%, RMM-30 ■, RMM-60 ■, RMM-90 ■ & RMM-180 ■)

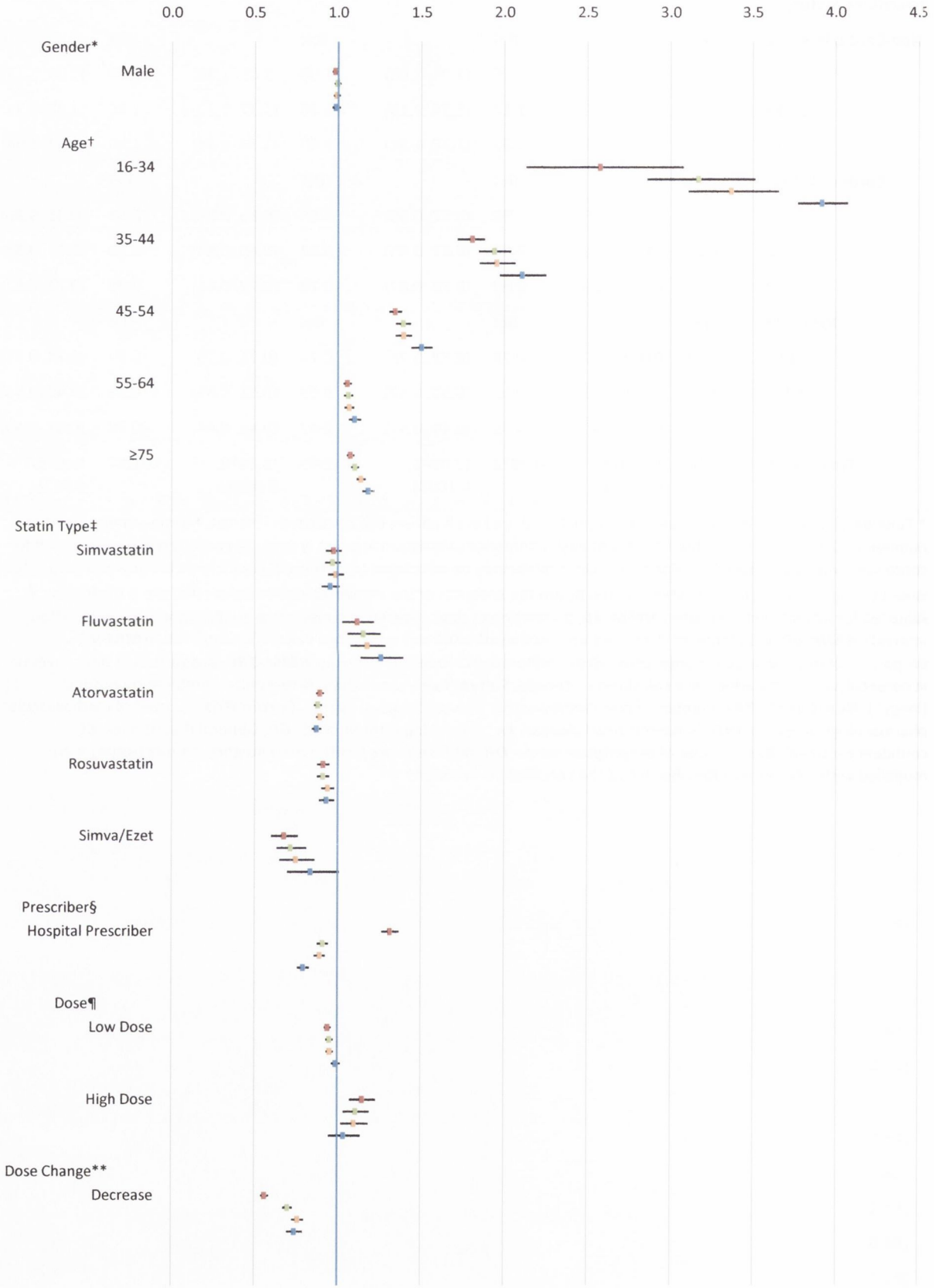
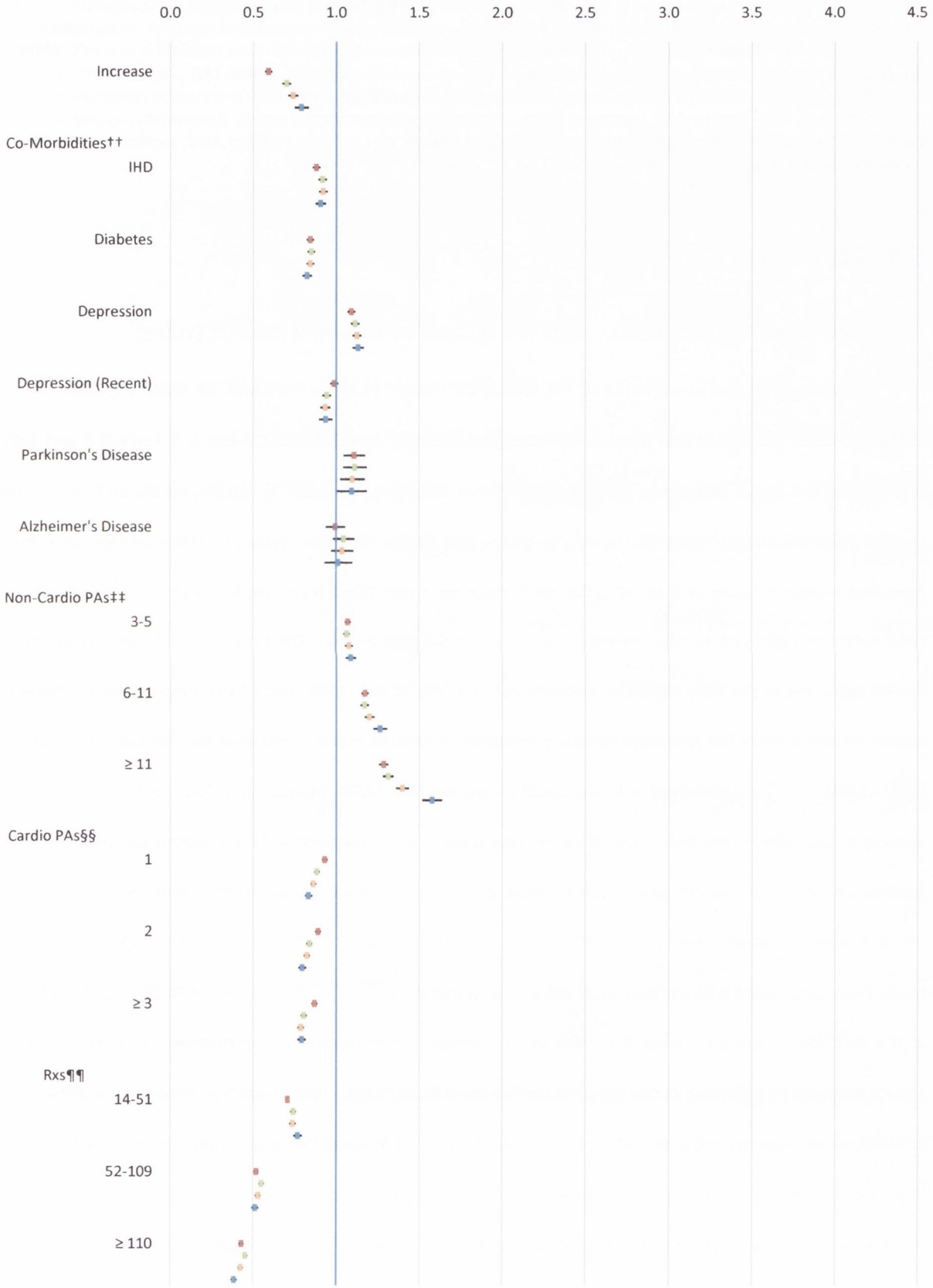


FIGURE 5.5 (CONTINUED): WHISKER PLOT OF ODDS RATIOS WITH 95% CI FROM THE MULTIVARIATE GEE REGRESSION ANALYSIS OF REPEATED MEASURE STATIN NON-ADHERENCE (PDC < 80%, RMM-30 ■, RMM-60 ■, RMM-90 ■ & RMM-180 ■)



■ = RMM-30. ■ = RMM-60. ■ = RMM-90. ■ = RMM-180. * Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. ***RMM-30***, proportion of days covered in consecutive 30 day adherence calculation intervals. ***RMM-60***, proportion of days covered in consecutive 60 day adherence calculation intervals. ***RMM-90***, proportion of days covered in consecutive 90 day adherence calculation intervals. ***RMM-180***, proportion of days covered in consecutive 180 day adherence calculation intervals. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio.

5.4 Discussion

5.4.1 Repeated Measure Model Results – A Comparison with Previous Studies

Non-adherence was identified in 42.7%, 45.3%, 47.3% and 45.1% of the RMM-30, RMM-60, RMM-90 and RMM-180 study cohorts at two years after treatment initiation (see Table 5.2, Table 5.3, Table 5.4 and Table 5.5 above). The mean adherence rates for patients at this time were 62.7%, 63.2%, 63.3% and 64.0%. The median adherence rates were 93.3%, 86.7%, 83.3% and 83.3%. Six prior studies of statin adherence using a repeated measure model and prescription refill data were identified from the literature.[38, 61-65] Synopses of their methodologies and results are presented in Table 5.8 (see below). The proportion of patients identified as non-adherent in the four repeated measure cohorts falls at the upper end of the range of non-adherence results obtained from the previous repeated measure models of statin adherence for the same time period (27% - 54%).[38, 61-64] In agreement with the results from the four RMM analyses (see Table 5.7 above), younger and older age (above and below 65-74 years) was universally associated with non-adherence in these prior studies. The effect of gender varied across these studies with female sex associated with increased odds of non-adherence in some analyses.[62, 64] Where assessed, the number of pharmacological agents received by a patient was associated with an increased risk of non-adherence.[38, 61, 62, 64] This is similar to the results obtained in the four RMM models, where the odds of non-adherence increased as the number of pharmacological agents received by a patient in the previous twelve months increased. The distinction between cardiovascular pharmacological agents and non-cardiovascular agents was not made in these previous studies. This may be an important distinction to make as there was a reduced odds of non-adherence associated with increasing numbers of cardiovascular agents in the RMM-30, 60, 90 and 180 cohorts. The reduction in the odds of non-adherence associated with diabetes and ischaemic heart disease observed in the four RMM cohorts is similar

to that observed in previous studies.[38, 61, 62, 64] The effect of dose or dose changes on the odds of non-adherence was not assessed in any of these studies; however, the effect of post-statin-initiation follow-up was assessed in the study by Benner.[62] This study demonstrated that patients who are followed-up after statin initiation have reduced odds of non-adherence. This is similar to the finding in the four RMM cohorts that patients with a change in dose, either increase or decrease, after statin initiation have reduced odds of non-adherence.

TABLE 5.8: SYNOPSES OF REPEATED MEASURE MODEL STUDIES OF STATIN ADHERENCE USING PRESCRIPTION REFILL DATA

Study	Length	Population	N	Interval	Adh <80%	Mean
Benner[38] 2002	1 – 10 years or until death or loss of eligibility	Medicaid & PAAD, males & females, >65 years old, initial users (1.5 years)	34,501	3 months x4 6 months	79% @ 3 months 56% @ 6 months 50% @ 1 year **35% @ 2 years*** 35% @ 5 years 42% @ 10 years	60% @ 3 months 43% @ 6 months - **47% @ 2 years*** 26% @ 5 years 32% @ 10 years
Benner[62] 2004	1 – 3 years or until death or loss of eligibility **Note** – patients required to have a minimum of 1 year follow-up	Insurance database, males & females, >18 years old, initial users (1 year)	19,422	3 months	51% @ 3 months 36% @ 6 months 30% @ 1 year **27% @ 2 years** 25% @ 3 years	74% @3months 51% @6months 43% @1 year **39% @ 2 years** 38% @ 3 years
Chapman[64] 2005	0.25 – 3 years or until death or loss of eligibility	Insurance database, males and females, >18 years old, initial users (1 year), with concomitant anti-hypertensive drugs (within 90 days of statin initiation)	8,406	3 months	53% @ 3 months 43% @ 6 months 43% @ 9 months 42% @ 1 year 41% @ 1.25 years 43% @ 1.5 years 42% @ 1.75 years **42% @ 2 years** 40% @ 2.25 years 39% @ 2.5 years 41% @ 2.75 years 43% @ 3 years	-
Benner[61] 2005	0.33 – 3 years or until death or loss of eligibility **Note** – patients required to have a minimum of 1 year follow-up	Insurance database, males & females, >18 years old, initial users (1 year), with at least 1 lipid measurement in year before statin initiation and at months 2-3 post statin initiation	14,480	3 months	59% @ 3 months 40% @ 6 months 34% @ 1 year 31% @ 1.5 years **28% @ 2 years** 22% @ 3 years	-

Study	Length	Population	N	Interval	Adh <80%	Mean
Caspard[63] 2005	0.5 – 3 years or until death or loss of eligibility **Note** – patients required to have a minimum of 183 days follow-up	HMO database, males & females, all ages, initial users (1 year), with baseline LDL measurement of ≥ 130 mg/dl	4,776	6 months	64% @ 6 months 55% @ 1 year **54% @ 2 years*** 53% @ 3years	-
Gibson[65] 2006	3 years	Insurance database, males & females, >18 years old, initial users (1 year)	142,341	1 month	-	-

* Two year non-adherence value estimated from reported results. ***Length***, length of study. ***Population***, Characteristics of study cohort. ***N***, number of patients in the study. ***Interval***, adherence calculation interval used in study. ***Adh < 80%***, proportion of the study population with an adherence rate less than 80% if reported. ***Mean***, the mean adherence rate for the study population if reported.

5.4.2 Advantages of Repeated Measure Models of Adherence & GEE Analysis

Repeated measure models of adherence, coupled with generalised estimating equation analysis offer a number of advantages over single measure models of adherence. The most important of these is the ability to describe the longitudinal nature of medication-taking behaviour. Repeated measure adherence models can take account of a patient's transition from adherent to non-adherent behaviour and vice versa. They can also account for the timing of non-adherence.

Variable follow-up times can be appropriately accommodated in GEE analyses subject to the limitation that missing data, due to variable follow-up, must be missing completely at random. This requires that the probability of "*missingness*" is completely independent of the outcome variables for both missing and observed outcomes.[72] In the context of repeated measure adherence analysis the causes of variable follow-up lengths must, therefore, be completely independent of the adherence outcomes for patients with complete and incomplete follow-ups. This is likely to be the case for patients with variable follow-up due to differences in the time of recruitment to the study cohort, as long as the risk of non-adherence can be said not to vary with respect to the date of treatment initiation. Whether or not the requirement for data to be missing completely at random is satisfied in the case of patients with reduced follow-up due to loss of eligibility for a prescription refill scheme or in the case of patients who have died – the latter of which may, quite plausibly, be dependent on a patient's adherence – is uncertain. The full implications of the requirement for data to be

missing completely at random, with respect to the assessment of adherence over the length of a patient's treatment episode, are discussed below (see Section 5.4.3.2).

The ability to appropriately handle time-varying covariates in GEE analyses allows the more precise attribution of non-adherence risk to covariates that may change over time. The accurate attribution of non-adherence risk in repeated measure models is however limited by a number of factors. Firstly, the correct assignment of a covariate value to an adherence calculation interval may prove difficult in patients where the covariate value changes during the interval. Secondly, the correct assignment of non-adherence risk to a time-varying covariate is dependent on the accurate identification of the timing of non-adherence. This is dependent on what conclusions can and cannot be derived from repeated adherence measures about the temporal relationship between gaps in prescription refills and a patient's underlying true medication-taking behaviour (see Section 5.4.3.1 below).

GEE analyses of repeated measure adherence data also offer the advantage of being able to appropriately analyse adherence outcomes as a continuous variable; this presents the opportunity to avoid the, sometimes arbitrary, dichotomisation of continuous adherence rates into adherent and non-adherent. The analysis of adherence rates as a continuous variable was not conducted in this study, an example of its implementation can however be found in the study of adherence to osteoporosis treatments conducted by Solomon et al.[66]

5.4.3 Limitations of Repeated Measure Models of Adherence

Despite the advantages that repeated measure models of adherence offer over single measure models there are a number of limitations to both the repeated calculation of adherence over consecutive intervals and the subsequent analysis of results that call the utility of the method into question.

5.4.3.1 Adherence Calculation Intervals & Upper Limits of Adherence

Some authors have suggested that repeated measure adherence rates may be interpreted as upper limits of adherence (see Section 1.3.1.2 on page 33).[64] This is not an accurate interpretation, as a patient's true adherence rate may be higher than that calculated in a repeated measure interval. This is best illustrated through an example. Consider the simulated 720 day prescription refill history shown in Figure 5.6 (see below). The daily adherence rates for this patient, calculated using the upper limit of adherence Equation 1.1 (see page

34), are shown in Figure 5.7 (see below). These adherence rates represent the upper limit of adherence for this patient; the maximum adherence rate they could have achieved at any time point had they displayed perfect adherence with each prescription refill they received from the date of treatment initiation. It is not possible to conclude from the prescription refill data what this patient's true adherence is, only that at any given time it lies on or below the calculated values in Figure 5.7. It is therefore possible that this patient's adherence never dropped below 80% as there was always enough medication available to cover at least 80% of the days at any time point.

Considerably different results are obtained by recalculating these adherence rates using 30, 60, 90 and 180 day repeated measure intervals. The same patient is identified as having between seven and one non-adherent episodes (PDC < 80%) and is categorised as non-adherent for 240 days (33%), 300 days (42%), 360 days (50%) and 180 days (25%) respectively (see Figure 5.8, Figure 5.9, Figure 5.10 & Figure 5.11 below). As with the upper limit of adherence calculations in Figure 5.7 (see below) it is possible that this patient may not have taken all of the medication assigned to an interval and their true adherence rate may therefore lie on or below the rates calculated in these repeated measures. It is, however, also possible that their true adherence rate could be greater than that calculated in these repeated measures. This is because repeated measure adherence calculations assume that all medication assigned to a prior adherence calculation interval is consumed in that interval. This is not necessarily the case and patients may carry over medication supplies from one interval to the next. It is thus impossible to ascertain the maximum number of days' supply a patient had available to them in an adherence calculation interval and, therefore, repeated measure adherence rates cannot be interpreted as upper limits of adherence.

This limitation of repeated adherence measures can be expressed in similar terms to the essential requirement for pharmacy systems, from which prescription refill data is collected, to be closed (see Section 1.3.1 on page 32). For the adherence calculations based on prescription refills to be considered valid (i.e. upper limits of adherence, see Section 1.3.1.2 on page 33) the pharmacy system from which they are obtained must be "*closed*"; that is, a patient must be unable or extremely unlikely to obtain medication from an unrecorded source outside of the pharmacy system. A similar criterion can be said to apply to individual adherence calculations within a closed pharmacy system. For an adherence calculation to be considered a valid upper limit of adherence, the interval over which adherence is calculated must be closed. That is, a patient must be

unable or extremely unlikely to carry unrecorded medication into an adherence calculation interval from any previous interval.

In the case of single measure models (see Chapter 4 on page 55), where adherence calculation intervals are defined as the length of time from treatment initiation to a predefined point, this is achieved by defining treatment initiation as the first prescription for the treatment of interest prior to which no prescriptions were received for an extended period of time (e.g. 1 year). This definition of treatment initiation makes it unlikely that a patient will carry forward medication from a previous treatment episode into the adherence calculation interval. In repeated measure adherence calculations the requirement for an adherence calculation interval to be closed is not met, as it is likely that a patient will carry forward medication which has not been consumed from intervals immediately preceding the adherence calculation interval of interest. The basic requirements that apply to prescription refill data for the valid calculation of adherence rates (a closed pharmacy system) cannot, therefore, be applied to the calculation of adherence rates using repeated measure methodology.

Based on these limitations it is difficult to draw conclusions about what information, if any, repeated adherence measures provide about a patient's medication-taking behaviour, or exactly how their results can be interpreted in light of the fact that they do not represent either a patient's true adherence rate or an upper limit of adherence. While upper limit of adherence measures can at least be considered a specific but insensitive measure of non-adherence, repeated adherence measures are neither a specific nor a sensitive measure of non-adherence.

In addition to this, a further examination of the simulated repeated measure results from the various interval lengths (see Figure 5.8, Figure 5.9, Figure 5.10 & Figure 5.11 below) shows considerable variation in both the adherence rates obtained and the timing of non-adherence episodes. This variation is not reflected in the aggregated results from the RMM-30, 60, 90 and 180 models (see Figure 5.1, Figure 5.2, Figure 5.3 & Figure 5.4 above), most likely due to an averaging of the effect. Nevertheless, the extreme variation raises concerns about the sensitivity of adherence results and covariate model results to changes in the length of the adherence calculation interval. This may also explain in part the differences in the odds ratios for non-adherence risk assigned to some covariates; in particular age. It is possible that repeated measure adherence models may be significantly influenced by the length of the adherence calculation interval. Without well

defined clinical reasoning or objective evidence for the selection of one adherence calculation interval length over the other it is difficult to advocate an appropriate one for use.

FIGURE 5.6: SIMULATED 720 DAY PRESCRIPTION REFILL HISTORY

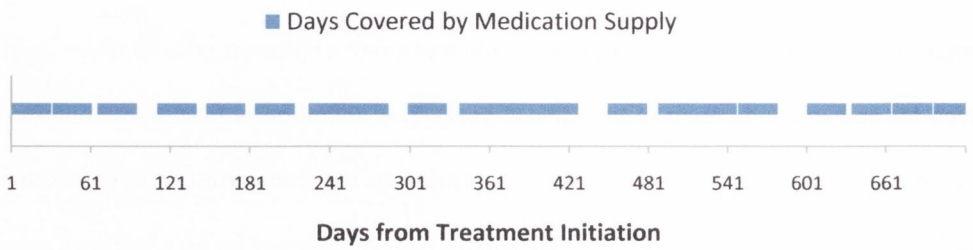


FIGURE 5.7: DAILY UPPER LIMIT OF ADHERENCE VALUES FOR A SIMULATED 720 DAY PRESCRIPTION REFILL HISTORY (SEE FIGURE 5.6 ABOVE)

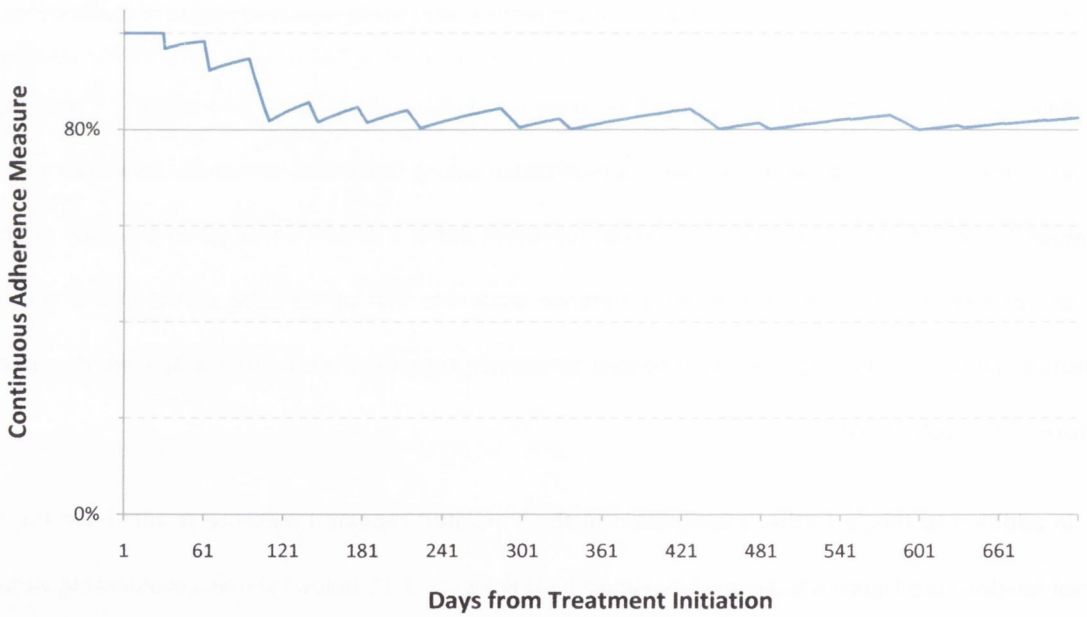


FIGURE 5.8: 30 DAY REPEATED MEASURE ADHERENCE VALUES FOR A SIMULATED 720 DAY PRESCRIPTION REFILL HISTORY (SEE FIGURE 5.6 ABOVE)

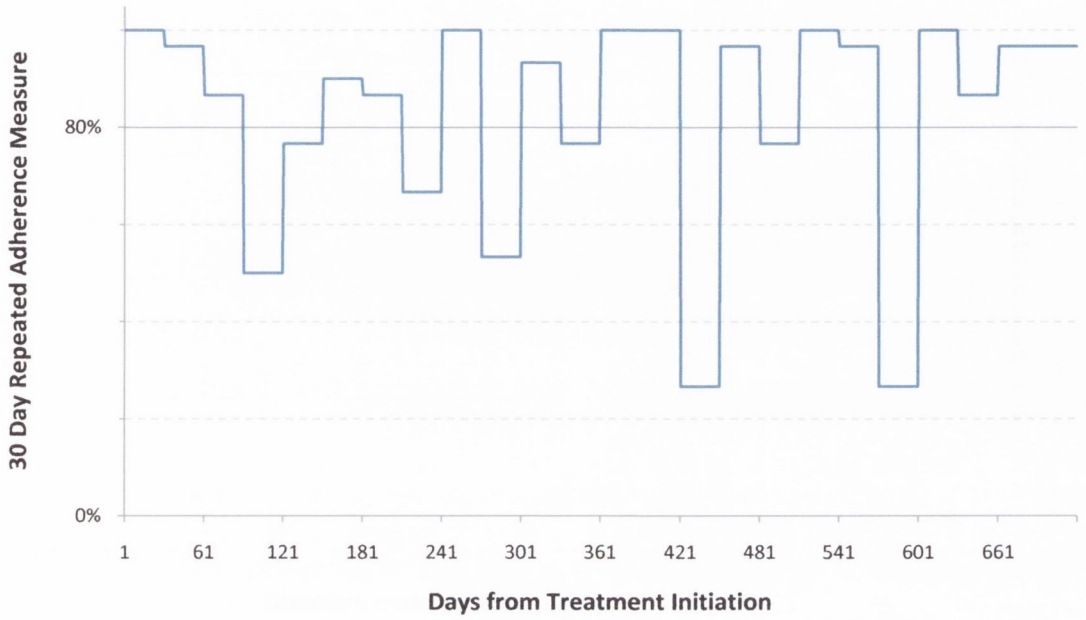


FIGURE 5.9: 60 DAY REPEATED MEASURE ADHERENCE VALUES FOR A SIMULATED 720 DAY PRESCRIPTION REFILL HISTORY (SEE FIGURE 5.6 ABOVE)

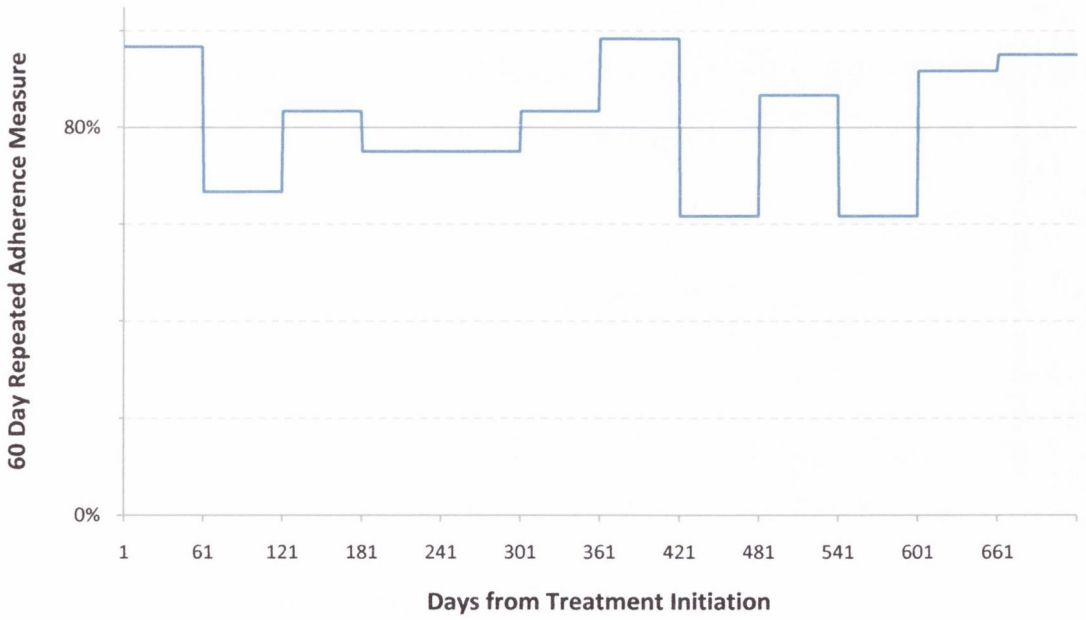


FIGURE 5.10: 90 DAY REPEATED MEASURE ADHERENCE VALUES FOR A SIMULATED 720 DAY PRESCRIPTION REFILL HISTORY (SEE FIGURE 5.6 ABOVE)

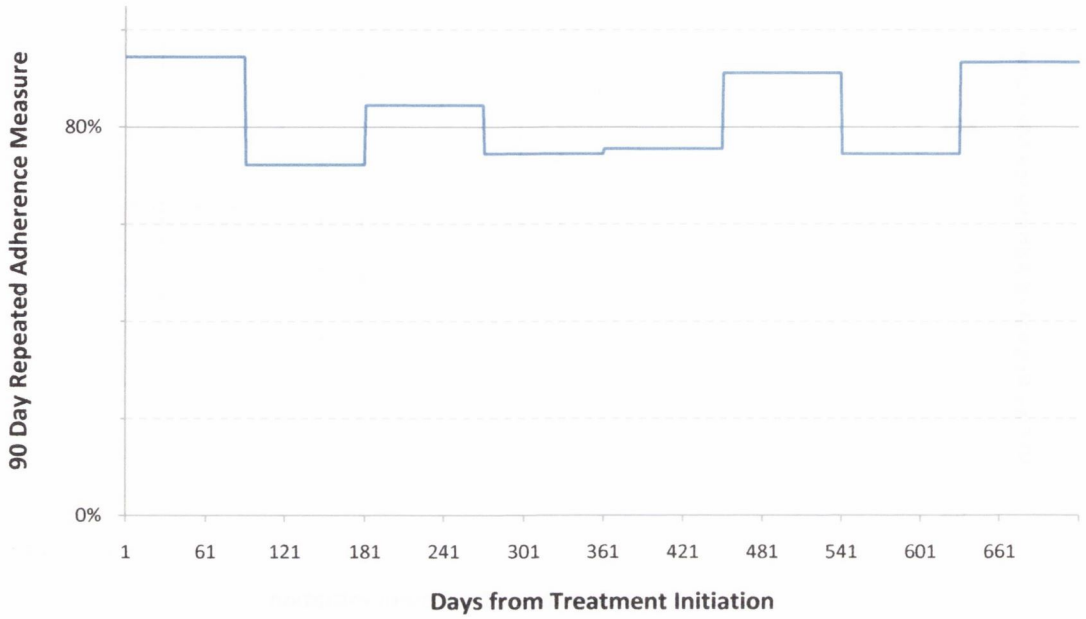
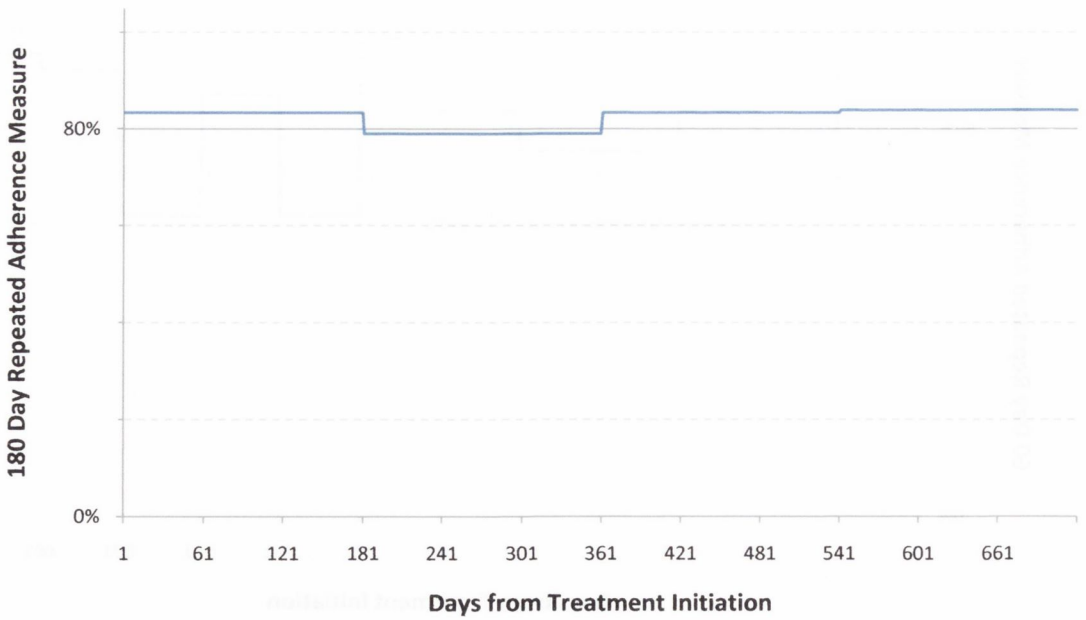


FIGURE 5.11: 180 DAYS REPEATED MEASURE ADHERENCE VALUES FOR A SIMULATED 720 DAY PRESCRIPTION REFILL HISTORY (SEE FIGURE 5.6 ABOVE)



5.4.3.2 Adherence Observation Period: Length of Follow-Up

In the RMM-30, 60, 90 and 180 adherence analyses and in all of the previously identified repeated measure adherence analyses[38, 61-68] adherence measures were repeated over the length of a patient's complete follow-up. As discussed in Section 4.4.3 (see page 75) this approach allows inclusion of the time after a patient has discontinued treatment in the calculation of adherence values and may result in the misclassification of patients who become non-persistent as non-adherent. It would be preferable to take repeated adherence measures over the length of time that a patient can reasonably be expected to be continuing with treatment.

While GEE analyses of repeated measure adherence models can handle variable follow-up times, this ability, as stated in Section 5.4.2 (see above), is subject to the limitation that missing data due to variable follow-up must be missing completely at random. For adherence data, missing due to non-persistence, to be considered missing completely at random, there must be no correlation between the risk of non-persistence and the adherence outcomes of both persistent and non-persistent patients. It is unlikely that this criterion is fulfilled as non-persistent patients are also likely to be those patients who have a higher risk of non-adherence.[23] The missing adherence data produced by non-persistence cannot be considered an ignorable non-response mechanism and GEE analyses cannot, therefore, be used for the analysis of results from studies that take repeated adherence measures over the length of a patient's treatment episode. The repeated measurement of a patient's adherence over the length of their treatment episode is also limited, in the same way as single measures (see Section 4.4.3 on page 75), by the inability of prescription refill data to provide accurate estimates of adherence in patients who receive only one prescription or patients who become non-persistent at an early stage in their treatment.

5.5 Summary

Statin adherence was measured in a cohort of GMS patients using prescription refill data from the HSE-PCRS pharmacy claims database. A repeated measure model of adherence was employed for the calculation of adherence rates and the results were analysed using a generalised estimating equations analysis with a binomial distribution a logit link function and an unstructured working correlation matrix. The adherence rate results were within the range of results obtained from previous repeated measure studies of statin

adherence.[38, 61-65] The results from the GEE covariate analysis were also broadly similar to those obtained in the previous statin studies.[38, 61-65] The calculation and analysis of adherence using the repeated measure model addresses a number of the limitations of single measure models (see Section 4.4.5 on page 78). Most notable among these is the ability of repeated measure models to take account of the longitudinal nature of adherence behaviour, the timing of non-adherence, the time-varying properties of covariates and variations in the length of patients' follow-up.

There are however some limitations to the repeated measure model. Firstly, the methodological and clinical rationale for the selection of an adherence rate calculation interval is not clear and variations in the length of this interval may produce significant variation in the adherence rates obtained for individual patients. Secondly, it is difficult to draw conclusions about what information, if any, repeated measure adherence rates provide about a patient's medication-taking behaviour, or exactly how their adherence rate results can be interpreted in light of the fact that they do not represent either a patient's true adherence or an upper limit of adherence. Finally, the requirement for missing data to be missing completely at random in GEE analyses does not allow the exclusion of non-persistent behaviour from the repeated measure model to measure adherence. This is because missing adherence data due to non-persistence cannot be considered an ignorable non-response mechanism.

5.6 Conclusion

Repeated measure models of adherence address many of the limitations of single measure models and in doing so provide considerably more analytic detail for the exploration of adherence behaviour. They are, however, limited; by the lack of objective evidence to validate the choice of an adherence calculation interval; by the imprecise nature of the adherence estimates they provide; and by the fact that their analysis does not allow the appropriate assessment of adherence over the length of a patient's treatment episode.

CHAPTER SIX

6 STATIN ADHERENCE – TIME TO NON-ADHERENCE MODEL

6.1 INTRODUCTION

Time to non-adherence models of medication-taking behaviour are based upon the identification of the time at which a patient's upper limit of adherence drops below a particular level. They provide an estimation of the length of time a patient can be expected to take a therapy at a specific intensity; where the intensity can be defined in terms of both the level of non-adherence (e.g. < 80%) and the length of the non-adherent episode (e.g. 180 days). As with the repeated measure model of adherence presented in Chapter 5 (see page 83), time to non-adherence models can take account of the longitudinal nature of medication-taking behaviour. The application of a time to non-adherence model to statin adherence in the GMS population is described here. The advantages and disadvantages of this method are discussed with reference to the measurement of adherence, the identification of non-adherent risk factors and the distinction between nono-adherent and non-persistent behaviours.

6.2 METHODS

Time to non-adherence models of medication-taking behaviour have been used infrequently for the analysis of adherence and where they have been applied, the methodology has been inconsistently defined.[75-77] Two prior studies of statin adherence using time to non-adherence methodology were identified from the literature.[75, 76] The first of these was undertaken using prescription refill data[75] and the second using pill count data[76] (see Section 1.2 on page 30) from a clinical trial[78] of statin efficacy. Unfortunately, both of these adherence studies combine the time to non-adherence results with time to non-persistence data (see Chapter 7 on page 139) to give a composite measure of adherence and persistence. This makes an assessment of the methodology used and an interpretation of the adherence results obtained difficult. The only identified study, in which time to non-adherence was measured and analysed independently, was of adherence to osteoporosis

medications using electronic medication event monitors (MEMS®[i]).[77] In this study, patients were defined as adherent if their measured adherence was above a threshold of 75% at the end of one year's follow-up. For patients with an adherence rate of less than 75% at this time, the last date upon which their adherence was above 75% was identified as their time to non-adherence. This methodology is limited by the possibility that time to non-adherence results may be influenced by the choice of follow-up length. This is because non-adherent events are defined with reference to the length of follow-up. As adherence rates may rise as well as fall, patients identified as having a non-adherent event over the defined follow-up may not be identified as having the same event, or any event at all, as the length of follow up is increased. The possibility that a patient may progress from having a non-adherent event to not having a non-adherent event, as the length of specified follow-up is increased, is unsatisfactory. The calculation and analysis of time to non-adherence in this study was therefore undertaken using a variation of this methodology.

6.2.1 Calculation of Proportion of Days Covered

Daily adherence rates were calculated using the proportion of days covered methodology (See Section 4.2.1 on page 55). A PDC value was calculated for *every day* in a patients follow-up using Equation 6.1 (see below). The number of assigned doses in each adherence calculation was determined from the constructed longitudinal database of medication supply (see Section 3.3 on page 46). The calculated proportion of days covered measure has a maximum value of 100% and may be interpreted as an upper limit of adherence as the adherence calculation interval, from treatment initiation onwards, can be considered closed (see Section 1.3.1.2 on Page 33).

EQUATION 6.1: PROPORTION OF DAYS COVERED FOR THE TIME TO NON-ADHERENCE MODEL

$$Proportion\ of\ Days\ Covered\ (Time\ to\ Non\ Adherence\ Model\ \%) = \left[\sum_{\delta=\alpha}^{\beta} \delta \Big/ \beta\right] \times 100$$

Where α denotes the first day of a patient's treatment, β denotes the day on which adherence is to be calculated and δ denotes the days supply (1 or 0) assigned to each day (see Section 1.3.1.2 on page 33 & Section 3.3 on page 46).

[i] Medication Electronic Monitoring System®, Aardex, Zug, Switzerland.

6.2.2 Defining Non-Adherence as an Event

Non-adherence has customarily been defined by an adherence rate of less than a specified permissible level (e.g. < 80%); in practice however, as adherence rates can rise as well as fall, the degree of non-adherence experienced by a patient is also dependent on the length of any non-adherent episode (see Section 4.4.5.1 on page 78). To account for the two-dimensional nature of non-adherence, non-adherent events in this study were defined by both the level of non-adherence and the length of the non-adherent episode.

Four non-adherent episode lengths were chosen to illustrate the influence of episode length on time to non-adherence results. These were 1 day, 90 days, 180 days and 360 days. As with the two previous statin adherence analyses (see Chapters 4 & 5 on pages 55 & 83) non-adherence was defined as PDC of less than 80% (see Section 3.2 on page 46). A patient's time to non-adherence was identified as the length of time from treatment initiation to the first time that their adherence rate dropped below 80% for at least 1 day (TNA-80/1[i]), 90 consecutive days (TNA-80/90[ii]), 180 consecutive days (TNA-80/180[iii]) or 360 consecutive days (TNA-80/360[iv]). The event date was taken as the first day of the non-adherent episode. Patients who became lost to follow-up (see Section 3.5.1 on page 49) within the defined non-adherent episode length were not identified as non-adherent. The time to non-adherence was ascertained for each of the four non-adherent event definitions.

6.2.3 Statistical Analysis

The SAS® PROC LIFETEST procedure was used to construct Kaplan-Meier plots from which the cumulative rates of non-persistence for the TNA-80/1, TNA-80/90, TNA-80/180 and TNA-80/360 models were estimated. Univariate and multivariate Cox regression models with time varying covariates were constructed for each of the time to non- adherence analyses using the SAS® PROC PHREG procedure. Censoring in this study was random[v] with observations censored at the time of loss to follow-up or end of follow-up, whichever occurred first. Tied events in the Cox regression model were handled using the method proposed by Efron.[79, 80] Crude

---

[i] Time to non-adherence model defined as a PDC of < 80% for at least 1 day.

[ii] Time to non-adherence model defined as a PDC of < 80% for at least 90 consecutive days.

[iii] Time to non-adherence model defined as a PDC of < 80% for at least 180 consecutive days.

[iv] Time to non-adherence model defined as a PDC of < 80% for at least 360 consecutive days.

[v] Censoring is considered random when observations are terminated for reasons that are not under the control of the investigator.

and adjusted hazard ratios and 95% confidence intervals are presented for independent covariates. Multivariate analyses were adjusted for all included covariates. Significance at $p < 0.05$ was assumed. SAS® version 9.1[i] was used for all analyses.

6.2.4 Covariates Included in the Time to Non-Adherence Models

Patient gender and the following time-varying covariates were included in the model; age, current statin type, current statin dose, current statin prescriber, statin dose change, all co-morbidities and the number of non-cardiovascular pharmacological agents, cardiovascular pharmacological agents and prescription items received by a patient in the prior 365 days. Values for the time-varying covariates were taken on the day of adherence calculation. A full description of these covariates can be found in Section 3.6 (see page 49).

6.3 Results

6.3.1 Time to Non-Adherence – Study Cohort

The time to non-adherence methodology did not require the exclusion of any patients from the source study cohort (see Chapter 3 on page 43). The characteristics of the patients included in the time to non-adherence analyses can be found in Table 3.2 (see page 53) and described in Section 3.7.2 (see page 52).

6.3.2 Time to Non-Adherence – Results

The Kaplan Meier curves for each of the four non-adherent event definitions are shown in Figure 6.1 (TNA-80/1), Figure 6.2 (TNA-80/90), Figure 6.3 (TNA-80/180) and Figure 6.4 (TNA-80/360) below. A selection of results from these Kaplan-Meier curves is presented in Table 6.1, Table 6.2, Table 6.3 and Table 6.4, also below. The curves show that, for the majority of non-adherent patients, non-adherence occurs in the first 180 days after treatment initiation. Thereafter, the number of patients experiencing an initial non-adherent event decreases.

The results from these Kaplan-Meier analyses can be used to estimate the probability of a number of adherence outcomes. For example, in the 720 days after treatment initiation the cumulative probability of a

[i] SAS Institute, Cary, NC, USA.

patient never having an adherence rate of less than 80% was 29.6%[i] (see Table 6.1 below). The probability of a patient having an adherence rate of less than 80% for at least one day was 70.4% and the probability of a patient having an adherence rate of less than 80% for a sustained period of 90, 180 or 360 consecutive days was 59.7%, 52.6% and 45.0% respectively (see Table 6.2, Table 6.3, & Table 6.4 below).

[i] Calculated as one minus the probability that a patient had an adherence rate of less than 80% for at least one day prior to 720 days follow-up.

FIGURE 6.1: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 1 DAY (TNA-80/1)

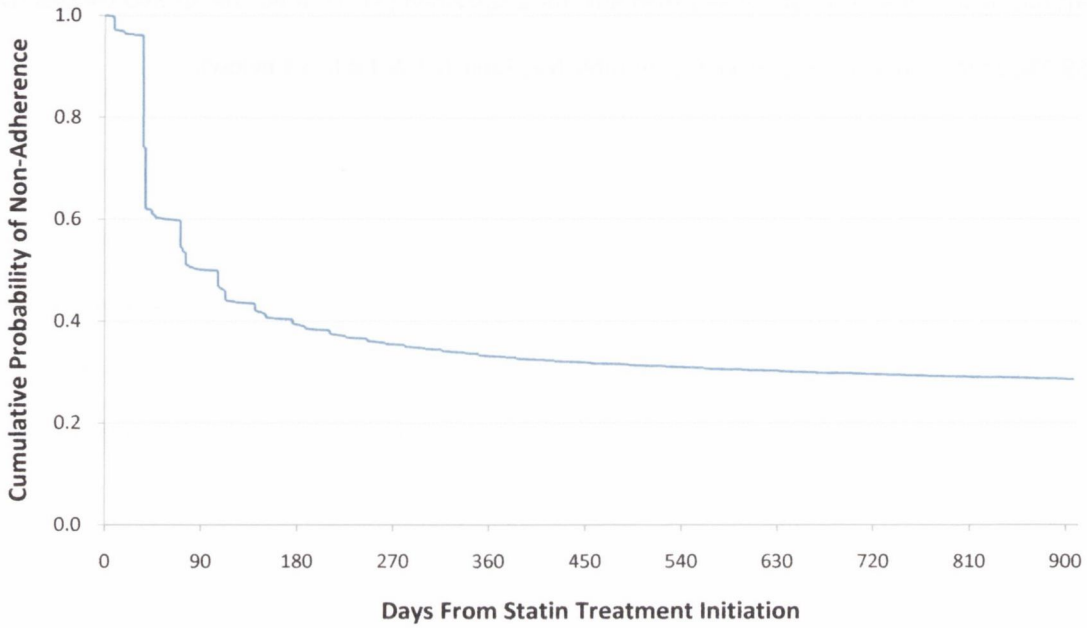


TABLE 6.1: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 1 DAY (TNA-80/1)

Day	Cumulative Probability of Non-Adherence (%)	95% CI (%)	Adherent (N)	Non-Adherent (N)	Censored (N)
30	3.8	(3.7, 4.0)	74,374	2,984	2,006
60	40.0	(39.7, 40.4)	46,056	30,893	2,415
90	49.9	(49.5, 50.2)	38,282	38,415	2,667
180	60.6	(60.3, 61.0)	29,594	46,587	3,183
270	64.5	(64.2, 64.9)	23,175	49,361	6,828
360	66.8	(66.5,67.1)	18,241	50,744	10,379
450	68.0	(67.7, 68.4)	13,684	51,352	14,328
540	69.0	(68.7, 69.3)	9,884	51,720	17,760
630	69.7	(69.3, 70.0)	8,368	51,926	19,070
720	70.4	(70.0, 70.7)	5,818	52,095	21,451
810	70.9	(70.5, 71.3)	2,645	52,176	24,543
900	71.3	(70.9, 71.7)	496	52,199	26,669

TNA-80/1, time to an adherence rate of less than 80% for at least 1 day. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

FIGURE 6.2: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 90 CONSECUTIVE DAYS (TNA-80/90)

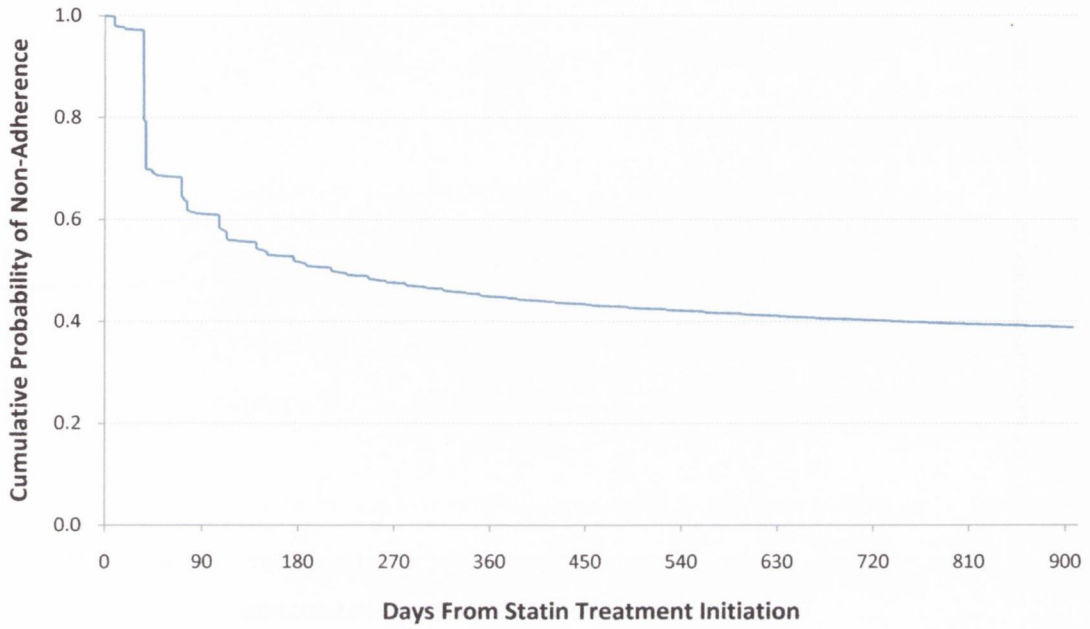


TABLE 6.2: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 90 CONSECUTIVE DAYS (TNA-80/90)

Day	Cumulative Probability of Non-Adherence (%)	95% CI (%)	Adherent (N)	Non-Adherent (N)	Censored (N)
30	2.8	(2.7, 2.9)	75,164	2,161	2,039
60	31.6	(31.2, 31.9)	52,353	24,343	2,668
90	38.9	(38.6, 39.2)	46,196	29,923	3,245
180	48.3	(47.9, 48.6)	38,022	36,916	4,426
270	52.4	(52.0, 52.7)	30,155	39,773	9,436
360	55.1	(54.7, 55.5)	24,043	41,354	13,967
450	56.6	(56.2, 56.9)	18,560	42,074	18,730
540	57.9	(57.5, 58.2)	13,859	42,570	22,935
630	58.8	(58.5, 59.2)	11,464	42,869	25,031
720	59.7	(59.3, 60.1)	7,993	43,089	28,282
810	60.5	(60.1, 60.9)	3,996	43,212	32,156
900	61.1	(60.7, 61.6)	684	43,247	35,433

TNA-80/90, time to an adherence rate of less than 80% for at least 90 consecutive days. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

FIGURE 6.3: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 180 CONSECUTIVE DAYS (TNA-80/180)

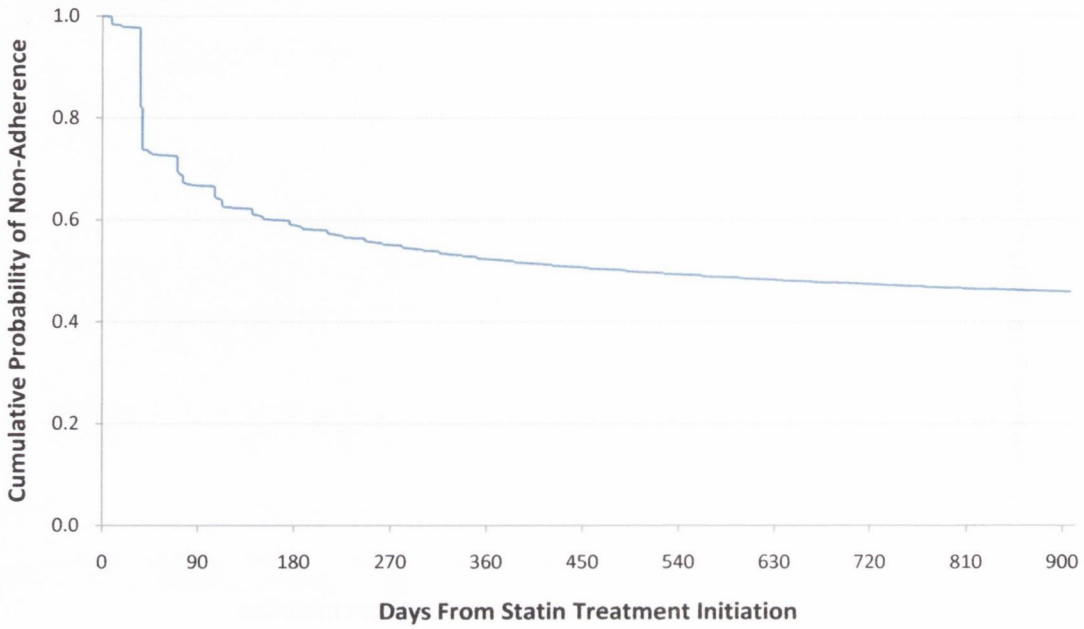


TABLE 6.3: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 180 CONSECUTIVE DAYS (TNA-80/180)

Day	Cumulative Probability of Non-Adherence (%)	95% CI (%)	Adherent (N)	Non-Adherent (N)	Censored (N)
30	2.2	(2.1, 2.3)	75,588	1,737	2,039
60	27.4	(27.0, 27.7)	55,605	21,091	2,668
90	33.3	(32.9, 33.6)	50,530	25,589	3,245
180	41.0	(40.7, 41.4)	43,141	31,385	4,838
270	44.9	(44.5, 45.3)	34,280	34,042	11,042
360	47.7	(47.3, 48.0)	27,559	35,641	16,164
450	49.3	(48.9, 49.6)	21,544	36,396	21,424
540	50.7	(50.3, 51.0)	16,372	36,933	26,059
630	51.7	(51.3, 52.0)	13,365	37,240	28,759
720	52.6	(52.2, 53.0)	9,237	37,462	32,665
810	53.5	(53.0, 53.9)	4,683	37,596	37,085
900	54.0	(53.7, 54.3)	784	37,633	40,947

TNA-80/180, time to an adherence rate of less than 80% for at least 180 consecutive days. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

FIGURE 6.4: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 360 CONSECUTIVE DAYS (TNA-80/360)

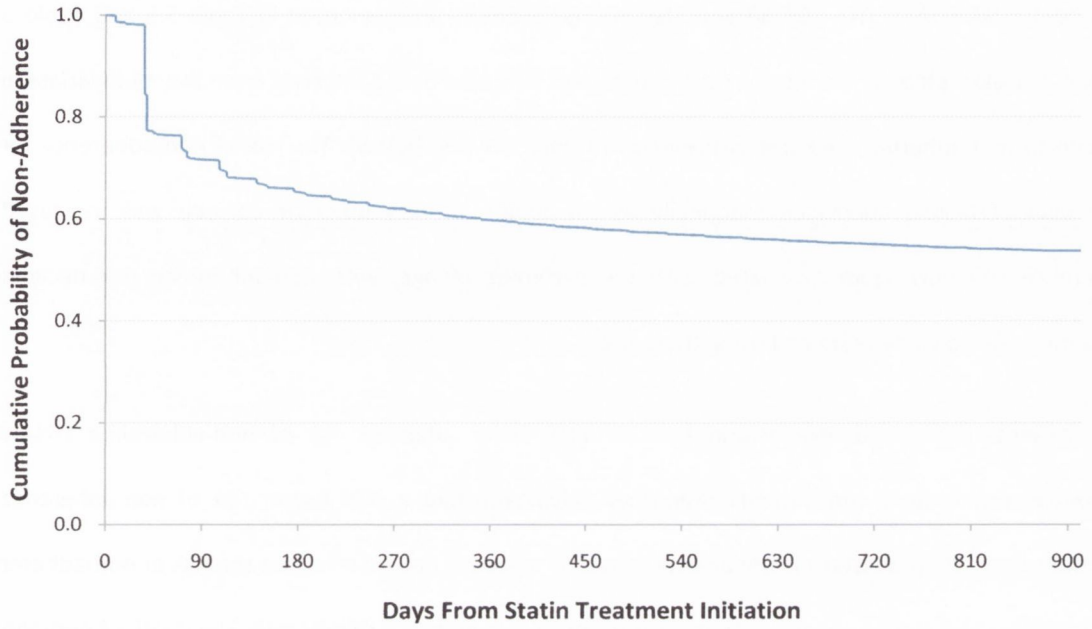


TABLE 6.4: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-ADHERENCE (PDC < 80%) FOR AT LEAST 360 CONSECUTIVE DAYS (TNA-80/360)

Day	Cumulative Probability of Non-Adherence (%)	95% CI (%)	Adherent (N)	Non-Adherent (N)	Censored (N)
30	1.9	(1.8, 1.9)	75,886	1,439	2,039
60	23.6	(23.3, 23.9)	58,514	18,182	2,668
90	28.4	(28.1, 28.7)	54,283	21,836	3,245
180	34.7	(34.4, 35.1)	47,934	26,592	4,838
270	37.9	(37.5, 38.2)	38,474	28,759	12,131
360	40.2	(39.9, 40.6)	30,869	30,073	18,422
450	41.7	(41.3, 42.0)	24,143	30,768	24,453
540	43.0	(42.7, 43.4)	18,518	31,273	29,573
630	44.0	(43.6, 44.4)	14,942	31,566	32,856
720	45.0	(44.6, 45.3)	10,228	31,781	37,355
810	45.8	(45.4, 46.2)	5,149	31,901	42,314
900	46.3	(45.8, 46.7)	889	31,935	46,540

TNA-80/360, time to an adherence rate of less than 80% for at least 360 consecutive days. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

6.3.3 Cox Regression Analyses – Univariate & Multivariate Models

The results from the univariate and multivariate Cox regression models of time to non-adherence for the TNA-80/1, TNA-80/90, TNA-80/180 and TNA-80/360 analyses are presented in Table 6.5 and Table 6.6 (see below). Whisker plots of the hazard ratio results and 95% confidence intervals from the multivariate analyses of time to non-adherence are also presented in Figure 6.5 (see below). The risk of non-adherence for males (reference; females) decreased marginally as the length of non-adherent episode was increased. Non-adherence risk was again associated with the extremes of age, with non-adherence risk declining with increasing age up to 74 years and rising thereafter.

Patients prescribed atorvastatin had an 11% lower adjusted risk of non-adherence (TNA-80/360, reference; pravastatin) and patients prescribed fluvastatin had a 30% higher risk of non-adherence (TNA-80/360, reference; pravastatin). The dose received by a patient had no effect on the risk of non-adherence but patients who had a dose change (either increase or decrease) had a significantly lower risk of non-adherence across each of the adherence episode length definitions.

In the adjusted model a diagnosis of Parkinson's disease or depression was associated with an increased risk of non-adherence, although a recent diagnosis of depression was not. Patients receiving treatments for ischaemic heart disease or diabetes had a 12% and 13% reduction in the adjusted risk of non-adherence respectively (TNA-80/360). The risk of non-adherence was higher for patients receiving non-cardiovascular pharmacological agents. The number cardiovascular agents prescribed was, however, only associated with a modest reduction in the risk of non-adherence after adjusting for other covariates in the model. The largest reductions in non-adherence risk were associated with increasing numbers of prescription items received by a patient. The reduction in the adjusted risk of non-adherence for patients receiving 14-51 and ≥ 110 prescription items in the prior twelve months was 24% and 53% respectively (TNA-80/360, reference ≤ 13 prescription items).

TABLE 6.5: RESULTS FROM THE UNIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-ADHERENCE FOR 1, 90, 180 & 360 DAYS (TNA-80/1, TNA-80/90, TNA-80/180 & TNA-80/360)

Model Covariates	TNA-80/1		TNA80/90		TNA80/180		TNA80/360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Gender								
Male	0.99	(0.97, 1.00)	0.98	(0.96, 1.00)	0.97	(0.95, 0.99)	0.96	(0.94, 0.98)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	2.42	(2.31, 2.54)	2.76	(2.63, 2.90)	2.86	(2.71, 3.01)	2.53	(2.39, 2.68)
35-44*	1.65	(1.58, 1.72)	1.81	(1.74, 1.90)	1.92	(1.83, 2.01)	1.88	(1.79, 1.97)
45-54*	1.37	(1.33, 1.41)	1.45	(1.40, 1.50)	1.50	(1.45, 1.55)	1.50	(1.44, 1.55)
55-64*	1.10	(1.07, 1.13)	1.13	(1.10, 1.16)	1.15	(1.12, 1.19)	1.16	(1.13, 1.20)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.05	(1.03, 1.07)	1.06	(1.03, 1.08)	1.05	(1.02, 1.08)	1.02	(0.99, 1.05)
Statin Type								
Simvastatin*	0.99	(0.95, 1.03)	0.99	(0.95, 1.03)	0.99	(0.95, 1.04)	0.98	(0.94, 1.04)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.21	(1.13, 1.28)	1.24	(1.16, 1.33)	1.28	(1.19, 1.37)	1.31	(1.21, 1.42)
Atorvastatin*	0.91	(0.89, 0.93)	0.88	(0.86, 0.90)	0.87	(0.85, 0.89)	0.85	(0.83, 0.88)
Rosuvastatin*	0.97	(0.94, 1.00)	0.96	(0.92, 0.99)	0.96	(0.92, 0.99)	0.96	(0.92, 1.00)
Simva/Ezet*	0.85	(0.74, 0.98)	0.92	(0.80, 1.07)	1.00	(0.86, 1.16)	1.03	(0.87, 1.20)
Prescriber								
GP Prescriber*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.97	(0.95, 1.00)	0.87	(0.84, 0.90)	0.78	(0.75, 0.81)	0.73	(0.70, 0.76)
Dose								
Low Dose*	0.99	(0.97, 1.01)	0.99	(0.97, 1.01)	0.99	(0.97, 1.01)	0.99	(0.97, 1.02)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	1.07	(1.01, 1.14)	1.05	(0.98, 1.12)	1.03	(0.95, 1.11)	0.99	(0.91, 1.07)
Dose Change								
No Dose Change*	Ref	-	Ref	-	Ref	-	Ref	-
Dose Decrease*	0.81	(0.75, 0.87)	0.90	(0.83, 0.96)	0.92	(0.86, 0.99)	0.87	(0.80, 0.95)
Dose Increase*	0.82	(0.77, 0.87)	0.86	(0.81, 0.92)	0.86	(0.80, 0.91)	0.83	(0.77, 0.89)
Co-morbidities								
IHD*	0.83	(0.81, 0.85)	0.79	(0.77, 0.82)	0.77	(0.74, 0.79)	0.73	(0.71, 0.76)
Diabetes*	0.87	(0.85, 0.89)	0.85	(0.83, 0.87)	0.84	(0.81, 0.86)	0.79	(0.76, 0.81)
Depression*	1.05	(1.03, 1.07)	1.05	(1.03, 1.08)	1.07	(1.05, 1.09)	1.07	(1.04, 1.10)
Depression(Recent)*	1.13	(1.09, 1.17)	1.17	(1.12, 1.22)	1.19	(1.14, 1.24)	1.18	(1.13, 1.23)
Parkinson's Disease*	1.00	(0.94, 1.05)	1.00	(0.94, 1.06)	0.99	(0.93, 1.06)	0.98	(0.91, 1.06)
Alzheimer's Disease*	1.01	(0.95, 1.07)	0.97	(0.91, 1.04)	0.95	(0.89, 1.02)	0.87	(0.80, 0.94)

Model Covariates	TNA-80/1		TNA80/90		TNA80/180		TNA80/360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Prescribing History								
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	0.93	(0.90, 0.96)	0.93	(0.89, 0.96)	0.92	(0.89, 0.95)	0.91	(0.88, 0.95)
6 - 11	0.90	(0.87, 0.92)	0.89	(0.86, 0.92)	0.89	(0.86, 0.92)	0.89	(0.86, 0.92)
≥ 11	0.94	(0.91, 0.97)	0.93	(0.90, 0.97)	0.94	(0.91, 0.97)	0.94	(0.91, 0.98)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.80	(0.78, 0.82)	0.78	(0.76, 0.80)	0.76	(0.74, 0.78)	0.75	(0.72, 0.77)
2	0.72	(0.70, 0.74)	0.67	(0.66, 0.69)	0.64	(0.62, 0.66)	0.63	(0.61, 0.65)
≥ 3	0.66	(0.64, 0.67)	0.60	(0.59, 0.62)	0.57	(0.55, 0.58)	0.54	(0.53, 0.56)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-	Ref	-
14-51	0.72	(0.70, 0.74)	0.72	(0.70, 0.74)	0.72	(0.69, 0.74)	0.74	(0.71, 0.76)
52-109	0.59	(0.57, 0.60)	0.56	(0.54, 0.57)	0.54	(0.53, 0.56)	0.55	(0.53, 0.57)
≥ 110	0.53	(0.51, 0.54)	0.48	(0.47, 0.50)	0.45	(0.44, 0.47)	0.44	(0.43, 0.46)

* Time-varying covariates, value taken from the day of each adherence calculation. † Time-varying covariates, number in 12 months prior to the day of each adherence calculation. ***TNA-80/1***, time to an adherence rate of less than 80% for at least 1 day. ***TNA-80/90***, time to an adherence rate of less than 80% for at least 90 consecutive days. ***TNA-80/180***, time to an adherence rate of less than 80% for at least 180 consecutive days. ***TNA-80/360***, time to an adherence rate of less than 80% for at least 360 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

TABLE 6.6: RESULTS FROM THE MULTIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-ADHERENCE FOR 1, 90, 180 & 360 DAYS (TNA-80/1, TNA-80/90, TNA-80/180 & TNA-80/360)

Multivariate‡ Model Covariates	TNA-80/1		TNA80/90		TNA80/180		TNA80/360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Gender								
Male	0.98	(0.96, 0.99)	0.97	(0.95, 0.99)	0.96	(0.94, 0.98)	0.96	(0.94, 0.98)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	2.18	(2.08, 2.29)	2.42	(2.30, 2.54)	2.45	(2.32, 2.58)	2.13	(2.02, 2.26)
35-44*	1.53	(1.47, 1.60)	1.67	(1.60, 1.74)	1.75	(1.67, 1.83)	1.69	(1.61, 1.78)
45-54*	1.30	(1.27, 1.34)	1.37	(1.33, 1.41)	1.40	(1.35, 1.45)	1.39	(1.34, 1.44)
55-64*	1.08	(1.05, 1.11)	1.10	(1.07, 1.13)	1.12	(1.08, 1.15)	1.12	(1.09, 1.16)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.14	(1.12, 1.17)	1.17	(1.14, 1.20)	1.18	(1.15, 1.21)	1.16	(1.12, 1.19)
Statin Type								
Simvastatin*	0.98	(0.94, 1.02)	0.98	(0.94, 1.02)	0.98	(0.93, 1.02)	0.97	(0.92, 1.02)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.17	(1.09, 1.25)	1.21	(1.12, 1.30)	1.24	(1.15, 1.34)	1.30	(1.19, 1.41)
Atorvastatin*	0.92	(0.90, 0.94)	0.90	(0.88, 0.93)	0.90	(0.87, 0.92)	0.89	(0.86, 0.91)
Rosuvastatin*	0.97	(0.94, 1.00)	0.95	(0.91, 0.98)	0.94	(0.91, 0.98)	0.94	(0.90, 0.98)
Simva/Ezet*	0.83	(0.72, 0.95)	0.89	(0.77, 1.03)	0.96	(0.83, 1.12)	1.00	(0.85, 1.17)
Prescriber								
GP Prescriber*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	1.09	(1.06, 1.13)	0.99	(0.96, 1.03)	0.91	(0.87, 0.95)	0.86	(0.82, 0.90)
Dose								
Low Dose*	1.00	(0.98, 1.02)	1.00	(0.98, 1.02)	1.00	(0.98, 1.03)	1.01	(0.98, 1.03)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	1.04	(0.97, 1.11)	1.01	(0.93, 1.09)	0.98	(0.91, 1.07)	0.93	(0.85, 1.01)
Dose Change								
No Dose Change*	Ref	-	Ref	-	Ref	-	Ref	-
Dose Decrease*	0.83	(0.77, 0.89)	0.92	(0.85, 0.99)	0.95	(0.88, 1.02)	0.90	(0.83, 0.98)
Dose Increase*	0.82	(0.77, 0.87)	0.87	(0.81, 0.92)	0.86	(0.81, 0.92)	0.84	(0.78, 0.91)
Co-morbidities								
IHD*	0.94	(0.91, 0.96)	0.92	(0.90, 0.95)	0.91	(0.88, 0.94)	0.88	(0.85, 0.91)
Diabetes*	0.93	(0.91, 0.96)	0.92	(0.90, 0.95)	0.92	(0.89, 0.95)	0.87	(0.84, 0.90)
Depression*	1.13	(1.10, 1.16)	1.14	(1.12, 1.17)	1.17	(1.14, 1.20)	1.18	(1.15, 1.22)
Depression(Recent)*	0.96	(0.92, 1.00)	0.97	(0.92, 1.01)	0.96	(0.92, 1.01)	0.94	(0.90, 0.99)
Parkinson's Disease*	1.08	(1.02, 1.14)	1.10	(1.03, 1.17)	1.11	(1.03, 1.18)	1.11	(1.03, 1.20)
Alzheimer's Disease*	1.06	(1.00, 1.12)	1.03	(0.97, 1.10)	1.02	(0.95, 1.10)	0.95	(0.87, 1.03)

Multivariate‡ Model Covariates	TNA-80/1		TNA80/90		TNA80/180		TNA80/360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Prescribing History								
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	1.03	(1.01, 1.06)	1.04	(1.01, 1.07)	1.04	(1.01, 1.08)	1.06	(1.02, 1.09)
6 - 11	1.04	(1.02, 1.07)	1.06	(1.03, 1.09)	1.08	(1.05, 1.11)	1.10	(1.06, 1.13)
≥ 11	1.02	(1.00, 1.05)	1.04	(1.01, 1.07)	1.06	(1.02, 1.09)	1.08	(1.04, 1.12)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.96	(0.94, 0.98)	0.97	(0.94, 1.00)	0.97	(0.95, 1.00)	0.97	(0.94, 1.00)
2	0.97	(0.95, 0.99)	0.99	(0.96, 1.02)	0.98	(0.95, 1.01)	0.96	(0.93, 0.99)
≥ 3	0.96	(0.94, 0.98)	0.97	(0.95, 1.00)	0.98	(0.95, 1.00)	0.96	(0.93, 0.99)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-	Ref	-
14-51	0.72	(0.70, 0.74)	0.73	(0.71, 0.75)	0.73	(0.70, 0.75)	0.76	(0.73, 0.78)
52-109	0.60	(0.58, 0.61)	0.57	(0.56, 0.59)	0.56	(0.55, 0.58)	0.58	(0.56, 0.60)
≥ 110	0.53	(0.52, 0.55)	0.49	(0.48, 0.51)	0.47	(0.45, 0.49)	0.47	(0.46, 0.49)

* Time-varying covariates, value taken from the day of each adherence calculation. † Time-varying covariates, number in 12 months prior to the day of each adherence calculation. ‡ Adjusted for all included covariates. ***TNA-80/1***, time to an adherence rate of less than 80% for at least 1 day. ***TNA-80/90***, time to an adherence rate of less than 80% for at least 90 consecutive days. ***TNA-80/180***, time to an adherence rate of less than 80% for at least 180 consecutive days. ***TNA-80/360***, time to an adherence rate of less than 80% for at least 360 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

FIGURE 6.5: WHISKER PLOT OF HAZARD RATIOS WITH 95% CI FROM THE MULTIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-ADHERENCE (PDC < 80%) FOR 1, 90, 180 & 360 DAYS (TNA-80/1 ■, TNA-80/90 ■, TNA-80/180 ■ & TNA-80/360 ■)

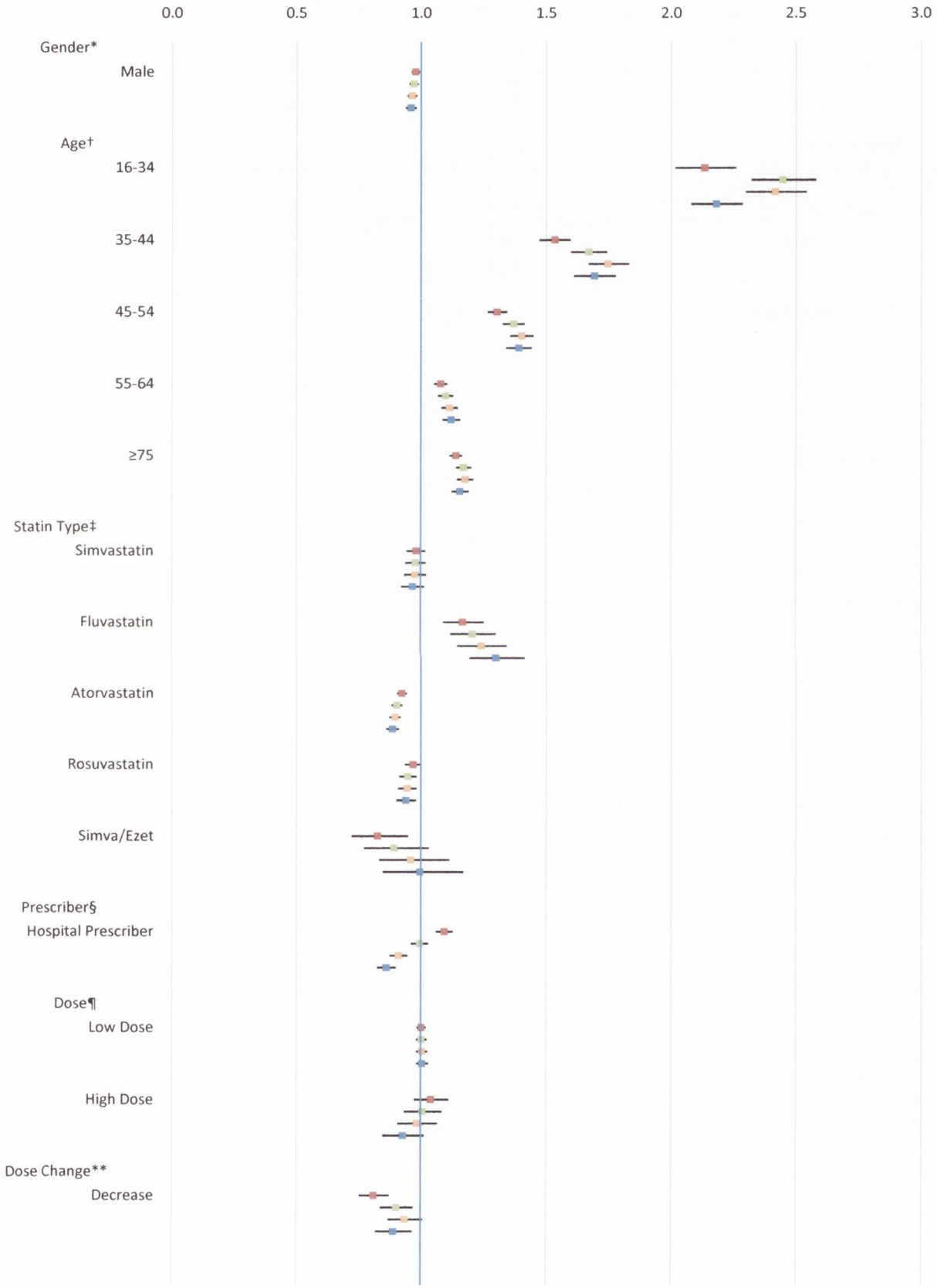
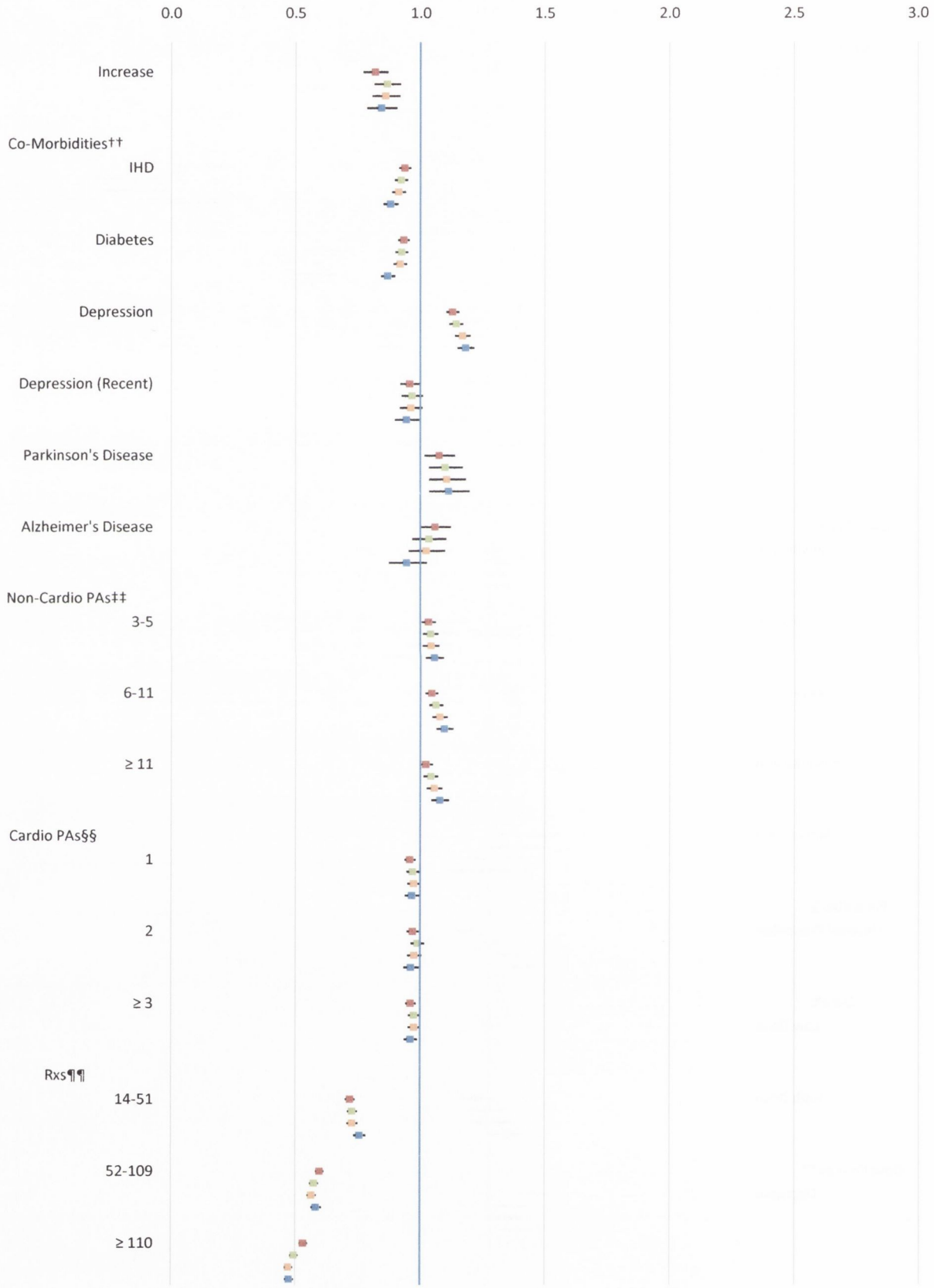


FIGURE 6.5 (CONTINUED): WHISKER PLOT OF HAZARD RATIOS WITH 95% CI FROM THE MULTIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-ADHERENCE FOR 1, 90, 180 & 360 DAYS (TNA-80/1 ■, TNA-80/90 ■, TNA-80/180 ■ & TNA-80/360 ■)



■ = TNA-80/1. ■ = TNA-80/90. ■ = TNA-80/180. ■ = TNA-80/360* Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. ***TNA-80/1***, time to an adherence rate of less than 80% for at least 1 day. ***TNA-80/90***, time to an adherence rate of less than 80% for at least 90 consecutive days. ***TNA-80/180***, time to an adherence rate of less than 80% for at least 180 consecutive days. ***TNA-80/360***, time to an adherence rate of less than 80% for at least 360 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio.

6.4 Discussion

6.4.1 Time to Non-Adherence Model Results – A Comparison of Episode Lengths

To illustrate the influence of the length of non-adherent episode on time to non-adherence results, four episode lengths were chosen for inclusion in this study (1, 90, 180 & 360 days). As can be seen from the Kaplan-Meier curves for each of these analyses (see Figure 6.1, Figure 6.2, Figure 6.3 & Figure 6.4 above) there is considerable variation in the probability of a patient experiencing a non-adherent event, with the probability decreasing as the length of the defined non-adherent episode was increased. At 720 days after treatment initiation the probability of a patient having a non-adherent episode of 1 day or longer was 70.4% (see Table 6.1 above). This probability decreased to 45.0% when the non-adherent episode length was increased to 360 days (see Table 6.4 above). Despite the considerable variation in the probability of a patient experiencing a non-adherent episode, the pattern of non-adherence risk identified in the Cox regression covariate analyses remained consistent across the four non-adherence definitions, although the magnitude of risk does vary for some covariates (see Table 6.6 & Figure 6.5 above). The effect of prescriber on non-adherence risk is the one exception to this; with patients prescribed a statin by a hospital prescriber having an increased risk of experiencing a short non-adherent event but a reduced risk of experiencing an extended non-adherent episode. This discrepancy may reflect the inability of HSE-PCRS prescription refill data to account for time spent as a hospital inpatient.

Although there is variation in the hazard ratio estimates and in the probability of having a non-adherent event across the four models this is as a result of quantifiable differences in the definition of a non-adherent event; not as is the case with repeated measure models due to arbitrary differences in the length of interval

selected for adherence rate calculations. The selection of a non-adherent episode length to use in time to non-adherence analyses should ideally be based upon objective evidence and a consideration of clinical relevance, i.e. what length of non-adherent episode will result in a clinically significant reduction in treatment efficacy? Unfortunately, for many treatments, there is little objective evidence to support this choice. The non-adherent episode length of 1 day used in the TNA-80/1 analysis provides a strict definition of statin non-adherence; it is, however, doubtful that an adherence rate of less than 80% for a single day would be of any clinical significance for statin therapy. In contrast, a statin adherence rate of less than 80% for 360 days or longer (TNA-80/360) could, most likely, be considered clinically significant. The appropriate choice of non-adherent episode length, for statin treatment, may therefore lie between the TNA-80/1 and TNA-80/360 adherence definitions.

It must, however, be remembered that adherence rates calculated from prescription refill data are only interpretable as upper limits of adherence and as such represent a hypothetical situation whereby a patient exhibits perfect adherence with the supply of treatment received (see Section 1.3.1.2 on page 33). It is unlikely that a patient will achieve this adherence rate and the concept of a single non-adherent episode of a defined length may not, therefore, be reflected in a patient's true adherence behaviour. Non-adherent events should instead be interpreted as a cumulative reflection of the adherence behaviour up to that point; with the length of non-adherent episode indicative of the intensity of non-adherent behaviour. The implications this has for the accuracy of temporal links between non-adherent events and covariate values are discussed in Section 6.4.3 (see below).

6.4.2 Advantages of Time to Non-Adherence Models

Time to non-adherence models offer a number of important advantages over conventional single measure models of adherence and repeated measure models. The first of these is the ability to define non-adherent events in two dimensions; the level of non-adherence and the length of the non-adherent episode. This is a considerably more precise method of defining non-adherence in comparison to definitions that utilize adherence level alone. In non-adherence definitions such as these, no distinction is made between patients that have been non-adherent for a single day or for a sustained period of time. There may therefore be considerable heterogeneity in the adherence behaviours of patients identified as non-adherent using the simple definition of an adherence rate < 80%. This simple non-adherence definition also allows the inappropriate classification of patients with very short non-adherent episodes, of little or no clinical

significance, as non-adherent. The addition of episode length to the definition of non-adherence reduces the variation in behaviours identified as non-adherent, allows the more appropriate classification of patients as non-adherent and may therefore increase the precision of any estimates from predictive models of adherence behaviour.

The timing of non-adherent events and temporal variations in non-adherence risk are the primary analytic focus of time to non-adherence models. The results from these models are amenable to survival analysis and therefore offer a number of analytic advantages. Time dependent covariates can be appropriately handled in the analyses of times to non-adherence, allowing a more accurate assignment of non-adherence risk to covariates that may change over the course of a patient's follow-up. However, as with repeated measure models of adherence (see Section 5.4.3.1 on page 107), this is dependent on what conclusions can and cannot be derived from time to non-adherence measures about the temporal relationship between prescription refills and a patient's true underlying medication-taking behaviour (see Section 6.4.3 below).

Variable follow-up times can also be accommodated in survival analyses of time to non-adherence results by varying the censoring definition. This is, however, subject to the limitation that censoring due to variable follow-up must be non-informative.[80] Non-informative censoring has been described as:

> *"Conditionally on the values of any explanatory variable, the prognosis for any individual who has survived to c_i should not be affected if the individual is censored at c_i. That is, an individual who is censored at c should be representative of all those subjects with the same covariate values who survive to c."*[81]

As with the repeated measure models of adherence (see section 5.4.2 on page 106) this is likely to be the case for patients with variable follow-up due to differences in the time of recruitment to the study cohort. Whether or not the requirement for censoring to be non-informative is satisfied in the case of patients with variable follow-up due to loss of eligibility for a prescription refill scheme or in the case of patients who have died is uncertain. The full implications of the requirement for censoring to be non-informative, in the context of variable follow-up times due to treatment discontinuation, are discussed below (see Section 6.4.3).

6.4.3 Limitations of Time to Non-Adherence Models

As discussed in Section 6.4.1 above, the lack of objective evidence to support the choice of an appropriate non-adherent episode length limits the interpretability of time to non-adherence results. Without evidence to support the choice of a non-adherent episode length it is difficult to accurately establish the clinical significance of the results from time to non-adherence models. This is, however, more a limitation of the imprecise way in which non-adherence has been defined in studies measuring the impact of non-adherence on treatment outcomes. The definitions of non-adherence used in these studies allow the inclusion of non-adherent episodes of any length when assessing the clinical significance of non-adherence. It can be argued that the ability to exclude very short non-adherent episodes from time to non-adherence event definitions will increase the specificity of the measure and may increase the likelihood that the non-adherence identified in these models will be of clinical significance.

The use of upper limits of adherence in time to non-adherence analyses raises concerns about the accuracy of temporal links between the true timing of a patient's non-adherence, the timing of non-adherent events identified using prescription refill data, and the subsequent assignment of non-adherence risk to a time varying covariate in predictive analyses. This is because non-adherence may occur at an earlier time than that identified in time to non-adherence models using upper limit of adherence measurements; non-adherence risk may therefore be assigned to covariate values that relate to a time after non-adherence has occurred. The limitations introduced by upper limits of adherence to covariate analyses are common to all prescription refill studies of medication-taking behaviour and are discussed in detail in Section 1.3.1.2 (see page 33).

Adherence in this time to non-adherence model is measured over the length of a patient's follow-up. As discussed in Section 4.4.3 (see page 75) this allows the inclusion of time after treatment discontinuation in adherence calculations. A considerable number of patients will therefore be incorrectly identified as non-adherent due to treatment discontinuation. It may appear possible to modify the censoring definition in time to non-adherence analyses to accommodate the assessment of a patient's adherence over the length of their treatment episode, by allowing patients' observations to be censored at the time of treatment discontinuation. However, as discussed in Section 6.4.2 (see above) the ability of survival analysis models to handle variable follow-up times is dependent on the assumption that censoring due to variable follow-up is non-informative. This is similar to the requirement for missing data to be missing completely at random in the

GEE analyses of repeated measure models of adherence (see Section 5.4.3.2 on page 113). In the case of censoring due to treatment discontinuation this would require that patients discontinuing treatment be no more or less likely to become non-adherent than those continuing treatment. It is, however, reasonable to suspect that non-adherence is positively correlated with non-persistence and patients who are likely to become non-persistent are also likely to become non-adherent.[23] The use of non-persistence as a censoring variable will therefore produce a downward bias in the estimated non-adherence probability, since individuals with better adherence are assumed to be representative of the population. Furthermore if a particular subgroup of patients is more likely to discontinue treatment, e.g. younger patients, this will lead to an artefactual tendency for younger patients to have a longer time to non-adherence, introducing bias to covariate estimates of non-adherence risk. In addition to the biases introduced by the informative censoring of patients discontinuing treatment, the use of censoring will not account for the fact that early treatment discontinuation, prevents the accurate calculation of a patient's adherence rate.

Lastly; while time to non-adherence analyses recognise the dynamic nature of medication-taking behaviour, they only identify the first non-adherent event experienced by a patient. Patients may return to adherent behaviour after this first event and go on to have subsequent non-adherent events. The return to adherent behaviour does not however contradict the fact that the criteria for a non-adherent event were originally met by a patient.

6.5 Summary

The length of time from statin initiation to the first non-adherent event was measured in a cohort of GMS patients using prescription refill data from the HSE-PCRS pharmacy claims database. Non-adherent events were defined in two dimensions; the level of non-adherence (PDC < 80%) and the length of non-adherent episode. Four non-adherent episode lengths were selected for use in the analysis (1 day, 90 days, 180 days & 360 days) to illustrate the effect of variations in the non-adherent event definition on times to non-adherence.

The results from these time to non-adherence analyses provide a detailed representation of non-adherent behaviours with the ability to estimate the probability of a broad range of non-adherent outcomes at any point in a patient's follow-up. 720 days after treatment initiation the probability of a patient having an

adherence rate of less than 80% for at least one day was 70.4% (see Table 6.1 above) and the probability of a patient having an adherence rate of less than 80% for a sustained period of 90, 180 or 360 consecutive days was 59.7%, 52.6% and 45.0% respectively (see Table 6.2, Table 6.3, & Table 6.4 above). The rationale for the selection of a non-adherent episode length to use in time to non-adherence analyses should ideally be based upon objective evidence and a consideration of clinical relevance. In the case of statin therapy, where objective evidence for the selection of a non-adherent episode length is lacking, it may be reasonable to suspect that an adherence rate of less than 80% for between 180 and 360 consecutive days would be clinically relevant. The Cox regression analyses of the four time to non-adherence models in this study produce patterns of non-adherence risk for covariates that are similar to those observed in single and repeated measure models of adherence (see Chapter 4 & Chapter 5 on pages 55 & 83). Shorter times to non-adherence are associated with the extremes of age. Longer times to non-adherence are associated with the use of certain statins (atorvastatin, rosuvastatin) and treatment for co-morbidities such as diabetes and ischaemic heart disease. There is minimal variation in the hazard rates for non-adherence across the four non-adherent event definitions.

The advantages of time to non-adherence models also include the increased precision provided by a two dimensional definition of non-adherence and the ability to account for the temporal variations in adherence behaviour, covariate values and their associated non-adherence risk. Time to non-adherence models are also suitable for the analysis of non-adherence in patients with variable follow-up times, although the appropriate analysis of time to non-adherence over the length of a patient's treatment episode is not possible with conventional survival analyses techniques as the censoring of patients' data due to treatment discontinuation cannot be considered non-informative.

6.6 Conclusion

As with repeated measure models, time to non-adherence models are capable of providing considerable analytical detail for the assessment of medication-taking behaviour. In contrast, however, the ability to more precisely define non-adherence and the use of upper limits of adherence allows a degree more certainty about the association between adherence rates calculated from prescription refill data and a patient's true adherence rate.

Time to non-adherence models are limited by the lack of objective evidence to validate the choice of non-adherent episode length and by the fact that their analysis using standard survival techniques does not allow for the censoring of patient data after treatment discontinuation; this precludes the assessment of time to non-adherence over the length of a patient's treatment episode. It may be feasible to overcome this limitation by treating non-persistence as a separate event rather than a censoring variable in time to non-adherence analyses. This possibility and methods for identifying non-persistence are explored further in Chapters 7 & 8 (see pages 139 & 163).

CHAPTER SEVEN

7 STATIN PERSISTENCE – PERMISSIBLE GAP MODEL

7.1 INTRODUCTION

A significant limitation of the three models of adherence presented in Chapters 4, 5, and 6 is their inability to appropriately incorporate treatment discontinuation or non-persistence into adherence calculations and analyses. This results in the misclassification of adherent patients as non-adherent and the incorrect assignment of non-adherence risk to covariates that are associated with an increased risk of non-persistence (see Section 4.4.3 on page 75). In models of medication-taking behaviour, adherence rates should preferably be calculated over the time that a patient can reasonably be expected to be taking treatment, i.e. from initiation to discontinuation of treatment. The incorporation of non-persistence into adherence analyses requires the identification of methodology that allows the consistent identification of treatment discontinuation from prescription refill data. A number of models have been proposed for this purpose, these include the anniversary model, the minimum refills model, the adherence model, the hybrid model and the permissible gap model. Comprehensive descriptions and evaluations of these models can be found in the reviews by Johnson,[82] Sikka,[21] Andrade,[17] Caetano,[20] Halpern,[35] Cramer[41] and Hudson.[60] The permissible gap model is the most widely recommended[21, 35, 41, 82] and commonly used[17] of these methods and its application to statin persistence in the GMS population is described here. The advantages and disadvantages of this model are discussed.

7.2 METHODS

Medication persistence is defined as: the duration of time from initiation to discontinuation of therapy [41] (see Section 1.1 on page 29), where treatment discontinuation generally refers to patients stopping medication use with no intention of restarting treatment.[35] Translating this definition of non-persistence into an operational definition for use with prescription refill data is limited by the difficulty determining a patient's *"intentions"* regarding treatment discontinuation from prescription refill databases. Whether a patient intends to restart treatment must therefore be inferred from prescription refill patterns.

In permissible gap models of persistence this is achieved by defining treatment discontinuation in terms of the maximum allowable time between the expected end of a patient's current medication supply and the subsequent refilling of a prescription, if any. Permissible gap models have been generally accepted as the most appropriate method for the assessment of treatment persistence using prescription refill data. There is, however little consensus on what permissible gap length to use in analyses, or on what criteria to use in the selection of a permissible gap length. In the fourteen permissible gap statin persistence studies identified from the literature[42, 50, 53, 56, 58, 63, 75, 83-89] (see Table 7.7 below) the length of permissible gap used ranged from 7 days to 180 days with a modal length of 180 days. Permissible gaps based on the number of days' supply in a preceding prescription or the length of a patient's follow-up, were also used in some analyses.[53, 56, 84]

The suggested criteria for the selection of a permissible gap include a consideration of the pharmacological properties of the drug and the clinical relevance of the missed doses: such that the permissible gap length reflects the maximum allowable time that a patient could go without medication and not anticipate reduced or suboptimal outcomes.[41] In most situations, however, there may be little or no objective evidence to support this selection and where short gaps in medication-taking are considered of clinical significance these gaps may not necessarily be interpretable as intentional treatment discontinuation. Alternatively, it has been proposed that as the identification of treatment discontinuation using permissible gap methodology does not preclude a patient from restarting treatment, the permissible gap length should reflect the minimum period of medication disuse that distinguishes non-persistent behaviour from non-adherence.[35]

In the selection of a permissible gap length, consideration must also be given to the likelihood that a gap in prescription refills does not automatically imply a gap of the same duration (or any gap at all) in medication-taking by a patient. This is because patients may cover a prescription refill gap with untaken medication from previously filled prescriptions. This possibility is more likely with shorter permissible gaps, for example there is no guarantee that a gap in prescription refills of 7 days or even 30 days, as used in a number of the identified statin persistence studies, represents an actual gap in patients' medication-taking. It is however unlikely that a patient will have retained enough medication from previous prescriptions to cover a lengthy prescription refill gap, of for example 180 days. Therefore, in the selection of a suitable permissible gap for persistence analyses, consideration should be given firstly to the length of gap in a patient's actual medication taking that signifies

treatment discontinuation and secondly to the length of gap in prescription refills that may correspond to this underlying gap in medication taking. There is little empirical evidence available to support either of these considerations.

7.2.1 Identification of Non-Persistence

Four permissible gap lengths were chosen to illustrate the influence of gap length on time to non-persistence results. These were 90 days, 180 days, 270 days and 360 days. Using these permissible gap lengths, non-persistence was identified as the first time in a patient's history of medication supply (see Section 3.3 on page 46) that the number of consecutive days without an assigned dose exceeded the permissible gap length. In other words; a patient was identified as non-persistent if the length of time between the end of their current available medication supply (assuming perfect adherence with the medication received) and a future prescription refill (if any) exceeded the permissible gap length. The time to non-persistence was taken as the length of time from treatment initiation to the last assigned day of treatment prior to the defined permissible gap of 90 days (PER-G90[i]), 180 days (PER-G180[ii]), 270 days (PER-G270[iii]) or 360 days (PER-G360[iv]). Patients who became lost to follow-up (see Section 3.5.1 on page 49) within the permissible gap were not identified as non-persistent.

7.2.2 Statistical Analysis

The SAS® PROC LIFETEST procedure was used to construct Kaplan-Meier plots from which the cumulative rates of non-persistence for the PER-G90, PER-G180, PER-G270 and PER-G360 models were estimated. Univariate and multivariate Cox regression models with time varying covariates were constructed for each of the time to non-persistence analyses using the SAS® PROC PHREG procedure. Censoring in this study was random[v] with observations censored at the time of loss to follow-up or end of follow-up, whichever occurred first. Tied events in the Cox regression model were handled using the method proposed by Efron.[79, 80] Crude and adjusted hazard ratios and 95% confidence intervals are presented for independent covariates.

---

[i] Non-persistence defined by a permissible gap in treatment of 90 days or greater.
[ii] Non-persistence defined by a permissible gap in treatment of 180 days or greater.
[iii] Non-persistence defined by a permissible gap in treatment of 270 days or greater.
[iv] Non-persistence defined by a permissible gap in treatment of 360 days or greater.
[v] Censoring is considered random when observations are terminated for reasons that are not under the control of the investigator.

Multivariate analyses were adjusted for all included covariates. Significance at $p < 0.05$ was assumed. SAS® version 9.1[i] was used for all analyses.

7.2.3 Covariates Included in the Permissible Gap Models

Patient gender and the following time-varying covariates were included in the time to non-persistence model; age, current statin type, current statin dose, current statin prescriber, statin dose change, all co-morbidities and the number of non-cardiovascular pharmacological agents, cardiovascular pharmacological agents and prescription items received by a patient in the prior 365 days. Values for the time-varying covariates were taken on the day of persistence evaluation. A full description of these covariates can be found in Section 3.6 (see page 49).

7.3 Results

7.3.1 Permissible Gap Model – Study Cohort

The permissible gap methodology for persistence measurement did not require the exclusion of any patients from the source study cohort (see Chapter 3 on page 43). The characteristics of the patients included in the time to non-persistence analyses can be found in Table 3.2 (see page 53) and are described in Section 3.7.2 (see page 52).

7.3.2 Permissible Gap Model – Time to Non-Persistence Results

The Kaplan Meier curves for each of the four non-persistent event definitions are shown in Figure 7.1 (PER-G90) Figure 7.2 (PER-G180), Figure 7.3 (PER-G270) and Figure 7.4 (PER-G360) below. A selection of results from these Kaplan-Meier curves is presented in Table 7.1, Table 7.2, Table 7.3 and Table 7.4 also below. These results indicate that, a considerable number of patients fill only a single prescription prior to becoming non-persistent and for the majority of non-persistent patients, non-persistence occurs in the first 180 days after treatment initiation. The cumulative probability of non-persistence 30 days after treatment initiation (i.e. after approximately one prescription refill) was 16.6%, 13.2%, 11.6% and 10.2% respectively for the PER-G90, PER-G180, PER-G270 and PER-G360 non-persistence definitions. By day 180 the cumulative probability of having a non-persistent event increased to 28.3%, 21.8%, 18.6% and 16.1% respectively.

[i] SAS Institute, Cary, NC, USA.

There is considerable variation in the estimated cumulative probabilities of non-persistence across the four non-persistence definitions, with the probability of a patient experiencing a non-persistent event decreasing as the length of the permissible gap used to define non-persistence is increased. For example, 720 days after treatment initiation the cumulative probability of non-persistence decreases from 41.4% to 24.5% as the length of the permissible gap is increased from 90 days to 360 days. The difference in estimated cumulative probabilities between successively longer permissible gaps does however decrease from 8.8% to 4.5% to 3.6% as the length of the permissible gap is increased from 90 to 180 days, from 180 to 270 days and from 270 to 360 days.

FIGURE 7.1: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-PERSISTENCE WITH A PERMISSIBLE GAP OF 90 DAYS (PER-G90)

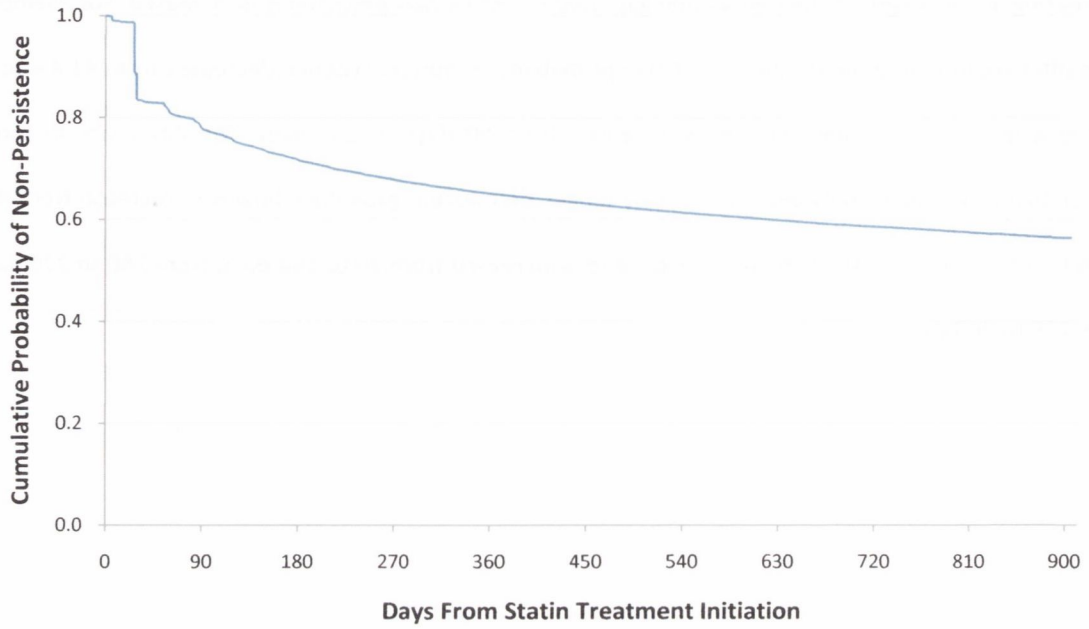


TABLE 7.1: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-PERSISTENCE (PER-G90)

Day	Cumulative Probability of Non-Persistence (%)	95% CI (%)	Persistent (N)	Non-Persistent (N)	Censored (N)
30	16.6	(16.3, 16.8)	64,558	12,817	1,989
60	19.1	(18.9, 19.4)	61,914	14,800	2,650
90	22.2	(21.9, 22.4)	59,041	17,092	3,231
180	28.3	(28.0, 28.6)	53,134	21,720	4,510
270	32.2	(31.8, 32.5)	43,292	24,385	11,687
360	34.8	(34.5, 35.2)	35,498	25,972	17,894
450	36.9	(36.5, 37.2)	28,226	26,973	24,165
540	38.7	(38.3, 39.0)	21,815	27,693	29,856
630	40.1	(39.7, 40.5)	17,405	28,161	33,798
720	41.4	(41.0, 41.8)	11,761	28,474	39,129
810	42.5	(42.1, 42.9)	5,849	28,651	44,864
900	43.6	(43.1, 44.1)	1,007	28,725	49,632

PER-G90, time to a gap in prescription refills of at least 90 consecutive days. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

FIGURE 7.2: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-PERSISTENCE WITH A PERMISSIBLE GAP OF 180 DAYS (PER-G180)

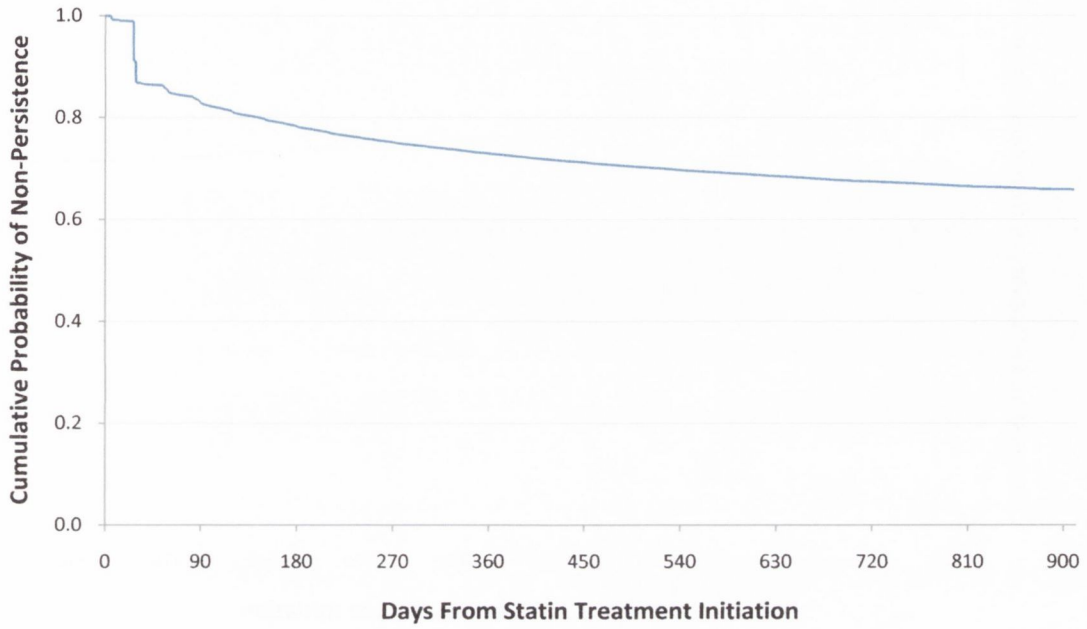


TABLE 7.2: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-PERSISTENCE (PER-G180)

Day	Cumulative Probability of Non-Persistence (%)	95% CI (%)	Persistent (N)	Non-Persistent (N)	Censored (N)
30	13.2	(13.0, 13.4)	67,155	10,220	1,989
60	15.1	(14.9, 15.4)	65,027	11,687	2,650
90	17.3	(17.0, 17.5)	62,811	13,322	3,231
180	21.8	(21.5, 22.1)	57,814	16,734	4,816
270	24.9	(24.6, 25.2)	47,680	18,856	12,828
360	27.1	(26.7, 27.4)	39,472	20,136	19,756
450	28.8	(28.5, 29.1)	31,603	21,003	26,758
540	30.3	(30.0, 30.6)	24,707	21,597	33,060
630	31.5	(31.1, 31.9)	19,867	21,981	37,516
720	32.6	(32.2, 32.9)	13,553	22,244	43,567
810	33.5	(33.1, 33.9)	6,615	22,390	50,359
900	34.1	(33.6, 34.6)	1,146	22,430	55,788

PER-G180, time to a gap in prescription refills of at least 180 consecutive days. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

FIGURE 7.3: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-PERSISTENCE WITH A PERMISSIBLE GAP OF 270 DAYS (PER-G270)

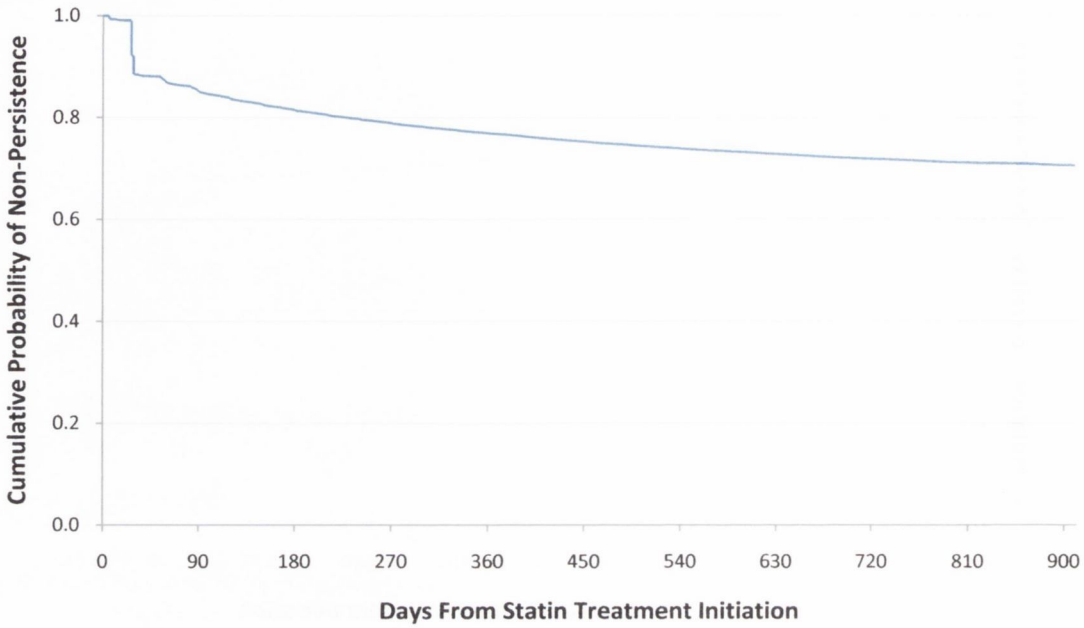


TABLE 7.3: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-PERSISTENCE (PER-G270)

Day	Cumulative Probability of Non-Persistence (%)	95% CI (%)	Persistent (N)	Non-Persistent (N)	Censored (N)
30	11.6	(11.3, 11.8)	68,430	8,945	1,989
60	13.2	(12.9, 13.4)	66,520	10,194	2,650
90	14.9	(14.7, 15.2)	64,594	11,539	3,231
180	18.6	(18.3, 18.9)	60,281	14,267	4,816
270	21.1	(20.8, 21.4)	49,976	16,015	13,373
360	23.1	(22.8, 23.4)	41,363	17,158	20,843
450	24.7	(24.4, 25.0)	33,152	17,953	28,259
540	26.1	(25.7, 26.4)	25,979	18,492	34,893
630	27.1	(26.8, 27.4)	20,912	18,827	39,625
720	28.1	(27.7, 28.4)	14,263	19,060	46,041
810	28.8	(28.4, 29.2)	6,980	19,180	53,204
900	29.4	(28.9, 29.8)	1,208	19,213	58,943

PER-G270, time to a gap in prescription refills of at least 270 consecutive days. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

FIGURE 7.4: KAPLAN-MEIER PLOT OF THE CUMULATIVE PROBABILITY OF STATIN NON-PERSISTENCE WITH A PERMISSIBLE GAP OF 360 DAYS (PER-G360)

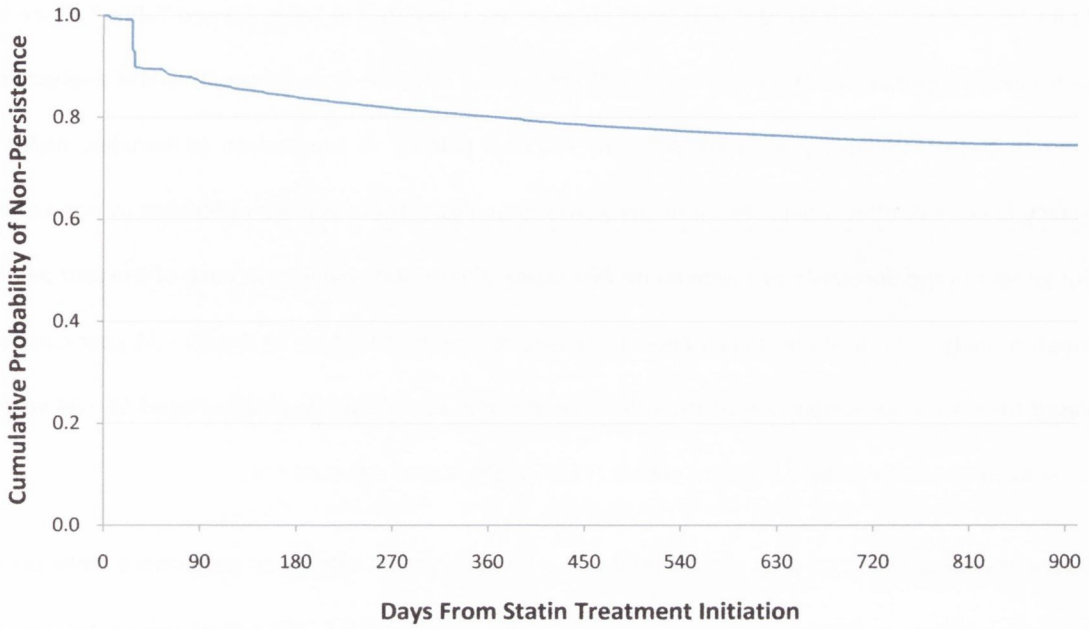


TABLE 7.4: SELECTED CUMULATIVE PROBABILITIES OF STATIN NON-PERSISTENCE (PER-G360)

Day	Cumulative Probability of Non-Persistence (%)	95% CI (%)	Persistent (N)	Non-Persistent (N)	Censored (N)
30	10.2	(10.0, 10.4)	69,465	7,910	1,989
60	11.6	(11.3, 11.8)	67,764	8,950	2,650
90	13.1	(12.8, 13.3)	66,036	10,097	3,231
180	16.1	(15.8, 16.3)	62,198	12,350	4,816
270	18.2	(17.9, 18.4)	51,917	13,797	13,650
360	19.8	(19.5, 20.1)	43,016	14,761	21,587
450	21.5	(21.1, 21.8)	34,367	15,566	29,431
540	22.7	(22.3, 23.0)	26,987	16,039	36,338
630	23.6	(23.2, 23.9)	21,740	16,325	41,299
720	24.5	(24.2, 24.8)	14,818	16,549	47,997
810	25.1	(24.8, 25.5)	7,266	16,649	55,449
900	25.5	(25.1, 25.9)	1,259	16,670	61,435

PER-G360, time to a gap in prescription refills of at least 360 consecutive days. ***Day***, number of days from statin initiation. ***CI***, confidence interval. ***N***, number of patients.

7.3.3 Cox Regression Analyses – Univariate & Multivariate Models

The results of from the univariate and multivariate Cox regression models of time to non-persistence for the PER-G90, PER-G180, PER-G270 & PER-G360 analyses are presented in Table 7.5 and Table 7.6 (see below). Whisker plots of the hazard ratio results and 95% confidence intervals from the multivariate analyses of time to non-persistence are also presented in Figure 7.5 (see below). In comparison to females, males had a marginally lower risk of non-persistence in the PER-G90 analysis. There was no difference in non-persistence risk for gender in the univariate or multivariate PER-G180, 270 or 360 analyses. In each of the four persistence definition models the risk of non-persistence decreased as age increased up to the 65 - 74 year category and increased thereafter. In comparison to the reference group of 65 - 74 years, patients aged 16 - 34 years were the most likely to become non-persistent with a 271% - 289% higher adjusted risk.

Patients had a 10% (PER-G90) to 14% (PER-G360) lower adjusted risk of non-persistence while prescribed atorvastatin (reference; pravastatin) and a 32% (PER-G90) to 41% (PER-G360) higher risk of non-persistence while prescribed fluvastatin (reference; pravastatin). Patients prescribed rosuvastatin had a slightly reduced risk of non-persistence and there was no difference in persistence risk for patients prescribed simvastatin or simvastatin/ezetimibe combinations (Inegy®, reference; pravastatin). Patients receiving a low dose of statin had a reduced adjusted risk of non-persistence across all four models (reference; intermediate dose). There was no difference in non-persistence risk for patients receiving higher doses. Dose increases had no effect on non-persistence risk but a dose decrease increased the adjusted risk of non-persistence by up to 30% (reference, no dose change)

In the adjusted models of non-persistence, patients receiving treatments for ischaemic heart disease had up to a 13% (PER-G360) reduced risk of experiencing a non-persistent event and patients receiving treatments for diabetes had up to a 23% (PER-G360) reduced risk of experiencing a non-persistent event. The adjusted risk of non-persistence was higher for patients receiving treatment for Parkinson's disease and depression. There was no difference non-persistence risk for patients receiving treatment for Alzheimer's disease and in the adjusted models a recent diagnosis of depression was only associated with non-persistence in the PER-G270 analysis. The adjusted risk of non-persistence was higher for patients receiving any more than two different non-cardiovascular pharmacological agents in the previous twelve months (reference; 0-2 non-cardiovascular pharmacological agents). There was no difference in adjusted non-persistence risk for patients receiving any

number of cardiovascular pharmacological agents in the prior twelve months. The largest reductions in non-persistence risk were associated with increasing numbers of prescription items received by a patient, although this association did appear to decrease as the length of permissible gap was increased. The reduction in the adjusted risk of non-adherence for patients receiving 14-51 and ≥ 110 prescription items in the prior twelve months was 22%-10% and 46%-31% respectively (reference ≤ 13 prescription items).

TABLE 7.5: RESULTS FROM THE UNIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-PERSISTENCE (PER-G90, PER-G180, PER-G270 & PER-G360)

Model Covariates	PER-G90		PER-G180		PER-G270		PER-G360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Gender								
Male	0.97	(0.95, 0.99)	0.98	(0.95, 1.00)	0.97	(0.95, 1.00)	0.97	(0.94, 1.00)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	4.26	(4.04, 4.50)	4.46	(4.20, 4.73)	4.39	(4.13, 4.68)	4.22	(3.95, 4.51)
35-44*	2.22	(2.11, 2.34)	2.34	(2.21, 2.48)	2.36	(2.23, 2.51)	2.32	(2.18, 2.48)
45-54*	1.56	(1.50, 1.63)	1.53	(1.46, 1.60)	1.50	(1.43, 1.58)	1.47	(1.40, 1.55)
55-64*	1.16	(1.12, 1.20)	1.16	(1.11, 1.21)	1.15	(1.10, 1.20)	1.12	(1.07, 1.17)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.15	(1.12, 1.19)	1.19	(1.15, 1.23)	1.21	(1.16, 1.25)	1.22	(1.18, 1.27)
Statin Type								
Simvastatin*	1.00	(0.95, 1.05)	0.97	(0.92, 1.03)	0.95	(0.89, 1.02)	0.94	(0.87, 1.00)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.34	(1.23, 1.45)	1.37	(1.26, 1.50)	1.42	(1.29, 1.56)	1.47	(1.33, 1.62)
Atorvastatin*	0.86	(0.83, 0.88)	0.85	(0.82, 0.87)	0.83	(0.80, 0.86)	0.83	(0.80, 0.86)
Rosuvastatin*	0.93	(0.89, 0.97)	0.92	(0.88, 0.97)	0.91	(0.87, 0.96)	0.91	(0.86, 0.96)
Simva/Ezet*	1.00	(0.85, 1.19)	0.98	(0.81, 1.19)	1.09	(0.89, 1.32)	1.04	(0.84, 1.29)
Prescriber								
GP Prescriber*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.78	(0.74, 0.81)	0.79	(0.75, 0.83)	0.78	(0.74, 0.83)	0.76	(0.72, 0.81)
Dose								
Low Dose*	0.93	(0.91, 0.95)	0.91	(0.89, 0.94)	0.91	(0.88, 0.94)	0.91	(0.89, 0.94)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	0.98	(0.90, 1.07)	1.06	(0.97, 1.17)	1.09	(0.98, 1.20)	1.09	(0.98, 1.22)
Dose Change								
No Dose Change*	Ref	-	Ref	-	Ref	-	Ref	-
Dose Decrease*	1.23	(1.15, 1.32)	1.25	(1.16, 1.35)	1.24	(1.14, 1.35)	1.25	(1.15, 1.37)
Dose Increase*	1.02	(0.95, 1.08)	1.05	(0.98, 1.13)	1.09	(1.01, 1.17)	1.06	(0.98, 1.16)
Co-morbidities								
IHD*	0.79	(0.76, 0.81)	0.79	(0.76, 0.82)	0.78	(0.75, 0.81)	0.78	(0.74, 0.81)
Diabetes*	0.81	(0.78, 0.84)	0.78	(0.75, 0.81)	0.76	(0.73, 0.79)	0.73	(0.70, 0.77)
Depression*	1.16	(1.13, 1.19)	1.18	(1.15, 1.22)	1.20	(1.16, 1.24)	1.21	(1.17, 1.25)
Depression(Recent)*	1.34	(1.27, 1.40)	1.37	(1.30, 1.44)	1.40	(1.32, 1.48)	1.35	(1.27, 1.44)
Parkinson's Disease*	1.14	(1.06, 1.22)	1.20	(1.11, 1.30)	1.21	(1.11, 1.32)	1.24	(1.13, 1.36)
Alzheimer's Disease*	1.01	(0.93, 1.09)	1.01	(0.92, 1.10)	1.06	(0.96, 1.16)	1.02	(0.92, 1.13)

Model Covariates	PER-G90		PER-G180		PER-G270		PER-G360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Prescribing History								
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	0.92	(0.88, 0.96)	0.94	(0.89, 0.99)	0.96	(0.91, 1.02)	0.98	(0.92, 1.04)
6 - 11	0.94	(0.90, 0.98)	0.97	(0.93, 1.02)	1.02	(0.97, 1.07)	1.04	(0.99, 1.10)
≥ 11	1.10	(1.06, 1.15)	1.16	(1.11, 1.22)	1.22	(1.16, 1.28)	1.26	(1.19, 1.33)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.76	(0.73, 0.78)	0.76	(0.73, 0.79)	0.77	(0.74, 0.80)	0.79	(0.75, 0.82)
2	0.66	(0.64, 0.69)	0.69	(0.67, 0.72)	0.71	(0.68, 0.74)	0.73	(0.70, 0.76)
≥ 3	0.61	(0.59, 0.63)	0.63	(0.61, 0.65)	0.64	(0.62, 0.67)	0.66	(0.64, 0.69)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-	Ref	-
14-51	0.77	(0.75, 0.80)	0.79	(0.76, 0.83)	0.83	(0.80, 0.87)	0.88	(0.84, 0.92)
52-109	0.56	(0.54, 0.58)	0.58	(0.55, 0.60)	0.61	(0.59, 0.64)	0.67	(0.64, 0.70)
≥ 110	0.51	(0.49, 0.53)	0.54	(0.52, 0.57)	0.58	(0.55, 0.61)	0.63	(0.60, 0.67)

* Time-varying covariates, value taken from the day of each adherence calculation. † Time-varying covariates, number in 12 months prior to the day of each adherence calculation. ***PER-G90***, Non-persistence defined by a permissible gap in treatment of 90 days or greater. ***PER-G180***, Non-persistence defined by a permissible gap in treatment of 180 days or greater. ***PER-G270***, Non-persistence defined by a permissible gap in treatment of 270 days or greater. ***PER-G360***, Non-persistence defined by a permissible gap in treatment of 360 days or greater. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

TABLE 7.6: RESULTS FROM THE MULTIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-PERSISTENCE (PER-G90, PER-G180, PER-G270 & PER-G360)

Multivariate‡ Model Covariates	PER-G90		PER-G180		PER-G270		PER-G360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Gender								
Male	0.97	(0.95, 0.99)	0.98	(0.95, 1.01)	0.98	(0.95, 1.01)	0.98	(0.95, 1.01)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	3.71	(3.52, 3.92)	3.89	(3.66, 4.13)	3.86	(3.62, 4.11)	3.75	(3.50, 4.01)
35-44*	2.03	(1.93, 2.14)	2.14	(2.00, 2.27)	2.18	(2.05, 2.31)	2.16	(2.02, 2.30)
45-54*	1.46	(1.40, 1.52)	1.42	(1.36, 1.49)	1.40	(1.34, 1.48)	1.38	(1.31, 1.46)
55-64*	1.12	(1.09, 1.16)	1.12	(1.08, 1.17)	1.11	(1.06, 1.16)	1.08	(1.03, 1.14)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.27	(1.23, 1.31)	1.29	(1.25, 1.34)	1.30	(1.25, 1.35)	1.31	(1.25, 1.36)
Statin Type								
Simvastatin*	0.99	(0.94, 1.05)	0.97	(0.91, 1.03)	0.95	(0.89, 1.01)	0.93	(0.87, 1.00)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.32	(1.21, 1.44)	1.32	(1.20, 1.45)	1.37	(1.23, 1.51)	1.41	(1.27, 1.57)
Atorvastatin*	0.90	(0.87, 0.92)	0.89	(0.86, 0.92)	0.87	(0.84, 0.90)	0.86	(0.83, 0.90)
Rosuvastatin*	0.94	(0.90, 0.98)	0.94	(0.90, 0.99)	0.94	(0.89, 0.99)	0.93	(0.88, 0.99)
Simva/Ezet*	0.95	(0.80, 1.12)	0.92	(0.76, 1.11)	1.02	(0.84, 1.24)	0.98	(0.79, 1.21)
Prescriber								
GP Prescriber*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.88	(0.84, 0.92)	0.88	(0.84, 0.93)	0.87	(0.83, 0.92)	0.84	(0.79, 0.89)
Dose								
Low Dose*	0.95	(0.93, 0.98)	0.94	(0.91, 0.96)	0.94	(0.91, 0.97)	0.94	(0.91, 0.97)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	0.91	(0.83, 1.00)	0.99	(0.89, 1.09)	0.99	(0.88, 1.10)	0.97	(0.87, 1.10)
Dose Change								
No Dose Change*	Ref	-	Ref	-	Ref	-	Ref	-
Dose Decrease*	1.27	(1.18, 1.36)	1.30	(1.20, 1.40)	1.28	(1.18, 1.40)	1.30	(1.19, 1.42)
Dose Increase*	0.99	(0.92, 1.05)	1.01	(0.94, 1.08)	1.05	(0.97, 1.13)	1.03	(0.95, 1.12)
Co-morbidities								
IHD*	0.91	(0.88, 0.95)	0.90	(0.86, 0.93)	0.88	(0.84, 0.92)	0.87	(0.83, 0.91)
Diabetes*	0.87	(0.84, 0.90)	0.82	(0.79, 0.86)	0.79	(0.76, 0.83)	0.76	(0.73, 0.80)
Depression*	1.20	(1.17, 1.24)	1.21	(1.17, 1.25)	1.20	(1.16, 1.25)	1.20	(1.16, 1.25)
Depression(Recent)*	1.03	(0.98, 1.09)	1.06	(1.00, 1.12)	1.09	(1.02, 1.16)	1.06	(0.98, 1.13)
Parkinson's Disease*	1.21	(1.12, 1.30)	1.25	(1.16, 1.36)	1.25	(1.14, 1.36)	1.26	(1.15, 1.38)
Alzheimer's Disease*	1.04	(0.96, 1.13)	1.03	(0.94, 1.13)	1.07	(0.97, 1.17)	1.01	(0.91, 1.12)

Multivariate‡ Model Covariates	PER-G90		PER-G180		PER-G270		PER-G360	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Prescribing History								
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	1.08	(1.04, 1.12)	1.11	(1.06, 1.16)	1.11	(1.06, 1.16)	1.10	(1.05, 1.16)
6 - 11	1.11	(1.08, 1.15)	1.15	(1.11, 1.20)	1.14	(1.10, 1.19)	1.14	(1.09, 1.19)
≥ 11	1.07	(1.04, 1.11)	1.10	(1.05, 1.14)	1.10	(1.06, 1.15)	1.10	(1.05, 1.16)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.99	(0.95, 1.02)	1.00	(0.96, 1.04)	1.00	(0.96, 1.04)	1.00	(0.96, 1.04)
2	0.97	(0.94, 1.00)	0.97	(0.94, 1.01)	0.96	(0.92, 1.00)	0.96	(0.91, 1.00)
≥ 3	0.98	(0.95, 1.01)	0.99	(0.95, 1.02)	0.98	(0.95, 1.02)	0.99	(0.96, 1.03)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-	Ref	-
14-51	0.78	(0.75, 0.81)	0.81	(0.77, 0.84)	0.85	(0.81, 0.89)	0.90	(0.86, 0.95)
52-109	0.58	(0.56, 0.60)	0.61	(0.58, 0.64)	0.66	(0.63, 0.69)	0.72	(0.69, 0.76)
≥ 110	0.54	(0.51, 0.56)	0.58	(0.55, 0.60)	0.63	(0.60, 0.66)	0.69	(0.66, 0.73)

***** Time-varying covariates, value taken from the day of each adherence calculation. **†** Time-varying covariates, number in 12 months prior to the day of each adherence calculation. **‡** Adjusted for all included covariates. ***PER-G90***, Non-persistence defined by a permissible gap in treatment of 90 days or greater. ***PER-G180***, Non-persistence defined by a permissible gap in treatment of 180 days or greater. ***PER-G270***, Non-persistence defined by a permissible gap in treatment of 270 days or greater. ***PER-G360***, Non-persistence defined by a permissible gap in treatment of 360 days or greater. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

FIGURE 7.5: WHISKER PLOT OF HAZARD RATIOS WITH 95% CI FROM THE MULTIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-PERSISTENCE (PER-G90 ■, PER-G180 ■, PER-G270 ■ & PER-G360 ■)

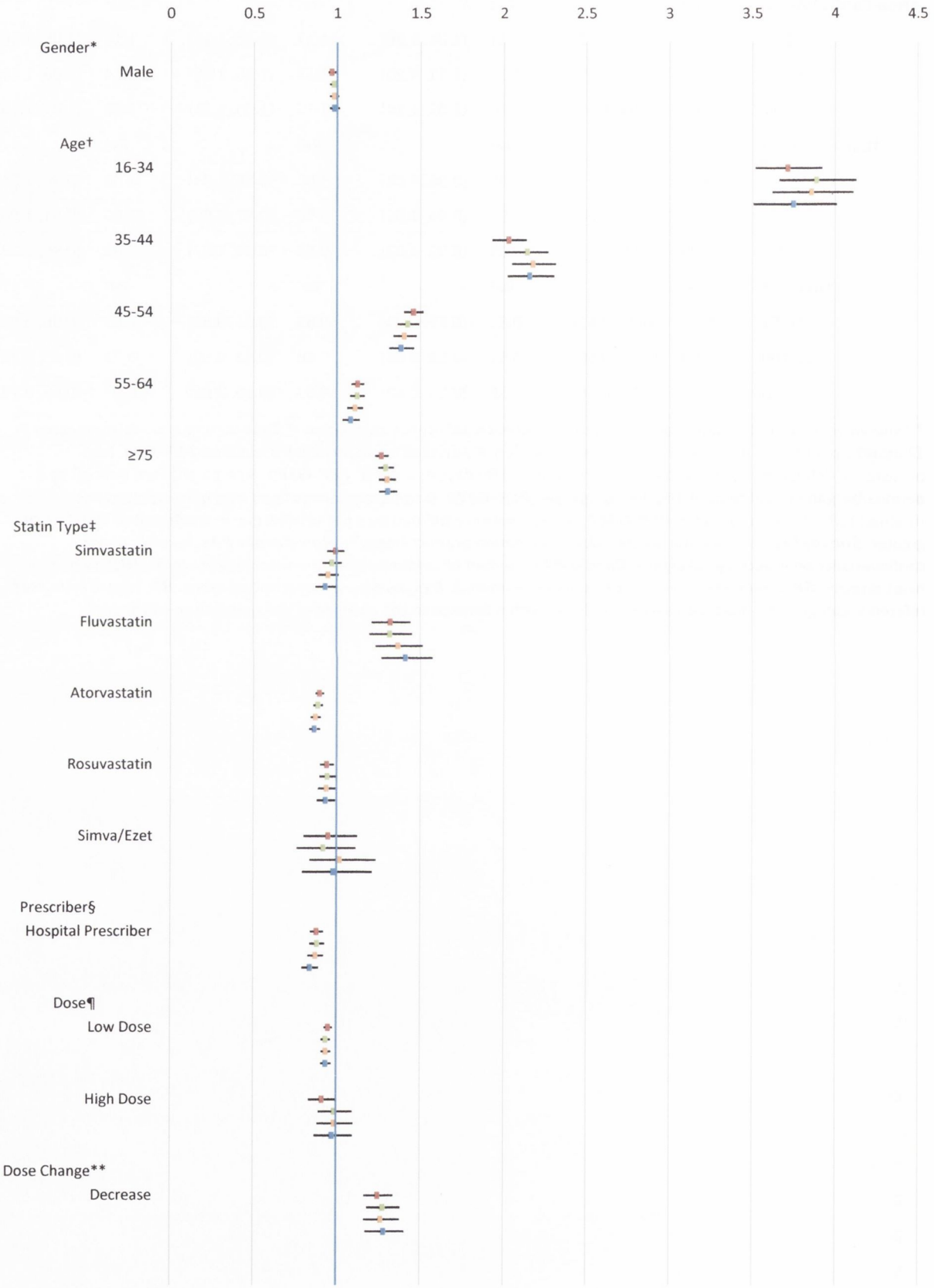
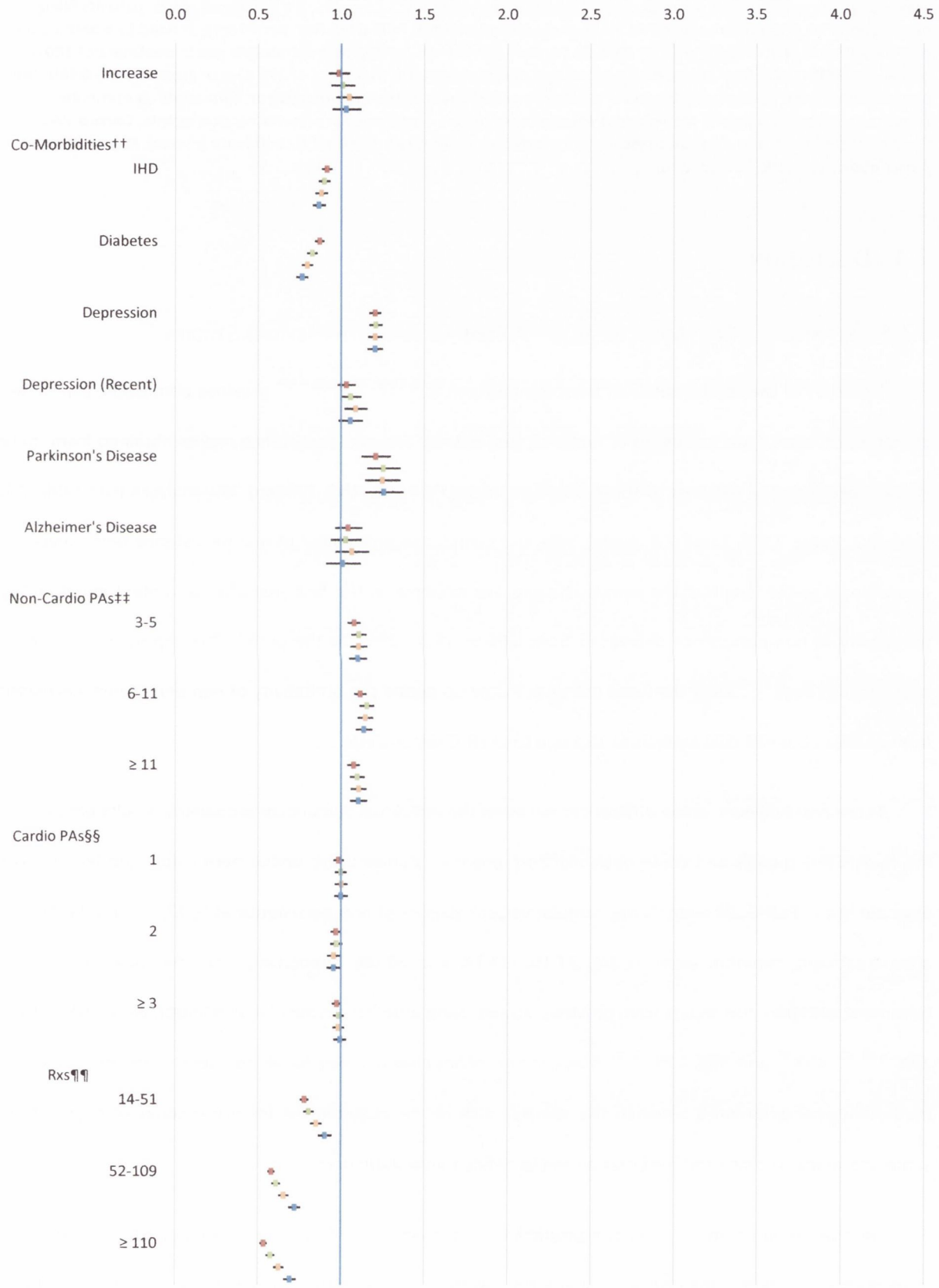


FIGURE 7.5 (CONTINUED): WHISKER PLOT OF HAZARD RATIOS WITH 95% CI FROM THE MULTIVARIATE COX REGRESSION ANALYSIS OF TIME TO STATIN NON-PERSISTENCE (PER-G90 ■, PER-G180 ■, PER-G270 ■ & PER-G360 ■)



■ = PER-G90. ■ = PER-G180. ■ = PER-G270. ■ = PER-G360. * Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. ***PER-G90***, Non-persistence defined by a permissible gap in treatment of 90 days or greater. ***PER-G180***, Non-persistence defined by a permissible gap in treatment of 180 days or greater. ***PER-G270***, Non-persistence defined by a permissible gap in treatment of 270 days or greater. ***PER-G360***, Non-persistence defined by a permissible gap in treatment of 360 days or greater. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio.

7.4 Discussion

7.4.1 Permissible Gap Model Results – A Comparison with Previous Studies

Synopses of the results obtained from the fourteen[42, 50, 53, 56, 58, 63, 75, 83-89] previous permissible gap studies of statin persistence are presented in Table 7.7 (see below). The non-persistence results obtained from these studies follow similar patterns to those obtained in the PER-G90, 180, 270 and 360 analyses (see Table 7.1, Table 7.2, Table 7.3 & Table 7.4 above), with the cumulative probability of non-persistence being inversely proportional to the length of the permissible gap. For example, in the first year after treatment initiation the probability of non-persistence decreased from 67% to 15% - 29% as the permissible gap increased from 7 days[84] to 180 days.[83, 85] Over the same one year follow-up period the probability of non-persistence decreased from 34.8% in the PER-G90 analysis to 19.8% in the PER-G360 analysis.

There are, however, some differences between the individual cumulative probability results obtained in the four PER-G models and those obtained from previous studies using similar permissible gap lengths. For example In the PER-G180 analysis the cumulative probabilities of non persistence at 6, 12, 18 and 24 months after treatment initiation were 21.8%, 27.1%, 30.3% and 32.6% respectively. For the same times after treatment initiation, the results from previous studies using a similar permissible gap length were 20%[63], 15%-29%[63, 83, 85], 40%[85] and 35%-47%.[63, 85] These minor inconsistencies may be attributable to demographic and methodological differences between the studies, such as the requirement for prescription co-payments in some pharmacy schemes and the criteria used to define initial statin users.

Despite the variation in cumulative probability results across the four time to non-persistence definitions there is little variation in the Cox regression estimates from the covariate analyses of these models (see Table

7.5, Table 7.6 & Figure 7.5 above). This indicates that the assignment of non-persistence risk to covariates is robust to changes in the length of permissible gap between 90 to 360 days. It should be noted that this may not be the case for permissible gaps of shorter than 90 days duration. The effect of gender on persistence risk was only significant In the PER-G90 model, with males having a marginal reduction in the risk of non-persistence. This is similar to the results from previous studies where there was either no difference between genders[42, 56, 87, 89] or a very slight reduction in the risk of non-persistence for males.[63, 75, 88] Where assessed, increasing age was universally associated with a reduced risk of non-persistence in these prior studies,[42, 56, 58, 63, 75, 87-89] with some studies showing an increase in risk beyond the age of 75 years.[75] These covariate results for age are confirmed by those from the four PER-G analyses.

Mantel-Teeuwisse et al.[87] assessed the effect of statin type on non-persistence risk and obtained similar results to those in the four PER-G analyses, with atorvastatin associated with the lowest risk of non-persistence and fluvastatin the highest. None of the studies examined the effect of statin prescriber, statin dose or statin dose changes on non-persistence risk. The presence of a pre-existing cardiovascular morbidity, such as ischaemic heart disease, was associated with a reduced risk of non-persistence in all of the studies that included this covariate[56, 58, 75, 84, 87, 89] and in each of the four PER-G models. The effect of diabetes did, however, vary across these studies. None of the studies identified examined the effect of a recent history of depression, Parkinson's disease or Alzheimer's disease on non-persistence risk, although patients prescribed psychotropic agents did have an increased risk of non-persistence in one study.[87] Prior cardiovascular prescription drug use was associated with either no effect [42] or a small reduced risk of non-persistence,[75] confirming the lack of non-persistence risk observed with cardiovascular prescription drug use in the PER-G models.

TABLE 7.7: SYNOPSES OF TIME TO STATIN NON-PERSISTENCE STUDIES USING PERMISSIBLE GAP MODELS & PRESCRIPTION REFILL DATA

Study	Length	Population	N	Gap	Non-Persistence	Median
Catalan[84] 2000	0.5 – 7 years or until death	Quebec RAMQ database, males & females, 45 – 64 years old, initial users (not defined), with at least 4 months between statin initiation and death	983	Longest of either 50% of first Rx length or 7 days	67% @ 1 year 87% @ 5 years	-
Ellis[58] 2004	3.9 years or until loss of eligibility switch to a non-statin treatment or death	Insurance database, males & females, ≥ 18 years old, initial users (no definition) **Note** – patients filling only a single prescription were excluded from the study	2,601	7 days	-	3.4 -3.7 years
Thiebauld[50] 2005	1 year or until death or loss of eligibility	Insurance database, males & females, 18-65 years old, initial users (1 year)	38,886	15 days 30 days 60 days	15 days 48% @ 1 year 60 days 21% @ 1 year	-
Larsen[42] 2002	5 years or until death	Odense OPED database, males & females, any age, initial users (1 year)	3,623	30 days	**40% @ 2 years***	3.5 years
Abraha[75] 2003	0.5 – 4.5 years or until death or loss of eligibility	Umbrian prescription database, males & females, any age, initial users (1 year)	39,222	30 days	-	-
Mantel-Teeuwise[87] 2004	2 years or until death or loss of eligibility	Netherland PHARMO database, males and females, and age, initial users (2 years)	8,335	45 days	39% @ 1 year **54% @ 2 years**	-
Perreault[89] 2005	1.5 – 3.5 years or until death or loss of eligibility	Quebec RAMQ database, males & females, 50 – 64 years old, primary & secondary prevention cohorts, initial users (1 year)	35,412	60 days	1° Prevention 35% @ 6 months **55% @ 2 years*** 65% @ 3 years 2° Prevention 29% @ 6 months **48% @ 2 years*** 55% @ 3 years	-
Perreault[88] 2005	1.5 – 3.5 years or until death or loss of eligibility	Quebec RAMQ database, males & females, 50 – 64 years old, primary prevention cohort, initial users (1 year)	25,733	60 days	23% @ 6 months **52% @ 2 years*** 61% @ 3 years	-

Study	Length	Population	N	Gap	Non-Persistence	Median
Andrade[83] 1995	2 years or until death	Insurance database, males & females, any age, initial users (not defined), with a diagnosis of hyperlipidaemia	2,369	180 days	15% @ 1 year	-
Maitland-van der Zee[86] 2003	3 years or until death	Rotterdam study pharmacy records, males & females, ≥ 55 years old, initial users (6 months)	798	180 days	-	-
Caspard[63] 2005	3 years or until death or loss of eligibility **Note** – patients required to have a minimum of 183 days follow-up	HMO database, males & females, any age, initial users (6 months), baseline low density lipoprotein ≥ 130mg/dl	4,776	183 days	20% @ 6 months 26% @ 1 year **35% @ 2 years** 39% @ 3 years	-
Kamal-Bahl[85] 2007	0.5 – 3 years or until loss of eligibility or end of follow-up	Ingenix Lab/Rx database, males & females, ≥ 20 years old, initial users (1 year)	161,450	180 days	29% @ 1 year 40% @ 1.5 years **47% @ 2 years**	27.5 months
Grant[56] 2004	0.25 – 3 years or until death or loss of eligibility	Insurance database, males & females, any age, initial users (90 days)	4,518	To end of follow-up	32% @ 1 year	-
Lachaine[53] 2006	2 years or until treatment switch or end of follow-up	Quebec RAMQ database, males & females, any age, initial users (1 year)	14,076	To end of follow-up	**17% @ 2 years**	-

* Two year non-persistence value estimated from reported results. ***Length***, length of study or patient observation period. ***Population***, source and characteristics of study cohort. ***N***, number of patients in the study. ***Gap***, length of permissible gap used in non-persistence definition. ***Non-Persistence***, proportion of the study population identified as non-persistent, if reported. ***Median***, the time to 50% of the study cohort becoming non-persistent, if reported. ***Rx***, prescription.

7.4.2 Non-Persistence Results – Implications for Adherence Analyses.

In Section 4.4.3 (see page 75) the advantages of assessing adherence over the length of a patient's treatment episode rather than the duration of follow-up were discussed. It was suggested that this approach was preferable as it does not permit inclusion of a *"terminal gap"*[19] – the time between treatment discontinuation and the end of follow-up – in adherence calculations; thus avoiding the misclassification as non-adherent of adherent patients who become non-persistent.

The high rates of early non-persistence observed in the four PER-G analyses of persistence underline the importance of measuring a patient's adherence over the length of time that they can reasonably be expected

to be taking treatment. In the PER-G180 analysis for example, by one year after treatment initiation 1 in 4 patients will have become non-persistent with a gap in prescription refills of at least 180 consecutive days; by two years this will have increased to 1 in 3 patients (Table 7.2 see page 145). It is unlikely that a gap in prescription refills of 180 days or longer can be attributed to non-adherence and the continued measurement of adherence over this time in such a high proportion of the study cohort is likely to result in a significant overestimation of the number of non-adherent patients.

The inclusion of the time after non-persistence in adherence analyses is also likely to produce an upward biasing of non-adherence risk for covariates that are associated with an increased risk of non-persistence. For example; in adherence models that do not account for treatment discontinuation, such as the time to non-adherence model (Chapter 6, see page 115), the repeated measure adherence model (Chapter 5, see page 83) and most of the single measure adherence models (Chapter 4, see page 55), younger age (16-34 years) was associated with the highest risk of non-adherence. An examination of the non-persistence risk estimates for the same age category (Table 7.6, see above) shows that patients aged 16-34 years also have a markedly increased risk of non-persistence suggesting that at least some proportion of the increased risk of non-adherence observed for this population may be accounted for by the inappropriate handling of treatment discontinuation in these models.

7.4.3 Limitations of Permissible Gap Models of Persistence

As discussed in Section 7.2 (see above), the length of permissible gap that is most appropriate for persistence analysis is open to question and this has been cited as the most significant limitation of the permissible gap methodology.[20, 21, 60] Suggestions that the selection of a permissible gap length should be based entirely on clinical and pharmacological considerations of the medication in question[41] are limited by the lack of objective evidence to support this choice for many treatments. The selection of a permissible gap based solely on these considerations also ignores the likelihood that a gap in prescription refills does not necessarily imply a gap of equal duration, or any gap, in medication-taking by a patient. This making the accurate identification of treatment gaps from prescription refill gaps difficult.

The considerable variation observed in the cumulative probabilities of non-persistence across the four persistence models in this study initially indicates that the selection of a permissible gap length is key to the

appropriate analysis of persistence behaviour. This variation in cumulative probabilities does not, however, result in significant variation in the assignment of non-persistence risk to covariates in the Cox regression models. This suggests that, where the goal of persistence analysis is the evaluation of non-persistence risk for various covariates, the selection of a permissible gap length may not be critical. Nevertheless, effort should be made to select a permissible gap length that, at the very least, reflects the minimum period of medication disuse that distinguishes non-persistent behaviour from non-adherence and sensitivity analyses should be performed to confirm the robustness of predictive covariate model results to variations in the permissible gap length.

Short permissible gap lengths, of less than 90 days for example, may not allow the distinction between non-adherence and non-persistence to be made; as it is conceivable that a patient may retain enough medication from previous prescription refills to continue treatment during this gap, albeit with poor adherence. Short gaps in prescription refills may, therefore, be more appropriately handled as part of adherence analyses. It should be noted that the taking of any amount of medication is consistent with the definition of persistence[41] (see Section 1.1 on page 29) and patients with varying degrees of non-adherence will therefore continue to be considered persistent with treatment. As a result it is important to view persistence results in conjunction with adherence measurements to allow an assessment of the proportion of patients who become non-adherent prior to treatment discontinuation.

7.5 Summary

Statin persistence was measured in a cohort of GMS patients using prescription refill data from the HSE-PCRS pharmacy claims database. The length of time from statin initiation to non-persistence was calculated using a permissible gap model. Four permissible gap lengths were selected for use in the analyses (90 days, 180 days, 270 days & 360 days) with non-persistence defined as the first time in a patient's history of medication supply that the number of consecutive days without an assigned dose exceeded the permissible gap length.

The results from the Kaplan Meier analyses of time to non-persistence for the four PER-G models followed the same pattern as those from previously published permissible gap studies of statin persistence, with the cumulative probability of non-persistence being inversely proportional to the length of permissible

gap. For example; at 720 days after treatment initiation the cumulative probability of non-persistence decreases from 41.4% to 24.5% as the length of the permissible gap is increased from 90 days to 360 days. The variation in non-persistence probability across the four permissible gap lengths did not however produce significant variation in the non-persistence risk assigned to covariates in the Cox regression analyses. This suggests that, where the goal of persistence analysis is the evaluation of non-persistence risk for various covariates, the selection of a permissible gap length may not be critical.

The high rates of early non-persistence observed in these models underline the need to exclude the time after non-persistence from adherence analyses. The continued measurement of adherence after non-persistence is likely to result in a significant overestimation of the number of non-adherent patients and a corresponding bias in the assignment of non-adherence risk to covariates that are associated with non-persistence, for example younger age.

7.6 Conclusion

The use of permissible gap methodology for the analysis treatment persistence produces easily interpreted results and is widely accepted as the most appropriate method for evaluating persistence from prescription refill data. Although the method is limited by the lack of objective evidence for the selection of a permissible gap; the choice of permissible gap, while affecting probability estimates for non-persistence, appears to have little effect on the covariate estimates of non-persistence risk. The high rates of non-persistence indicate that the incorporation of persistence measurements into adherence analyses may have a significant effect on adherence rates and covariate estimates of non-adherence risk. A method facilitating this will be discussed and implemented in Chapter 8 (see page 163).

CHAPTER EIGHT

8 STATIN ADHERENCE & PERSISTENCE – COMPETING RISKS MODEL

8.1 INTRODUCTION

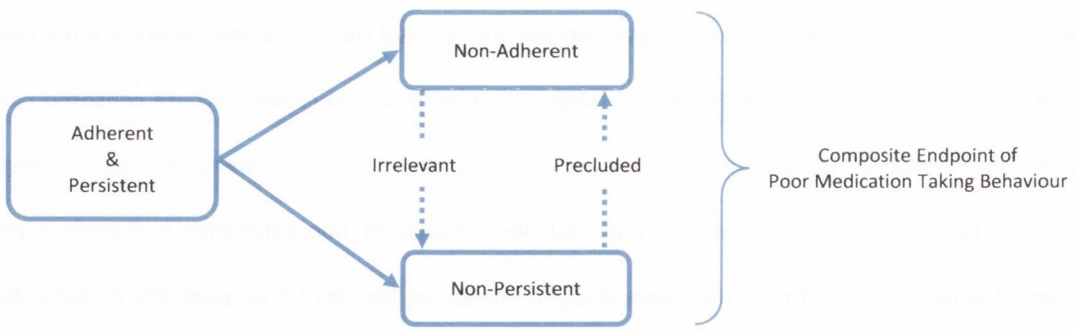
The inability to appropriately account for treatment discontinuation (non-persistence) in models of adherence risk has been the shared and most significant limitation of each of the three adherence models presented (single measure, repeated measure & time to non-adherence). The measurement of non-adherence and non-persistence using a common metric – time – in the time to non-adherence model and the time to non-persistence model (see Chapters 6 & 7 on pages 115 & 139) does however present the opportunity to overcome this limitation. This chapter proposes a method that combines these two measures, allowing the appropriate partitioning of their contributions to poor medication taking and the correct assignment of risk estimates to individual covariates for both behaviours.

8.1.1 NON-ADHERENCE & NON-PERSISTENCE AS COMPETING RISKS

The difficulty incorporating non-persistence times into time to non-adherence models can be thought of in terms other than the informative nature of the censoring this produces. Consider the example of a cause specific model of time to non-adherence where non-persistence times are used as a censoring variable. In the Kaplan-Meier analysis of this model, censored patients are treated as if they could still experience the event of interest after censoring has occurred. However, unlike truly censored observations where censored patients continue to have a risk for the outcome of interest, patients who discontinue treatment are no longer at further risk of becoming non-adherent and their risk for subsequent non-adherence is therefore zero (a patient cannot adhere to a treatment they have stopped taking, see Section 1.1 on page 29). As patients who can no longer fail are treated as if they could fail the Kaplan-Meier model overestimates the cumulative probability for non-adherence and hence underestimates the corresponding adherence probability[90] (see example in Table 8.1 below). The Kaplan-Meier estimator is therefore not an appropriate statistic for non-adherence in the presence of non-persistence because it estimates the probability of non-adherence occurring in an imaginary patient who can never discontinue treatment.

Instead of treating non-persistence as a censoring variable in a time to non-adherence model, it is more appropriate to think of non-adherence and non-persistence as competing risks for the composite outcome of poor medication-taking behaviour; where poor medication-taking behaviour is defined as either non-adherence or non-persistence. These two behaviours represent the two reasons a patient may fail to take a treatment correctly, namely; not acting in accordance with the prescribed interval and dosage of the treatment (non-adherence) and discontinuing the treatment prematurely (non-persistence). The modelling of these two behaviours as competing risks makes empirical sense as patients are simultaneously at risk of both non-adherence and non-persistence and the occurrence of either event fulfils the definition for the composite outcome of poor medication-taking behaviour while respectively precluding or making irrelevant the subsequent occurrence of the competing event (see Figure 8.1 below). The occurrence of non-adherence is precluded by non-persistence as it is not possible to measure the quality of treatment execution in patients who are not taking treatment. The occurrence of non-adherence can be thought of as making irrelevant the subsequent discontinuation of treatment by a patient because non-adherence is the defining event for this patient. In other words, non-persistence is likely to be of greater relevance in patients who are adherent to treatment and it may be advantageous to distinguish between treatment discontinuation in adherent patients versus non-adherent patients.

FIGURE 8.1: COMPETING RISKS MODEL OF NON-ADHERENCE & NON-PERSISTENCE



In a competing risks medication-taking behaviour model such as this, the use of individual Kaplan-Meier estimates for each of the cause specific outcomes leads to internal inconsistencies as the probability of having the composite outcome of a poor medication-taking behaviour event is not equal to the sum of the individual probabilities of having a non-adherent or non-persistent event.[91] This is illustrated in Table 8.1 (see below)

where the Kaplan-Meier cumulative event incidences are estimated for a sample of ten patients in a cause specific non-adherence model, with censoring for non-persistence; a cause specific non-persistence model, with censoring for non-adherence; and a composite non-adherence/non-persistence model. In this illustration the cumulative incidences for the outcomes of interest are calculated using Equation 8.1[90] and Equation 8.2[90] (see below). The first of these, Equation 8.1, is used to calculate the Kaplan-Meier cumulative probability of being event free at each time point. The Kaplan-Meier estimate of the cumulative event incidence is calculated from this result, using Equation 8.2 or more simply as one minus the cumulative probability of being event free $[1 - S_{KM}^{event(1)}(t_x)]$.[91]

EQUATION 8.1: KAPLAN-MEIER ESTIMATE OF THE CUMULATIVE EVENT FREE PROBABILITY

$$S_{KM}^{event(1)}(t_x) = S_{KM}^{event(1)}(t_{x-1}) \times \frac{number\ of\ event(1)\ free\ patients\ at\ t_x}{number\ of\ patients\ at\ risk\ of\ event(1)\ prior\ to\ t_x}$$

Where $S_{KM}^{event(1)}$ denotes the Kaplan-Meier cumulative event(1) free probability, t_x denotes the time at which the current estimation is made and t_{x-1} denotes the time immediately prior to t_x.

EQUATION 8.2: KAPLAN-MEIER ESTIMATE OF THE CUMULATIVE EVENT INCIDENCE

$$CI_{KM}^{event(1)}(t_x) = CI_{KM}^{event(1)}(t_{x-1}) + S_{KM}^{event(1)}(t_{x-1}) \times \frac{number\ of\ event(1)\ at\ t_x}{number\ of\ patients\ at\ risk\ of\ event(1)\ prior\ to\ t_x}$$

Where $CI_{KM}^{event(1)}$ denotes the Kaplan-Meier cumulative event(1) incidence, $S_{KM}^{event(1)}$ denotes the Kaplan-Meier cumulative event(1) free probability (see Equation 8.1 above), t_x denotes the time at which the current estimation is made and t_{x-1} denotes the time immediately prior to t_x.

The inconsistencies in the Kaplan-Meier estimation of cumulative incidences for this competing risk sample data are illustrated by the fact that, after both event types have occurred the cumulative incidences of the individual events sum to greater than the estimated cumulative incidence of the combined events.[i] In addition, the sum of the individual cumulative incidences for the last two events in the series is greater than one. The overestimation of Kaplan-Meier cumulative incidences in these cause specific models of competing risks arises from the assumption that patients experiencing a competing risk either remain at risk of the event

[i] The probability of $A \cup B$ is equal to the sum of the probability of A and the probability of B, minus the probability of A and B (the probability of A and B is by definition equal to zero in a competing risks situation, as the occurrence of one type of event precludes or makes irrelevant the occurrence of the other).

of interest or their risk for the event is not affected by the occurrence of the competing risk. This results in the incorrect estimation of the event free survival probability. For example; the probability of a patient being event free prior to the first non-adherent event in the sample data (patient number 4 at time 17) is estimated at one. This estimation is, however, based upon the assumption that all patients were at risk of non-adherence immediately prior to this event. This is not an accurate assumption, as two patients had become non-persistent prior to this time and they were therefore no longer at risk of becoming non-adherent. The probability of a patient being event free prior to this first non-adherent event is therefore less than the estimated value of one and the Kaplan-Meier calculation of the cumulative incidence of non-adherence is overestimated as a result.

The Cox regression model is also inappropriate in a competing risks situation such as this, because the cause specific hazard function for a competing risk does not have a direct interpretation in terms of survival probability.[90] The estimated effect of a covariate on non-adherence in a cause specific model may therefore be very different from the effect of the covariate in the presence of non-persistence.

The use of cause specific Kaplan-Meier and Cox regression models is therefore not adequate for the estimation of individual event probabilities and covariate effects in a competing risks situation. Additive cumulative incidence function models[92-94] have been proposed as a more appropriate method for competing risks as they can properly partition the event probabilities and the effects of a covariate on poor medication-taking behaviour into their component parts.[91]

TABLE 8.1: KAPLAN-MEIER ESTIMATED CUMULATIVE INCIDENCES OF NON-ADHERENCE, NON-PERSISTENCE AND COMPOSITE NON-ADHERENCE/NON-PERSISTENCE FOR A SAMPLE OF TEN PATIENTS, CALCULATED USING EQUATION 8.1 & EQUATION 8.2.

Patient	Time	Event	Number At Risk	CI_{KM}^{NonAdh}	CI_{KM}^{NonPer}	$CI_{KM}^{NonAdh + NonPer}$
1	10	Non-Per	10	$0 + 1 \times \left(\frac{0}{10}\right)$	$0 + 1 \times \left(\frac{1}{10}\right)$	$0 + 1 \times \left(\frac{1}{10}\right)$
				= 0.0	**= 0.1**	**= 0.1**
2	12	EFU	9	$0 + 1 \times \left(\frac{0}{9}\right)$	$0.1 + 0.9 \times \left(\frac{0}{9}\right)$	$0.1 + 0.9 \times \left(\frac{0}{9}\right)$
				= 0.0	**= 0.1**	**= 0.1**
3	15	Non-Per	8	$0 + 1 \times \left(\frac{0}{8}\right)$	$0.1 + 0.9 \times \left(\frac{1}{8}\right)$	$0.1 + 0.9 \times \left(\frac{1}{8}\right)$
				= 0.0	**= 0.213**	**= 0.213**
4	17	Non-Adh	7	$0 + 1 \times \left(\frac{1}{7}\right)$	$0.213 + 0.787 \times \left(\frac{0}{7}\right)$	$0.213 + 0.787 \times \left(\frac{1}{7}\right)$
				= 0.143	**= 0.213**	**= 0.325**
5	18	EFU	6	$0.143 + 0.857 \times \left(\frac{0}{6}\right)$	$0.213 + 0.787 \times \left(\frac{0}{6}\right)$	$0.325 + 0.675 \times \left(\frac{0}{6}\right)$
				= 0.143	**= 0.213**	**= 0.325**
6	20	Non-Per	5	$0.143 + 0.857 \times \left(\frac{0}{5}\right)$	$0.213 + 0.787 \times \left(\frac{1}{5}\right)$	$0.325 + 0.675 \times \left(\frac{1}{5}\right)$
				= 0.143	**= 0.37**	**= 0.46**
7	24	Non-Adh	4	$0.143 + 0.857 \times \left(\frac{1}{4}\right)$	$0.37 + 0.63 \times \left(\frac{0}{4}\right)$	$0.46 + 0.54 \times \left(\frac{1}{4}\right)$
				= 0.357	**= 0.37**	**= 0.595**
8	27	Non-Adh	3	$0.357 + 0.643 \times \left(\frac{1}{3}\right)$	$0.37 + 0.63 \times \left(\frac{0}{3}\right)$	$0.595 + 0.405 \times \left(\frac{1}{3}\right)$
				= 0.571	**= 0.37**	**= 0.730**
9	29	Non-Per	2	$0.571 + 0.429 \times \left(\frac{0}{2}\right)$	$0.37 + 0.63 \times \left(\frac{1}{2}\right)$	$0.730 + 0.270 \times \left(\frac{1}{2}\right)$
				= 0.571	**= 0.685**	**= 0.865**
10	30	EFU	1	$0.571 + 0.429 \times \left(\frac{0}{1}\right)$	$0.37 + 0.63 \times \left(\frac{0}{1}\right)$	$0.865 + 0.135 \times \left(\frac{0}{1}\right)$
				= 0.571	**= 0.685**	**= 0.865**

Time, number of days from treatment initiation to non-persistence (***Non-Per***) non-adherence (***Non-Adh***) or end of follow-up (***EFU***). ***Number at Risk***, number of patients in cohort who have not had an event up to this time i.e. all adherent and persistent patients who have not reached the end of follow-up. CI_{KM}^{NonAdh}, Kaplan-Meier estimate of the cumulative incidence of non-adherence with non-persistence censored. CI_{KM}^{NonPer}, Kaplan-Meier estimate of the cumulative incidence of non-persistence with non-adherence censored. $CI_{KM}^{NonAdh + NonPer}$, Kaplan-Meier estimate of the cumulative incidence of either non-adherence or non-persistence.

8.1.2 Additive Cumulative Incidence Function Models for Competing Risk Analyses

8.1.2.1 Cumulative Incidence Functions

Competing risk probabilities can be summarised by the cumulative incidence function. This estimates the rate at which patients who could become non-adherent or non-persistent are becoming non-adherent. The

cumulative incidence of non-adherence in the presence of non-persistence as a competing risk can be calculated using Equation 8.3 (see below). This is similar to the Kaplan-Meier method used in Section 8.1.1 (see above), the difference lies in the probability of an event free survival immediately prior to the estimation of the cumulative incidence. In the Kaplan-Meier method this probability is the probability of being adherent ($S_{KM}^{event(1)}$, see Equation 8.1 above) whereas it is the probability of being adherent and persistent in the competing risks cumulative incidence estimation ($S_{KM}^{event(1)+event(2)}$, see Equation 8.3 below). The cumulative incidence of non-adherence in the presence of non-persistence as a competing risk can therefore be thought of as the probability of a patient becoming non-adherent at a specified time given that the patient was both adherent and persistent up to that time. It should be noted that the cumulative incidence function makes no assumptions about the relationship between the competing risks, such as independence.

The calculation of cumulative incidences in the presence of a competing risk is illustrated in Table 8.2 (see below), using the same sample data used in Section 8.1.1. In this competing risks illustration, the inconsistencies observed in the Kaplan-Meier estimation of cumulative incidences are not repeated (see Table 8.1 above). The cumulative incidences for the individual competing risks of non-adherence and non-persistence correctly sum to the cumulative incidence for the composite outcome.

EQUATION 8.3: COMPETING RISKS ESTIMATE OF THE CUMULATIVE EVENT INCIDENCE

$$CI_{CR}^{event(1)}(t_x) = CI_{CR}^{event(1)}(t_{x-1}) + S_{KM}^{event(1)+event(2)}(t_{x-1}) \times \frac{number\ of\ event(1)\ at\ t_x}{number\ at\ risk\ of\ event(1)\ prior\ to\ t_x}$$

Where $CI_{KM}^{event(1)}$ denotes the competing risks cumulative event incidence for event(1) in the presence of event(2), $S_{KM}^{event(1)+event(2)}$ denotes the Kaplan-Meier cumulative event free probability for the composite outcome of event(1) and event(2) (see Equation 8.1 above), t_x denotes the time at which the current estimation is made and t_{x-1} denotes the time immediately prior to t_x.

TABLE 8.2: COMPETING RISKS CUMULATIVE INCIDENCES OF NON-ADHERENCE, NON-PERSISTENCE AND COMPOSITE NON-ADHERENCE/NON-PERSISTENCE FOR A SAMPLE OF TEN PATIENTS, CALCULATED USING EQUATION 8.1 & EQUATION 8.3.

Patient	Time	Event	Number At Risk	CI_{CR}^{NonAdh}	CI_{CR}^{NonPer}	$CI_{KM}^{NonAdh + NonPer}$
1	10	Non-Per	10	$0 + 1 \times \left(\frac{0}{10}\right)$	$0 + 1 \times \left(\frac{1}{10}\right)$	$0 + 1 \times \left(\frac{1}{10}\right)$
				= 0.0	**= 0.1**	**= 0.1**
2	12	EFU	9	$0 + 0.9 \times \left(\frac{0}{9}\right)$	$0.1 + 0.9 \times \left(\frac{0}{9}\right)$	$0.1 + 0.9 \times \left(\frac{0}{9}\right)$
				= 0.0	**= 0.1**	**= 0.1**
3	15	Non-Per	8	$0 + 0.9 \times \left(\frac{0}{8}\right)$	$0.1 + 0.9 \times \left(\frac{1}{8}\right)$	$0.1 + 0.9 \times \left(\frac{1}{8}\right)$
				= 0.0	**= 0.213**	**= 0.213**
4	17	Non-Adh	7	$0 + 0.787 \times \left(\frac{1}{7}\right)$	$0.213 + 0.787 \times \left(\frac{0}{7}\right)$	$0.213 + 0.787 \times \left(\frac{1}{7}\right)$
				= 0.112	**= 0.213**	**= 0.325**
5	18	EFU	6	$0.112 + 0.675 \times \left(\frac{0}{6}\right)$	$0.213 + 0.675 \times \left(\frac{0}{6}\right)$	$0.325 + 0.675 \times \left(\frac{0}{6}\right)$
				= 0.112	**= 0.213**	**= 0.325**
6	20	Non-Per	5	$0.112 + 0.675 \times \left(\frac{0}{5}\right)$	$0.213 + 0.675 \times \left(\frac{1}{5}\right)$	$0.325 + 0.675 \times \left(\frac{1}{5}\right)$
				= 0.112	**= 0.348**	**= 0.460**
7	24	Non-Adh	4	$0.112 + 0.54 \times \left(\frac{1}{4}\right)$	$0.348 + 0.54 \times \left(\frac{0}{4}\right)$	$0.46 + 0.54 \times \left(\frac{1}{4}\right)$
				= 0.247	**= 0.348**	**= 0.595**
8	27	Non-Adh	3	$0.248 + 0.405 \times \left(\frac{1}{3}\right)$	$0.348 + 405 \times \left(\frac{0}{3}\right)$	$0.595 + 0.405 \times \left(\frac{1}{3}\right)$
				= 0.382	**= 0.348**	**= 0.730**
9	29	Non-Per	2	$0.383 + 0.270 \times \left(\frac{0}{2}\right)$	$0.348 + 0.270 \times \left(\frac{1}{2}\right)$	$0.730 + 0.270 \times \left(\frac{1}{2}\right)$
				= 0.382	**= 0.483**	**= 0.865**
10	30	EFU	1	$0.383 + 0.135 \times \left(\frac{0}{1}\right)$	$0.483 + 0.135 \times \left(\frac{0}{1}\right)$	$0.865 + 0.135 \times \left(\frac{0}{1}\right)$
				= 0.382	**= 0.483**	**= 0.865**

Time, number of days from treatment initiation to non-persistence (***Non-Per***) non-adherence (***Non-Adh***) or end of follow-up (***EFU***). ***Number at Risk***, number of patients in cohort who have not had an event up to this time i.e. all adherent and persistent patients who have not reached the end of follow-up. CI_{CR}^{NonAdh}, competing risk estimate of the cumulative incidence of non-adherence. CI_{CR}^{NonPer}, competing risk estimate of the cumulative incidence of non-persistence. $CI_{KM}^{NonAdh + NonPer}$, Kaplan-Meier estimate of the cumulative incidence of either non-adherence or non-persistence.

8.1.2.2 Regression on the Cumulative Incidence Function

The Cox regression analysis is appropriate for use in models with a single endpoint where there is a one to one correspondence between the hazard rate and the survival probability as estimated by the Kaplan-Meier estimator. This one to one relationship between the hazard rate and the survival probability does not hold for competing risks models, as estimates of the probability that a patient has experienced an event depend on the hazard rates for all the competing risks. To overcome this difficulty a number of regression models based on

the competing risk cumulative incidence functions have been proposed. These include the "*proportional hazards*" model developed by Fine and Gray[93, 94] and the "*pseudo-value*" approach proposed by Andersen, Klein and Rosthøj.[92, 95] The latter of these two methods was selected for use in this study, primarily because of the availability of published macros[96, 97] to fit the model in SAS®.

8.2 Methods

When competing risks are present there are three possible ways to proceed with their analysis. Firstly, an analysis of the event of interest, ignoring or treating the competing risks as a censored variable. Secondly, an analysis of the joint events as a single composite endpoint. Thirdly, an analysis of the competing risks independently. As discussed in Section 8.1 (see above) the first approach is incorrect as it leads to a biased Kaplan-Meier estimator and Cox regression model. The second approach, while correct, may be too limited to address many relevant research questions. However, the combination of the second and third methods provides a comprehensive approach to the analysis of competing risks that can adequately address general as well as more specific study questions. For this study therefore, the times to non-adherence and non-persistence were analysed as separate competing risks and as a composite endpoint. Two separate models were constructed using varying definitions of poor medication-taking behaviour.

8.2.1 Identification of Time to Non-Adherence

The time to non-adherence was identified using the methodology described in Section 6.2 (see page 115). A non-adherent episode length of 180 days was chosen for the competing risks analysis and non-adherence was defined as a PDC of less than 80%. A patient's time to non-adherence was identified as the length of time from treatment initiation to the first time that their adherence rate dropped below 80% for at least 180 consecutive days (CRM-A180[i]). The non-adherent episode length of 180 days was chosen for this analysis because it represents a level of non-adherence that may reasonably be expected to have a negative effect on clinical outcomes (see Section 6.4.1 on page 131).

Patients were not classified as non-adherent if they were also identified as lost to follow-up (see Section 3.5.1 on page 49) prior to the end of the 180 day non-adherent episode length. These patients were classified

[i] Competing risks model of time to non-adherence defined as a PDC of < 80% for at least 180 consecutive days.

as lost to follow-up instead. In patients who had both a non-adherent and a non-persistent (see Section 8.2.2 below) event; non-adherence was only identified as the defining event for a patient if non-persistence occurred after the end of the 180 day non-adherent episode length.

8.2.2 Identification of Time to Non-Persistence

The time to non-persistence was identified using the methodology described in Section 7.2.1 (see page 141). Two permissible gap lengths were chosen to illustrate the influence of gap length on the competing risks model results. These were 180 days and 360 days. Using these permissible gap lengths, non-persistence was identified as the first time in a patient's history of medication supply (see Section 3.3 on page 46) that the number of consecutive days without an assigned dose exceeded the permissible gap length. The time to non-persistence was taken as the length of time from treatment initiation to the last assigned day of treatment prior to the defined permissible gap of 180 days (CRM-P180[i]) or 360 days (CRM-P360[ii]). The two competing risks models were identified by the acronyms CRM-A180P180[iii] and CRM-A180P360[iv].

Patients were not classified as non-persistent if they were also identified as lost to follow-up (see Section 3.5.1 on page 49) at any time prior to the end of the permissible gap. These patients were classified as lost to follow-up instead. In patients who had both a non-persistent and a non-adherent (see section 8.2.1 above) event; non-persistence was only identified as the defining event for a patient if it occurred prior to the end of the 180 day non-adherent episode length.

8.2.3 Identification of Time to Composite Endpoint (Non-Adherence/Non-Persistence)

The definitions of non-adherence and non-persistence described in Sections 8.2.1 and 8.2.2 (see above) preclude the simultaneous identification of a patient as both non-adherent and non-persistent. This is because; where both events occurred in a patient's history, the earlier of these two events was identified as

---

[i] Competing risks model of time to non-persistence defined by a permissible gap in treatment of ≥ 180 days.

[ii] Competing risks model of time to non-persistence defined by a permissible gap in treatment of ≥ 360 days.

[iii] Competing risks model of time to non-adherence defined as a PDC of < 80% for at least 180 consecutive days or non-persistence defined by a permissible gap in treatment of ≥ 180 days.

[iv] Competing risks model of time to non-adherence defined as a PDC of < 80% for at least 180 consecutive days or non-persistence defined by a permissible gap in treatment of ≥ 360 days.

the defining endpoint for that patient. Therefore the time to a patient's defining endpoint, either non-adherence or non-persistence, was taken as the time to the composite endpoint for that patient.

8.2.4 Statistical Analysis

Cumulative incidence functions for the competing risks – non-adherence and non-persistence – were calculated using the SAS® macro *incid*[96] (see Appendix 2, Section A2.3 on page 221). These functions were used to estimate the cumulative incidence of non-adherence in the presence of non-persistence as a competing risk (and vice versa) for each of the models CRM-A180P180 and CRM-A180P360. The cumulative incidences of the composite outcome non-adherence/non-persistence were calculated in the standard way using a Kaplan-Meier estimator (SAS® PROC LIFETEST).

8.2.4.1 Regression Modelling Based on Pseudo-Values of the Competing Risk Cumulative Incidence Functions

Univariate and multivariate regression modelling based on the competing risk cumulative incidence functions for non-adherence and non-persistence was carried out using the pseudo-value approach developed by Andersen, Klein and Rosthøj.[92, 95] This technique allows the direct regression modelling of the cumulative incidence function using pseudo-values based on the difference between the complete sample and the "*leave-one-out*" estimators of relevant survival quantities (jack-knife procedure).[95] These pseudo-values are then used in a generalised estimating equation regression analysis to model the effects of covariates on the outcome of interest. The pseudo-value model can incorporate time-dependent covariates but requires that a series of time points be pre-specified for the calculation of corresponding pseudo-values. It has been suggested that the use of anywhere between five and twenty time points evenly spaced on the event scale (i.e. roughly equal numbers of events between time points) is adequate.[98, 99] For this analysis nineteen time points were selected, these were days 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 360, 450, 54, 630, 720 and 900. A detailed description of the pseudo-value methodology and a comparison of its use with other methods have been published.[92, 98, 99]

The pseudo-values for the cumulative incidence functions can be calculated using the SAS® macros *pseudoci*[97] (see Appendix 2, Section A2.1 on page 217) and *cuminc*[97] (see Appendix 2, Section A2.2 on page 220). A guide to the application of these macros has been published by Klein et al[95] and Rosthøj et al.[100] The

SAS® macro *pseudoci* computes a set of pseudo-values for each competing risk at the pre-specified time points, using the output from the *cuminc* macro. This macro uses the SAS® PROC PHREG procedure to obtain crude hazard rates by fitting two Cox regression models, one for each competing risk and repeating this process for each observation in the data set with a different patient deleted from the analysis for each iteration (jack-knife procedure). This yields the cumulative crude hazard rate which is converted to the hazard rate at the event times and subsequently combined to generate the cumulative incidence functions. This is a computationally intensive analysis requiring for each model the use of almost 160,000 individual PROC PHREG procedures and taking approximately 240 hours for the analysis of the 79,364 patients in the study cohort.

Once the pseudo-values have been computed they are used as the dependent variables in a generalised estimating equation (PROC GENMOD, see Section 5.2.3.1 on page 85) to estimate the β regression coefficients for covariates associated with the competing risks. As recommended,[95, 98, 99] the dependent variable distribution for this GEE analysis was specified as normal; the link function used in the transformation of the dependent variable was the complementary log-log function and the correlation structure of the dependent variable was specified as independent. The complementary log-log function gives a proportional hazards representation when applied to a survival function[98, 101] allowing the exponentiated β regression coefficients from the analyses to be interpreted as hazard ratios or more appropriately as sub-distribution hazard ratios. The term sub-distribution is derived from the fact that while a survival distribution function tends to 1 the cumulative incidence function tends to the raw proportion of events, hence it is also called a sub-distribution function. Hazard ratios estimated from these functions are therefore referred to as sub-distribution hazard ratios. [101, 102] Crude and adjusted sub-distribution hazard ratios with 95% confidence intervals are presented for independent categorical variables. Multivariate analyses were adjusted for all included covariates. Significance at $p < 0.05$ was assumed. SAS®, version 9.1[i] was used for all analyses

8.2.4.2 Cox Regression Modelling of the Composite Endpoint

Univariate and multivariate Cox regression models (SAS® PROC PHREG) with time varying covariates were constructed for the composite non-adherence/non-persistence event endpoints in each of the models (CRM-

[i] SAS Institute, Cary, NC, USA.

A180P180 and CRM-A180P360). Censoring in these analyses was considered random[i] with observations censored at the time of loss to follow-up or end of follow-up, whichever occurred first. Tied events in the Cox regression model were handled using the method proposed by Efron.[79, 80] Crude and adjusted hazard ratios and 95% confidence intervals are presented for independent covariates. Multivariate analyses were adjusted for all included covariates. Significance at $p < 0.05$ was assumed. SAS®, version 9.1 was used for all analyses.

8.2.5 Covariates Included in the Competing Risk Models

Patient gender and the following time-varying covariates were included in the competing risks and composite outcome models; age, current statin type, current statin dose, current statin prescriber, statin dose change, all co-morbidities and the number of non-cardiovascular pharmacological agents, cardiovascular pharmacological agents and prescription items received by a patient in the prior 365 days. Values for the time-varying covariates were taken on the day of persistence or adherence evaluation (i.e. at each of the nineteen time points selected for the pseudo-value analysis). A full description of these covariates can be found in Section 3.6 (see page 49).

8.3 Results

8.3.1 Competing Risks Model Study Cohort

The permissible gap methodology for persistence estimation and time to non-adherence methodology for adherence estimation did not require the exclusion of any patients from the source study cohort (see Chapter 3 on page 43). The characteristics of the patients included in the competing risks analyses can therefore be found in Table 3.2 (see page 53) and are described in Section 3.7.2 (see page 52).

8.3.2 Non-Adherence, Non-Persistence & Composite Outcome Cumulative Incidences

The cumulative incidence curves for the two competing risk models are shown in Figure 8.2 (CRM-A180P180) and Figure 8.3 (CRM-A180P360) below. A selection of results from these cumulative incidence plots is presented in Table 8.3 and Table 8.4, also below. At two years after statin treatment initiation the cumulative incidence of non-adherence varied from 24.7% to 31.0% and the cumulative incidence of non-

[i] Censoring is considered random when observations are terminated for reasons that are not under the control of the investigator.

persistence varied from 28.3% to 20.3% for the CRM-A180P180 and CRM-A180P360 models respectively. While the cumulative incidences for the individual competing risks differ between the two models, the cumulative incidences for the composite outcomes are remarkably similar (CRM-A180P180, 53.0%; CRM-A180P360, 51.3%). This is because as the permissible gap defining non-persistence is lengthened from 180 to 360 days the cumulative incidence of non-persistence reduces and the cumulative incidence of non-adherence increases.

The results from these cumulative incidence curves can be used to estimate the probability of a number of medication-taking behaviour outcomes. For example in the CRM-A180P180 model (see Figure 8.2 and Table 8.3 below) the cumulative probability of a patient becoming non-adherent in the two years after treatment initiation, assuming that they were both adherent and persistent prior to the event, is 28.3%. The corresponding cumulative incidence for non-persistence is 24.7% and overall just over half (53.0%) of patients will have experienced a non-adherent or a non-persistent event in the first two years after treatment initiation.

FIGURE 8.2: CUMULATIVE INCIDENCE PLOTS OF STATIN NON-ADHERENCE (CRM-A180 ■) & STATIN NON-PERSISTENCE (CRM-P180 ■) AS COMPETING RISKS & COMPOSITE STATIN NON-ADHERENCE & NON-PERSISTENCE (CRM-A180P180 ■)

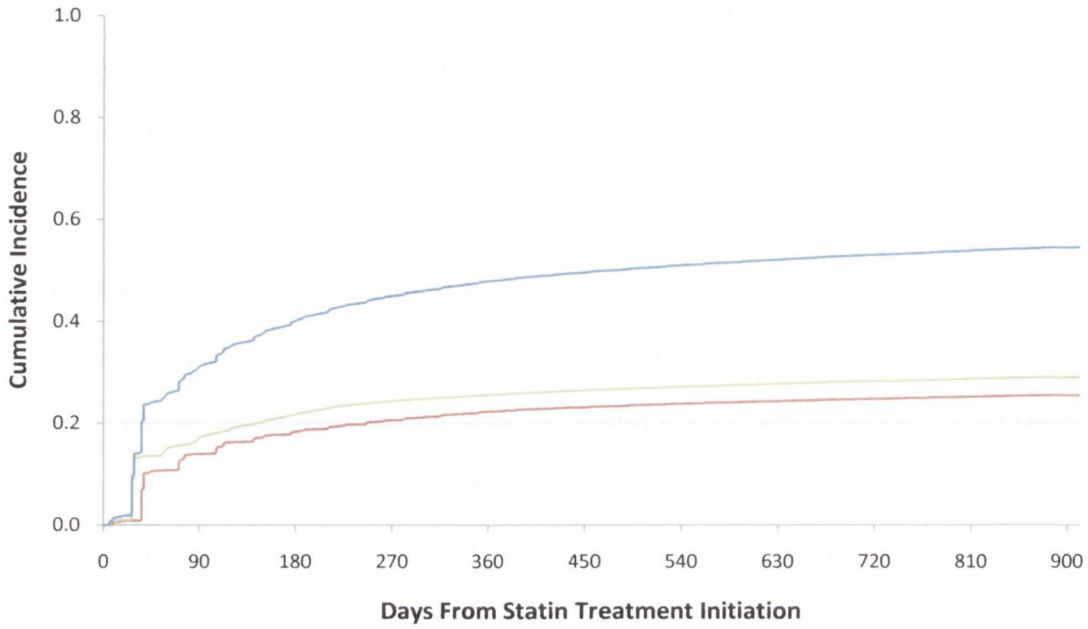


TABLE 8.3: SELECTED CUMULATIVE INCIDENCES OF STATIN NON-ADHERENCE (CRM-A180) & STATIN NON-PERSISTENCE (CRM-P180) AS COMPETING RISKS & COMPOSITE STATIN NON-ADHERENCE & NON-PERSISTENCE (CRM-A180P180)

	CRM-A180		CRM-P180		CRM-A180P180		N-Adh	N-Per	Adh & Per	Cen
Day	(%)	95% CI (%)	(%)	95% CI (%)	(%)	95% CI (%)	N	N	N	N
30	0.9	(0.8, 0.9)	13.2	(13.0, 13.4)	14.1	(13.8, 14.3)	678	10,220	66,477	1,989
60	10.8	(10.6, 11.0)	15.1	(14.9, 15.4)	25.9	(25.6, 26.2)	8,303	11,687	56,724	2,650
90	14.9	(13.7, 14.2)	17.3	(17.0, 17.5)	31.2	(30.9, 31.6)	10,744	13,322	52,067	3,231
180	18.3	(18.1, 18.6)	21.8	(21.5, 22.1)	40.2	(39.8, 40.5)	13,997	16,734	43,817	4,816
270	20.6	(20.3, 20.9)	24.4	(24.1, 24.7)	45.0	(44.6, 45.3)	15,548	18,484	34,326	11,006
360	22.3	(22.0, 22.6)	25.6	(25.3, 25.9)	47.9	(47.5, 48.3)	16,535	19,175	27,493	16,161
450	23.1	(22.8, 23.4)	26.5	(26.1, 26.8)	49.6	(49.2, 49.9)	16,919	19,598	21,469	21,378
540	23.8	(23.5, 24.2)	27.2	(26.8, 27.5)	51.0	(50.6, 51.4)	17,196	19,870	16,268	26,030
630	24.3	(24.0, 24.6)	27.8	(27.4, 28.1)	52.1	(51.7, 52.5)	17,339	20,047	13,249	28,729
720	24.7	(24.4, 25.1)	28.3	(27.9, 28.6)	53.0	(52.6, 53.4)	17,451	20,165	9,143	32,605
810	25.2	(24.8, 25.5)	28.7	(28.3, 29.0)	53.9	(53.5, 54.3)	17,516	20,228	4,639	36,981
900	25.5	(25.1, 25.9)	29.0	(28.6, 29.4)	54.5	(54.0, 54.9)	17,535	20,251	774	40,804

Day, number of days from statin initiation. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P180***, competing risks time to a gap in prescription refills of at least 180 consecutive days. ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***N-Adh***, non-adherent patients. ***N-Per***, non-persistent patients. ***Adh & Per***, adherent & persistent patients. ***Cen***, censored patients. ***CI***, confidence interval. ***N***, number of patients.

FIGURE 8.3: CUMULATIVE INCIDENCE PLOTS OF STATIN NON-ADHERENCE (CRM-A180 ■) & STATIN NON-PERSISTENCE (CRM-P360 ■) AS COMPETING RISKS & COMPOSITE STATIN NON-ADHERENCE & NON-PERSISTENCE (CRM-A180P360 ■)

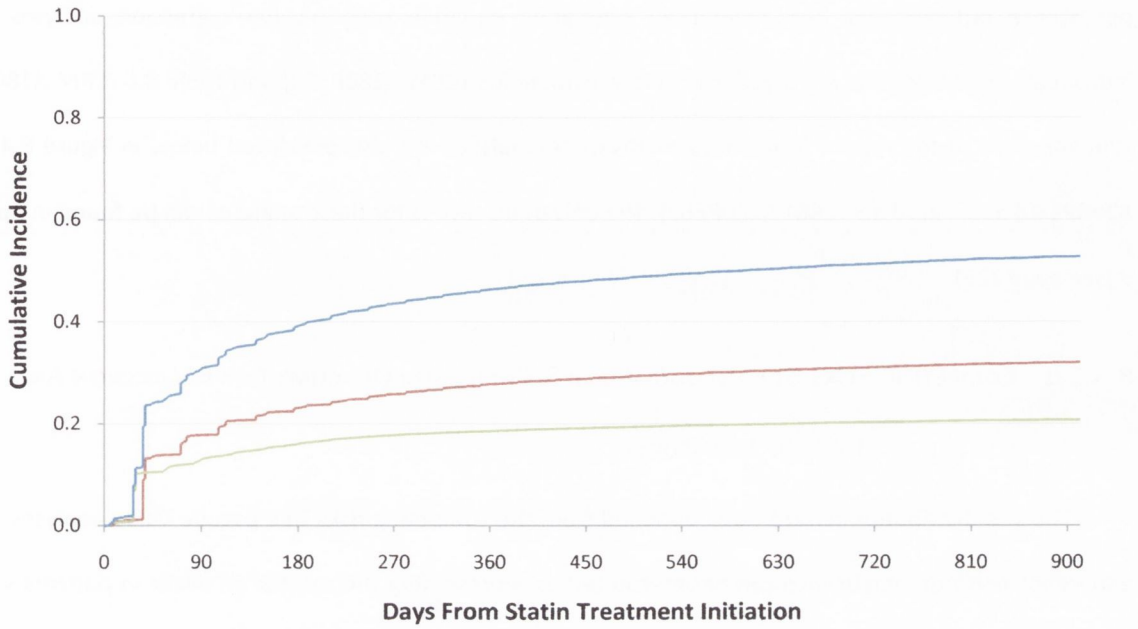


TABLE 8.4: SELECTED CUMULATIVE INCIDENCES OF STATIN NON-ADHERENCE (CRM-A180) & STATIN NON-PERSISTENCE (CRM-P360) AS COMPETING RISKS & COMPOSITE STATIN NON-ADHERENCE & NON-PERSISTENCE (CRM-A180P360)

	CRM-A180		CRM-P360		CRM-A180P360		N-Adh	N-Per	Adh & Per	Cen
Day	(%)	95% CI (%)	(%)	95% CI (%)	(%)	95% CI (%)	N	N	N	N
30	1.1	(1.1, 1.2)	10.2	(10.0, 10.4)	11.4	(11.1, 11.6)	886	7,910	68,579	1,989
60	13.9	(13.7, 14.1)	11.6	(11.3, 11.8)	25.5	(25.2, 25.8)	10,713	8,950	57,051	2,650
90	17.8	(17.5, 18.1)	13.1	(12.8, 13.3)	30.9	(30.5, 31.2)	13,680	10,097	52,356	3,231
180	23.1	(22.8, 23.4)	16.1	(15.8, 16.4)	39.2	(38.8, 39.5)	17,638	12,350	44,560	4,816
270	25.8	(25.5, 26.1)	17.8	(17.5, 18.0)	43.6	(43.2, 43.9)	19,483	13,496	35,030	11,355
360	27.8	(27.5, 28.1)	18.6	(18.3, 18.9)	46.4	(46.0, 46.7)	20,617	13,957	27,837	16,953
450	28.8	(28.5, 29.2)	19.2	(18.9, 19.4)	48.0	(47.6, 48.3)	21,103	14,235	21,635	22,391
540	29.8	(29.4, 30.1)	19.6	(19.3, 19.9)	49.4	(49.0, 49.8)	21,452	14,408	16,371	27,133
630	30.4	(30.0, 30.8)	19.9	(19.6, 20.2)	50.4	(50.0, 50.7)	21,648	14,501	13,340	29,875
720	31.0	(30.6, 31.4)	20.3	(20.0, 20.6)	51.3	(50.9, 51.7)	21,792	14,582	9,202	33,788
810	31.6	(31.2, 32.0)	20.6	(20.3, 20.9)	52.2	(51.8, 52.6)	21,880	14,623	4,664	38,197
900	32.0	(31.5, 32.4)	20.7	(20.4, 21.0)	52.7	(52.2, 53.1)	21,902	14,633	781	42,048

Day, number of days from statin initiation. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P360***, competing risks time to a gap in prescription refills of at least 360 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days. ***N-Adh***, non-adherent patients. ***N-Per***, non-persistent patients. ***Adh & Per***, adherent & persistent patients. ***Cen***, censored patients. ***CI***, confidence interval. ***N***, number of patients.

8.3.3 Competing Risks GEE & Cox Regression Analyses – Multivariate Models

The results of from the multivariate Cox regression analyses of the composite non-adherence and non-persistence outcome and the generalised estimating equation pseudo-value regression analyses of the individual competing risks are presented below in Table 8.5 (CRM-A180P180) and Table 8.6 (CRM-A180P360). Whisker plots of the results from these multivariate analyses are also presented below in Figure 8.4 (CRM-A180P180) and Figure 8.5 (CRM-A180P360). The univariate results for these analyses can be found in Appendix 3 (see page 225).

8.3.3.1 Competing Risks GEE Pseudo-Value & Composite Outcome Cox Regression Analyses for the CRM-A180P180 Model

The sub-distribution hazard rates obtained from the competing risks GEE pseudo-value analyses of non-adherence and non-persistence can be interpreted as representing the risk for an event in patients who are both adherent and persistent with treatment. There was no difference between males and females in the adjusted risk for non-adherence, non-persistence or the composite outcome of the two. Patients younger than 55 years and older than 74 years had a higher adjusted risk of non-persistence in comparison to the 65-74 year age category. This increased risk was considerable for patients under the age of 45, with patients in the youngest age category having a 138% increased risk of non-persistence (reference 65-74 years). The pattern of risk was appreciably different for age in the competing risks model of non-adherence. Non-adherence risk increased with age up to the 45-54 years age category, reducing thereafter. In comparison to the reference age category, 65-74 years, patients between the ages of 45-54 and 55-64 years had an increased risk of non-adherence; there was no difference in non-adherence risk for patients over the age of 75 years. Patients in the youngest age category, 16-34 years, had the lowest risk of non-adherence. A comparison of non-adherence and non-persistence risk estimates within the various age groups shows that patients in the 16-34 year age category have the highest risk of non-persistence but also the lowest risk of non-adherence. As age increased the risks of non-adherence and non-persistence converge to being roughly equal for the 45-54 year and 65-74 year age categories.

With the exception of the simvastatin/ezetimibe combination (Inegy®) there was no significant difference between the risk of non-adherence for the five statins, pravastatin, simvastatin, fluvastatin, atorvastatin and

rosuvastatin. Differences between statins did however occur in the risk of non-persistence, with patients prescribed fluvastatin having an increased risk of non-persistence (26%) and patients prescribed atorvastatin or rosuvastatin having a reduced risk of non-persistence (14% & 12%). The composite outcome hazard ratio results for these four statins followed a similar pattern to the results for non-persistence. Patients prescribed the simvastatin/ezetimibe combination had a reduced risk of non-persistence and an increased risk of non-adherence in comparison to pravastatin. The composite outcome results for patients prescribed this combination showed no difference in the risk of poor-medication-taking behaviour in comparison to pravastatin.

Patients prescribed a statin by a hospital prescriber were significantly less likely to be either non-adherent or non-persistent with treatment with an 11% and a 9% reduction in the risk of each event respectively and an 11% reduction in the risk of the composite outcome. In comparison to patients receiving an intermediate statin dose there was no significant difference in the risk of the composite outcome of non-adherence or non-persistence for patients receiving a low or a high statin dose. The individual competing risks analyses did however show that low doses were associated with a reduced risk of non-persistence and an increased risk of non-adherence. This association was reversed for patients receiving a high statin dose. For patients receiving a modification to the dose of statin they received, either a decrease or an increase, the risk of non-adherence was greater than that for patients remaining on the same dose, but the risk of non-persistence was reduced.

With the exception of patients receiving medications for Parkinson's disease who had a reduced risk of non-adherence, none of the co-morbidities included in the competing risks model were associated with a change in the risk of non-adherence. In contrast, patients receiving treatments for ischaemic heart disease, diabetes or a recent diagnosis of depression had a lower risk of non-persistence and patients receiving treatments for Parkinson's disease or a history of depression were at increased risk of non-persistence.

As the number prescriptions for non-cardiovascular pharmacological agents received by a patient in the prior twelve months increased there was a corresponding increase in the risk of both non-adherence and non-persistence. The magnitude of non-persistence risk was higher than that of non-adherence. There was a marginal reduction in the risk of non-adherence for patients receiving any more than one cardiovascular

pharmacological agent in the prior twelve months. There was a similar reduction in the risk of non-persistence for patients receiving one or more of these agents. The number of prescription items a patient had dispensed to them over the past twelve months was inversely associated with the risk of non-adherence, non-persistence and the composite outcome of the two endpoints.

8.3.3.2 Competing Risks GEE Pseudo-Value & Composite Outcome Cox Regression Analyses for the CRM-A180P360 Model

Results from the competing risks GEE pseudo-value regression analysis and the composite outcome Cox regression analysis of the CRM-A180P360 model followed a similar pattern to the results obtained for the CRM-A180P180 model with little, if any, difference in either the direction or magnitude of risk assigned to covariate values (see Table 8.6 below).

TABLE 8.5: RESULTS FROM THE MULTIVARIATE COMPETING RISKS ANALYSIS OF CRM-A180 & CRM-P180 & THE MULTIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P180

Multivariate Model Covariates	CRM-A180P180 (Cox)		CRM-A180 (Pseudo)		CRM-P180 (Pseudo)	
	HR	(95% CI)	S-HR	(95% CI)	S-HR	(95% CI)
Gender						
Male	0.99	(0.97, 1.01)	0.97	(0.94, 1.01)	1.02	(0.99, 1.05)
Female	Ref	-	Ref	-	Ref	-
Age						
16-34*	2.45	(2.32, 2.58)	0.69	(0.62, 0.78)	2.38	(2.22, 2.56)
35-44*	1.62	(1.54, 1.69)	0.94	(0.87, 1.01)	1.72	(1.63, 1.83)
45-54*	1.31	(1.27, 1.36)	1.20	(1.14, 1.26)	1.22	(1.17, 1.28)
55-64*	1.09	(1.06, 1.12)	1.10	(1.05, 1.14)	1.00	(0.96, 1.04)
65-74*	Ref	-	Ref	-	Ref	-
≥75*	1.19	(1.16, 1.22)	1.00	(0.96, 1.04)	1.23	(1.19, 1.28)
Statin Type						
Simvastatin*	0.99	(0.95, 1.04)	1.02	(0.96, 1.09)	0.95	(0.89, 1.01)
Pravastatin*	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.25	(1.15, 1.35)	1.01	(0.90, 1.13)	1.26	(1.14, 1.39)
Atorvastatin*	0.89	(0.87, 0.92)	0.97	(0.94, 1.01)	0.86	(0.83, 0.89)
Rosuvastatin*	0.94	(0.90, 0.98)	1.02	(0.96, 1.07)	0.88	(0.83, 0.93)
Simva/Ezet*	0.93	(0.80, 1.08)	1.17	(1.03, 1.33)	0.79	(0.67, 0.92)
Prescriber						
GP Prescriber*	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.89	(0.85, 0.92)	0.89	(0.85, 0.95)	0.91	(0.86, 0.95)
Dose						
Low Dose*	1.01	(0.99, 1.03)	1.10	(1.07, 1.14)	0.94	(0.91, 0.97)
Intermediate Dose*	Ref	-	Ref	-	Ref	-
High Dose*	0.98	(0.91, 1.07)	0.85	(0.77, 0.93)	1.14	(1.03, 1.27)
Dose Change						
No Dose Change*	Ref	-	Ref	-	Ref	-
Dose Decrease*	1.11	(1.04, 1.19)	1.76	(1.67, 1.84)	0.55	(0.51, 0.58)
Dose Increase*	1.00	(0.94, 1.06)	1.79	(1.71, 1.88)	0.43	(0.40, 0.45)
Co-morbidities						
IHD*	0.94	(0.91, 0.98)	0.99	(0.95, 1.03)	0.89	(0.86, 0.93)
Diabetes*	0.88	(0.85, 0.90)	1.04	(1.00, 1.08)	0.82	(0.79, 0.86)
Depression*	1.09	(1.06, 1.12)	0.99	(0.95, 1.02)	1.18	(1.14, 1.22)
Depression(Recent)*	0.94	(0.89, 0.98)	0.99	(0.95, 1.04)	0.90	(0.87, 0.94)
Parkinson's Disease*	1.07	(1.00, 1.15)	0.89	(0.81, 0.98)	1.23	(1.13, 1.33)
Alzheimer's Disease*	0.99	(0.92, 1.06)	1.04	(0.95, 1.13)	0.94	(0.86, 1.02)

Multivariate Model Covariates	CRM-A180P180 (Cox)		CRM-A180 (Pseudo)		CRM-P180 (Pseudo)	
	HR	(95% CI)	S-HR	(95% CI)	S-HR	(95% CI)
Prescribing History						
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-
3 - 5	1.08	(1.04, 1.13)	1.25	(1.20, 1.29)	1.50	(1.45, 1.55)
6 - 11	1.32	(1.27, 1.37)	1.34	(1.28, 1.40)	1.88	(1.81, 1.96)
≥ 11	1.80	(1.72, 1.88)	1.56	(1.49, 1.63)	2.71	(2.59, 2.83)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-
1	0.88	(0.85, 0.90)	0.95	(0.92, 0,98)	0.98	(0.94,1.01)
2	0.83	(0.81, 0.86)	0.91	(0.88, 0.95)	0.92	(0.88, 0.96)
≥ 3	0.81	(0.79, 0.84)	0.92	(0.89, 0.96)	0.93	(0.89, 0.97)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-
14-51	0.71	(0.69, 0.73)	1.07	(1.03, 1.12)	0.53	(0.51, 0.55)
52-109	0.50	(0.48, 0.52)	0.81	(0.78, 0.85)	0.29	(0.28, 0.31)
≥ 110	0.38	(0.36, 0.40)	0.60	(0.57, 0.64)	0.23	(0.21, 0.24)

* Time-varying covariates, value taken from the day of each adherence/persistence evaluation. † Time-varying covariates, number in 12 months prior to the day of each adherence/persistence evaluation. ***Cox***, Cox regression model. ***Pseudo***, competing risks pseudo-value generalised estimating equation regression model. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P180***, competing risks time to non-persistence defined by a permissible gap in treatment of 180 days or greater. ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***S-HR***, sub-distribution hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

FIGURE 8.4: WHISKER PLOT OF RESULTS FROM THE MULTIVARIATE COMPETING RISKS ANALYSIS OF CRM-A180 (■) & CRM-P180 (■) & THE MULTIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P180 (■).

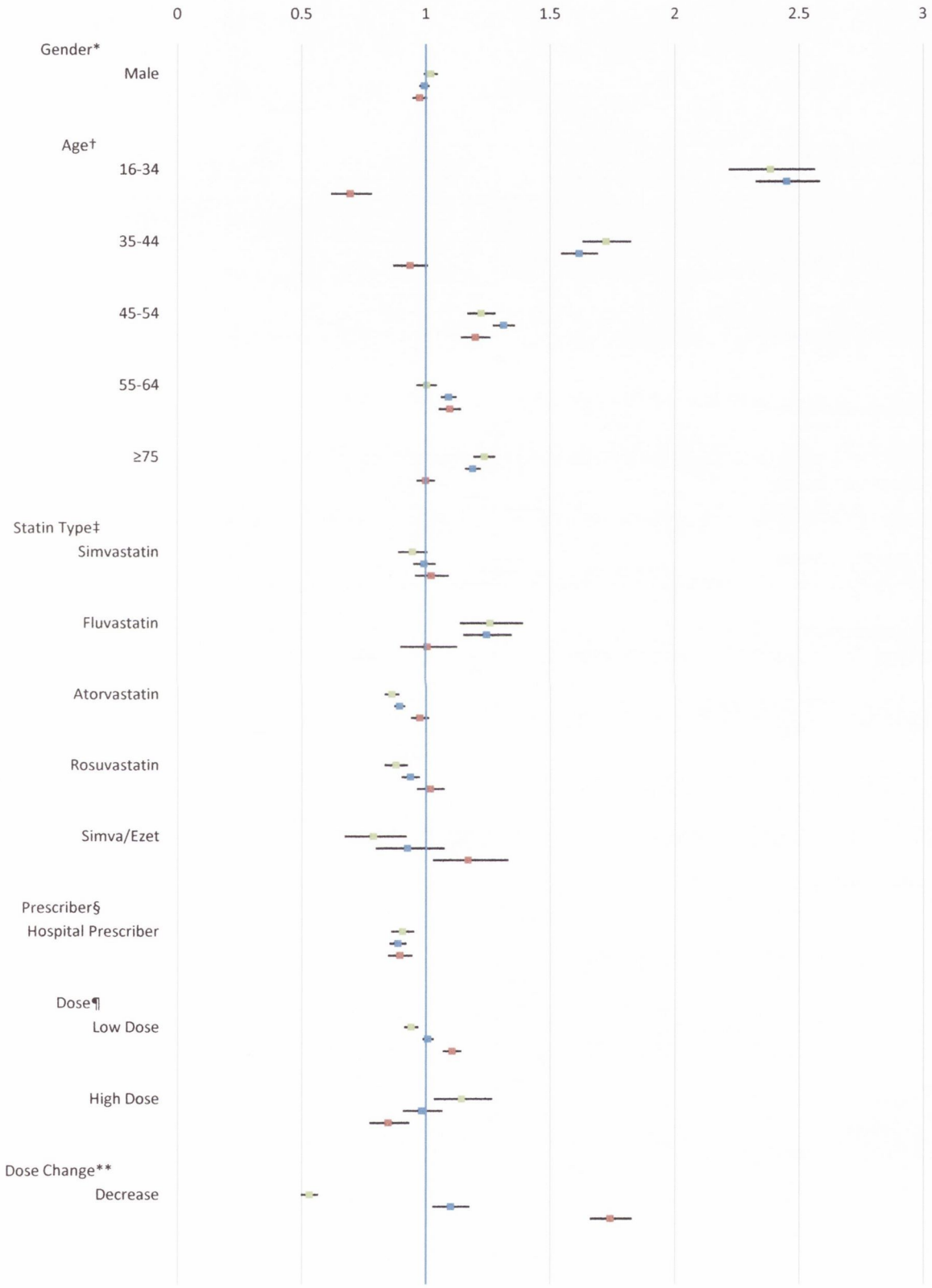
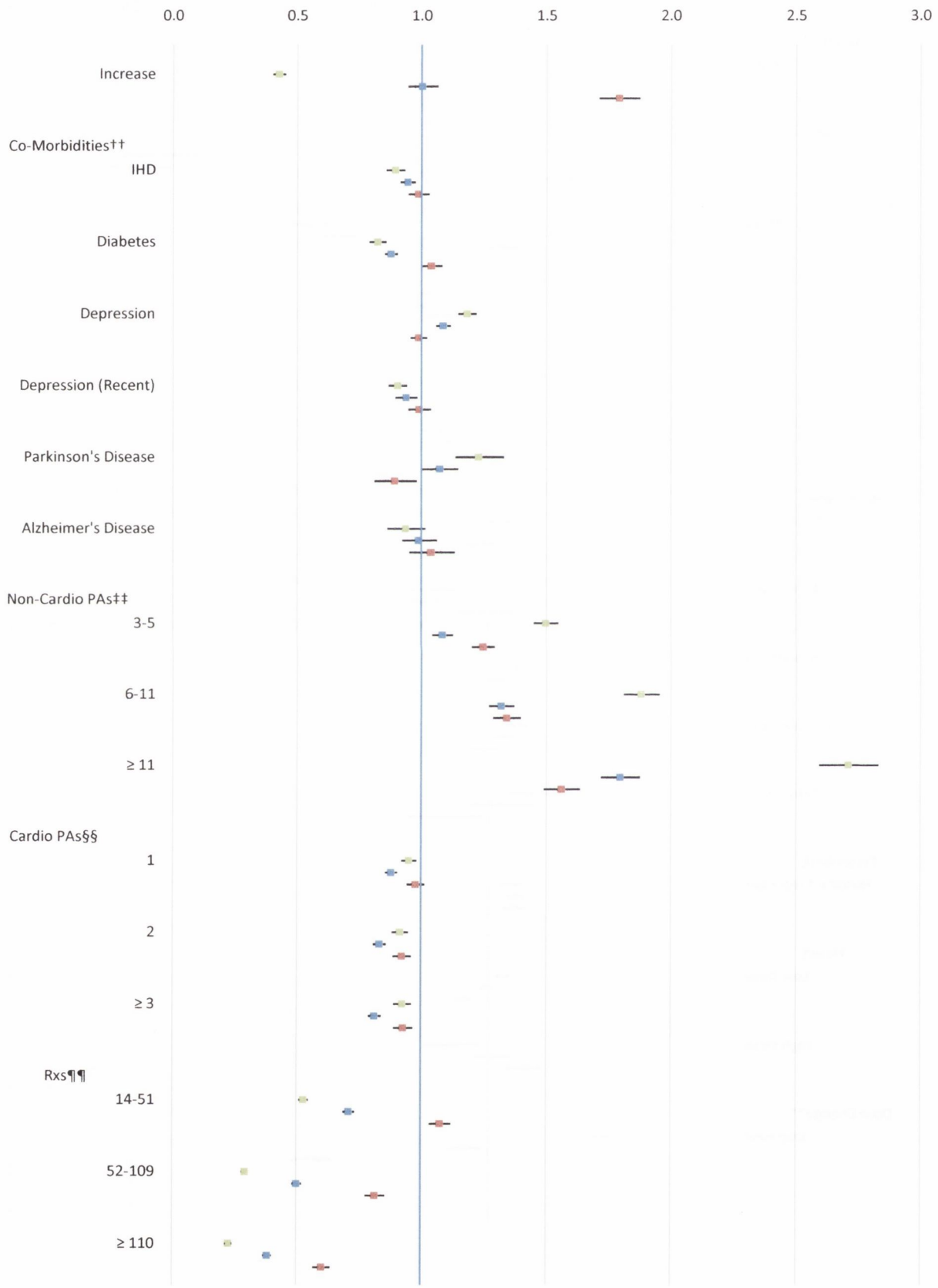


FIGURE 8.4 (CONTINUED): WHISKER PLOT OF RESULTS FROM THE MULTIVARIATE COMPETING RISK ANALYSIS OF CRM-A180 (■) & CRM-P180 (■) & THE MULTIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P180 (■).



= Sub-distribution hazard ratios for CRM-A180 from the GEE pseudo-value competing risk analysis of the CRM-A180P180 model. = Sub-distribution hazard ratios for CRM-P180 from the GEE pseudo-value competing risk analysis of the CRM-A180P180 model. = Hazard ratios for the composite outcome of CRM-A180P180. * Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P180***, competing risks time to a gap in prescription refills of at least 180 consecutive days. ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items.

TABLE 8.6: RESULTS FROM THE MULTIVARIATE COMPETING RISKS ANALYSIS OF CRM-A180 & CRM-P360 & THE MULTIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P360

Multivariate Model Covariates	CRM-A180P360 (Cox)		CRM-A180 (Pseudo)		CRM-P360 (Pseudo)	
	HR	(95% CI)	S-HR	(95% CI)	S-HR	(95% CI)
Gender						
Male	0.99	(0.97, 1.01)	0.98	(0.96, 1.01)	1.01	(0.97, 1.04)
Female	Ref	-	Ref	-	Ref	-
Age						
16-34*	1.99	(1.88, 2.11)	0.80	(0.72, 0.88)	2.26	(2.08, 2.46)
35-44*	1.52	(1.45, 1.60)	0.98	(0.92, 1.04)	1.74	(1.63, 1.86)
45-54*	1.28	(1.23, 1.32)	1.21	(1.16, 1.27)	1.19	(1.13, 1.26)
55-64*	1.08	(1.05, 1.11)	1.11	(1.07, 1.15)	0.97	(0.92, 1.02)
65-74*	Ref	-	Ref	-	Ref	-
≥75*	1.16	(1.13, 1.20)	1.02	(0.99, 1.06)	1.23	(1.17, 1.28)
Statin Type						
Simvastatin*	0.98	(0.94, 1.03)	1.04	(0.98, 1.10)	0.91	(0.84, 0.98)
Pravastatin*	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.26	(1.17, 1.37)	1.03	(0.93, 1.14)	1.30	(1.16, 1.47)
Atorvastatin*	0.90	(0.87, 0.92)	0.97	(0.94, 1.00)	0.86	(0.82, 0.89)
Rosuvastatin*	0.94	(0.90, 0.98)	1.03	(0.98, 1.08)	0.85	(0.80, 0.91)
Simva/Ezet*	0.94	(0.81, 1.10)	1.25	(1.11, 1.40)	0.67	(0.53, 0.83)
Prescriber						
GP Prescriber*	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.87	(0.84, 0.91)	0.89	(0.85, 0.93)	0.86	(0.81, 0.92)
Dose						
Low Dose*	1.02	(1.00, 1.05)	1.12	(1.09, 1.15)	0.92	(0.88, 0.95)
Intermediate Dose*	Ref	-	Ref	-		-
High Dose*	0.95	(0.88, 1.04)	0.85	(0.78, 0.92)	1.17	(1.03, 1.34)
Dose Change						
No Dose Change*	Ref	-	Ref	-	Ref	-
Dose Decrease*	1.08	(1.00, 1.15)	1.76	(1.69, 1.84)	0.34	(0.31, 0.38)
Dose Increase*	0.99	(0.93, 1.06)	1.76	(1.69, 1.83)	0.27	(0.25, 0.30)
Co-morbidities						
IHD*	0.94	(0.91 , 0.98)	0.98	(0.94, 1.02)	0.87	(0.83, 0.92)
Diabetes*	0.87	(0.85, 0.90)	1.03	(0.99, 1.07)	0.76	(0.72, 0.80)
Depression*	1.08	(1.05, 1.11)	1.03	(1.00, 1.06)	1.15	(1.11, 1.19)
Depression(Recent)*	0.93	(0.89, 0.98)	0.97	(0.93, 1.01)	0.91	(0.87, 0.95)
Parkinson's Disease*	1.05	(0.98, 1.13)	0.95	(0.88, 1.04)	1.21	(1.10, 1.33)
Alzheimer's Disease*	0.94	(0.88, 1.01)	1.02	(0.94, 1.10)	0.87	(0.79, 0.97)

Multivariate Model Covariates	CRM-A180P360 (Cox)		CRM-A180 (Pseudo)		CRM-P360 (Pseudo)	
	HR	(95% CI)	S-HR	(95% CI)	S-HR	(95% CI)
Prescribing History						
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-
3 - 5	1.08	(1.04, 1.13)	1.33	(1.29, 1.38)	1.50	(1.44, 1.56)
6 - 11	1.31	(1.26, 1.36)	1.48	(1.43, 1.54)	1.87	(1.78, 1.96)
≥ 11	1.75	(1.67, 1.83)	1.80	(1.73, 1.88)	2.64	(2.50, 2.78)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-
1	0.87	(0.85, 0.90)	1.00	(0.97, 1.04)	0.91	(0.88, 0.95)
2	0.82	(0.80, 0.85)	0.96	(0.92, 0.99)	0.87	(0.83, 0.91)
≥ 3	0.80	(0.77, 0.83)	0.98	(0.94, 1.02)	0.83	(0.79, 0.87)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-
14-51	0.73	(0.71, 0.76)	0.88	(0.85, 0.92)	0.61	(0.58, 0.64)
52-109	0.53	(0.51, 0.55)	0.61	(0.58, 0.64)	0.37	(0.35, 0.39)
≥ 110	0.40	(0.38, 0.42)	0.43	(0.41, 0.46)	0.30	(0.28, 0.33)

***** Time-varying covariates, value taken from the day of each adherence/persistence evaluation. **†** Time-varying covariates, number in 12 months prior to the day of each adherence/persistence evaluation. ***Cox***, Cox regression model. ***Pseudo***, competing risks pseudo-value generalised estimating equations regression model. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P360***, competing risks time to a gap in prescription refills of at least 360 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***S-HR***, sub-distribution hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

FIGURE 8.5: WHISKER PLOT OF RESULTS FROM THE MULTIVARIATE COMPETING RISKS ANALYSIS OF CRM-A180 (■) & CRM-P360 (■) & THE MULTIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P360 (■)

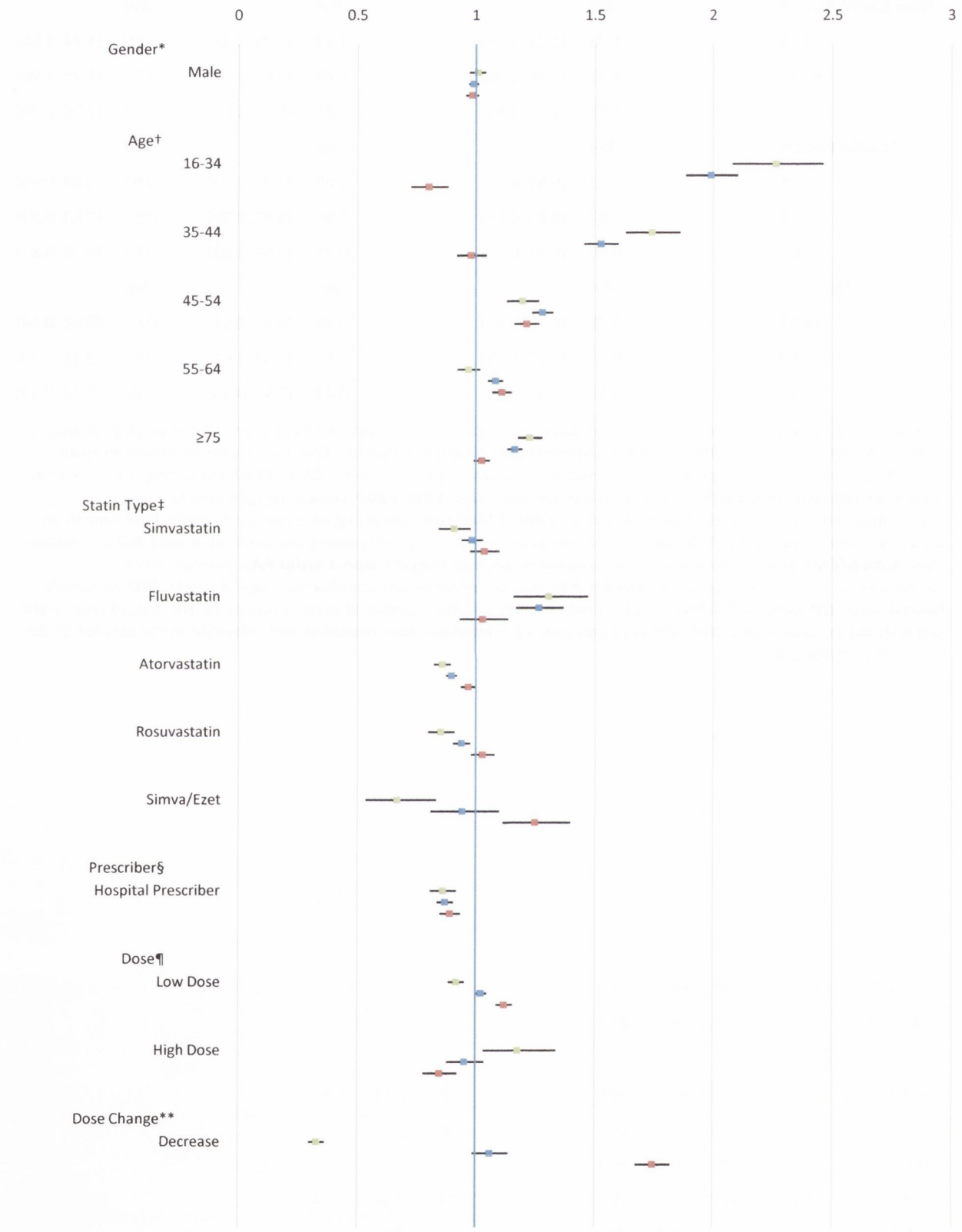
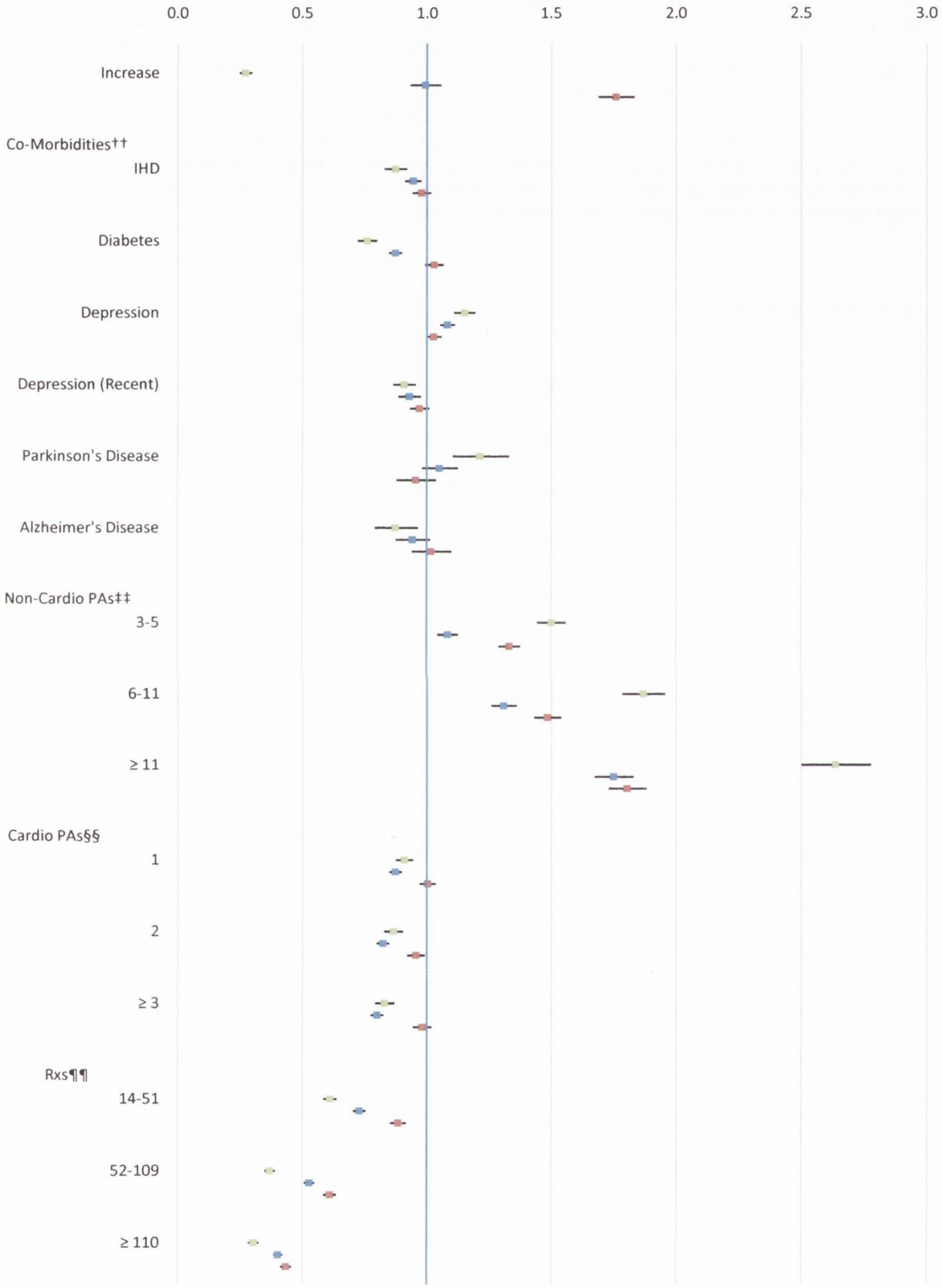


FIGURE 8.4 (CONTINUED): WHISKER PLOT OF RESULTS FROM THE MULTIVARIATE COMPETING RISK ANALYSIS OF CRM-A180 (■) & CRM-P360 (■) & THE MULTIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P360 (■)



= Sub-distribution hazard ratios for CRM-A180 from the GEE pseudo-value competing risk analysis of the CRM-A180P360 model. = Sub-distribution hazard ratios for CRM-P360 from the GEE pseudo-value competing risk analysis of the CRM-A180P360 model. = Hazard ratios for the composite outcome of CRM-A180P360. * Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P360***, competing risks time to a gap in prescription refills of at least 360 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items.

8.4 Discussion

The rationale behind the calculation of adherence rates over the length of a patient's treatment episode and the methodological difficulties this introduces when applied to prescription refill data have been discussed in detail previously (see Section 4.4.3, Section 5.4.3.2 & Section 6.4.3 on pages 75, 113 & 134) but can be summarised briefly as: if non-adherence and non-persistence are considered separate behaviours the measurement of adherence beyond the time that a patient has discontinued treatment underestimates adherence rates and biases estimates of non-adherence risk for covariates that are associated with non-persistence. The calculation and analysis of adherence rates over the length of a patient's treatment episode presents the opportunity to overcome these two limitations by providing a distinction between non-adherent and non-persistent behaviours. The analysis of these adherence rate estimates is however complicated by the inaccurate adherence estimates obtained for patients receiving only a single prescription and the systematic nature of non-persistence which produces variable follow-up times that cannot be considered to vary at random. This precludes the use of standard models for the analysis of data with variable follow-up times such as generalised estimating equation models for repeated adherence measures or survival models for time to non-adherence measures. Methods that can account for the non-random or informative nature of non-persistence are therefore required for the appropriate analysis of adherence models that exclude the time after treatment discontinuation from adherence calculations.

The purpose of this chapter was to demonstrate a method that allowed the estimation of adherence rates over the length of a patient's treatment episode (i.e. up to non-persistence) and the accurate assignment of non-adherence risk to covariates based on these adherence estimates. A competing risks model of non-

adherence and non-persistence was selected for this purpose because it specifically addresses the methodological difficulties introduced by the informative nature of non-persistence. This is achieved by changing the focus of analysis away from making inferences about the chance of non-adherence occurring in patients who are adherent, towards making inferences about the chance of non-adherence occurring in patients who are adherent and persistent. This approach allows the partitioning of the contributions of non-adherence and non-persistence to poor medication-taking behaviour and the correct assignment of risk estimates to individual covariates for both. The results obtained in this competing risks analysis illustrate the large biases introduced to non-adherence probability estimates and covariate risk estimates when the time after treatment discontinuation is not excluded from adherence rate calculations.

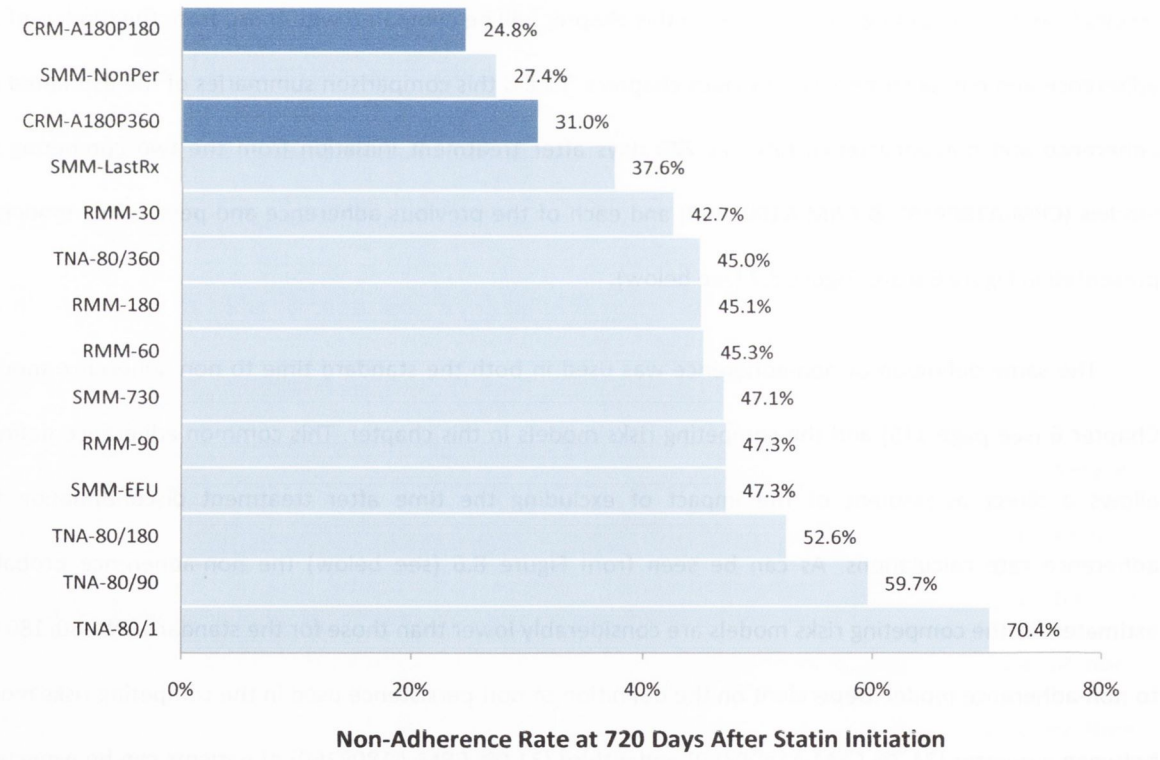
8.4.1 Non-Adherence & Non-Persistence Competing Risks – Cumulative Incidences

No previous studies utilizing a competing risks model for the analysis of adherence and persistence with prescription refill data were identified from the literature. For the purposes of this discussion, therefore, the results from the competing risks analyses in this chapter will be compared with those from the models of non-adherence and non-persistence in previous chapters. To aid this comparison summaries of the estimated non-adherence and non-persistence rates at 720 days after treatment initiation from the two competing risks models (CRM-A180P180 & CRM-A180P360) and each of the previous adherence and persistence models are presented in Figure 8.6 and Figure 8.7 (see below).

The same definition of non-adherence was used in both the standard time to non-adherence model in Chapter 6 (see page 115) and the competing risks models in this chapter. This common adherence definition allows a direct assessment of the impact of excluding the time after treatment discontinuation from adherence rate calculations. As can be seen from Figure 8.6 (see below) the non-adherence probability estimates for the competing risks models are considerably lower than those for the standard TNA-80/180 time to non-adherence model. Dependent on the definition of non-persistence used in the competing risks models, between a quarter (24.7% CRM-A180P180) and a third (31.0% CRM-A180P360) of patients can be expected to have a non-adherent episode in the two years following treatment initiation. Using the same definition of adherence this estimate of non-adherence probability rises to more than half (52.6% TNA-80/180) when adherence rates calculated after treatment discontinuation are not excluded.

A comparison of the adherence results from the competing risks models with those from the other adherence models shows a similar pattern; with the rate of non-adherence considerably lower in the competing risks models (see Figure 8.6 below). The only standard models with similar non-adherence rate results to those obtained in the competing risks analyses are the single measure models; SMM-LastRx (37.6%) and SMM-NonPer (27.4%). This is because both of these models exclude all or at least some proportion of the time after treatment discontinuation from adherence calculations. These two single measure models do however have limitations that discourage their use in the modelling and analysis of adherence behaviour; namely their inability to account for variable follow-up times and the inaccurate adherence estimate produced by early non-persistence (see Section 4.4.5 on page 78).

FIGURE 8.6: SUMMARY OF ESTIMATED NON-ADHERENCE RATES AT 720 DAYS AFTER TREATMENT INITIATION FOR THE COMPETING RISKS MODELS (CRM-A180P180 & CRM-A180P360), THE SINGLE MEASURE MODELS (SMM), THE REPEATED MEASURE MODELS (RMM) AND THE TIME TO NON-ADHERENCE MODELS (TNA)



■ = Competing risks adherence model. ■ = Non-competing risks adherence model. ***Single Measure Model***, see Chapter 4 on page 55. ***Repeated Measure Model***, see Chapter 5 on page 83. ***Time to Non-Adherence Model***, see Chapter 6 on page 115. ***SMM-720***, proportion of days covered at 720 days follow-up. ***SMM-EFU***, proportion of days covered at 720 days follow-up or end of follow-up. ***SMM-LastRx***, proportion of days covered at 720 days follow-up or last statin prescription. ***SMM-NonPer***, proportion of days covered at 720 days follow-up or non-persistence. ***RMM-30***, proportion of days covered in consecutive 30 day adherence calculation intervals. ***RMM-60***, proportion of days covered in

consecutive 60 day adherence calculation intervals. ***RMM-90***, proportion of days covered in consecutive 90 day adherence calculation intervals. ***RMM-180***, proportion of days covered in consecutive 180 day adherence calculation intervals. ***TNA-80/1***, time to an adherence rate of less than 80% for at least 1 day. ***TNA-80/90***, time to an adherence rate of less than 80% for at least 90 days. ***TNA-80/180***, time to an adherence rate of less than 80% for at least 180 days. ***TNA-80/360***, time to an adherence rate of less than 80% for at least 360 days. ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days.

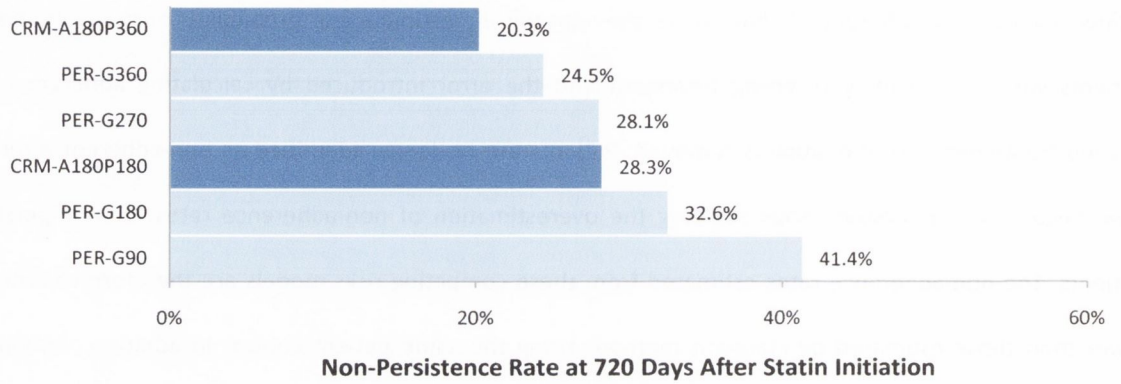
The estimates of non-adherence obtained in the competing risks models can be considered a more refined measure of adherence behaviour as they specifically estimate the probability of non-adherence in patients who are currently receiving treatment and the error introduced by calculating adherence rates beyond treatment discontinuation is removed. Patients are no longer identified as non-adherent after they have become non-persistent, thus avoiding the overestimation of non-adherence rates for non-persistent patients. The non-adherence rates estimated from these competing risks models are therefore considerably lower than those estimated by standard methods using the same patient cohort. In addition, without the ambiguity introduced by non-persistence, these adherence rate estimates will allow more appropriate comparisons of non-adherence probabilities between treatments or covariates that have different baseline non-persistence rates (see Section 8.4.3 below).

The same definitions of non-persistence were used in both the standard time to non-persistence model in Chapter 7 (see page 139) and the competing risks models in this chapter. These common persistence definitions allow a direct assessment of the impact of including time to non-adherence as a competing risk in time to non-persistence models. The summary of non-persistence estimates in Figure 8.7 (see below) shows that the cumulative incidence results from the competing risks model of non-persistence do not differ greatly from the estimates for standard models of time to non-persistence. In models using the same definition of non-persistence there is approximately a 4% reduction in the probability of non-persistence for the competing risks models in comparison to the standard models. The discrepancy between the two can be accounted for by patients who become non-adherent prior to discontinuing treatment in the competing risks model.

While it is still possible and not incorrect to continue modelling non-persistence using the standard time to non-persistence model demonstrated in Chapter 7 (see page 139), the competing risks model of non-persistence provides a different perspective on the analysis of persistence behaviour by allowing the assessment of non-persistence risk specifically in patients who are adherent to treatment. Non-persistence

models with similar intent to this but different methodology have been published.[23] In these models, non-adherence was incorporated into time to non-persistence models by including it as a time dependent covariate, giving what can be considered a bi-directional non-adherence/non-persistence multi-state model.[103]

FIGURE 8.7: SUMMARY OF ESTIMATED NON-PERSISTENCE RATES AT 720 DAYS AFTER TREATMENT INITIATION FOR THE COMPETING RISKS MODELS (CRM-A180P180 & CRM-A180P360) AND THE TIME TO NON-PERSISTENCE MODELS (PER-G)



■ = Competing risks persistence model. ■ = Non-competing risks persistence model. ***Time to Non-Persistence Model***, see Chapter 7 on page 139. ***PER-G90***, time to a gap in prescription refills of at least 90 days. ***PER-G180***, time to a gap in prescription refills of at least 180 days. ***PER-G270***, time to a gap in prescription refills of at least 270 days. ***PER-G360***, time to a gap in prescription refills of at least 360 days. ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days.

The cumulative incidence estimates obtained for the composite outcome of poor medication-taking behaviour represent the sum of the cumulative incidences for the individual competing risks; non-adherence and non-persistence. These composite estimates provide a comprehensive representation of poor medication-taking behaviour that is difficult to obtain using results from standard models. Combining the non-adherence and non-persistence estimates from standard models of adherence and persistence is impractical because neither estimate represents an exclusive measure of a single behaviour. Therefore, combinations of standard estimates for the two behaviours result in an over-estimation of the composite outcome rate. For example; the composite outcome rate at 720 days for the non-adherence definition TNA-80/180 and the non-persistence definition PER-G180 is 85.2% in the standard time to event models (52.6% TNA-80/180 + 32.6% PER-G180, see Table 6.3 on page 122 & Table 7.2 on page 145). This is considerably higher than the composite

rate of 53.0% obtained in the competing risks time to event model (24.7% CRM-A180 + 28.3% CRM-P180, see Table 8.3 above).

8.4.2 Comparison with Results from Electronic Medication Event Monitor Studies

The inclusion of the time after treatment discontinuation in the calculation of adherence rates from prescription refill records produces adherence rate estimates that are consistently lower than those obtained from studies using electronic medication event monitors.[23] This discrepancy has traditionally been attributed to the presence of a Hawthorne effect[26] i.e. the possibility that the act of observing a patient with electronic monitors produces a short term improvement their medication taking behaviour. While this may be a factor, a consideration of the differences between the adherence outcomes measured by the two techniques is also required. In contrast to prescription refill studies of adherence, studies of adherence using electronic medication event monitors generally report adherence results exclusive of the effect of non-persistence. The fact that one method measures non-adherence exclusively and the other a composite of non-adherence and non-persistence may explain more of the observed difference between the results obtained from the two methods than the potential for a Hawthorne effect.

The exclusion of the time after non-persistence from adherence calculations in the competing risks model should produce adherence estimates that are more comparable to those obtained from studies using electronic medication event monitors. Four studies of statin adherence using electronic medication event monitors were identified from the literature.[104-108] Synopses of their methodologies and results are presented in Table 8.7 (see below). The results from three of these studies are not suitable for comparison with the competing risk adherence results. The study by Kruse et al[106] only measured adherence over a four week period; a length of time that is too short to provide meaningful adherence estimations with prescription refill data. The study by Stilley et al[108] did not exclude the time after treatment discontinuation from estimates of adherence. The study by Schwed et al[107] reported only a mean adherence rate for the study cohort, no estimation of the number of non-adherent patients was provided.

The remaining study by Cheng et al[104, 105] assessed statin adherence behaviour over six months in 83 established users of statin therapy. The rate of non-adherence, defined as an adherence rate of < 80%, was 15.7% at six months in this cohort of patients. The non-adherence rate estimates obtained in the competing

risks model at six months are higher than this (18.3% CRM-A180P180, 23.1 % CRM-A180P360, see Table 8.3 & Table 8.4 above), although the difference is considerably less than observed with models of adherence that do not account for non-persistence. A number of factors may have contributed to the variation. First, the cohort of patients in the study by Cheng et al[104, 105] was a selected population who had agreed to partake in the study and were pre-existing users of statins, both of these factors may have predisposed the participants to better adherence behaviour than the cohort selected from the GMS database. Second, although both sets of results estimate the rate of non-adherence, there are significant differences in the way in which non-adherence is defined. While the standard 80% adherence rate cut-off for statin non-adherence, used in the study by Cheng et al,[104, 105] has been validated with reference to clinical outcomes (see Section 3.2 on page 46), there is currently no objective evidence linking the non-adherent events identified in time to non-adherence models with clinical outcomes. A true assessment of the comparability of the two methodologies will require their application to the same set of medication histories.

TABLE 8.7: SYNOPSES OF STATIN ADHERENCE STUDIES USING ELECTRONIC MEDICATION EVENT MONITORS

Study	Length	Population	N	Adh <80%	Mean
Kruse[106] 1993	4 weeks or until treatment discontinuation	Males & females, any age, familial hyperlipidaemia, initial & established users	24	-	88.7% @ 4 weeks
Schwed[107] 1999	6 months or until treatment discontinuation	Male outpatients, 20 - 70 years old, primary type 2 hyperlipidaemia, initial & established users	40	-	82.4% @ 6 months
Cheng[104, 105] 2004	6 months or until treatment discontinuation	Males & females, any age, established users (less than 1 year)	83	15.7% @ 6 months	-
Stilley[108] 2004	6 months **Note** – Adherence rate estimated over 6 months for all patients	Males & females, 24 – 60 years old, primary hyperlipidaemia, initial users	153	50.0% @ 6 months*	-

* Adherence measured over 6 months for all patients, the time after treatment discontinuation was not excluded from the adherence estimate. ***Length***, length of study. ***Population***, Characteristics of study cohort. ***N***, number of patients in the study. ***Adh < 80%***, proportion of the study population with an adherence rate, defined as number of doses taken on correct day, of less than 80%, if reported. ***Mean***, the mean adherence rate for the study population, if reported.

8.4.3 Non-Adherence & Non-Persistence Competing Risks – Regression Analyses

The use of common non-adherence and non-persistence definitions allows a direct comparison of the covariate risk estimates obtained in the competing risks regression models (CRM-A180P180 & CRM-A180P360, see Table 8.5 & Table 8.6 above) and the standard time to event regression models (TNA-80/180 see Table 6.6 on page 127 & PER-G180, PER-G360 see Table 7.6 on page 152). The results from these regression models are compared in Sections 8.4.3.1, 8.4.3.2 and 8.4.3.3 below, with specific reference to differences in covariate risk estimates and the methodological implications of these. To aid this comparison, whisker plots of the aggregated results from these analyses are presented in Appendix 4 (see Figure A4.1 on page 233 & Figure A4.2 on page 230).

8.4.3.1 Demographic Covariates

In both of the competing risks models the covariate risk estimates obtained for males (reference females) do not differ greatly from those obtained in standard models using corresponding event definitions. There was however a striking change in the estimates for non-adherence risk associated with age. In the standard TNA-80/180 time to non-adherence model the highest risk of non-adherence was associated with the 16-34 year age category and non-adherence risk decreased with age up to the 65-74 year age category, increasing thereafter. This risk profile is considerably altered in both of the competing risks time to non-adherence models, where the lowest risk of non-adherence is associated with the 16-34 year age category and non adherence risk increases with age up to the 45-54 year age category, decreasing thereafter. The most notable change in non-adherence risk occurred for patients between the ages of 16 and 44 years (reference 65-74 years). Non-adherence risk was considerably lower for these patients in the competing risks models, resulting in a reversal of the direction of non-adherence risk. Non-adherence risk was also decreased, but to a lesser extent, in the 45-54 year and ≥ 75 year age categories.

There was no change in the pattern of non-persistence risk or the direction of effect for any of the age categories in either of the competing risks models although there was a reduction in non-persistence risk estimates across each of the age categories. The highest risk of non-persistence remained associated with the 16-34 year age category in both of the competing risks models. This risk decreased in magnitude with age, up to the 65-74 year age category and increased thereafter.

8.4.3.2 Treatment Covariates

Unlike the results from the standard TNA-80/180 regression analysis, where the use of certain statins was associated with an increased or a decreased risk of non-adherence, there was no difference in non-adherence risk between the five individual statins included in the competing risks time to non-adherence models (simvastatin, fluvastatin, atorvastatin, rosuvastatin; reference pravastatin). This was with the exception of the ezetimibe/simvastatin combination product (Inegy®), for which there was an increase in the risk of non-adherence and a reduced risk of non-persistence. Otherwise, there was minimal change in the non-persistence risk for the individual statins in the competing risks model; with patients prescribed fluvastatin continuing to have an increased risk of non-persistence and patients prescribed atorvastatin or rosuvastatin having a reduced risk of non-persistence. With respect to non-adherence risk, these results provide little evidence to support the choice of one statin type over the other. Patients prescribed atorvastatin, rosuvastatin or the simvastatin ezetimibe combination were, however, less likely to be identified as non-persistent.

8.4.3.3 Co-Morbidity & Prescribing History Covariates

In comparison to the standard TNA-80/180 model of non-adherence, where the presence of certain co-morbidities was associated with an increased or decreased risk of non-adherence, the presence of an identified co-morbidity in the competing risks models did not alter the risk of non-adherence. With the exception of a slightly lower non-adherence risk for Parkinson's disease in the CRM-A180P180 model. Patients receiving treatments for ischaemic heart disease, diabetes, depression, recent depression or Alzheimer's disease were no more or less likely to be non-adherent than those who had not received treatment for these conditions. In contrast to this, the altered risk of non-persistence associated with co-morbidity in the standard models did remain in the competing risks models with a reduced risk of non-persistence for ischaemic heart disease, diabetes, recent depression and an increased risk of non-persistence for depression and Parkinson's disease.

8.4.3.4 Interpretation of Competing Risks Regression Analysis Results

Much of the change that is observed in non-adherence risk estimates for covariates in the competing risks models can be attributed primarily to the exclusion of the time after treatment discontinuation from adherence calculations. As discussed in Section 8.4.1 (see above) the exclusion of the time after treatment

discontinuation results in a lower cumulative incidence of non-adherence. This change in non-adherence risk is, however, not uniform across all patients in the study cohort; but occurs specifically in those patients who are identified as non-persistent. There is, therefore, a greater change in non-adherence risk for covariates associated with a high risk of non-persistence.

The results from the competing risks regression analyses of non-adherence and non-persistence represent the risk of an event in patients who are both adherent and persistent with treatment. The regression results for non-adherence must consequently be interpreted in the light of the covariate estimates for non-persistence and vice versa. For example, while the risk of non-persistence is very high in younger patients (16-34 years), patients in this age category who persist with treatment have the lowest risk of non-adherence. In addition it must be remembered that the competing risks model makes no assumptions about the relationship, i.e. independence, between the competing risks (the assumption that the two behaviours are not independent is the rationale for use of the competing risks model). The impact of these unknown and inestimable interactions on the interpretation of non-adherence and non-persistence regression analysis results is therefore unclear. For this reason it is incorrect to assume that, upon the removal of one cause of failure the risk of failure from the other cause will remain unchanged. For example; a successful intervention to improve treatment persistence may also result in a change in adherence risk, as those additional patients who now persist with treatment as a result of the intervention may have a higher or lower non-adherence risk than patients who would have persisted with treatment without the intervention.

8.4.4 Considerations for the Selection of a Permissible Gap Length

The criteria for selecting a permissible gap length to define non-persistence are discussed in detail in section 7.4.3 (see page 160). In this it is suggested that the length of permissible gap should reflect the minimum period of medication disuse that distinguishes non-persistent behaviour from non-adherent behaviour. This is of particular relevance in the competing risks model of non-adherence and non-persistence, as it is the length of permissible gap that simultaneously defines the minimum gap in prescription refills that is considered non-persistence and the maximum gap in prescription refills that is considered non-adherence. For example; as the length of permissible gap is increased, the maximum length of gap in prescription refills that can be included in adherence calculations also increases. Adherence rate estimates for patients previously

identified as non-persistent will therefore be reduced and many of these patients will be reclassified as non-adherent as a result.

The permissible gap length also defines the minimum adherence rate that can be measured. For example; consider a patient who receives prescriptions for 30 days' of treatment. If a permissible gap of 90 days is used to define non-persistence the maximum gap that this patient can have between successive 30 day prescriptions, without being classified as non-persistent, is $30 + 89$ days. The minimum adherence rate that is measureable for this patient is therefore $30/(30 + 89) = 25.2\%$.[i] To record an adherence rate lower than this, the patient would need to have a gap in treatment of 90 days or greater and would therefore be classified as non-persistent instead. It may therefore be wise to use a permissible gap of sufficient length to accommodate the identification of the broadest range of adherence rates. The minimum measureable adherence rates for permissible gaps of 180 and 360 days, assuming a prescription length of 30 days, are 14.4% and 7.7% respectively.

In both of the competing risks models, increasing the permissible gap length from 180 days to 360 days results in a decrease in the estimated cumulative incidence of non-persistence and a corresponding increase in the estimated cumulative incidence of non-adherence. Despite this variation, there is little change in the risk estimates obtained for covariates in the pseudo-value GEE regression analyses. This indicates that the competing risks regression models of medication-taking behaviour are reasonably robust to variations in persistence definition. It is difficult to establish whether or not the stability observed in these results will be maintained for permissible gap lengths above or below the 180 day and 360 day lengths used in this study. It may therefore be reasonable to conduct sensitivity analyses to confirm the robustness of covariate risk estimates to variations in the permissible gap length.

8.4.5 Competing Risk Adherence Estimates in Patients with Early Non-Persistence

The inability of prescription refill data to provide accurate adherence estimates in patients who become non-persistent after receiving no more than a single prescription or very few prescriptions has the potential to significantly bias results from models based upon these estimations (see Section 4.4.3 on page 75). The use of

[i] The number of days' supply divided by the number of days' supply plus the permissible gap length less one

competing risks methodology allows these inaccurate adherence estimates to be disregarded in patients who discontinue treatment at an early stage. This is because patients who discontinue therapy soon after initiation do not persist with treatment for long enough to allow them to fulfil the criteria for a non-adherent event[i]. These patients are therefore classified as having a non-persistent event and the occurrence of early non-persistence can be thought of as masking or preventing the identification of a patient's true adherence behaviour. The inability to accurately measure a patient's adherence rate due to early non-persistence can be regarded as exactly the same process whereby the occurrence of non-persistence at any time in the competing risks model prevents the subsequent identification of a non-adherent event. In both instances non-persistence acts as a competing risk preventing the identification of non-adherence; their influence on the evaluation and interpretation of non-adherence risk estimates in the competing risks model can therefore be considered equivalent.

8.4.6 Advantages of Competing Risk Models of Adherence & Persistence

The most important advantage of the competing risks methodology presented in this chapter is its ability to appropriately account for treatment discontinuation in models of non-adherence risk. This has a number of distinct benefits for the analysis of both adherence and persistence behaviour. The competing risks model appropriately handles the difficulties introduced to adherence models by the exclusion of the terminal gap from adherence calculations. namely; the inability of prescription refill data to provide accurate estimates of adherence in patients with very short treatment episodes (see Section 8.4.5 above) and the non-random, variable nature of the follow-up times produced by non-persistence (see Section 8.1.2 above). By facilitating the analysis of adherence rates estimated over the length of a patient's treatment episode, the competing risks model avoids both the underestimation of adherence rates for patients who discontinue treatment and the subsequent biasing of non-adherence risk for covariates that are associated with an increased risk of non-persistence. The adherence rate estimates that are obtained from this model reflect adherence behaviour over the time that a patient can reasonably be expected to be taking treatment. In comparison to the adherence estimates obtained from the single measure, repeated measure or time to non-adherence models, this is a

[i] For a patient to be identified as having a non-adherent event non-persistence cannot occur before the end of the non-adherent episode (see Section 8.2.1, Identification of Time to Non-Adherence).

more refined estimate of adherence that acknowledges the difference between non-adherent and non-persistent behaviours.

The modelling of non-adherence and non-persistence as competing risks allows the partitioning of their contributions to poor medication-taking behaviour so that cumulative incidence estimates exclusive to a single outcome can be obtained. These individual risk estimates permit a better assessment of the type of behaviour that is likely to contribute to poor medication-taking behaviour. Most importantly however the competing risks model allows the appropriate comparison of adherence rate estimates between cohorts, treatments types or covariates with different underlying persistence behaviours and vice versa. The separate assignment of non-adherence and non-persistence risk to individual covariates allows a distinction to be made between the risk factors that predict non-adherence and the risk factors that predict non-persistence.

8.4.7 Limitations of Competing Risk Models of Adherence & Persistence

In addition to the standard limitations that apply to the use of prescription refill data for the analysis of medication-taking behaviour (see Section 1.3.4 on page 37) there are a number of limitations specific to the competing risks model of non-adherence and non-persistence. As discussed in Chapters 6 and 7 (see Section 6.4.3 and Section 7.4.3 on pages 134 & 160), the lack of objective evidence to support the choice of an appropriate definition for a non-adherent event or a non-persistent event limits the interpretability of the results. This is of particular relevance in the competing risks model, as variations in the definition of one event have the potential to affect the results obtained for both events. The interpretation of results from the competing risks model is further complicated by the fact that no assumptions about the relationship between non-adherence and non-persistence are made (see Section 8.4.3.4 above). Cumulative incidence and covariate risk estimates for one event must therefore be interpreted with reference to results for the competing event and it is not possible to ascertain what effect the removal of one cause of failure will have on the competing cause of failure.

8.5 Summary

Statin adherence and persistence were measured in a cohort of GMS patients using prescription refill data from the HSE-PCRS pharmacy claims database. Non-adherent events were defined in two dimensions; the level of non-adherence (PDC < 80%) and the length of non-adherent episode (180 days). Non-persistent events

were defined using a permissible gap of either 180 days or 360 days. The results from these measures were used to construct models of non-adherence and non-persistence as competing risks for the composite outcome of poor medication-taking behaviour. In these competing risks models patients were simultaneously at risk for both non-adherence and non-persistence and the occurrence of either event fulfilled the definition for the composite outcome of poor medication-taking behaviour, while respectively precluding or making irrelevant the subsequent occurrence of the competing event. Additive cumulative incidence functions for competing risks were used to estimate the probability of experiencing a non-adherent or a non-persistent event and risk estimates for individual covariates were obtained using the pseudo-value approach proposed by Andersen, Klein and Rosthøj[92, 95] for regression on cumulative incidence functions. The composite endpoint of poor medication-taking behaviour (non-adherence or non-persistence) was also modelled using a Kaplan-Meier estimator to calculate the cumulative event incidence and a Cox regression model to estimate the risk of poor medication-taking behaviour for individual covariates.

The results from these competing risks models show cumulative incidence estimates for non-adherence that are considerably lower than those obtained from models that do not exclude the time after treatment discontinuation from analyses. In the 720 days after treatment initiation the probability of a patient experiencing a non-adherent event was 24.7% in the competing risks model (CRM-A180P180) as compared to 52.6% in the standard time to non-adherence model (TNA-80/180). This difference illustrates the substantial overestimation of non-adherence rates that occurs in standard models of non-adherence. The cumulative incidence estimates for non-persistence from the competing risks models are marginally lower than those obtained in the standard model of non-persistence. In the 720 days after treatment initiation the probability of a patient experiencing a non-adherent event was 28.3% in the competing risks model (CRM-A180P180) as compared to 32.6% in the standard time to non-persistence model (PER-G180). The difference between the two estimates represents patients who have become non-adherent prior to discontinuing treatment in the competing risks model.

The event probabilities for the individual competing risks did vary with the length of permissible gap used in the competing risks model (CRM-P180 or CRM-P360), there was however little change in the cumulative incidence for the composite outcome of non-adherence or non-persistence (53.0% versus 51.3% at 720 days) or in the risk estimates obtained for individual covariates in regression analyses. The ability to differentiate

between non-adherent and non-persistent behaviours in the competing risks regression analyses produces risk estimate for covariate that are, in some cases, markedly different to those obtained from standard models of non-adherence and non-persistence. This is illustrated by the results obtained for age covariates in the competing risks model, where the pattern of non-adherence risk is appreciably different to that obtained in the standard time to non-adherence model.

By allowing the separation of non-persistent behaviour from estimates of non-adherence, competing risk models avoid the underestimation of adherence rates for patients who discontinue treatment and the subsequent biasing of non-adherence risk for covariates that are associated with an increased risk of non-persistence. This approach provides a representation of medication-taking behaviours that is not attainable with standard models of non-adherence and non-persistence. The advantages of the competing risks methodology include the ability to obtain estimates of non-adherence and non-persistence incidence that are exclusive to the specific outcome. Most importantly however, the competing risks model allows the appropriate comparison of non-adherence estimates between cohorts, treatments types or covariates with different underlying persistence behaviours and vice versa.

8.6 Conclusion

The ability of the competing risks models to appropriately account for non-persistence in models of non-adherence risk avoids both the underestimation of adherence rates for patients who discontinue treatment and the subsequent biasing of non-adherence risk for covariates that are associated with an increased risk of non-persistence. This makes it possible to differentiate between the behaviours that contribute to poor medication taking and the risk factors that predict non-adherence and non-persistence.

The competing risks model of non-adherence and non-persistence can therefore be considered a more appropriate method for the analysis of medication-taking behaviour than the standard models of adherence presented in previous chapters. The implications of the competing risk results for clinical outcomes with statin therapy and the design and targeting of interventions to address non-adherence and non-persistence are discussed in Chapter 9 (see Page 205)

CHAPTER NINE

9 COMPETING RISKS MODEL – IMPLICATIONS OF RESULTS

9.1 CLINICAL IMPLICATIONS – ADHERENCE & PERSISTENCE IN THE GMS POPULATION

Prescription refill studies that do not measure adherence exclusive of treatment discontinuation have consistently reported high rates of non-adherence with statin therapy (see Table 4.5 & Table 5.8 on pages 73 & 105). The fact that these adherence estimates represent composites of adherence and persistence has rarely been acknowledged and this has led to confusion in their interpretation. It is a widely held belief that the quality of treatment execution by patients prescribed statin therapy is extremely poor.[26, 109] The results from the competing risk analysis of medication taking behaviours indicate that non-adherence to statin therapy is not as prevalent as suggested by these previous studies; with less than a quarter of patients in the GMS cohort experiencing a significant non-adherent episode within the first two years of treatment (dependant on the definition of non-persistence used, see Table 8.3 on page 176). Nevertheless, while these rates of non-adherence are lower than previously estimated, taken in conjunction with estimates of non-persistence there remains a greater than 50% probability that a patient will experience either a non-adherent or a non-persistent event within the first two years of initiating treatment. Conversely these results can be interpreted as a less than a 50% probability that a patient will be both adherent and persistent with statin therapy in the first two years of treatment.

In the absence of evidence to the contrary it can be assumed that there is a difference between statin non-adherence and statin non-persistence with respect to their individual influence on cardiovascular morbidity and mortality. The impact of these two medication taking behaviours on clinical outcomes should therefore be considered separately. A number of *"on-treatment"*[5] studies have assessed the correlation between statin medication taking behaviours and clinical outcomes.[2-5, 8, 15, 16, 110]

In four of these on-treatment studies, adherence rates were calculated from study enrolment up to either the end of follow-up or the occurrence of an event of interest.[2, 3, 15, 16] In the remaining two studies adherence was assessed over the length of time that patients were receiving treatment.[4, 5] All of these on-

treatment studies demonstrated superior outcomes in patients who are adherent to treatment. Unfortunately, it is difficult to adapt these results to provide accurate estimates for the effect of non-adherence in the competing risks model because of the significant differences in the adherence measures used. A number of the on-treatment studies calculate adherence rates inclusive of the time after treatment discontinuation and all of the studies use a single measure of adherence at a defined point as opposed to the non-adherent event definition used in the competing risks model. Nevertheless, the ability to exclude short non-adherent episodes from time to non-adherence event definitions increases the specificity of the measure and may increase the likelihood that the non-adherence identified in these models will be of clinical significance. Future work in this area may include the use of more specific measures of non-adherent behaviour in on-treatment analyses.

In a recent study by Daskalopoulou et al[8] the effect of non-persistence with statin therapy post myocardial infarction (MI) was assessed. Patients who discontinued statin therapy for at least the 90 day period after experiencing an MI had a significantly increased risk of all cause mortality in the 90 to 365 day period post MI. In a similar study by Colivicchi et al[110] the effect of non-persistence with statin therapy post ischaemic stroke was assessed. Patients who discontinued statin therapy in the 365 days after experiencing an ischaemic stroke had a significantly increased risk of all cause mortality during that time. Based upon these studies it is reasonable to expect that the rates of statin non-persistence observed in the GMS cohort will have a detrimental impact on treatment outcomes; in particular the high rates of early non-persistence which can be considered equivalent to patients receiving no treatment at all.

The ability of a treatment to maintain therapeutic drug action in the face of occasional, variably long lapses in dosing has been termed *"forgiveness"*.[111, 112] The forgiveness of a specific treatment has been defined as the threshold of adherence above which the marginal benefits of additional adherence are negligible;[113] or more specifically as the post-dose duration of effective action minus the recommended dosing interval.[111, 112] With respect to statins forgiveness refers to the ability of certain statins, with longer half lives, to maintain efficacy with alternate day, twice weekly or even once weekly dosing.[114-118] The capacity of prescription refill records to assess adherence with reference to the forgiveness of a specific treatment is limited. This is because prescription refill records do not provide the necessary analytical detail to allow the accurate identification of these types of behaviour; a gap in prescription refilling does not necessarily correspond to a gap of the same length in medication taking.

9.2 Implications for Interventions to Improve Adherence & Persistence

The ability to distinguish between those who do not take their treatment correctly and those who do not take it at all, in conjunction with an understanding of the risk factors for each behaviour, provides important information for the targeting and tailoring of effective interventions to tackle poor medication taking behaviours. There is evidence to suggest that interventions to improve medication taking behaviours can have a differential effect on adherence and persistence outcomes.[30] Patients who are non-persistent may require interventions aimed at influencing their perceptions about the risks and benefits of treatment[119]— to re-motivate and reinforce the need for treatment. Whereas, patients who are non-adherent have at least acknowledged the need for treatment, and may instead require interventions aimed at facilitating the integration of their dosing into their daily routine.[120, 121] Therefore while the use of a dosing aid, such as a pill box, may have the potential to improve the accuracy with which patients execute a treatment regimen it is unlikely that an intervention such as this will persuade non-persistent patients of the need to continue with treatment. This distinction underlines the need to adequately convey the rationale for and importance of treatment in addition to addressing ways of integrating dosing into daily routines.

Results from the competing risks model of statin adherence and persistence illustrate the importance of correctly identifying the mode of poor medication taking behaviour. For example; in a younger population (16-34 years) where the risk of statin non-adherence is low by comparison to other age categories, the use of interventional techniques to improve treatment execution may not be the most efficient use of resources. It may be of considerably greater benefit to target factors that contribute to statin discontinuation as this is the behaviour for which a younger population has the highest risk. It should be noted however that an effective intervention to increase persistence with treatment may also influence the risk of non-adherence once the adherence behaviours of previously non-persistent patients are incorporated into the non-adherence risk estimation. This is because the competing risks model makes no assumptions about the independence of non-adherence and non-persistence. It is also worthwhile noting the pattern of non-adherent and non-persistent events, the majority of which occur after the filling of a single prescription or within the first 90 days of treatment. This suggests that interventions timed to coincide with the initiation of treatment and the following few months may provide the most benefit.

9.3 Implications for Future Work

It is worthwhile noting that because the competing risks model of adherence and persistence takes no account of event history it is essentially Markovian in nature.[103] Markov models have been used previously for the modelling of medication taking behaviours using prescription refill records;[36] however, none of the identified studies examined adherence as a distinct behaviour exclusive of persistence. It is possible that a Markov model may provide a viable opportunity to assess adherence behaviour beyond the first non-adherent event in the competing risks model. This is an area of research that requires further exploration.

CHAPTER TEN

10 CONCLUSION

Prescription refill records are too coarse to ever fully reveal the subtleties and complexities of a patient's underlying medication taking behaviour. Unlike techniques such as directly observed therapy and electronic medication event monitors, the unit of analysis is the complete prescription refill, not the individual dose. Prescription refill records are consequently a rather blunt instrument for the estimation of adherence. Measures of adherence derived from prescription refill records must be interpreted in the light that the quality of a patient's treatment execution can only be inferred from the timeliness of their prescription refilling and the finer details of medication taking behaviours, such as the timing of doses, drug holidays and white coat compliance, cannot be observed. The fact that the pattern of adherence to individual doses cannot be observed from prescription refill records does not invalidate the adherence measures derived from prescription refill data. When appropriately interpreted prescription refill records provide a unique opportunity to efficiently describe the medication taking behaviours of large populations, over long periods of time, in a truly objective manner.

The challenge for researchers using prescription refill records has been to develop models of adherence measurement that capture patients' medication-taking behaviours in an accurate and concise way. This has resulted in a proliferation of proposed methodologies for the measurement and subsequent analysis of adherence, using prescription refill data. An increasing body of evidence[29, 30] and opinion[28, 35, 41] supporting the need for a distinction between non-adherence and non-persistence have however led to criticism of many of these proposed prescription refill adherence measure models, because they fail to or are unable to differentiate between the two behaviours.[22, 23]

The analysis of adherence rate estimates exclusive of non-persistence is complicated by two factors. The systematic nature of non-persistence which produces variable follow-up times that cannot be considered to vary at random and the fact that adherence rate estimates for patients with very short follow-up times, in particular patients who receive only a single prescription, cannot be considered accurate. These difficulties preclude the use of standard repeated measure models and time to non-adherence models for the analysis of

adherence measures exclusive of non-persistence. A number of attempts have been made to exclude persistence behaviour from adherence measures using single measure models. These models are however significantly limited by both the general weaknesses of single measure adherence models and their inability to appropriately handle the bias introduced to adherence estimates by patients with a single or very few prescription refills.

The competing risks model proposed in this thesis presents the opportunity to appropriately account for non-persistence in the measurement and analysis of adherence. This is achieved by changing the focus of analysis away from making inferences about the chance of non-adherence occurring in patients who are adherent, towards making inferences about the chance of non-adherence occurring in patients who are both adherent and persistent. This approach allows the partitioning of the contributions of non-adherence and non-persistence to poor medication taking behaviour and the correct assignment of risk estimates to covariates for both.

As expected the estimated rates of non-adherence from the competing risks model were considerably lower than those obtained from models of adherence that do not exclude the time after non-persistence. By specifically estimating the probability of non-adherence in patients who are persistent with treatment the competing risks adherence model provides a clearer understanding of the way in which non-adherence contributes to medication taking behaviour. The removal of the error introduced by calculating adherence rates beyond treatment discontinuation allows a more appropriate comparison of non-adherence probabilities between treatments or covariates that have different baseline non-persistence rates. In addition, whereas previously it was not possible to combine estimates of non-adherence and non-persistence derived from prescription refill data, the competing risks model allows the accurate composite estimation of medication taking behaviours. This permits an estimation of the number of patients who can be expected to both persist-with and adhere-to treatment.

The disparity observed between the results obtained by the competing risks regression model and standard adherence regression models illustrates the considerable bias introduced to non-adherence risk estimates by non-persistence. By facilitating the analysis of adherence exclusive of non-persistence the competing risks model avoids the biasing of non-adherence risk for covariates that are associated with non-

persistence. The separate assignment of non-adherence and non-persistence risk to individual covariates allows a distinction to be made between the risk factors that predict each behaviour. This provides valuable information about the type of behaviour that is likely to contribute to poor medication taking in a specific cohort of patients and may in turn allow the targeting of interventions specific to the behaviour. The interpretation of the risk estimates from the competing risks model does however require some care. The results from the competing risks regression analysis of non-adherence and non-persistence represent the risk of an event in patients who are both adherent and persistent to treatment. The non-adherence risk estimates must therefore be interpreted with reference to the risk estimates obtained for non-persistence and vice versa.

This thesis has been based upon the hypothesis that the appropriate exclusion of non-persistent behaviour from adherence analyses will provide more accurate estimates of non-adherent behaviour and more robust risk estimates for covariates associated with this behaviour. For this purpose the competing risks model of time to non-adherence and time to non-persistence was proposed. This adherence measure model has the ability to account for both the non-random or informative nature of non-persistence, and the biased adherence rate estimates obtained for patients with very short follow-up times. By allowing the exclusion of non-persistent behaviour from adherence analyses, and vice versa, the competing risks model separates the duration and intensity of treatment into distinct but complementary measures of medication taking behaviour. These two measures are capable of individually addressing the questions: How long has the patient continued to take the medication in an effort to treat the disease? Has the patient taken enough medication during that time period to treat the disease?

APPENDIX ONE

A1 APPENDIX 1

A1.1 REPEATED MEASURE MODEL – CORRELATION MATRIX SENSITIVITY ANALYSIS

The results from the univariate and multivariate models of non-adherence (RMM-90) for the two specified working correlation matrices are presented in Table A1.1 (see below). The working correlation matrices used in the multivariate analyses of these two models are shown in Table A1.2 and Table A1.3 (see below). While there are some minor differences between the results obtained in the autoregressive and unstructured correlation GEE models in both the univariate and multivariate analyses; in general there is a high level of agreement between the two sets of results. This suggests that the specification of the mean model structure (binomial) is appropriate and that the β regression estimates are robust to a miss-specification of the correlation structure.[72]

TABLE A1.1: RESULTS FROM THE UNIVARIATE & MULTIVARIATE GENERALISED ESTIMATING EQUATION REGRESSION ANALYSES OF STATIN NON-ADHERENCE FOR THE RMM-90 STUDY COHORT WITH A BINOMIAL VARIANCE DISTRIBUTION A COMMON LOGIT LINK FUNCTION AND EITHER AN UNSTRUCTURED OR AUTOREGRESSIVE WORKING CORRELATION MATRIX

Model Covariates	Univariate AR		Multivariate AR‡		Univariate US		Multivariate US‡	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Gender								
Male	0.98	(0.96, 1.00)	0.99	(0.97, 1.01)	0.98	(0.96, 1.00)	0.99	(0.97, 1.01)
Female	Ref	-	Ref	-	Ref	-	Ref	-
Age								
16-34*	4.62	(4.16, 5.14)	3.64	(3.28, 4.04)	4.04	(3.66, 4.46)	3.37	(3.06, 3.71)
35-44*	2.43	(2.29, 2.58)	1.98	(1.87, 2.10)	2.30	(2.18, 2.43)	1.95	(1.85, 2.07)
45-54*	1.62	(1.56, 1.68)	1.41	(1.36, 1.47)	1.56	(1.50, 1.61)	1.39	(1.35, 1.44)
55-64*	1.14	(1.10, 1.17)	1.08	(1.04, 1.11)	1.12	(1.09, 1.16)	1.07	(1.04, 1.10)
65-74*	Ref	-	Ref	-	Ref	-	Ref	-
≥75*	1.04	(1.01, 1.06)	1.19	(1.16, 1.22)	1.02	(1.00, 1.05)	1.14	(1.11, 1.17)
Statin Type								
Simvastatin*	0.98	(0.93, 1.03)	1.00	(0.92, 1.02)	1.00	(0.95, 1.05)	0.99	(0.94, 1.04)
Pravastatin*	Ref	-	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.27	(1.17, 1.39)	1.20	(1.10, 1.32)	1.23	(1.13, 1.34)	1.18	(1.07, 1.29)

Model Covariates	Univariate AR		Multivariate AR‡		Univariate US		Multivariate US‡	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Atorvastatin*	0.85	(0.83, 0.88)	0.88	(0.86, 0.91)	0.86	(0.84, 0.88)	0.89	(0.87, 0.91)
Rosuvastatin*	0.92	(0.88, 0.96)	0.92	(0.88, 0.96)	0.93	(0.89, 0.97)	0.94	(0.90, 0.98)
Simva/Ezet*	0.80	(0.70, 0.91)	0.79	(0.69, 0.91)	0.73	(0.64, 0.85)	0.75	(0.65, 0.86)
Prescriber								
GP Prescriber*	Ref	-	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.80	(0.77, 0.83)	0.90	(0.87, 0.94)	0.79	(0.76, 0.82)	0.89	(0.86, 0.93)
Dose								
Low Dose*	0.97	(0.95, 0.99)	0.96	(0.94, 0.99)	0.98	(0.96, 1.00)	0.95	(0.93, 0.97)
Intermediate Dose*	Ref	-	Ref	-	Ref	-	Ref	-
High Dose*	1.07	(1.00, 1.15)	1.10	(1.02, 1.19)	1.06	(0.99, 1.14)	1.10	(1.02, 1.18)
Dose Change								
No Dose Change*	Ref	-	Ref	-	Ref	-	Ref	-
Dose Decrease*	0.81	(0.78, 0.85)	0.80	(0.76, 0.84)	0.79	(0.75, 0.82)	0.78	(0.74, 0.81)
Dose Increase*	0.81	(0.78, 0.85)	0.75	(0.72, 0.78)	0.81	(0.78, 0.83)	0.74	(0.71, 0.77)
Co-morbidities								
IHD*	0.76	(0.74, 0.78)	0.94	(0.91, 0.97)	0.76	(0.74, 0.79)	0.92	(0.89, 0.95)
Diabetes*	0.77	(0.75, 0.80)	0.85	(0.82, 0.87)	0.79	(0.76, 0.81)	0.84	(0.82, 0.87)
Depression*	1.10	(1.07, 1.13)	1.15	(1.12, 1.18)	1.08	(1.06, 1.11)	1.12	(1.09, 1.15)
Depression(Recent)*	1.07	(1.04, 1.11)	0.93	(0.90, 0.96)	1.03	(1.00, 1.06)	0.93	(0.90, 0.96)
Parkinson's Disease*	1.02	(0.96, 1.10)	1.10	(1.02, 1.18)	1.04	(0.97, 1.11)	1.10	(1.02, 1.17)
Alzheimer's Disease*	1.00	(0.93, 1.07)	1.04	(0.97, 1.11)	0.99	(0.93, 1.06)	1.03	(0.97, 1.10)
Prescribing History								
Non-Cardio PAs† ≤ 2	Ref	-	Ref	-	Ref	-	Ref	-
3 - 5	0.93	(0.91, 0.96)	1.11	(1.08, 1.14)	0.95	(0.93, 0.97)	1.08	(1.05, 1.10)
6 - 11	0.91	(0.89, 0.93)	1.28	(1.25, 1.32)	0.93	(0.91, 0.96)	1.20	(1.17, 1.23)
≥ 11	0.94	(0.91, 0.96)	1.59	(1.54, 1.64)	0.95	(0.93, 0.98)	1.40	(1.36, 1.44)
Cardio PAs† ≤ 0	Ref	-	Ref	-	Ref	-	Ref	-
1	0.75	(0.73, 0.77)	0.83	(0.81, 0.85)	0.80	(0.78, 0.81)	0.86	(0.85, 0.88)
2	0.65	(0.63, 0.67)	0.79	(0.77, 0.81)	0.71	(0.70, 0.73)	0.82	(0.80, 0.84)
≥ 3	0.58	(0.57, 0.59)	0.76	(0.74, 0.79)	0.64	(0.63, 0.66)	0.79	(0.77, 0.81)
Rxs† ≤ 13	Ref	-	Ref	-	Ref	-	Ref	-
14-51	0.80	(0.78, 0.82)	0.69	(0.67, 0.71)	0.82	(0.80, 0.84)	0.74	(0.72, 0.76)
52-109	0.54	(0.53, 0.56)	0.45	(0.43, 0.46)	0.61	(0.60, 0.63)	0.53	(0.51, 0.55)
≥ 110	0.44	(0.42, 0.45)	0.34	(0.33, 0.35)	0.50	(0.49, 0.52)	0.42	(0.41, 0.44)
Time								
Time (Ln)*§	0.0271	(0.0244, 0.0297)	0.0538	(0.0508, 0.0568)	0.0248	(0.0223, 0.0273)	0.0506	(0.0478, 0.0534)

* Time-varying covariates, value taken from the first day of each adherence calculation interval. † Time-varying covariates, number in 12 months prior to the first day of each adherence calculation interval. § Beta (β) coefficients are presented for

continuous variables instead of odds ratios. ‡ Adjusted for all included covariates. ***RMM-90***, proportion of days covered in consecutive 90 day adherence calculation intervals. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***Ln***, natural logarithmic scale. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***OR***, odds ratio. ***AR***, autoregressive working correlation matrix. ***US***, unstructured working correlation matrix. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

TABLE A1.2: AUTOREGRESSIVE WORKING CORRELATION MATRIX FOR THE MULTIVARIATE GEE ANALYSIS OF RMM-90

Interval (Days)	1-90	91-180	181-270	271-360	361-450	451-540	541-630	631-720	721-810	811-900
1-90	1.0000									
91-180	0.4941	1.0000								
181-270	0.2441	0.4941	1.0000							
271-360	0.1206	0.2441	0.4941	1.0000						
361-450	0.0596	0.1206	0.2441	0.4941	1.0000					
451-540	0.0294	0.0596	0.1206	0.2441	0.4941	1.0000				
541-630	0.0145	0.0294	0.0596	0.1206	0.2441	0.4941	1.0000			
631-720	0.0072	0.0145	0.0294	0.0596	0.1206	0.2441	0.4941	1.0000		
721-810	0.0036	0.0072	0.0145	0.0294	0.0596	0.1206	0.2441	0.4941	1.0000	
811-900	0.0018	0.0036	0.0072	0.0145	0.0294	0.0596	0.1206	0.2441	0.4941	1.0000

TABLE A1.3: UNSTRUCTURED WORKING CORRELATION MATRIX FOR THE MULTIVARIATE GEE ANALYSIS OF RMM-90

Interval (Days)	1-90	91-180	181-270	271-360	361-450	451-540	541-630	631-720	721-810	811-900
1-90	1.0000									
91-180	0.4167	1.0000								
181-270	0.3544	0.4956	1.0000							
271-360	0.3077	0.4066	0.4895	1.0000						
361-450	0.3318	0.3976	0.4732	0.5403	1.0000					
451-540	0.3022	0.4290	0.4267	0.4687	0.5618	1.0000				
541-630	0.2582	0.3642	0.4973	0.4256	0.5046	0.5579	1.0000			
631-720	0.2645	0.3306	0.3894	0.4844	0.4458	0.5047	0.5334	1.0000		
721-810	0.2723	0.3118	0.3877	0.3777	0.4878	0.4370	0.5207	0.5047	1.0000	
811-900	0.3124	0.2432	0.4661	0.4894	0.5284	0.4966	0.5950	0.6659	0.6867	1.0000

APPENDIX TWO

A2 APPENDIX 2

The SAS macro PSEUDOCI (see Section A2.1 below) was originally written to calculate the competing risks pseudo-values for relapse or death in studies of bone marrow transplantation for patients with haematologic malignancy. The computationally intensive jack-knife procedure used in this macro did not cause difficulties in these analyses because the number of patients included was small. However because of the large number of patients included in the competing risks model of statin adherence it was not possible to obtain results from the PSEUDOCI macro within an acceptable time frame. The estimated time to run a single analysis was several months. For this reason a number of modifications were made to the PSEUDOCI macro to the increase the efficiency of the data handling steps and to allow the analysis to be run in batches on multiple computers. The additions to the PSEUDOCI macro code in Section A2.1 below are underlined and the deletions appear as ~~strikethrough~~. These modifications were tested using the sample dataset and results provided by Klein et al.[95]

A2.1 SAS MACRO PSEUDOCI[97]

```
/*assign libref to datapb1*/
libname datapb9 'G:\GMS\GMSProjects\METHODS\Methods\lipid therapy\StatDat2
(methods) b\CR Batch';
run;

%macro pseudoci(datain,x,r,d,howmany,datatau,dataout);

/*
MACRO COMPUTES PSEUDOVALUES BASED ON THE CUMUALTIVE INCIDENCE FUNCTION FOR
BOTH OF TWO COMPETING RISKS TIME
      INPUTS:
      DATAIN            INPUT DATA SET
      X                 TIME VARIABLE
      R                 INDICCATOR OF FIRST COMPETING RISK (1-YES, 0-NO)
      D                 INDICATOR OF SECOND COMPETING RISK (1-YES, 0-NO)
      HOWMANY           SAMPLE SIZE
      DATATAU           SUBSET OF INPUT DATA SET AT WHICH PSEUDO VALUES ARE
                        COMPUTED DATA SET HAS SINGLE VARIABLE "TIME"
      DATAOUT           OUTPUT DATA SET WHICH CONATINS THE PSEUDO VALUES AT
                        EACH TIME POINT (PSUK,K=1,...,HOWMANY)
*/
proc sort data=&datain; by &x;

data keep; set &datatau;
find=1;

proc sort data=keep; by time;
```

```
data point; set &datain;
time=&x;
keep=1;
data point; merge point keep; by time;
keep time find keep;

data useme; set point;
retain temp -1;
if keep = 1 then temp=time;
tuse=temp;
if find ne 1 then delete;
&x=tuse;

t = &x;
data useme; set useme;
by t;
if first.t;

proc print;

/*
PREPARE DATA SET WITH MISSING VALUES FOR DEADK AND RELAPSEK TO BE USED IN
COMPUTING ESTIMATED CUMULATIVE INCIDENCE WITH KTH OBSERVATION DELETED
*/
proc sort data=&datain;
by &x;
data newdat; set &datain ;
id+1;
array iobsd(&howmany) dead1-dead&howmany;
array iobsr(&howmany) relapse1-relapse&howmany;
do j=1 to &howmany;
iobsd(j)=&d;
iobsr(j)=&r;
if j=id then do; iobsr(j)=.; iobsd(j)=.; end;
end;

data out; set newdat;
drop dead1-dead&howmany relapse1-relapse&howmany;

/*
COMPUTE CI FOR 1ST (CIRALL) AND 2ND (CIDALL) FOR FULL SAMPLE, STORE IN SALL
*/
%cuminc(newdat,&x,&r,&d,sall,cirall,cidall);

%do ip=1 %to &howmany;

data newdat1;  set &datain ;
id+1;
dead=&d;
relapse=&r;
if &ip=id then do; relapse=.; dead=.; end;

/*
COMPUTE CI FOR 1ST (CIRALL) AND 2ND (CIDALL) FOR REDUCED SAMPLE, STORE IN
SIP
*/
%cuminc(newdat newdat1,&x,relapse&ip,dead&ip,stemp,cir1,cid1);

/*
COMPUTE PSEUDOVALUES FOR BOTH RISK AT EVERY DATA POINT AND ADD TO FILE
```

```
*/
data ps; merge sall stemp; by &x;
retain cirtemp 0;
retain cidtemp 0;
if cir1=. then cir1=cirtemp;
cirtemp=cir1;
rpsu&ip=&howmany*cirall- (&howmany-1)*cir1;
if cid1=. then cid1=cidtemp;
cidtemp=cid1;
dpsu&ip=&howmany*cidall- (&howmany-1)*cid1;

data out; merge out ps useme; by &x;
if find ne 1 then delete;
keep time rpsu1-rpsu&ip dpsu1-dpsu&ip &x;

data psfile.a&ip; set ps;
keep time rpsu&ip dpsu&ip &x find;

run;
%end;

data out1; set out;
keep &x;
%do ip=1 %to 1000;
data out1; merge out psfile.a&ip; by &x;
if find ne 1 then delete;
run;
%end;

data out2; set out;
keep &x;
%do ip=1 %to 2000;
data out2; merge out2 psfile.a&ip; by &x;
if find ne 1 then delete;
run;
%end;

data out3; set out;
keep &x;
%do ip=1 %to 3000;
data out3; merge out3 psfile.a&ip; by &x;
if find ne 1 then delete;
run;
%end;
.
.
.
data out#; set out;
keep &x;
%do ip=1 %to &howmany;
data out#; merge out# psfile.a&ip; by &x;
if find ne 1 then delete;
run;
%end;

data out; merge out out1 out2 out3...out#; by &x;
if find ne 1 then delete;
keep time rpsu1-rpsu&howmany dpsu1-dpsu&howmany &x;
run;

data &dataout; set newdat;
```

```
data all; set out;
array yr(&howmany) rpsu1-rpsu&howmany;
array yd(&howmany) dpsu1-dpsu&howmany;
do j=1 to &howmany;
rpseudo=yr(j);
dpseudo=yd(j);
id=j;
output;
end;
keep id time rpseudo dpseudo;
proc sort data=all; by id;
data &dataout; merge &dataout all;
by id;
retain otime -1;
retain oid -1;
if id eq oid and otime=time then delete;
else do; oid=id; otime=time; end;

%mend;
```

A2.2 SAS MACRO CUMINC[97]

```
%macro cuminc(datain,x,re,de,dataout,cir,cid);

/*
THIS MACRO COMPUTES THE CUMULATIVE INCIDENCE FUNCTIONS FOR BOTH COMPETING
RISKS USING PROC PHREG OUTPUT
      INPUTS:
      DATAIN            NAME OF INPUT DATA SET CONTAINING
      X                 TIME TO EVENT
      RE                INDICCATOR OF FIRST COMPETING RISK (1-YES, 0-NO)
      DE                INDICATOR OF SECOND COMPETING RISK (1-YES, 0-NO)
      DATAOUT           NAME OF OUTPUT DATA SET CONTAINING
      CIR               CUMULATIVE INCIDENCE FUNCTION FOR 1ST COMPETING
                        RISK
      CID               CUMULATIVE INCIDENCE FUNCTION FOR 2ND COMPETING
                        RISK
*/
data work; set &datain;
t=&x;
r=&re;
d=&de;
zero=0;

/*
COMPUTE CRUDE CUMUALTIVE HAZARD FOR FIRST COMPETING RISK
*/
proc phreg data=work noprint;
model t*r(0)=zero;
output out=rel logsurv=chr /method=emp;

/*
COMPUTE CRUDE CUMUALTIVE HAZARD FOR SECOND COMPETING RISK
*/
proc phreg data=work noprint;
model t*d(0)=zero;
output out=dead logsurv=chd /method=emp;

/*
```

```
COMPUTE CUMULATIVE INCIDENCE
*/
data both; merge rel dead; by t;
retain s 1
retain cr 0;
retain cd 0;
retain cumincr 0;
retain cumincd 0;
hr=-(cr+chr);
hd=-(cd+chd);

/*
NOTE HR AND HD ARE THE JUMPS IN THE CUMUALTIVE CRUDE HAZARDS AT THIS TIME
*/
cr=-chr;
cd=-chd;
cir=cumincr+hr*s;
cumincr=cir;
cid=cumincd+hd*s;
cumincd=cid;
s=s*(1-hr-hd);
/*
NOTE S IS KAPLAN-MEIER ESTIMATE IGNORING CAUSE OF FAILURE
*/
data &dataout; set both;
&x=t;
&cir=cir; &cid=cid;
keep &x &cir &cid;

%mend;
```

A2.3 SAS MACRO INCID[96]

```
%macro incid(data,group,relp,trm,time,out=);

/* THIS MACRO COMPEUTS THE CUMULATIVE INCIDENCES FOR BOTH COMPETING RISKS
      INPUTS:
      DATA              NAME OF INPUT DATASET CONTAINING
      GROUP             STRATIFYING VARIABLE IF REQUIRED (E.G. AGE)
      RELP              INDICCATOR OF FIRST COMPETING RISK (1-YES, 0-NO)
      TRM               INDICATOR OF SECOND COMPETING RISK (1-YES, 0-NO)
      TIME              TIME TO EVENT
      OUT=              NAME OF OUTPUT DATA SET
*/

data lc_one; set &data;
a=&time;
b=&relp;
c=&trm;
d=&group;
keep a b c d;

proc sort data=lc_one; by descending a;
/*
proc sort data=lc_one; by d;
*/
proc iml;
```

```
use lc_one; read all into x;
n=nrow(x);
ngrp=max(x[ ,4]);
gnum=J(1,ngrp,0);
do k=1 to n;
gnum[1,x[k,4]] = gnum[1,x[k,4]]+1;
end;

t=J(1,n,0);
t[1,1]=x[1,1];
ntime=1;
tnow=x[1,1];
do j=2 to n;
if x[j,1] <tnow then do; ntime=ntime+1; t[1,ntime]=x[j,1]; tnow=x[j,1];
end;
end;

relap=J(ntime,ngrp,0);
trm=J(ntime,ngrp,0);
atrisk=J(ntime,ngrp,0);
do k=1 to ntime;
do j=1 to n;
ax=x[j,1]; at=t[1,k]; ag=x[j,4]; ad=x[j,3]; ar=x[j,2];
if x[j,1] =t[1,k] then do; relap[k,ag]=relap[k,ag]+ar;
trm[k,ag]=trm[k,ag]+ad; end;
if x[j,1] >= t[1,k] then atrisk[k,ag]=atrisk[k,ag]+1;
end;
end;

lfs=J(ntime,ngrp,-1);
ci_rel=J(ntime,ngrp,-1);
ci_trm=J(ntime,ngrp,-1);
vci_rel=J(ntime,ngrp,-1);
vci_trm=J(ntime,ngrp,-1);
index=J(ntime,1,0);
tt=t(t[1,1:ntime]);
do ig=1 to ngrp;
p=1;
cr=0;
cd=0;
do j=1 to ntime ;
index[j,1]=j;
k=ntime-j+1;
if atrisk[k,ig] >0 then do;
cr=cr+relap[k,ig]*p/atrisk[k,ig];
cd=cd+trm[k,ig]*p/atrisk[k,ig];
p=p*(1-(trm[k,ig]+relap[k,ig])/atrisk[k,ig]);
lfs[k,ig]=p;
ci_rel[k,ig]=cr;
ci_trm[k,ig]=cd;
end;

else do; lfs[k,ig]=.; ci_rel[k,ig]=.; ci_trm[k,ig]=.; end;
end;

do j=1 to ntime;
know=ntime-j+1;
vr=0; vd=0;
if ci_rel[know,ig] = . then do; vci_rel[know,ig]=.; vci_trm[know,ig]=.;end;
else do;
do k=1 to ntime;
```

```
jnow=ntime-k+1;
if tt[jnow,1] <= tt[know,1] then do;
wr=(trm[jnow,ig]+relap[jnow,ig])/atrisk[jnow,ig]**2;
wr=wr*lfs[jnow,ig]*(ci_rel[know,ig]-ci_rel[jnow,ig])**2;
q=(relap[jnow,ig]/atrisk[jnow,ig]**2)*lfs[jnow,ig]**2;
q=q*(1-2*(ci_rel[know,ig]-ci_rel[jnow,ig]));
vr=vr+wr+q;
wd=(trm[jnow,ig]+relap[jnow,ig])/atrisk[jnow,ig]**2;
wd=wd*lfs[jnow,ig]*(ci_trm[know,ig]-ci_trm[jnow,ig])**2;
q=trm[jnow,ig]/atrisk[jnow,ig]**2*lfs[jnow,ig]**2;
q=q*(1-2*(ci_trm[know,ig]-ci_trm[jnow,ig]));
vd=vd+wd+q;
end;
end;
end;

vci_rel[know,ig]=sqrt(vr);
vci_trm[know,ig]=sqrt(vd);
end;
end;

nn=ngrp*ntime;
yout=j(nn,6,0);
k=0;
do is=1 to ngrp;
do it=1 to ntime;
k=k+1;
yout[k,1]=tt[it,1];
yout[k,2]=is;
yout[k,3]=ci_rel[it,is];
yout[k,4]=vci_rel[it,is];
yout[k,5]=ci_trm[it,is];
yout[k,6]=vci_trm[it,is];
end;
end;

create dout from yout;
append from yout;
close dout;
quit;
data io; set dout;
time=col1;
group=col2;
CI1=col3;
SE_CI1=col4;
CI2=col5;
SE_CI2=col6;
if CI1 =. then se_ci1=.;
if CI2=. then se_ci2=.;
drop col1-col6;
proc sort data=io; by time;
proc sort data=io; by group;
proc print data=io;
data &out; set io;

%mend;
```

A3 APPENDIX 3

A3.1 COMPETING RISKS COX & GEE REGRESSION ANALYSES – UNIVARIATE MODELS

The results of from the univariate Cox regression analyses of non-adherence and non-persistence as a composite outcome and the generalised estimating equation pseudo-value regression analyses of the individual competing risks are presented below in Table A3.1 (CRM-A180P180, univariate competing risks), and Table A3.2 (CRM-A180P360, univariate competing risks).

TABLE A3.1: RESULTS FROM THE UNIVARIATE COMPETING RISKS ANALYSIS OF CRM-A180 & CRM-P180 & THE UNIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P180

Univariate Model Covariates	CRM-A180P180 (Cox)		CRM-A180 (Pseudo)		CRM-P180 (Pseudo)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Gender						
Male	0.97	(0.95, 0.99)	0.96	(0.93, 0.99)	0.99	(0.96, 1.02)
Female	Ref	-	Ref	-	Ref	-
Age						
16-34*	3.08	(2.92, 3.24)	0.75	(0.67, 0.84)	3.40	(3.16, 3.64)
35-44*	1.92	(1.84, 2.01)	1.01	(0.94, 1.08)	2.22	(2.10, 2.35)
45-54*	1.49	(1.44, 1.54)	1.28	(1.22, 1.34)	1.43	(1.36, 1.50)
55-64*	1.15	(1.12, 1.19)	1.13	(1.08, 1.17)	1.07	(1.02, 1.11)
65-74*	Ref	-	Ref	-	Ref	-
≥75*	1.05	(1.02, 1.08)	0.91	(0.88, 0.94)	1.10	(1.06, 1.13)
Statin Type						
Simvastatin*	0.99	(0.95, 1.04)	1.05	(0.98, 1.12)	0.94	(0.89, 1.00)
Pravastatin*	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.28	(1.19, 1.38)	1.02	(0.92, 1.14)	1.33	(1.22, 1.46)
Atorvastatin*	0.86	(0.84, 0.89)	0.98	(0.94, 1.02)	0.80	(0.78, 0.83)
Rosuvastatin*	0.95	(0.92, 0.99)	1.21	(1.04, 1.16)	0.87	(0.83, 0.91)
Simva/Ezet*	0.99	(0.85, 1.15)	1.31	(1.15, 1.49)	0.77	(0.66, 0.89)
Prescriber						
GP Prescriber*	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.78	(0.75, 0.81)	0.82	(0.77, 0.86)	0.79	(0.75, 0.83)
Dose						

Univariate Model Covariates	CRM-A180P180 (Cox)		CRM-A180 (Pseudo)		CRM-P180 (Pseudo)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Low Dose*	0.98	(0.96, 1.00)	1.05	(1.02, 1.08)	0.96	(0.94, 0.99)
Intermediate Dose*	Ref	-	Ref	-		-
High Dose*	1.03	(0.96, 1.11)	0.93	(0.85, 1.02)	1.06	(0.97, 1.16)
Dose Change						
No Dose Change*	Ref	-	Ref	-	Ref	-
Dose Decrease*	1.12	(1.05, 1.20)	1.83	(1.75, 1.92)	0.53	(0.50, 0.57)
Dose Increase*	1.03	(0.97, 1.09)	1.70	(1.63, 1.77)	0.44	(0.42, 0.47)
Co-morbidities						
IHD*	0.77	(0.75, 0.80)	0.89	(0.86, 0.93)	0.73	(0.70, 0.76)
Diabetes*	0.84	(0.81, 0.86)	0.99	(0.95, 1.03)	0.76	(0.73, 0.79)
Depression*	1.08	(1.06, 1.11)	0.98	(0.95, 1.01)	1.16	(1.13, 1.19)
Depression(Recent)*	1.22	(1.17, 1.27)	1.06	(1.02, 1.11)	1.21	(1.16, 1.26)
Parkinson's Disease*	1.01	(0.95, 1.08)	0.82	(0.75, 0.91)	1.20	(1.11, 1.29)
Alzheimer's Disease*	0.96	(0.90, 1.03)	0.96	(0.89, 1.05)	0.99	(0.91, 1.07)
Prescribing History						
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-
3 - 5	0.93	(0.90, 0.97)	1.16	(1.12, 1.19)	0.87	(0.85, 0.90)
6 - 11	0.91	(0.88, 0.94)	1.13	(1.10, 1.17)	0.80	(0.78, 0.82)
≥ 11	0.98	(0.94, 1.01)	1.11	(1.07, 1.15)	0.86	(0.84, 0.89)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-
1	0.76	(0.74, 0.79)	0.73	(0.71, 0.75)	0.98	(0.95, 1.02)
2	0.66	(0.64, 0.68)	0.60	(0.58, 0.62)	0.86	(0.83, 0.89)
≥ 3	0.58	(0.56, 0.59)	0.53	(0.51, 0.54)	0.80	(0.77, 0.83)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-
14-51	0.77	(0.75, 0.79)	1.28	(1.24, 1.32)	0.66	(0.64, 0.68)
52-109	0.57	(0.55, 0.68)	1.02	(0.99, 1.06)	0.42	(0.41, 0.43)
≥ 110	0.48	(0.47, 0.59)	0.80	(0.77, 0.83)	0.38	(0.37, 0.40)

***** Time-varying covariates, value taken from the day of each adherence/persistence evaluation. **†** Time-varying covariates, number in 12 months prior to the day of each adherence/persistence evaluation. ***Cox***, Cox regression model. ***Pseudo***, competing risks pseudo-value generalised estimating equation regression model. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P180***, competing risks time to non-persistence defined by a permissible gap in treatment of 180 days or greater. ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***S-HR***, sub-distribution hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

TABLE A3.2: RESULTS FROM THE UNIIVARIATE COMPETING RISKS ANALYSIS OF CRM-A180 & CRM-P360 & THE UNIVARIATE COX REGRESSION ANALYSIS OF THE COMPOSITE OUTCOME CRM-A180P360

Univariate Model Covariates	CRM-A180P360 (Cox)		CRM-A180 (Pseudo)		CRM-P360 (Pseudo)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Gender						
Male	0.96	(0.94, 0.98)	0.97	(0.94, 1.00)	0.98	(0.95, 1.01)
Female	Ref	-	Ref	-	Ref	-
Age						
16-34*	2.52	(2.38, 2.66)	0.90	(0.82, 0.99)	3.24	(2.98, 3.51)
35-44*	1.82	(1.73, 1.90)	1.10	(1.03, 1.17)	2.22	(2.08, 2.37)
45-54*	1.45	(1.40, 1.50)	1.32	(1.26, 1.38)	1.38	(1.30, 1.45)
55-64*	1.14	(1.11, 1.18)	1.14	(1.10, 1.19)	1.03	(0.99, 1.09)
65-74*	Ref	-	Ref	-	Ref	-
≥75*	1.03	(1.00, 1.06)	0.92	(0.89, 0.95)	1.12	(1.07, 1.16)
Statin Type						
Simvastatin*	0.99	(0.95, 1.04)	1.06	(1.00, 1.13)	0.90	(0.84, 0.97)
Pravastatin*	Ref	-	Ref	-	Ref	-
Fluvastatin*	1.28	(1.19, 1.38)	1.05	(0.95, 1.15)	1.39	(1.25, 1.54)
Atorvastatin*	0.87	(0.84, 0.89)	0.97	(0.94, 1.00)	0.78	(0.75, 0.81)
Rosuvastatin*	0.96	(0.93, 1.00)	1.11	(1.06, 1.16)	0.82	(0.78, 0.87)
Simva/Ezet*	0.99	(0.85, 1.16)	1.39	(1.23, 1.56)	0.63	(0.51, 0.76)
Prescriber						
GP Prescriber*	Ref	-	Ref	-	Ref	-
Hospital Prescriber*	0.76	(0.74, 0.80)	0.80	(0.77, 0.84)	0.76	(0.72, 0.81)
Dose						
Low Dose*	1.00	(0.98, 1.02)	1.06	(1.04, 1.09)	0.95	(0.92, 0.99)
Intermediate Dose*	Ref	-	Ref	-	Ref	-
High Dose*	1.01	(0.94, 1.09)	0.94	(0.86, 1.02)	1.08	(0.97, 1.20)
Dose Change						
No Dose Change*	Ref	-	Ref	-	Ref	-
Dose Decrease*	1.08	(1.00, 1.15)	1.82	(1.75, 1.90)	0.34	(0.31, 0.37)
Dose Increase*	1.00	(0.94, 1.06)	1.64	(1.58, 1.69)	0.29	(0.26, 0.31)
Co-morbidities						
IHD*	0.77	(0.75, 0.79)	0.87	(0.84, 0.90)	0.70	(0.67, 0.74)
Diabetes*	0.83	(0.81, 0.86)	0.97	(0.93, 1.00)	0.72	(0.68, 0.75)
Depression*	1.07	(1.05, 1.10)	1.00	(0.97, 1.03)	1.16	(1.12, 1.20)
Depression(Recent)*	1.19	(1.14, 1.24)	1.10	(1.05, 1.14)	1.19	(1.13, 1.24)
Parkinson's Disease*	0.99	(0.92, 1.06)	0.86	(0.79, 0.94)	1.22	(1.11, 1.33)
Alzheimer's Disease*	0.92	(0.85, 0.99)	0.94	(0.87, 1.01)	0.95	(0.87, 1.05)

Univariate Model Covariates	CRM-A180P360 (Cox)		CRM-A180 (Pseudo)		CRM-P360 (Pseudo)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Prescribing History						
†Non-Cardio PAs ≤ 2	Ref	-	Ref	-	Ref	-
3 - 5	0.93	(0.90, 0.97)	1.11	(1.08, 1.14)	0.91	(0.88, 0.94)
6 - 11	0.91	(0.88, 0.95)	1.07	(1.04, 1.10)	0.85	(0.82, 0.88)
≥ 11	0.96	(0.93, 1.00)	1.05	(1.02, 1.09)	0.93	(0.90, 0.96)
†Cardio PAs ≤ 0	Ref	-	Ref	-	Ref	-
1	0.77	(0.75, 0.79)	0.94	(0.91, 0.97)	0.73	(0.71, 0.76)
2	0.66	(0.64, 0.68)	0.81	(0.79, 0.84)	0.62	(0.59, 0.64)
≥ 3	0.58	(0.56, 0.59)	0.76	(0.73, 0.78)	0.52	(0.50, 0.54)
†Rxs ≤ 13	Ref	-	Ref	-	Ref	-
14-51	0.78	(0.76, 0.81)	1.11	(1.08, 1.15)	0.71	(0.69, 0.74)
52-109	0.59	(0.57, 0.61)	0.84	(0.81, 0.87)	0.47	(0.45, 0.49)
≥ 110	0.49	(0.48, 0.51)	0.66	(0.63, 0.68)	0.44	(0.42, 0.46)

***** Time-varying covariates, value taken from the day of each adherence/persistence evaluation. **†** Time-varying covariates, number in 12 months prior to the day of each adherence/persistence evaluation. ***Cox***, Cox regression model. ***Pseudo***, competing risks pseudo-value generalised estimating equations regression model. ***CRM-A180***, competing risks time to an adherence rate of less than 80% for at least 180 consecutive days. ***CRM-P360***, competing risks time to a gap in prescription refills of at least 360 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***GP***, General Practitioner. ***CI***, confidence interval. ***Rxs***, number of prescription items. ***HR***, hazard ratio. ***S-HR***, sub-distribution hazard ratio. ***Ref***, reference category, co-morbidities were modelled with reference to the absence of the specified co-morbidity.

APPENDIX FOUR

A4 APPENDIX 4

A4.1 COMPETING RISKS & STANDARD TIME TO EVENT RESULTS – WHISKER PLOTS

The non-adherence risk estimate results from the multivariate Cox regression analyses of the standard time to non-adherence model (TNA-80/180) and the multivariate GEE pseudo-value regression analysis of the competing risks models (CRM-A180P180 & CRM-A180P360) are presented as a whisker plot in Figure A4.1 (see below).

The non-persistence risk estimate results from the multivariate Cox regression analyses of the standard time to non-persistence models (PER-G180 & PER-G360) and the multivariate GEE pseudo-value regression analysis of the competing risks models (CRM-A180P180 & CRM-A180P360) are presented as a whisker plot in Figure A4.2 (see below).

FIGURE A4.1: WHISKER PLOT OF NON-ADHERENCE RISK ESTIMATES FROM THE MULTIVARIATE ANALYSIS OF CRM-A180P180 (■), CRM-A180P360 (■) & TNA-80/180 (■) MODELS.

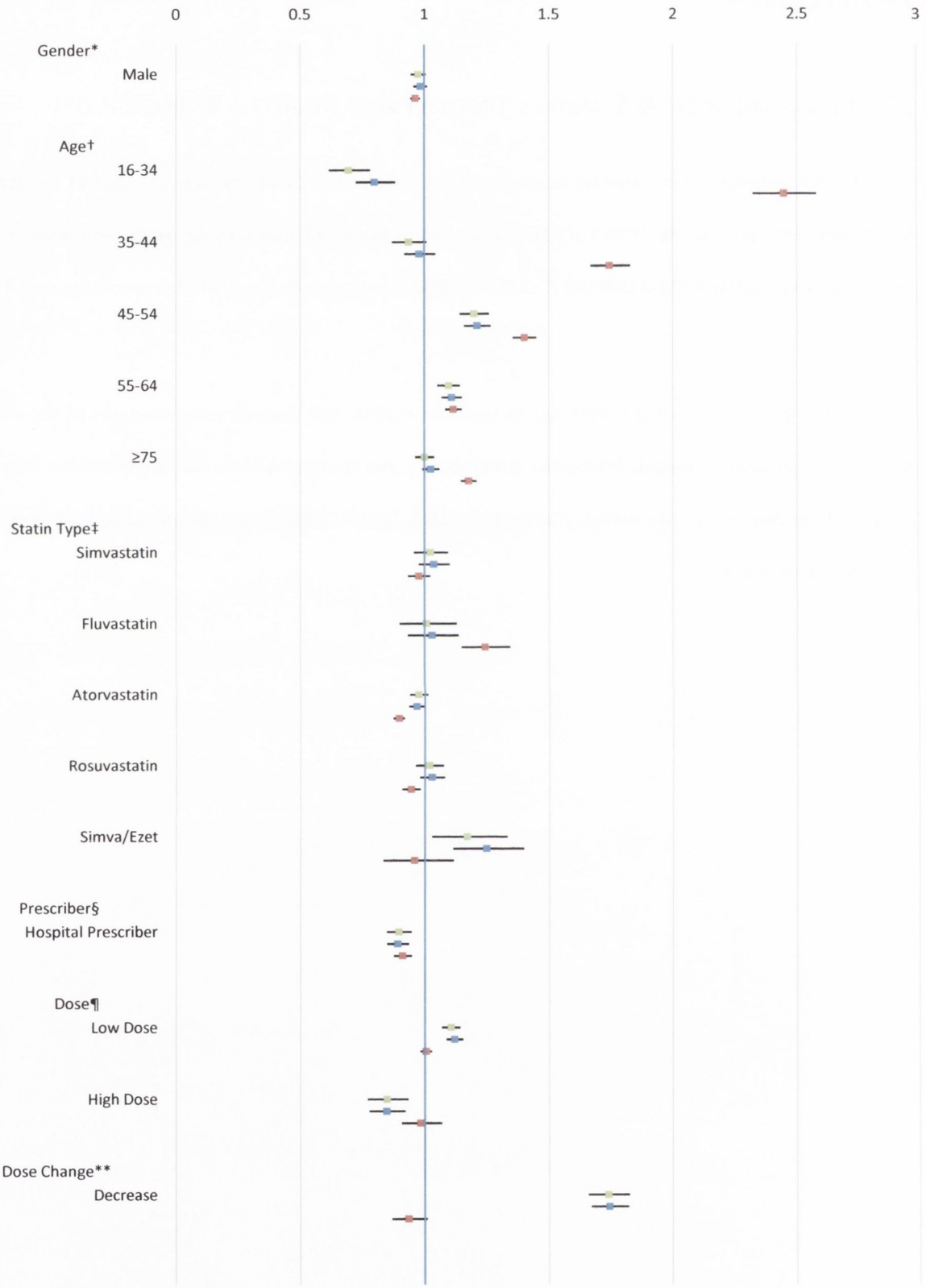
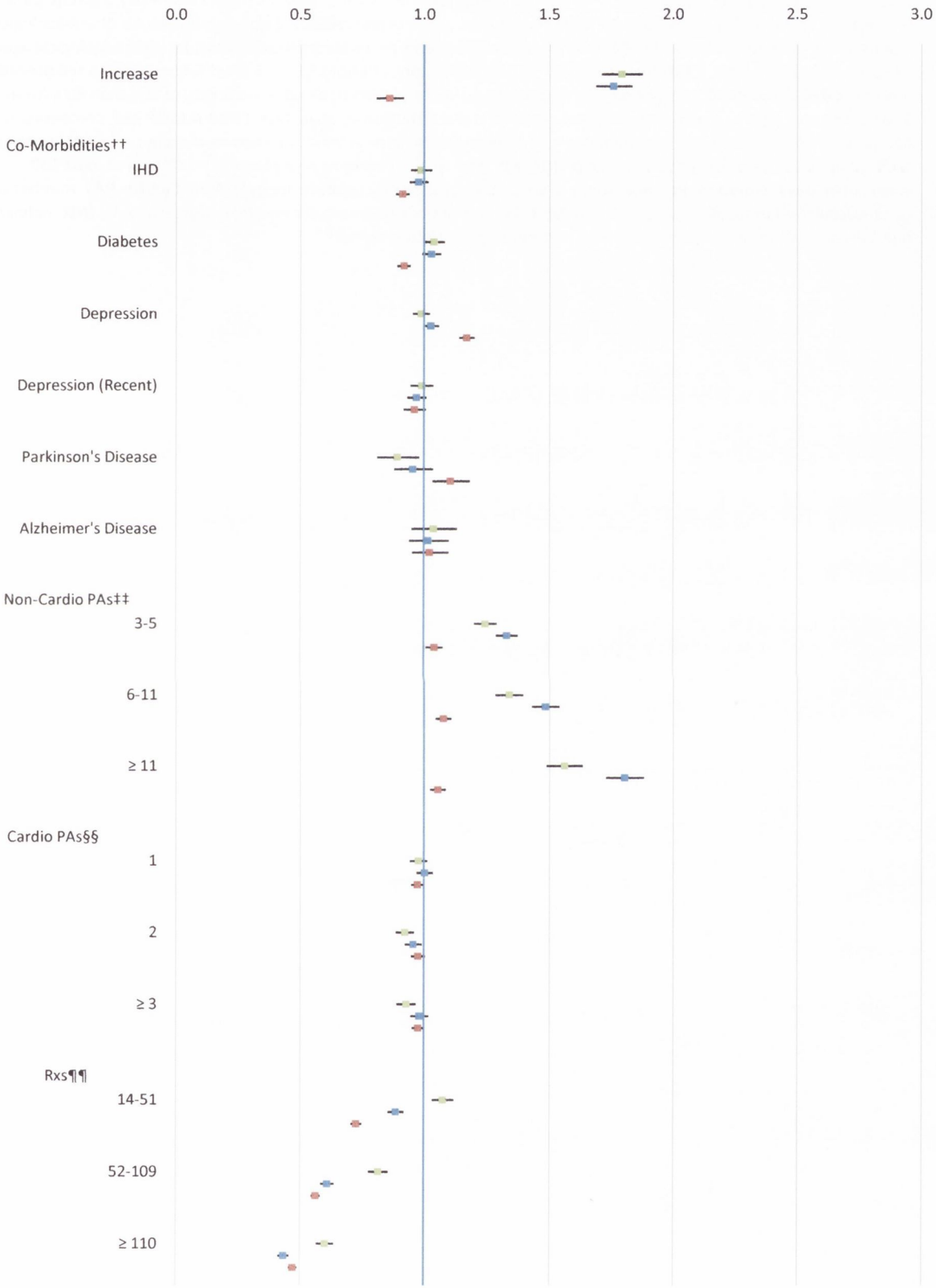


FIGURE A4.1 (CONTINUED): WHISKER PLOT OF NON-ADHERENCE RISK ESTIMATES FROM THE MULTIVARIATE ANALYSIS OF CRM-A180P180 (), CRM-A180P360 () & TNA-80/180 () MODELS.



= Sub-distribution hazard ratios for CRM-A180 from the GEE pseudo-value competing risk analysis of the CRM-A180P180 model. = Sub-distribution hazard ratios for CRM-A180 from the GEE pseudo-value competing risk analysis of the CRM-A180P360 model. = Hazard ratios for TNA-80/180 from the Cox regression analysis of the standard time to non-adherence models. * Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days. ***TNA-80/180***, time to an adherence rate of less than 80% for at least 180 consecutive days. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items.

FIGURE A4.2: WHISKER PLOT OF NON-PERSISTENCE RISK ESTIMATES FROM THE MULTIVARIATE ANALYSIS OF CRM-A180P180 (■), CRM-A180P360 (■), PER-G180 (■) & PER-G360 (■) MODELS

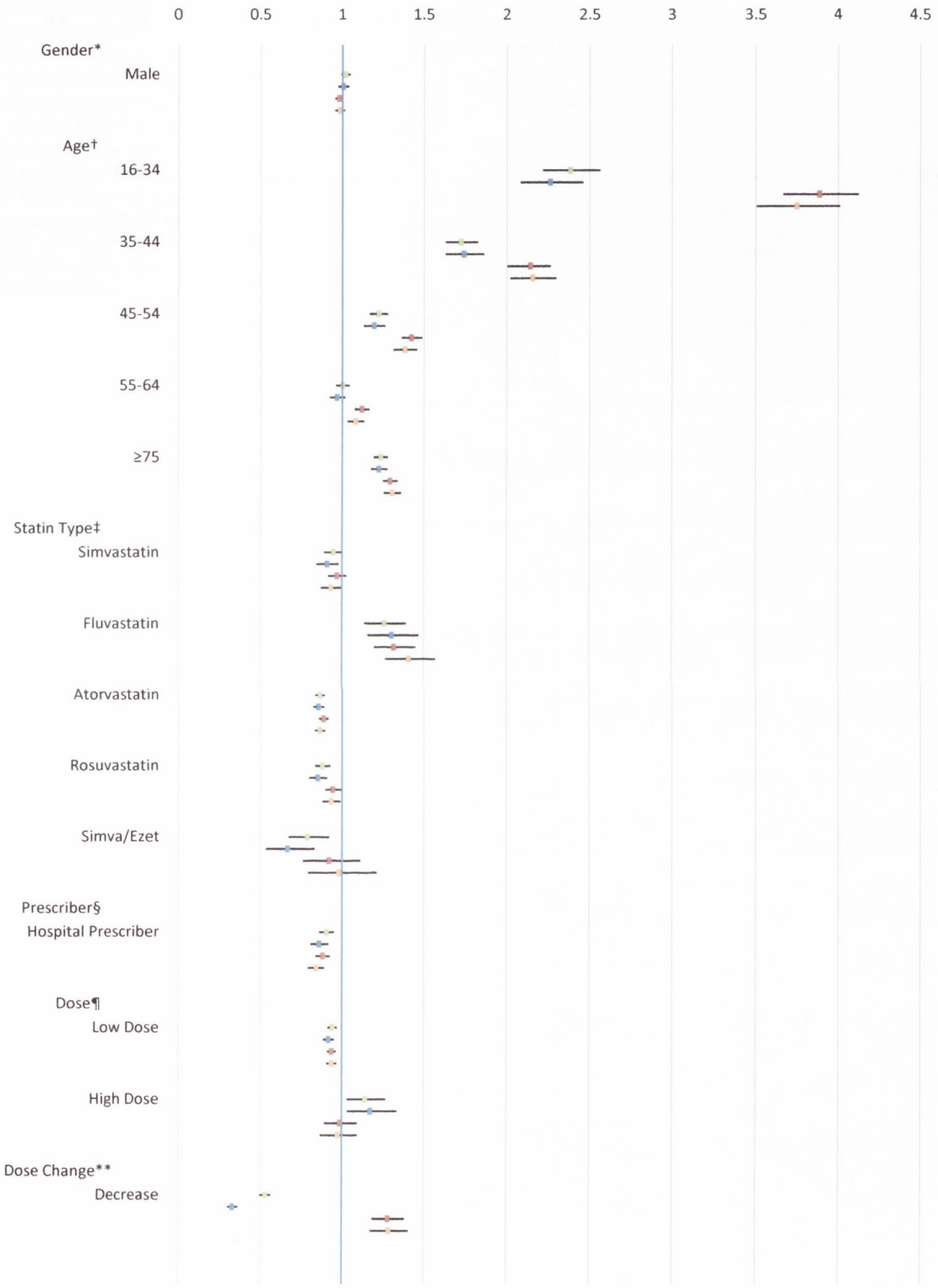
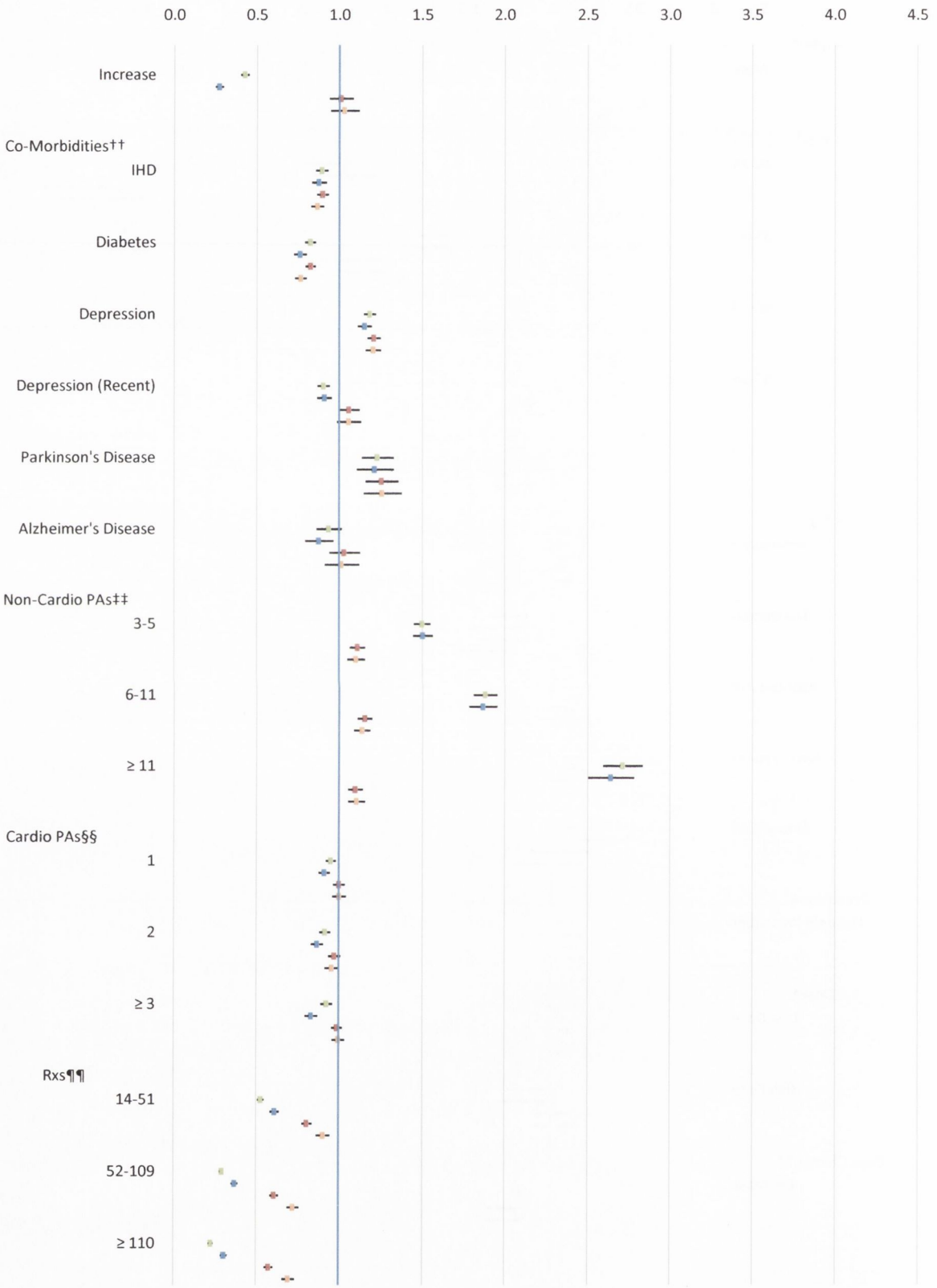


FIGURE A4.2 (CONTINUED): WHISKER PLOT OF NON-PERSISTENCE RISK ESTIMATES FROM THE MULTIVARIATE ANALYSIS OF CRM-A180P180 (■) & CRM-A180P360 (■) & THE MULTIVARIATE ANALYSIS OF THE PER-G180 (■) & PER-G360 (■) STANDARD MODELS



= Sub-distribution hazard ratios for CRM-P180 from the GEE pseudo-value competing risk analysis of the CRM-A180P180 model. = Sub-distribution hazard ratios for CRM-P360 from the GEE pseudo-value competing risk analysis of the CRM-A180P360 model. = Hazard ratios for PER-G180 from the Cox regression analysis of the standard time to non-adherence models PER-G180. = Hazard ratios for PER-G360 from the Cox regression analysis of the standard time to non-adherence models PER-G360. * Reference group: females. † Reference group: patients aged 65-74 years. ‡ Reference group: patients receiving pravastatin. § Reference group: patients prescribed statin by a general practitioner. ¶ Reference group: patients receiving an intermediate statin dose. **Reference group: patients without dose change. †† Reference group: patients without the co-morbidity of interest. ‡‡ Reference group: patients prescribed ≤ 2 non-cardiovascular pharmacological agents in the preceding 12 months. §§ Reference group: patients prescribed ≤ 0 cardiovascular pharmacological agents in the preceding 12 months. ¶¶ Reference group: patients filling prescriptions for ≤ 13 prescription items in the preceding 12 months. . ***CRM-A180P180***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 180 consecutive days. ***CRM-A180P360***, competing risks composite estimate of time to an adherence rate of less than 80% for at least 180 consecutive days or a gap in prescription refills of at least 360 consecutive days. ***PER-G180***, Time to non-persistence defined by a permissible gap in treatment of 180 days or greater. ***PER-G360***, Time to non-persistence defined by a permissible gap in treatment of 360 days or greater. ***Simva/Ezet***, simvastatin & ezetimibe combination product (Inegy®). ***Non-Cardio PAs***, number of non-cardiovascular pharmacological agents. ***Cardio PAs***, number of cardiovascular pharmacological agents. ***IHD***, ischaemic heart disease. ***CI***, confidence interval. ***Rxs***, number of prescription items.

REFERENCES

1. Lerner BH, Gulick RM, Dubler NN. Rethinking nonadherence: historical perspectives on triple-drug therapy for HIV disease. Ann Intern Med 1998;129:573-8.

2. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. Heart 2002;88:229-33.

3. Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. Br J Clin Pharmacol 2008;66:110-6.

4. Valuck RJ, Williams SA, MacArthur M, et al. A retrospective cohort study of correlates of response to pharmacologic therapy for hyperlipidemia in members of a managed care organization. Clin Ther 2003;25:2936-57.

5. Compliance and adverse event withdrawal: their impact on the West of Scotland Coronary Prevention Study. Eur Heart J 1997;18:1718-24.

6. Peterson AM, McGhan WF. Pharmacoeconomic impact of non-compliance with statins. Pharmacoeconomics 2005;23:13-25.

7. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. Health Econ 2001;10:601-15.

8. Daskalopoulou SS, Delaney JA, Filion KB, Brophy JM, Mayo NE, Suissa S. Discontinuation of statin therapy following an acute myocardial infarction: a population-based study. Eur Heart J 2008.

9. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615-22.

10. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301-7.

11. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.

12. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349-57.

13. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001-9.

14. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

15. Bouchard MH, Dragomir A, Blais L, Berard A, Pilon D, Perreault S. Impact of adherence to statins on coronary artery disease in primary prevention. Br J Clin Pharmacol 2007;63:698-708.

16. Perreault S, Dragomir A, Blais L, Berard A, Lalonde L, White M. Impact of adherence to statins on chronic heart failure in primary prevention. Br J Clin Pharmacol 2008.

17. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf 2006;15:565-74; discussion 75-7.

18. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother 2006;40:1280-88.

19. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 1997;50:105-16.

20. Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. Clin Ther 2006;28:1411-24; discussion 0.

21. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care 2005;11:449-57.

22. Urquhart J. Pharmionics: research on what patients do with prescription drugs. Pharmacoepidemiol Drug Saf 2004;13:587-90.

23. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ 2008;336:1114-7.

24. Cramer J, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value in Health 2008;11:44-7.

25. Steiner JF, Earnest MA. The language of medication-taking. Ann Intern Med 2000;132:926-30.

26. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.

27. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther 2001;26:331-42.

28. Steiner JF, Gardner EM. Assessing medication adherence from pharmacy records. Pharmacoepidemiology and Drug Safety 2006;15:575-7.

29. Tremlett H, Van der Mei I, Pittas F, et al. Adherence to the immunomodulatory drugs for multiple sclerosis: contrasting factors affect stopping drug and missing doses. Pharmacoepidemiol Drug Saf 2008.

30. Vrijens B, Belmans A, Matthys K, de Klerk E, Lesaffre E. Effect of intervention through a pharmaceutical care program on patient adherence with prescribed once-daily atorvastatin. Pharmacoepidemiol Drug Saf 2006;15:115-21.

31. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999;21:1074-90; discussion 3.

32. Maronde RF, Chan LS, Larsen FJ, Strandberg LR, Laventurier MF, Sullivan SR. Underutilization of antihypertensive drugs and associated hospitalization. Med Care 1989;27:1159-66.

33. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990;263:1653-7.

34. Steiner JF, Fihn SD, Blair B, Inut TS. Appropriate reductions in compliance among well-controlled hypertensive patients. J Clin Epidemiol 1991;44:1361-71.

35. Halpern MT, Khan ZM, Schmier JK, et al. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. Hypertension 2006;47:1039-48.

36. Girard P, Blaschke TF, Kastrissios H, Sheiner LB. A Markov mixed effect regression model for drug compliance. Stat Med 1998;17:2313-33.

37. Grubisic M G-SF, Nichol MB, Yu A, Zhang Y, Cabilio P. Conceptualization and validation of a new metric – Sum of Squares Adherence Index (SSAI). In: ESPACOMP - European Symposium on PAtient COMpliance and Persistence. Bonn (Germany); 2006.

38. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. Jama 2002;288:455-61.

39. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007;10:3-12.

40. Schultz JS, O'Donnell JC, McDonough KL, Sasane R, Meyer J. Determinants of compliance with statin therapy and low-density lipoprotein cholesterol goal attainment in a managed care population. Am J Manag Care 2005;11:306-12.

41. Cramer J, Roy A, Burrell A, et al. Medication Compliance and Persistence: Terminology and Definitions. Value in Health 2007;doi:10.1111/j.1524-4733.2007.00213.x.

42. Larsen J, Andersen M, Kragstrup J, Gram LF. High persistence of statin use in a Danish population: compliance study 1993-1998. Br J Clin Pharmacol 2002;53:375-8.

43. Statistical Analysis of Claims and Payments: Health Services Executive Finance Shared Services Primary Care Reimbursement Services; 2006.

44. ATC Classification Index with DDDs: World Health Organisation Collaborating Centre for Drug Statistics Methodology; 2008.

45. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333:15.

46. Gray J, Majeed A, Kerry S, Rowlands G. Identifying patients with ischaemic heart disease in general practice: cross sectional study of paper and computerised medical records. BMJ 2000;321:548-50.

47. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. JAMA 1998;279:1458-62.

48. Gibson TB, Mark TL, Axelsen K, Baser O, Rublee DA, McGuigan KA. Impact of statin copayments on adherence and medical care utilization and expenditures. Am J Manag Care 2006;12 Spec no.:SP11-9.

49. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. Arch Intern Med 2006;166:332-7.

50. Thiebaud P, Patel BV, Nichol MB, Berenbeim DM. The effect of switching on compliance and persistence: the case of statin treatment. Am J Manag Care 2005;11:670-4.

51. Larsen J, Vaccheri A, Andersen M, Montanaro N, Bergman U. Lack of adherence to lipid-lowering drug treatment. A comparison of utilization patterns in defined populations in Funen, Denmark and Bologna, Italy. Br J Clin Pharmacol 2000;49:463-71.

52. Wei L, MacDonald TM, Watson AD, Murphy MJ. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study. Pharmacoepidemiol Drug Saf 2007;16:385-92.

53. Lachaine J, Rinfret S, Merikle EP, Tarride JE. Persistence and adherence to cholesterol lowering agents: evidence from Regie de l'Assurance Maladie du Quebec data. Am Heart J 2006;152:164-9.

54. Campione JR, Sleath B, Biddle AK, Weinberger M. The influence of physicians' guideline compliance on patients' statin adherence: a retrospective cohort study. Am J Geriatr Pharmacother 2005;3:229-39.

55. Kopjar B, Sales AE, Pineros SL, Sun H, Li YF, Hedeen AN. Adherence with statin therapy in secondary prevention of coronary heart disease in veterans administration male population. Am J Cardiol 2003;92:1106-8.

56. Grant RW, O'Leary KM, Weilburg JB, Singer DE, Meigs JB. Impact of concurrent medication use on statin adherence and refill persistence. Arch Intern Med 2004;164:2343-8.

57. LaFleur J, Thompson CJ, Joish VN, Charland SL, Oderda GM, Brixner DI. Adherence and persistence with single-dosage form extended-release niacin/lovastatin compared with statins alone or in combination with extended-release niacin. Ann Pharmacother 2006;40:1274-9.

58. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. J Gen Intern Med 2004;19:638-45.

59. Sung JC, Nichol MB, Venturini F, Bailey KL, McCombs JS, Cody M. Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. Am J Manag Care 1998;4:1421-30.

60. Hudson M, Rahme E, Richard H, Pilote L. Comparison of measures of medication persistency using a prescription drug database. Am Heart J 2007;153:59-65.

61. Benner JS, Pollack MF, Smith TW, Bullano MF, Willey VJ, Williams SA. Association between short-term effectiveness of statins and long-term adherence to lipid-lowering therapy. Am J Health Syst Pharm 2005;62:1468-75.

62. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. Pharmacoeconomics 2004;22 Suppl 3:13-23.

63. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. Clin Ther 2005;27:1639-46.

64. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med 2005;165:1147-52.

65. Gibson TB, Mark TL, McGuigan KA, Axelsen K, Wang S. The effects of prescription drug copayments on statin adherence. Am J Manag Care 2006;12:509-17.

66. Solomon DH, Avorn J, Katz JN, et al. Compliance with osteoporosis medications. Arch Intern Med 2005;165:2414-9.

67. Palepu A, Tyndall MW, Joy R, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. Drug Alcohol Depend 2006;84:188-94.

68. Breekveldt-Postma NS, Koerselman J, Erkens JA, Lammers JW, Herings RM. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. Respir Med 2007;101:1398-405. Epub 2007 Mar 23.

69. Ghisletta P, Spini D. An Introduction to Generalized Estimating Equations and an Application to Assess Selectivity Effects in a Longitudinal Study on Very Old Individuals. Journal of Educational and Behavioral Statistics 2004;29:421-37.

70. Hu FB, Goldberg J, Hedeker D, Flay BR, Pentz MA. Comparison of population-averaged and subject-specific approaches for analyzing repeated binary outcomes. Am J Epidemiol 1998;147:694-703.

71. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121-30.

72. Zorn CJW. Generalized Estimating Equation Models for Correlated Data: A Review with Applications. American Journal of Political Science 2001;45:470-90.

73. Ballinger GA. Using Generalized Estimating Equations for Longitudinal Data Analysis. Organizational Research Methods 2004;7:127-50.

74. How to estimate relative risk in SAS using PROC GENMOD for common outcomes in cohort studies? (Accessed 11th March 2008, at http://www.ats.ucla.edu/stat/sas/faq/relative_risk.htm.)

75. Abraha I, Montedori A, Stracci F, Rossi M, Romagnoli C. Statin compliance in the Umbrian population. Eur J Clin Pharmacol 2003;59:659-61.

76. Lesaffre E, Kocmanova D, Lemos PA, Disco CM, Serruys PW. A retrospective analysis of the effect of noncompliance on time to first major adverse cardiac event in LIPS. Clin Ther 2003;25:2431-47.

77. Clowes JA, Peel NF, Eastell R. The impact of monitoring on adherence and persistence with antiresorptive treatment for postmenopausal osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab 2004;89:1117-23.

78. Serruys PW, De Feyter PJ, Benghozi R, Hugenholtz PG, Lesaffre E. The Lescol(R) Intervention Prevention Study (LIPS): a double-blind, placebo-controlled, randomized trial of the long-term effects of fluvastatin after successful transcatheter therapy in patients with coronary heart disease. Int J Cardiovasc Intervent 2001;4:165-72.

79. Efron B. The Efficiency of Cox's Likelihood Function for Censored Data. Journal of the American Statistical Association 1977;76:312-9.

80. Allison PD. Survival Analysis Using SAS®: A Practical Guide. 9th ed. Cary, NC: SAS Institute Inc.; 1995.

81. Cox DRO, D. Analysis of Survival Data. London: Chapman and Hall; 9184.

82. Johnson ES, Mozaffari E. Measuring patient persistency with drug therapy using methods for the design and analysis of natural history studies. Am J Manag Care 2002;8:S249-54.

83. Andrade SE, Walker AM, Gottlieb LK, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? N Engl J Med 1995;332:1125-31.

84. Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. Value Health 2000;3:417-26.

85. Kamal-Bahl SJ, Burke T, Watson D, Wentworth C. Discontinuation of lipid modifying drugs among commercially insured United States patients in recent clinical practice. Am J Cardiol 2007;99:530-4.

86. Maitland-van der Zee AH, Stricker BH, Klungel OH, et al. Adherence to and dosing of beta-hydroxy-beta-methylglutaryl coenzyme A reductase inhibitors in the general population differs according to apolipoprotein E-genotypes. Pharmacogenetics 2003;13:219-23.

87. Mantel-Teeuwisse AK, Goettsch WG, Klungel OH, de Boer A, Herings RM. Long term persistence with statin treatment in daily medical practice. Heart 2004;90:1065-6.

88. Perreault S, Blais L, Dragomir A, et al. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. Eur J Clin Pharmacol 2005;61:667-74.

89. Perreault S, Blais L, Lamarre D, et al. Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol 2005;59:564-73.

90. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res 2007;13:559-65.

91. Klein JP. Modelling competing risks in cancer studies. Stat Med 2006;25:1015-34.

92. Andersen PK, Klein JP, Rosthoj S. Generalised linear models for correlated pseudo-observations, with applications to multi-state models. Biometrika 2003;90:15-27.

93. Fine JP. Regression modeling of competing crude failure probabilities. Biostat 2001;2:85-97.

94. Fine JP, Gray Robert J. A Proportional Hazards Model for the Subdistribution of Competing Risk. Journal of the American Statistical Association 1999;94:496-509.

95. Klein JP, Gerster M, Andersen PK, Tarima S, Perme MP. SAS and R functions to compute pseudo-values for censored data regression. Comput Methods Programs Biomed 2008;89:289-300.

96. SAS Macro For Cumulative Incidence Functions (Accessed 26th June 2008, at http://www.biostat.mcw.edu/software/incidence.txt.)

97. SAS Macros to find pseudo-values for censored data. (Accessed 26th June 2008, at http://www.biostat.mcw.edu/software/P-V_sas%20functions.txt.)

98. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. Biometrics 2005;61:223-9.

99. Logan BR, Zhang MJ, Klein JP. Regression models for hazard rates versus cumulative incidence probabilities in hematopoietic cell transplantation data. Biol Blood Marrow Transplant 2006;12:107-12.

100. Rosthoj S, Andersen PK, Abildstrom SZ. SAS macros for estimation of the cumulative incidence functions based on a Cox regression model for competing risks survival data. Comput Methods Programs Biomed 2004;74:69-75.

101. Ambrogi FB, Elia. Boracchi, Patrizia. Clinical useful measures for the study of competing risks in survival analysis. In: 28th Annual Conference of the International Society for Clinical Biostatistics. Alexandropoulis, Greece; 2007.

102. Resche-Rigon M, Azoulay E, Chevret S. Evaluating mortality in intensive care units: contribution of competing risks analyses. Crit Care 2006;10:R5.

103. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389-430.

104. Cheng CW, Woo KS, Chan JC, Tomlinson B, You JH. Association between adherence to statin therapy and lipid control in Hong Kong Chinese patients at high risk of coronary heart disease. Br J Clin Pharmacol 2004;58:528-35.

105. Cheng CW, Woo KS, Chan JC, Tomlinson B, You JH. Assessing adherence to statin therapy using patient report, pill count, and an electronic monitoring device. Am J Health Syst Pharm 2005;62:411-5.

106. Kruse W, Nikolaus T, Rampmaier J, Weber E, Schlierf G. Actual versus prescribed timing of lovastatin doses assessed by electronic compliance monitoring. Eur J Clin Pharmacol 1993;45:211-5.

107. Schwed A, Fallab CL, Burnier M, et al. Electronic monitoring of compliance to lipid-lowering therapy in clinical practice. J Clin Pharmacol 1999;39:402-9.

108. Stilley CS, Sereika S, Muldoon MF, Ryan CM, Dunbar-Jacob J. Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. Ann Behav Med 2004;27:117-24.

109. Tsuyuki RT, Bungard TJ. Poor adherence with hypolipidemic drugs: a lost opportunity. Pharmacotherapy 2001;21:576-82.

110. Colivicchi F, Bassi A, Santini M, Caltagirone C. Discontinuation of statin therapy and clinical outcome after ischemic stroke. Stroke 2007;38:2652-7.

111. Urquhart J. Pharmacodynamics of variable patient compliance: implications for pharmaceutical value. Adv Drug Deliv Rev 1998;33:207-19.

112. Urquhart J. The electronic medication event monitor. Lessons for pharmacotherapy. Clin Pharmacokinet 1997;32:345-56.

113. Shaya FT, Khoury ACE. Developing benchmarks for adherence studies. Expert Review of Pharmacoeconomics & Outcomes Research 2005;5:229-32.

114. Hughes DA, Walley T. Predicting "real world" effectiveness by integrating adherence with pharmacodynamic modeling. Clin Pharmacol Ther 2003;74:1-8.

115. Stern RH, Abel RB. Rate of low-density lipoprotein cholesterol and apolipoprotein B changes on initiation and discontinuation of atorvastatin treatment. J Clin Pharmacol 1997;37:291-6.

116. Sampietro T, Galetta F, Bionda A. Behavior of Lp(a) and apoproteins (A1, B, C2, C3, E) during and after therapy with simvastatin. Cardiovasc Drugs Ther 1995;9:785-9.

117. Metz CA, Lucas KH. Alternate-day dosing of HMG-CoA reductase inhibitors for cholesterol reduction. Ann Pharmacother 2001;35:496-500.

118. Matalka MS, Ravnan MC, Deedwania PC. Is alternate daily dose of atorvastatin effective in treating patients with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin Study (ADDAS). Am Heart J 2002;144:674-7.

119. McGinnis B, Olson KL, Magid D, et al. Factors related to adherence to statin therapy. Ann Pharmacother 2007;41:1805-11.

120. Rosen MI, Rigsby MO, Salahi JT, Ryan CE, Cramer JA. Electronic monitoring and counseling to improve medication adherence. Behav Res Ther 2004;42:409-22.

121. Rigsby MO, Rosen MI, Beauvais JE, et al. Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention. J Gen Intern Med 2000;15:841-7.