# Assessing the risks associated with warfarin therapy and related methodological considerations

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July 2007

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy

## PREFACE

This thesis was prepared according to the McGill university rules for a thesis by manuscript as found at: http://www.mcgill.ca/gps/programs/thesis/guidelines/preparation/ and described in section I part C. It consists of three manuscripts which are intended for publication in the peer-reviewed literature and have the common theme of methodological issues arising from describing adverse events related to warfarin in the General Practice Research Database (GPRD).

### Contributions of Authors

I (Joseph Delaney) wrote the thesis and the first drafts for all of manuscripts. I authored or co-authored all associated ethics protocols. I extracted the data from the GPRD and developed the databases on which this thesis is based. I had primary responsibility for all statistical analyses and sole responsibility for the statistical analysis for the first two papers. I had the original research ideas for the second and third papers.

Dr. Suissa had the responsibility for day to day supervision. He gave advice on the research questions on all three thesis papers and on the validity of the study designs. He was an important source of advice on approaches to presenting results and greatly improved the quality of the abstracts. He helped re-develop the approach to the second paper making it much more precise and focused.

Dr. Lucie Opatrny had the original research idea for the first paper. She was an extremely involved collaborator in the development of this paper and the process

of interpreting the results. She was involved in all aspects of the writing of the paper.

Dr. James Brophy substantially improved the first paper by making key suggestions for refocusing the scientific question, revising the draft and in critically commenting on the results.

Dr. Robert Platt had an important role in developing the statistical approaches in the second paper and in critically revising the intellectual content (especially the statistical content) of the paper.

Dr. Erica Moodie had an important role in developing the statistical approaches in the third paper and in critically revising the intellectual content (especially the statistical content) of the paper.

**Statement of Originality**

The first paper in this thesis is the first study to consider the risks associated with warfarin use in the GPRD using population based comparators. This allowed us to properly measure drug-drug interactions between warfarin and other drugs. It also allowed us to provide estimates of the size of these drug-drug interactions. It is also the first GPRD study on warfarin that directly modelled alcohol abuse as a confounder instead of using it as an exclusion criterion. In addition, it is the first study to estimate the magnitude of the channelling bias that exists for the co-prescription of warfarin and aspirin.

The second thesis paper represents the first systematic simulations of the properties of inverse probability of treatment weighted marginal structural models in the presence of effect modification. It is also the first real example (as opposed to hypothetical example) of marginal structural models being applied to study warfarin. It is also an implementation of marginal structural models in case-

control data and an example of where important differences can occur between marginal and conditional estimates in a practical example across the general population.

The third paper is the first study to validate the blood pressure measures recorded in the GPRD as an outcome for a pharmacoepidemiology study. It is also the first study to apply multiple imputation to improving the handling of missing values for blood pressure in the GPRD.

# ACKNOWLEDGMENTS

I would like to acknowledge my supervisor, Dr. Samy Suissa, and my committee members (Dr. Lucie Opatrny and Dr. James Brophy). Without their ideas, mentorship and good will this thesis could not have happened.

I would also like to thank Dr. Erica Moodie who became involved on short notice and made invaluable contributions to the statistics in this thesis. I would like to thank Dr. Robert Platt stimulating my interest in statistical modeling. I would also like to thank my thesis abstract translator, Dr. Christel Renoux, and my proof-readers, Dr. Stella Daskalopoulou and Dr. Verena Schneider-Lindner.

I want to thank my friends and colleagues at McGill University who made my years here better than they should have been. In particular: Marie-Pierre Sylvestre, Verena Schneider-Lindner, Kristian Filion, Linda Levesque and Raluca Ionescu-Ittu all taught me about both science and life. They are all in many of the categories below as well as being important influences in my life and career.

I also want to thank the other students in causal inference (Dana Teltsch, Jack Ishak, Sheila McDonald, Machelle Wilchesky) for inspiring conversations. I want to thank the students in Biostatistics for challenging me to think more and assume less (Marie-Eve Beauchamp, Ella Huszti, Genevieve Lefebvre, Katia Charland). And, not to forget a major part of my time at McGill, the Epidemiology and Biostatistics Student Society has been filled with many wonderful students (including Caroline Hebert, Jacqueline Quail and Karen Roberts). The last summer with the "RVH gang" has been great as well; going for drinks with Charlotte Van Der Avoort, Glen Stacey, Sarah Vahey, Stella Daskalopoulou, Ana Blagojevic and Chrissy St. Germaine has helped keeping me sane as I struggled to finish my thesis. There were some great conversations about epidemiology in there as well.

I also want to thank Diane Gaudreau and Sophie Dell-Aneillo for showing me the ropes at the Division of Clinical Epidemiology when I first arrived and being there ever since – especially when we ventured into learning about the GPRD.

I would like to thank the Canadian Institutes of Health Research (CIHR) and the Canadian Foundation for Innovation for funding the acquisition of the GPRD by McGill University.

# ABSTRACT

Warfarin is an anticoagulant medication that is used for the prevention and treatment of venous and arterial thrombotic complications. The evaluation of the risks associated with warfarin therapy, and its interaction with other drugs, poses important methodological challenges. In this thesis, we studied two of these risks and assessed techniques to address these methodological challenges using data from the United Kingdom's General Practice Research Database (GPRD).

First, we conducted a case-control study to examine the risk of gastrointestinal bleeding associated with warfarin use. We identified 4028 cases and 40171 matched controls from 2000 through 2005. Using conditional logistic regression, we found an increased risk of bleeding associated with warfarin use [adjusted odds ratio (OR) 2.15; 95% confidence interval (CI):1.81 to 2.54]. We also observed an increased risk due to drug-drug interactions between warfarin and other anti-thrombotic drugs. We also observed evidence of channelling bias as warfarin users were less likely to be prescribed other anti-thrombotic drugs.

Second, as warfarin has many weak interactions, we re-analyzed our case-control study using a marginal structural model to assess the overall impact of effect modification. This analysis produced a different estimate (for the population level instead of the individual level) for the risk of bleeding associated with warfarin [OR 17.2; 95% CI: 6.5 to 37.7] than analysis with conditional logistic regression. The impact of effect modification on these estimates was then assessed with a Monte Carlo simulation study.

Third, we created a cohort of patients given their first prescription of warfarin, ibuprofen, statins, or rofecoxib/celecoxib from 2001 through 2003 to study whether GPRD blood pressure data was of sufficient quality to model longitudinal increases in blood pressure as an adverse event. We compared different approaches to handling missing data. A hypothesized increase in systolic blood

pressure when initiating warfarin therapy was not supported with an observed reduction of 0.23 mmHg (95% CI:-0.78 to 0.31).

Studying warfarin adverse events poses several methodological challenges including channeling bias, unmeasured interactions and missing data. However, the careful application of statistical and epidemiological technique can provide improved risk estimates.

# RÉSUMÉ

Le traitement par Warfarine est utilisé pour la prévention et le traitement d'événements thrombotiques artériels et veineux. L'évaluation des risques associés au traitement par warfarine et son interaction avec d'autres médicaments représentent des défis méthodologiques importants. Dans cette thèse, nous étudions ces risques et évaluons les techniques pour relever ces défis méthodologiques en utilisant les données de la base de données *General Practice Research Database* (GPRD).

Dans un premier temps, nous avons réalisé une étude cas-témoins pour évaluer le risque de saignement gastro-intestinal associé à l'utilisation de la warfarine. Nous avons identifié 4028 cas et 40171 contrôles appariés, entre 2000 et 2005. En utilisant une régression logistique conditionnelle, nous avons constaté une augmentation du risque de saignement chez les patients sous warfarine [rapport des cotes ajusté (RC) 2.15 (intervalle de confiance à 95 % (IC) :1.81–2.54)]. Nous avons également observé un risque augmenté en raison d'une interaction médicamenteuse entre la warfarine et d'autres médicaments antithrombotiques. Enfin, nous avons mis en évidence un biais d'indication lié à la moindre probabilité de prescription d'autres médicaments antithrombotiques chez les utilisateurs de warfarine.

La warfarine ayant de nombreuses faibles interactions, nous avons, dans un deuxième temps analysé notre étude cas-témoins en utilisant un modèle structurel marginal pour évaluer l'impact global d'une modification d'effet. Cette analyse a produit une estimation différente (au niveau de la population et non d'un individu) du risque de saignement associé à la warfarine [RC 17.2 (IC à 95 % : 6.5–37.7)] de celle obtenue par la régression logistique conditionnelle. L'impact d'une modification d'effet sur ces estimations a alors été évalué par une étude de simulation de Monte-Carlo.

Enfin, nous avons créé une cohorte de patients selon leur première prescription de warfarine, ibuprofène, statines, ou rofécoxibe/célécoxibe entre 2001 et 2003. Nous avons étudié si les données de tension artérielle de la base GPRD étaient de qualité suffisante pour modéliser l'augmentation longitudinale de la tension artérielle en tant qu'événement indésirable. Nous avons comparé différentes approches pour la prise en compte des données manquantes. L'hypothèse d'une augmentation de la tension artérielle systolique à l'initiation du traitement par warfarine n'a pas été confirmée avec une réduction observée de 0.23 mmHg (IC à 95%:-0.78–0.31).

L'étude des effets indésirables liés à l'utilisation de la warfarine représente plusieurs défis méthodologiques tels que la présence de biais d'indication, d'interactions non mesurées et de données manquantes. L'application prudente de techniques statistiques et épidémiologiques permet cependant d'améliorer les estimations de risque obtenues.

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# Chapter 1

# Introduction

The discovery of warfarin dates to the 1920's when mouldy silage made from sweet clover was associated with an outbreak of fatal bleeding in cattle [1]. Initially used as a rat poison, warfarin was approved for human use in 1954 as an anticoagulant and it is now the most widely used anticoagulant in the world [1]. However, since warfarin overdoses can lead to death from bleeding complications, the use of warfarin requires careful monitoring with laboratory testing. These tests track the degree of anticoagulation through the international normalized ratio (INR) to prevent under or over-anticoagulation [1].

One of the important clinical and scientific challenges with warfarin therapy is balancing its risks and benefits. Despite its proven efficacy at reducing thrombotic events [2], warfarin therapy is also associated with serious bleeding and even fatal bleeding episodes [2]. While warfarin has other known side effects such as skin necrosis and hair loss [1], the side effect of significant levels of bleeding is the most serious and common.

Warfarin also has broad range of interactions with a variety of other drugs [3] that can increase the risk of adverse events when used in combination. To make matters even more complicated, there are many instances where patients are at extremely high risk of thrombotic events (often due to surgical recovery from percutaneous transluminal coronary angioplasty involving a stent) and require treatment with these potentially dangerous drug combinations [4]. In these cases, the risk of death due to bleeding is felt to be outweighed by an overall improved outcome due to the reduction in other extremely serious outcomes (such as reduced rates of a second myocardial infarction or stent thrombosis).

Previous population-based research on warfarin using prescription claims databases from the province of Quebec, Canada, has demonstrated that combinations of warfarin with other antithrombotic medications can lead to a surprisingly high rate of bleeding complications [5]. This research also shows that these multi-drug combinations are not rare and could thus have an important public health impact [5].

Given all of the complexities associated with warfarin therapy, it should not be surprising that there are several methodological problems with correctly studying the risks and benefits of exposure to this drug in the context of the general population. These methodological problems are in addition to the general problems that are encountered in all database research, such as missing data on the outcome or unmeasured confounders. For instance, since warfarin is well known as a drug with many contraindications, physicians may directly account for these contra-indications in their warfarin prescription decisions. This could cause strong channelling bias [6] and prevent the easy interpretation of the effects seen in an epidemiological study.

The goal of this thesis is to consider a number of methodological challenges associated with estimating the risk of warfarin adverse events in a population-based primary care database.

To derive estimates of the risks associated with warfarin therapy despite these challenges, we will employ a variety of statistical techniques. The goal of these approaches is to derive valid estimates of the elevated risks of adverse outcomes seen in patients who are exposed to warfarin. These statistical techniques include marginal structural models [7], linear mixed models [8], and multiple imputation [9]. As well, we will employ traditional epidemiological study design techniques, such as the risk-set sampled nested case control design, to remove issues of temporality from these studies [10].

By approaching the analysis of warfarin in this more sophisticated way, we provide a better estimate of the real-world risks of adverse outcomes associated with exposure to this drug. While there are known important benefits to warfarin therapy, a clear appreciation of the potential risks with therapy involved allows the most informed possible therapeutic decisions on the part of both clinicians and patients.

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# Chapter 2

# Background and Literature Review

The most important source of potential methodological problems in this study is due to the nature of the data that are being used. This study is situated in a clinical database. Clinical databases, such as the General Practice Research Database (GPRD), are a collection of medical information recorded by the General Practitioner in the course of managing patients rather than a systematically followed medical cohort. Because these data are not actively and systematically collected, it requires careful analysis to obtain estimates that can be properly interpreted as the mechanisms by which data are collected can be an important source of bias.

So we begin our background discussion by considering the source of the data for this study, how they are stored and their inherent strengths and limitations.

## 2.1 The General Practice Research Database

The GPRD is a United Kingdom (UK) clinical database based on the medical records of more than 400 UK general practices covering 3.2 million patients at any point in time [1-5]. The validity of the database has been extensively described in previous literature [1-5]. However, most of these validity studies were conducted before the year 2000; possibly because the validity of the GPRD database is now well accepted.

This database contains four types of information on patients enrolled in GPRD practices:

1) Medical codes for the diagnosis of health events/conditions including hospitalizations

2) Demographic and lifestyle information describing patients

3) Prescriptions issued by general practitioners

4) Laboratory test results

To date, the focus of most validation studies in the GPRD have been on the medical codes [4] although work has been done on validating codes for prescriptions issued and the demographic variables [1].

The key problem with the lifestyle variables as collected in the GPRD is due to missing data as these variables may not be systematically recorded for all patients which limits their utility as potential confounders in a statistical model [1]. However, the presence of missing lifestyle variable data is not necessarily a major limitation. Having even limited information on a confounding variable, such as smoking, is an improvement over prescription claims databases that lack this information entirely [6]. Furthermore, missing data can be accounted for in a variety of ways, including the use of multiple imputation [7], in order to obtain valid inferences. The quality of these inferences depend on the rate of missing data for the variable in question, but studies have shown good performance of multiple imputation on medical data when the proportion of missing data is less than 60% [7].

Prescription drug information in the GPRD is recorded based on prescriptions issued by general practitioners rather than prescriptions filled (as would be the case in prescription claims databases) [1]. This makes the GPRD an ideal setting to judge the impact of the prescribing behaviour of the general practitioner on health outcomes. While we never know if the prescription is filled, we know what the effect of the physician prescribing is on the outcome. This can be a much more direct measure of the effectiveness of the physician's behaviour on altering the patient's outcomes through prescribing drug therapy.

The medical codes that are used to diagnose diseases have been validated in the GPRD. These codes capture actual events with varying levels of sensitivity and specificity tending to be more specific than sensitive. However, "hard" outcomes that represent important events such as myocardial infarction [4], cancer [4], gastrointestinal bleeding [4], schizophrenia [2] and death [1] are generally well recorded and very specific. There is less complete information in the GPRD medical codes on the minor complications (like an episode of breathing problems) of chronic diseases, such as diabetes or asthma, although the presence of the disease itself is usually very well recorded [1].

Participating general practices are not required to record consultations with medical specialists (even if many of them do) making this variable differentially recorded and of questionable value in medical research [2]. In particular, this can lead to misleading inferences if the general practice is not controlled for (often by matching) in the data analysis.

Another known limitation of the GPRD is the lack of linkage to other health care databases in the UK [3]. This is especially problematic with hospitalization information, which is not systematically captured by the GPRD. While hospitalizations are required to be reported back to the general practitioner by the hospital, there is some evidence form the earlier GPRD validation studies that this reporting may not be well documented in the database. For example, 55% of hospitalizations were found to not have been captured by the database in a 1991 study [5]. Later GPRD studies find a much higher rate for the proper recording of hospitalization information (85% in a 1999 validation study) [1]. This suggests that GPRD information on hospitalization prior to the mid-1990's should be interpreted with caution. Even in modern GPRD studies, the cause of hospitalization may not be recorded in the database – especially for minor events. Despite this, the improvements in recording of medical information have played an important role in increasing the validity and utility of the GPRD for medical

research. As a result of this improved information, many studies in the GPRD currently use information only after the year 2000 to improve data quality.

In summary, the GPRD is a broadly validated database with a wealth of important information on outpatient health care that covers a large proportion of the UK population. The GPRD is broadly representative of the UK general population on factors such as age and sex [1-5]. This makes the GPRD an ideal setting for studies on drug therapy as we can infer the impact of drug therapy on GPRD patients to the whole of the UK population.

**2.2 Previous Research on Warfarin**

There is a broad literature on antithrombotic medications. A search for "warfarin" in PubMed up to May 3rd, 2007 yielded 12, 952 articles. A similar search for "aspirin" yields 39,594 articles. A search for "clopidogrel" yields 2,690 articles.

The majority of studies on these drugs are clinical trial reports, commentaries or observational studies (although some animal and pharmacokinetic studies are present). Commentaries interpret the results of previous studies and provide opinions or guidance to practitioners. The clinical trial information on these drugs is extensive and, in the case of warfarin, has a long history. Systematic reviews of antithrombotic drugs, such as warfarin, often use other systematic reviews as the units of observation [8]. In essence, this gives us a meta-analysis of meta-analyses which highlights the depth of research on warfarin involving randomized trials that is present in the literature.

Our goal is to consider the observational evidence since we are concerned that the close monitoring of patients in clinical trials, or even in prospective cohort studies, could under-represent risks of adverse events in patients exposed to warfarin who are in the community and receive the normal standard of care.

To better understand the risks associated with warfarin exposure at the population level, it is typically necessary to have databases that capture information at the population level. Clinical trials often lack the required information on potential adverse outcomes due to inadequate follow-up time or due to lack of power to detect rare but important adverse outcomes (such as death due to adverse drug effects).

The main choices for population level coverage are either clinical databases such as the GPRD [1] or prescription claims databases such as the *Régie de l'Assurance Maladie du Québec* (RAMQ) [6]. Some research has been done in the RAMQ prescription claims databases on warfarin [9, 10], clopidogrel [11] and aspirin [12-16] with studies considering both protective and adverse outcomes associated with these drugs. However, these studies are typically restricted to patients over 65 years of age due to the coverage of the database. Furthermore, this database lacks information regarding certain key confounders, such as alcohol abuse. The lack of these confounders could impact the validity of these studies given that alcohol can increase the antithrombotic effect of warfarin even at low doses [17]. This potential limitation also applies to other prescription-claims databases such as the medical databases of Saskatchewan, in which a single study on the antithrombotic warfarin was also conducted [18], or the medical databases of Ontario which have been used for numerous studies of warfarin [19-29].

Most of these database studies have shown a higher risk of bleeding in patients prescribed warfarin. However, some of these studies lack information on the distribution of important confounders. For example, a study in the medical databases of Ontario on potential drug interactions between warfarin and antidepressant medications was unable to assess the possible confounding effects of alcohol abuse [23] which is associated with both depression and some of the adverse outcomes (such as gastro-intestinal bleeds). While these studies can still add valuable information to the medical literature, it is necessary to extend these

studies to settings where there is information on these confounding factors – such as in clinical databases.

There have been previous studies on warfarin in the GPRD which is probably the best known example of a clinical database. We will now focus on these previous studies to survey what work has been done in the context of clinical databases and to motivate areas that this research can be extended to other GPRD researchers.

### 2.3 Previous GPRD Research on Antithrombotic Drugs

A number of studies on antithrombotic drugs have been conducted using the General Practice Database (GPRD). The primary drug of interest to us is the antithrombotic agent warfarin. While the use of warfarin reduces the risk of serious thrombotic events, it does so at the cost of increased bleeding risk. We searched PubMed for any article on antithrombotic agents using the search terms "general practice research database" in conjunction with "aspirin", "warfarin" and "clopidogrel". As noted before, we conducted our search up to May 3rd, 2007.

There have been a limited number of studies on warfarin prescriptions in the GPRD to date. There are three studies on the treatment patterns for patients with atrial fibrillation (which is an important indication for warfarin therapy) [30-32] and two studies on the bleeding risk of patients who are exposed to warfarin [33-34]. The previous studies on treatment patterns are drug utilization studies and, therefore, do not directly address the question of drug efficacy but rather determine the level to which treatment for medical conditions is in accordance with evidence-based treatment guidelines.

The first study we are considering was on warfarin and bleeding and conducted by Hollowell et al. [33]. This study was restricted to a group of

patients in the GPRD for which an indication for warfarin could be identified. All patients in this study were currently exposed to warfarin so the reference group was warfarin users with no other drug prescriptions. This study also used a very tight definition of exposure (current use being a prescription in the past 30 days) and a relatively restricted age range (40 to 85 years) based on the group of patients that the authors considered to be most clinically relevant. The authors focused their study on estimating the incidence rate of bleeding in these exposed patients but did consider age, sex and clinical indication as independent predictors of risk. They used a cohort approach to their study design and so were able to estimate the actual rate of bleeding in the GPRD. However, because they restricted their study to patients currently exposed to warfarin, they were unable to compare the relative rates of bleeding between patients exposed to warfarin and similar patients who were unexposed.

A second study on warfarin and bleeding by Gasse et al. [34] was conducted entirely within a cohort of patients with atrial fibrillation. While this study had the key advantage of insuring that the patients are more similar than with a general population cohort (as the patients in the general population may have a diverse set of indications for warfarin therapy), this focus has the downside of overlooking large groups of patients in which warfarin is extensively used. As with Hollowell et al. [33], this study was restricted to a cohort of current warfarin users and the authors estimated the risk of using drugs in combination with warfarin versus the use of warfarin alone. This approach does not allow the assessment of drug-drug interactions since there was no unexposed group (as all patients were exposed to warfarin), although it could document the increased levels of risk for bleeding episodes in patients who were also taking drugs such as aspirin in combination with warfarin.

In a third study and the second by Gasse et al., Gasse et al. [34] documented an increased risk associated with aspirin use among those patients who were also exposed to warfarin. The high rate of bleeding that they reported

was much larger than the rate that is typically seen for aspirin alone. So this study acts as an indirect test of interaction between aspirin and warfarin by suggesting that the addition of aspirin to a patient's drug therapy leads to greater risks of bleeding among patients who are already exposed to warfarin. The authors were also able to consider a broad range of other drugs that might interact with warfarin to increase bleeding risk by pooling these drugs and considering the number of potentially interacting drugs taken at the same time as warfarin. This approach was a way to avoid the lack of power due to the rare nature of some of these interactions. However, the increase in power came at the cost of losing specificity as to which drugs were the primary drivers of increased rates of adverse drug events.

In addition, the authors chose to exclude patients with some of the key confounders such as a history of alcohol use. While restriction is a valid approach to controlling for confounding, not including these patients creates the possibility of underestimating the actual risk in the general population. It also removes the ability of the authors to test for whether alcohol use is associated with an increased risk of bleeding among patients exposed to some of the study drugs.

To our knowledge, this thesis is the first study in the GPRD to consider clopidogel as a primary drug exposure or to attempt to quantify its association with an increased risk of bleeds. No articles were located in PubMed in evolving both clopiogrel and the GPRD, although this drug has been widely studied in other databases and the possible risks of clopidogrel exposure are extensively reported in the clinical trials literature.

There are twenty published studies on the prescription of aspirin in the GPRD that we were able to locate in our PubMed search. These studies range from risk studies on increased risk of bleeding to documenting the potentially protective effects of aspirin on the development of cancer.

Four GPRD studies examined treatment patterns of drugs including aspirin in patients diagnosed with either atrial fibrillation or heart failure [30-32, 35] and three also looked at warfarin utilization in these populations [30-32]. Ten studies looked at potentially protective effects of aspirin therapy on cancer [36-40], myocardial infarction [41-44] and Parkinson's disease [45].

The study on aspirin use and the rate of Parkinson's disease found no effect of aspirin exposure. The protective effect of aspirin on myocardial infarction is well known from the clinical trials literature. Less clear, however, is whether the GPRD is an ideal environment to study the association between aspirin use and the development of cancer. Patients with health-seeking behaviours may take aspirin as part of their "health promotion" regime, but these patients may also engage in other behaviours (improved diet, increased exercise) that are protective against cancer. This confounding of health seeking behaviour and aspirin use is difficult to tackle in the GPRD and it makes the small protective effects of aspirin use on the rate of cancer that are seen by these studies difficult to interpret.

The authors of one study looked at aspirin as a small part of a larger validation study that compared the data quality in the GPRD to data quality in the health improvement network database [46]. This validation study used the validity of the GPRD as the gold standard level of validity for clinical practice databases. This use of the GPRD as a gold standard is a mark of the degree of confidence that researchers have in GPRD validity.

The last six studies in the GPRD involving aspirin involved evaluating bleeding risk upon exposure to drugs. Two of these studies used aspirin as a covariate in the study of other drugs [47-48] and the risk of gastro-intestinal bleeding (anti-depressants and cyclical etidronate). These studies were not specifically designed to answer questions about the risks associated with aspirin and appeared to be mainly focused on controlling confounding between aspirin

use and the use of the primary drug under study. One study, previously mentioned for its discussion of warfarin, also considered the risk of bleeding associated with aspirin but only among patients who were already exposed to warfarin [34]. However, this effect is difficult to interpret outside of the context of a patient population that is being treated with warfarin as the increased risk associated with aspirin use is likely to be some combination of a real aspirin effect and a drug-drug interaction.

The last two studies considered the increased risk of gastrointestinal bleeding among patients who were prescribed aspirin [49-50]. The study by de Abajo et al. [50] found a slightly higher risk associated with aspirin than that reported by Henandez-Diaz et al. [49]. Interestingly, de Abajo et al. also found a slightly higher risk among the patients prescribed entric coated aspirin than those patients who were prescribed regular (non-entric coated) cardio-protective aspirin. This finding of increased risk of gastro-intestinal bleeding among patients who were exposed to a protective agent is compatible with previous reports. These reports suggest that drugs that are intended for use in high risk patients might be subject to channelling bias and this makes it difficult to obtain an unbiased estimate of risk in a database study [51].

While not antithrombotic agents, there have also been GPRD studies on other drugs that are given for indications similar to that of aspirin and have similar possible side effects. These studies include ones on non-aspirin non-steroidal anti-inflammatory drugs [51-53], acetaminophen (paracetamol) [54] and steroids [55]. Some of these studies have also considered GI complications with drug use and have found consistent results of drug use being associated with an increased risk of bleeding as compared with GPRD studies on aspirin.

However, there is currently a lack of population level studies on adverse effects for warfarin and clopidogrel in the GPRD. With warfarin, the previous GPRD studies have considered only warfarin users without population based

comparison groups. Without these comparison groups, it is impossible to rule out other reasons for observing the size of the bleeding risk associated with drug use. It is also impossible to determine which part of the effect of another drug, such as aspirin, in users of warfarin is due to the aspirin itself and which part of the effect is a drug-drug interaction.

Therefore, further work on adverse events associated with warfarin therapy in the GPRD has the potential to enrich our understanding of the potential risks of prescribing this drug in the UK general population.

**2.4 GPRD studies and matching**

Cohort studies are not typically conducted using the GPRD because of the clustered nature of the database. Different practices in the GPRD have different standards for recording diagnostic codes [2] which need to be accounted for in the analysis of GPRD studies. This bias could arise because of differences in the distribution of practice-related factors (such as recording of some types of medical codes such as specialist visits) between the exposed and the unexposed. This difference in recording practices is not as serious of an issue in certain studies where both the exposure and the outcome are either prescriptions issued or records of test information as the recording of these data is standardized across the GPRD [1]. However, it is never good practice not to account for the potential recording differences GPRD medical practices.

When looking at an outcome or primary exposure that is a diagnostic code in the GPRD, it is therefore important to account for the variability in diagnostic code recording between different GPRD practices [1,2]. One way to account for this variability is to match incident cases with a referent group from the same practice. This approach to handling confounding by practice is popular among GPRD researchers due to the number of practices in the database (>400) which makes the use of indicator variable methods inefficient [1-2]. Another alternative

to handle this issue with practice-related confounding would be to use a random-effects model (in which each practice had its own unique intercept) but this has not been a common approach in GPRD studies due to the computational issues in implementing these models in large database studies.

In addition, an extra advantage of the matching on practice approach is that it naturally extends to matching on calendar time as well. By matching on both calendar time and practice, the analyst is thus able to also control for the changes in individual-level practice recording policy over time. Since the quality of information recorded by practices increases over time, this is actually important.

The analysis of cohort data using a matched case-control design has been widely described [56-60]. While this study design is often called the nested case control study [59-60], there is some ambiguity about this terminology as nested case control has also been used in the epidemiological literature to mean a regular case control study nested within a cohort even if this cohort is not explicitly defined or followed – as all cases and controls ultimately come from some population cohort [56]. This definition seems sub-optimal as all case-control studies could be considered to be nested case-control studies and this seems to remove any useful meaning from the definition.

An alternative name for this type of approach, when one considers the hazard functions as being constant over time, is that of incidence density sampling [57]. This idea of comes from Miettinen and his early work on case-control studies [61]. This type of analysis often gives an average rate ratio instead of an instantaneous rate ratio unless the time bands selected are quite narrow (as the width of the time bands goes to zero, we get a hazard ratio instead of a rate ratio).

The basic principle that underlies this type of "nested case control" design is to obtain a sample of person-moments who are representative of the "person-

time experience out of which the cases arise" [61]. The odds ratios given by the analysis of these study designs will approximate the rate ratio without any need for a rare disease assumption [56]. While there is a slight cost in precision when the case is matched to less than 20 controls [60] this is typically extremely low in the very large studies usually conducted in the GPRD [56].

However, when the controls are sampled randomly from the population that is at risk at the time of the event, we can describe the controls as being selected using risk set sampling [60, 62, 63]. The key requirement for this approach is that the controls must be selected as a random sample of the population which is at risk for the event at the exact same time as the case occurs (i.e. the members of the case's risk set). Risk set sampling of the controls allows the estimates from the nested case control study with risk set sampling to directly approximate those of a prospective cohort study [57]. We can interpret the estimates derived from this approach to data analysis as representing the baseline cumulative hazard ratio (the same parameter estimated from a cohort study that begins at baseline and does not account for any changes in the proportionality of the hazard ratio) [60]. This design also removes assumptions about the prevalence of the exposure across the life of the cohort [64] and is a natural environment to introduce other important matching criteria.

The risk set sampled nested case-control study design is the most logical approach to analysis of GPRD data that does not involve more complex techniques (such as the use of random effects models). This is especially important when the medical codes are either the primary exposure or are used to define the study outcome. The reason for this is that most of the differences between practices cannot be directly observed in the data and must be accounted for using either matching or clustered data analysis.

While there are frequency-matched cohort studies that have been conducted in the GPRD [65, 66], these studies typically already match on either

the time that exposure begins or the time of outcome as well as practice. Because they sub-sample the unexposed population, it is not trivial to correct the estimates obtained from these studies to get the actual underlying rate of events in the GPRD population. Therefore, these approaches do not seem to bring any substantial advantages to the analysis of GPRD data above and beyond those that are seen with matched case control studies, although small advantages are possible with cohort approaches [61]. In particular, issues due to censoring are less visible in a nested case-control analysis. However, censoring is not the critical issue in GPRD studies that it would be in a prospective study of an exposure-outcome relationship as participants typically drop-out of randomized controlled trials and prospective cohort studies at much larger rates than patients change general practices.

In the case of a database like the GPRD, the underlying structure of the data makes a risk set sampled nested case control study the most attractive way to estimate the rate ratio of events in an unbiased way. However, this analytical approach does come with the disadvantage of not giving a direct estimate of the rates of disease in the population but only in the relative increase in rate among the exposed as compared to the unexposed.

However, the advantage of using a method of analysis that can use matching to partially control for potential unmeasured confounding by practice-related factors is important and this limitation in choice of study design is a small disadvantage when compared to the ability of GPRD data to answer a broad class of interesting medical questions that arise in the primary care of patients. In this thesis, we will first illustrate the use of a nested case control design to directly answer a medical question to show the use of standard technique. Later on, we will show that this is not the only option when we apply a random effects model to GPRD data as an analytic alternative.

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# Chapter 3

## Drug-Drug interactions between antithrombotic medications and the risk of gastro-intestinal haemorrhage

This chapter contains a greatly expanded version of a manuscript that was submitted to the Canadian Medical Association Journal.

This paper describes bleeding as an adverse effect of exposure to warfarin. This is the best known warfarin adverse effect. The novelty in the papers comes from looking at warfarin in conjunction with other antithrombotic drug therapies.

Therefore, the primary focus of this paper is on evaluating drug-drug interactions between antithrombotic medications leading to increased risk of bleeding. To have a clear example of bleeding, we picked a single major type of bleeding for which hospitalization is certain (gastrointestinal bleeds).

It also contains a discussion of channelling bias away from specific medications in the General Practice Research Database (GPRD). This occurs when physicians avoid giving a medication to a patient due to concerns that it may interact with other medications that the patient is on. It presents evidence that this channelling is happening differently among users of warfarin and clopidogrel.

Particular care was used to adjust for confounding in this example, including those variables such as alcohol. This is especially important given the evidence of drug channelling due to risk factors. The estimates of the rate ratio for some drugs, such as anti-depressants, were significantly impacted by the inclusion of alcohol abuse as a confounder.

The contributions of authors are listed in the preface to the thesis.

# Drug-Drug interactions between antithrombotic medications and the risk of gastro-intestinal bleeding

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**ABSTRACT**

**Background**: Anticoagulants and antiplatelet drugs (such as warfarin, clopidogrel and aspirin) are key therapeutic agents in patients who have conditions such as atrial fibrillation and venous thrombo-embolism. However, these drugs are known to increase bleeding risk and the total magnitude of any increased bleeding risk associated with the combination of these drugs is unclear.

**Objective:** To assess the risk of antithrombotic drug combinations on the rate of gastrointestinal (GI) bleeds across a general population.

**Design:** Population-based, retrospective case-control study in the United Kingdom General Practice Research Database (GPRD) from the year 2000 through the year 2005 matched on physician practice, patient age and calendar date. All patients had at least 3 years of follow-up in the database. Index date was defined as the date of first-ever GI bleed for the cases and their matched controls. Drug exposure was measured by any prescription issued in the 90 days before the index date.

**Participants:** 4028 cases of GI bleeding and 40171 controls.

**Results:** The co-prescribing of aspirin with either clopidogrel [rate ratio (RR): 3.9; 95% confidence interval (CI): 2.8 to 5.5] or warfarin [RR: 6.5; 95% CI: 4.2 to 9.8] was associated with an increased risk of a GI bleed over the risk observed with individual drugs. There was also evidence of drug channelling in that patients exposed to warfarin were less likely to be co-prescribed other medications that also increase bleeding risk. After adjusting for age and sex, patients who were prescribed clopidogrel were as likely as the general population to be prescribed either aspirin [RR: 1.00; 95% CI: 0.82 to 1.22] or a non-steroidal anti-inflammatory drug [RR: 0.97; 95% CI: 0.74 to 1.27]. In contrast, warfarin

users were much less likely to be prescribed aspirin [RR: 0.22; 95% CI:0.18 to 0.28] or an NSAID [RR: 0.44; 95% CI:0.34 to 0.56].

**Interpretation:** Drug combinations involving antiplatelet and anticoagulants are associated with a high risk of GI bleeding. Physicians should continue their current practice of exercising caution when co-prescribing antithrombotic medications.

**Word Count:** 3474

**Abstract Word Count:** 282

**Tables:** 5

**Figures**: 2

## INTRODUCTION

Gastro-intestinal (GI) bleeding is a significant source of morbidity and mortality. Reports suggesting an incidence rate of GI bleed as high as 103 per 100,000 people in the population [1]. It is well known that non-steroidal anti-inflammatory agents (NSAIDs) [2], warfarin [3] and antiplatelet therapies [4] all independently increase the risk of a GI bleed.

Previous work on the effect of combining these drugs has strongly supported the notion that the combination therapy with anticoagulant and antiplatelet drugs can lead to an increase in major bleeding episodes [6-9]. Since approximately 1% of the UK population is on warfarin therapy [3] and many patients are simultaneously prescribed antiplatelet agents for concomitant disease or consume over-the-counter NSAIDs for symptom control [5], it is important to determine the increased risk of bleeding that combinations of these drugs may cause. Since it is possible that these therapies may become more widespread, it is important to extend this work to the general population as well as selected hospital-based populations. This information would be especially informative with newer COX-2 inhibiting NSAIDS agents as they are thought to have a lower overall risk of GI bleed [10], and little population data currently exist on their interaction with other medications.

Database studies have played an important role in finding risk factors for GI hemorrhages particularly in terms of adverse drug reactions [11-15]. The objective of this study was to document the evidence of effect modification between anti-thrombotic agents, based on contemporary practice standards, outside the context of a controlled clinical trial. This will enable us to assess the practical current risk of upper GI bleeds among patients on combinations of warfarin and anti-platelet agents.

## METHODS

The General Practice Research Database (GPRD) is a United Kingdom (UK) based clinical database thatcontains information on a few million patients at the general practice level [16-21]. This is an extensively validated database that provides information on the community care of patients as the General Practitioner (Family Doctor) is the center of primary care in the UK [16-21]. This database is also ideal for pharmacoviligance and the finding of rare adverse drug events, such as drug-drug interactions, in the general population [21].

Using the GPRD we identified all cases with a first diagnosis of upper GI bleed in the recorded using either a READ or OMXIS medical code in the database between Jan 1st, 2000 and December 31st, 2005 by a General Practitioner reporting to the GPRD. For a list of GI bleed codes used to identify outcomes in this study please refer to Table 3.5. We focused on the first-ever event (with at least 3 years of follow-up) in order to focus on people who did not have a specific drug contra-indication due to previous GI bleeds.

The date of the medical event as recorded in the GPRD was defined as the index date for the case. Up to ten controls were randomly selected for every case matched on GPRD practice, age (plus or minus 2 years) and the index date of the case was allocated to its controls. All patients in this study (cases or controls) were required to have at least 3 years of follow-up time prior to the index date to enable an adequate assessment of the patient's medical history.

### Exposure Definition

Our main exposure was anti-thrombotic drugs. We defined exposure to a drug as being any prescription for a pharmaceutical agent in the 90 days prior to the index date.

In order to control for confounding, we assembled a list of drugs previously considered to be either protective against GI bleed or to promote GI bleed. We adjusted for any use of these agents. We considered the following drugs as potential confounders: proton pump inhibitors, diuretics, $H_2$ antagonists, antidepressants, antibiotics, corticosteroids and paracetamol. All drugs were defined using the British National Formulary classification system [22].

**Co-morbidity Definition**

We defined the presence of a co-morbid condition as being any previous history (as defined by a GPRD medical code) for a medical condition being recorded in the database prior to the index date. In order to control for confounding, we considered a broad range of indicators of patient morbidity as well as risk factors for GI bleeds or indications for warfarin use.

We considered as covariates a past history of the following diseases: gastro-esophageal reflux, peptic ulcer disease, a recorded positive test for Helicobacter Pylori, a moderately high blood pressure reading in the past 1 year (systolic blood pressure above 160 or diastolic blood pressure above 100), a mildly high blood pressure reading in the past year but no high reading (systolic blood pressure above 140 or diastolic blood pressure above 85), no blood pressure reading in the past year (missing data), liver failure, renal failure, rheumatoid arthritis, other types of arthritis (either unspecified or oesteo-arthritis), diabetes (either type I or type II), cancer (any type), chronic obstructive pulmonary disease and any form of dementia. We also examined the indication for warfarin use, including cardiac arrthymia [23], pulmonary embolism, deep vein thrombosis, congestive heart failure, myocardial infarct, angina and stroke.

We also adjusted for the demographic characteristics of the cases and controls including age, sex, smoking status, body mass index (BMI) and history of heavy alcohol use as recorded in GPRD medical codes. A BMI of under 18 was considered underweight, a BMI above 30 but less than 40 to be obese and a BMI of 40 or higher to indicate morbid obesity. A positive history of smoking (current or past) was grouped together as a single smoking variable given the known limitations in the GPRD [24] for this variable.

**Data Analysis**

The primary data analysis was done using conditional logistic regression to analyze a nested case-control study [25]. This design was required to enable us to match by GPRD practice and account for potential recording and therapeutic practice differences between practices. All covariates were entered into the model as well as interaction terms between anti-coagulants and NSAIDs to model effect modification. Odds ratios for the outcome were computed and used as an approximation of the rate ratio (RR) for users of these medications [25]. We estimated both the RR for the interaction term (showing risk above and beyond that of a single medication) as well as the RR for drug combinations (showing the total increase risk among those patients who were exposed to many agents as compared to those exposed to none).

We also modeled the probability of being prescribed aspirin or an NSAID among the controls (who are a random sample of the population from which the cases arose) adjusting for age and sex in order to test for channelling bias in who is co-prescribed these medications. A special problem for warfarin in particular was that some of the drug-drug interactions are well known and this may cause the physician to avoid co-prescriptions. This is slightly different from confounding by indication as it is confounding by "contra-indication" although it is the same idea.

All analyses were performed using SAS version 9.1.3 software.

## RESULTS

There were 4028 cases identified in our study with a first episode of GI bleeding and matched by age, general practice and index date to 40171 controls. The demographic and lifestyle characteristics of the cases and controls are described in Table 3.1. Male sex and being underweight were associated with an increased risk for GI bleeding. Other variables associated with an increased risk for bleeding included a history of heavy alcohol use and a history of past or current smoking.

There were a number of co-morbid conditions that we observed to be related to a higher rate of GI bleeding after adjustement (Table 3.1). These included liver failure, renal failure, dementia and having COPD. Of note, people on corticosteroid therapy did not have an increased risk of GI bleed (adjusted RR 0.90; 95% CI: 0.81 to 1.00) although only a small number of patients were exposed to oral agents (as opposed to inhaled or topical agents).

The strong effect of heavy alcohol use (adjusted RR: 4.00; 95% CI: 3.45 to 4.63) on the risk of GI bleeds is important to note. If it is related to any drug use, it has the potential to be an extremely important confounder not generally available in prescription claims databases. Since alcohol abuse is a strong contra-indication for warfarin use but also promotes GI bleeding, it was a potentially important confounder.

For single agent use, the risk of GI bleed on warfarin therapy was similar, if higher, than that observed among users of clopidogrel alone (Table 3.2). There was an increased risk of GI bleed among the users of NSAIDs.

The rate of co-prescription of NSAIDs and warfarin was lower than would be expected by chance alone. We used the rate of prescription to the overall control population to estimate the number of users of warfarin and clopidogrel that would be exposed to ibuprofen, aspirin and other NSAIDs if these sub-populations had been prescribed drugs at the same rate as the age-matched UK general population (Table 3.3). For example, if we apply the rates of prescription of ibuprofen in the control population as a whole to the population exposed to warfarin, we would have expected 38 patients to be exposed to both ibuprofen and warfarin. Instead only 17 patients were actually exposed to both agents in the study. This pattern of lower rates of co-prescribing did not persist in the clopidogrel sub-population.

We can estimate the size of this effect. After adjusting for age and sex, being prescribed clopidogrel had no effect on the rate of aspirin prescription [RR: 1.00; 95% CI: 0.82 to 1.22] or an NSAID [RR: 0.97; 95% CI: 0.74 to 1.27]. In contrast, warfarin users were much less likely to be prescribed aspirin [RR: 0.22; 95% CI:0.18 to 0.28] or an NSAID [RR: 0.44; 95% CI: 0.34 to 0.56].

Patients on either celecoxib or rofecoxib showed a higher risk of GI bleed (RR = 1.64) than those patients exposed to no NSAID of any kind. We lacked sufficient sample size to test for effect modification with these drugs (Table 3.4).

We did find an important effect modification (26) between co-prescription for aspirin and warfarin as well as for co-prescription of aspirin and clopidogrel (Table 3.4) on the rate of GI bleed. We can see the rate ratios for exposure to each of these agents in Figure 3.2.

We also tested for evidence of a warfarin-paracetamol effect modification due to suggestions in the literature of a mechanism for a drug interaction that could give rise to this (27) but the test for effect modification did not reach significance (p=0.06). We did, however, continue to see a higher risk for users of

paracetamol for GI bleeding [RR: 1.47; 95% CI: 1.35 to 1.60] as compared to non-users. We did not find a protective effect for proton pump inhibitors on the rate of GI Bleed when comparing those patients who were exposed to these agents as compared to those patients who were not (Table 3.1).

**INTERPRETATION**

The goal of this study was to determine the excess risk caused by the combinations of the anti-thrombotic agents such as aspirin, clopidegel and warfarin. We also intended to document the surplus risk caused by the combination of these agents with NSAIDS. The main new finding of this study was to document large size of the effect modification between clopidogrel and aspirin (RR = 3.90 for patients exposed to both agents as compared to patients exposed to neither). If we combined this effect with the effect observed between warfarin and aspirin then the size of the potential risk increase becomes even larger for patients who are exposed to all three agents; although we were unable to directly observe any meaningful number of cases exposed to all three agents in this population. Therefore, any discussion of the effect of exposure to all three antithrombotic agents simultaneously remains speculative.

While we lacked the power to properly assess the effect modification of warfarin with cyclooxygenase-2 (COX-2) inhibiting NSAIDs on the risk of GI bleeding, it was interesting to note that exposure to these drugs was associated with a significant increase in risk of GI bleeding when compared to patients unexposed to any of the drugs detailed in Table 1. Our finding of increased risk among users of COX-2 selective inhibitors (both rofecoxib and celecoxib in this study) is supported by previous studies on these drugs [28-29] that also showed increased bleeding risk among patients who were exposed to these agents. In addition, given the limited evidence for protection against GI bleeding supplied by these studies, the use of these agents should be further weighed in the balance

against recent highly publicized data about cardiovascular [30] and renal failure [31] risks related to the use of COX-2 inhibitors.

However, as we did not find a protective effect of proton pump inhibitors on the risk of GI bleed, it is possible that the confounding that was present with these drugs has also influenced the estimates for the COX-2 inhibitors.

**Methodological Issues**

Our study supports a previous study in the GPRD that has suggested channeling bias [32] in the prescription of drugs to warfarin users [33] due to the low rate of co-prescription of drugs like ibuprofen and aspirin observed in the database. Both our study and MacDonald et al. [33] suggest that careful patient-based prescribing practice of warfarin therapy reduces the rate of GI bleeds that would otherwise be experienced in the UK. It is unknown what criteria physicians use clinically to determine elevated risk of bleed and how this perception of increased risk may affect their prescribing choices, although some work has indicated that physicians base prescription choice more on potential risks than benefits [34].

We evidence of confounding by indication in this study with the "elevated risk" seen with proton pump pump inhibitors as these drugs are given to high risk patients. This risk increased has been seen in previous observational studies of GI bleed [35] and occurs because proton pump inhibitor use is a marker for greatly elevated risk. Clinical trial evidence confirms that these drug are actually protective and, therefore, this is confounding by indication [36] and that these drugs are actually protective.

The channeling bias seen with warfarin should be in the direction of reducing the size of an adverse effect by making risky drug combination less likely. This is supported by the low rate of drug co-prescription for warfarin with

drugs known to interact with it to increased bleeding that we noted in the database. Therefore, we should interpret the estimates of risk seen between warfarin and NSAIDs/aspirin to the "lower limit" of the actual effect size as there is likely to be channeling away from high risk patients.

This pattern of lower co-prescription did not persist with clopidogrel and aspirin. This suggests that physicians are less aware of the risks of co-prescription with clopidogrel or are deciding that the benefits of co-prescribing these drugs outweigh the risks. This might be especially true if the patients prescribed both clopidogrel and aspirin had a recent procedure with a risk of complications such as percutaneous transluminal coronary angioplasty involving a stent [37], where the risk of stent thrombosis may be felt to outweigh the risk of bleed. However, because of the limitations of the GPRD, it was not possible to assess the history of these hospital-based procedures among the patients in our study [16]. If most patients who are exposed to this drug combination have recently had surgery then it is possible that the excess risk of the drug combination may be balanced by the known benefits of coronary surgery [38] and the lower risk of post-surgical complications [37].

In observational studies there is always the possibility of unknown confounders that could influence the results of our study despite our extensive attempts to broadly control for confounding. Our definition of co-morbidity was developed to account for the possibility that some conditions are likely to be recorded only once upon the patient's admission to a practice in order to maximize the chances of detecting potential confounders. Given the broad range of conditions that we have controlled for, it seems unlikely that there is a strong unmeasured confounder that could completely explain our results. The ability for studies in the GPRD to control for potential confounders such as past readings of clinical blood pressure, alcohol use and smoking are key advantages that this study has over prescription claims database studies on these drugs [6, 29].

Other issues common to large database studies with secondary use of data were also present. These include missing data (which we account for using indicator variables) and the selective recording of other variables (such as blood pressure). In addition, some important variables such as smoking or alcohol use are relatively crudely defined. It would have been an advantage to have a more complete definition of smoking such as pack-years smoked, for example.

A more abstract approach to confounding, like that of counterfactuals, might motivate a different type of analysis such as a marginal structural model approach. This type of analytic approach might be a logical extension of this approach as it makes fewer parametric assumptions about the relationships in the data [39].

Because we have prescriptions written but not filled, it is possible that some of the patients classified as exposed are actually unexposed. However, this misclassification would make the exposed and the unexposed more similar and result in a bias towards a null effect. It is also possible that warfarin use could involve some degree of cumulative risk and, in such a case, use of a fixed time window to measure exposure may not be the ideal approach [40]. However, cohort studies of warfarin use do not seem to reveal any evidence of an increase in risk over time [41] suggesting that the fixed time window approach is appropriate for this study question.

The 90 day exposure window is another potential limitation. In the GPRD there are some assumptions required to calculate duration of prescription and this can be especially difficult to establish when studying a drug like warfarin where the dose may be modified mid-prescription due to the results of laboratory tests [42]. This may result in slightly lower estimates of risk due to exposure misclassification. However, the reverse (misclassifying users as non-users) would seem to be the greater risk here. Not only would it reduce our power to look at drug-drug interactions, but it would also induce a misclassification bias that could

be at least as large by placing exposed patients among the controls. As problems with the drug might be part of why a longer time window occurs between refills (as warfarin doses are dynamically changed during treatment) this could actually remove some of the highest risk patients who give the most important information as to the risk associated with warfarin exposure.

**Clinical Interpretation**

The combination of warfarin and aspirin has a stronger effect in this study than that seen in a recent meta-analysis of clinical trials [43]. While this could be due to residual confounding, it is more likely due to the higher risk observed with warfarin outside of the tightly controlled setting of a clinical trial where monitoring of the degree of anti-coagulation in patients may be more frequent [44], and patient comorbid factors are fewer. Studies have shown that patients in community practice often do not have precisely controlled anticoagulation [42]. The translation of clinical trial results to clinical practice can be tricky when the trial involves intensive monitoring of high risk patients that might not be available in routine care.

While this study is a step forward, more research is needed to better understand the overall burden of risk due to co-prescription of aspirin and clopidogrel. This is especially true given current suggestions in the literature that the effect modification could have been in the opposite direction [45] which would have predicted much less risk than we observed.

Studies have shown that up to half of some types of adverse bleeding events in warfarin users may be due to adverse drug reactions [46] and it would be surprising if clopidogrel did not have similar increased risks associated with drug combinations (although the mechanisms may differ). Physicians need to weigh the increased risk of GI bleed against the known therapeutic benefits of these drugs; especially when using them in combination. Providing evidence of

the empirical risk of treatment in the community is an important step forward in balancing the risk of GI bleeds with the known benefits of these drugs.

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**Table 3.1: Characteristics of Upper gastro-intestinal (GI) Bleed Case-Control Population and relationship (odds ratio) between each characteristics and the first episode of Upper GI Bleed**

| Covariates | Cases (N=4028) | Controls (N=40171) | Crude Odds Ratio | Adjusted Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|---|
| **Personal Characteristics** | | | | | |
| Age (year) Mean [Range] | 69.3 [18-104] | 69.1 [18-105] | 1.06 | 1.05 | 1.03 to 1.08 |
| Male Sex | 2171 | 17237 | 1.58 | 1.50 | 1.40 to 1.62 |
| Female Sex | 1857 | 22934 | 1.00 | 1.00 | n/a |
| Body Mass Index | | | | | |
| < 18 | 105 | 690 | 1.57 | 1.52 | 1.21 to 1.91 |
| 30 to 39.9 | 514 | 4780 | 1.11 | 0.96 | 0.86 to 1.07 |
| 40 + | 56 | 399 | 1.48 | 1.07 | 0.78 to 1.45 |
| Missing BMI | 1064 | 10666 | 1.03 | 1.22 | 1.11 to 1.35 |
| 18 to 29.9 | 2289 | 23636 | 1.00 | 1.00 | n/a |
| Blood Pressure (BP) | | | | | |
| Moderately High Blood Pressure | 959 | 8848 | 0.83 | 0.90 | 0.81 to 1.01 |
| Mildly High Blood Pressure | 978 | 8264 | 0.90 | 0.93 | 0.83 to 1.04 |
| No BP reading in the past year | 1350 | 17541 | 0.55 | 0.71 | 0.64 to 0.78 |
| Normal Blood Pressure | 741 | 5518 | 1.00 | 1.00 | n/a |
| Smoking | | | | | |
| Smoker | 1797 | 13780 | 1.58 | 1.23 | 1.15 to 1.34 |
| No Smoking Recorded | 468 | 5689 | 0.93 | 0.94 | 0.82 to 1.08 |
| Non-Smoker | 1763 | 5689 | 1.00 | 1.00 | n/a |
| Heavy Alcohol Use | 395 | 791 | 5.90 | 4.00 | 3.45 to 4.63 |
| **Comorbid Conditions (patients with a history of these conditions)*** | | | | | |
| Acid Reflux Disease | 431 | 3321 | 1.35 | 0.88 | 0.78 to 0.99 |
| Peptic Ulcer | 76 | 403 | 1.91 | 1.25 | 0.95 to 1.64 |
| H. Pylori | 56 | 228 | 2.50 | 1.91 | 1.38 to 2.64 |
| Pulmonary Embolism | 89 | 410 | 2.21 | 1.33 | 1.03 to 1.74 |
| Deep vein | 139 | 907 | 1.55 | 1.03 | 0.84 to 1.26 |

| | | | | | |
|---|---|---|---|---|---|
| Thrombosis | | | | | |
| Myocardial Infarct | 358 | 2014 | 1.87 | 1.04 | 0.91 to 1.20 |
| Angina | 672 | 4477 | 1.66 | 1.00 | 0.90 to 1.11 |
| Stroke | 329 | 1489 | 2.38 | 1.56 | 1.35 to 1.79 |
| Arrthymia | 536 | 3362 | 1.73 | 1.11 | 0.99 to 1.25 |
| Congestive Heart Failure | 472 | 2290 | 2.34 | 1.33 | 1.17 to 1.52 |
| Rheumatoid Arthritis | 101 | 616 | 1.65 | 1.16 | 0.92 to 1.47 |
| Other Arthritis | 1252 | 10841 | 1.26 | 0.94 | 0.86 to 1.02 |
| Diabetes | 512 | 3204 | 1.71 | 1.27 | 1.13 to 1.42 |
| Cancer | 143 | 852 | 1.73 | 1.59 | 1.31 to 1.94 |
| Dementia | 171 | 1029 | 1.74 | 1.76 | 1.46 to 2.12 |
| Liver Failure | 89 | 62 | 14.69 | 7.00 | 4.78 to 10.27 |
| Renal Failure | 125 | 490 | 2.60 | 1.57 | 1.26 to 1.95 |
| COPD | 354 | 1875 | 2.04 | 1.41 | 1.23 to 1.62 |
| **Drug Related Covariates**** | | | | | |
| Antibiotics | 1009 | 5990 | 1.93 | 1.47 | 1.34 to 1.60 |
| Antidepressants | 632 | 3702 | 1.84 | 1.30 | 1.17 to 1.44 |
| Corticosteroids | 599 | 4729 | 1.32 | 0.90 | 0.81 to 1.00 |
| Diuretics | 1370 | 10348 | 1.58 | 1.05 | 0.96 to 1.14 |
| H2 Antagonists | 268 | 1287 | 2.18 | 1.83 | 1.58 to 2.13 |
| Paracetamol | 1336 | 7934 | 2.18 | 1.47 | 1.35 to 1.60 |
| Proton Pump Inhibitors | 930 | 3985 | 2.83 | 2.07 | 1.88 to 2.28 |

* Previous history of condition in GPRD medical records prior to index date

** Any prescription issued in the 90 days prior to the index date

**Table 3.2: Association of Warfarin/Clopidogrel and Non-steroidal anti-inflammatory Agents with the risk of GI haemorrhage**

| Agent* | Cases (N=4028) | Controls (N=40171) | Crude Rate Ratio | Rate Ratio*** | 95% Confidence Interval |
|---|---|---|---|---|---|
| No exposure | 2124 (52.7%) | 28264 (70.4%) | 1.00 (Reference) | 1.00 (Reference) | Reference |
| **Antithrombotic Agent** | | | | | |
| Warfarin | 281 (7.0%) | 1130 (2.8%) | 2.64 | 1.94 | 1.61 to 2.34 |
| Clopidogrel | 160 (4.0%) | 532 (1.3%) | 3.16 | 1.67 | 1.27 to 2.20 |
| **NSAIDs** | | | | | |
| Ibuprophen | 210 (5.2%) | 1340 (3.3%) | 1.60 | 1.42 | 1.20 to 1.67 |
| Aspirin | 1122 (27.9%) | 7350 (18.3%) | 1.85 | 1.39 | 1.26 to 1.53 |
| Cox 2 inhibitors | 129 (3.2%) | 630 (1.6%) | 2.12 | 1.64 | 1.31 to 2.06 |
| Other NSAIDs** | 495 (12.3%) | 2469 (6.2%) | 2.16 | 1.92 | 1.71 to 2.15 |

* Any prescription issued in the 90 days before the index date

** This class includes aclofenac, dexketoprofen, diclofenac, diflunisal, etodolac, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid.

*** adjusted for all of the variables in table 1 as well as anticoagulant/NSAID use

**NSAID= Non-steroidal anti-inflammatory drug**
**COX 2 = Cyclooxygenase-2**

**Table 3.3: Difference between expected prescriptions in the study controls of two separate drugs assuming no drug contra-indications and the observed prescriptions in the data**

| Number of Prescriptions by Agent | Warfarin User | | Clopidogrel User | |
|---|---|---|---|---|
| | Expected | Observed | Expected | Observed |
| Ibuprofen | 38 | 17 | 18 | 17 |
| Aspirin | 207 | 82 | 98 | 133 |
| Other NSAIDs | 70 | 36 | 33 | 28 |

**NSAID= Non-steroidal anti-inflammatory drug**

**Table 3.4: Estimates of the magnitude of the effect modification between NSAIDs and Warfarin/Clopidogrel on the risk of GI haemorrhage. Reference is exposure to none of the antithrombotic agents in the study. GPRD data from 2000 to 2005.**

| Agent | Cases (N=4028) | Controls (N=40171) | Effect Modification Rate Ratio* (95% CI) | Estimated Rate Ratio of users of drug combination (95% CI) |
|---|---|---|---|---|
| No exposure | 2124 (52.7%) | 28264 (70.4%) | 1.00 (Reference) | 1.00 (Reference) |
| **Warfarin Effect Modification*** | | | | |
| Warfarin*Ibuprofen | 11 (0.3%) | 17 (0.04%) | 2.57 (1.09 to 6.09) | 6.63 (2.84 to 15.46) |
| Warfarin*Aspirin | 48 (1.2%) | 82 (0.2%) | 2.23 (1.46 to 3.41) | 6.48 (4.25 to 9.87) |
| Warfarin*Cox 2 | 6 (0.2%) | 9 (0.0%) | 1.37 (0.44 to 4.30) | 4.62 (1.48 to 14.43) |
| Warfarin*Other NSAIDs | 19 (0.5%) | 36 (0.1%) | 0.95 (0.50 to 1.81) | 3.26 (1.74 to 6.12) |
| **Clopidogrel Effect Modification** | | | | |
| Clopidogrel*Ibuprofen | 8 (0.2%) | 17 (0.04%) | 1.17 (0.44 to 3.10) | 2.84 (1.09 to 7.40) |
| Clopidogrel*Aspirin | 73 (1.8%) | 133 (0.3%) | 1.75 (1.17 to 2.64) | 3.90 (2.78 to 5.47) |
| Clopidogrel*Cox 2 | 9 (0.2%) | 19 (0.1%) | 0.98 (0.40 to 2.44) | 2.60 (1.09 to 6.23) |
| Clopidogrel*Other NSAIDs | 15 (0.4%) | 28 (0.3%) | 0.91 (0.43 to 1.94) | 2.93 (1.38 to 6.21) |

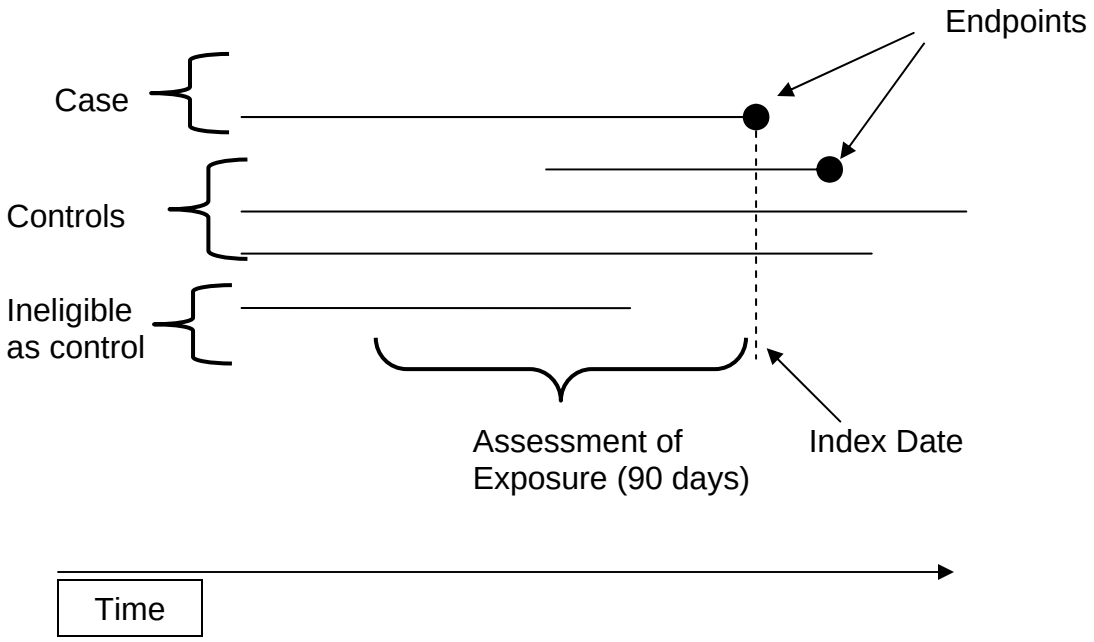
*adjusted for all of the variables in table 1 as well as anticoagulant/NSAID use and terms to test for effect modification

**Table 3.5: Medical codes (READ/OXMIS codes) used to define a serious and clear episode of GI haemorrhage in the GPRD database**

| GPRD Medical Code | Term Type | Read / OXMIS Code* | Read / OXMIS Term |
|---|---|---|---|
| 207375 | READ | J68zz00 | Gastrointestinal tract haemorrhage NOS |
| 211264 | OXMIS | 569 MH | INTESTINAL HAEMORRHAGE |
| 211265 | OXMIS | 569 MI | HAEMORRHAGE GASTROINTESTINAL |
| 234580 | READ | J68z200 | Upper gastrointestinal haemorrhage |
| 243602 | READ | J68..00 | Gastrointestinal haemorrhage |
| 243603 | READ | J68z.11 | GIB - Gastrointestinal bleeding |
| 252731 | READ | J68z000 | Gastric haemorrhage NOS |
| 280274 | READ | J68z.00 | Gastrointestinal haemorrhage unspecified |
| 298679 | READ | J68z100 | Intestinal haemorrhage NOS |
| 304156 | OXMIS | 5339DB | DUODENAL ULCER BLEEDING |
| 304252 | OXMIS | 569 M | GI BLEEDING |
| 306674 | OXMIS | 569 ME | UPPER GASTROINTESTINAL HAEMORRHAGE |

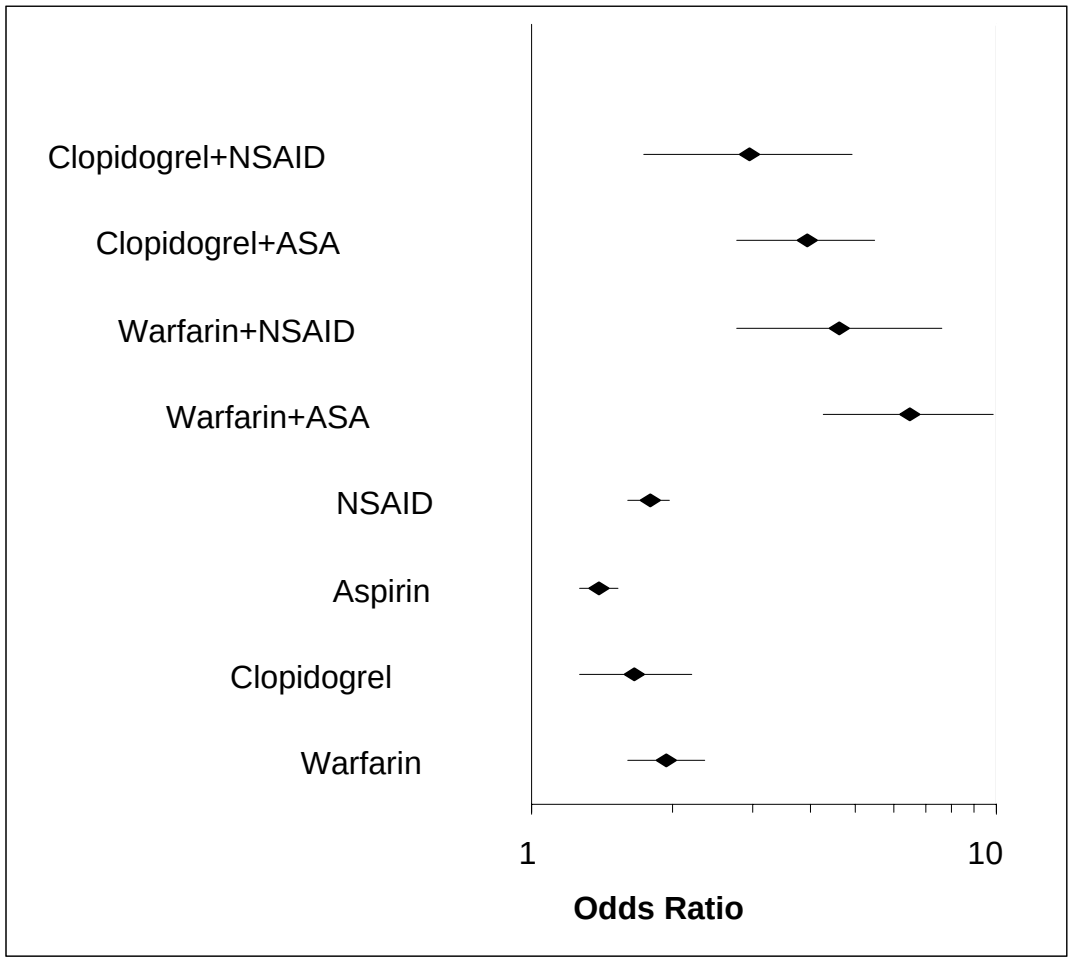
* READ and OXMIS are UK based medical coding schemes used to classify medical events.

**Figure 3.1 Schematic of the case-control design using incidence density sampling**




There is one case and 4 possible controls. One control is not eligible because it was censored before the index date. One control later becomes a case but is still an eligible control at the time shown. The drug exposure is assessed for the case and the three potential controls at starting the data before the index date and for a time period going backwards (90 days in this study)

**Figure 3.2: Forest plot of the odds ratio of gastro-intestinal bleeding for patients prescribed: aspirin (ASA), clopidogrel, warfarin as well as non-steroidal anti-inflammatory drugs (NSAIDs) whether alone or in combination.**



## Chapter 4

## Comparing a marginal structural model to logistic regression in the presence of baseline effect modification

This chapter contains a manuscript that will be submitted to Pharmacoepidemiology and Drug Safety.

Like the previous paper, the adverse effect of warfarin that are considering here is upper gastro-intestinal bleeding.

The focus of this paper was to consider cases where the estimate of the odds ratio as given by a logistic regression analysis might differ from that given by a marginal structural model. As both estimates have slightly different interpretations, it is important to understand when these models give different answers and the implications of these answers.

Marginal structural models model the counterfactual (the same as a randomized control trial) which is "what is the effect of treating the whole population versus treating nobody?" Adjusted logistic regression models estimate the effect with the covariates that are adjusted for or "what is the effect of treating vs. not treating people with an identical covariate pattern"

The difference between the individual estimates (the conditional effect) and the population effect (the marginal effect) was first observed by Gail, Wiand and Piantadosi in their 1984 Biometrics paper. There they discussed how the estimate of effect given by a clinical trial could be altered by statistical adjustment if there was a non-linear relationship between the exposure, outcome and a confounder. While this is not bias, the difference in effects can show important properties of the data.

The largest difference between conditional and marginal effects occurs because of effect modification. This made it the ideal object of study for this thesis.

This is also relevant because Marginal Structural Models can control for time-varying confounders in a way that regression cannot. However, alternative explanations for differences between the results of these approaches (regression analysis vs. marginal structural models) should also be considered. Since a clinical trial always gives a marginal estimate, a higher concordance between the results of observational data analyzed using Marginal Structural Models and randomized control trials would thus be expected – even if the Marginal Structural Models had no improved control of confounding relative to traditional analysis.

The contributions of authors are listed in the preface to the thesis.

# Comparing a marginal structural logistic model to a logistic regression model in the presence of baseline effect modification

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**Running Head:** Effect Modification and Marginal Structural Models

**Type:** Original Report

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**Abstract**

**Introduction:** The proper interpretation of the results of different statistical modeling approaches is a key step to properly describing a drug-outcome relationship. The interpretation depends on whether the statistical model used is estimating an individual-level (conditional) or a population-level (marginal) effect.

**Methods:** We present the results of a Monte Carlo simulation study in which we show that strong interactions can create a difference between the marginal effect of exposure on outcome (as estimated by a marginal structural logistic model) and the conditional effect (as estimated by an adjusted logistic regression model). We illustrate this approach using a real database example from the General Practice Research Database. We consider the effect of warfarin on gastro-intestinal bleeding, in a study of 4030 cases and 79239 controls from the years 2000 to 2005.

**Results:** We estimated the conditional Odds Ratio (OR) of a gastro-intestinal bleed among patients prescribed warfarin as 2.09 (95% Confidence Interval (CI):1.74,2.50) using adjusted logistic regression, and the marginal OR as 17.22 (95% CI:6.46,37.65) using a marginal structural logistic model. This large difference in estimates suggests that there may be non-linear relationships or effect modification between warfarin exposure and the risk of gastro-intestinal bleeding.

**Conclusions:** Divergences between the marginal and conditional estimates of the effect of an exposure on an outcome can be taken as suggestive of either non-linearity or effect modification in the exposure-outcome relationship under study.

**Keywords:** effect modification; warfarin; marginal structural models; statistical models; epidemiology.; General Practice Research Database (GPRD)

**Word Count:** 4585

**Abstract Word Count:** 228

**Tables:** 4

**Figures**: 0

**What this study adds**

1) Examples have entered the literature showing differences between the results of marginal structural models and traditional regression approaches. We provide an example of this phenomenon using the drug warfarin.

2) We demonstrate, using simulations, the size of the effect modifier required in order to create the sort of large differences being observed.

3) We show that the effect modifier must have the opposite sign compared to the exposure in order to generate the pattern of results seen (here and elsewhere) solely due to effect modification.

## INTRODUCTION

Logistic regression with adjustment for candidate confounders is currently the standard analytical approach to analyzing observational epidemiological data with binary outcomes, such as the effect of treatment with prescription drugs on an adverse outcome [1,2]. Logistic regression generates an estimated odds ratio (OR) which can be used to approximate the ratio of event rates (rate ratio, RR) between exposed and unexposed subjects [2, 3].

However, regression is not the only analytical technique used to analyze observational data. Marginal structural models (MSMs) are an alternative for the analysis of pharmacoepidemiology studies [4-6] although other alternatives exist [7]. MSMs are models for the marginal causal effect of exposure on potential outcomes; the parameters are typically estimated using inverse probability of treatment weighting (IPTW). MSMs rely on two important assumptions. The first assumption, common to all observational research including regression, is that there are no unmeasured confounders [8]. The second assumption is that there are no impossible treatment combinations (the experimental treatment assumption) [9].

The MSM approach generates a pseudopopulation through IPTW reweighting; the pseudopopulation includes potentially counterfactual outcomes for all subjects under each treatment condition. Since we have the complete set

of counterfactual outcomes in the pseudopopulation, we can directly contrast the outcomes of subjects under treatment and non-treatment. Very rare treatment combinations can reduce the stability of the estimate of the MSM and result in a loss of normality of the estimates in finite samples. This is due to the presence of large weights distorting the pseudopopulation [4]. However, stabilization of the weights resolves this issue in most practical problems [4].

Adjusted logistic regression and marginal structural logistic models give estimates of the parameters of a model that have different interpretations. The parameter estimated by a marginal model is the effect of giving the treatment to everyone in the entire source population relative to withholding it from everyone. This parameter is very logically connected to the difference between counterfactuals - the contrast between treating everybody in the population versus treating nobody in the population. This gives a MSM a direct causal interpretation.

This marginal effect is different from the conditional effect that is estimated by adjusted logistic regression. The conditional effect is the effect of the exposure within each stratum of the collection of covariates in the statistical model [10, 11]. This is the effect of treatment at the individual level. As noted by Gail et al., when the relationship between the response variable and exposure (treatment and covariates) is linear, the conditional effect and marginal effect are equivalent [12]. Marginal and conditional estimates of the odds ratio will differ,

however, when the relationships are not linear or when effect modification is present [13-14]. This can occur even in the case of an estimate from a clinical trial [12]. This feature of the odds ratio and hazard ratio, sometimes referred to as non-collapsibility, is often considered a disadvantage of the odds ratio [15-16]. However, odds ratios do become effectively collapsible when the outcome is rare, in which case the conditional and marginal estimates will be similar [17].

This difference between marginal and conditional effects has been previously reported in both a real example [18] and in a teaching example [11]. The real example looked at the effect of administering thrombolytic therapy (tissue plasminogen activator or t-PA) as a post-stroke treatment to reduce the risk of death [18]. This study, by Kurth et al., found large differences in the estimates for the odds ratio (OR) of the outcome between treated and untreated when different modeling techniques were used. In particular, the estimate from multivariate logistic regression was OR=1.9 while the estimate of the IPTW model was OR=10.8 [18]. More interestingly, the unadjusted regression estimate was OR=3.4 so the two techniques moved the estimate in opposite directions relative to the crude [18]. This evidence was consistent with the possibility that there was a difference between the effect of the drug at the population level and at the individual level. The IPTW model correctly estimated what would be the effect of the drug if it were given to the entire population even in cases where the drug should not be prescribe.

The goal of the present study was to use a series of simulated datasets to introduce ``hidden'' effect modification to generate cases where the crude estimate of the effect of an exposure on an outcome lay between an adjusted logistic model (conditional effect) and an IPTW model (marginal effect). The effect modifier was hidden, or unknown, because a known effect modifier would be explicitly modeled in both adjusted regression models and MSMs. These simulations illustrated that a difference between the parameters estimated by a MSM and the conditional estimates of the parameters could be due to the presence of effect modification or non-linearity in the data. We then explored both effect modification and non-linearity using Monte-Carlo simulations.

## MATERIALS AND METHODS

There are two components to this study: a Monte-Carlo simulation study and an illustration based on empirical data.

### Monte-Carlo study

In this Monte Carlo simulation study, we aim to show that by introducing effect modification into the data, we can cause the conditional and the marginal estimates to diverge.

*Assumptions and Approach*

Our study goal was to develop a simulation approach that was consistent with the structure of data reported by Kurth et al. [18]. As a basic assumption, we assumed a scenario where there was a relatively rare treatment (such as t-PA) and outcome (such as death). This was consistent with the treatment rate observed in the Kurth et al. study where the authors reported only 212 treated patients compared to 6057 patients who were not treated [18]. Among the patients population in the study by Kurth et al., only 469 deaths were reported [18].

We considered a situation with a single exposure $X_E$ with two levels (0/1) and a single covariate (which was also a potential confounder) ($X_C$) with three levels (0/1/2). To explore the effect of the interaction between the exposure ($X_E$) and covariate ($X_C$) on the marginal and conditional estimates we used a strong interaction so that the effect could be clearly seen. To make this interaction more complex, we assumed that the relationship between the covariate and outcome was linear but that the relationship between the interaction and outcome was quadratic.

*Generation of Outcome*

We estimated the probability of a positive outcome from the logistic regression equation:

$$P(Y=1) = \frac{e^{\Omega}}{1+e^{\Omega}}$$

where $\Omega$ was given by:

$$\Omega = \lambda_0 + \lambda_1 X_E + \lambda\_2 X_C + \lambda_3 X_E (X_C)^2 + \lambda_4 X_C X_E$$

We set $\lambda_0 = -4.595$ which yielded an approximately 1% chance of a positive outcome when both $X_E$ and $X_C$ are equal to zero. We manipulated $\lambda_1$, $\lambda_2$ and $\lambda_3$ across scenarios to create different relationships between the exposure, covariate and outcome. In all cases, we have considered the case where $\lambda_4 = 0$.

*Data Generation*

We set the level of exposure to be $P(X_E=1) = 5\%$ when $X_C = 0$. We started by generating two levels of a covariate with the following distribution: $P(X_C = 0) = 70\%$, $P(X_C = 1) = 20\%$ and $P(X_C=2) = 10\%$. Since it was required that the covariate affect both the treatment and the outcome in order for the covariate to be a confounder [19], we set $P(X_E=1) = 2\%$ when $X_C = 1$ and $P(X_E=1) = 1\%$ when $X_C = 2$.

We used a sample size of 20000 observations to create a large enough sample size to identify rare events. Our least likely combination of covariates was $X_C$ =2 and $X_E$=1 which occurred in only 0.1% of observations (giving an average of 20 observations in a given random sample). Much smaller numbers of observations would be liable to make the influence of a rare covariate/exposure combination (which was one of our assumptions) too difficult to detect in our simulations as there might not be any events with this combination of exposure and covariate in some of the independent random samples. However, 20000 observations was three times the size of Kurth's study [17]. A study based on larger sample size than this would be unrealistic in the context of a typical pharmacoepidemiology study.

We generated 1000 independent random samples of this data which was sufficient to allow us to systematically evaluate the performance of various candidate models.

All generation of the independent random samples was done using SAS version 9.1.3 running on a Windows XP platform with coding done by one author (JD).

*Scenarios*

We explored the following scenarios for these models to systematically test the properties of these models in the presence of interactions:

1) Changes in the measure of effect ($\lambda_1$= 0 or $\lambda_1$ = 0.68925) between a null effect of exposure and a real effect.

2) Changes in the intensity of the covariate $\lambda_2$ = - 0.68925, $\lambda_2$ = 0 and $\lambda_2$ = 0.68925). This enabled us to consider cases where there was no effect of the covariate on the outcome, where the covariate protects against the outcome and where the covariate promotes the outcome.

3) Changes in the interaction effect ($\lambda_3$= 0 vs. $\lambda_3$= 0.919). This enabled us to compare cases where the summary of the conditional odds ratios approaches that of the marginal odds ratio to those where there was substantial difference.

Altering the size of the different parameters for $\lambda_1$ would simply alter the size of the conditional effect. Altering $\lambda_2$ would increase or decrease the size of the potential confounding.

*Statistical Analysis*

We considered 4 logistic regression models in order to analyze this data representing various degrees of complexity. The names of these models correspond to the columns in Tables 1 and 2 of the results section. The models were:

1) The crude model:

$$\text{Logit } [P(Y=1)] = \beta_0 + \beta_1 X_E$$

2) The adjusted model:

$$\text{Logit } [P(Y=1)] = \beta_0 + \beta_1 X_E + \beta_2 X_C$$

3) The linear interaction model:

$$\text{Logit } [P(Y=1)] = \beta_0 + \beta_1 X_E + \beta_2 X_C + \beta_3 X_E X_C$$

4) The true model:

$$\text{Logit } [P(Y=1]] = \beta_0 + \beta_1 X_E + \beta_2 X_C + \beta_3 X_E X_C^2$$

where Y was an outcome (0/1), $X_E$ was our drug exposure (0/1) and $X_C$ was our confounding variable (0/1/2).

The marginal structural logistic model was specified as:

$$\text{Logit } [P(Y_X=1)] = \beta_0 + \beta_1 X_E$$

where $Y_X$ was the weighted outcome Y. This model was fit by a weighted logistic regression with weights given by:

$$w_1 = \frac{P_E}{P_{E_i}}$$

for the exposed observations and

$$w_0 = \frac{1 - P_E}{1 - P_{E_i}}$$

in the unexposed, where $P_E$ was the overall probability of exposure in the cohort and $P_{E_i}$ was the probability of a given observation, i, getting the treatment received given their covariate pattern [11]. We modeled the individual probability of exposure using logistic regression, which is typically sufficient, although non-parametric approaches can also be used [5, 8]. The form of the model was:

$$\text{Logit}\,[P(X_E=1)] = \gamma_0 + \gamma_1 X_C$$

where $X_E$ was the exposure status and $X_C$ was the covariate status.

We presented the mean estimate of the odds ratio for the event of interest as well as the mean estimate of $\beta_1$ across scenarios. We also presented the variance, bias and mean squared error (MSE) for each of these 12 scenarios [20-21]. Bias was based on the true value $\beta_1$ from the logistic model used to generate the outcomes given random data. We also estimated bias for MSMs in the scenarios without interactions term where the marginal and conditional effect should be identical.

In this study we used the conditional effect as the basis for comparing differences between these approaches. The use of conditional estimate as the standard for reporting effects is a common decision [22] as individual effects are often the parameter of most interest to the medical decision maker [14]. Marginal effects give the estimate across the population without reference to the individual [12] and most medical decisions are made within the context of the characteristics of the individual patient.

*Sensitivity testing of the assumptions for collapsibility*

Collapsibility occurs when the measure of association between two parameters remains constant across a series of strata [15].

To explore the conditions under which the summary of conditional odds ratios (across all strata) was collapsible and the conditional and marginal odds

ratios are equivalent, we considered a series of scenarios designed to demonstrate when the conditional and marginal effects differ. We contrasted rare and common exposures/outcomes as well as different underlying relationships between the exposure and outcome. In all cases, we set $\lambda_1$ and $\lambda_2$ equal to 0.68925. In all scenarios we considered a $\lambda_3 = 0.0919$; this less extreme value for $\lambda_3$ illustrated the difference in estimates of the size of the effect of the exposure $\beta_1$ between the models in the absence of extremely strong effect modifiers and non-linear covariates.

To generate a common (as opposed to a rare) covariate, we set the level of exposure to be $P(X_E=1) = 50\%$, $P(X_E=1) = 20\%$ when $X_C=1$ and $P(X_E=1) = 10\%$ when $X_C=2$. This was exactly a 10 fold increase over the probability of exposure in the rare case defined above.

As part of our sensitivity testing of our simulation assumptions, we considered different data generating equations to examine different assumptions about the relationship between the response variable, exposure and covariate. The first example was a linear equation:

$$\Omega = \lambda_0 + \lambda_1 X_E + \lambda_2 X_C$$

The second example was one with a quadratic covariate:

$$\Omega = \lambda_0 + \lambda_1 X_E + \lambda_2 X_C + \lambda_3 X_C^2$$

The third example was a linear effect modifier:

$$\Omega = \lambda_0 + \lambda_1 X_E + \lambda_2 X_C + \lambda_3 X_C X_E$$

This last case differed from the primary model considered in our study in that the effect of the covariate was linear and not quadratic. In these scenarios we replaced the "True Model" with a model with a "Quadratic covariate model" specified as:

$$\text{Logit}\,[P(Y=1)] = \beta_0 + \beta_1 X_E + \beta_2 X_C + \beta_3 X_C^2$$

These scenarios allowed us to explore the impact of the assumptions that we made in our primary set of simulations.

*Illustration*

We illustrated the concepts under study in a population-based, retrospective case-control study in the United Kingdom's General Practice Research Database (GPRD) [23].

We identified 4030 cases of upper GI bleeding in the GPRD between the years 2000 and 2005. Each case was matched on index date with up to 20 potential controls drawn the general population and satisfying the matching criterion yielding a total of 79239 controls. Both cases and controls were required to have at least 3 years of information in the database. The matching on index date requires us to assume that the population was stationary (or independent of time) [24]. This assumption required that the population was stable (which is true in a dynamic cohort like the GPRD that samples a relatively fixed fraction of a stable, large population) and that the incidence rate of the disease was constant over time [24]. The range of events across the study period was between 759 and 840 (with no trend) suggesting that our assumption of a stationary population was approximately met in this population (over this time period and for this outcome).

It is not required that the rate of drug prescriptions be stable over time which is important as GPRD prescribing patterns can vary strongly over time [25]. It would also have been possible to use a higher degree of matching with this type of study design when computing the conditional effect of treatment [26], but a design matched only on time was used to make the two modeling approaches directly comparable.

The primary exposure of interest was the prescription medication warfarin which was known to be associated with bleeding complications [27]. Patients were considered exposed to warfarin if they received at least one prescription for

warfarin in the preceding 90 days. We used three modeling strategies: a crude regression estimate from conditional logistic regression, a multivariate estimate using conditional logistic regression and a marginal structural model [25].

The multivariate models were adjusted for a broad range of potential confounders including: age, sex, body mass index, clinical blood pressure, smoking, heavy alcohol use, GI disease (acid reflux, peptic ulcer, positive test for H. Pylori), indications for warfarin use (pulmonary embolism, deep vein thrombosis, stroke, arrthymia), general comorbidity (angina, myocardial infraction, congestive heart failure, arthritis, diabetes, cancer, dementia, liver or renal failure and chronic obstructive pulmonary disease) or other drugs associated with bleeds (non-steroidal anti-inflammatory drugs including aspirin, paracetamol, gastric acid suppressants, corticosteroids, antibiotics, antidepressants, clopidogrel and heparin). To adequately assess potential confounders we considered medical records recorded at any time since the patient was enrolled in the database but before the index date. Blood pressure was assessed in the year before the index date. Drug exposure was measured by any prescription being issued in the 90 days before index date.

The odds ratios were generated using conditional logistic regression. For the marginal structural model, we developed a probability of treatment model using information on the controls [24] (who can be seen as a random sample of the source population from which the cases arise) using all available covariates to

estimate the probability of getting the treatment received given the patient's covariate pattern. We applied this model to all of the observations in the study and inverted it to obtain the weights. We then stabilized the weights using the baseline probability of getting the treatment received [1, 2]. We created confidence intervals for the IPTW-based parameter estimate using bootstrapping [28].

## RESULTS

The results from our five candidate models where we designed the scenarios for the true effect of the interaction to be zero are presented in Table 1. Here we see that all models do well in controlling for confounding except for the crude model. All models perform well in terms of accuracy (MSE). These simulations enable us to verify that the marginal and conditional effects are equivalent given our rare outcome study assumptions. This was important as, if the outcome were common, differences between these estimates could be due to other causes than effect modification.

The marginal and conditional estimates were similar in these scenarios because we defined all of our effects as linear and did not have any effect modification [12].

### Simulated Data for Effect Modification

The results where we have designed the scenarios to have a non-linear interaction between the covariate and the exposure are presented in Table 2. Only the true logistic model performs well at modeling the conditional effect of exposure across all scenarios. The model with the linear interaction term tends to systematically overcorrect for the interaction and has extremely high variance between estimates. However, failing to statistically adjust for the interaction between the covariate and the exposure, as with the adjusted model and the crude model, results in overstating the effect of exposure on outcome.

The results from MSMs in these scenarios differ from all of the logistic models. It was important to note that the estimate from the MSM was always greater than that of the true model because the positive interaction term $\lambda_3 = 0.919$ created greater changes at the population level among those observations with a non-zero covariate term.

When the covariate was negative $\lambda_2 = -0.68925$ we observe the expected reduction in the size of the effect of the adjusted model as compared to the crude model, This was because a negative confounding covariate caused the model to overestimate the association between the exposure and outcome. When the covariate and the interaction are in opposite directions, you can get the crude estimate lying between the conditional and marginal estimates as seen in cases 7 and 8.

Increasing the size of the interaction had a fairly direct impact on the marginal effects. Increasing $\lambda_3$ to 1.8238 for case 12 gave a mean estimate for the effect of treatment, $\beta_1$, across 1000 simulations for the IPTW-based estimate of $\beta_1$=2.537 and for the true model gave an estimate of $\beta_1$=0.637. Likewise, decreasing $\lambda_3$ to 0.4595 gave a mean estimate of $\beta_1$over 1000 simulations for the MSM of $\beta_1$=1.445 and for the true model $\beta_1$=0.658. Of course, the impact on the odds ratio estimated by the MSM for $\beta_1$ due to varying $\lambda_3$ will also depend on the distribution of the covariate in the overall population.

**Simulated Data for Non-linearity**

To demonstrate the conditions under which the marginal and conditional effects would diverge, we conducted a sensitivity analysis on the results of case 6 from Table 1. These results are presented in Table 3. We see that the variability between estimates was greatly reduced in the scenario the common outcome and exposure when compared to the scenario with rare exposure and outcome. This sensitivity analysis verifies that the odds ratio is non-collapsible for common exposures even in the absence of an interaction term [14, 17]. However, the mean odds ratio across simulations remained the same for the rare exposure until the linear effect modifier was introduced when they diverged.

**Real Data Illustration**

The results of our case control study designed to illustrate a difference between conditional and marginal effects in real data are presented in Table 4. In this case, we see a divergence between the estimate of the OR with adjusted logistic regression and the estimate of the OR given by the MSM. The results are consistent with previous hypotheses of effect modification by age in warfarin studies [11]. Part of this was because the cases (mean age=69.0 years) were older than the source population (mean age=48.2 years). When we restricted the analysis to the portion of the population over 60, the estimates became more similar, suggesting that the effect of warfarin differs in older vs. younger patients.

## DISCUSSION

The objective of this study was to use simulated data to demonstrate how a hidden effect modification can give rise to differences between the conditional effect given by logistic regression and the marginal effect given by an IPTW-based MSM. When there is a large difference between the parameter estimates of an adjusted logistic regression model and a marginal structural model, effect modification in the data is a possible cause.

The Kurth et al. study, which motivated this study, evaluated an exposure-outcome relationship between tPA post-strike and death. In this analysis, statistical adjustment for potential confounders reduced a crude estimate of the

effect of t-PA treatment on mortality from OR=3.4 (95% CI:2.3, 4.9) to OR=1.9 (95% CI:1.2, 3.1). However, when estimates for the counterfactual effect of treatment were derived using inverse probability of treating weighting (IPTW), an estimate of OR=11.8 (95% CI:2.5, 47.0) was obtained. The authors resolved this using stratification by propensity scores above 5% and determined that the "correct" estimate for the IPTW-based model was OR=1.1 (95% CI:0.6, 1.9). These results were compared to a meta-analysis of RCT results which estimated the effect as OR 1.2 (95% CI:0.9, 1.4) [18]. This effect could be explained due to either true effect modification or unmeasured confounding among "unusual" (and thus very highly weighted) patients.

One result of our simulation study was to show the dramatic size of the effect modification that would be required to generate this level of difference in estimates. Another was to rule out reasonable levels of non-linearity as a potential alternate explanation for difference between conditional (statistical adjustment) and marginal (IPTW-based) results. Finally, we demonstrated that the effect modification term needs to have an opposite sign from the confounder in order for statistical adjustment and IPTW to shift the estimate in opposite direction relative to the crude estimate. This suggests important properties about the possible mechanisms that could lead to this type of effect modification and the interpretation of these results and is consistent with the hypothesized mechanism of Stürmer et al. [11].

The conditional effect is the "stratum specific" or estimate of effect of treatment on the individual. The marginal effect is the effect of either treating or not treating across the entire population. Deviations between these estimates for rare outcomes appear to only occur in the presence of either effect modification or a non-linear relationship between the treatment, response variable and covariates [12-14]. The results of the primary simulation study show two scenarios that are consistent with the pattern of divergent point estimates seen in Kurth et al. [18] (cases 7 and 8 from Table 2). This may suggest that there is either effect modification or non-linearity is a possible explanation for the relationship between the exposure and outcome in that study [18].

The empirical bias in the parameter estimates from the true model and linear interaction model show less bias than the adjusted model when there is a covariate with an effect on the outcome but the true effect of the interaction is zero. This is surprising because the one would expect the correctly specified model show equal or better performance than the over-specified models. A plausible explanation is that these two models correct for "chance confounding" by including variables that are pure predictors of exposure in the model [29]. This sort of behavior has been seen in variable selection studies for propensity score-based models [29] where the inclusion of pure risk factors improves the parameter estimates for the same reason. The improved performance of rich models for propensity score is further discussed by Robins et al. where it is shown that including extraneous surrogate variables can improve precision [30].

However, the MSE is lower for the adjusted model than the true model when there is no interaction but a confounding covariate is present. The crude model has the best MSE when there is no interaction and the covariate has no effect on the outcome suggesting that it is the most accurate in this case.

One limitation to our approach is that, while a difference between marginal and conditional estimates may indicate the presence of effect modification, it may not be possible to identify this interaction, to properly specify it once identified or to distinguish it from non-linearity in the covariate. Failure to properly specify the functional form of a complex relationship can lead to complex residual confounding although advanced techniques do exist to deal with relationships between exposure and outcome that do not have a simple functional form [31]. It is also important to note that these results only apply to baseline effect modification and that time-varying effect modifiers require special treatment [32-33].

The difference in results in Table 4 between the general population and those restricted to age 60+ are almost certainly due to the unusual nature of young patients who are both exposed to warfarin and have gastro-intestinal bleeds. These patients are very rare and, therefore, are given very high weights. If these patients also have other unusual characteristics that are not captured in the database, than the difference in estimates between OR=17.2 and OR=4.2 for the Marginal Structural Model analysis could be due to unmeasured confounding of

these rare but heavily re-weighted observations. This is similar to what was found by Kurth et al. as their IPTW-based estimate was much closer to the null when they stratified their analysis by propensity score [18].

The results of this Monte-Carlo study suggest an additional sensitivity analysis that could be used to detect effect modification or non-linearity in the data for a pharmacoepidemiology study. The increased use of sensitivity analysis is an important part of richly describing medical data and properly interpreting [34-35]. If the results of a MSM differ greatly from a logistic regression analysis then one can justify the decision to systematically test for one or more important effect modifiers or to introduce non-linear regression techniques. Given that properly specified effect modification will provide a richer description of the data and allow better understanding of the effect of drug therapy, any improvements in detecting these features are an important contribution to improving our understanding of the effects of drugs in populations.

## Ethical Review

Ethical review for this study was done by the Independent Scientific Advisory Committee for MHRA database research

## Funding

This study was funded by the Canadian Institutes of Health Research (CIHR) and the Canadian Foundation for Innovation.

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**Table 4.1:** Comparison of parameter estimates (where $\beta_1$ is the estimator of the treatment effect) by type and specification of model with no interaction present. Results from 1000 Simulated datasets with 20,000 observations each: Estimates for no interaction term ($\lambda_3 = 0$)

| $\lambda_1$ | $\lambda_2$ | Parameter Estimated | Crude Model | Adjusted Model | Linear Interaction Model | True Model | Marginal Structural Model* |
|---|---|---|---|---|---|---|---|
| **Case 1: No true effect of exposure, negative confounder** | | | | | | | |
| 0 | - 0.68925 | Odds Ratio | 1.12 | 0.99 | 1.00 | 1.01 | 0.99 |
| | | $\beta_1$ | 0.031 | -0.089 | -0.085 | -0.069 | -0.104 |
| | | Bias | - 0.031 | 0.089 | 0.085 | 0.069 | 0.104 |
| | | Variance | 0.182 | 0.183 | 0.192 | 0.186 | 0.204 |
| | | MSE | 0.183 | 0.191 | 0.199 | 0.191 | 0.215 |
| **Case 2: True effect of exposure, negative confounder** | | | | | | | |
| 0.68925 | - 0.68925 | Odds Ratio | 2.24 | 1.99 | 2.00 | 2.02 | 1.98 |
| | | $\beta_1$ | 0.770 | 0.650 | 0.652 | 0.663 | 0.640 |
| | | Bias | -0.081 | 0.039 | 0.037 | 0.026 | 0.049 |
| | | Variance | 0.082 | 0.082 | 0.087 | 0.085 | 0.094 |
| | | MSE | 0.089 | 0.084 | 0.088 | 0.086 | 0.096 |
| **Case 3: No true effect of exposure, no confounder** | | | | | | | |
| 0 | 0 | Odds Ratio | 0.99 | 0.99 | 1.00 | 1.02 | 0.99 |
| | | $\beta_1$ | -0.086 | -0.086 | -0.082 | -0.066 | 0.112 |
| | | Bias | 0.086 | 0.086 | 0.082 | 0.066 | 0.112 |
| | | Variance | 0.172 | 0.174 | 0.188 | 0.180 | 0.230 |
| | | MSE | 0.179 | 0.181 | 0.195 | 0.184 | 0.243 |
| **Case 4: True effect of exposure, no confounder** | | | | | | | |
| 0.68925 | 0 | Odds Ratio | 1.98 | 1.98 | 2.00 | 2.02 | 1.97 |
| | | $\beta_1$ | 0.649 | 0.649 | 0.654 | 0.664 | 0.632 |
| | | Bias | 0.040 | 0.040 | 0.035 | 0.025 | 0.057 |
| | | Variance | 0.076 | 0.077 | 0.085 | 0.082 | 0.101 |
| | | MSE | 0.078 | 0.079 | 0.086 | 0.083 | 0.104 |
| **Case 5: No true effect of exposure, positive confounder** | | | | | | | |
| 0 | 0.68925 | Odds Ratio | 0.78 | 0.99 | 1.00 | 1.01 | 1.01 |
| | | $\beta_1$ | -0.318 | -0.073 | -0.081 | -0.063 | -0.093 |
| | | Bias | 0.318 | 0.073 | 0.081 | 0.063 | 0.093 |
| | | Variance | 0.142 | 0.144 | 0.182 | 0.170 | 0.226 |
| | | MSE | 0.243 | 0.149 | 0.189 | 0.174 | 0.235 |
| **Case 6: True effect of exposure, positive confounder** | | | | | | | |
| 0.68925 | 0.68925 | Odds Ratio | 1.55 | 1.98 | 2.00 | 2.01 | 2.00 |
| | | $\beta_1$ | 0.407 | 0.654 | 0.653 | 0.661 | 0.644 |
| | | Bias | 0.282 | 0.035 | 0.036 | 0.028 | 0.045 |
| | | Variance | 0.064 | 0.065 | 0.083 | 0.077 | 0.106 |
| | | MSE | 0.144 | 0.066 | 0.084 | 0.078 | 0.108 |

* with no effect modification present, conditional effect = marginal effect under our rare outcome assumption so we will present bias and mean square error for the Marginal Structural Model.

**Table 4.2:** Comparison of parameter estimates (where $\beta_1$ is the estimator of the treatment effect) by type and specification of model with a strong interaction present. Results from 1000 Simulated datasets with 20000 observations each: Estimates for with an interaction term ($\lambda_3 = 0.919$).

| $\lambda_1$ | $\lambda_2$ | Parameter Estimated | Crude Model | Adjusted Model | Linear Interaction Model | True Model | Marginal Structural Model |
|---|---|---|---|---|---|---|---|
| **Case 7: No true effect of exposure, negative confounder** | | | | | | | |
| 0 | - 0.68925 | Odds Ratio | 1.46 | 1.32 | 0.94 | 1.00 | 2.34 |
| | | $\beta_1$ | 0.316 | 0.209 | -0.157 | -0.081 | 0.740 |
| | | Bias | - 0.316 | - 0.209 | 0.157 | 0.081 | n/a |
| | | Variance | 0.143 | 0.148 | 0.210 | 0.185 | 0.258 |
| | | MSE | 0.243 | 0.192 | 0.235 | 0.192 | n/a |
| **Case 8: True effect of exposure, negative confounder** | | | | | | | |
| 0.68925 | - 0.68925 | Odds Ratio | 2.89 | 2.63 | 1.87 | 1.99 | 4.52 |
| | | $\beta_1$ | 1.030 | 0.934 | 0.585 | 0.651 | 1.454 |
| | | Bias | -0.341 | -0.245 | -0.104 | 0.038 | n/a |
| | | Variance | 0.065 | 0.069 | 0.093 | 0.081 | 0.117 |
| | | MSE | 0.181 | 0.129 | 0.104 | 0.082 | n/a |
| **Case 9: No true effect of exposure, no confounder** | | | | | | | |
| 0 | 0 | Odds Ratio | 1.80 | 1.86 | 0.87 | 0.99 | 4.40 |
| | | $\beta_1$ | 0.547 | 0.580 | -0.235 | -0.084 | 1.425 |
| | | Bias | -0.547 | -0.580 | 0.235 | 0.084 | n/a |
| | | Variance | 0.089 | 0.094 | 0.218 | 0.169 | 0.122 |
| | | MSE | 0.388 | 0.430 | 0.273 | 0.176 | n/a |
| **Case 10: True effect of exposure, no confounder** | | | | | | | |
| 0.68925 | 0 | Odds Ratio | 3.33 | 3.51 | 1.77 | 1.99 | 7.56 |
| | | $\beta_1$ | 1.180 | 1.230 | 0.527 | 0.654 | 1.995 |
| | | Bias | -0.491 | -0.541 | 0.162 | 0.035 | n/a |
| | | Variance | 0.045 | 0.049 | 0.097 | 0.076 | 0.057 |
| | | MSE | 0.286 | 0.342 | 0.123 | 0.077 | n/a |
| **Case 11: No true effect of exposure, positive confounder** | | | | | | | |
| 0 | 0.68925 | Odds Ratio | 1.94 | 2.61 | 0.79 | 0.99 | 6.14 |
| | | $\beta_1$ | 0.635 | 0.933 | -0.333 | -0.075 | 1.789 |
| | | Bias | - 0.635 | - 0.933 | 0.333 | 0.075 | n/a |
| | | Variance | 0.054 | 0.056 | 0.236 | 0.149 | 0.052 |
| | | MSE | 0.457 | 0.926 | 0.347 | 0.155 | n/a |
| **Case 12: True effect of exposure, positive confounder** | | | | | | | |
| 0.68925 | 0.68925 | Odds Ratio | 3.10 | 4.25 | 1.69 | 1.99 | 8.67 |
| | | $\beta_1$ | 1.116 | 1.430 | 0.475 | 0.653 | 2.144 |
| | | Bias | -0.427 | -0.741 | 0.214 | 0.036 | n/a |
| | | Variance | 0.033 | 0.035 | 0.105 | 0.071 | 0.032 |
| | | MSE | 0.215 | 0.584 | 0151 | 0.072 | n/a |

* with effect modification present, conditional effect ≠ marginal effect under our rate outcome assumption so we do not present bias or mean square error for the marginal structural model.

**Table 4.3:** Sensitivity Analysis for marginal versus conditional effects. Results from 1000 Simulated datasets with 20000 observations each: all cases have the same exposure and confounder effect size ($\lambda_1 = 0.68925$, $\lambda_2 = 0.68925$ ). Common exposures are 10 times as likely as rare exposures.

| $\lambda_0$ | $\lambda_3$ | Parameter Estimated | Crude Model | Adjusted Model | Quadratic Confounder Model | Linear Interaction Model | Marginal Structural Model |
|---|---|---|---|---|---|---|---|
| **Case `13: Rare Exposure and Outcome, Linear Model** | | | | | | | |
| -4.595 | 0 | Odds Ratio | 1.55 | 1.98 | 1.98 | 2.00 | 2.00 |
| | | $B_1$ | 0.407 | 0.654 | 0.654 | 0.653 | 0.644 |
| | | Variance | 0.0637 | 0.0651 | 0.0652 | 0.0828 | 0.1058 |
| **Case 14: Rare Exposure and Outcome; Quadratic Model** | | | | | | | |
| -4.595 | 0.0919 | Odds Ratio | 1.42 | 2.00 | 1.99 | 2.02 | 2.01 |
| | | $\beta_1$ | 0.325 | 0.662 | 0.656 | 0.666 | 0.648 |
| | | Variance | 0.0617 | 0.0639 | 0.0640 | 0.0827 | 0.1083 |
| **Case 15: Rare Exposure and Outcome, Linear Effect Modifier** | | | | | | | |
| -4.595 | 0.0919 | Odds Ratio | 1.60 | 2.05 | 2.05 | 2.00 | 2.15 |
| | | $\beta_1$ | 0.437 | 0.686 | 0.686 | 0.653 | 0.718 |
| | | Variance | 0.627 | 0.0642 | 0.0643 | 0.0819 | 0.1045 |
| **Case 16: Common Exposure and Outcome, Linear Model** | | | | | | | |
| -0.60 | 0 | Odds Ratio | 1.49 | 1.99 | 1.99 | 1.99 | 1.96 |
| | | $\beta_1$ | 0.397 | 0.689 | 0.689 | 0.689 | 0.674 |
| | | Variance | 0.0008 | 0.0009 | 0.0009 | 0.0011 | 0.0009 |
| **Case 17: Common Exposure and Outcome; Quadratic Model** | | | | | | | |
| -0.60 | 0.0919 | Odds Ratio | 1.41 | 2.00 | 1.99 | 2.01 | 1.95 |
| | | $\beta_1$ | 0.341 | 0.694 | 0.689 | 0.699 | 0.666 |
| | | Variance | 0.0007 | 0.0009 | 0.0009 | 0.0011 | 0.0009 |
| **Case 18: Common Exposure and Outcome, Linear Effect Modifier** | | | | | | | |
| -0.60 | 0.0919 | Odds Ratio | 1.50 | 2.02 | 2.03 | 1.99 | 2.02 |
| | | $\beta_1$ | 0.406 | 0.704 | 0.705 | 0.689 | 0.700 |
| | | Variance | 0.0007 | 0.0009 | 0.0009 | 0.0011 | 0.0009 |

**Table 4.4:** Comparison of the effect of warfarin exposure on the risk of gastro-intestinal bleeding using different analytical techniques with different interpretations in a case control study; data from the General Practice Research Database (2000to 2005)

| **All ages** | **Cases (N=4030)** | **Controls (N=792391)** | **Odds Ratio** | **95% Confidence Interval** |
|---|---|---|---|---|
| Unexposed | 3747 (93.0%) | 39041 (99.0%) | 1.00 | Reference |
| Crude estimate | 281 (7.0%) | 810 (1.0%) | 7.23 | 6.28, 8.31 |
| Adjusted (age+sex only) estimate | 281 (7.0%) | 810 (1.0%) | 2.81 | 2.42, 3.25 |
| Adjusted Estimate | 281 (7.0%) | 810 (1.0%) | 2.09 | 1.74, 2.50 |
| Marginal Structural Model | 281 (7.0%) | 810 (1.0%) | 17.22 | 6.46, 37.65* |
| **Age > 60** | **Cases (N=2903)** | **Controls (N=20741)** | **Odds Ratio** | **95% Confidence Interval** |
| Unexposed | 2655 (91.5%) | 20074 (96.8%) | 1.00 | Reference |
| Crude estimate | 248 (8.5%) | 667 (3.2%) | 2.72 | 2.32, 3.20 |
| Adjusted (age+sex only) estimate | 248 (8.5%) | 667 (3.2%) | 2.43 | 2.05, 2.87 |
| Adjusted Estimate | 248 (8.5%) | 667 (3.2%) | 1.87 | 1.52, 2.30 |
| Marginal Structural Model | 248 (8.5%) | 667 (3.2%) | 4.22 | 1.73, 9.27* |

* 95% confidence interval estimated by 1000 iterations of an empirical bootstrap

## 4.3 Supplementary Material

The following three tables show additional results based on the second thesis paper that were beyond the scope of the published article.

The first table presents the results of the marginal structural model analysis with matching for age and time. The results in the actual paper do not contain any matching. The time matching does not matter as the population is stationary. But the age matching reduces the size of the point estimate considerably. It also makes the estimate partially conditioned and thus less directly interpretable.

The second two tables are just additional simulations to test model assumptions. The first repeats table 3 with much larger sizes of effect modifiers and non-linear terms. This table demonstrates that the rare disease assumption is not sufficient to ensure equality of the conditional and marginal estimates when the effect size of the non-linear term is very large.

The last table shows how much a smaller covariate impacts the results of the second table in the paper. Here we see that the separation between the marginal and conditional effects is clearly being driven by the interaction and not the covariate.

**Table 4.5: Sensitivity analysis for matched data: Comparison of the effect of Warfarin exposure on GI Bleed using different analytical techniques with different interpretations in a GPRD case control study**

| Analytical Technique | Cases (N=4028) | Controls (N=40171) | Odds Ratio | 95% Confidence Interval |
|---|---|---|---|---|
| Unexposed | 3747 (93.0%) | 39041 (97.2%) | 1.00 | Reference |
| Crude estimate | 281 (7.0%) | 1130 (2.8%) | 2.64 | 2.31 - 3.03 |
| Adjusted Estimate | 281 (7.0%) | 1130 (2.8%) | 2.15 | 1.81 – 2.54 |
| Marginal Structural Model | 281 (7.0%) | 1130 (2.8%) | 5.12 | 2.86 – 8.80* |

* 95% confidence interval estimated by 1000 iterations of an empirical bootstrap

**Table 4.6: Sensitivity Analysis for marginal versus conditional effects with large interaction/non-linear term. Results from 1000 Simulated datasets with 20000 observations each: all cases have the same exposure and confounder effect size ($\lambda_1 = 0.68925$, $\lambda_2 = 0.68925$ ). Common exposures are 10 times as rare exposures**

| $\lambda_0$ | $\lambda_3$ | Parameter Estimated | Crude Model | Adjusted Model | Quadratic Confounder Model | Linear Interaction Model | Marginal Structural Model |
|---|---|---|---|---|---|---|---|
| **Case `19: Rare Exposure and Outcome, Linear Model** | | | | | | | |
| -4.595 | 0 | Odds Ratio | 1.55 | 1.98 | 1.98 | 2.00 | 2.00 |
| | | $B_1$ | 0.407 | 0.654 | 0.654 | 0.653 | 0.644 |
| | | Variance | 0.0637 | 0.0651 | 0.0652 | 0.0828 | 0.1058 |
| **Case 20: Rare Exposure and Outcome; Quadratic Model** | | | | | | | |
| -4.595 | 0.919 | Odds Ratio | 0.53 | 2.20 | 2.00 | 3.01 | 1.53 |
| | | $\beta_1$ | -0.634 | 0.767 | 0.669 | 1.052 | 0.415 |
| | | Variance | 0.0306 | 0.0482 | 0.0440 | 0.1076 | 0.0299 |
| **Case 21: Rare Exposure and Outcome, Linear Effect Modifier** | | | | | | | |
| -4.595 | 0.919 | Odds Ratio | 2.33 | 3.08 | 3.09 | 2.00 | 4.79 |
| | | $\beta_1$ | 0.827 | 1.104 | 1.105 | 0.654 | 1.539 |
| | | Variance | 0.0434 | 0.0451 | 0.452 | 0.785 | 0.0582 |
| **Case 22: Common Exposure and Outcome, Linear Model** | | | | | | | |
| -0.60 | 0 | Odds Ratio | 1.49 | 1.99 | 1.99 | 1.99 | 1.96 |
| | | $\beta_1$ | 0.397 | 0.689 | 0.689 | 0.689 | 0.674 |
| | | Variance | 0.0008 | 0.0009 | 0.0009 | 0.0011 | 0.0009 |
| **Case 23: Common Exposure and Outcome; Quadratic Model** | | | | | | | |
| -0.60 | 0.919 | Odds Ratio | 1.07 | 2.03 | 1.99 | 2.06 | 1.82 |
| | | $\beta_1$ | 0.083 | 0.710 | 0.689 | 0.721 | 0.599 |
| | | Variance | 0.0008 | 0.0011 | 0.0010 | 0.0011 | 0.0007 |
| **Case 24: Common Exposure and Outcome, Linear Effect Modifier** | | | | | | | |
| -0.60 | 0.919 | Odds Ratio | 1.60 | 2.23 | 2.25 | 1.99 | 2.37 |
| | | $\beta_1$ | 0.469 | 0.805 | 0.813 | 0.689 | 0.861 |
| | | Variance | 0.0008 | 0.0009 | 0.0009 | 0.0010 | 0.0008 |

**Table 4.7: Sensitivity Analysis for when the effect of the covariate is smaller than the effect of the exposure. Results from 1000 Simulated datasets with 20000 observations each. Estimates for covariate term ($\lambda_2 = 0.344625$) and data generated with same interaction structure as Table 4.2.**

| $\lambda_1$ | $\lambda_3$ | Parameter Estimated | Crude Model | Adjusted Model | Linear Interaction Model | True Model | Marginal Structural Model |
|---|---|---|---|---|---|---|---|
| **Case 25: No true effect of exposure, no interaction** | | | | | | | |
| 0 | 0 | Odds Ratio | 0.89 | 0.99 | 1.00 | 1.02 | 0.99 |
| | | $\beta_1$ | -0.189 | -0.085 | -0.081 | -0.062 | -0.117 |
| | | Variance | 0.164 | 0.165 | 0.186 | 0.177 | 0.235 |
| **Case 26: True effect of exposure, no interaction** | | | | | | | |
| 0.68925 | 0 | Odds Ratio | 1.79 | 1.98 | 2.02 | 2.01 | 1.99 |
| | | $\beta_1$ | 0.547 | 0.651 | 0.653 | 0.662 | 0.637 |
| | | Variance | 0.072 | 0.073 | 0.084 | 0.080 | 0.108 |
| **Case 27: No true effect of exposure, interaction** | | | | | | | |
| 0 | 0.919 | Odds Ratio | 1.95 | 2.26 | 0.83 | 0.99 | 5.54 |
| | | $\beta_1$ | 0.634 | 0.781 | -0.284 | -0.081 | 1.677 |
| | | Variance | 0.067 | 0.071 | 0.228 | 0.161 | 0.073 |
| **Case 28: True effect of exposure, interaction** | | | | | | | |
| 0.68925 | 0.919 | Odds Ratio | 3.37 | 3.99 | 1.72 | 1.99 | 8.73 |
| | | $\beta_1$ | 1.200 | 1.361 | 0.496 | 0.655 | 2.145 |
| | | Variance | 0.039 | 0.0426 | 0.098 | 0.071 | 0.044 |

**Chapter 5**

# Modeling blood pressures changes after drug treatment in the general practice research database

This chapter contains a manuscript that has been submitted to Pharmacoepidemiology and Drug Safety.

The adverse effect of warfarin considered in this paper is a hypothesized increase in systolic blood pressure among patients who are prescribed warfarin therapy. This is an unexpected adverse effect that was reported in the secondary analysis of a very small clinical trial of warfarin therapy. While it is unlikely that such a finding is not by chance, the existence of such an effect would be of clinical importance. This is because it could become important to alter blood pressure medications when beginning warfarin therapy if this therapy was leading to important rises in systolic blood pressure.

However, before we can answer this question, we need to find out of the data in the GPRD can give answers that are comparable to those found in randomized control trials on changes in blood pressures. Therefore, the primary focus of this paper is validating the blood pressure information in the General Practice Research Database in order to be able to examine this hypothesis about the effect of warfarin on blood pressure. This validation is done using drugs with well known effects on blood pressure from clinical trials. Multiple approaches to modeling this data are considered and the results are compared with each other.

The contributions of authors are listed in the preface to the thesis.

# Validating the effects of drug treatment on blood pressure in the General Practice Research Database

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**Running Head:** VALIDATING THE EFFECTS OF DRUG TREATMENT

**Type:** Original Report

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**ABSTRACT**

**Purpose:** Observational studies using clinical databases, such as the United Kingdom's General Practice Research Database (GPRD), may provide an alternative to clinical trial data for detecting longitudinal changes in blood pressure due to drug exposures that vary over time. Blood pressure data measured at variable intervals and often missing present a particular methodological challenge to the analysis of such studies.

**Methods:** To assess effects on blood pressure, we extracted from the GPRD several cohorts of new drug users of warfarin (n=21,532), ibuprofen (n=92,037), proton pump inhibitors (n=153,695), statins (n=118,704), rofecoxib (n=6,399) and celecoxib (n=6,217) from 2001 through 2003. Several blood pressure readings were missing either before or after initiating therapy. We compared the results of analysis using a linear mixed model with a pre-post quasi-experimental design, using the multiple imputation approach to account for missing data.

**Results:** There was evidence that the missing blood pressure data were not missing completely at random as subjects with more blood pressure readings tended to have higher recorded values. For statins, the mixed model estimated a change in systolic blood pressure of -3.80 mmHg (99% confidence interval: -3.97 to -3.63), similar to the quasi-experimental model and to the -4.00 mmHg estimated from clinical trials. Sensitivity analyses indicate that these estimates are robust. For rofecoxib, the change in systolic blood pressure were 2.20 mmHg

(99% confidence interval: 1.09 to 3.32) and 1.21 mmHg (99% confidence interval: 0.21 to 2.22) for the two methods respectively, again confirming the findings of randomized trials.

**Conclusion:** With appropriate statistical techniques, GPRD blood pressure data can be used to estimate blood pressure changes secondary to drug therapy.

**Keywords:** linear mixed models; blood pressure; random effects; multiple imputation; General Practice Research Database (GPRD)

**Word Count:** 3896
**Abstract Word Count:** 267
**Tables:** 6
**Figures**: 2

**What this study adds**

1) Blood pressure data in clinical databases, such as the General Practice Research Database, can provide valid estimates of the effect of drug treatment on blood pressure

2) Missing data need to be accounted for when using blood pressure data in a clinical database

3) Estimates of blood pressure changes in clinical database studies are robust to modest departures from the assumption that the data are missing at random and different approaches yield similar estimates

## 1. INTRODUCTION

Blood pressure is an important biologic parameter that is predictive of cardiovascular outcomes [1]. Elevated blood pressure is widely targeted for reduction in order to decrease the mortality and morbidity due to cardiovascular disease [1]. It is estimated that roughly half of deaths due to coronary heart disease can be attributed to sub-optimal blood pressure control [1]. Therefore, the detection of drugs that may unexpectedly effect blood pressure is an important public health issue.

However, acquiring information on and developing estimates of population level blood pressure changes due to drug exposures is challenging [2]. The individual effects of medications are frequently estimated using data from randomized controlled trials whose participants may not be representative of the general population. One means of obtaining such information on the population level effects of treatment on blood pressure is through clinical practice databases where blood pressure is recorded as part of routine care. However, before these data can be used to estimate population level effects, it is important to verify that the estimates of drug effects obtained from such data are comparable to those obtained from randomized controlled trials.

Clinical databases are often prone to missing information. Subjects enrolled in these databases may not visit their physician in a given time frame or the physician may choose not to measure the blood pressure of a specific subject. This creates a problem of missing blood pressure data. The issue of missing blood pressure data has been previously considered as part of studying drop-outs from clinical trials [3, 4] and missed visits in prospective cohort studies [5]. In this study, we will apply similar approaches to clinical databases where the data tend to be less balanced than in studies with regular follow-up visits.

## 2. DESCRIPTION OF THE PROBLEM

The General Practice Research Database (GPRD) is a large clinical database that stores the medical treatment information of about 3.2 million residents of the United Kingdom (UK) at any point in time [6]. The GPRD has been operating in different forms since 1988 and contains over 50 million person-years of data. The data recorded in the GPRD include prescriptions issued, clinical diagnoses, demographic/lifestyle data, laboratory tests and blood pressure readings.

The GPRD is a very rich database source of population level information on blood pressure. However, the blood pressure readings in the GPRD are taken by general practitioners at patient visits and so are recorded at irregular intervals. Furthermore, some subjects (possibly the healthiest subjects) will have no recorded blood pressure values in the GPRD at all. Therefore, it is important to validate the results of analyses using GPRD blood pressure data by comparing these results with previously validated sources.

A common source of information on the effects of medications is randomized clinical trials which are considered the current gold standard. Comparisons of results from GPRD data with those derived from randomized controlled trial data can determine if these data sources are in broad agreement. If so, the GPRD has the additional advantage that it can then be used to estimate the effects of a drug on blood pressure in populations that are often excluded or under-represented in clinical trials such as the very elderly [5].

In addition, GPRD data on blood pressure can be used to examine epidemiological questions when blood pressure data from randomized clinical trials are not readily available. One example is warfarin, a drug that has a long history of adverse event reports [7]. A recent study reported a new possible side

effect of warfarin: increased systolic blood pressure [8]. We will attempt to replicate this finding using GPRD blood pressure data.

Therefore, the objectives of this study were:

1) To validate the blood pressure data in the GPRD. To do this we use three classes of drugs with known effects on blood pressure as well as two separate approaches to modeling the data. These results will then be compared to those found by randomized controlled trials.

2) To illustrate the use of GPRD blood pressure data by testing for clinically meaningful effect of a drug (warfarin) where the effects on blood pressure are not known from clinical trials and are debated in the literature.

We defined a clinically meaningful result as a change of 2 points (mmHg) in systolic blood pressure based on previous definitions [9].

## 3. DESCRIPTION OF THE COHORT

We formed a series of cohorts of new users of different medications. We focused on new users to avoid the confounding that may arise with medication effects among prevalent users [10]. The medications that we considered for this study are statins (known to lower blood pressure), non-steroidal anti-inflammatory drugs or NSAIDs (known to increase blood pressure), warfarin (unknown effect on blood pressure) and proton pump inhibitors (uninvolved with blood pressure changes). None of these medications are directly used to treat hypertension.

We defined the index date for a subject as the date of the first ever prescription of any study drug (a statin, warfarin, an NSAID or a proton pump inhibitor) for each subject since their initial enrolment in the GPRD. All subjects were required to have been enrolled in the GPRD for at least one year prior to this index date to verify that they were new users of the medication and had not been prescribed the drug in a previous medical practice.

We distinguish between types of NSAID (ibuprofen, rofecoxib, celecoxib) as they are thought to have different effects on blood pressure. We wanted to replicate the increasing effect of NSAIDs on blood pressure as a function of their Cox 2 selectivity. However, to exclude switchers from one type of NSAID to another, we only considered subjects for whom one of these three NSAIDs was the first ever NSAID prescription issued to this subject in the GPRD.

We focused this study on blood pressure changes in a stable and relatively healthy population to increase the comparability of participants in the GPRD and the RCTs to which we compare our results. Therefore all subjects who transferred out of the GPRD within two years of their index date were excluded. This included all subjects who died within the 2 year period after their first prescription. Consequently, we have a full three years of information on all subjects in this study.

In order to mimic the results obtained from clinical trials as precisely as possible, an intention to treat (ITT) analysis was used where subjects are classified as treated from the date of their first prescription and persisting throughout follow-up. This approximation is less biased for drugs with many repeat prescriptions in this population (statins, warfarin) than for drugs with low levels of repeated prescribing (ibuprofen). This is because the ITT approach assumes that once a subject becomes exposed they have perfect adherence to therapy. If adherence is good, then ITT is a good approximation. However, with poor adherence there will be misclassification of exposure so that treatment

exposure may be overestimated. This typically results in a biased estimate of the treatment effect towards the null, leading to an underestimate of the effect of the drug on blood pressure.

## 4. MIXED MODELS APPROACH

Our primary analytical strategy used linear mixed models [11] to account for the pattern with which blood pressure information is recorded in the GPRD. Blood pressure readings on the same subject will be correlated over time. Linear mixed models take this correlation into account and can accommodate variations from the population average blood pressure trajectories that may occur at the individual level.

Following Diggle [12], we modeled blood pressure as a vector response variable, $Y_i$ for individual i using a linear mixed model with a random effect for both time (allowing different subjects to have different blood pressure trajectories) and intercept (allowing subjects to have different baseline blood pressures). The statistical model used was:

$$Y_i = \beta X_i + U_i Z_i + e_i$$

where $Y_i$ is the response variable (blood pressure readings for person i), $X_i$ is a matrix of covariates that have fixed effects, and $Z_i$ is a matrix of covariates that have random effects (typically a subset of $X_i$; in our case we assume random intercepts and slopes in time so that $Z_i$ is a matrix whose first column is a vector of 1's and whose second is the vector of time). The vector of fixed coefficients is $\beta$ and $U_i$ is a multivariate Normal vector with zero mean that accounts for person i's deviation from the population-average fixed effect. The vector of error terms is represented by $e_i$; these are also Normally distributed with zero mean.

The explicit model for the unadjusted linear mixed model using only time, t, and treatment, d (0 or 1), as covariates can be expressed as:

$$Y_i = \beta_0 + \beta_1 t_i + \beta_2 d_i + U_{0i} + U_{1i} t_i + e_i$$

In this model, $X_i = (1, t_i, d_i)$ and $Z_i = (1, t_i)$. Here $\beta_0$ is the untreated population average blood pressure at time zero (one year prior to the first drug prescription), $\beta_1$ represents population-average blood pressure changes over time and $\beta_2$ represents the effect of treatment on blood pressure. The deviations $U_i$ and $e_i$ were assumed to be mutually independent. The random effects, $U_{0i}$ and $U_{1i}$, were assumed to have mean zero and to be Normally distributed. The random intercept, $U_{0i}$, represents the subject-specific deviation from the population-average blood pressure at time zero. The random slope, $U_{1i}$, represents the subject-specific deviation from the population average trajectory of blood pressures over time [13].

The mixed model approach allowed us to efficiently handle the unbalanced structure in the clinical database where subjects have different measures at different times [13]. As a further advantage, linear mixed models are unbiased when the data are missing at random or missing completely at random so long as the mean model and correlation structure are correctly specified [14].

We adjusted for the baseline population characteristics that are presented in Table 5.1. Repeat prescriptions of the treatment were not considered in our analysis as an intention to treat approach was taken, an approach that has been used in other studies [15]. We used 99% confidence intervals as the large cohorts allowed for a high level of precision in our estimates.

All blood pressure readings in the first 90 days after beginning the new medication were excluded to ensure that the medication had sufficient time to affect blood pressure. Analyses were conducted using SAS 9.1.3 using the PROC MIXED procedure using restricted maximum likelihood (REML).

## 5. PRE-POST DESIGN WITH MULTIPLE IMPUTATION

Another strategy we employed to deal with the effect of treatment on blood pressure was to analyze the data using a pre-post quasi-experimental design with the decision to begin prescribing medication to the subjects as the "policy change" [16]. In this design, the last blood pressure reading taken before the beginning of drug treatment (up to one year before) was taken to be the baseline blood pressure. The first reading measured one year post-therapy initiation was taken as the outcome. An illustration of the quasi-experimental design is given in Figure 5.1.

The main challenge with this approach was that some subjects had no blood pressure measures either before or after beginning therapy. These missing values are unlikely to be missing completely at random. Therefore, an analysis based entirely on complete cases was inappropriate [17]. A good choice for this approach was multiple imputation [18] which is a well validated approach to estimating missing values when the data are missing at random [19]. Multiple imputation yields improved estimates of the variance over conventional single imputation techniques by accounting for variability in the imputation procedure [18].

Multiple imputation was used to estimate the unobserved blood pressures by modeling blood pressure as a function of a broad range of covariates representing both the demographic, clinical and medication use characteristics of the cohort. Estimation was performed using PROC MI in SAS with a multiple chain full imputation using the MCMC method and 10 copies. Using a richer model for the imputation step than for the primary analysis can improve coverage and reduce the size of confidence intervals [20] and so this did not impact the validity of our results.

### 5.1 Missing not at random sensitivity analysis

Following van Buuren et al. [5], we performed an analysis to determine the sensitivity of the pre-post design treatment effect estimates to the assumption that data were missing not at random (MNAR) due to unrecorded predictors. We considered the case where subjects with missing information had an increase of either 1 mmHg or 2 mmHg of SBP above what was predicted by the imputation model These results were then compared with the results found in the quasi-experimental study which assumed that data were missing at random to determine whether estimates were robust to small violations of this assumption.

### 5.2 Effect of blood pressure measurement density on mortality

To further explore the comparability of the GPRD with other studies of blood pressure, a new cohort was formed in which we no longer excluded subjects who died or were censored in the two years after beginning treatment. In this cohort, we considered how the number of blood pressure readings at baseline or the absence of baseline blood pressure information predicted mortality in the two years post-treatment. We focused this sub-analysis on the warfarin and statins cohorts to determine whether the number of blood pressure measurements were predictive of all-cause mortality. This also allowed us examine whether the effect of the number of blood pressure readings varied between relatively healthy subjects (statin users) and much sicker subjects (warfarin users).

The association between number of blood pressure measurements and mortality was estimated using a Cox proportional hazards model [21] with the outcome being time to death. The index date for this analysis was taken to be the date that the subject began drug therapy for either warfarin or a statin. Subjects who transferred out of their GPRD practice in this two year time window were censored. We defined three fixed-time exposure categories based on the number

of blood pressure recordings available before the index date when therapy begins: no blood pressure readings at baseline, between 1 and 3 blood pressure readings at baseline (reference) and 4 or more blood pressure readings at baseline.

Since all of the measurements were taken before the index date (baseline) and used to predict future mortality, this study is not subject to immortal time bias [22]. If we wanted to model the effect of blood pressure readings after baseline, some version of time-dependent Cox would be required to account for the time-varying nature of post-treatment blood pressure readings [23] as well as their change in prognostic significance over time [24].

## 6. RESULTS

The results of the linear mixed models analysis are presented in Table 5.2. These results indicate a clinically important change [9] in SBP for two drugs: statins, which decrease SBP by 3.8 mmHg (99% confidence interval (CI): 3.63 to 3. 97), and rofecoxib, which increases SBP by 2.2 mmHg (99% CI: 1.09 to 3.32).

Using the pre-post quasi-experimental design approach to the analysis with multiple imputation to account for the missing blood pressure values suggested that the patients with missing data had different average blood pressures than those with recorded blood pressures. Table 5.3 shows the pattern of baseline systolic blood pressure based on the pattern of blood pressure reporting in the data.

From Table 5.4 we observe that ibuprofen, with an increase in SBP of 0.53 mmHg (99% CI: 0.17 to 0.90), and rofecoxib, with an increase of SBP of 1.21 mmHg (99% CI: 0.21 to 2.22), are associated with statistically significant changes. However, neither drug showed a clinically meaningful increase in systolic blood pressure due to therapy. Statins continue to show a strong effect in

reducing systolic blood pressure compared to proton pump inhibitors with a reduction of 3.81 mmHg (99% CI: 3.54 to 4.08) in systolic blood pressure. Sensitivity analyses for blood pressure being MNAR in Table 5.4 suggests that estimates of the change in blood pressure are robust to small underestimates of blood pressure in subjects with missing baseline or exit blood pressure readings.

Figure 5.2 shows the absolute values of the estimates using a complete case approach to the missing data as compared to using multiple imputation.

The estimates for the effect of the number of blood pressure measurements on mortality are found in Table 5.5. The results suggest that the subjects who are missing blood pressure information at baseline have higher mortality than those with recorded information. In particular, close follow-up (as marked by more than 3 visits with a blood pressure reading taken in a one year period) appears to be protective against mortality in the next two years. Sensitivity analyses indicate that including the subjects who perish in the follow-up period in the mixed model has no impact on the statistical inference (Table 5.6).

To examine the size of bias that could be caused by changes in antihypertensive drug use, we conducted an additional sensitivity analysis: we included antihypertensive drugs (by class including: beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, calcium channel blockers and alpha blockers) in the random effects model for systolic blood pressure. We obtained an adjusted estimate for the change in systolic blood pressure of 0.16 (95% CI: -0.38 to 0.70) for warfarin and -3.22 (95% CI: -3.39 to -3.05) for statins.

## 7. CONCLUSIONS

The effect of statin treatment on blood pressure is consistent with the effect observed in clinical trials for subjects with blood pressure profiles

comparable to those we captured in the GPRD [25]. Two different approaches gave similar answers for the effect of statin therapy on blood pressure with a linear mixed model estimating a decrease of 3.80 mmHg (99% CI: 3.63 to 3.97) and the quasi-experimental design estimating a decrease of 3.81 mmHg (99% CI: 3.54 to 4.08).

These estimates are both qualitatively similar to a meta-analysis of clinical trial which predicted a drop of approximately 4.00 mmHg in subjects with the blood pressure range of the subjects included in this study [25]. The meta-analysis reviewed 20 clinical trials in which statins were used, blood pressures were recorded and concomitant antihypertensive treatment was not altered [25]. The estimates were larger for subjects with systolic blood pressure above > 130 mmHg or diastolic blood pressure > 80 mmHg. The baseline characteristics of the subjects in the GPRD analyzed here are similar to the subgroup with elevated blood pressure that was considered in the meta-analysis. The decrease in diastolic blood pressure of 2.18 mmHg (99% CI: 2.09 to 2. 28) given by the linear mixed model is, however, larger than the decrease of 1.24 mmHg (95% CI: -2.57 to 0.10) predicted by the meta-analysis. However, the estimate derived from the GPRD data is within the 95% confidence interval found by the meta-analysis.

The estimates for NSAIDs are lower than expected [26]. This is likely explained by low adherence as few subjects refilled prescriptions for these drugs in this population. ITT approaches in observational studies always run the risk of a strong bias toward the null when adherence is low [27]. Nevertheless, the estimates correctly rank the ordering of the change in blood pressure by the degree of Cox-2 selectivity of each type of NSAID.

The unexpected effect of warfarin on blood pressure found by Krishnan et al. [8] was not replicated in this study. The GPRD is a very rich database containing information on a large number of subject characteristics. Thus, it is unlikely that the analysis of warfarin effects performed here suffers from any

substantial bias due to confounding. The ability to search for unexpected drug effects in a large and unselected population database is one of the strengths of the GPRD.

As expected, proton pump inhibitors do not cause clinically important (or statistically significant) changes in blood pressure. The small increase seen in the mixed model analysis is entirely due to subjects on long term NSAID therapy also being prescribed proton pump inhibitors. This small effect is removed completely if we adjust for post-baseline NSAID exposure.

An ITT approach was taken in all of the analyses presented in this study. It is unlikely that the decision to discontinue prescriptions, especially for medications indicated for long term use, is random. If the reason for discontinuation is related to other unmeasured subject characteristics, an "as treated" (observational) analysis could produce biased estimates. This may be especially true of blood pressure where general lifestyle effects, such as salt intake, may affect blood pressure and also be linked to the probability of being adherent to a medication.

The statistical approach used in this study is not suitable for drugs that are prescribed for hypertension or for examining the effects of drug treatment regimes that change over time. In cases where treatment is time-varying, unbiased estimation may require the use of different techniques from those used here such as a structural nested mean model [28]. The need for these special models arises because the decision of the physician either to treat or to discontinue treatment is typically a function of the subject's time-varying treatment history. Traditional regression techniques will not give valid estimates in the presence of time-varying confounders [29] in a longitudinal setting especially if some of the variables are intermediate between the treatment and the outcome [30].

The estimates of missing blood pressure given by the pre-post design using multiple imputation support the notion that, on average, subjects who do not have blood pressure values recorded in a one year time span have lower blood pressure than those who do. However, we also observe that subjects who are missing blood pressure readings are also at higher risk of mortality as reported by van Buuren et al. [5]. This suggests that subjects who are more ill are less likely to have a reading recorded. However, it is not clear if the increase in mortality is due to a lower intensity of follow-up or poorer underlying health status.

The sensitivity analysis for MNAR data indicate that estimates from the pre-post design analysis were robust to small increases in the modelled blood pressure of the subjects with missing data. Therefore, even if the multiple imputation approach leads to small underestimates of the true blood pressure of subjects with missing values, the direction of the change in blood pressure is correctly estimated. Including censored subjects (i.e. subjects who die in the 2 years post-treatment) in the mixed model produces remarkably consistent results.

It is also possible that changes in antihypertensive therapy could have acted as a time varying confounder that should be adjusted for in the statistical model [23, 31]. The prevalence of antihypertensive drug therapy increases over time in both the statin and the warfarin groups. This is expected as both groups are likely to have some level of cardiovascular disease and likely experience increasing disease severity with time. However, these groups do not show similar changes in blood pressure despite similar rises in intensity of therapy suggesting that the observed changes in blood pressure are an effect of the drugs and not of changes in adjunct therapies.

Modeling unexpected blood pressure changes due to drug treatment is feasible in clinical databases such as the GPRD and other databases with similar characteristics [32]. The use of random effects models makes it possible to

account for the unbalanced nature of clinical data and allows valid inferences to be made about the effect of medications on blood pressure.

**Ethical Review:** Ethical review for this study was done by the Independent Scientific Advisory Committee for MHRA database research

**Funding:** This study was funded by the Canadian Institutes of Health Research (CIHR) and the Canadian Foundation for Innovation.

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**Table 5.1: A description of characteristics for new drug user cohort. All variables are measured at baseline (date of 1st Rx) unless otherwise stated. Data from the General Practice Research Database from 2001 through 2003.**

| | Statin | Proton Pump Inhibitor | Ibuprofen | Celecoxib | Rofecoxib | Warfarin |
|---|---|---|---|---|---|---|
| Number of Patients | 118,704 | 153,695 | 92,032 | 6,217 | 6,399 | 21,532 |
| **Baseline Covariates** | | | | | | |
| Age [SD] | 64.5 [11.2] | 56.5 [16.3] | 51.5 [17.0] | 62.5 [15.6] | 61.4 [15.8] | 67.5 [13.1] |
| % Male | 53.7 | 44.8 | 44.3 | 40.1 | 41.4 | 53.0 |
| % Alcohol Abuse | 2.9 | 3.4 | 2.4 | 2.3 | 2.2 | 2.6 |
| % Myocardial Infarct | 12.9 | 4.2 | 2.0 | 3.5 | 3.7 | 10.5 |
| % Stroke | 5.3 | 2.0 | 0.9 | 1.5 | 1.9 | 6.7 |
| % Congestive Heart Failure | 4.4 | 2.7 | 1.1 | 2.1 | 2.2 | 12.3 |
| % Arrythmia | 7.9 | 4.8 | 2.3 | 4.8 | 4.0 | 39.5 |
| % Pulmonary Embolism | 1.3 | 0.9 | 0.4 | 0.7 | 0.9 | 10.1 |
| % Deep Vein Thrombosis | 2.1 | 1.7 | 0.8 | 1.7 | 1.6 | 17.7 |
| % Diabetes | 24.6 | 5.9 | 4.4 | 5.9 | 5.5 | 9.5 |
| % Gastro-intestinal bleed | 0.4 | 0.6 | 0.1 | 0.4 | 0.4 | 0.6 |
| % Renal Failure | 1.2 | 0.7 | 0.1 | 0.1 | 0.2 | 1.7 |
| % Liver Failure | 0.1 | 0.2 | 0.2 | 0.3 | 0.4 | 0.1 |
| % Arthritis | 25.9 | 21.5 | 6.7 | 19.2 | 19.0 | 30.5 |
| Num Hosp Prev Year | 0.3 [1.1] | 0.3 [1.3] | 0.1 [0.6] | 0.1 [0.7] | 0.1 [0.7] | 0.6 [1.7] |
| **Covariates measured at one year after baseline** | | | | | | |
| Number of Rx refills | 8.1 | 3.4 | 0.6 | 1.9 | 2.0 | 7.8 |

**Table 5.2: Effect of beginning drug treatment on blood pressure (using an intention to treat approach). Analysis is with a longitudinal linear mixed model. Data from the general practice research database from 2001 through 2003.**

| | Number | Crude Change in Blood Pressure | Adjusted Change in Blood Pressure | 99% Confidence Interval |
|---|---|---|---|---|
| **1) Systolic Blood Pressure** | | | | |
| *Statin* | 118,704 | -4.18 | -3.80 | -3.97 to -3.63 |
| *Proton Pump Inhibitor* | 153,695 | 0.13 | 0.51 | 0.29 to 0.74 |
| *Ibuprofen* | 92,032 | 1.11 | 1.17 | 0.86 to 1.49 |
| *Celecoxib* | 6,217 | 1.03 | 1.30 | 0.22 to 2.38 |
| *Rofecoxib* | 6,399 | 2.01 | 2.20 | 1.09 to 3.32 |
| *Warfarin* | 21,532 | -1.01 | -0.23 | -0.78 to 0.31 |
| **2) Diastolic Blood Pressure** | | | | |
| *Statin* | 118,704 | -2.40 | -2.18 | -2.28 to -2.09 |
| *Proton Pump Inhibitor* | 153,695 | 0.18 | 0.26 | 0.13 to 0.38 |
| *Ibuprofen* | 92,032 | 0.71 | 0.67 | 0.49 to 0.85 |
| *Celecoxib* | 6,217 | 0.44 | 0.45 | -0.14 to 1.05 |
| *Rofecoxib* | 6,399 | 1.16 | 1.10 | 0.50 to 1.70 |
| *Warfarin* | 21,532 | -1.00 | -0.70 | -1.00 to -0.39 |

**Table 5.3: Effect of study drugs on systolic blood pressure (SBP) and diastolic blood pressure (DBP) relative to change observed in proton pump inhibitor users (control drug). Quasi-experimental pre-post study design analyzed with linear regression. Data from the General Practice Research Database from 2001 through 2003.**

| | Crude SBP | Adjusted SBP (99% confidence interval) | Crude DBP | Adjusted DBP (99% confidence interval) |
|---|---|---|---|---|
| *Full Analysis* | | | | |
| *Statin* | -5.13 | -3.81 (-4.08 to -3.54) | -3.08 | -2.25 (-2.45 to -2.06) |
| *Ibuprofen* | 0.90 | 0.53 (0.17 to 0.90) | 0.44 | 0.15 (-0.19 to 0.49) |
| *Celebrex* | 0.43 | 0.48 (-0.62 to 1.58) | -0.01 | 0.17 (-0.51 to 0.85) |
| *Rofecoxib* | 1.05 | 1.21 (0.21 to 2.22) | 0.41 | 0.39 (-0.49 to 1.27) |
| *Warfarin* | -2.21 | -0.00 (-1.10 to 1.10) | -1.78 | -0.47 (-0.94 to 0.00) |
| *Sensitivity Analysis (+1 mmHg for missing value)* | | | | |
| *Statin* | -5.10 | -3.76 (-4.06 to -3.46) | -3.05 | -2.21 (-2.38 to -2.04) |
| *Ibuprofen* | 0.89 | 0.52 (0.15 to 0.89) | 0.44 | 0.14 (-0.20 to 0.47) |
| *Celebrex* | 0.42 | 0.47 (-0.62 to 1.58) | -0.02 | 0.16 (-0.52 to 0.85) |
| *Rofecoxib* | 1.32 | 1.20 (0.20 to 2.20) | 0.39 | 0.38 (-0.50 to 1.26) |
| *Warfarin* | -2.21 | 0.03 (-1.07 to 1.14) | -1.79 | -0.44 (-0.90 to 0.03) |
| *Sensitivity Analysis (+2 mmHg for missing value)* | | | | |
| *Statin* | -5.06 | -3.72 (-4.01 to -3.42) | -3.02 | -2.17 (-2.34 to -2.00) |
| *Ibuprofen* | 0.89 | 0.51 (0.14 to 0.87) | 0.43 | 0.12 (-0.22 to 0.46) |
| *Celebrex* | 0.40 | 0.47 (-0.63 to 1.57) | -0.04 | 0.16 (-0.52 to 0.84) |
| *Rofecoxib* | 1.29 | 1.19 (0.18 to 2.19) | 0.36 | 0.37 (-0.51 to 1.25) |
| *Warfarin* | -2.20 | 0.07 (-1.04 to 1.17) | -1.77 | -0.40 (-0.87 to 0.07) |

**Table 5.4: Hazard ratio (HR) for all-cause mortality (in the two years first drug prescription) based on number of blood pressure readings in the year before first drug prescription. Drugs considered are warfarin and statins. Analysis is with Cox proportional hazards model. Data from the General Practice Research Database from 2001 through 2003.**

| | Patients | Deaths | Crude HR | Adjusted HR | 99% Confidence Interval |
|---|---|---|---|---|---|
| *Warfarin* | | | | | |
| *No BP readings* | 9,524 (35.6%) | 1643 (40.8%) | 1.14 | 1.13 | 1.01 to 1.25 |
| *1-3 readings* | 10,760 (40.2%) | 1662 (41.3%) | 1.00 | 1.00 | Reference |
| *4+ readings* | 6,482 (24.2%) | 722 (17.9%) | 0.70 | 0.67 | 0.59 to 0.76 |
| *Statin* | | | | | |
| *No BP readings* | 25,422(19.6%) | 1309 (23.4%) | 1.24 | 1.23 | 1.11 to 1.36 |
| *1-3 readings* | 67,109 (51.9%) | 2816 (50.3%) | 1.00 | 1.00 | Reference |
| *4+ readings* | 36,852 (28.5%) | 1475 (25.3%) | 0.95 | 0.88 | 0.81 to 0.96 |

**Table 5.5: Sensitivity analysis for selection bias. Effect of beginning drug treatment on blood pressure (using an intention to treat approach). Analysis is with a longitudinal linear mixed model. This is a sensitivity analysis that includes both the population that remains across the study period as well as patients who die or are censored in the 2 years after beginning drug therapy. Data from the general practice research database from 2001 through 2003.**

| | Number | Crude Change in Blood Pressure | Adjusted Change in Blood Pressure | 99% Confidence Interval |
|---|---|---|---|---|
| **1) Systolic Blood Pressure** | | | | |
| *Statin* | 129,458 | -4.20 | -3.80 | -3.97 to -3.63 |
| *Proton Pump Inhibitor* | 179,714 | -0.13 | 0.33 | 0.11 to 0.54 |
| *Ibuprofen* | 102,273 | 1.00 | 1.08 | 0.78 to 1.39 |
| *Celecoxib* | 7,005 | 0.83 | 1.13 | 0.08 to 2.18 |
| *Rofecoxib* | 7,354 | 1.75 | 1.95 | 0.88 to 3.03 |
| *Warfarin* | 26,793 | -1.28 | -0.52 | -1.04 to 0.00 |
| **2) Diastolic Blood Pressure** | | | | |
| *Statin* | 129,458 | -2.39 | -2.16 | -2.26 to -2.07 |
| *Proton Pump Inhibitor* | 179,714 | 0.16 | 0.23 | 0.11 to 0.35 |
| *Ibuprofen* | 102,273 | 0.68 | 0.64 | 0.47 to 0.82 |
| *Celecoxib* | 7,005 | 0.52 | 0.52 | -0.06 to 1.10 |
| *Rofecoxib* | 7,354 | 1.20 | 1.14 | 0.57 to 1.72 |
| *Warfarin* | 26,793 | -1.12 | -0.83 | -1.12 to -0.54 |

**Figure 5.1: Quasi-experimental pre-post study design used to evaluate changes in blood pressure in cohort of new users of medication. Policy change is the decision to prescribe medication (index date).**

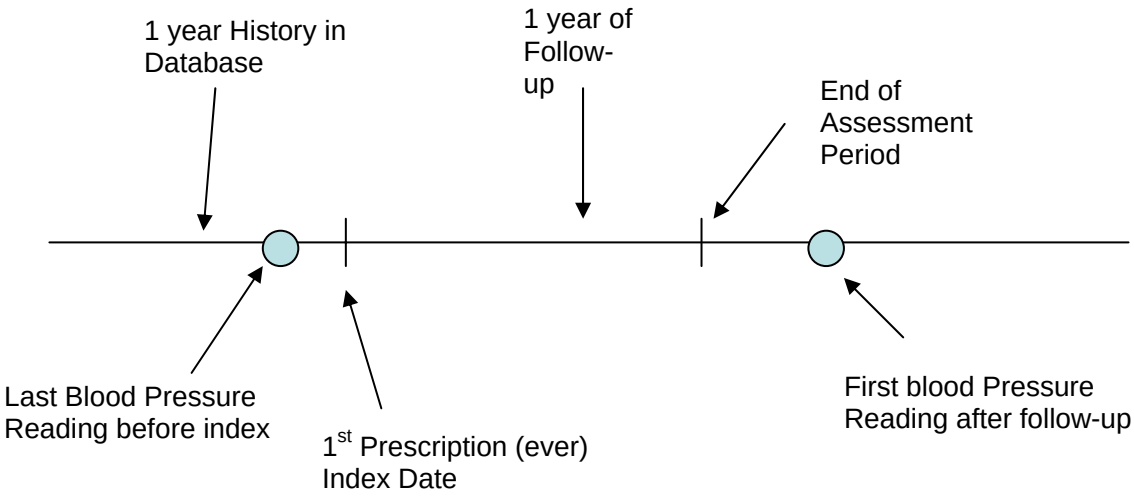
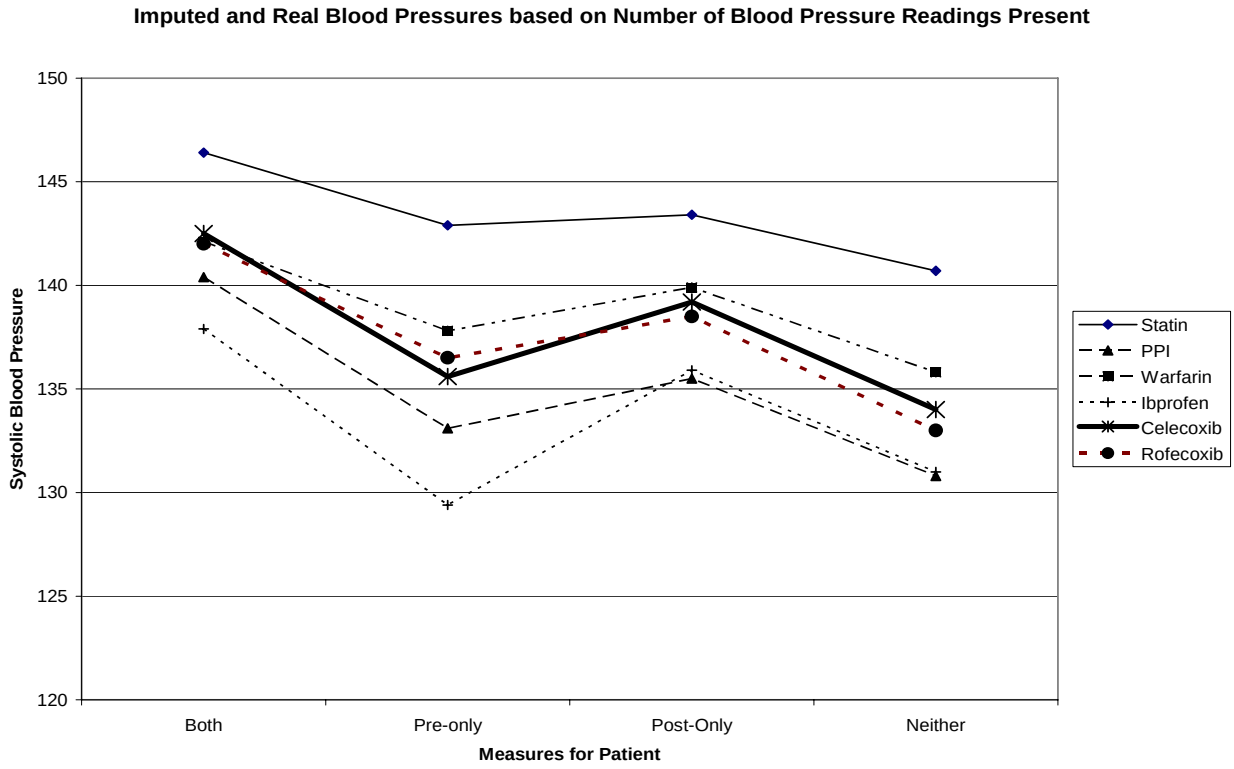


**Figure 5.2: Imputed and measured baseline systolic blood pressure by cohort and by measurement information available pre and post index date (1st ever prescription) by drug class. Data from the General Practice Research Database from 2001 through 2003. Means presented are from observed blood pressure data only (where both measurements were recorded), from observed and imputed blood pressure measures (where only one of pre- and post-treatment measurements was recorded), or from imputed blood pressure data only (where both pre- and post-treatment measurements were missing).**



## 5.3 Supplementary Material

The following 4 figures and one table are additional information for the paper in this chapter. The figures show the performance of the multiple imputation for systolic blood pressure (both pre- and post- treatment) in the statins cohort for the quasi-experimental study. They are intended as illustrative examples of the good properties that the imputation had in this study.

The table shows the properties of the imputed data in the quasi-experimental study by category of missingness. Of general interest is that patients with missing baseline blood pressure values seemed to show less effect of drug exposure on blood pressure. Whether this is a property of the patients with missing blood pressure values in the GPRD or evidence of missing not at random will require further validation work.

**Figure 5.3: Time plots for multiple imputation of systolic blood pressure pre-intervention in the Statins cohort**

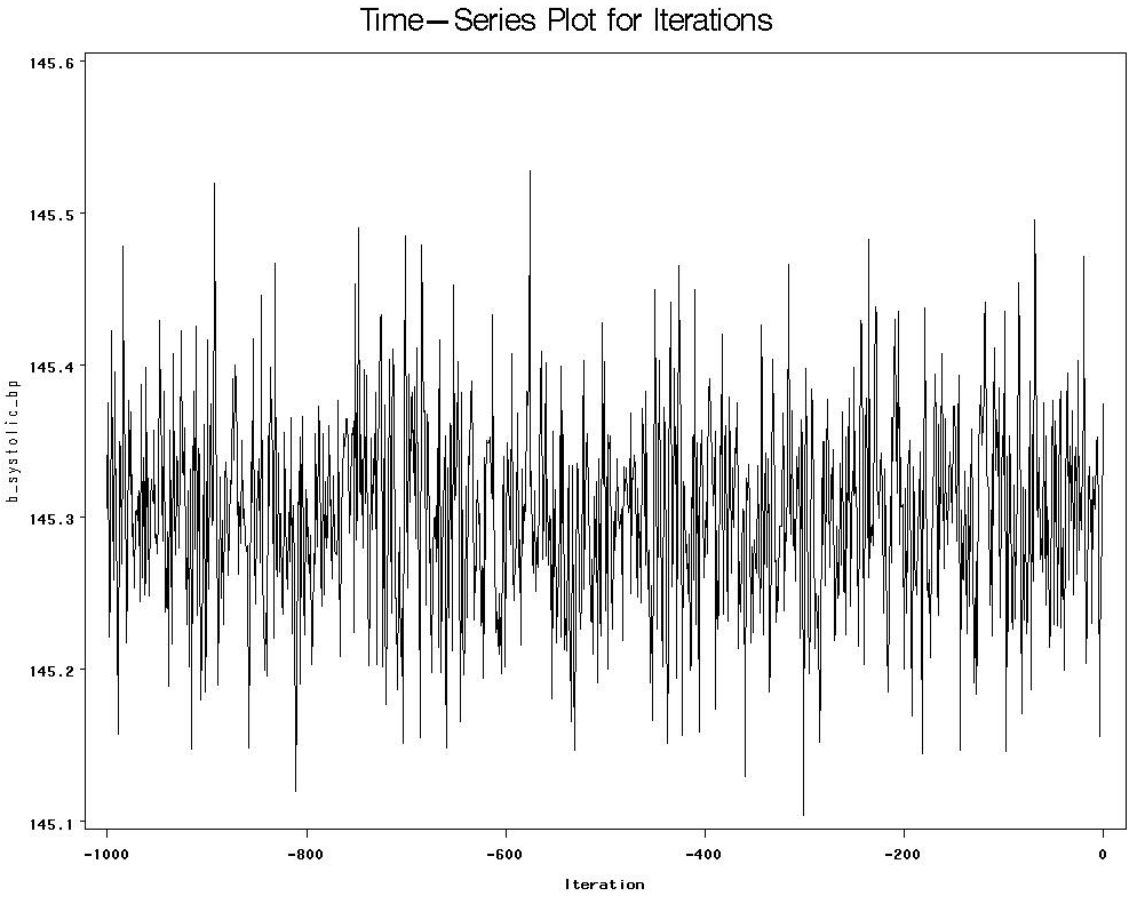


**Figure 5.4: Time plot for multiple imputation of systolic blood pressure post intervention in the Statins cohort**

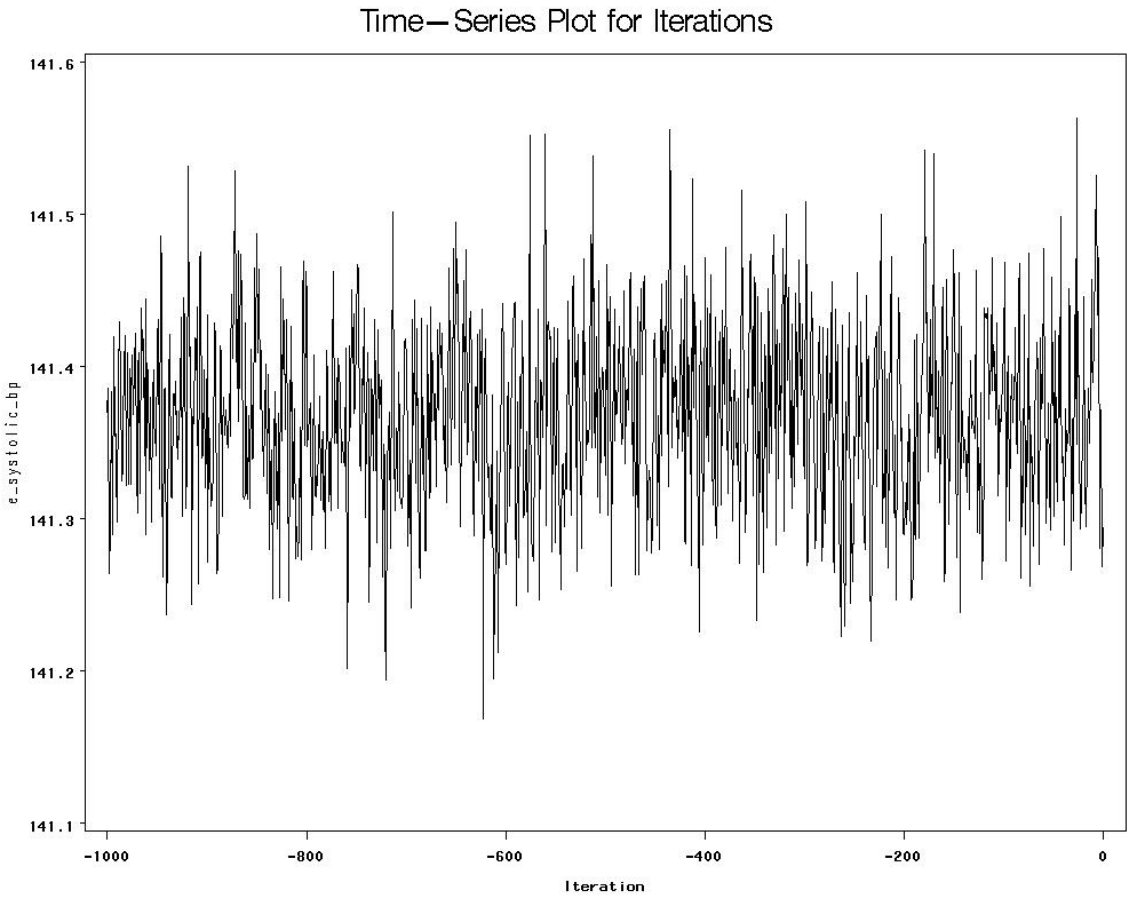


**Figure 5.5: Autocorrelation plot for multiple imputation of systolic blood pressure pre intervention in the Statins cohort**

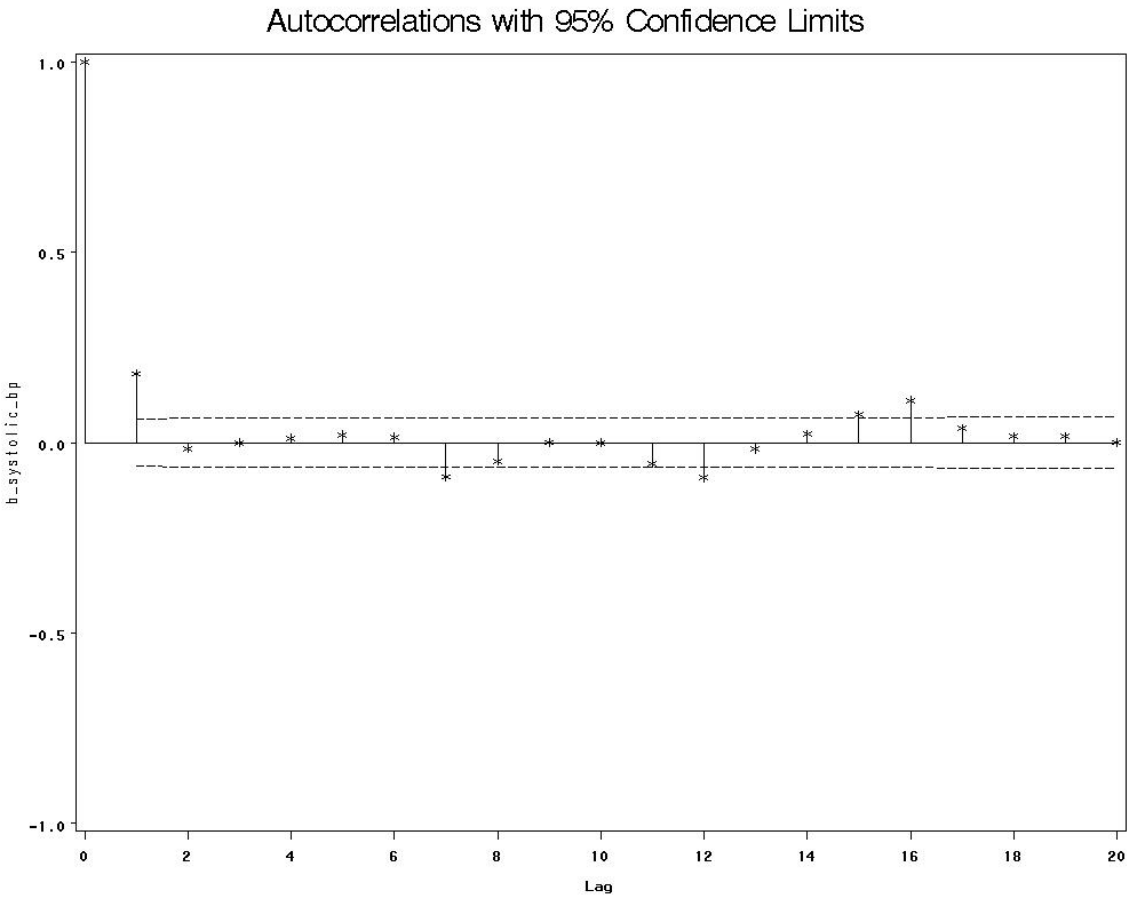


**Figure 5.6: Auto-correlation plot for multiple imputation of systolic blood pressure post intervention in the Statins cohort**

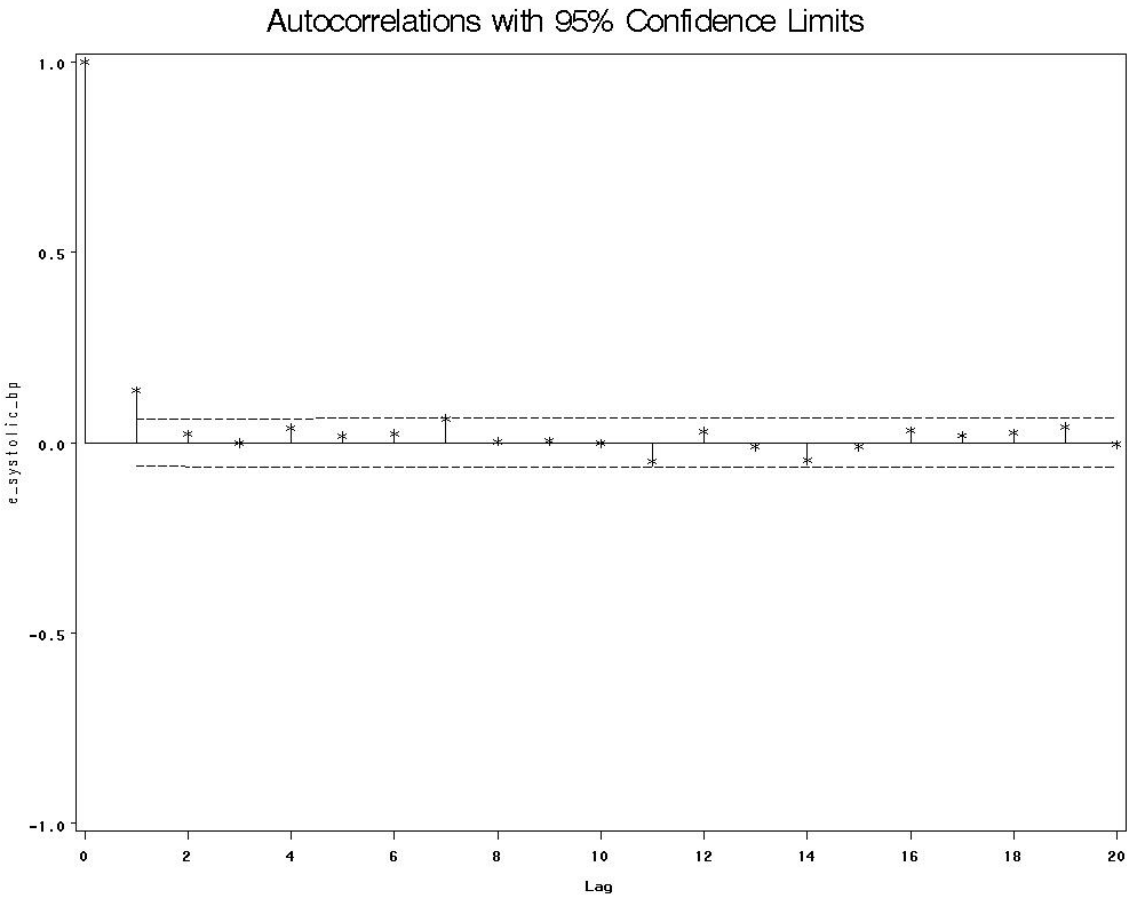


**Table 5.7: Imputed Effects for Missing Blood Pressure by drug class and status of missing data in the General Practice Research Database [GPRD, 1st Rx 2000 to 2003]. Data from second manuscript (*Modeling blood pressures changes after drug treatment in the general practice research database*)**

| Measure | Both baseline and 1 year BP measured | Baseline BP but no 1 year BP | No baseline BP but 1 year BP measured | Neither baseline or 1 year BP measured |
|---|---|---|---|---|
| **Statin** | N = 83,650 | N = 11,969 | N = 16,528 | N = 6,557 |
| *Systolic Blood Pressure (baseline)* | 146.4 | 142.9 | 143.4 | 140.7 |
| *Systolic Blood Pressure (exit)* | 142.4 | 140.1 | 138.6 | 137.9 |
| *Delta Systolic Blood Pressure* | -4.0 | -2.8 | -4.8 | -2.7 |
| *Diastolic Blood Pressure (baseline)* | 82.7 | 82.6 | 82.6 | 82.6 |
| *Diastolic Blood Pressure (exit)* | 80.0 | 80.6 | 79.5 | 80.6 |
| *Delta Systolic Blood Pressure* | -2.7 | -2.0 | -3.1 | -2.1 |
| **Proton Pump Inhibitor** | N = 54,330 | N = 21,900 | N = 32,334 | N = 45,131 |
| *Systolic Blood Pressure (baseline)* | 140.4 | 133.1 | 135.5 | 130.8 |
| *Systolic Blood Pressure (exit)* | 140.5 | 134.9 | 136.8 | 132.8 |
| *Delta Systolic Blood Pressure* | 0.2 | 1.8 | 1.3 | 2.0 |
| *Diastolic Blood Pressure (baseline)* | 80.6 | 79.3 | 80.3 | 79.5 |
| *Diastolic Blood Pressure (exit)* | 80.5 | 80.1 | 80.8 | 80.4 |
| *Delta Systolic Blood Pressure* | -0.2 | 0.8 | 0.5 | 1.0 |
| **Warfarin** | N = 11,365 | N = 2,752 | N = 4,126 | N = 3,289 |
| *Systolic Blood Pressure (baseline)* | 142.1 | 137.8 | 139.9 | 135.8 |
| *Systolic Blood Pressure (exit)* | 140.3 | 137.9 | 139.0 | 136.4 |

| Measure | Both baseline and 1 year BP measured | Baseline BP but no 1 year BP | No baseline BP but 1 year BP measured | Neither baseline or 1 year BP measured |
|---|---|---|---|---|
| *Delta Systolic Blood Pressure* | -1.8 | 0.0 | -0.9 | 0.6 |
| *Diastolic Blood Pressure (baseline)* | 81.6 | 80.7 | 81.3 | 80.4 |
| *Diastolic Blood Pressure (exit)* | 79.7 | 80.0 | 80.0 | 80.3 |
| *Delta Systolic Blood Pressure* | -1.8 | -0.7 | -1.3 | -0.1 |
| **Ibuprofen** | N = 24, 869 | N = 12,278 | N = 18,860 | N = 36,030 |
| *Systolic Blood Pressure (baseline)* | 137.9 | 129.4 | 133.5 | 128.5 |
| *Systolic Blood Pressure (exit)* | 138.9 | 131.9 | 135.9 | 131.0 |
| *Delta Systolic Blood Pressure* | 1.1 | 2.4 | 2.4 | 2.5 |
| *Diastolic Blood Pressure (baseline)* | 80.0 | 80.0 | 79.5 | 78.4 |
| *Diastolic Blood Pressure (exit)* | 80.3 | 79.1 | 80.6 | 79.5 |
| *Delta Systolic Blood Pressure* | 0.2 | 1.1 | 1.1 | 1.2 |
| **Celecoxib** | N = 2,415 | N = 827 | N = 1,352 | N = 1,623 |
| *Systolic Blood Pressure (baseline)* | 142.5 | 135.6 | 139.2 | 134.0 |
| *Systolic Blood Pressure (exit)* | 143.1 | 137.8 | 141.0 | 136.6 |
| *Delta Systolic Blood Pressure* | 0.7 | 2.2 | 1.7 | 2.6 |
| *Diastolic Blood Pressure (baseline)* | 80.8 | 79.7 | 80.9 | 80.1 |
| *Diastolic Blood Pressure (exit)* | 80.5 | 80.5 | 81.5 | 81.3 |
| *Delta Systolic Blood Pressure* | -0.2 | 0.8 | 0.5 | 1.2 |
| **Rofecoxib** | N = 2,257 | N = 851 | N = 1,450 | N = 1,841 |
| *Systolic Blood Pressure (baseline)* | 142.0 | 136..5 | 138.5 | 133.0 |
| *Systolic Blood Pressure (exit)* | 143.7 | 139.5 | 140.8 | 136.6 |
| *Delta Systolic Blood Pressure* | 1.7 | 3.0 | 2.3 | 3.5 |
| *Diastolic Blood Pressure (baseline)* | 80.3 | 79.9 | 80.7 | 79.6 |

| Measure | Both baseline and 1 year BP measured | Baseline BP but no 1 year BP | No baseline BP but 1 year BP measured | Neither baseline or 1 year BP measured |
|---|---|---|---|---|
| *Diastolic Blood Pressure (exit)* | 81.0 | 81.0 | 81.3 | 80.7 |
| *Delta Systolic Blood Pressure* | 0.7 | 1.1 | 0.7 | 1.2 |

# Chapter 6

# Conclusions

Warfarin is a powerful drug that has many well documented benefits in the reduction of adverse cardiovascular events in high-risk patients [1]. However, warfarin is a complex drug to study because it has a number of unfavourable properties from a pharmacoepidemiology point of view. It is known to have strong channelling bias due to prescribing guidelines [2], it has many different interactions with a large number of other drugs [3] and the duration of prescriptions is hard to quantify because the dose of the drug may be dynamically adjusted between prescriptions (making duration impossible to easily estimate) [4].

These same properties also make warfarin an excellent drug to focus methodology work around as there is potential to detect large differences between approaches with studies on this drug. Also, as a well understood drug, it is possible to have some guidance about what is or is not a credible answer.

This thesis provides elements necessary to improve the methodology of studies conducted in the General Practice Research Database (GPRD). We started with a series of methodological challenges in the GPRD including: detecting interactions, account for confounding by indication or channelling bias and the problem of missing data.

One of the most important elements of this thesis was the implementation of different approaches to statistical modeling of exposure-outcome relationships. While one should always use the simplest model that can answer the study question in a valid manner, sometimes the result of this decision is not a simple model. In many cases, the problem itself requires a complex model in order for

valid estimates to be obtained. In particular, the use of marginal structural models is an important step forward in handling time-varying confounders more appropriately as they are more able to handle the issues of time-varying confounding than regular regression approaches [5]. Understanding the properties of these models and the correct interpretation of their results is important as they become more common the epidemiological literature. Discussing how their interpretation is different and systematically testing their properties improved our understanding of these models.

Other modeling techniques, like linear mixed models [6] and multiple imputation [7], are not new techniques but have not always been applied as broadly as they might have been in epidemiological research. There are many advantages to including these techniques in the arsenal of the practicing epidemiologist who is doing research in the GPRD. This is especially true for the use of the test based data where data is unbalanced, patients often have missing data and repeated measures are common.

The GPRD, being based on practices, is a naturally clustered study environment [8]. Traditionally, this clustering has been handled by matching on GPRD practice. However, for some rare diseases or when there are tight matching requirements, this may result in the loss of cases when one can afford to lose them the least. Linear mixed models are another alternative that might be extended to handle cases where the epidemiologist does not want to match on GPRD practice but either the outcome or the exposure is a GPRD diagnostic code.

In the same vein, one of the key advantages of the GPRD over prescription claims databases is the presence of information on demographic characteristics such as smoking and body mass index. However, it is squandering invaluable data to not to use the best possible technique to account for this missing data in the analysis of GRPD studies. The introduction of multiple imputation as a

technique to handle missing data, while not the only good choice, is a logical way forward [7].

There are two other logical next steps to improving modeling for pharmacoepidemiology studies in the GPRD. One step is to introduce Bayesian models for which contain priors for the measurement error in the data. Large database studies often systematically under-represent the amount of uncertainty in the data as the systematic error may be much greater than the random error [9]. We began the process of trying to be more explicit about uncertainty by increasing the size of the confidence intervals in the last manuscript, but a more formal approach would be much more appropriate.

The other logical step is to formally introduce longitudinal marginal structural models to account for time-varying nature of many of the confounders in the GPRD. This is especially important in dynamic treatment regimes where standard approaches are unable to account for the past history of the patient correctly [10]. In particular, good studies need to be done comparing the estimates from marginal structural models to estimates obtained from time dependent Cox models.

Our careful work on confounding in the GPRD is also important to note. We built extremely large models to try and broadly adjust for the health status of the patients in these studies -- taking full advantage of the statistical power that we have in GPRD studies to create large models. We also tried to demonstrate channelling bias away from high risk drug combinations that are well known to general practitioners by comparing the well known high risk combination to a more recent and less well known combination.

In addition, our work on marginal versus conditional effects also gives us some insight into this potential source of bias. By comparing the results of the logistic regression and the marginal structural model we are actually able to

estimate how much risk warfarin would pose in the absence of this "good prescribing practice". After all, the marginal effect represents what would happen if the patients in the GPRD were randomized to warfarin irrespective of their covariates. In that sense, our second paper is able to uniquely document the beneficial effects of prescription policy and awareness of adverse drug effects among physicians.

Like any observational study, the studies in this thesis have a number of limitations. In particular, we are always vulnerable to the influence of unknown confounders on our estimates. It is possible to do sensitivity analyses to determine how robust your results are to unmeasured confounders. This is especially true if the magnitude of the confounding relationship can be estimated from external information (other studies, for example). However, there is no way to ensure against the presence of unknown confounding.

We also have to assume that we have exchangeability between the exposed and unexposed when we construct our marginal structural model – that within a given covariate pattern we can exchange the exposed and the unexposed. While this is an explicit assumption for marginal structural models, if there are unexchangeable subjects in the analysis it is not immediately clear that conditional logistic regression will be able to estimate exposure-outcome effects in an unbiased manner either.

There are also the special problems that are unique to pharmacoepidemiology studies. Here we can have confounding by indication (channelling bias) where the drug is being given to patients at high risk. We see this clearly in the effect of proton pump inhibitors (a highly protective drug) in the first study (where they appear to be risky due to confounding by indication). There is also the problem of reverse causality due to protopathic bias (as it is essential that the drug exposure precedes the outcome and not be marker for the outcome having already happened). Where this does not hold and the drug

therapy is being given to treat the early symptoms of the outcome then we would have a case of reverse causality. This is a plausible explanation for the results seen in the first paper for proton pump inhibitors and the risk of gastrointestinal bleeding where a protective drug appears to increase risk.

However, despite the limitations of databases such as the GPRD, there is a lot of valuable information that can be extracted from them that are able to answer questions on adverse effects that may not be available from other sources. In some cases the hurdle is ethical – we are unable to randomize patients to a given exposure because it is known to be harmful (the classic example being smoking). Or current clinical trial information could be too sparse to find an effect or it could fail to include the relevant sub-group for a specific study question.

In other cases, there may be no currently relevant clinical trial information the time required to do a series of experimental studies may be too long. This is especially true of extremely severe adverse events (such as death) or for exposures with long onset times before the outcome occurs. While the length of time that the GPRD has excellent data recoding is mostly post-2000, over time researchers using this database will gain the ability to ask longer term questions.

Lastly, there are many cases where the results of clinical trials may not generalize to the general population or to situations of standard practice. The patients in the experiments may be sub-selected such that particular groups (including high risk groups) may be excluded. As a result, the tightly controlled nature of the clinical trial environment may not match the reality of actual clinical practice. This is especially relevant with a drug like warfarin where there are a lot of contra-indications and extensive monitoring options. It may simply not be feasible to replicate the expertise or the environment of the clinical trial in "real world" settings.

Because of these limitations with non-observational approaches to pharmacoepidemiology, it is important to develop approaches to the analysis of observational data that allow one to make the best inferences possible given the data available. Given the high cost of data acquisition and the amount of effort that is put into developing a database like the GPRD, it only makes sense to analyze studies based on this data with care. We have seen the potential harm that poor methodology can do with the many studies containing immortal time bias that gravely mislead patients and physicians alike.

By providing guidance on how to handle potential methodological problems (interactions, channelling bias, missing data), we improve the ability of researchers to perform more validobservational studies in the GPRD.

In terms of substantive conclusions, this thesis and provides new insights into the link between warfarin use and serious bleeding episodes in the general practice setting. We show the practical effect of drug-drug interactions in a real-world setting and demonstrate that the risk shown in the trials is not greatly increased despite less stringent monitoring. We are also able to more broadly document the interaction of warfarin with drugs that it would not be routinely tested in combination with for a clinical trial. We also demonstrate the magnitude of additional bleeding risk that warfarin therapy would have if applied to everyone making it clear that careful population selection is important for techniques like marginal structural models. Finally, we look at another possible adverse drug outcome for warfarin (increases in systolic blood pressure) and conclude that we can find no evidence to support this hypothesis.

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# Appendix I : Ethics Approval from the United Kingdom ISAC Approval (Papers 1 and 2) and SEAG (Paper 3)

The following are the 4 ethics approvals used for these research projects (2 from the UK and 2 from McGill). The protocol on gastro-intestinal bleeding covers the first two studies while the protocol on primary prevention of cardiovascular disease covers the third thesis paper.

GPRD

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## SEAG EVALUATION OF PROTOCOLS

## FEED-BACK TO APPLICANTS

**CONFIDENTIAL** *by e-mail*

**PROTOCOL NO:** 758

**PROTOCOL TITLE:** The use of statins in the primary prevention of cardiovascular disease: influence of BMI

**APPLICANT:** Samy Suissa, PhD, McGill University, Division of Clinical Epidemiology, Royal Victoria Hospital

| APPROVED ☐ | APPROVED SUBJECT TO MINOR AMENDMENT (resubmission not required) ☒ | REVISION/ RESUBMISSION REQUESTED ☐ | REJECTED ☐ |
|---|---|---|---|

**COMMENTS**

Protocol 758 is approved subject to the investigators noting the following comments by SEAG and making appropriate amendments.

Cholesterol units are different in UK? ">200" without stated units is meaningless. Different parts of the UK may use different units and they may have changed over time. The researchers will need to convert milli-equivalents, milli-moles and milligrams into a single unit of measurement.

Use of the guidelines at the time of analysis will invalidate any criticism of the treatment provided by GPs.

Information obtained should include major diagnoses as not all the endpoints to be studied involve hospitalisation.

Apart from debating the exact threshold of cholesterol level requiring treatment, the researchers might study the effects of levels of HDL and LDL as factors influencing prescribing.

There have been large calendar effects upon the indications for the treatment of cholesterol levels.

**DATE:** 15 November 2005

Centre universitaire de santé McGill
McGill University Health Centre

Bureau d'éthique de la recherche
Office of Research Ethics

May 29, 2007

Dr. Samy Suissa
Div. of Clinical Epidemiology
RVH, Room R4.29

**REB NO. BMB 07-002**

**RE: Warfarin in the General Practice Research Database: Adverse Effects Interactions and Benefits**

Dear Dr. Suissa:

We are pleased to inform you that the above referenced study was found to be within ethical guidelines for conduct at the McGill University Health Centre. Approval for the study protocol dated March 29, 2006 was provided via expedited review of the Chair on May 28, 2007 and will be reported to the Research Ethics Board (REB) at its meeting of July 4, 2007. It was also noted that no consent form is required. This decision will be entered accordingly into the minutes. At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840.

All research involving human subjects requires review at a recurring interval and the current study approval is in effect until May 27, 2008. An Application for Continuing Review must be submitted to the REB prior to the expiration of approval to comply with the regulation for continuing review of "at least once per year".

The Research Ethics Boards (REBs) of the McGill University Health Centre are registered REBs working under the published guidelines of the Tri-Council Policy Statement, in compliance with the "Plan d'action ministériel en éthique de la recherche et en intégrité scientifique" (MSSS, 1998) and the Food and Drugs Act (7 June 2001); and acting in conformity with standards set forth in the (US) Code of Federal Regulations governing human subjects research, function in a manner consistent with internationally accepted principles of good clinical practice.

We wish to advise you that this document completely satisfies the requirement for Research Ethics Board Attestation as stipulated by Health Canada.

Should any revision to the research or other unanticipated development occur prior to the next required review, please advise the REB promptly and prior to initiating any revision.

Sincerely,

L. Moroz, M.D.
Chair, Biomedical-B Committee
RVH Research Ethics Board

Independent Scientific Advisory Committee
for MHRA database research

## ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING GPRD DATA

## FEED-BACK TO APPLICANTS

| CONFIDENTIAL | | | *by e-mail* |
|---|---|---|---|
| **PROTOCOL NO:** | 06_040R | | |
| **PROTOCOL TITLE:** | Warfarin in the general practice research database: adverse effects, interactions and benefits | | |
| **APPLICANT:** | Dr Samy Suissa, Professor of Department of Epidemiology Biostatistics / McGill University, Royal Victoria Hospital | | |
| **APPROVED** ☒ | **APPROVED SUBJECT TO MINOR AMENDMENT (resubmission not required)** ☐ | **REVISION/ RESUBMISSION REQUESTED** ☐ | **REJECTED** ☐ |
| **COMMENTS:** | Protocol 06_040R is approved. | | |
| **DATE:** | 25 September 2006 | | |

**Medicines and Healthcare products Regulatory Agency**
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January 23, 2007

Dr. Samy Suissa
Clinical Epidemiology
Royal Victoria Hospital
687 Pine Avenue West – Room R4.29
Montreal, Quebec
H3A 1A1

Dear Dr. Suissa,

We are writing in response to your request for continuing review for the study A11-M98-05B entitled "The Use of Statins in the Primary Prevention of Cardiovascular Disease: Influence of BMI"

The progress report was reviewed and we are pleased to inform you that full Board re-approval for the study was provided on **January 22, 2007** valid until **November 27, 2007**. The certification of annual review has been enclosed.

We ask that you take note of the investigator's responsibility to assure that the current protocol and consent document are deposited on an annual basis with the Research Ethics Board of each hospital where patient enrollment or data collection is conducted.

Should any modification or unanticipated development occur prior to the next review, please advise the IRB promptly.

Yours sincerely,

Serge Gauthier, MD
Chair
Institutional Review Board

cc: Chris Delaney
A11-M98-05B

## Appendix 2: Variables used in Multiple Imputation for Chapter 5 (Modeling blood pressures changes after drug treatment in the general practice research database)

Number of the following drugs as prescribed in the year prior to index date: beta blockers, ace inhibitors, arbs, calcium channel blockers, alpha blockers, statins, ibuprofen, celecoxib, rofecoxib, warfarin, diuretics and insulin

Blood pressure readings taken between baseline and one year: number, mean systolic blood pressure, mean diastolic blood pressure

Clinical diagnoses in the GPRD database at baseline for: hypertension, angina, diabetes, cancer, chronic obstructive pulmonary disease, stroke, arrhythmia, liver failure, renal failure, arthritis, serious blood clots, myocardial infarction, congestive heart failure and alcohol abuse.

Demographic characteristics: sex, age, body mass index, smoking, drinking, and calendar year at baseline

Number of the following drugs as prescribed in the year after index date
beta blockers, ace inhibitors, arbs, calcium channel blockers, alpha blockers, statins, ibuprofen, celecoxib, rofecoxib, warfarin, diuretics, insulin, aspirin, proton pump inhibitors, corticosteroids and paracetomol.

Outcome variables (in imputation as parameters being estimated for missing): Baseline systolic blood pressure, baseline diastolic blood pressure, Systolic blood pressure at one year, and Diastolic blood pressure at one year.

## Appendix 3: SAS code used for Models in Chapter 5 (Modeling blood pressures changes after drug treatment in the general practice research database)

Mixed Models

```
proc mixed data=z METHOD=REML;
  model systolic_bp =treated time /Solution DDFM=BW cl alpha=0.01;
  random Intercept time/subject=id type=un;
  repeated /subject=id type=ar(1);
      title 'Intent to Treat Model for Statin';
      title2 'Treated is main effect [post 1st Statin Rx]';
run;

proc mixed data=z METHOD=REML;
  model systolic_bp =treated time Pulmonary_embolism age_baseline male
     alcohol chf dvt gi_bleed MI stroke arrythmia diabetes
      num_hosp liver_failure renal_failure arthritis/Solution DDFM=BW cl
alpha=0.01;
  random Intercept time/subject=id type=un;
  repeated /subject=id type=ar(1);
    title 'Intent to Treat Model for Statin';
    title2 'Treated is main effect [post 1st Statin Rx]';
run;
```

Multiple Imputation

```
proc mi data=bps out=bps_mi_2 seed=8499244 nimpute=10;
    where match=2; /* Statins Group Only */
  mcmc impute=full chain=multiple timeplot acfplot nbiter=1000 niter=1000
    initial=em (maxiter=1000);
  var  b_systolic_bp b_diastolic_bp e_systolic_bp e_diastolic_bp
     /* Baseline Drug Therapy*/
     num_beta_blocker num_ace_inhibitor num_arb num_ccb num_alpha_blocker
     num_statin num_ibuprofen num_celebrex num_vioxx num_warfarin
     num_diuretic num_insulin
     /* Blood Pressures during follow-up */
     num_IBP mean_ISBP mean_IDBP
     /* Medical Codes at Baseline */
     prev_hypertension angina diabetes cancer copd stroke arrythmia
     liver_failure renal_failure arthritis dvt  MI chf
     /* Demographic Charactertistics */
     alcohol male age_baseline BMI smoker drinker event_year
     /* Drug Therapy during follow-up */
     num_insulin_base num_beta_blocker_base num_ace_inhibitor_base
     num_arb_base num_ccb_base num_diuretic_base num_alpha_blocker_base
```

```
    num_celebrex_base num_asa_base num_statin_base num_ppi_base
    num_cortico_base  num_paracetamol_base;
run;
```

Quasi-Experimental Analysis Code for Systolic Blood Pressure

```
data x;
  set gprd.Imputed_bp;
   if match =8 or match =2; /* match=2 is statins, match=8 is proton pump
inhibitors */
   if match =2 then statin=1;
   else statin=0;
run;

proc sort data=x;
  by _imputation_;
run;

/* Crude Estimate */
proc reg outest=parmcov covout data= x;
   by _imputation_;
  model delta_sbp=statin;
run;

proc mianalyze data=parmcov;
   modeleffects statin;
run;

/* Adjusted Estimate */
proc reg outest=parmcov covout data= x;
  by _imputation_;
   model delta_sbp= statin prev_hypertension angina diabetes cancer copd stroke
         arrythmia liver_failure renal_failure arthritis dvt  MI chf
         alcohol male age_baseline BMI smoker drinker
         num_beta_blocker  num_arb num_ccb num_alpha_blocker
         num_ace_inhibitor num_ibuprofen num_celebrex num_vioxx
         num_warfarin num_diuretic num_insulin ;
run;

proc mianalyze data=parmcov;
modeleffects statin;
run;
```

# Appendix 4: Annotated code for Marginal Structural Models in a Case Control Setting

```
/*
SAS code for Marginal Structural Models (annotated version)
Date:April 10, 2006
Programmer: Chris Delaney
->Based on code in Hernan 2000 and ideas in Newman 2006
This is a set of code designed to determine the relationship between an exposure and
outcome.  Exposure is 90 day exposure to Warfarin (warfarin)
*/

*Set SAS Library;
libname gprd 'C:\Temporary\';

data q_msm;
 set gprd.communitycohort2;
run;

/* Model Selection for probability of Treatment model – here we us all major covariates
but sub-selection may be important with smaller databases due to narrow strata.
NOTE: Model is built using controls only!*/

proc logistic data=q_msm descending;
where case=0;
model  warfarin = antidepressants  plavix heparin  vioxx celebrex ibuprofen asa
  naproxen_plus paracetamol diuretic abx_90d corticosteroids h2_block ppi
  acid_reflux peptic_ulcer H_pylori alcohol Pulmonary_embolism chf dvt mi angina
  stroke afib liver_failure renal_failure r_arthritis other_arthritis diabetes cancer copd
  age underweight obese morbid_obese missing_bmi smoker no_smoker_rec dementia
  no_bp_reading male high_bp med_bp;
title 'Propensity Model for IPTW; we can do full model because sample size > 40,000';
run;
/*
Now we take the model derived above and implement it into IPTW weights
*/

data x_msm;
set q_msm;

x=  -5.9690+
 antidepressants       *   -0.1308+
 plavix              *   -2.4986+
 heparin              *    1.6436+
 vioxx               *   -0.7720+
 celebrex             *   -0.7046+
 ibuprofen            *   -0.9249+
 asa                *   -2.8815+
 naproxen_plus         *   -0.8055+
 paracetamol          *    0.3585+
```

```
diuretic            *    0.9520+
abx_90d             *    0.0242+
corticosteroids     *    0.1342+
H2_block            *    0.0207+
ppi                 *   -0.2342+
acid_reflux         *   -0.0959+
peptic_ulcer        *    0.2053+
h_pylori            *    0.3979+
alcohol             *    0.1024+
Pulmonary_embolism  *    2.4518+
chf                 *    0.4249+
dvt                 *    1.7863+
mi                  *    0.4509+
angina              *    0.4654+
stroke              *    0.9611+
afib                *    3.3969+
liver_failure       *   -0.3718+
renal_failure       *   -0.1468+
r_arthritis         *    0.0675+
other_arthritis     *  -0.00899+
diabetes            *    0.0993+
cancer              *    0.1815+
copd                *   -0.0996+
age                 *    0.0100+
underweight         *    0.0131+
obese               *    0.1034+
morbid_obese        *   -0.4259+
missing_bmi         *   -0.1160+
smoker              *    0.1591+
no_smoker_rec       *   -0.1716+
dementia            *   -0.5850+
no_bp_reading       *   -0.4801+
male                *    0.6237+
high_bp             *   -0.0875+
med_bp              *    0.1287;
;
/* This gives probability of treatment and acts as a propensity score.  In Marginal
Structural Models we will use something slightly different*/

p=exp(x);
prob =p/(1+p);

/*Now we define the Inverse Probability of Treatment weight.  it's not time dependent so
we take the probability of receiving the treatment that you actually got as our probability
of treatment for stabilizing the weights */

if warfarin=1 then IPTW=1/prob;  /*exposed*/
else IPTW =(1/(1-prob));              /*unexposed*/

/*Stabilized Weights */
```

```
if warfarin=1 then s_iptw=IPTW*0.0280865;
else s_iptw=IPTW*(1- 0.0280865);
run;

/*Crude Estimate of Effect */
proc phreg  nosummary data= x_msm;
  model timefake*case(0)=  warfarin  /rl ties=discrete;
  strata match;
  title ' Statin and warfarin Exposure in GI Bleed Cohort: Crude Effect of Warfarin';
run;

/* This is the adjusted Conditional Logistic Regression */

proc phreg  nosummary data=  x_msm;
 model timefake*case(0)= antidepressants warfarin plavix heparin vioxx celebrex
   ibuprofen asa naproxen_plus paracetamol diuretic abx_90d  corticosteroids
   h2_block ppi acid_reflux peptic_ulcer H_pylori alcohol Pulmonary_embolism chf dvt
   mi angina stroke afib liver_failure renal_failure r_arthritis other_arthritis diabetes
   cancer copd age underweight obese morbid_obese missing_bmi smoker no_smoker_rec
   dementia  no_bp_reading male high_bp med_bp
    int_vioxx_war int_celebrex_warfarin  int_ibu_warfarin int_naprox_warfarin
    int_asa_war  int_vioxx_plavix  int_celebrex_plavix int_ibu_plavix int_naprox_plavix
    int_asa_plavix  int_war_plavix_asa int_para_war int_war_cort /rl ties=discrete;
  strata match;
  title ' NSAID and warfarin Exposure in GI Bleed Cohort: Full Analytic Model';
 run;

/* Marginal Structural Model using stabolized weights.
NOTE: the confidence intervals are computed below */

proc genmod data=x_msm descending ;
class practice_id;
model case = warfarin /link=logit dist=bin;
estimate 'warfarin' warfarin 1/exp;
scwgt s_IPTW;
repeated subject=practice_id;
title 'Marginal Structral Model for Warfarin in GI Bleed Cohort';
run;

/* This is the inference for the Marginal Structural Model.  It is a bootstrap method; the
alternative is a robust sandwich estimator.  1000 repetitions appear to work well. We do
1000 sampels of size N from our dataset and see how much the coverage is of the 1000
samples.  */

data parms;
run;

%MACRO boot;
%DO i = 1 %to 1000;
          DATA analysis;
           choice = INT(RANUNI(23456+&i)*n)+1;
```

```
          SET x POINT = choice NOBS = n;
          j+1;
          IF j > n THEN STOP;
         RUN;

proc genmod data=analysis descending;
   ods output Estimates=outests;
   ods listing exclude Estimates;
class match;
model case = warfarin /link=logit dist=bin;
estimate 'warfarin' warfarin 1/exp;
scwgt s_IPTW;
run;
DATA PARMS;
 SET PARMS outests;
 if ChiSq>0 then delete; *includes both the beta and the RR! this step
                    ensures that we keep only the RR.  There are
                    probably cleaner ways to code this;
run;

%END;
%MEND;

%boot

/*
This looks at the output from the 1000 samples.  Note the min/max for range of data and
also consider the mean which should be the same as the point estimate of the MSM
defined
above or very close
*/

PROC means DATA=parms;
run;

*We have one junk parameter for n =1, this gets rid of it;
data aaa;
 set parms;
 if _N_=1 then delete;
run;

proc sort data=aaa;
 by Estimate;
run;

data aaa;
 set aaa;
 num=_N_;
run;

Proc Print;
```

```
where num=26;
title 'Lower Confidence Interval Limit';
run;

Proc Print;
where num=975;
title 'Upper Confidence Interval Limit';
run;

*This should give a valid Marginal Structural Model in the case control setting;
```

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