ADVERSE DRUG INTERACTION WITH WARFARIN PLUS AMIODARONE

INCREASED HOSPITALIZATION FOR HEMORRHAGES IN PATIENTS TAKING AMIODARONE WITH WARFARIN: A POPULATION-BASED COHORT STUDY

By

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ABSTRACT

BACKGROUND

Amiodarone is believed to inhibit the hepatic metabolism of warfarin, potentiating its hypoprothrombinemic effect and increasing the risk of hemorrhage. The consequences of this drug interaction on important clinical outcomes are unknown.

METHODOLOGY

Using linked health administrative databases, we conducted a population-based retrospective cohort study among Ontario residents aged 66 years or older who had been treated with warfarin therapy for at least 6 months. Within this group, we identified subjects who initiated amiodarone while on warfarin. Each of these subjects was matched to a subject not treated with amiodarone on age, sex, year of cohort entry, and a high dimensional propensity score. The primary outcome was a hospitalization due to a hemorrhagic event within 30 days of follow-up. In a secondary analysis, we examined in-hospital mortality following hospitalization for major hemorrhage.

RESULTS

We identified 60,497 eligible patients between July 1, 1994 and March 31, 2009. Of these, 11,665 (19.3%) received a new prescription for amiodarone while receiving ongoing warfarin therapy and 7,124 (61.1%) of these were matched to a subject who was not exposed to amiodarone while receiving warfarin therapy. The median age at cohort

entry of the matched cohort was 76 years, 51.6% in the cohort were male, 14.5% lived in a rural location, 2.8% had a bleed in the past year, and 21.6% had a diagnosis of congestive heart failure in the past year. Fifty-six amiodarone recipients experienced a hemorrhagic event (0.8%) as compared to 23 individuals (0.3%) in the non-exposed group at 30 day follow-up (adjusted hazard ratio (HR) = 2.45; 95% CI, 1.49 to 4.02). Seven patients in the amiodarone group died after hospitalization for a hemorrhage versus four in the non-exposed group (adjusted HR = 1.74; 95% CI, 0.25 to 12.24).

CONCLUSION

Initiation of amiodarone in patients on chronic warfarin therapy was associated with a two-fold increase in the risk of hospitalization due to a hemorrhagic event. Physicians should closely monitor the response to warfarin following initiation of amiodarone.

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LIST OF ABBREVIATIONS AND SYMBOLS

AF = Atrial fibrillation
ASA = Aspirin
AV = Atrioventricular
CHF = Congestive heart failure
CIHI = Canadian Institute of Health Information
COX-2 = Cyclooxygenase-2
CYP = Cytochrome P450
DAD = Discharge abstract database
e.g. = For example
EMR = Electronic medical records
GI = Gastrointestinal
HDPS = High dimensional propensity score
HR = Hazard ratio
ICES = Institute for Clinical Evaluative Sciences
i.e. = That is; in other words
INR= International normalized ratio
IPTW = Inverse probability of treatment weighting
IV = Intravenous
MI = Myocardial infarction
MRDx = Most responsible diagnosis
NPV = Negative predictive value
NSAID = Non-steroidal anti-inflammatory drug
ODB = Ontario Drug Benefit
OHIP= Ontario Health Insurance Plan
OR = Odds ratio
PPV = Positive predictive value
PSM = Propensity score matching
PT = Prothrombin time
RCT = Randomized control trial
RPDB = Registered Persons Database
RR = Relative risk
SA = Sinoatrial
SDF = Standardized difference
SSRI = Selective serotonin reuptake inhibitor
$T_{1/2}$ = half-life
UGIB = Upper gastrointestinal bleeding
UK = United Kingdom
VKA = Vitamin K antagonist
VTE = venous thromboembolism
95% CI = 95% confidence interval
χ^2 = Chi-squared

1.0 INTRODUCTION

Hemostasis is an essential mechanism by which bleeding at the site of an injury is stopped.[1] Multiple pathways work in concert to initiate, perpetuate, and finally stop a coagulation cascade. This coagulation cascade is a series of enzymatic reactions which lead to fibrin (or clot) formation.[1] Ultimately, the coagulation cascade is responsible for forming insoluble fibrin to stop bleeding while maintaining vascular patency.[1,2] However, for diseases such as venous thrombosis and atrial fibrillation in which clot formation is the genesis of negative cardiovascular outcomes, inhibition of coagulation is warranted. While the human body has innate mechanisms in place to balance the effects of the coagulation cascade, pharmacological interventions in the form of anticoagulants are needed to prevent fibrin formulation. As a class of drugs, they inhibit specific coagulation factors which are crucial in the coagulation cascade.[1] However, anticoagulants are amongst the top 10 drugs cited as having patient safety concerns in North America.[3] This may largely be due to the risk of bleeding associated with over anticoagulation. This class of drugs consist of vitamin K antagonists (VKAs), heparin and derivative substances, direct thrombin inhibitors and factor X inhibitors. The focus of this study will be on the VKA, warfarin and how it interacts with amiodarone.

1.1. Warfarin

Warfarin is the most commonly used VKA in North America and perhaps worldwide.[4,5] In 2010, the number of prescriptions dispensed from Canadian retail pharmacies was estimated to be 5.5 million nationwide; a 5.5% increase from the

previous year.[6] In Canada, it is indicated for patients with atrial fibrillation (AF) or prosthetic heart valves, and for the prevention and treatment of venous thromboembolism (VTE).[7]

Vitamin K is a cofactor which enables conformational changes in the coagulation factors II, VII, IX, X, in the extrinsic pathway part of the coagulation cascade.[8] As a VKA, warfarin produces its antithrombotic effects by inactivating the proportion of these functional vitamin K-dependent clotting factors via interference with the vitamin K regeneration cycle in the liver.[8] Warfarin is a racemic mixture of two optically-active enantiomers; R and S-isomer.[8] Moreover, the S-isomer is roughly 5 times more potent than the R-isomer.[9-11] This is important to note considering certain drugs stereoselectively interact with warfarin (i.e. specifically inhibit or potentiate only one isomer's function). Specifically, S-warfarin is metabolized by cytochrome P450 (CYP) isoenzyme 2C9, a hepatic enzyme which is also a target of many other drugs.[8,10,11]

Due to its narrow therapeutic window, it is necessary to monitor the anticoagulant effects of warfarin using the international normalized ratio (INR). The INR reflects the pharmacodynamic response to warfarin.[7,8] The therapeutic range of INR for most indications including atrial fibrillation is between 2.0 and 3.0, based on evidence that INRs outside this range are associated with increased adverse thrombotic or bleeding events.[7,12,13] The most common adverse effect of warfarin is hemorrhage.[4,14,15] The annual risk of major bleeds (defined as bleeds that were intracranial or retroperitoneal, or bleeds that directly resulted in death, hospitalization or blood transfusion) is estimated to

be between 0.8-6.6% which includes intracranial hemorrhage at an annual rate of 0.3-0.5%.[14] The case-fatality rate for major bleeding in a systematic review was summarized at 13% but may be as high as 46% for intracranial hemorrhages.[14] This bleeding risk may be partly due to drug-drug interactions with warfarin, some of which are not fully understood. In one systematic review of drug and food interactions with warfarin, 181 articles regarding 120 drugs or foods were retrieved and analyzed.[16] 128 (70%) of these articles reported potentiation of warfarin's anticoagulant effects while 28 (15%) reported no effect or inhibition. More importantly, 82% of these articles were rated as poor quality studies and 85% of them were case reports. This highlights the paucity of high quality drug interaction data which could guide clinicians when prescribing warfarin to patients.

1.2. Amiodarone

Amiodarone was originally developed in 1962 as an anti-anginal agent due to its coronary vasodilatory properties.[17] However, since the discovery of its cardiac action potential slowing properties, amiodarone has become one of the most commonly prescribed anti-arrhythmic agents worldwide.[18] In particular, amiodarone (available in oral and intravenous formulations) accounts for over 30% of prescriptions for anti-arrhythmic agents (this classification does not include common beta-blockers) in North America and this market share has been steadily increasing. In 2010, there were estimated to be more than 30,000 users of amiodarone in Ontario alone (OPDB personal communication, June 2010) It is primarily used for symptomatic rapid atrial fibrillation

where beta-blockers and digoxin have failed to control the heart rate, and for refractory ventricular arrhythmias.[17,18]

The electrophysiological effects of amiodarone are complex and not fully understood.[17,18] However it is postulated that in acute therapy, amiodarone inhibits inward sodium (Vaughn-Williams class I) and inward calcium channels (Vaughn-Williams class IV), and has non-competitive anti-adrenergic effects in cardiac tissue.[19,20] These effects depress automaticity of the sinoatrial (SA) node, resulting in decreased heart rate during sinus rhythm, conduction slowing and increased refractoriness in the atrioventricular (AV) node.[19] In chronic amiodarone therapy, outward potassium channels are inhibited resulting in prolongation of the action potential duration and effective refractory period.

The pharmacokinetic profile of amiodarone is different from other antiarrhythmic agents. Amiodarone absorption is slow and variable.[21-27] The onset of action is between 2 days to 2 weeks for oral amiodarone although it is much quicker with the intravenous (IV) formulation. It takes 1 week to 5 months to observe the peak effects of oral amiodarone.[23-27] Metabolism of the active parent drug occurs extensively in the liver and via CYP 2C8 and 3A4. Moreover, amiodarone is converted into its main active metabolite, N-desethylamiodarone.[23,28,29] Due to the fat-soluble nature of amiodarone, terminal half life ($T_{1/2}$) is long ranging between 26 to 107 days and the duration of effects after discontinuation continue for an additional 7 to 50 days.[22-27]

Amiodarone may inhibit several CYP P450 and P-glycoprotein pathways important in drug metabolism (further details below).[22,30,31] This potentially results in increased serum concentrations of other drugs and may increase the risk of side effects associated with them. Moreover, amiodarone is a substrate of CYP P450 enzymes and may itself be inhibited by other CYP substrates.[30]

1.3. The interaction between warfarin and amiodarone

Adverse events due to drug interactions, are associated with polypharmacy defined as 5 or more drugs taken concurrently, and increased age.[32-35] Interactions can have either a pharmacokinetic or a pharmacodynamic mechanism. In a pharmacokinetic interaction, the affected drug's pharmacokinetic profile (i.e. absorption, distribution, metabolism, and elimination) is altered.[36] A pharmacodynamic interaction involves the disruption between the relationship of a drug's concentration and its clinical effect(s) in the patient.[37] This may occur through synergistic, additive or antagonistic effects which results in increased or decreased drug response in the body.

Pharmacokinetically, amiodarone likely inhibits the hepatic metabolism of (S)-warfarin via CYP 2C9, thereby potentiating the anticoagulant effects of warfarin.[38,39] *In vivo,* amiodarone and its metabolites have been shown to inhibit warfarin hydroxylation to its metabolites in human hepatic microsomes.[31] This suggests amiodarone inhibits cytochrome P450 isoenzymes and, in particular, CYP 2C9 which converts (S)-warfarin into an active metabolite, (S)-7-hydroxywarfarin. In a non-randomized kinetic study of 30 patients, warfarin clearance was found to be roughly 55% lower in amiodarone-treated

patients compared to patients treated with warfarin alone.[31] Furthermore, amiodarone concentrations were significantly and directly correlated to racemic warfarin concentrations. Previous small observational and *in vivo* pharmacokinetic studies with a total sample size of less than 200 suggest a dose-dependent interaction results in an increase in the INR or prothrombin time (PT) following the initiation of amiodarone therapy. [21,31,38,40-47] In one retrospective chart review of 70 patients seen in an American anticoagulation clinic, the combination of amiodarone and warfarin lead to an increased risk of INR values greater than 5, most common during the first 12 weeks after initiation of amiodarone.[21] Although bleeding does occur within therapeutic INR levels, increases in INRs above 5 are more directly associated with a higher risk of major and intracranial bleeding.[13]

Few studies have looked at more clinically relevant outcomes such as major hemorrhagic events. One observational study by Zhang *et al.* of 1,260 subjects newly or continuously treated with warfarin and amiodarone concluded that there was no increase in the risk of hemorrhage compared to warfarin treatment alone.[48] But the study involved a relatively small number of patients with limited overlap of drug therapy and a short observation period (7 days) for hemorrhagic events.

We sought to examine the association between initiation of amiodarone and the risk of hemorrhage in community-dwelling seniors who have been receiving warfarin therapy for at least 6 months.

1.4. Ontario's health care administrative databases

A vast amount of health information is collected and stored in Ontario's linked health care administrative databases. This patient-related information includes demographics, hospital data, physician diagnoses and billings, drug data, vital statistics, and home care data for all eligible Ontario citizens. The anonymized linked data resource has been managed at Institute for Clinical Evaluative Sciences (ICES) for many years and has supported multiple drug safety and effectiveness studies including drug interaction topics.[49,50-53] Four administrative databases were used to address our research question: the Canadian Institute of Health Information Discharge Abstract Database, Ontario Drug Benefit database, Ontario Health Insurance Plan database, and Registered Persons database. These are described further below.

1.4.1. Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD)

CIHI is an independent, not-for-profit organization mandated to provide health information on the Canadian health care system and its users.[54] Health information collected range from data on organ replacement to hospitalization records. In particular, the DAD maintained by CIHI provides a wealth of health information useful in conducting epidemiological studies. Per year, more than 1 million discharge records are available on Canadians dating back to 1988.[55] The DAD comprises demographic, administrative (e.g. length of stay), and clinical data (e.g. procedures performed, admitting diagnosis, comorbidities, discharge diagnoses) on Canadian residents.

Within the CIHI data holdings, the International Statistical Classification of Diseases and Related Health Problems, tenth enhanced Canadian revision (ICD-10-CA), ninth revision (ICD-9) and Clinical Modification (ICD-9-CM) revision of standardized codes are used to systematically code diseases, injuries, and causes of death.[56] Similarly, the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP), procedure section of the ICD-9-CM, and Canadian Classification of Health Interventions (CCI) are used to classify therapeutic and diagnostic interventions.[57] ICD-9, and CCP were replaced by ICD-10-CA and CCI in Canada between 2001 and 2006 (2002 in Ontario). The newer versions allowed for a single set of national standards for diagnoses, and interventions which accommodated more comprehensive scope and improved the specificity of coding.[58,59]

Accuracy of codes used in the CIHI datasets is variable and dependent on 2 main factors: diagnosis type, and information type (diagnostic, procedural, demographic).[60,61] Diagnosis type involves how and when a diagnosis is made in relation to a patient's hospital stay, including most responsible diagnosis (MRDx), pre-admission comorbidity, post-admission comorbidity, secondary diagnosis, external cause/place/activity, and service transfer diagnoses (**Table 1, Appendix 1**).[60] MRDx is the diagnosis which accounts for the greatest portion of the length of stay or use of health care services during hospitalization but is not necessarily the reason for hospitalization. A type 1 diagnosis or pre-admission comorbidity is defined as a significant condition existing prior to admission. A condition is significant when at least one of these three criteria is met: 1) it

has significant influence on treatment received; 2) it requires additional treatment beyond treatment for pre-existing condition; and 3) it increases length of stay by equal or greater than 24 hours. A type 2 diagnosis or post-admission comorbidity is a condition that develops during hospitalization and meets one of the criteria for significance as outlined above. A type 3 diagnosis or secondary diagnosis is a condition which is not categorized as a significant comorbidity but is present. A type 9 diagnosis is analogous to ICD-9 External-cause-of-injury codes (E-codes) and represents external causes of morbidity or mortality (e.g. motor vehicle accident, drug overdose) and is mandatory to include when associated with injury. Types W,X, and Y codes represent ICD-10-CA service transfer diagnoses and are associated with first, second, and third transfer in service while hospitalized.

In general, the MRDx is coded more accurately than other diagnosis types.[60,61] For example, the sensitivity and positive predictive value (PPV) of chronic ischemic heart disease (IHD) as MRDx was 0.83 (95% CI; 0.80 to 0.85) and 0.92 (95% CI; 0.90 to 0.94) compared to chart abstraction by ICES-trained abstractors, respectively.[60] However when examining the validity of IHD coding as a pre or post-admission comorbidity, sensitivity and PPV dropped to 0.79 (95% CI; 0.75 to 0.83) and 0.42 (95% CI; 0.39 to 0.45), respectively.[60] The second factor which influences coding accuracy is information type. Demographic (non-medical) information (e.g. age, admission date), and procedure-driven codes (e.g. implantation of an internal device, biopsy, magnetic resonance imaging) are generally coded extremely accurately.[60,61] In comparison, sensitivity and PPV of

diagnosis-driven codes are generally lower than procedure-driven codes. This makes intuitive sense since there is very little room for interpretation of a surgical repair of the intestine, for example, compared to a diagnosis of irritable bowel syndrome. The closer examination of coding accuracy for the outcome measures in our study was one of the methodological issues addressed in this thesis (see Section 3.9.2).

1.4.2. Ontario Drug Benefit (ODB) Database

The ODB database stores information on prescription claims covered by the ODB formulary which is administered by the Ministry of Health and Long Term Care.[55,62] Eligible drug products, nutritional supplies or diabetic testing agents (e.g. glucose test strips) listed in the ODB Formulary or Comparative Drug Index, are reimbursed by the province if prescribed by an authorized Ontario healthcare professional.[63] The ODB does not cover most over-the-counter medications, supplements, compression stockings, dentures, hearing aids, eye glasses, or diabetic supplies (e.g. lancets, glucometers). Medications not listed in the formulary are considered for reimbursement on a case-by-case basis through the ministry's Exceptional Access Program. Eligible beneficiaries include individuals 65 years or older, residents of long term care facilities, residents of Homes for Special Care and individuals on social assistance from the Ontario government (i.e. welfare, family benefits, individuals in the Trillium drug program) – in total approximately 2.8 million Ontario residents each year receiving $3.8 billion CAN.[64] Roughly 60% of recipients of ODB coverage are Ontario seniors over the age of 65 years.[65] The main data elements available include drug name, brand, dosage form, drug

identification number, quantity dispensed, number of days supplied, cost, long term care indicator, and encrypted patient/physician identifiers.[55]

Unlike the CIHI-DAD, coding in the ODB is consistently accurate. Of the 5155 dispensed prescriptions abstracted in one validation study, the overall error rate was less than 1%. The majority of errors related to incorrect prescribing physician or instructions submitted to the ODB database.[65]

1.4.3. Ontario Health Insurance Plan (OHIP) dataset

In Ontario, selected health care services are publicly insured. Most physicians and laboratories bill the provincial government through the OHIP within a fee-for-service structure.[55,66,67] Main data elements of the OHIP database include encrypted patient and physician identifiers, service provided, associated diagnosis, date of service, and physician specialty. However, results from laboratory procedures are not currently captured in the database.[55] Unfortunately, very little research has been published concerning the reliability of billing diagnoses codes or laboratory codes used in the OHIP dataset. What little has been published indicates a variability in the accuracy of coding that is highly dependent on the type of service rendered. For example, mental health care provision in a primary health care setting was found to be coded quite accurately in the OHIP dataset when validated with medical chart abstraction but OHIP codes were moderately accurate in identifying intensive care unit admission as compared to a critical care patient registry.[66,68]

1.4.4. Registered Persons Database (RPDB)

The RPDB's main data elements include encrypted patient identifier for all residents who have received an Ontario health card number, date of birth, sex, date of death, postal code of residence, OHIP eligibility over time, and date of last contact with the health care system.[69]

1.5. Methodological challenges of confounding using health care administrative databases

A confounding variable or confounder is both associated with the exposure and is also an independent risk factor of the outcome.[70,71] Methodological issues surrounding confounding are a major concern in observational studies. Treatment allocation in observational studies is not randomized and the indication for treatment not only predicts the treatment (hopefully) but also often predicts the risk of future outcomes. Therefore, indication can be a source of confounding and produce unbalanced prognostic factors between study groups.[70,71] This source of confounding occurs because physicians and other health care providers seek to provide care to patients who are most likely to benefit, often those who are sickest or who have certain risk factors..[70] Failure to control for the risk factors can result in erroneously concluding that the exposure is associated with negative (or positive) outcomes. Several techniques to reduce confounding have been published. These include, but are not limited to, multivariable regression, instrumental variable analysis, and propensity score methods.

Multivariable regression analysis allows for covariate adjustment in the regression model.[72-74] While the technique enables one to control for many variables simultaneously, the number of covariates in the model is restricted by number of events per variable. Generally, at least 10 to 15 events are recommended per independent variable to reduce the risk of bias of the regression coefficients in either the positive or negative direction.[75,76]

Instrumental variable analysis attempts to adjust for unknown confounding or hidden bias. The instrumental variable is a measured variable associated with the exposure or treatment but does not directly affect the outcome measure.[73] Three main assumptions must be met in order for a variable to be an appropriate instrument: (1) the variable must be correlated with the exposure variable, (2) it must not be associated with observed confounders, and (3) it must not be directly associated with the outcome variable except along the causal pathway.[72,77,78,79] The amount of variation in the exposure variable that is induced by the instrumental variable is used to estimate effect on outcome commonly using two-stage ordinary least square regression.[72,77,80] An example of an instrumental variable is randomization because it satisfies all three necessary criteria: it determines treatment allocation (exposure), is not correlated with other covariates if randomization is performed appropriately, and does not directly affect the outcome of interest.[77] By definition, randomization of treatment assignment does not occur in an observational study. Previously, physician prescribing preference, regional

variation/demographic location, facility-prescribing patterns, patient history/financial status, and calendar time have been used as instruments.

The third method to reduce confounding is use of propensity scores which is explored more in depth below.

1.5.1. Propensity score methods

To reduce confounding, propensity score (PS) methods can be used to balance measured baseline covariates between exposed and unexposed patients.[81] The propensity score reflects the probability between 0 and 1 of receiving the exposure - in this case a new prescription for amiodarone, conditional on other observed baseline covariates in the individual.[81] This probability is calculated by logistic regression in which the exposure status is regressed on to measured baseline covariates.[81] Four propensity score methods are common in the medical literature: covariate adjustment using propensity score, stratification based on propensity score, inverse probability of treatment of weighting (IPTW), and propensity score matching (PSM).[81-84] A variation of propensity score matching named high dimensional propensity score (HDPS) matching was recently published in 2009.[85] These methods are further described below.

1.5.1.1. Covariate adjustment using propensity score

In covariate adjustment using propensity score, the outcome is regressed on to variables denoting exposure status and propensity score. Simply, the propensity score is incorporated in the final regression model estimating effect of exposure on outcome of

interest. Thus, the effect of the exposure on outcome is adjusted for the probability of developing the exposure.[82-84] This is the most common propensity score method used in medical literature.[86-88] However, the method assumes that the exposure effect is being compared between exposed and non-exposed individuals with similar propensity scores.[82]

1.5.1.2. Stratification based on propensity score

In stratification based on propensity score, the effect of the exposure on outcome is estimated within propensity score-defined strata.[82,84] Typically, ranked propensity scores are equally divided into five strata.[82,84] Then, stratum-specific exposure effects on outcome are estimated and pooled to determine an overall exposure effect.[82,84] From one study, this method has been shown to eliminate approximately 90% of bias associated with measured confounders.[89]

1.5.1.3. Inverse probability of treatment weighting (IPTW)

The inverse probability of treatment (IPTW) is mathematically defined as E/PS + (1-E)/(1-PS), where E denotes the dichotomous treatment or exposure status and PS denotes the propensity score.[82,84] This is interpreted as an exposed individual's inverse probability of being exposed and similarly, a non-exposed individual's inverse probability of not being exposed.[82,84] Weighting by this method results in an artificial population with exposure status independent of measured baseline covariates.[90]

1.5.1.4. Propensity score matching

In propensity score matching, propensity scores are used to match individuals from the exposed to the individuals in the non-exposed groups resulting in matched-pair data.[82,84] Various approaches to matching exist. However, the most common is nearest neighbour pair-matching without replacement within specified calipers of the propensity score.[81,91] Pairing of an exposed individual and non-exposed individual is formed when their propensity scores fall within a certain distance of each other (calipers).[81,91] The caliper is calculated by multiplying an arbitrarily set fraction by the standard deviation of the propensity scores within the study population (i.e. caliper equals 0.2 times the standard deviation). Once pairs are formed, absolute or relative risk can be estimated by comparing the proportion of exposed individuals with the outcome to the proportion of unexposed individuals with the outcome.[84]

1.5.1.5. Performance of the different propensity score methods

The performance of the different propensity score methods can be measured by how well each method balances relevant baseline covariates (i.e. variables that were important in predicting outcome) between groups with an inherent assumption that balanced covariates result in an unbiased effect estimate .[82-84] Balance in each baseline characteristic can be measured by the standardized difference, which is the difference in sample means using pooled standard deviation units.[92,93] This allows for a measure that is not affected by imbalance between group sizes.[82] It has been shown in one study by Austin that all PS methods reduce standardized differences in baseline characteristics

considerably.[82] However, PSM and inverse probability of treatment weighting (IPTW) removes a larger proportion than the other two methods.[82] When correlation between baseline covariates is 0%, IPTW performs slightly better than PSM in balancing baseline characteristics. However, as correlation increases, PSM is marginally better than IPTW.[82]

Perhaps a more rigorous approach to performance is how well effect estimates produced using propensity score methods reflect results on the same question produced in RCTs. A literature search revealed that few studies are published comparing propensity score methods to RCT findings. More studies have been published concerning how well the propensity score methods balance baseline characteristics. In one case-study, PSM resulted in a risk ratio for all-cause mortality with statin therapy that was near identical to an estimate produced in a previously conducted meta-analysis of RCTs although estimates produced by direct regression methods, propensity score stratification, IPTW, and covariate adjustment were also similar to RCT estimates.[94]

1.5.2. High dimensional propensity score (HDPS) matching

Conventional PSM requires the investigator to decide which baseline covariates to include in the propensity score model. Given that administrative databases may contain thousands of variables that could potentially be confounding, it could be difficult to identify all covariates to include. A variation of regular propensity score matching with user-defined baseline covariates is HDPS matching; a relatively new method developed by Schneeweiss *et al.* which is both empirically and user-driven.[85] This semi-automated approach allows an investigator to match groups based on context knowledge or expertise

of the specific research question and empirically-derived covariates using a HDPS algorithm the investigator may not have considered or known were important. The algorithm has important steps: identification of datasets, empirically derivation of prevalent codes, assessment of recurrence, prioritization of codes, HDPS model building

Prior to introducing user-defined covariates in the propensity model for subsequent matching, a large number of empirically-derived covariates from different administrative datasets or dimensions are identified for inclusion in the propensity score model.[85] Firstly, prevalent codes from each database are identified. Prevalence is calculated as the proportion of subjects with a given code at least once during a look-back period prior to cohort entry (e.g. 1 year).

These codes are then assessed for recurrence within each patient (i.e. how frequently the code was recorded for each patient) during the look-back period whereby each prevalent code is categorized into occurring $\geq$ 1, $\geq$ median number of times, and $\geq$ 75th percentile. These categories are coded as binary variables. As an example, they could be coded as CovX_once, CovX_median, CovX_frequent to represent covariate X's occurrence of $\geq$ 1, $\geq$ median number of times, or $\geq$ 75th percentile, respectively. If covariate A occurred once, CovX_once equals one while CovX_median and CovX_frequent both equal zero. A covariate which occurs greater than the 75th percentile of times would result in all three binary variables equally one. As a result of recurrence assessment, each prevalent code is split up into these three recurrence variables. As a result, the *n* x 3 most prevalent and recurrent codes are selected from each dataset. The

number of prevalent codes, *n*, is determined by the user. However, Schneeweiss *et al*. have previously used a cut-off threshold of 200 covariates from each database.[85]

An important next step in building the HDPS model is prioritization of covariates across the databases in terms of how well each covariate reduces potential confounding. Covariates should not be conditional on exposure or other covariates (i.e. exposure status does not influence the covariate) as it has been shown that inclusion of covariates associated with the exposure but not the outcome increases the uncertainty of the effect estimate without reducing confounding.[95]

Next, the top *k* number of empirically-derived covariates, user-defined covariates (i.e. covariates included *a priori* based on investigator's judgement and knowledge) and two-way interaction terms are incorporated in a multivariate logistic regression model to produce an HDPS. Of note, *k*, can range between 200 to 500 covariates with little effect on the effect estimate.[85] After an HDPS is calculated, the use of the HDPS is similar to regular PSM.

1.5.2.1. Performance of high dimensional propensity score matching

Overall, HDPS matching so far has been as effective to slightly more effective than standard PSM in producing effect estimates similar to those produced from randomized control trials (RCTs) and in reducing confounding.[85,96] For example, HDPS matching was evaluated against standard PSM in a case study by Schneeweiss *et al.* of the risk of severe GI complications with initiation of selective cyclooxygenase-2 (COX-2)

inhibitors as compared to initiation of NSAIDs among 49,653 American seniors.[85] Results indicated that the GI protective effects of COX-2 inhibitors was more pronounced using HDPS matching than standard PSM with 15 predefined variables; a conclusion echoed by RCT findings.[85]

The greatest strength of HDPS matching is the ability to identify a large number of baseline characteristics along with predefined characteristics that could potentially be confounding. However, the process prevents the investigator from critically appraising each step of the process. It is uncertain whether there are serious consequences of using this method given the paucity of published data comparing HDPS matching and regular PSM. A recently published cohort study by Toh *et al.* using electronic medical records (EMR) databases in the United Kingdom (UK) compared semi-automated HDPS matching (i.e. combination of empirically-derived and investigator-derived covariate selection) to investigator-derived PSM in the context of initiation of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or selective Cyclooxygenase-2 (COX-2) inhibitors, and the risk of upper gastrointestinal bleeding (UGIB).[97] Of 455,185 patients between the ages of 40 and 84 years during the study period between January 1st, 2000 and December 31st, 2008, 411,616 UK subjects were identified as new users of non-selective NSAIDs while 43,569 subjects were identified as new users of COX-2 inhibitors. In the investigator-derived approach, investigators selected *a priori* known risk factors for adjustment in the logistic regression model used to estimate OR of bleeding associated with COX-2 inhibitor use as compared to NSAID use. The OR

calculated was 0.81 (95% CI, 0.52 to 1.27) adjusted for known risk factors which indicated a 16% non-statistically significant reduction of UGIB associated with COX-2 inhibitor initiation as compared to NSAID initiation. In the semi-automated HDPS matching approach similar to the one previously described in subsection 1.5.1, it yielded a very similar OR of 0.78 (95% CI, 0.49 to 1.22). Two main limitations of HDPS matching were highlighted in the study. Firstly, the approach lacks theoretical justification since hundreds of covariates were empirically derived using a computer algorithm.[97,98] This could be likened to "data dredging", in which one attempts to massage and scour available data for any variables related to the outcome. Therefore, there is a risk of introducing bias if these associations are anomalies and identifying baseline variables as important confounders using the HDPS approach that are truly not clinically relevant to the cause-effect relationship. The second limitation to HDPS matching is the inability of the approach to control for time-varying exposure status or confounders. The approach can only attempt to control for differences in baseline characteristics (i.e. characteristics present prior to exposure) and does not deal with changes in baseline characteristics which may occur between exposure and outcome.[97] This constraint is ubiquitous to all PS methods and not just to the HDPS approach.

Ultimately, the study by Toh *et al.* prompts the question of whether or not HDPS matching provides a more accurate effect estimate than regular, investigator-driven PSM. More research into this method and other forms of automatic selection of confounders is required before they can be used reliably.[97]

2. OBJECTIVES

To characterize the risk of hospitalization for hemorrhage and in-hospital death associated with the concomitant use of warfarin and amiodarone compared to warfarin use alone amongst Ontario seniors. The null hypothesis was that the addition of amiodarone does not lead to a significant increase in the rate of hemorrhage or in-hospital death in elderly chronic users of warfarin.

3. METHODS

3.1. Study design

Our study was a retrospective cohort study. In a retrospective cohort design, patients are separated by exposure status and followed forward in time to an outcome of interest. Strength of association is measured by relative risk (RR) or odds ratio (OR). A case-control study design was considered as an alternative to a retrospective cohort study. In a case-control study design, outcome status in the cohort is initially identified and patients are categorized as being cases (i.e. have the outcome of interest) or controls (i.e. do not have the outcome) followed by looking back and determining exposure status. An OR is the only measure of association produced in a case control study. Though, when event rates are rare, the OR approximates RR. The disadvantages of the case-control study design include recall bias, in which individuals with the outcome of interest are more likely to remember risk factors. Previous interaction studies by ICES investigators

using similar data have been case-control in design[99-102], yet we decided a retrospective cohort study design was more appropriate in this study because it would allow us to incorporate time-to-event analysis; a feature not feasible in a case-control study design. Moreover, there was no clear advantage of designing a case-control study over a retrospective cohort study.

3.2. Setting

We conducted a population-based retrospective propensity-matched cohort study using data from linked health care databases in Ontario, Canada between July 1, 1994 and March 31, 2009. Accordingly, the earliest date a patient could be included in the cohort was July 1, 1994. We selected this cohort entry date because the data quality and data collection process underwent significant upgrades and revisions during a few years prior to this date. As well, we required a look-back window of 1 year to collect baseline characteristics. Thus, baseline variables were collected from as early as July 1, 1993. The last possible date for inclusion in the cohort was March 31, 2009. We initially planned to follow patients for 1 year after cohort entry. Thus, the final follow-up date was set at March 31, 2010 for the possibility that a patient would be accrued on March 31, 2009. This date allowed inclusion of the most recent, research-ready data. A detailed study time frame is available in **Figure 1** (Appendix 2).

3.3. Data source

The use of administrative databases was discussed previously in section 1.3. Briefly, hospitalization data were obtained from the DAD which contains detailed diagnostic and procedural information. Prescription claims data were obtained from ODB database, which records medications reimbursed by the Ontario government for residents 65 years or older. Physician billing information was obtained from the OHIP database. We used the RPDB to determine demographic characteristics of the cohort, including age, gender, and socioeconomic status (using the neighbourhood income quintile).

3.4. Privacy concerns

Immediately after ICES receives patient health information, the data are stripped of any personal identifiers (e.g. name, address, phone number) and each patient's health card number is encrypted.[103,104] This encrypted health card number allows ICES personnel to link each patient's health information across multiple administrative databases. Health information is not examined on an individual basis by ICES analysts. Instead, analysts execute macros (i.e. programming instructions that enable computers to extract the necessary health information). Therefore, the information obtained by analysts was aggregated into cohorts.

3.5. Data collection

Since the encrypted data can only be handled by ICES analysts and scientists, a data collection protocol (DCP) for this study was created. The purpose of this document

was to provide specific technical instructions to the analyst who was responsible for extracting the data. These instructions include how the cohort was defined, what baseline characteristics were examined, and how the results were analyzed. The full DCP can be found in **Appendix 3.**

3.6. Ethics approval

The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. ICES is a 'prescribed entity' under Ontario's health information privacy legislation, the Personal Health Information Protection Act of 2004. Thus, patient consent is not required by ICES for the purpose of analysis, evaluation of health care utilization in Ontario or conduct of epidemiological studies. However, high standards are in health information privacy are expected to be upheld. Because of the recurring nature of epidemiologic studies carried out at ICES, an expedited ethics approval process has been developed. Three forms were submitted for approval; a privacy impact assessment (PIA) form, project activation worksheet (PAW), and an ICES collaborating researcher non-disclosure agreement **(Appendix 4 to 6)**.

3.7. Design and matching

The cohort consisted of Ontario patients 66 years or older who received at least two warfarin prescriptions over the study period. To ensure they were ongoing warfarin users prior to study inclusion, they had to have had a prescription for warfarin filled within 0-90 days *and* within 90-180 days prior to cohort entry. We selected 66 as the age

of cohort entry because seniors over the age of 65 are able to submit prescription claims to ODB for coverage of many medications. These individuals had universal access to physicians' services, hospital care, and prescription drug coverage.

We excluded patients if they had an invalid identifier, were less than 66 years old, were missing information on age and gender, died on the cohort entry date, had no prescription for warfarin within 0-90 days or 90-180 days prior to cohort entry date or received amiodarone within 365 days prior to cohort entry date. In defining the last two exclusion criteria, we were able to include a cohort of individuals likely on continuous warfarin therapy for at least 180 days and who were sure to have no residual use or effect of past use of amiodarone during the study period.

The cohort entry date was defined as the date of the first prescription for amiodarone during the study period for exposed individuals. For those in the non-exposed group, cohort entry date was randomly assigned based on the distribution of cohort entry dates among the exposed cohort. For example, if more exposed individuals were included between 2004 and 2007, a greater portion of non-exposed individuals would be randomly selected from that time period. Exposed patients were matched to an unexposed patient based on age at cohort entry (within 2 years), sex, year of cohort entry, and an HDPS (within 1 caliper).

As previously discussed in section 1.4, several techniques to address confounding are available. Multivariate regression in the form of a Cox proportional hazard model was used. However, it was not the primary technique to reduce confounding.

Instrumental variable was not used because of the difficulty in identifying instruments that uphold the three assumptions. We explored propensity score methods and felt that HDPS algorithm allowed us to empirically identify a large number of measured baseline covariates available in administrative databases.

In the algorithm, we identified all records in the CIHI-DAD, OHIP and ODB databases in the year prior to cohort entry for all patients in our cohort, and included these *a priori* as dimensions in the HDPS algorithm. In total, there were five datasets or dimensions created (ODB claims, DAD diagnosis codes, DAD procedural codes, OHIP fee codes, and OHIP diagnosis codes). As previously discussed, the 200 most prevalent covariates from each dimension were selected and ranked based on each covariate's potential ability to reduce confounding.[85,96] We retained the 500 highest ranking covariates across all datasets and, in combination with investigator-defined covariates (i.e. age, gender, Charlson Comorbidity Index, prior bleeding, history of congestive heart failure, number of PT/INR tests 30 days prior to cohort entry date, and number of distinct drugs in past 1 year), were entered in a propensity score model using multivariate logistic regression. The HDPS matching algorithm is illustrated in **Figure 2**.

3.8. Patient characteristics

Baseline characteristics of study patients included demographics, income quintile (based on calculations by Statistics Canada)[105], measures of health care use (hospitalizations in past year, prothrombin time test (billing term used to indicate INR) in past 30 days, residence in long term care facility), Charlson comorbidity index[106], prior

bleeding, history of congestive heart failure (CHF), and concomitant prescription drug use suspected of interacting with warfarin. The Charlson comorbidity index accurately reflects the 1 year patient mortality and is based on weighted comorbidities: myocardial infarction (MI), CHF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, liver disease, ulcer disease, diabetes, hemiplegia, tumor(s), renal disease, acquired immune deficiency syndrome, metastatic solid tumor(s), leukemia and lymphoma.[106-108] Split into 5 ordinal categories (0 through 4), each point increase represents a 2.3% (95% CI, 1.9 to 2.8) increase in relative risk of 1-year mortality.[108]

3.9. Outcome definitions

Patients were followed from the cohort entry date to the first of: outcome, death from any cause, or 30 days maximum follow-up. The primary outcome was hospitalization for hemorrhage, defined as an inpatient hospital admission due to bleeding; including intracranial, gastrointestinal, genitourinary and other types of hemorrhage identified using the *ICD-9* and *ICD-10-CA* (**Table 2**). This list was derived from a previously published ICD validation study by Arnason *et al.*[15] A more detailed description of these codes is available in the DCP (**Appendix 2**)

There were three options for selecting diagnosis codes from hospitalization data: all diagnoses, most responsible diagnoses, and admission diagnoses. Within each definition, several diagnosis types were used. For all diagnoses, diagnosis types included pre-admission comorbidities (type 1), post-admission comorbidities (type 2), most

responsible diagnosis (type M), secondary diagnoses (Type 3), external codes (type 9), and service transfer diagnoses (types W, X, Y). Most responsible diagnoses (type M) included those diagnoses that were responsible for the person's longest length of stay in hospital regardless of whether it was a pre-admission or post-admission comorbidity. Admission diagnoses included types 1, W, X, Y, and M (but excluded if also coded as a post-admission comorbidity). The first two options were excluded because they included post-admission comorbidity which raised the possibility of that bleeding was caused by another factor during hospitalization extraneous to amiodarone initiation. For this reason, only diagnoses present at the time of admission (types 1, W, X, Y, and M) were considered in the outcome definition. Most responsible diagnosis (type M) was only considered in the admission diagnosis if it was not also a post-admission comorbidity. As previously mentioned, it was conceivable that a condition for which a patient was hospitalized for (or had as a previous comorbidity) did not end up being the main factor for the patient's length of stay. Another diagnosis after hospitalization could have been the main attributable factor for length of stay in hospital.

In a secondary analysis, all deaths occurring during a hospitalization for a hemorrhagic event were considered as outcomes. Only the first occurrence of an outcome was considered among subjects who experienced multiple outcomes over the study period.

3.9.1. Accuracy of codes used to define outcome

A key methodology issue with using administrative codes is how well information documented in medical charts such as admitting diagnosis is translated into ICD-9-CM or ICD-10-CA codes found in databases. In general, these codes were used on death certificates and hospital discharge abstracts to classify diseases. In these hospital discharge abstracts, health records analysts by reviewing physicians' discharge forms and health professional charting, determine the coding for the most responsible diagnosis, pre and post-admission co-morbidities, secondary diagnoses and admitting diagnosis in post-hospitalization of patients.[15]

As outlined in **Table 2**, several codes representing bleeding were used. Thus, we had to first determine how accurate or valid these ICD codes were for bleeding. Validity is reflected in the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).[109] The sensitivity of a bleeding code measures how likely the code is present in the database for patients who had a true bleed as recorded in the hospital medical chart (**Table 3**). Specificity measures how likely the code would not be present for patients who did not have a bleed in hospital. PPV reflects the likelihood that somebody with a code for bleeding actually experienced a bleed. NPV reflects the likelihood that somebody lacking the code in the database truly did not have a bleed.

A literature search resulted in two pertinent Canadian validation studies of ICD-9 codes for bleeding (**Table 4**).[15,110] No Canadian validation studies of ICD-10 coding for bleeding were found. In a well designed validation study of 616 patients, Arnason *et al.*

validated ICD-9-CM codes for bleeding (defined as either major or definite) against re-abstraction of hospital discharge data from an Ottawa tertiary care hospital.[15] Major bleeds were clinically overt and had at least one of the following: a) the patient was hospitalized for the bleeding; b) the haemoglobin level dropped more than 20 mg/dl; or c) at least 2 U of packed red blood cells were transfused. Definite bleeds required at least one of the following: a) documentation of a direct visualization of blood by a physician; b) imaging consistent with bleeding; c) imaging of a bleeding source accompanied by signs of bleeding. For definite bleeding, the ICD-9-CM codes had sensitivity, specificity, PPV, and NPV of 93%, 88%, 91%, and 91%, respectively. For major bleeding, the ICD-9-CM codes had sensitivity, specificity, PPV and NPV of 94%, 83%, 87%, and 92%, respectively. PPVs for diagnosis type of major and definite bleeding were also calculated. For definite bleeding, PPV for MRDx, pre-admission comorbidity, post-admission comorbidity, and secondary diagnosis were 96%, 86%, 73%, and 71%, respectively. For major bleeding, PPV for MRDx, pre-admission comorbidity, post-admission comorbidity, and secondary diagnosis were 92%, 78%, 65%, and 65%, respectively. Thus the likelihood a positive ICD code for bleeding is in fact recorded as a definite bleed in a hospital chart is over 70% but as low as 65% if the bleed was recorded as major. Furthermore, an MRDx of either major or definite bleeding is most accurate followed by pre-admission comorbidity. In an older study by Raiford *et al.* of 1,762 hospitalized patients, PPV of ICD-9 for GI bleeding and UGIB were 88% and 78%, respectively.[110] Sensitivity and specific could not be calculated in this study because raw data was not available. Moreover, NPV could not be calculated because unlike the study

by Arnason *et al.*, negative controls were not used.[110] We also identified a validation study by Leonard *et al.* on the accuracy of ICD-9 E-codes compared to a medical record review.[111] These E-codes can identify warfarin toxicity resulting in hemorrhages or other major bleeds. However, these codes were shown to have very low sensitivity (25.5%) and PPV (46.6%) for warfarin possibly due to underutilization of warfarin-specific E-codes or to the possibility that bleeding is not specific to warfarin and may occur in other disease states. Unfortunately, we could not find validation studies estimating the accuracy of service transfer diagnoses.

Since only diagnoses present at the time of admission (types 1, W, X, Y, and M) were considered in the outcome definition, we extrapolated that sensitivity, specificity, PPV, and NPV of our bleeding codes were approximately 80% or greater. However, there is uncertainty as to the accuracy of type W, X, or Y codes and how many of these diagnosis types would be present in our study.

3.10. Statistical analysis

We used standardized differences (SDF) to compare the baseline characteristics between groups. While there is no consensus on how small this difference should be, values greater than 0.10 (10%) suggest meaningful residual imbalance between groups.[82] We made this comparison prior to HDPS matching and after matching. To incorporate the paired nature of the study design, we used Cox proportional hazards regression and specified clustering by pair in the model in order to measure the robust estimates of standard error. From the regression model, we estimate the hazard ratio (HR) and 95%

confidence interval (CI) for the association between initiation of amiodarone use during warfarin therapy and hospitalization for hemorrhage. We performed two tests of proportionality of hazards to evaluate whether the assumption that covariates were independent with respect to time and their hazards were constant over the study period: a goodness-of-fit chi-squared (χ^2) test and a log-minus-log (or log-log) plot.[112] Under the null hypothesis in the χ^2 test (i.e. $p>0.05$), the data should not deviate from the theoretical Cox proportional hazard model.[112] The log-log plot converts the survival or hazard function of each group to a logarithm scale. To create the log-log plot, the logarithm of the survival function is calculated.[112] The value is converted into a positive value (because the logarithm of the survival function would be a negative number) and logged again. This value is plotted on the y-axis with the logarithm of follow-up time on the x-axis. At each time point, the curves should approximately be an equal distance apart similar to other time points. If the curves diverge, converge, or cross over, one cannot assume the hazard (of developing the outcome) is constant over time. Visual representation of bleeding over time between both groups was produced in the form of an unadjusted Kaplan-Meier survival curve and number of patients with bleeding over time. We adjusted the regression model for any imbalanced variables after propensity score matching (i.e. standard difference greater than 0.10) by including the variables in the final regression model. All analyses were performed by the ICES analyst using SAS version 9.2 (SAS Institute, Cary, North Carolina).

4. RESULTS

We identified 60,497 patients on warfarin therapy. Of these, 11,665 (19.3%) were started on amiodarone during warfarin therapy while 48,832 were on warfarin therapy alone.

4.1. Baseline characteristics prior to matching

Prior to HDPS matching, several imbalances were observed in baseline characteristics (**Table 5**). Notably, major imbalances (i.e. SDF greater than 0.10) were seen in CHF (SDF, 0.83), median hospitalizations within 1 year prior to cohort entry (SDF, 0.56), year of cohort entry (SDF, 0.41), age at cohort entry date (SDF, 0.36), missing Charlson scores (SDF, 0.33), median number of drugs prescribed in past year (SDF, 0.28), long term care status (SDF, 0.24), selective serotonin reuptake inhibitor (SSRI) use (SDF, 0.14), Charlson scores greater than 2 (SDF, 0.12 to 0.17), sex (SDF, 0.11), and bleeding in past year (SDF, 0.11). Thus, as compared to patients on warfarin only, patients on both warfarin and amiodarone tended to have higher Charlson scores, be on more medications, were more likely to be male, were hospitalized slightly more, and were previously diagnosed with bleeding and CHF. However, they were slightly younger, less likely to be on an SSRI, and less likely to be residing in a long term care facility.

4.2. Cohort after matching

Of the 11,665 subjects started on amiodarone, 7124 (61.1%) of these were successfully matched to a subject who was not exposed to amiodarone while receiving warfarin therapy. Following HDPS matching, exposed individuals were well-matched to unexposed individuals on characteristics with the exception of median number of hospitalizations per group in past one year where difference in median was one and the standardized difference was 0.10 (previously, 0.56 before HDPS matching). Thus, we adjusted for this variable in our regression model. Excluding hospitalization, standardized differences were less than 0.06 (**Table 6)**.

4.3. Tests of proportionality of hazards

From the goodness-of-fit the χ^2 test with one degree of freedom, *p* was 0.9978 (i.e. greater than χ^2) which suggests our data conformed to expected values and that hazards in both group were constant over the study period. Our log-minus-log plot indicated that the hazard function did not change over time since the two curves are roughly parallel and do not cross each other.

4.4. Bleeding and death

Among the 7,124 patients who started amiodarone, we identified 56 (0.8%) patients who had been hospitalized for hemorrhage within the subsequent 30 days. Of these, 7 (14%) died before discharge. In the matched control group, 23 (0.3%) patients were hospitalized for hemorrhage. We found a statistically significant increase in risk of

hemorrhage following initiation of amiodarone among patients receiving warfarin (unadjusted HR, 2.43; 95% CI, 1.50 to 3.96 and adjusted HR, 2.45; 95% CI, 1.49 to 4.02). We calculated a number needed to harm of 216. The Kaplan-Meier curve visually shows a divergence in the hazards of each group. Over the 30-day observation window, probability of remaining hemorrhage-free drops at steady but greater rate in the exposed group as compared to the unexposed group (**Figure 4**).

Seven patients in the amiodarone group died after hospitalization for a hemorrhage versus four in the non-exposed group. We found no statistically significant association between amiodarone use and death while hospitalized for bleeding (unadjusted HR, 1.75; 95% CI, 0.51 to 5.98 and adjusted HR, 1.74; 95% CI, 0.25 to 12.24). Study findings are provided in **Table 7**. **Tables 8** and **9** show the baseline characteristics of patients who bled and died, respectively, in both groups.

5. DISCUSSION

Our findings suggest a two-fold increased risk of hospitalization for bleeding within the first month of concomitant use of amiodarone with ongoing warfarin therapy as compared to ongoing warfarin use alone. However, no association was observed between the combination of the two medications and death after hospitalization for bleeding. This may have been due to the small number of deaths and thus, our analysis was underpowered to see a significant result. Overall, roughly 1% of patients co-

prescribed amiodarone and warfarin were hospitalized with a hemorrhage within 30 days, and 12.5% of these patients died during their hospital visit. This is a high 30 day case-fatality rate and merits further research.

Our findings differ from those reported by Zhang *et al.* who did not detect excess overt bleeding within 7 days of initiation of amiodarone while on warfarin (OR, 0.98; 95% CI, 0.83 to 1.16).[48] We compare our results mainly to this study because to our knowledge, it is the only study published in which clinical outcomes were measured potentially as a result of the interaction. Previously studies have either looked at the effects of the interaction on INR values or warfarin dose adjustment only.[10,13,17,38,40-47] As highlighted in section 1.3., the study by Zhang *et al.* was an administrative claims analysis of 17,895 American patients who were on warfarin therapy during October 1, 2003, to September 30, 2004. In their study, 40.3% of these individuals were on warfarin for less than 120 days, 14.1% were on warfarin for 121 to 180 days, and 45.7% were on warfarin for greater than 180 days. Of the 17,895 patients on warfarin, 1,260 subjects (7%) were identified as being on amiodarone as well.[48] Our cohort provides a much larger sample with a longer follow-up for outcomes among well-matched patient groups.[48] Moreover, we selected the majority of our ICD codes for bleeding which have been previously validated. Our results are consistent with a biologically and pharmacologically plausible explanation and with other evidence which has shown that the interaction leads to supratherapeutic INR values.[21,31,38,40-47]

Several limitations exist in our study which merit further discussion. Firstly, we could not assess unmeasured variables such as use of non-prescription medications or diets which interact with anticoagulation control. While HDPS matching did an excellent job balancing several measured baseline covariates between both groups as evident in the small standardized differences of the means at baseline, no method of adjustment can assure balance of unmeasured covariates. This is problematic in the study of warfain because warfarin has several documented drug and food interactions.[16] In particular, the use of "over the counter" aspirin could not be examined, which is an important confounder since evidence suggests that co-administration of low-dose aspirin with an oral anticoagulant is associated with a 2-fold increased risk of upper GI bleeding.[83] Secondly, we could not directly measure INR control and identify patients at risk of bleeding or determine a correlation between hospitalization for bleeding and supratherapeutic INR values. Unfortunately, we did not have access to a laboratory database to obtain INR values for subjects. This data would be useful to determining level of control and time in therapeutic range. More importantly, poor INR control is predictive of hemorrhagic events.[13] Therefore, we are unable to comment on the degree of INR control while a patient is on warfarin. Thirdly, we lost roughly 40% of eligible subjects due to stringent matching criteria. This was likely attributable to matching exposed individuals to controls based on the HDPS. With the trade-off in smaller sample size however, we were able to select well-matched groups based on baseline characteristics. A fourth limitation is our inability to look at discontinuation of either amiodarone or warfarin during follow-up. This is due to the fact that medications

claimed by patients and captured in the ODB database will not have any information concerning discontinuation. We could only look at ODB prescription claims and frequency of claims to estimate length of therapy. Since we were looking at a 30 day follow-up, it is conceivable patients were receiving prescription refills for greater than 30 days. A fifth limitation concerning medication use is the lack of data on warfarin dose adjustments. This would have provided useful information in reinforcing our assertion that haemorrhaging was associated with the interaction. It has been previously shown that the interaction between warfarin and amiodarone leads to an increased INR.[21,31,38,40-47] This supratherapeutic increase in INR often results in warfarin dose reduction. From one small observational study, the interaction led to a 44% mean maximum reduction in the warfarin maintenance doses seven weeks after initiation of amiodarone.[38] It was recommended that for patients initiated on amiodarone at 100, 200, 300, and 400 mg per day, the dose of warfarin should be reduced by 25%, 30%, 35%, and 40%, respectively. In our study, if we could have shown that exposed individuals had a greater number of warfarin dose adjustments than the control group, it would corroborate our hypothesis that the interaction leads to variable INR which ultimately lead to a clinically adverse outcome. A sixth limitation of our study was setting a follow-up of 30 days. On one hand, having a shorter follow-up may have increased the likelihood that hospitalization for bleeding was associated with amiodarone initiation. If follow-up was longer, this also may have allowed physicians more time to act on INRs out of therapeutic range and thus decreasing the chance of observing a bleed. However, oral amiodarone absorption is slow and variable with an observed peak effect between 1 week to 5 months.[21-27] Another

limitation is the lack of information on the prevalence of atrial fibrillation and myocardial infarction at baseline. While they were included in our HDPS model, we did not measure prevalence at baseline. Thus, we are unsure if these two variables were balanced after matching. Bleeding is not likely a sequelae of atrial fibrillation. However, other factors such as aspirin use may have an influence on bleeding in patients with atrial fibrillation. In myocardial infarction, literature suggests there may be an increased risk of bleeding after an MI.[113-115] Reasons include antiplatelet and antithrombolytic therapy, hypoperfusion of the gastrointestinal tract, and stress gastritis associated with MIs.[113] A *post hoc* analysis of atrial fibrillation and MI rates is necessary in the future to rule out these two variables as potential confounders. Finally, the validity of the outcome codes we used for bleeding is still a concern (see section **3.9.1.**). Depending on the diagnosis type, accuracy could be highly variable. To ensure we were using codes representative of events in hospital, a validation study was a crucial initial step in our type of study that was not performed.

The introduction of amiodarone therapy to elderly patients receiving chronic warfarin for at least 6 months was associated with a two-fold increased risk of hospitalization for bleeding. Although deaths were too few for power to declare a difference, the trend suggests that the hospitalization for bleeding was harmful overall. At the least, hospitalization is an inconvenience and is associated with a decrease in quality of life in some circumstances.[116-118] Clinicians need to be aware of the level of risk involved with the combination of both medications. Since warfarin and amiodarone are

frequently co-prescribed in elderly patients with atrial fibrillation, closer monitoring of anticoagulation control over the first month of co-prescribing may be necessary to minimize adverse events.

6. APPENDIX 1: Tables

Table 1. Common diagnosis types used in the Canadian Institute of Health Information discharge abstract database (CIHI-DAD)

Type	Name	Description
M	Most Responsible Diagnosis (MRDx)	The diagnosis that accounts for the greatest portion of the length of stay or use of health care services during hospitalization. This diagnosis may not necessarily be the reason for hospitalization.
1	Pre-admission comorbidity	Conditions that existed prior to admission and are significant*
2	Post-admission comorbidity	Conditions that develop during hospitalization and are significant.* These conditions can potentially be categorized as a MRDx if it meets the definition of a MRDx.
3	Secondary diagnosis	Conditions that are not categorized as significant comorbidities* but are present.
9	External cause, place or activity	External causes of morbidity or mortality (e.g. motor vehicle accident) and is mandatory to include when associated with injury
W,X,Y	Service transfer diagnoses	ICD-10-CA diagnosis codes signifying most responsible for 1st, 2nd, and 3rd transferred service

*Significant comorbidities must meet at least of these three criteria: 1) significant influence on treatment received; 2) requirement of additional treatment beyond treatment for pre-existing condition; and 3) increase in length of stay $\geq$ 24 hours.

Source: Juurlink D, Preyra C, Croxford A, Austin P, Tu J, Laupacis A**.** Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: Institute for Clinical Evaluative Sciences; 2006.

Table 2: International Classification of Diseases (ICD), 9th and 10th edition codes used to identify bleeding.

Outcome	ICD-9 code	ICD-10 code
Intracerebral bleeding	430, 431, 432.0, 432.1, 432.9	I60, I61, I620, I621, I629
Upper gastrointestinal bleeding	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 5332, 5334, 5336, 5340, 534.2, 534.4, 534.6, 578.0, 578.1, 578.9	I850, I9820, I983, K2210, K2212, K2214, K2216, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K920, K921, K3180, K6380
Lower	569.3, 578.1, 578.9	K5520, K625, K922

gastrointestinal bleeding		
Other	287.8, 287.9, 459.0, 596.7, 599.7, 627.1, 719.1, 784.8, 786.3	N020 to N029, K661, N938, N939, N950, R041, R042, R048, R049, R310, R311, R318, R58, D683, H356, H431, H450, M250

Table 3: Diagnostic tests in the context of bleeding

		Diagnosis from medical chart review	
		True bleeding confirmed	No bleeding confirmed
ICD code for bleeding	Present	*TP*	*FP*
	Absent	*FN*	*TN*

Sensitivity = TP/TP+FN	Positive predictive value = TP/TP+FP
Specificity = TN/FP+TN	Negative predictive value = FN/FN+TN

* TP = true positive, FP = false positive, FN = false negative, TN = true negative

Table 4. Validation studies for bleeding in Canadian databases

Validation studies										
Authors	**Database**	**"Gold Standard"**	**No. of patients**	**Specific outcome of interest/ code used**	**Diagnosis types**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Kappa**
Bleeding										
Arnason *et al.*[15]	Hospital discharge abstracts database (Ottawa)	Medical records	616	ICD-9CM codes for definite bleeding*	All types (with focus on Type M)	93	88	91	91	----
Arnason *et al.*[15]	Hospital discharge abstracts database (Ottawa)	Medical records	616	ICD-9CM codes for major bleeding**	All types (with focus on Type M)	94	83	87	92	----
Raiford *et al.*[110]	Saskatchewan Hospital Services Plan database	Medical records	1,762	ICD-9 CM codes for hemorrhage of rectum/anus, hematemesis, melena, unspecific intestinal bleeding	Discharge diagnosis (Type unspecified)	----	-----	83 (Specific) 68 (UGIB) 21 (site-specific lesion)	----	----

Type 1 = pre-admit comorbidity, Type 2 = post-admit comorbidity

*'"Definite bleeding" required at least one of the following: a) documentation of a direct visualization of blood by a physician; b) imaging consistent with bleeding (such as CT scan showing intracranial hemorrhage); c) imaging of a bleeding source accompanied by signs of bleeding (for example, endoscopy diagnosing a duodenal ulcer and physician documentation of melena).' (Arnason *et al*., 2006)

**"Bleeds were classified as "major" if they were clinically overt and had at least one of the following: a) the patient had to be admitted to a hospital for the bleeding problem; b) the haemoglobin dropped more than 20 mg/dl as a result of the bleed; or c) at least 2 U of packed red blood cells were transfused as a result of the bleed." (Arnason, *et al*., 2006)

[15] Arnason T, Wells PS, van Walraven C, Forster AJ. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. Thromb Res. 2006;118(2):253-62.

[110] Raiford DS, Gutthann SP,Rodriguez LAG. Positive predictive value of ICD-9 codes in the identification of cases of complicated peptic ulcer disease in the Saskatchewan hospital automated database. Epidemiology. 1996;7:101-104.

Table 5. Baseline characteristics ***prior*** to high dimensional propensity score matching with standardized differences.

Variable	Warfarin Alone	Warfarin + Amiodarone	Standardized difference of the mean
	N=48,832	**N=11,665**	
Demographics			
Median age at cohort entry (IQR)	78 (73-83)	75 (71-80)	0.36
Male	23,766 (48.7%)	6,320 (54.2%)	0.11
Rural location	7,842 (16.1%)	1,597 (13.7%)	0.07
*Income Quintile**			
1	9,966 (20.4%)	2,270 (19.5%)	0.02
2	10,556 (21.6%)	2,472 (21.2%)	0.01
3	9,807 (20.1%)	2,280 (19.5%)	0.01
4	9,006 (18.4%)	2,169 (18.6%)	0
5	9,320 (19.1%)	2,447 (21.0%)	0.05
Missing	177 (0.4%)	27 (0.2%)	0.02
Year of cohort entry			
1994	256 (0.5%)	447 (3.8%)	0.41
1995	553 (1.1%)	382 (3.3%)	0.41
1996	916 (1.9%)	438 (3.8%)	0.41
1997	1,407 (2.9%)	560 (4.8%)	0.41
1998	2,188 (4.5%)	873 (7.5%)	0.41
1999	2,682 (5.5%)	915 (7.8%)	0.41
2000	3,350 (6.9%)	947 (8.1%)	0.41
2001	4,263 (8.7%)	1,051 (9.0%)	0.41
2002	4,514 (9.2%)	971 (8.3%)	0.41
2003	4,202 (8.6%)	833 (7.1%)	0.41
2004	4,225 (8.7%)	786 (6.7%)	0.41

2005	4,546 (9.3%)	872 (7.5%)	0.41
2006	4,716 (9.7%)	868 (7.4%)	0.41
2007	4,944 (10.1%)	757 (6.5%)	0.41
2008	4,839 (9.9%)	779 (6.7%)	0.41
2009	1,231 (2.5%)	186 (1.6%)	0.41
Measures of health care use			
Median number of hospitalizations in past year (IQR)	1 (0-1)	0 (0-2)	0.56
Mean number of PT tests in past 30 days ± standard deviation	1.28± 1.28	1.32± 1.46	0.04
Co-morbidity			
Charlson Comorbidity Index			
0	14,278 (29.2%)	3,311 (28.4%)	0.02
1	8,022 (16.4%)	2,267 (19.4%)	0.08
2	5,654 (11.6%)	1,817 (15.6%)	0.12
3	3,302 (6.8%)	1,178 (10.1%)	0.13
4	3,882 (7.9%)	1,490 (12.8%)	0.17
Missing	13,694 (28.0%)	1,602 (13.7%)	0.33
Hemorrhage in past 1 year	725 (1.5%)	340 (2.9%)	0.11
Congestive heart failure in past 1 year	3,106 (6.4%)	3,644 (31.2%)	0.83
Residence in long-term care facility	5,141 (10.5%)	437 (3.7%)	0.24
Median number of distinct drugs prescribed in past 1 year (IQR)	10 (7-14)	11 (8-15)	0.28
≤ 5	7,531 (15.4%)	951 (8.2%)	0.21
6-10	19,215 (39.3%)	4,015 (34.4%)	0.1
11-15	13,425 (27.5%)	3,832 (32.9%)	0.12
16-20	5,944 (12.2%)	1,838 (15.8%)	0.11
21-26	2,145 (4.4%)	791 (6.8%)	0.11

≥ 27	572 (1.2%)	238 (2.0%)	0.08
Medication use (Evidence of at least one prescription of the following in the past 60 days prior to cohort entry date)			
NSAIDs/non COX-2 inhibitor/non ASA	2,036 (4.2%)	495 (4.2%)	0
COX-2 inhibitor	1,215 (2.5%)	189 (1.6%)	0.06
Anti-platelet agents by prescription – ASA, ticlopidine, clopidogrel, dipyridamole, dypridamole/ASA combination)	1,057 (2.2%)	400 (3.4%)	0.08
Acetaminophen and combinations	7,726 (15.8%)	1,658 (14.2%)	0.04
Gastroprotective medications (H_2 receptor antagonists, misoprostol, proton pump inhibitors, sucralfate)	10,528 (21.6%)	2,369 (20.3%)	0.03
Selective serotonin receptor inhibitors	448 (7.1%)	395 (6.2%)	0.03
Corticosteroids (excluding topical or aerosol formulations)	1,858 (3.8%)	539 (4.6%)	0.04
Statins	12,031 (24.6%)	2,805 (24.0%)	0.01
Antibiotic use (Evidence of at least one prescription of the following in the past 14 days prior to cohort entry date)			
Trimethoprim/sulfamethoxazole	154 (0.3%)	31 (0.3%)	0.01
Fluroquinolone	653 (1.3%)	152 (1.3%)	0
Metronidazole	63 (0.1%)	16 (0.1%)	0

*****Income quintiles are calculated by dividing income into 5 categories (i.e. 1 through 5). A household size-adjusted measure of household income based on the 2006 Statistics Canada census is used to define level of income. There are no set (monetary) value ranges for the quintiles as it depends on neighbourhood.[105]

NB: Abbreviations include non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitor, aspirin (ASA), and histamine 2 (H2) receptor antagonists

Table 6. Baseline characteristics ***after*** high dimensional propensity score matching with standardized differences.

Variable	Warfarin Alone	Warfarin + Amiodarone	Standardized difference of the mean
	N=7,124	**N=7,124**	

Demographics			
Median age at cohort entry (IQR)	76 (71-81)	76 (71-81)	0
Male	3,674 (51.6%)	3,674 (51.6%)	0
Rural location	1,054 (14.8%)	1,015 (14.2%)	0.02
*Income Quintile**			
1	1,402 (19.7%)	1,410 (19.8%)	0
2	1,586 (22.3%)	1,480 (20.8%)	0.04
3	1,425 (20.0%)	1,416 (19.9%)	0
4	1,320 (18.5%)	1,293 (18.1%)	0.01
5	1,369 (19.2%)	1,505 (21.1%)	0.05
Missing	22 (0.3%)	20 (0.3%)	0.01
Year of cohort entry			
1994	40 (0.6%)	40 (0.6%)	0
1995	116 (1.6%)	116 (1.6%)	0
1996	193 (2.7%)	193 (2.7%)	0
1997	275 (3.9%)	275 (3.9%)	0
1998	421 (5.9%)	421 (5.9%)	0
1999	480 (6.7%)	480 (6.7%)	0
2000	630 (8.8%)	630 (8.8%)	0
2001	723 (10.1%)	723 (10.1%)	0
2002	679 (9.5%)	679 (9.5%)	0
2003	566 (7.9%)	566 (7.9%)	0
2004	532 (7.5%)	532 (7.5%)	0
2005	566 (7.9%)	566 (7.9%)	0

2006	637 (8.9%)	637 (8.9%)	0
2007	570 (8.0%)	570 (8.0%)	0
2008	562 (7.9%)	562 (7.9%)	0
2009	134 (1.9%)	134 (1.9%)	0
Measures of health care use			
Median number of hospitalizations in past year (IQR)	1 (0-1)	0 (0-1)	0.1
Mean number of PT tests in past 30 days ± standard deviation	1.34±1.35	1.32 ±1.43	0.01
Co-morbidity			
Charlson Comorbidity Index			
0	2,136 (30.0%)	2,100 (29.5%)	0.01
1	1,304 (18.3%)	1,293 (18.1%)	0
2	1,067 (15.0%)	1,021 (14.3%)	0.02
3	674 (9.5%)	644 (9.0%)	0.01
4	862 (12.1%)	837 (11.7%)	0.01
Missing	1,081 (15.2%)	1,229 (17.3%)	0.06
Hemorrhage in past 1 year	199 (2.8%)	194 (2.7%)	0
Congestive heart failure in past 1 year	1,537 (21.6%)	1,535 (21.5%)	0
Residence in long-term care facility	241 (3.4%)	312 (4.4%)	0.05
Median number of distinct drugs prescribed in past 1 year (IQR)	11 (8-15)	11 (8-15)	0.02
≤ 5	694 (9.7%)	675 (9.5%)	0.01
6-10	2,462 (34.6%)	2,586 (36.3%)	0.04
11-15	2,254 (31.6%)	2,233 (31.3%)	0.01
16-20	1,112 (15.6%)	1,042 (14.6%)	0.03
21-26	457 (6.4%)	452 (6.3%)	0

≥ 27	145 (2.0%)	136 (1.9%)	0.01
Medication use (Evidence of at least one prescription of the following in the past 60 days prior to cohort entry date)			
NSAIDs/non COX-2 inhibitor/non ASA	255 (3.6%)	310 (4.4%)	0.04
COX-2 inhibitor	162 (2.3%)	140 (2.0%)	0.02
Anti-platelet agents – ASA, ticlopidine, clopidogrel, dipyridamole, dypridamole/ASA combination)	246 (3.5%)	216 (3.0%)	0.02
Acetaminophen and combinations	1,095 (15.4%)	1,037 (14.6%)	0.02
Gastroprotective medications (H_2 receptor antagonists, misoprostol, proton pump inhibitors, sucralfate)	1,572 (22.1%)	1,492 (20.9%)	0.03
Selective serotonin receptor inhibitors	539 (7.6%)	437 (6.1%)	0.06
Corticosteroids (excluding topical or aerosol formulations)	324 (4.5%)	339 (4.8%)	0.01
Statins	1,919 (26.9%)	1,857 (26.1%)	0.02
Antibiotic use (Evidence of at least one prescription of the following in the past 14 days prior to cohort entry date)			
Trimethoprim/sulfamethoxazole	21 (0.3%)	23 (0.3%)	0.01
Fluroquinolone	83 (1.2%)	100 (1.4%)	0.02
Metronidazole	6 (0.1%)	13 (0.2%)	0.03

*Income quintiles are calculated by dividing income into 5 categories (i.e. 1 through 5). A household size-adjusted measure of household income based on the 2006 Statistics Canada census is used to define level of income. There are no set (monetary) value ranges for the quintiles as it depends on neighbourhood.[105]

NB: Abbreviations include non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitor, aspirin (ASA), and histamine 2 (H2) receptor antagonists

Table 7. Hospitalization for bleeding and hospitalization for bleeding resulting in death.

	Warfarin alone	**Warfarin + Amiodarone**
Number of individuals	N=7,124	N=7,124
Total follow-up (person years)	581.4	577.4

Follow-up (days ± standard deviation)	29.81 ± 1.86	29.60 ± 2.78
Hospitalization for a hemorrhagic event (primary event)		
Number of patients with a hemorrhage	23	56
Incidence	0.3%	0.8%
NNH	N/A	216
Unadjusted hazard ratio (95% CI)	N/A	2.43 (1.50 -3.96)
Adjusted hazard ratio (95% CI)	N/A	2.45 (1.49 - 4.02)
Hospitalization for bleeding resulting in death		
Number of deaths	4	7
Incidence	0.06%	0.1%
Unadjusted hazard ratio (95% CI)	N/A	1.75 (0.51 - 5.98)
Adjusted hazard ratio (95% CI)	N/A	1.74 (0.25 -12.24)

Abbreviations: NNH = number need to harm, CI = confidence interval

Table 8: Comparison of baseline characteristics of patients who bled between groups

Variable	Warfarin Alone	Warfarin + Amiodarone	Standardized difference of the mean
	N=23	N=56	
Demographics			
Median age at cohort entry (IQR)	79 (73-83)	78 (72-83)	0.11
Male	14 (60.9%)	38 (67.9%)	0.15
Year of cohort entry			
1996	1 (4.3%)	0	0.07
1997	1 (4.3%)	2 (3.6%)	0.07
1998	1 (4.3%)	2 (3.6%)	0.07
1999	3 (13.0%)	3 (5.4%)	0.07
2000	1 (4.3%)	3 (8.9%)	0.07
2001	0	6 (10.7%)	0.07
2002	2 (8.7%)	6 (10.7%)	0.07

2003	4 (17.4%)	4 (7.1%)	0.07
2004	3 (13.0%)	6 (10.7%)	0.07
2005	0	3 (5.4%)	0.07
2006	0	6 (10.7%)	0.07
2007	2 (8.7%)	7 (12.5%)	0.07
2008	3 (13.0%)	6 (10.7%)	0.07
2009	2 (8.7%)	0	0.07
Measures of health care use			
Median number of hospitalizations in past year (IQR)	1 (0-2)	1 (0-2)	0.34
Mean number of PT tests in past 30 days ± standard deviation	1.61 ± 1.34	1.16 ± 1.20	0.36
Co-morbidity			
Hemorrhage in past 1 year	2 (8.7%)	4 (7.1%)	0.06
Congestive heart failure in past 1 year	8 (34.8%)	19 (33.9%)	0.02
Median number of distinct drugs prescribed in past 1 year (IQR)	12 (8-15)	13 (10-15)	0.02
Medication use (Evidence of at least one prescription of the following in the past 60 days prior to cohort entry date)			
NSAIDs/non COX-2 inhibitor/non ASA	1 (4.3%)	3 (5.4%)	0.05
COX-2 inhibitor	0	2 (3.6%)	0.23
Anti-platelet agents – ASA, ticlopidine, clopidogrel, dipyridamole, dypridamole/ASA combination)	1 (4.3%)	2 (3.6%)	0.04
Acetaminophen and combinations	6 (26.1%)	6 (10.7%)	0.43
Gastroprotective medications (H_2 receptor antagonists, misoprostol, proton pump inhibitors, sucralfate)	5 (21.7%)	14 (25.0%)	0.08
Selective serotonin receptor inhibitors	2 (8.7%)	4 (7.1%)	0.06
Corticosteroids (excluding topical or aerosol formulations)	0	3 (5.4%)	0.28
Statins	6 (26.1%)	15 (26.8%)	0.02

Antibiotic use (Evidence of at least one prescription of the following in the past 14 days prior to cohort entry date)			
Trimethoprim/sulfamethoxazole	0	0	N/A
Fluroquinolone	0	4 (7.1%)	0.33
Metronidazole	0	0	N/A

NB: Abbreviations include non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitor, aspirin (ASA), and histamine 2 (H2) receptor antagonists

Table 9: Comparison of baseline characteristics of patients who died between groups

Variable	Warfarin Alone	Warfarin + Amiodarone	Standardized difference of the mean
	N=4	N=7	
Demographics			
Median age at cohort entry (IQR)	81 (75-86)	78 (74-86)	0.14
Male	2 (50.0%)	6 (85.7%)	0.78
Year of cohort entry			
1998	0	1 (14.3%)	0.61
1999	1 (25.0%)	1 (14.3%)	0.61
2000	1 (25.0%)	0	0.61
2002	1 (25.0%)	0	0.61
2004	1 (25.0%)	3 (42.9%)	0.61
2006	0	2 (28.6%)	0.61
Measures of health care use			
Median number of hospitalizations in past year (IQR)	2 (1-2)	2 (1-2)	0.57
Mean number of PT tests in past 30 days ± standard deviation	2.50 ± 0.58	1.14 ± 1.46	1.11
Co-morbidity			
Hemorrhage in past 1 year	0	1 (14.3%)	0.47
Congestive heart failure in past 1 year	2 (50.0%)	4 (57.1%)	0.13
Median number of distinct drugs prescribed in	7	16	2.59

past 1 year (IQR)	(5-11)	(14-18)	
Medication use (Evidence of at least one prescription of the following in the past 60 days prior to cohort entry date)			
NSAIDs/non COX-2 inhibitor/non ASA	0	1 (14.3%)	0.47
COX-2 inhibitor	0	0	N/A
Anti-platelet agents – ASA, ticlopidine, clopidogrel, dipyridamole, dypridamole/ASA combination)	0	0	N/A
Acetaminophen and combinations	1 (25.0%)	1 (14.3%)	0.25
Gastroprotective medications (H_2 receptor antagonists, misoprostol, proton pump inhibitors, sucralfate)	0	0	N/A
Selective serotonin receptor inhibitors	0	1 (14.3%)	0.47
Corticosteroids (excluding topical or aerosol formulations)	0	0	N/A
Statins	1 (25.0%)	1 (14.3%)	0.25
Antibiotic use (Evidence of at least one prescription of the following in the past 14 days prior to cohort entry date)			
Trimethoprim/sulfamethoxazole	0	0	N/A
Fluroquinolone	0	1 (14.3%)	0.47
Metronidazole	0	0	N/A

NB: Abbreviations include non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitor, aspirin (ASA), and histamine 2 (H2) receptor antagonists

APPENDIX 2: Figures

Figure 1: Study time frame

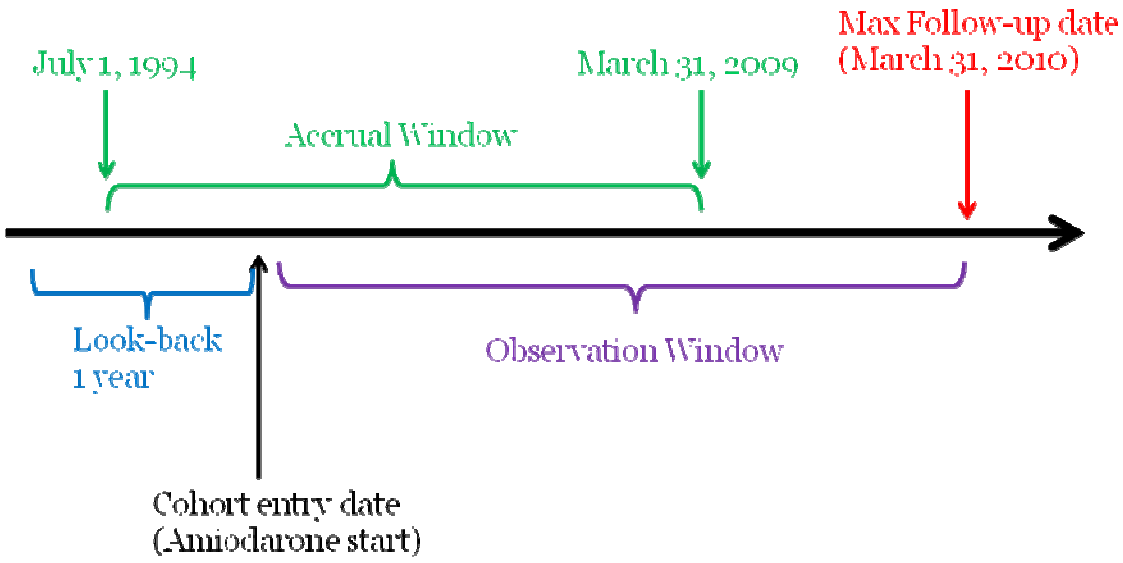


Figure 2: High dimensional propensity score algorithm

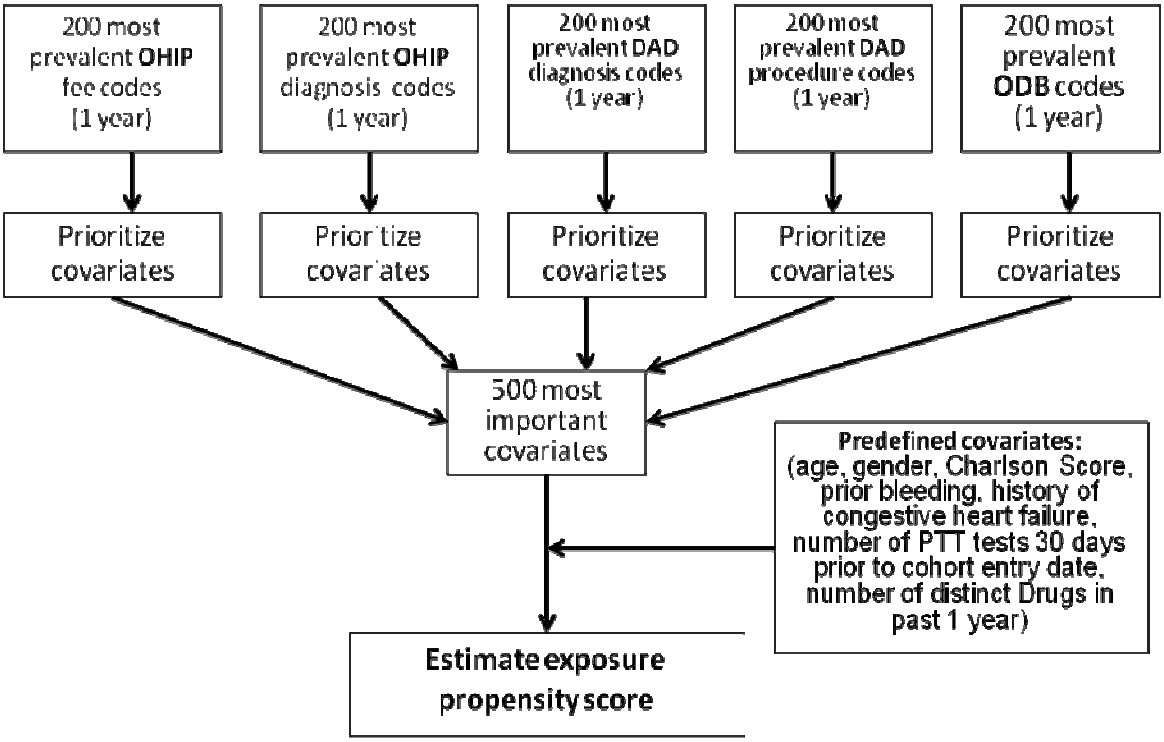


Figure 3: Log-minus-log plot (test for proportionality of hazards)

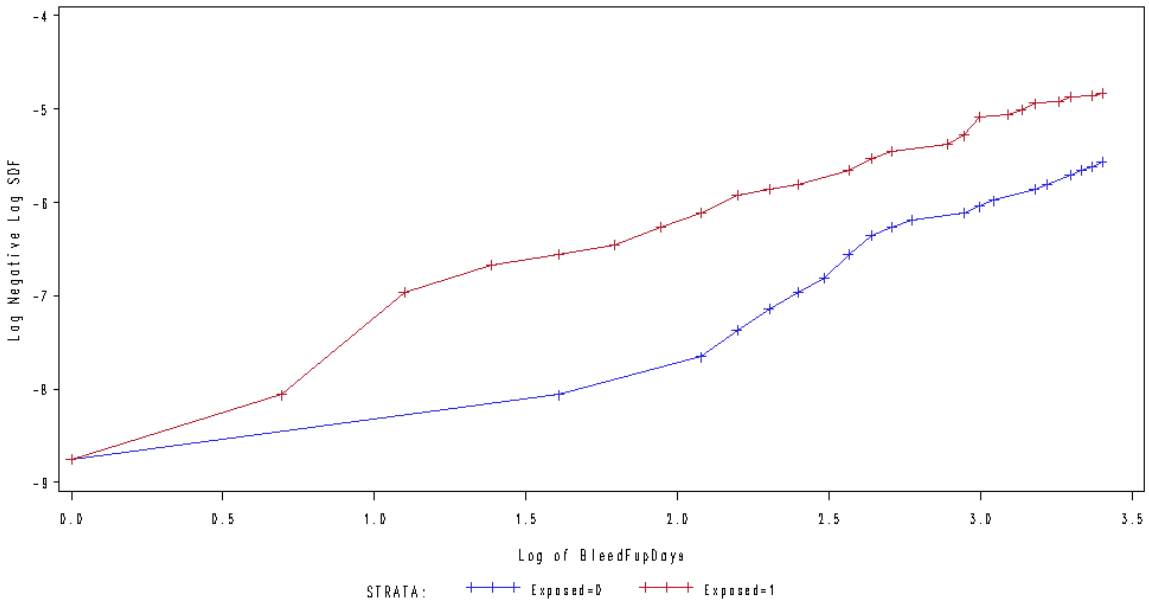
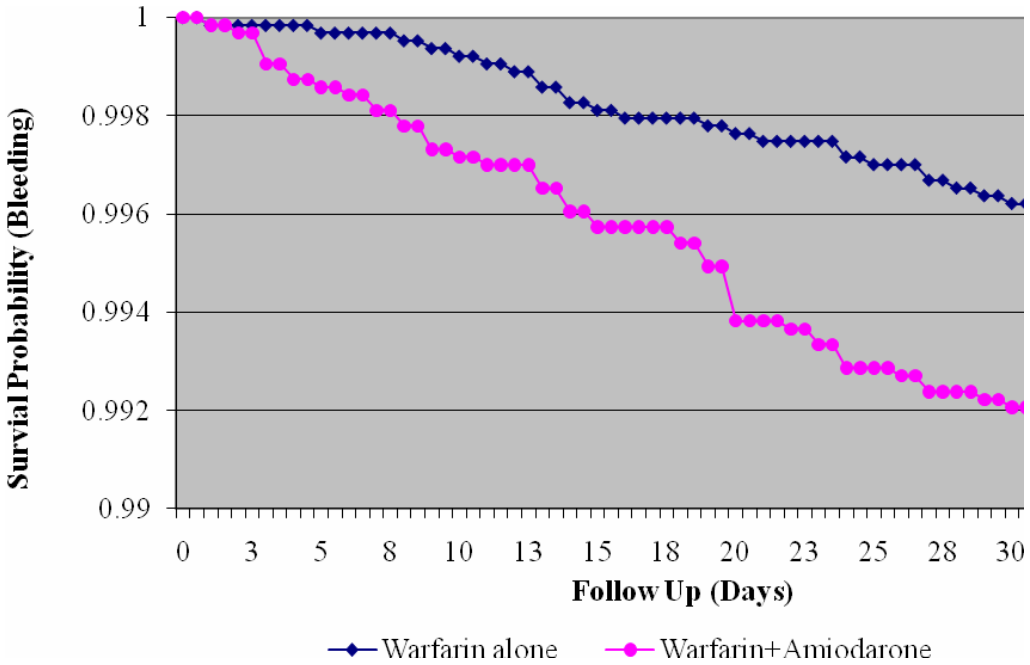


Figure 4: Unadjusted Kaplan-Meier survival curve for bleeding (primary outcome).



Appendix 3: Data collection protocol (DCP)

Hemorrhage during warfarin therapy associated with the addition of amiodarone: a population-based cohort study

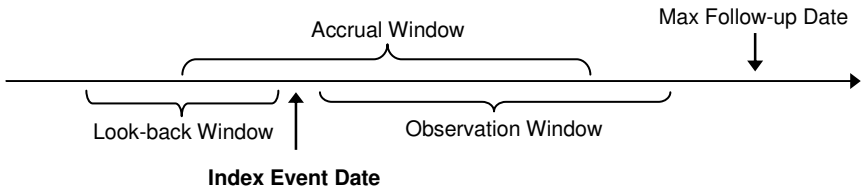
Name and Number of Study	Hemorrhage during warfarin therapy associated with the addition of amiodarone: a population-based cohort study Project Number: 2011 0760 136 000
PI and P&B Contacts	• Anne Holbrook • Jason Lam • Muhammad Mamdani • David Juurlink • Mike Paterson • Tara Gomes
PIA Approved?	Yes
DCP update history	Version 1: Nov. 2, 2010 (JL) Version 2: Nov. 5, 2010 (JL) Version 3: Nov. 9, 2010 (JL, TG edit) Version 4: Nov. 10, 2010 (JL) Version 5: Nov. 22, 2010 (JL, MP edit) Version 6: Nov. 27, 2010 (JL) Version 7: Nov. 29, 2010 (JL, AH edit) Version 8: Nov. 30, 2010 (JL, group edit) Version 9: Dec. 21-22, 2010 (JL) Version 10: Jan. 14, 2010 (JL) Version 11: January 18, 2011 (TG, JL)
Short Description of Research Question	To examine whether exposure to concomitant warfarin and amiodarone lead to higher risk of major bleeding and death in-hospitalization within 30 days compared to warfarin therapy alone
List of Datasets Used	• ODB • CIHI-DAD • OHIP

Defining the Cohort

Nest Definition	Subject Prescribed Warfarin at some point over the study period. Nest Entry date = Date of first warfarin prescription over the study period
Index Event and Cohort Entry Date	<u>Exposed individuals:</u> Prescription for amiodarone following Nest Entry Date Cohort entry date = date of first amiodarone prescription following nest entry date <u>Unexposed individuals:</u> No prescription for amiodarone following Nest Entry

	Date Cohort entry date randomly assigned based on distribution of cohort entry dates among the exposed cohort.
Exclusions (In order)	• Invalid IKN • Missing Age or Gender • <66 years old • Death on cohort entry date • No warfarin prescription within 0-90 days prior to cohort entry date • No warfarin prescription within 91-180 days prior to cohort entry date • Among exposed and unexposed – exclude if any use of amiodarone in the 365 days prior to cohort entry date.
Size of Cohort	To be determined

Time Frame Definitions



Accrual Start/End Dates	Beginning of Accrual Period for cohort: July 1, 1994 End of Accrual Period for cohort: March 31, 2009
Max Follow-up Date	End of follow-up Period: March 31, 2010
When does observation window terminate?	From date of cohort entry to first of: • Major Bleeding event • Death • End of follow-up (30 days)
Lookback Window(s)	• 1 year for co-morbid conditions (including previous major bleeding events) • 1 year for ODB medications • Look back 180 days from cohort entry date for prescription claim for warfarin

Variable Definitions

Main Exposure or Risk Factor	Exposed Cohort: • Current users of warfarin (**dclass VKA)** • New users of amiodarone (**dclass AMIO)** : • New use: 365 days to look back to define new use. Unexposed

	• Current warfarin users only

Baseline Characteristics	**Demographics (at cohort entry)**
	• Age at cohort entry: median (IQR), mean (SD)
	• Female sex
	• Year of cohort entry
	• Rural location at cohort entry
	• Socioeconomic status at cohort entry
	  ○ Neighbourhood Income Quintiles calculated by FSA, (report as missing, 1, 2, 3, 4, 5)
	
	Measure of health care use (prior to cohort entry date):
	• Number of hospitalizations in past year (median, IQR)
	• Prothrombin time (PT) test in past 30 days (OHIP feecode L445)
	• Living in LTC home:
	  ○ Use LTC flag on ODB record closest to and prior to the cohort entry date. For exposed, this will be the date of amiodarone Rx. For unexposed, it will be for some other recent drug.
	
	Co-morbidity (based on information within 1 year of cohort entry date)
	• Charlson score: Median (IQR), categories. If no hospitalizations, report as missing.
	• Prior major bleeding (Please see Appendix)
	• Congestive heart failure
	• Number of distinct drugs (based on drug name) used in past 1 year reported as median (IQR)
	
	Concomitant Medication Use (Evidence of at least one prescription of the following in the past 60 days prior to cohort entry date except if stated otherwise)
	1) Anti-platelets
	  - ASA **(dclass = ASA)**
	  - TICLOPIDINE HCL', 'CLOPIDOGREL BISULFATE', 'DIPYRIDAMOLE', dypridamole/ASA combination **(dclass = APLAT)**
	2) NSAIDs/ non COX-2 inhibitor/ non ASA, **(dclass = NSAID)**
	3) COX-2 inhibitor **(dclass = COX2)**
	4) Acetaminophen and combinations **(dclass = ACET)**
	5) Gastroprotective medications
	  - H_2 antagonists, **(dclass = H2RA)**
	  - misoprostol [excluding Arthrotec], sucralfate **(dclass GASTRO)**
	  - proton pump inhibitors **(dclass PPI)**
	6) Selective serotonin receptor inhibitors, **(dclass SSRI)**
	7) Fluoroquinolones (within 14 days prior to cohort entry date), **dclass ABX_FQ**

	8) Septra (within 14 days prior to cohort entry date), **dclass ABX_TMX** 9) Metronidazole (within 14 days prior to cohort entry date), **dclass ABX_MET** 10) Corticosteroids (excluding topical creams/ointments), **dclass STEROID** 11) Statins (**dclass STATINS) –** includes combination product (Amlodipine + Atorvastatin

Propensity Score Definition	<u>High-Dimensional Propensity Model (using methods developed by Sebastian Schneeweiss):</u>
	• This method allows various large datasets including large amounts of observational data to be input into macro. The top 500 most important variables are kept, and propensity score is calculated for these variables.
	  ○ 1 year ODB claims (based on drug name)
	  ○ 1 years CIHI-DAD data (dxcode ICD9 and ICD10)
	  ○ 1 year CIHI-DAD data (incode/prcode, ICD9 and 10)
	  ○ 1 year OHIP feecodes
	  ○ 1 year OHIP dxcodes
	  • The 200 most prevalent empirical covariates to consider <u>from each of the above datasets</u>
	  • The number of empirical covariates to include in the resulting propensity score = 500
	  • Also include age, gender, Charlson Score, prior bleeding, history of congestive heart failure, number of PTT tests 30 days prior to cohort entry date, number of distinct Drugs in past 1 year in model.

Propensity Score Matching	**Matching Variables:** Matching Ratio: Match 1 Unexposed to each Exposed individual on: • Propensity score: Caliper = 0.2 x Standard Deviation • Age at cohort entry date within +/- 2 years • Sex • Year of cohort entry date

Outcome Definitions	• **Hospitalizations for major bleeding:**
	Use CIHI-DAD only:
	  ○ Diagnosis codes: Please see Appendix
	  ○ Diagnosis Type: Admission Diagnosis (admitdx)
	  ○ For hospitalizations, DAD source: Inpatient
	• **Death in-hospitalization (Secondary outcome)**
	Use CIHI-DAD only:
	  ○ Diagnosis codes: Please see Appendix
	  ○ Diagnosis Type: Admission Diagnosis
	  ○ For hospitalizations, DAD source: Inpatient

- Only count if Hospitalization discharge disposition = ‘07’ (died on discharge).

Analysis Plan

Propensity Score Matching:

- Exposed individuals will be matched to cohort of unexposed individuals based on matching variables outlined above
- Number unexposed to match to each exposed: 1

Statistical Analyses:

- **Descriptive Analyses:**
    - Table created comparing baseline characteristics between unexposed and exposed *prior* to propensity score matching
    - Table created comparing baseline characteristics between unexposed and exposed *after* propensity score matching – analyst must check to see that propensity score matching has created cohort where exposed and unexposed are similar. If not, may have to add more variables to propensity score matching algorithm, or match on other variables
    - List all continuous, categorical and dichotomous variables for Table 1

For each outcome, the following can be computed:

Cox Proportional Hazards Model – Incorporates time-to-event

- Incorporates the paired nature of the matched study design
- Unadjusted Kaplan-Meier survival curve
- Test of proportionality of hazards: Log-Log Survival curve and time-dependent covariates
- Adjusted KM-curve based on mean of all covariates in adjusted model
- If proportional hazards assumption holds, run unadjusted model with only exposure variables included.
- If proportional hazards assumption holds, run adjusted model with exposure and covariates of interest included:
    - Covariates to include in model:

- Tables 2b and 2c created (based on mock table below)

NEW: TIME-TO-EVENT DESCRIPTIVE ANALYSIS:

- Assess time to event: from cohort entry date to event date (in days).
- Provide frequency distribution of time-to-event.
- If events are clustered around the 25-30 day period, may want to consider options for longer follow-up time (NOTE: this would be complicated since would require rules included in design to ensure continued use of warfarin and amiodarone)

Table 1a: Baseline characteristics for each exposure group: Prior to Propensity Score matching			
Variable	**Warfarin + Amiodarone**	**Warfarin alone**	**Standardized Difference**
Number	N	N	
Demographics			
Age			
Median (IQR)	Median (IQR)	Median (IQR)	
Male	N=, (%)	N=, (%)	
Income based socioeconomic status			
Quintile 1	N=, (%)	N=, (%)	
Quintile 2	N=, (%)	N=, (%)	
Quintile 3	N=, (%)	N=, (%)	
Quintile 4	N=, (%)	N=, (%)	
Quintile 5	N=, (%)	N=, (%)	
Missing	N=, (%)	N=, (%)	
Rural Location	N=, (%)	N=, (%)	
Year of cohort entry			
1994	N=, (%)	N=, (%)	
1995	N=, (%)	N=, (%)	
1996	N=, (%)	N=, (%)	
1997	N=, (%)	N=, (%)	
1998	N=, (%)	N=, (%)	
1999	N=, (%)	N=, (%)	
2000	N=, (%)	N=, (%)	
2001	N=, (%)	N=, (%)	
2002	N=, (%)	N=, (%)	
2003	N=, (%)	N=, (%)	
2004	N=, (%)	N=, (%)	
2005	N=, (%)	N=, (%)	
2006	N=, (%)	N=, (%)	
2007	N=, (%)	N=, (%)	
2008	N=, (%)	N=, (%)	
2009	N=, (%)	N=, (%)	
Measure of health care use			
Number of hospitalizations in past year	Median (IQR)	Median (IQR)	
Number of PT tests in past 30 days	Mean (SD)	Mean (SD)	
Co-morbidity			
Charlson Comorbidity Index			
Median (IQR)	Median (IQR)	Median (IQR)	
0	N=, (%)	N=, (%)	
1	N=, (%)	N=, (%)	
2	N=, (%)	N=, (%)	

3	N=, (%)	N=, (%)	
4	N=, (%)	N=, (%)	
> 4	N=, (%)	N=, (%)	
Missing	N=, (%)	N=, (%)	
Prior major bleeding	N=, (%)	N=, (%)	
Congestive heart failure	N=, (%)	N=, (%)	
No. of patients living in LTC facility	N=, (%)	N=, (%)	
Number of distinct drugs			
Median (IQR)	Median (IQR)	Median (IQR)	
≤ 5	N=, (%)	N=, (%)	
6-10	N=, (%)	N=, (%)	
11-15	N=, (%)	N=, (%)	
16-20	N=, (%)	N=, (%)	
21-26	N=, (%)	N=, (%)	
≥ 26	N=, (%)	N=, (%)	
Medication use			
NSAIDs/non COX-2 inhibitor/non ASA	N=, (%)	N=, (%)	
COX-2 inhibitor	N=, (%)	N=, (%)	
Anti-platelet agents – ASA, ticlopidine, clopidogrel, dipyridamole, dypridamole/ASA combination)	N=, (%)	N=, (%)	
Acetaminophen and combinations	N=, (%)	N=, (%)	
Gastroprotective medications (H2RAs, misoprostol, PPIs, sucralfate)	N=, (%)	N=, (%)	
Septra use within 14 days prior to index date	N =,(%)	N =, (%)	
Fluoroquinolones	N =,(%)	N =, (%)	
Metronidazole	N =,(%)	N =, (%)	
Corticosteroids	N =,(%)	N =, (%)	
SSRIs	N =,(%)	N =, (%)	
Statins	N =,(%)	N =, (%)	

Table 1b: Baseline characteristics for each exposure group: After Propensity Score matching			
Variable	**Warfarin + Amiodarone**	**Warfarin alone**	**Standardized Difference**
Number	N	N	
Demographics			
Age			

Median (IQR)	Median (IQR)	Median (IQR)	
Male	N=, (%)	N=, (%)	
Income based socioeconomic status			
Quintile 1	N=, (%)	N=, (%)	
Quintile 2	N=, (%)	N=, (%)	
Quintile 3	N=, (%)	N=, (%)	
Quintile 4	N=, (%)	N=, (%)	
Quintile 5	N=, (%)	N=, (%)	
Missing	N=, (%)	N=, (%)	
Rural Location	N=, (%)	N=, (%)	
Year of cohort entry			
1994	N=, (%)	N=, (%)	
1995	N=, (%)	N=, (%)	
1996	N=, (%)	N=, (%)	
1997	N=, (%)	N=, (%)	
1998	N=, (%)	N=, (%)	
1999	N=, (%)	N=, (%)	
2000	N=, (%)	N=, (%)	
2001	N=, (%)	N=, (%)	
2002	N=, (%)	N=, (%)	
2003	N=, (%)	N=, (%)	
2004	N=, (%)	N=, (%)	
2005	N=, (%)	N=, (%)	
2006	N=, (%)	N=, (%)	
2007	N=, (%)	N=, (%)	
2008	N=, (%)	N=, (%)	
2009	N=, (%)	N=, (%)	
Measure of health care use			
Number of hospitalizations in past year	Median (IQR)	Median (IQR)	
Number of PT tests in past 30 days	Mean (SD)	Mean (SD)	
Co-morbidity			
Charlson Comorbidity Index			
Median (IQR)	Median (IQR)	Median (IQR)	
0	N=, (%)	N=, (%)	
1	N=, (%)	N=, (%)	
2	N=, (%)	N=, (%)	
3	N=, (%)	N=, (%)	
4	N=, (%)	N=, (%)	
> 4	N=, (%)	N=, (%)	
Missing	N=, (%)	N=, (%)	
Prior major bleeding	N=, (%)	N=, (%)	
Congestive heart failure	N=, (%)	N=, (%)	
No. of patients living in LTC	N=, (%)	N=, (%)	

facility			
Number of distinct drugs			
Median (IQR)	Median (IQR)	Median (IQR)	
≤ 5	N=, (%)	N=, (%)	
6-10	N=, (%)	N=, (%)	
11-15	N=, (%)	N=, (%)	
16-20	N=, (%)	N=, (%)	
21-26	N=, (%)	N=, (%)	
≥ 26	N=, (%)	N=, (%)	
Medication use			
NSAIDs/non COX-2 inhibitor/non ASA	N=, (%)	N=, (%)	
COX-2 inhibitor	N=, (%)	N=, (%)	
Anti-platelet agents – ASA, ticlopidine, clopidogrel, dipyridamole, dypridamole/ASA combination)	N=, (%)	N=, (%)	
Acetaminophen and combinations	N=, (%)	N=, (%)	
Gastroprotective medications (H2RAs, misoprostol, PPIs, sucralfate)	N=, (%)	N=, (%)	
Septra use within 14 days prior to index date	N =,(%)	N =, (%)	
Fluoroquinolones	N =,(%)	N =, (%)	
Metronidazole	N =,(%)	N =, (%)	
Corticosteroids	N =,(%)	N =, (%)	
SSRIs	N =,(%)	N =, (%)	
Statins	N =,(%)	N =, (%)	

Table 2b: Cox Proportional Hazards Regression for Primary Analysis (Major bleeding)		
Statistic	**Warfarin + Amiodarone**	**Warfarin alone**
Number of individuals		
No. outcomes		
Mean follow-up time		
SD follow-up time		
Total follow-up (person years)		
No. outcomes per 1000 person years		
Q1 follow-up time		

Q3 follow-up time		
Median follow-up time		
Unadjusted HR		n/a
LCL Unadjusted HR		n/a
UCL Unadjusted HR		n/a
Adjusted HR		n/a
LCL Adjusted HR		n/a
UCL Adjusted HR		n/a
Adjusted No. Outcomes per 1000 person-years		n/a
NNT to Harm		n/a
NNT to Harm (using estimated probabilities)		n/a

Table 2c: Cox Proportional Hazards Regression for Secondary Analysis (Death)		
Statistic	**Warfarin + Amiodarone**	**Warfarin alone**
Number of individuals		
No. outcomes		
Mean follow-up time		
SD follow-up time		
Total follow-up (person years)		
No. outcomes per 1000 person years		
Q1 follow-up time		
Q3 follow-up time		
Median follow-up time		
Unadjusted HR		n/a
LCL Unadjusted HR		n/a
UCL Unadjusted HR		n/a
Adjusted HR		n/a
LCL Adjusted HR		n/a
UCL Adjusted HR		n/a
Adjusted No. Outcomes per 1000 person-years		n/a
NNT to Harm		n/a
NNT to Harm (using estimated probabilities)		n/a

Bleeding: ICD10 codes

Intracerebral	
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I620	Subdural haemorrhage (acute)(nontraumatic)
I621	Nontraumatic extradural haemorrhage
I629	Intracranial haemorrhage (nontraumatic), unspecified
Upper GI	
K920	Haematemesis
K921	Melaena
I850	Oesophageal varices with bleeding
I9820	Oesophageal varices in diseases classified elsewhere with bleeding
I983	Oesophageal varices with bleeding in disease classified elsewhere
K2210	Ulcer of oesophagus, acute with haemorrhage
K2212	Ulcer of oesophagus, acute with both haemorrhage and perforation
K2214	Ulcer of oesophagus, chronic or unspecified with haemorrhage
K2216	Ulcer of oesophagus, chronic or unspecified with both haemorrhage and perforation
K250	Gastric ulcer, acute with haemorrhage
K252	Gastric ulcer, acute with both haemorrhage and perforation
K254	Gastric ulcer, chronic or unspecified with haemorrhage
K256	Gastric ulcer, chronic or unspecified with both haemorrhage and perforation
K260	Duodenal ulcer, acute with haemorrhage
K262	Duodenal ulcer, acute with both haemorrhage and perforation
K264	Duodenal ulcer, chronic or unspecified with haemorrhage
K266	Duodenal ulcer, chronic or unspecified with both haemorrhage and perforation
K270	Peptic ulcer, acute with haemorrhage
K272	Peptic ulcer, acute with both haemorrhage and perforation
K274	Peptic ulcer, chronic or unspecified with haemorrhage
K276	Peptic ulcer, chronic or unspecified with both haemorrhage and perforation
K280	Gastrojejunal ulcer, acute with haemorrhage
K282	Gastrojejunal ulcer, acute with both haemorrhage and perforation
K284	Gastrojejunal ulcer, chronic or unspecified with haemorrhage
K286	Gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation
K290	Acute haemorrhagic gastritis
K6380	Angiodysplasia of small intestine, except duodenum with bleeding
K3180	Angiodysplasia of stomach and duodenum with bleeding
Lower GI	
K5520	Angiodysplasia of colon with bleeding
K625	Haemorrhage of anus and rectum
K922	Gastrointestinal haemorrhage, unspecified
Other	

N020	Recurrent and persistent haematuria, minor glomerular abnormality
N021	Recurrent and persistent haematuria, focal and segmental glomerular lesions
N022	Recurrent and persistent haematuria, diffuse membranous glomerulonephritis
N023	Recurrent and persistent haematuria, diffuse mesangial proliferative glomerulonephritis
N024	Recurrent and persistent haematuria, diffuse endocapillary proliferative glomerulonephritis
N025	Recurrent and persistent haematuria, diffuse mesangiocapillary glomerulonephritis
N026	Recurrent and persistent haematuria, dense deposit disease
N027	Recurrent and persistent haematuria, diffuse crescentic glomerulonephritis
N028	Recurrent and persistent haematuria, other
N029	Recurrent and persistent haematuria, unspecified
K661	Haemoperitoneum
N938	Other specified abnormal uterine and vaginal bleeding
N939	Abnormal uterine and vaginal bleeding, unspecified
N950	Postmenopausal bleeding
R041	Haemorrhage from throat
R042	Haemoptysis
R048	Haemorrhage from other sites in respiratory passages
R049	Haemorrhage from respiratory passages, unspecified
R310	Gross hematuria
R311	Microscopic hematuria
R318	Other and unspecified hematuria
R58	Haemorrhage, not elsewhere classified
D683	Haemorrhagic disorder due to circulating anticoagulants
H356	Retinal haemorrhage
H431	Vitreous haemorrhage
H450	Vitreous haemorrhage in diseases classified elsewhere
M250	Haemarthrosis,

ICD9 Codes for Bleeds:

Intracerebral	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432.0	Nontraum extradural hem
432.1	Subdural hemorrhage
432.9	Intracranial hemorr NOS
Upper gastrointestinal	
531.0	ac stomach ulcer w hem ac stomach ulcer w hem-obst
531.2	ac stomach ulc w hem/perf ac stomach ulc w hem/perf-obst
531.4	chr stomach ulc w hem

	chr stomach ulc w hem-obst
531.6	chr stomach ulc hem/perf chr stomach ulc hem/perf-obst
532.0	ac duodenal ulcer w hem ac duodenal ulcer w hem-obst
532.2	ac duodenal ulc w hem/perf ac duodenal ulc w hem/perf-obst
532.4	chr duoden ulcer w hem chr duoden ulcer w hem-obst
532.6	chr duoden ulc w hem/perf chr duoden ulc w hem/perf-obst
533.0	ac peptic ulc w hemorr ac peptic ulc w hemorr-obst
533.2	ac peptic ulc w hem/perf ac peptic ulc w hem/perf-obst
533.4	chr peptic ulcer w hem chr peptic ulcer w hem-obst
533.6	chr peptic ulc w hem/perf chr peptic ulc w hem/perf-obst
534.0	ac marginal ulcer w hem ac marginal ulcer w hem-obst
534.2	ac margin ulc w hem/perf ac margin ulc w hem/perf-obst
534.4	chr marginal ulcer w hem chr marginal ulcer w hem-obst
534.6	chr marg ulc w hem/perf chr marg ulc w hem/perf-obst
578.0	hematemesis
578.1	Blood in stool
578.9	Gastrointest Hemorr NOS
Lower gastrointestinal	
569.3	Rectal and anal hemorrhage
578.1	Blood in stool
578.9	Gastrointest Hemorr NOS
Other Bleeds	
287.8	Hemorrhagic Cond NEC
287.9	Hemorrhagic Cond NOS
596.7	Hemorrhage from throat
784.8	Hemorrhage from throat
599.7	Hematuria
627.1	Post menopausal bleeding
459.0	Hemorrhage NOS
719.1	Hemarthrosis
786.3	Hemoptysis

Drug list

DIN	Drug name	Drug formulation	Strength	Drug class
00010308	WARFARIN SODIUM	Tablet	5 mg	Vitamin K antagonist
00585629	WARFARIN SODIUM	Tablet	5 mg	Vitamin K antagonist
00585637	WARFARIN SODIUM	Tablet	10 mg	Vitamin K antagonist
00585645	WARFARIN SODIUM	Tablet	2.5 mg	Vitamin K antagonist
00585653	WARFARIN SODIUM	Tablet	2 mg	Vitamin K antagonist
01918311	WARFARIN SODIUM	Tablet	1 mg	Vitamin K antagonist
01918338	WARFARIN SODIUM	Tablet	1 mg	Vitamin K antagonist
01918346	WARFARIN SODIUM	Tablet	2.5 mg	Vitamin K antagonist
01918354	WARFARIN SODIUM	Tablet	5 mg	Vitamin K antagonist
01918362	WARFARIN SODIUM	Tablet	10 mg	Vitamin K antagonist
02007959	WARFARIN SODIUM	Tablet	4 mg	Vitamin K antagonist
02240205	WARFARIN SODIUM	Tablet	3 mg	Vitamin K antagonist
02242680	WARFARIN SODIUM	Tablet	1 mg	Vitamin K antagonist
02242681	WARFARIN SODIUM	Tablet	2 mg	Vitamin K antagonist
02242682	WARFARIN SODIUM	Tablet	2.5 mg	Vitamin K antagonist
02242683	WARFARIN SODIUM	Tablet	3 mg	Vitamin K antagonist
02242684	WARFARIN SODIUM	Tablet	4 mg	Vitamin K antagonist
02242685	WARFARIN SODIUM	Tablet	5 mg	Vitamin K antagonist
02242687	WARFARIN SODIUM	Tablet	10 mg	Vitamin K antagonist
02242924	WARFARIN SODIUM	Tablet	1 mg	Vitamin K antagonist
02242925	WARFARIN SODIUM	Tablet	2 mg	Vitamin K antagonist
02245618	WARFARIN SODIUM	Tablet	3 mg	Vitamin K antagonist
02242926	WARFARIN SODIUM	Tablet	2.5 mg	Vitamin K antagonist
02242927	WARFARIN SODIUM	Tablet	4 mg	Vitamin K antagonist
02242928	WARFARIN SODIUM	Tablet	5 mg	Vitamin K antagonist
02242929	WARFARIN SODIUM	Tablet	10 mg	Vitamin K antagonist
02244462	WARFARIN SODIUM	Tablet	1 mg	Vitamin K antagonist
02244463	WARFARIN SODIUM	Tablet	2 mg	Vitamin K antagonist
02244464	WARFARIN SODIUM	Tablet	2.5 mg	Vitamin K antagonist
02287498	WARFARIN SODIUM	Tablet	3 mg	Vitamin K antagonist
02244465	WARFARIN SODIUM	Tablet	4 mg	Vitamin K antagonist
02244466	WARFARIN SODIUM	Tablet	5 mg	Vitamin K antagonist
02244467	WARFARIN SODIUM	Tablet	10 mg	Vitamin K antagonist
02265273	WARFARIN SODIUM	Tablet	1 mg	Vitamin K antagonist
02265281	WARFARIN SODIUM	Tablet	2 mg	Vitamin K antagonist
02265303	WARFARIN SODIUM	Tablet	2.5 mg	Vitamin K antagonist
02265311	WARFARIN SODIUM	Tablet	3 mg	Vitamin K antagonist
02265338	WARFARIN SODIUM	Tablet	4 mg	Vitamin K antagonist
02265346	WARFARIN SODIUM	Tablet	5 mg	Vitamin K antagonist
2246194	AMIODARONE HCL	Tablet	200 mg	Antirhythmic agent
2036282	AMIODARONE HCL	Tablet	201 mg	Antirhythmic agent

2240604	AMIODARONE HCL	Tablet	202 mg	Antirhythmic agent
2239835	AMIODARONE HCL	Tablet	203 mg	Antirhythmic agent
2242472	AMIODARONE HCL	Tablet	204 mg	Antirhythmic agent
2245781	AMIODARONE HCL	Tablet	205 mg	Antirhythmic agent
2240071	AMIODARONE HCL	Tablet	206 mg	Antirhythmic agent
2243836	AMIODARONE HCL	Tablet	207 mg	Antirhythmic agent
00514004	DICLOFENAC SODIUM	Tablet	25MG	Non-steroidal anti-inflammatory drug
00514012	DICLOFENAC SODIUM	Tablet	50MG	Non-steroidal anti-inflammatory drug
00590827	DICLOFENAC SODIUM	Tablet	100MG	Non-steroidal anti-inflammatory drug
00632724	DICLOFENAC SODIUM	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
00632732	DICLOFENAC SODIUM	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
00782459	DICLOFENAC SODIUM	Tablet	75MG	Non-steroidal anti-inflammatory drug
00808539	DICLOFENAC SODIUM	Tablet	25MG	Non-steroidal anti-inflammatory drug
00808547	DICLOFENAC SODIUM	Tablet	50MG	Non-steroidal anti-inflammatory drug
00839175	DICLOFENAC SODIUM	Tablet	25MG	Non-steroidal anti-inflammatory drug
00839183	DICLOFENAC SODIUM	Tablet	50MG	Non-steroidal anti-inflammatory drug
00886017	DICLOFENAC SODIUM	Tablet	25MG	Non-steroidal anti-inflammatory drug
00886025	DICLOFENAC SODIUM	Tablet	50MG	Non-steroidal anti-inflammatory drug
01910175	DICLOFENAC SODIUM	Tablet	50MG	Non-steroidal anti-inflammatory drug
01910183	DICLOFENAC SODIUM	Tablet	25MG	Non-steroidal anti-inflammatory drug
02048698	DICLOFENAC SODIUM	Tablet	100MG	Non-steroidal anti-inflammatory drug
02091194	DICLOFENAC SODIUM	Tablet	100MG	Non-steroidal anti-inflammatory drug
02158582	DICLOFENAC SODIUM	Tablet	75MG	Non-steroidal anti-inflammatory drug
02162814	DICLOFENAC SODIUM	Tablet	75MG	Non-steroidal anti-inflammatory drug
02174677	DICLOFENAC SODIUM	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02174685	DICLOFENAC	Rectal	100MG	Non-steroidal anti-inflammatory

	SODIUM	suppository		drug
02228203	DICLOFENAC SODIUM	Tablet	75MG	Non-steroidal anti-inflammatory drug
02228211	DICLOFENAC SODIUM	Tablet	100MG	Non-steroidal anti-inflammatory drug
02231502	DICLOFENAC SODIUM	Tablet	25MG	Non-steroidal anti-inflammatory drug
02231503	DICLOFENAC SODIUM	Tablet	50MG	Non-steroidal anti-inflammatory drug
02231504	DICLOFENAC SODIUM	Tablet	75MG	Non-steroidal anti-inflammatory drug
02231505	DICLOFENAC SODIUM	Tablet	100MG	Non-steroidal anti-inflammatory drug
02231506	DICLOFENAC SODIUM	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02231508	DICLOFENAC SODIUM	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
02237786	DICLOFENAC SODIUM	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02237787	DICLOFENAC SODIUM	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
02241224	DICLOFENAC SODIUM	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02241225	DICLOFENAC SODIUM	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
01917056	DICLOFENAC SODIUM & MISOPROSTOL	Tablet	50MG/200MCG	Non-steroidal anti-inflammatory drug
02229837	DICLOFENAC SODIUM & MISOPROSTOL	Tablet	75MG/200MCG	Non-steroidal anti-inflammatory drug
00576131	DIFLUNISAL	Tablet	500MG	Non-steroidal anti-inflammatory drug
00587699	DIFLUNISAL	Tablet	250MG	Non-steroidal anti-inflammatory drug
02039486	DIFLUNISAL	Tablet	250MG	Non-steroidal anti-inflammatory drug
02039494	DIFLUNISAL	Tablet	500MG	Non-steroidal anti-inflammatory drug
02048493	DIFLUNISAL	Tablet	250MG	Non-steroidal anti-inflammatory drug
02048507	DIFLUNISAL	Tablet	500MG	Non-steroidal anti-inflammatory drug
02142023	ETODOLAC	Capsule	200MG	Non-steroidal anti-inflammatory drug

02142031	ETODOLAC	Capsule	300MG	Non-steroidal anti-inflammatory drug
02232318	ETODOLAC	Capsule	300MG	Non-steroidal anti-inflammatory drug
00328642	FENOPROFEN CALCIUM	Capsule	300MG	Non-steroidal anti-inflammatory drug
00345504	FENOPROFEN CALCIUM	Tablet	600MG	Non-steroidal anti-inflammatory drug
00638668	FLOCTAFENINE	Tablet	200MG	Non-steroidal anti-inflammatory drug
00754153	FLOCTAFENINE	Tablet	400MG	Non-steroidal anti-inflammatory drug
01902717	FLOCTAFENINE	Tablet	200MG	Non-steroidal anti-inflammatory drug
01902725	FLOCTAFENINE	Tablet	400MG	Non-steroidal anti-inflammatory drug
02017628	FLOCTAFENINE	Tablet	200MG	Non-steroidal anti-inflammatory drug
02017636	FLOCTAFENINE	Tablet	400MG	Non-steroidal anti-inflammatory drug
02244680	FLOCTAFENINE	Tablet	200MG	Non-steroidal anti-inflammatory drug
02244681	FLOCTAFENINE	Tablet	400MG	Non-steroidal anti-inflammatory drug
00593346	FLURBIPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
00593354	FLURBIPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
00600792	FLURBIPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
00647942	FLURBIPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
00675199	FLURBIPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
00675202	FLURBIPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
01912038	FLURBIPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
01912046	FLURBIPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
02020661	FLURBIPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
02020688	FLURBIPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
02100509	FLURBIPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory

				drug
02100517	FLURBIPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
02223066	FLURBIPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
02223074	FLURBIPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
00252409	IBUPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
00327794	IBUPROFEN	Tablet	300MG	Non-steroidal anti-inflammatory drug
00364142	IBUPROFEN	Tablet	400MG	Non-steroidal anti-inflammatory drug
00441643	IBUPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
00441651	IBUPROFEN	Tablet	300MG	Non-steroidal anti-inflammatory drug
00443182	IBUPROFEN	Capsule	200MG	Non-steroidal anti-inflammatory drug
00443190	IBUPROFEN	Capsule	300MG	Non-steroidal anti-inflammatory drug
00443204	IBUPROFEN	Capsule	400MG	Non-steroidal anti-inflammatory drug
00484911	IBUPROFEN	Tablet	600MG	Non-steroidal anti-inflammatory drug
00506052	IBUPROFEN	Tablet	400MG	Non-steroidal anti-inflammatory drug
00585114	IBUPROFEN	Tablet	600MG	Non-steroidal anti-inflammatory drug
00606197	IBUPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
00606200	IBUPROFEN	Tablet	300MG	Non-steroidal anti-inflammatory drug
00606219	IBUPROFEN	Tablet	400MG	Non-steroidal anti-inflammatory drug
00606227	IBUPROFEN	Tablet	600MG	Non-steroidal anti-inflammatory drug
00629324	IBUPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
00629332	IBUPROFEN	Tablet	300MG	Non-steroidal anti-inflammatory drug
00629340	IBUPROFEN	Tablet	400MG	Non-steroidal anti-inflammatory drug
00629359	IBUPROFEN	Tablet	600MG	Non-steroidal anti-inflammatory drug

00016039	INDOMETHACIN	Capsule	25MG	Non-steroidal anti-inflammatory drug
00016047	INDOMETHACIN	Capsule	50MG	Non-steroidal anti-inflammatory drug
00016233	INDOMETHACIN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
00337420	INDOMETHACIN	Capsule	25MG	Non-steroidal anti-inflammatory drug
00337439	INDOMETHACIN	Capsule	50MG	Non-steroidal anti-inflammatory drug
00463248	INDOMETHACIN	Capsule	75MG	Non-steroidal anti-inflammatory drug
00594466	INDOMETHACIN	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
00611158	INDOMETHACIN	Capsule	25MG	Non-steroidal anti-inflammatory drug
00611166	INDOMETHACIN	Capsule	50MG	Non-steroidal anti-inflammatory drug
00865850	INDOMETHACIN	Capsule	25MG	Non-steroidal anti-inflammatory drug
00865869	INDOMETHACIN	Capsule	50MG	Non-steroidal anti-inflammatory drug
01934139	INDOMETHACIN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
01934147	INDOMETHACIN	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02143364	INDOMETHACIN	Capsule	25MG	Non-steroidal anti-inflammatory drug
02143372	INDOMETHACIN	Capsule	50MG	Non-steroidal anti-inflammatory drug
02146932	INDOMETHACIN	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02146940	INDOMETHACIN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
02176130	INDOMETHACIN	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02176149	INDOMETHACIN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
02204541	INDOMETHACIN	Capsule	25MG	Non-steroidal anti-inflammatory drug
02204568	INDOMETHACIN	Capsule	50MG	Non-steroidal anti-inflammatory drug
02231799	INDOMETHACIN	Rectal suppository	50MG	Non-steroidal anti-inflammatory drug
02231800	INDOMETHACIN	Rectal	100MG	Non-steroidal anti-inflammatory

		suppository		drug
00336440	KETOPROFEN	Capsule	50MG	Non-steroidal anti-inflammatory drug
00499544	KETOPROFEN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
00566888	KETOPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
00663735	KETOPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
00761664	KETOPROFEN	Capsule	50MG	Non-steroidal anti-inflammatory drug
00761672	KETOPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
00761680	KETOPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
00761699	KETOPROFEN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
00790427	KETOPROFEN	Capsule	50MG	Non-steroidal anti-inflammatory drug
00790435	KETOPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
00817201	KETOPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
00842664	KETOPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
01913050	KETOPROFEN	Capsule	150MG	Non-steroidal anti-inflammatory drug
01913069	KETOPROFEN	Capsule	200MG	Non-steroidal anti-inflammatory drug
01926365	KETOPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
01926373	KETOPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
01926381	KETOPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
01926403	KETOPROFEN	Capsule	50MG	Non-steroidal anti-inflammatory drug
01926411	KETOPROFEN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
01981528	KETOPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
01981536	KETOPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
02015951	KETOPROFEN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug

02031175	KETOPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
02150808	KETOPROFEN	Capsule	50MG	Non-steroidal anti-inflammatory drug
02150816	KETOPROFEN	Tablet	50MG	Non-steroidal anti-inflammatory drug
02150824	KETOPROFEN	Tablet	100MG	Non-steroidal anti-inflammatory drug
02156083	KETOPROFEN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
02165481	KETOPROFEN	Rectal suppository	100MG	Non-steroidal anti-inflammatory drug
02172577	KETOPROFEN	Tablet	200MG	Non-steroidal anti-inflammatory drug
00864048	KETOROLAC TROMETHAMINE	Tablet	10MG	Non-steroidal anti-inflammatory drug
02162660	KETOROLAC TROMETHAMINE	Tablet	10MG	Non-steroidal anti-inflammatory drug
00155225	MEFENAMIC ACID	Capsule	250MG	Non-steroidal anti-inflammatory drug
02229452	MEFENAMIC ACID	Capsule	250MG	Non-steroidal anti-inflammatory drug
02229569	MEFENAMIC ACID	Capsule	250MG	Non-steroidal anti-inflammatory drug
02231208	MEFENAMIC ACID	Capsule	250MG	Non-steroidal anti-inflammatory drug
02242785	MELOXICAM	Tablet	7.5MG	Non-steroidal anti-inflammatory drug
02242786	MELOXICAM	Tablet	15MG	Non-steroidal anti-inflammatory drug
02247889	MELOXICAM	Tablet	7.5MG	Non-steroidal anti-inflammatory drug
02248031	MELOXICAM	Tablet	15MG	Non-steroidal anti-inflammatory drug
02248267	MELOXICAM	Tablet	7.5MG	Non-steroidal anti-inflammatory drug
02248268	MELOXICAM	Tablet	15MG	Non-steroidal anti-inflammatory drug
02248973	MELOXICAM	Tablet	7.5MG	Non-steroidal anti-inflammatory drug
02248974	MELOXICAM	Tablet	15MG	Non-steroidal anti-inflammatory drug
02250012	MELOXICAM	Tablet	7.5MG	Non-steroidal anti-inflammatory drug
02250020	MELOXICAM	Tablet	15MG	Non-steroidal anti-inflammatory

				drug
02255987	MELOXICAM	Tablet	7.5MG	Non-steroidal anti-inflammatory drug
02255995	MELOXICAM	Tablet	15MG	Non-steroidal anti-inflammatory drug
02258315	MELOXICAM	Tablet	7.5MG	Non-steroidal anti-inflammatory drug
02258323	MELOXICAM	Tablet	15MG	Non-steroidal anti-inflammatory drug
02083531	NABUMETONE	Tablet	500MG	Non-steroidal anti-inflammatory drug
02083558	NABUMETONE	Tablet	750MG	Non-steroidal anti-inflammatory drug
02238639	NABUMETONE	Tablet	500MG	Non-steroidal anti-inflammatory drug
02240867	NABUMETONE	Tablet	500MG	Non-steroidal anti-inflammatory drug
00299413	NAPROXEN	Tablet	125MG	Non-steroidal anti-inflammatory drug
00335193	NAPROXEN	Tablet	250MG	Non-steroidal anti-inflammatory drug
00522651	NAPROXEN	Tablet	250MG	Non-steroidal anti-inflammatory drug
00522678	NAPROXEN	Tablet	125MG	Non-steroidal anti-inflammatory drug
00525537	NAPROXEN	Tablet	500MG	Non-steroidal anti-inflammatory drug
00531022	NAPROXEN	Rectal suppository	500MG	Non-steroidal anti-inflammatory drug
00565350	NAPROXEN	Tablet	250MG	Non-steroidal anti-inflammatory drug
00565369	NAPROXEN	Tablet	125MG	Non-steroidal anti-inflammatory drug
00583367	NAPROXEN	Tablet	375MG	Non-steroidal anti-inflammatory drug
00587923	NAPROXEN	Oral suspension	25MG/ML	Non-steroidal anti-inflammatory drug
00589861	NAPROXEN	Tablet	500MG	Non-steroidal anti-inflammatory drug
00592277	NAPROXEN	Tablet	500MG	Non-steroidal anti-inflammatory drug
00600806	NAPROXEN	Tablet	375MG	Non-steroidal anti-inflammatory drug
00615307	NAPROXEN	Tablet	125MG	Non-steroidal anti-inflammatory drug

00615315	NAPROXEN	Tablet	250MG	Non-steroidal anti-inflammatory drug
00615323	NAPROXEN	Tablet	375MG	Non-steroidal anti-inflammatory drug
00615331	NAPROXEN	Tablet	500MG	Non-steroidal anti-inflammatory drug
00627097	NAPROXEN	Tablet	375MG	Non-steroidal anti-inflammatory drug
00756814	NAPROXEN	Rectal suppository	500MG	Non-steroidal anti-inflammatory drug
00788767	NAPROXEN	Tablet	750MG	Non-steroidal anti-inflammatory drug
00865621	NAPROXEN	Tablet	125MG	Non-steroidal anti-inflammatory drug
00865648	NAPROXEN	Tablet	250MG	Non-steroidal anti-inflammatory drug
00865656	NAPROXEN	Tablet	375MG	Non-steroidal anti-inflammatory drug
00865664	NAPROXEN	Tablet	500MG	Non-steroidal anti-inflammatory drug
02017237	NAPROXEN	Rectal suppository	500MG	Non-steroidal anti-inflammatory drug
02162415	NAPROXEN	Tablet	375MG	Non-steroidal anti-inflammatory drug
02162423	NAPROXEN	Tablet	500MG	Non-steroidal anti-inflammatory drug
02162431	NAPROXEN	Oral suspension	25MG/ML	Non-steroidal anti-inflammatory drug
02162458	NAPROXEN	Rectal suppository	500MG	Non-steroidal anti-inflammatory drug
02162474	NAPROXEN	Tablet	250MG	Non-steroidal anti-inflammatory drug
02162482	NAPROXEN	Tablet	375MG	Non-steroidal anti-inflammatory drug
02162490	NAPROXEN	Tablet	500MG	Non-steroidal anti-inflammatory drug
02177072	NAPROXEN	Tablet	750MG	Non-steroidal anti-inflammatory drug
02229690	NAPROXEN	Rectal suppository	500MG	Non-steroidal anti-inflammatory drug
02230477	NAPROXEN	Rectal suppository	500MG	Non-steroidal anti-inflammatory drug
02231327	NAPROXEN	Tablet	750MG	Non-steroidal anti-inflammatory drug
00491772	NAPROXEN SODIUM	Tablet	275MG	Non-steroidal anti-inflammatory

				drug
02027860	OXAPROZIN	Caplet	600MG	Non-steroidal anti-inflammatory drug
00010502	PHENYLBUTAZONE	Tablet	100MG	Non-steroidal anti-inflammatory drug
00021660	PHENYLBUTAZONE	Tablet	100MG	Non-steroidal anti-inflammatory drug
00093041	PHENYLBUTAZONE	Tablet	100MG	Non-steroidal anti-inflammatory drug
00258377	PHENYLBUTAZONE	Tablet	100MG	Non-steroidal anti-inflammatory drug
00312789	PHENYLBUTAZONE	Tablet	100MG	Non-steroidal anti-inflammatory drug
00525596	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
00525618	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
00632708	PIROXICAM	Rectal suppository	10MG	Non-steroidal anti-inflammatory drug
00632716	PIROXICAM	Rectal suppository	20MG	Non-steroidal anti-inflammatory drug
00642886	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
00642894	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
00695696	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
00695718	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
00836230	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
00836249	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
00865761	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
00865788	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
02139952	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
02139960	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
02144212	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
02144220	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug

02154420	PIROXICAM	Rectal suppository	10MG	Non-steroidal anti-inflammatory drug
02154463	PIROXICAM	Rectal suppository	20MG	Non-steroidal anti-inflammatory drug
02171813	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
02171821	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
02230066	PIROXICAM	Capsule	10MG	Non-steroidal anti-inflammatory drug
02230067	PIROXICAM	Capsule	20MG	Non-steroidal anti-inflammatory drug
02238028	PIROXICAM	Rectal suppository	20MG	Non-steroidal anti-inflammatory drug
00432369	SULINDAC	Tablet	200MG	Non-steroidal anti-inflammatory drug
00456888	SULINDAC	Tablet	150MG	Non-steroidal anti-inflammatory drug
00745588	SULINDAC	Tablet	150MG	Non-steroidal anti-inflammatory drug
00745596	SULINDAC	Tablet	200MG	Non-steroidal anti-inflammatory drug
00778354	SULINDAC	Tablet	150MG	Non-steroidal anti-inflammatory drug
00778362	SULINDAC	Tablet	200MG	Non-steroidal anti-inflammatory drug
02042576	SULINDAC	Tablet	150MG	Non-steroidal anti-inflammatory drug
02042584	SULINDAC	Tablet	200MG	Non-steroidal anti-inflammatory drug
00884367	TENOXICAM	Tablet	20MG	Non-steroidal anti-inflammatory drug
00589926	TIAPROFENIC ACID	Tablet	200MG	Non-steroidal anti-inflammatory drug
00589934	TIAPROFENIC ACID	Tablet	300MG	Non-steroidal anti-inflammatory drug
00893714	TIAPROFENIC ACID	Capsule	300MG	Non-steroidal anti-inflammatory drug
01924613	TIAPROFENIC ACID	Tablet	200MG	Non-steroidal anti-inflammatory drug
01924621	TIAPROFENIC ACID	Tablet	300MG	Non-steroidal anti-inflammatory drug
01989774	TIAPROFENIC ACID	Tablet	300MG	Non-steroidal anti-inflammatory drug
01989782	TIAPROFENIC ACID	Tablet	200MG	Non-steroidal anti-inflammatory

				drug
01989790	TIAPROFENIC ACID	Capsule	300MG	Non-steroidal anti-inflammatory drug
02136112	TIAPROFENIC ACID	Tablet	200MG	Non-steroidal anti-inflammatory drug
02136120	TIAPROFENIC ACID	Tablet	300MG	Non-steroidal anti-inflammatory drug
02179679	TIAPROFENIC ACID	Tablet	200MG	Non-steroidal anti-inflammatory drug
02179687	TIAPROFENIC ACID	Tablet	300MG	Non-steroidal anti-inflammatory drug
02221950	TIAPROFENIC ACID	Tablet	300MG	Non-steroidal anti-inflammatory drug
02221969	TIAPROFENIC ACID	Capsule	300MG	Non-steroidal anti-inflammatory drug
02230827	TIAPROFENIC ACID	Tablet	200MG	Non-steroidal anti-inflammatory drug
02230828	TIAPROFENIC ACID	Tablet	300MG	Non-steroidal anti-inflammatory drug
00364126	TOLMETIN SODIUM	Tablet	200MG	Non-steroidal anti-inflammatory drug
00484938	TOLMETIN SODIUM	Capsule	400MG	Non-steroidal anti-inflammatory drug
00632740	TOLMETIN SODIUM	Tablet	600MG	Non-steroidal anti-inflammatory drug
02076233	TOLMETIN SODIUM	Capsule	400MG	Non-steroidal anti-inflammatory drug
02239941	CELECOXIB	Capsule	100MG	COX-2 INHIBITOR
02239942	CELECOXIB	Capsule	200MG	COX-2 INHIBITOR
02241107	ROFECOXIB	Tablet	12.5MG	COX-2 INHIBITOR
02241108	ROFECOXIB	Tablet	25MG	COX-2 INHIBITOR
02241109	ROFECOXIB	Oral suspension	12.5MG/5ML	COX-2 INHIBITOR
02246621	VALDECOXIB	Tablet	10MG	COX-2 INHIBITOR
02246622	VALDECOXIB	Tablet	20MG	COX-2 INHIBITOR
10332	ASA	Tablet		Aspirin-based
10340	ASA	Tablet		Aspirin-based
36145	ASA	Tablet		Aspirin-based
40851	ASA	Tablet		Aspirin-based
92754	ASA	Tablet		Aspirin-based
95508	ASA & CAFFEINE & CODEINE	Tablet		Aspirin-based
95516	ASA & CAFFEINE & CODEINE	Tablet		Aspirin-based
108103	ASA & CAFFEINE &	Tablet		Aspirin-based

	CODEINE			
176192	ASA & CAFFEINE & CODEINE & BUTALBITAL	Capsule		Aspirin-based
176206	ASA & CAFFEINE & CODEINE & BUTALBITAL	Capsule		Aspirin-based
216666	ASA	Tablet		Aspirin-based
219843	ASA & CAFFEINE & CODEINE	Tablet		Aspirin-based
226327	ASA & CAFFEINE & BUTALBITAL	Capsule		Aspirin-based
229296	ASA	Tablet		Aspirin-based
275328	ASA & CAFFEINE & BUTALBITAL	Tablet		Aspirin-based
315117	ASA	Rectal suppository		Aspirin-based
315133	ASA	Rectal suppository		Aspirin-based
377961	ASA	Rectal suppository		Aspirin-based
406104	ASA & CODEINE PHOSPHATE	Tablet		Aspirin-based
406112	ASA & CODEINE PHOSPHATE	Tablet		Aspirin-based
419508	ASA	Tablet		Aspirin-based
451738	ASA	Rectal suppository		Aspirin-based
451746	ASA	Rectal suppository		Aspirin-based
604496	ASA & CAFFEINE & CODEINE	Tablet		Aspirin-based
604518	ASA & CAFFEINE & CODEINE	Tablet		Aspirin-based
785547	ASA	Rectal suppository		Aspirin-based
1905392	ASA	Caplet		Aspirin-based
2027917	SALSALATE	Tablet		Aspirin-based
2046253	ASA	Tablet		Aspirin-based
2150352	ASA	Tablet		Aspirin-based
2208156	ASA	Tablet		Aspirin-based
2237726	ASA	Tablet		Aspirin-based
2238645	ASA & CAFFEINE & CODEINE	Tablet		Aspirin-based
2242281	ASA	Tablet		Aspirin-based

9857146	ASA	Tablet		Aspirin-based
9857147	ASA	Tablet		Aspirin-based
608203	ASA & CAFFEINE & CODEINE & BUTALBITAL	Capsule		Aspirin-based
574392	OXYCODONE & ASA	Tablet		Aspirin-based
580236	OXYCODONE & ASA	Tablet		Aspirin-based
608157	OXYCODONE & ASA	Tablet		Aspirin-based
1916483	OXYCODONE & ASA	Tablet		Aspirin-based
2237701	TICLOPIDINE HCL	Tablet		Aspirin-based
2239744	TICLOPIDINE HCL	Tablet		Aspirin-based
2236848	TICLOPIDINE HCL	Tablet		Aspirin-based
2237560	TICLOPIDINE HCL	Tablet		Aspirin-based
2243587	TICLOPIDINE HCL	Tablet		Aspirin-based
2162776	TICLOPIDINE HCL	Tablet		Aspirin-based
895644	DIPYRIDAMOLE	Tablet		Aspirin-based
00067385	DIPYRIDAMOLE	Tablet		Aspirin-based
895652	DIPYRIDAMOLE	Tablet		Aspirin-based
67393	DIPYRIDAMOLE	Tablet		Aspirin-based
895660	DIPYRIDAMOLE	Tablet		Aspirin-based
452092	DIPYRIDAMOLE	Tablet		Aspirin-based
2242119	DIPYRIDAMOLE & ACETYLSALICYLIC ACID	Capsule		Aspirin-based
2238682	CLOPIDOGREL BISULFATE	Tablet		Aspirin-based
00013668	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00277193	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00291412	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00293482	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00330876	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00361046	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00373710	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00374148	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00389218	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00446114	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00482323	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00522511	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00524891	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00544981	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00545007	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00553328	ACETAMINOPHEN	Rectal suppository	120MG	Acetaminophen-based
00553336	ACETAMINOPHEN	Rectal	650MG	Acetaminophen-based

		suppository		
00559393	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00567663	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00589233	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00589241	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
00594814	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00631353	ACETAMINOPHEN	Oral drops	80MG/ML	Acetaminophen-based
00642401	ACETAMINOPHEN	Oral liquid	80MG/ML	Acetaminophen-based
00646156	ACETAMINOPHEN	Rectal suppository	325MG	Acetaminophen-based
00658049	ACETAMINOPHEN	Oral liquid	16MG/ML	Acetaminophen-based
01919385	ACETAMINOPHEN	Rectal suppository	120MG	Acetaminophen-based
01919393	ACETAMINOPHEN	Rectal suppository	325MG	Acetaminophen-based
01919407	ACETAMINOPHEN	Rectal suppository	650MG	Acetaminophen-based
01928244	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
01928260	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
01934805	ACETAMINOPHEN	Oral liquid	80MG/5ML	Acetaminophen-based
02027801	ACETAMINOPHEN	Oral liquid	80MG/ML	Acetaminophen-based
02046660	ACETAMINOPHEN	Rectal suppository	120MG	Acetaminophen-based
02046687	ACETAMINOPHEN	Rectal suppository	325MG	Acetaminophen-based
02046695	ACETAMINOPHEN	Rectal suppository	650MG	Acetaminophen-based
02230434	ACETAMINOPHEN	Rectal suppository	120MG	Acetaminophen-based
02230436	ACETAMINOPHEN	Rectal suppository	325MG	Acetaminophen-based
02230437	ACETAMINOPHEN	Rectal suppository	650MG	Acetaminophen-based
09857143	ACETAMINOPHEN	Tablet	325MG	Acetaminophen-based
09857144	ACETAMINOPHEN	Tablet	500MG	Acetaminophen-based
00293504	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	325MG & 30MG & 15MG	Acetaminophen-based
00293512	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	325MG & 30MG & 30MG	Acetaminophen-based
00372331	ACETAMINOPHEN & CAFFEINE &	Tablet	300MG & 30MG &	Acetaminophen-based

	CODEINE PHOSPHATE		15MG	
00372358	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 30MG & 30MG	Acetaminophen-based
00425370	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 15MG	Acetaminophen-based
00425389	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 30MG	Acetaminophen-based
00653241	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 15MG	Acetaminophen-based
00653276	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 30MG	Acetaminophen-based
00687200	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 15MG	Acetaminophen-based
00687219	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 30MG	Acetaminophen-based
02163926	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 30MG	Acetaminophen-based
02163934	ACETAMINOPHEN & CAFFEINE & CODEINE PHOSPHATE	Tablet	300MG & 15MG & 15MG	Acetaminophen-based
00396516	ACETAMINOPHEN & CODEINE PHOSPHATE	Tablet	300MG & 60MG	Acetaminophen-based
00608882	ACETAMINOPHEN & CODEINE PHOSPHATE	Tablet	300MG & 30MG	Acetaminophen-based
00621463	ACETAMINOPHEN &	Tablet	300MG &	Acetaminophen-based

	CODEINE PHOSPHATE		60MG	
00666130	ACETAMINOPHEN & CODEINE PHOSPHATE	Tablet	300MG & 30MG	Acetaminophen-based
00666149	ACETAMINOPHEN & CODEINE PHOSPHATE	Tablet	300MG & 60MG	Acetaminophen-based
00685143	ACETAMINOPHEN & CODEINE PHOSPHATE	Oral liquid	160MG & 8MG/5ML	Acetaminophen-based
00816027	ACETAMINOPHEN & CODEINE PHOSPHATE	Oral elixir	160MG & 8MG/5ML	Acetaminophen-based
02163918	ACETAMINOPHEN & CODEINE PHOSPHATE	Tablet	300MG & 60MG	Acetaminophen-based
02163942	ACETAMINOPHEN & CODEINE PHOSPHATE	Oral elixir	160MG & 8MG/5ML	Acetaminophen-based
00574384	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
00580201	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
00608165	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
01916475	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
01916548	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
02245758	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
02307898	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
02324628	OXYCODONE & Acetaminophen	Tablet	5MG & 325MG	Acetaminophen-based
00421480	SULFAMETHOXAZOLE	Tablet	500MG	Antibiotic
00013412	SULFAMETHOXAZOLE & PHENAZOPYRIDINE HCL	Tablet	500MG	Antibiotic
00270636	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	400MG & 80MG	Antibiotic

00270644	SULFAMETHOXAZOLE & TRIMETHOPRIM	Oral suspension	40MG & 8MG/ML	Antibiotic
00272469	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	400MG & 80MG	Antibiotic
00272485	SULFAMETHOXAZOLE & TRIMETHOPRIM	Oral suspension	40MG & 8MG/ML	Antibiotic
00368040	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	800MG & 160MG	Antibiotic
00371823	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	800MG & 160MG	Antibiotic
00445274	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	400MG & 80MG	Antibiotic
00445282	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	800MG & 160MG	Antibiotic
00510637	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	400MG & 80MG	Antibiotic
00510645	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	800MG & 160MG	Antibiotic
00516759	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	400MG & 80MG	Antibiotic
00516767	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	800MG & 160MG	Antibiotic
00550078	SULFAMETHOXAZOLE & TRIMETHOPRIM	Injectable solution	80MG/ML & 16MG/ML	Antibiotic
00726540	SULFAMETHOXAZOLE & TRIMETHOPRIM	Oral suspension	40MG & 8MG/ML	Antibiotic
00846465	SULFAMETHOXAZOLE & TRIMETHOPRIM	Oral suspension	40MG & 8MG/ML	Antibiotic
00865710	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	400MG & 80MG	Antibiotic

00865729	SULFAMETHOXAZOLE & TRIMETHOPRIM	Tablet	800MG & 160MG	Antibiotic
00865753	SULFAMETHOXAZOLE & TRIMETHOPRIM	Oral suspension	40MG & 8MG/ML	Antibiotic
00397474	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
00487872	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
00546232	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
00546240	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
00563560	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
00563579	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
00563587	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
00568449	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
00582409	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
00582417	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
00584215	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
00584282	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
00600059	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
00600067	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
00603678	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
00603686	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
00618616	CIMETIDINE	Tablet	800MG	Histamine-2 receptor antagonist
00653411	CIMETIDINE	Tablet	800MG	Histamine-2 receptor antagonist
00663727	CIMETIDINE	Tablet	800MG	Histamine-2 receptor antagonist
00749494	CIMETIDINE	Tablet	800MG	Histamine-2 receptor antagonist
00865796	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
00865818	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
00865826	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
00865834	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
01916769	CIMETIDINE	Tablet	800MG	Histamine-2 receptor antagonist
01916777	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
01916785	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
01916793	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
01916815	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
02227436	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
02227444	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
02227452	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
02227460	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
02229717	CIMETIDINE	Tablet	200MG	Histamine-2 receptor antagonist
02229718	CIMETIDINE	Tablet	300MG	Histamine-2 receptor antagonist
02229719	CIMETIDINE	Tablet	400MG	Histamine-2 receptor antagonist
02229720	CIMETIDINE	Tablet	600MG	Histamine-2 receptor antagonist
02229721	CIMETIDINE	Tablet	800MG	Histamine-2 receptor antagonist

00397482	CIMETIDINE HYDROCHLORIDE	Oral liquid	60MG/ML	Histamine-2 receptor antagonist
01916750	CIMETIDINE HYDROCHLORIDE	Oral liquid	60MG/ML	Histamine-2 receptor antagonist
02243085	CIMETIDINE HYDROCHLORIDE	Oral liquid	300MG/5ML	Histamine-2 receptor antagonist
00710113	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
00710121	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
00728128	FAMOTIDINE	Injectable solution	10MG/ML	Histamine-2 receptor antagonist
01953834	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
01953842	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
02022133	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
02022141	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
02024195	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
02024209	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
02196018	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
02196026	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
02237148	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
02237149	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
02240622	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
02240623	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
02242327	FAMOTIDINE	Tablet	20MG	Histamine-2 receptor antagonist
02242328	FAMOTIDINE	Tablet	40MG	Histamine-2 receptor antagonist
00778338	NIZATIDINE	Capsule	150MG	Histamine-2 receptor antagonist
00778346	NIZATIDINE	Capsule	300MG	Histamine-2 receptor antagonist
02177714	NIZATIDINE	Capsule	150MG	Histamine-2 receptor antagonist
02177722	NIZATIDINE	Capsule	300MG	Histamine-2 receptor antagonist
02220156	NIZATIDINE	Capsule	150MG	Histamine-2 receptor antagonist
02220164	NIZATIDINE	Capsule	300MG	Histamine-2 receptor antagonist
02240457	NIZATIDINE	Capsule	150MG	Histamine-2 receptor antagonist
02240458	NIZATIDINE	Capsule	300MG	Histamine-2 receptor antagonist
02246046	NIZATIDINE	Capsule	150MG	Histamine-2 receptor antagonist
02246047	NIZATIDINE	Capsule	300MG	Histamine-2 receptor antagonist
02231831	RANITIDINE BISMUTH CITRATE	Tablet	400MG	Histamine-2 receptor antagonist
00553379	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
00603791	RANITIDINE HCL	Injectable solution	25MG/ML	Histamine-2 receptor antagonist
00641790	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
00733059	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
00733067	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
00782386	RANITIDINE HCL	Oral liquid	15MG/ML	Histamine-2 receptor antagonist
00828556	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist

00828564	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
00828688	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
00828823	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
00865737	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
00865745	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
00905992	RANITIDINE HCL	Oral liquid	15MG/ML	Histamine-2 receptor antagonist
02207761	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
02207788	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
02212331	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
02212358	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
02212366	RANITIDINE HCL	Injectable solution	25MG/ML	Histamine-2 receptor antagonist
02212374	RANITIDINE HCL	Oral liquid	15MG/ML	Histamine-2 receptor antagonist
02230003	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
02230004	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
02241598	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
02241599	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
02242453	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
02242454	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
02242940	RANITIDINE HCL	Oral liquid	15MG/ML	Histamine-2 receptor antagonist
02243229	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
02243230	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
02248570	RANITIDINE HCL	Tablet	150MG	Histamine-2 receptor antagonist
02248571	RANITIDINE HCL	Tablet	300MG	Histamine-2 receptor antagonist
02280833	RANITIDINE HCL	Oral liquid	15MG/ML	Histamine-2 receptor antagonist
02244522	ESOMEPRAZOLE MAGNESIUM TRIHYDRATE	Tablet	40MG	Proton pump inhibitor
02165503	LANSOPRAZOLE	Capsule	15MG	Proton pump inhibitor
02165511	LANSOPRAZOLE	Capsule	30MG	Proton pump inhibitor
02249472	LANSOPRAZOLE	Tablet	30MG	Proton pump inhibitor
02280515	LANSOPRAZOLE	Capsule	15MG	Proton pump inhibitor
02280523	LANSOPRAZOLE	Capsule	30MG	Proton pump inhibitor
02293811	LANSOPRAZOLE	Capsule	15MG	Proton pump inhibitor
02293838	LANSOPRAZOLE	Capsule	30MG	Proton pump inhibitor
00846503	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
02119579	OMEPRAZOLE MAGNESIUM	Capsule	10MG	Proton pump inhibitor
02190915	OMEPRAZOLE MAGNESIUM	Tablet	20MG	Proton pump inhibitor
02230737	OMEPRAZOLE MAGNESIUM	Tablet	10MG	Proton pump inhibitor
02245058	OMEPRAZOLE	Capsule	20MG	Proton pump inhibitor

	MAGNESIUM			
02260867	OMEPRAZOLE MAGNESIUM	Tablet	20MG	Proton pump inhibitor
02296446	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
02320851	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
02329433	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
09857195	OMEPRAZOLE MAGNESIUM	Tablet	20MG	Proton pump inhibitor
09857267	OMEPRAZOLE MAGNESIUM	Tablet	20MG	Proton pump inhibitor
09857285	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
09857314	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
09857341	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
09857342	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
09857343	OMEPRAZOLE MAGNESIUM	Capsule	20MG	Proton pump inhibitor
00239616	PANTOPRAZOLE	Injectable solution	40MG/VIAL	Proton pump inhibitor
02229453	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02239616	PANTOPRAZOLE	Injectable solution	40MG/VIAL	Proton pump inhibitor
02285487	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02292920	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02299585	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02300486	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02301083	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02305046	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02307871	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02308703	PANTOPRAZOLE	Tablet	40MG	Proton pump inhibitor
02243796	RABEPRAZOLE SODIUM	Tablet	10MG	Proton pump inhibitor
02243797	RABEPRAZOLE SODIUM	Tablet	20MG	Proton pump inhibitor
02296632	RABEPRAZOLE SODIUM	Tablet	10MG	Proton pump inhibitor
02296640	RABEPRAZOLE SODIUM	Tablet	20MG	Proton pump inhibitor
02298074	RABEPRAZOLE	Tablet	10MG	Proton pump inhibitor

	SODIUM			
02298082	RABEPRAZOLE SODIUM	Tablet	20MG	Proton pump inhibitor
02310805	RABEPRAZOLE SODIUM	Tablet	10MG	Proton pump inhibitor
02310813	RABEPRAZOLE SODIUM	Tablet	20MG	Proton pump inhibitor
02314177	RABEPRAZOLE SODIUM	Tablet	10MG	Proton pump inhibitor
02314185	RABEPRAZOLE SODIUM	Tablet	20MG	Proton pump inhibitor
00632600	MISOPROSTOL	Tablet	200MCG	Other gastroprotective agents
00813966	MISOPROSTOL	Tablet	100MCG	Other gastroprotective agents
02240754	MISOPROSTOL	Tablet	100MCG	Other gastroprotective agents
02240755	MISOPROSTOL	Tablet	200MCG	Other gastroprotective agents
02244022	MISOPROSTOL	Tablet	100MCG	Other gastroprotective agents
02244023	MISOPROSTOL	Tablet	200MCG	Other gastroprotective agents
02244125	MISOPROSTOL	Tablet	0.2MG	Other gastroprotective agents
00506346	SUCRALFATE	Tablet	1G	Other gastroprotective agents
00836370	SUCRALFATE	Oral liquid	100MG/ML	Other gastroprotective agents
01924699	SUCRALFATE	Oral suspension	200MG	Other gastroprotective agents
02045702	SUCRALFATE	Tablet	1G	Other gastroprotective agents
02100622	SUCRALFATE	Tablet	1G	Other gastroprotective agents
02103567	SUCRALFATE	Oral suspension	200MG	Other gastroprotective agents
02125250	SUCRALFATE	Tablet	1G	Other gastroprotective agents
02134829	SUCRALFATE	Tablet	1G	Other gastroprotective agents
02238209	SUCRALFATE	Tablet	1G	Other gastroprotective agents
02239607	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02239608	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02246056	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02246057	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02246594	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02246595	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02248010	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02248011	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor

02248050	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02248051	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02248170	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02248171	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02251558	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02251566	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02252112	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02252120	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02285622	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02285630	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02293218	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02293226	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02304686	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02304694	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02306239	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02306247	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02313405	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02313413	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
02322781	CITALOPRAM HYDROBROMIDE	Tablet	20MG	Selective serotonin receptor inhibitor
02322803	CITALOPRAM HYDROBROMIDE	Tablet	40MG	Selective serotonin receptor inhibitor
09854539	CITALOPRAM HYDROBROMIDE	Rectal suppository	20MG	Selective serotonin receptor inhibitor
02263238	ESCITALOPRAM OXALATE	Tablet	10MG	Selective serotonin receptor inhibitor
02263254	ESCITALOPRAM	Tablet	20MG	Selective serotonin receptor

	OXALATE			inhibitor
00636622	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
01917021	FLUOXETINE HCL	Oral liquid	20MG/5ML	Selective serotonin receptor inhibitor
02018985	FLUOXETINE HCL	Capsule	10MG	Selective serotonin receptor inhibitor
02177579	FLUOXETINE HCL	Capsule	10MG	Selective serotonin receptor inhibitor
02177587	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
02192764	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
02216353	FLUOXETINE HCL	Capsule	10MG	Selective serotonin receptor inhibitor
02216361	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
02216582	FLUOXETINE HCL	Capsule	10MG	Selective serotonin receptor inhibitor
02216590	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
02231328	FLUOXETINE HCL	Oral liquid	20MG/5ML	Selective serotonin receptor inhibitor
02237814	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
02241371	FLUOXETINE HCL	Capsule	10MG	Selective serotonin receptor inhibitor
02241374	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
02242177	FLUOXETINE HCL	Capsule	10MG	Selective serotonin receptor inhibitor
02242178	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
02243486	FLUOXETINE HCL	Capsule	10MG	Selective serotonin receptor inhibitor
02243487	FLUOXETINE HCL	Capsule	20MG	Selective serotonin receptor inhibitor
01919342	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
01919369	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02218453	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02218461	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor

02231192	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02231193	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02231329	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02231330	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02239953	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02239954	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02240682	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02240683	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02240849	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02240850	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02247054	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02247055	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02255529	FLUVOXAMINE MALEATE	Tablet	50MG	Selective serotonin receptor inhibitor
02255537	FLUVOXAMINE MALEATE	Tablet	100MG	Selective serotonin receptor inhibitor
02087294	NEFAZODONE HCL	Tablet	50MG	Selective serotonin receptor inhibitor
02087375	NEFAZODONE HCL	Tablet	100MG	Selective serotonin receptor inhibitor
02087383	NEFAZODONE HCL	Tablet	150MG	Selective serotonin receptor inhibitor
02087391	NEFAZODONE HCL	Tablet	200MG	Selective serotonin receptor inhibitor
02237398	NEFAZODONE HCL	Tablet	100MG	Selective serotonin receptor inhibitor
02237399	NEFAZODONE HCL	Tablet	150MG	Selective serotonin receptor inhibitor
02237400	NEFAZODONE HCL	Tablet	200MG	Selective serotonin receptor inhibitor
02242823	NEFAZODONE HCL	Tablet	100MG	Selective serotonin receptor inhibitor
02242824	NEFAZODONE HCL	Tablet	150MG	Selective serotonin receptor

				inhibitor
02242825	NEFAZODONE HCL	Tablet	200MG	Selective serotonin receptor inhibitor
02245102	NEFAZODONE HCL	Tablet	100MG	Selective serotonin receptor inhibitor
02245103	NEFAZODONE HCL	Tablet	150MG	Selective serotonin receptor inhibitor
02245111	NEFAZODONE HCL	Tablet	200MG	Selective serotonin receptor inhibitor
02245203	NEFAZODONE HCL	Tablet	100MG	Selective serotonin receptor inhibitor
02245204	NEFAZODONE HCL	Tablet	150MG	Selective serotonin receptor inhibitor
02245205	NEFAZODONE HCL	Tablet	200MG	Selective serotonin receptor inhibitor
02245435	NEFAZODONE HCL	Tablet	100MG	Selective serotonin receptor inhibitor
02245436	NEFAZODONE HCL	Tablet	150MG	Selective serotonin receptor inhibitor
02245437	NEFAZODONE HCL	Tablet	200MG	Selective serotonin receptor inhibitor
01940473	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
01940481	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02027887	PAROXETINE HCL	Tablet	10MG	Selective serotonin receptor inhibitor
02240907	PAROXETINE HCL	Tablet	10MG	Selective serotonin receptor inhibitor
02240908	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02240909	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
02247751	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02247752	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
02247811	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02247812	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
02248012	PAROXETINE HCL	Tablet	10MG	Selective serotonin receptor inhibitor
02248013	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor

02248014	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
02248557	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02248558	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
02254751	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02254778	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
02262754	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02262762	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
02269430	PAROXETINE HCL	Tablet	20MG	Selective serotonin receptor inhibitor
02269449	PAROXETINE HCL	Tablet	30MG	Selective serotonin receptor inhibitor
01962779	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
01962817	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
02132702	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02238280	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02238281	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
02238282	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
02240481	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
02240484	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
02240485	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02242519	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02242520	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
02242521	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
02244838	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02244839	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor

				inhibitor
02244840	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
02245159	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02245160	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
02245161	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
02245787	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02245788	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
02245789	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
02287390	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
02287404	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
02287412	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
09854126	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
09854134	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
09854142	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
09854410	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
09854428	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
09854436	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
09857435	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
09857443	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
09857451	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor
09857460	SERTRALINE HCL	Capsule	25MG	Selective serotonin receptor inhibitor
09857478	SERTRALINE HCL	Capsule	50MG	Selective serotonin receptor inhibitor
09857486	SERTRALINE HCL	Capsule	100MG	Selective serotonin receptor inhibitor

02103680	VENLAFAXINE HCL	Tablet	37.5MG	Selective serotonin receptor inhibitor
02103702	VENLAFAXINE HCL	Tablet	75MG	Selective serotonin receptor inhibitor
02237279	VENLAFAXINE HCL	Capsule	37.5MG	Selective serotonin receptor inhibitor
02237280	VENLAFAXINE HCL	Capsule	75MG	Selective serotonin receptor inhibitor
02237282	VENLAFAXINE HCL	Capsule	150MG	Selective serotonin receptor inhibitor
02273969	VENLAFAXINE HCL	Capsule	37.5MG	Selective serotonin receptor inhibitor
02273977	VENLAFAXINE HCL	Capsule	75MG	Selective serotonin receptor inhibitor
02273985	VENLAFAXINE HCL	Capsule	150MG	Selective serotonin receptor inhibitor
02275023	VENLAFAXINE HCL	Capsule	37.5MG	Selective serotonin receptor inhibitor
02275031	VENLAFAXINE HCL	Capsule	75MG	Selective serotonin receptor inhibitor
02275058	VENLAFAXINE HCL	Capsule	150MG	Selective serotonin receptor inhibitor
02278545	VENLAFAXINE HCL	Capsule	37.5MG	Selective serotonin receptor inhibitor
02278553	VENLAFAXINE HCL	Capsule	75MG	Selective serotonin receptor inhibitor
02278561	VENLAFAXINE HCL	Capsule	150MG	Selective serotonin receptor inhibitor
02304317	VENLAFAXINE HCL	Capsule	37.5MG	Selective serotonin receptor inhibitor
02304325	VENLAFAXINE HCL	Capsule	75MG	Selective serotonin receptor inhibitor
02304333	VENLAFAXINE HCL	Capsule	150MG	Selective serotonin receptor inhibitor
02310279	VENLAFAXINE HCL	Capsule	37.5MG	Selective serotonin receptor inhibitor
02310287	VENLAFAXINE HCL	Capsule	75MG	Selective serotonin receptor inhibitor
02310295	VENLAFAXINE HCL	Capsule	150MG	Selective serotonin receptor inhibitor
02310317	VENLAFAXINE HCL	Capsule	37.5MG	Selective serotonin receptor inhibitor
02310325	VENLAFAXINE HCL	Capsule	75MG	Selective serotonin receptor inhibitor
02310333	VENLAFAXINE HCL	Capsule	150MG	Selective serotonin receptor

				inhibitor
02237334	CIPROFLOXACIN	Injectable solution	2MG/ML	Fluoroquinolone
02237514	CIPROFLOXACIN	Oral suspension	10G/100ML	Fluoroquinolone
00817163	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
00817171	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
00817198	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02155931	CIPROFLOXACIN HCL	Tablet	100MG	Fluoroquinolone
02155958	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02155966	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02155974	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02161737	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02161745	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02161753	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02229521	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02229522	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02229523	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02245647	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02245648	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02245649	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02246825	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02246826	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02246827	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02247339	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone

02247340	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02247341	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02247916	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02248437	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02248438	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02248439	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02248756	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02248757	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02248758	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02251787	CIPROFLOXACIN HCL	Tablet	1000MG	Fluoroquinolone
02266962	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02266970	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02267934	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02267942	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02267950	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02303728	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02303736	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02303744	CIPROFLOXACIN HCL	Tablet	750MG	Fluoroquinolone
02332132	CIPROFLOXACIN HCL	Tablet	250MG	Fluoroquinolone
02332140	CIPROFLOXACIN HCL	Tablet	500MG	Fluoroquinolone
02236839	LEVOFLOXACIN	Injectable solution	5MG/ML	Fluoroquinolone
02236841	LEVOFLOXACIN	Tablet	250MG	Fluoroquinolone
02236842	LEVOFLOXACIN	Tablet	500MG	Fluoroquinolone
02248262	LEVOFLOXACIN	Tablet	250MG	Fluoroquinolone

02248263	LEVOFLOXACIN	Tablet	500MG	Fluoroquinolone
02284677	LEVOFLOXACIN	Tablet	250MG	Fluoroquinolone
02284685	LEVOFLOXACIN	Tablet	500MG	Fluoroquinolone
02284707	LEVOFLOXACIN	Tablet	250MG	Fluoroquinolone
02284715	LEVOFLOXACIN	Tablet	500MG	Fluoroquinolone
02298635	LEVOFLOXACIN	Tablet	250MG	Fluoroquinolone
02298643	LEVOFLOXACIN	Tablet	500MG	Fluoroquinolone
02313979	LEVOFLOXACIN	Tablet	250MG	Fluoroquinolone
02313987	LEVOFLOXACIN	Tablet	500MG	Fluoroquinolone
02315424	LEVOFLOXACIN	Tablet	250MG	Fluoroquinolone
02315432	LEVOFLOXACIN	Tablet	500MG	Fluoroquinolone
02242965	MOXIFLOXACIN HCL	Tablet	400MG	Fluoroquinolone
00643025	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02229524	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02237682	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02246596	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02269627	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
00643025	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02229524	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02237682	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02246596	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02269627	NORFLOXACIN	Tablet	400MG	Fluoroquinolone
02243182	GATIFLOXACIN	Tablet	400MG	Fluoroquinolone
02237735	GREPAFLOXACIN HCL	Tablet	200MG	Fluoroquinolone
00028185	BETAMETHASONE	Tablet	.5MG	Corticosteroid
00028096	BETAMETHASONE SODIUM PHOSPHATE	Injectable solution	3MG & 3MG/ML	Corticosteroid
00036366	BETAMETHASONE SODIUM PHOSPHATE	Tablet	.5MG	Corticosteroid
00212385	BETAMETHASONE SODIUM PHOSPHATE	Oral pllets	.1MG	Corticosteroid
02060884	BETAMETHASONE SODIUM PHOSPHATE	Enema	.05MG	Corticosteroid
02052431	BUDESONIDE & SODIUM CHLORIDE	Enema	.02MG/ML	Corticosteroid
02229293	BUDESONIDE & SODIUM CHLORIDE	Capsule	3MG	Corticosteroid
00584711	CORTICOTROPIN	Injectable solution	40U	Corticosteroid
00584738	CORTICOTROPIN	Injectable solution	40U/5ML	Corticosteroid
00721107	CORTICOTROPIN	Injectable solution	40U/ML	Corticosteroid
09900004	CORTICOTROPIN	Injectable	80U/ML	Corticosteroid

		solution		
00016438	CORTISONE ACETATE	Tablet	5MG	Corticosteroid
00016446	CORTISONE ACETATE	Tablet	25MG	Corticosteroid
00249963	CORTISONE ACETATE	Tablet	25MG	Corticosteroid
00280437	CORTISONE ACETATE	Tablet	25MG	Corticosteroid
09854537	CORTISONE ACETATE	Tablet	5MG	Corticosteroid
00016462	DEXAMETHASONE	Tablet	.5MG	Corticosteroid
00213624	DEXAMETHASONE	Injectable solution	4MG/ML	Corticosteroid
00269026	DEXAMETHASONE	Injectable solution	4MG/ML	Corticosteroid
00285471	DEXAMETHASONE	Tablet	.75MG	Corticosteroid
00295094	DEXAMETHASONE	Tablet	.5MG	Corticosteroid
00349100	DEXAMETHASONE	Tablet	4MG	Corticosteroid
00354309	DEXAMETHASONE	Tablet	4MG	Corticosteroid
00489158	DEXAMETHASONE	Tablet	4MG	Corticosteroid
00501050	DEXAMETHASONE	Tablet	.5MG	Corticosteroid
00504416	DEXAMETHASONE	Tablet	4MG	Corticosteroid
00664227	DEXAMETHASONE	Injectable solution	4MG/ML	Corticosteroid
01964070	DEXAMETHASONE	Tablet	4MG	Corticosteroid
01964976	DEXAMETHASONE	Tablet	0.5MG	Corticosteroid
01977547	DEXAMETHASONE	Injectable solution	4MG/ML	Corticosteroid
02240684	DEXAMETHASONE	Tablet	.5MG	Corticosteroid
02240687	DEXAMETHASONE	Tablet	4MG	Corticosteroid
02250055	DEXAMETHASONE	Tablet	4MG	Corticosteroid
02261081	DEXAMETHASONE	Tablet	0.5MG	Corticosteroid
00029351	FLUDROCORTISONE ACETATE	Tablet	.1MG	Corticosteroid
02086026	FLUDROCORTISONE ACETATE	Tablet	.1MG	Corticosteroid
00030910	HYDROCORTISONE	Tablet	10MG	Corticosteroid
00030929	HYDROCORTISONE	Tablet	20MG	Corticosteroid
00230316	HYDROCORTISONE	Enema	100MG/60ML	Corticosteroid
00661856	HYDROCORTISONE	Rectal suspension	100MG/60ML	Corticosteroid
01925172	HYDROCORTISONE	Rectal suspension	100MG/60ML	Corticosteroid
02112736	HYDROCORTISONE	Rectal	100MG/60ML	Corticosteroid

		suspension		
09857120	HYDROCORTISONE	Injectable solution	100MG	Corticosteroid
00406708	HYDROCORTISONE ACETATE	Rectal suppository	40MG	Corticosteroid
00407836	HYDROCORTISONE ACETATE	Rectal suppository	10MG	Corticosteroid
02099179	HYDROCORTISONE ACETATE	Rectal suppository	10MG	Corticosteroid
02099187	HYDROCORTISONE ACETATE	Rectal suppository	40MG	Corticosteroid
00476285	HYDROCORTISONE ACETATE & ZINC SULFATE	Rectal suppository	10MG	Corticosteroid
00030600	HYDROCORTISONE SODIUM SUCCINATE	Injectable solution	100MG	Corticosteroid
00030619	HYDROCORTISONE SODIUM SUCCINATE	Injectable solution	250MG	Corticosteroid
00030627	HYDROCORTISONE SODIUM SUCCINATE	Injectable solution	500MG	Corticosteroid
00030635	HYDROCORTISONE SODIUM SUCCINATE	Injectable solution	1G	Corticosteroid
00888230	HYDROCORTISONE SODIUM SUCCINATE	Injectable solution	100MG	Corticosteroid
00030988	METHYLPREDNISOLONE	Tablet	4MG	Corticosteroid
00036129	METHYLPREDNISOLONE	Tablet	16MG	Corticosteroid
00030740	METHYLPREDNISOLONE ACETATE	Injectable solution	20MG/ML	Corticosteroid
00030759	METHYLPREDNISOLONE ACETATE	Injectable solution	40MG/ML	Corticosteroid
00030767	METHYLPREDNISOLONE ACETATE	Injectable solution	80MG/ML	Corticosteroid
01934325	METHYLPREDNISOLONE ACETATE	Injectable solution	20MG/ML	Corticosteroid
00030643	METHYLPREDNISOLONE SODIUM SUCCINATE	Injectable solution	40MG/ML	Corticosteroid
00030651	METHYLPREDNISOLONE SODIUM SUCCINATE	Injectable solution	125MG/VIAL	Corticosteroid
00030678	METHYLPREDNISOLONE SODIUM SUCCINATE	Injectable solution	500MG/VIAL	Corticosteroid

02152541	PREDNISOLONE SODIUM PHOSPHATE	Oral liquid	5MG/5ML	Corticosteroid
02230619	PREDNISOLONE SODIUM PHOSPHATE	Oral liquid	6.7MG/5ML	Corticosteroid
02245532	PREDNISOLONE SODIUM PHOSPHATE	Oral liquid	6.7MG/5ML	Corticosteroid
00021695	PREDNISONE	Tablet	5MG	Corticosteroid
00093629	PREDNISONE	Tablet	5MG	Corticosteroid
00210188	PREDNISONE	Tablet	5MG	Corticosteroid
00232378	PREDNISONE	Tablet	50MG	Corticosteroid
00252417	PREDNISONE	Tablet	50MG	Corticosteroid
00271373	PREDNISONE	Tablet	1MG	Corticosteroid
00312770	PREDNISONE	Tablet	5MG	Corticosteroid
00550957	PREDNISONE	Tablet	50MG	Corticosteroid
00598194	PREDNISONE	Tablet	1MG	Corticosteroid
00610623	PREDNISONE	Tablet	5MG	Corticosteroid
00015016	TRIAMCINOLONE	Tablet	2MG	Corticosteroid
00015024	TRIAMCINOLONE	Tablet	4MG	Corticosteroid
02194082	TRIAMCINOLONE	Tablet	2MG	Corticosteroid
02194090	TRIAMCINOLONE	Tablet	4MG	Corticosteroid
00029300	TRIAMCINOLONE ACETONIDE	Injectable solution	40MG/ML	Corticosteroid
00460761	TRIAMCINOLONE ACETONIDE	Injectable solution	10MG/ML	Corticosteroid
00990876	TRIAMCINOLONE ACETONIDE	Injectable solution	40MG/ML	Corticosteroid
01999761	TRIAMCINOLONE ACETONIDE	Injectable solution	10MG/ML	Corticosteroid
01999869	TRIAMCINOLONE ACETONIDE	Injectable solution	40MG/ML	Corticosteroid
02229540	TRIAMCINOLONE ACETONIDE	Injectable solution	10MG/ML	Corticosteroid
02229550	TRIAMCINOLONE ACETONIDE	Injectable solution	40MG/ML	Corticosteroid
09857128	TRIAMCINOLONE ACETONIDE	Injectable solution	200MG/5ML	Corticosteroid
00297151	TRIAMCINOLONE HEXACETONIDE	Injectable solution	20MG/ML	Corticosteroid
02194155	TRIAMCINOLONE HEXACETONIDE	Injectable solution	20MG/ML	Corticosteroid
00021555	METRONIDAZOLE	Tablet	250MG	Antibiotic
00024929	METRONIDAZOLE	Vaginal cream	10%	Antibiotic
00025615	METRONIDAZOLE	Tablet	250MG	Antibiotic
00025887	METRONIDAZOLE	Vaginal	500MG	Antibiotic

		suppository		
00489891	METRONIDAZOLE	Capsule	500MG	Antibiotic
00524557	METRONIDAZOLE	Injectable solution	5MG/ML	Antibiotic
00545066	METRONIDAZOLE	Tablet	250MG	Antibiotic
00584339	METRONIDAZOLE	Tablet	250MG	Antibiotic
00649074	METRONIDAZOLE	Injectable solution	5MG/ML	Antibiotic
00783137	METRONIDAZOLE	Capsule	500MG	Antibiotic
00870420	METRONIDAZOLE	Injectable solution	5MG/ML	Antibiotic
01926853	METRONIDAZOLE	Capsule	500MG	Antibiotic
01926861	METRONIDAZOLE	Vaginal cream	10%	Antibiotic
01926888	METRONIDAZOLE	Vaginal suppository	500MG	Antibiotic
01926896	METRONIDAZOLE	Tablet	250MG	Antibiotic
02248562	METRONIDAZOLE	Capsule	500MG	Antibiotic
00250724	METRONIDAZOLE & NYSTATIN	Vaginal suppository	500MG & 100000U	Antibiotic
00338338	METRONIDAZOLE & NYSTATIN	Vaginal cream	500MG & 100000U	Antibiotic
00439134	METRONIDAZOLE & NYSTATIN	Vaginal suppository	500MG & 100000U	Antibiotic
01926829	METRONIDAZOLE & NYSTATIN	Vaginal suppository	500MG & 100000U	Antibiotic
01926837	METRONIDAZOLE & NYSTATIN	Vaginal suppository	500MG & 100000U	Antibiotic
01926845	METRONIDAZOLE & NYSTATIN	Vaginal cream	500MG & 100000U/G	Antibiotic
02273233	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	5MG & 10MG	Statin (Antilipdemic agent)
02273241	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	5MG & 20MG	Statin (Antilipdemic agent)
02273268	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	5MG & 40MG	Statin (Antilipdemic agent)
02273276	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	5MG & 80MG	Statin (Antilipdemic agent)
02273284	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	10MG & 10MG	Statin (Antilipdemic agent)

02273292	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	10MG & 20MG	Statin (Antilipdemic agent)
02273306	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	10MG & 40MG	Statin (Antilipdemic agent)
02273314	AMLODIPINE BESYLATE & ATORVASTATIN	Tablet	10MG & 80MG	Statin (Antilipdemic agent)
02230711	ATORVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02230713	ATORVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02230714	ATORVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02243097	ATORVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02237325	CERIVASTATIN SODIUM	Tablet	.2MG	Statin (Antilipdemic agent)
02237326	CERIVASTATIN SODIUM	Tablet	.3MG	Statin (Antilipdemic agent)
02241466	CERIVASTATIN SODIUM	Tablet	.4MG	Statin (Antilipdemic agent)
02061562	FLUVASTATIN SODIUM	Capsule	20MG	Statin (Antilipdemic agent)
02061570	FLUVASTATIN SODIUM	Capsule	40MG	Statin (Antilipdemic agent)
02250527	FLUVASTATIN SODIUM	Tablet	80MG	Statin (Antilipdemic agent)
00795852	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
00795860	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02220172	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02220180	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02243127	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02243129	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02245822	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02245823	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02246013	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02246014	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02246542	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02246543	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02247056	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02247057	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02248572	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02248573	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02267969	LOVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02267977	LOVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
00893749	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)

00893757	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02222051	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02237373	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02237374	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02237375	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02243506	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02243507	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02243508	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02244350	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02244351	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02244352	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02246930	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02246931	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02246932	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02247008	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02247009	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02247010	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02247655	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02247656	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02247657	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02247856	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02247857	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02247858	PRAVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)

	SODIUM			
02248182	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02248183	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02248184	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02257092	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02257106	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02257114	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02284421	PRAVASTATIN SODIUM	Tablet	10MG	Statin (Antilipdemic agent)
02284448	PRAVASTATIN SODIUM	Tablet	20MG	Statin (Antilipdemic agent)
02284456	PRAVASTATIN SODIUM	Tablet	40MG	Statin (Antilipdemic agent)
02247162	ROSUVASTATIN CALCIUM	Tablet	10MG	Statin (Antilipdemic agent)
02247163	ROSUVASTATIN CALCIUM	Tablet	20MG	Statin (Antilipdemic agent)
02247164	ROSUVASTATIN CALCIUM	Tablet	40MG	Statin (Antilipdemic agent)
02265540	ROSUVASTATIN CALCIUM	Tablet	5MG	Statin (Antilipdemic agent)
00884324	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
00884332	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
00884340	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
00884359	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02240332	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02246582	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02246583	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02246584	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02246585	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02246737	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02247011	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02247012	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02247013	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02247014	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02247015	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02247067	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02247068	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02247069	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)

02247070	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02247071	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02247827	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02247828	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02247830	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02247831	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02247833	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02248103	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02248104	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02248105	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02248106	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02248107	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02250144	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02250152	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02250160	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02250179	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02250187	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02252619	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02252635	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02252643	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02252651	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02252678	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02265885	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02265893	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02265907	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02269252	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02269260	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02269279	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02269287	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02269295	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)
02281554	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02329131	SIMVASTATIN	Tablet	5MG	Statin (Antilipdemic agent)
02329158	SIMVASTATIN	Tablet	10MG	Statin (Antilipdemic agent)
02329166	SIMVASTATIN	Tablet	20MG	Statin (Antilipdemic agent)
02329174	SIMVASTATIN	Tablet	40MG	Statin (Antilipdemic agent)
02329182	SIMVASTATIN	Tablet	80MG	Statin (Antilipdemic agent)

Appendix 4: Privacy impact assessment (PIA) form

INSTITUTE FOR CLINICAL EVALUATIVE SCIENCES
PROJECT-SPECIFIC PRIVACY IMPACT ASSESSMENT FORM
(FOR ALL ICES PROJECTS)

A. PROJECT TITLE
Hemorrhage during warfarin therapy associated with amiodarone: a population-based cohort study

B. THE PROJECT		
Select the PHIPA Section that applies to this project as the privacy implications are different.		
1) Please indicate below whether this Project falls into PHIPA Section 45i and/or 45ii OR Section 44(iii). (see "Completing PIAs" document and/or Reference*)		
Section 45:		
i) The purpose of the project is analysis or compiling statistical information related to evaluation, monitoring, planning, resource allocation, service delivery and management of the health care system;	☒ Y	Sec. 45 i)
and/or		
ii) This project is creating infrastructure or a framework for the activity above?	☐ Y	Sec. 45 ii)
or		
Section 44:		
iii) Research purpose other than activities listed in Section 45 above (see "Completing PIAs" document or contact Privacy Office).	☐ Y	Sec. 44 iii)

2)	Has an electronic PIA and Proposal been submitted to the Program Administrator? (A DCP may be an acceptable substitute in some circumstances)	☒ Y	
3)	Is data planned for use in this project to be linked with other data sets?	☒ Y	
4)	Is the rationale for the planned data linkage described in the proposal (or in the DCP?) **If not, please append.**	☒ Y	☐ N
5)	From a Process and/or Technology perspective, is this project :		If yes, security consultation with CISO may be of benefit for this project
	• Introducing a novel methodology or direction?	☐ Y	
	• Introducing significant changes from an existing project?	☐ Y	
	• Implementing a new remote implementation?	☐ Y	
	• Introducing a new technology?	☐ Y	
6)	Is this a trainee / student / fellow project?	☒ Y	☐ N

7) If you answered "yes" in question 6, please identify the student's designation below:

☒ **MSc** ☐ **PhD** ☐ **Other** ____

8) Name the project participants / staff and provide contact details here.
Use pull-down lists under role to describe each person's activity.

At least one ICES scientist must be named for all projects as Investigator or Co-investigator.
Include affiliations/qualifications for all scientists who are <u>not</u> ICES scientists/adjunct scientists. You may provide affiliations/qualifications on an attached sheet or electronically.

NAME / AFFILIATION/ QUALIFICATIONS	ROLE	PHONE	E-MAIL
Anne Holbrook/McMaster, St. Joseph's/MD, MSc	Co-PI	905.522.1155 x 5269	holbrook@mcmaster.ca
Jason Lam/McMaster/BScPhm, MSc Candidate	Student	416-567-3888	lamj44@univmail.cis.mcmaster.ca
Muhammad Mamdani	Co-PI	416 864 3037	MamdaniM@smh.ca
David Juurlink	Co-investigator	3037	david.juurlink@ices.on.ca
Tara Gomes	Co-investigator	2746	tara.gomes@ices.on.ca
Michael Paterson	Co-investigator	3886	michael.paterson@ices.on.ca
Chelsea Hellings	RC	7460	chelsea.hellings@ices.on.ca
Hong Zheng	PB		hong.zheng@ices.on.ca
	PI		
	PI		
	PI		
	PI		
	PI		
	PI		

9) Please name team members who will have **access to the individual-level data**.
(Have you provided names and related qualifications as requested above?)

Assigned P&B Analyst

10) What types of data are being used? (check all that apply)
Identify those, which are being linked to administrative datasets.

Type	To be linked
☒ ICES Administrative Data	
☐ Survey	☐
☐ Registry	☐
☐ Primary clinical	☐
☐ Chart abstraction	☐
☐ Electronic Health Record	☐
☐ Web-based data collection	☐
☐ Other: (Please indicate below)	☐

11) What databases are being used? (check all that apply)
Indicate dates of data to be used. (Note: *Year* means year for which data is summarized.
Fiscal year is defined as: 1 April 2008 – 31 March 2009 = fiscal 2008.

Type	Fiscal year		
Administrative Databases		**Year**	
☒ CIHI-DAD	1991	to	2010
☐ CIHI-SDS		to	
☐ CIHI-NACRS		to	
☐ CIHI-CCRS		to	
☐ CIHI-NRS		to	
☒ ODB	1993	to	2010
☒ OHIP	1991	to	2010
☐ HCD		to	
☐ LOC		to	
☐ OMHRS		to	
☒ RPDB	N/A		
☐ CAPE	N/A		
☐ IPDB	N/A		
☐ CPDB	N/A		
☐ Other			
☐			
☐			

Composite Databases (i.e., OHIP + CIHI + ODB)	Day/Month/Yr
☐ Asthma*	
☐ CHF *	
☐ COPD*	
☐ Hypertension	
☐ MOMBaby	
☐ ODD	
☐ OMID	
☐ PIBD*	
☐ Other	
☐	

* Permission/notification required before use of asterisked datasets. Please contact Director, Data Management for details.

Restricted Databases - Registry		
☐ CCN* (approval required)		to
☐ OCR**		to
☐ RCSN †		to
☐ EFFECT		to
☐ OBSP*		
☐ Cytobase*		
Others: (Please indicate below)		
		to
		to

* Note: all studies planning use of CCN data must be approved by an external process.
** All studies planning use of Cancer Care Ontario databases (ie, OCR, OBSP, Cytobase) must be logged and submitted to Cancer Care Ontario by Chief Privacy Officer (contact for details) and approved by additional process.
† Written applications to the Stroke Network Publication Committee.

Surveys	Linked
☐ OHS	☐
☐ NPHS	☐
☐ CCHS	☐
☐ PCAS	☐
☐ OTHER:	☐

Other Databases		Year
☐ ARIS		to
☐ MIS		to
☐ OTR		to
☐ Custom Clinical dataset		to
☐ Others: (Please indicate below)		
		to

12) i) Is probabilistic linkage planned? ☐ **Y** ☒ **N**

ii) Please list any personal health information/data that will be collected and / or used in this study, which *potentially*, alone or *in combination*, could be associated *with increased risk to privacy* (identification of the individual).

☐ Birth date ☐ Postal Code ☐ Other (list below)

C. DATA SECURITY/PRIVACY IMPACT

A. Internal Projects:

1) Complies with all ICES policies / procedures ☒ **Y**

Describe perceived need for modification:

No perceived need for modification

B. External Projects (e.g. Chart abstraction, EHM/EMR, primary data collection) have special privacy and security data concerns.
ICES Staff Research Coordinator and/or Analyst should be designated for these projects.

1) Complies with all ICES policies / procedures ☐ **Y**
Describe perceived need for modification:

2) MRNs sent to hospitals in password-protected Excel files ☐ **Y**
(see SOP DM005)

3) For primary data collection projects using laptops/USB key/mobile devices:
- Encryption software in place. ☐ **Y**
- 2 levels of unique passwords must comply with ICES password policy. ☐ **Y**
- Anonymization at collection point: collected under unique study number. ☐ **Y**
- Data collection tool complies with ICES standards for primary databases on laptops. (see Mobile Devices Policy) ☐ **Y**

4) Are complete copies of reports / tests required? ☐ **Y** ☐ **N**
If Yes:
- Limited numbers of reports may be scanned where abstraction difficult or untenable. Consult the Privacy Office. ☐ **Y**
- Paper reports / tests will be de-identified; assigned a unique number only and couriered to ICES. ☐ **Y**

5) **Append methods describing encryption methods and protections, if you plan to transmit data back to ICES.** ☐ **Y**

D. PUBLIC BENEFIT
(Legislation requires completion of this section)

1) What is the public benefit of this Data use: (eg. Research that contributes to the effectiveness, quality, equity and efficiency of health care in Ontario) that are expected / anticipated from the project? Identify any potential impact.

According to the Institute for Safe Medication Practices Canada, anticoagulants are always amongst the top 10 drugs cited as patient safety concerns. Warfarin, an oral vitamin K antagonist, has been the near-exclusive anticoagulant used in the North American community-setting for patients, with occasional use of low-molecular-weight heparins. It is commonly indicated for the prevention and treatment of venous thromboembolism and pulmonary embolism in patients with atrial fibrillation, prosthetic heart valves, and as adjunct prophylaxis therapy in patients after an acute myocardial infarction or stroke. Yet due to its narrow therapeutic window, the most common adverse effect of warfarin is bleeding. The annual risks of major and intracranial bleeding are conservatively estimated to be between 0.8-6.6% and 0.3-0.5%, respectively. Yet the bleeding risk can potentially be compounded due to the numerous documented drug-drug interactions associated with warfarin use.

In particular, the interaction between amiodarone and warfarin has not been fully elucidated. Previous small studies have focused on the pharmacodynamic effects of the drug interaction. Yet few studies have looked at more clinically relevant outcomes such as bleeding. Thus, a well designed, observational study using population-based data may be best suited to explore the association between concomitant warfarin and amiodarone use and major bleeding. Our objective is to characterize this risk of major bleeding, and death in-hospitalization in order to minimize future interactions which may result in harm.

E. ESTIMATION OF HARM
(Legislation requires completion of this section)

Note: Cell sizes less than or equal to 5 cannot be reported without prior written approval from the President and CEO of ICES.

1) Please describe the level at which the results will be reported (e.g. level of individuals, institution or region – smallest units)

All data will only be reported in aggregate form. Cell sizes <= 5 will be suppressed

2) Describe any reasonably foreseeable harms that may arise from the use of the data. Are there any ways this study might identify, stigmatize, or otherwise harm patients, practitioners or institution(s)? How will these reasonably foreseeable harms be addressed?

There is no anticipated risk of harm to patients, practitioners or institutions in carrying out this study.

F. ALTERNATIVES
(Legislation requires completion of this section)

1) Is it possible to do this research without using personal health information? ☐ Y ☒ N

2) Were any alternative methods considered / rejected as less privacy-invasive for achieving the desired objectives? If so, please describe briefly (this provides a means of assessing any real / potential privacy-adverse impact which may be challenged by external sources). ☐ Y ☒ N

G. TIMEFRAME, DATA RETENTION/DESTRUCTION

1) What is the proposed time frame of the project:
- Anticipated start-up date: 30/11/2010 (dd/mm/yyyy)
- Anticipated completion date: 1/7/2011 (dd/mm/yyyy)

2) Retention and disposal policies.
Stipulate retention prior to dataset destruction period.
Notification to PI to be sent on: Apr-10 (mm/yy)
- Document shredding. ☐ Y
- Destruction of electronic media (magnetic and optical disks, cartridges, CDs). ☐ Y
- Dataset Destruction date: 01/10/2018 (dd/mm/yy):

H. FINANCIAL INFORMATION

1) What is the funding source for this study?

ICES – Core Budget *

* Do not use unless expenditures have been pre-approved and included in the ICES core budget.

- Ministry Workplan (MOHLTC)* ☐ Y
- ICES Funded (non-MOHLTC/non-grant)* ☐ Y

Externally Funded

- MOHLTC Program Funded (Special Projects) ☐ Y
- CCO ☐ Y
- Peer Reviewed Grant (Specify Source) ODPRN ☒ Y
- External Contract ☐ Y
- MOHLTC Third Party Funded (MOHLTC funds held at another institution.) ☐ Y
- Other funding source (Specify Source) ☐ Y

2) **PAW**: Have you completed and submitted a Project Activation Worksheet? ☒ Y

NOTE: A project TRIM number will not be assigned unless the budget section of the PAW is completed.

I. ETHICS APPROVAL STATUS

- Ethics approval sought by President and CEO and Chief Privacy Officer (anonymized data studies with administrative data) ☒ Y
- Chart abstraction study – ethics approval obtained (append copies of REB approval) ☐ Y
- Clinical study – ethics approval obtained (append copies of REB approval) (Include patient consent form ***if applicable***.) ☐ Y

J. COMPLIANCE WITH CORPORATE RULES FOR ALL STAFF

Is a data-sharing agreement required for this project? ☐ Y ☒ N

- If yes:
  - Has the Privacy Office and the Program Administrator been notified? **OR** ☐ Y ☐ N
  - Data sharing agreements have been signed. ☐ Y ☐ N
- Confidentiality agreements have been signed by ALL project staff. ☒ Y
- All project participants have been familiarized with ALL ICES privacy and confidentiality policies and procedures. ☒ Y
- Copies of proposal, Privacy Impact Assessment form and Project Activation Worksheets have been filed with the Program Administrator. Electronic copies of each of these have been sent to the ICES Privacy Office. ☒ Y
- If external Ethics approval has been sought, append copy to documents ☐ Y
- Cell sizes less than or equal to 5 cannot be reported (any exceptions must be approved in writing by ICES President and CEO). ☒ Y
- Your interest in the disclosure of the data for your research purpose will not result in actual, perceived or potential conflict of interest with your other duties as researcher. ☒ Y
- You have received and agree with ICES Media Relations Policy ☒ Y
- You have read and agree with the ICES Conflict of Interest Policy ☒ Y

K. SOP'S AND POLICIES

- You and your project team have reviewed all current Policies and SOP's applicable to this project ☒ Y ☐ N

If you selected "N" please find the up-to-date SOP's and Polices at the following locations:

- ICES Intranet – under "Policies and Forms"
- ICES Research Practice site

- For access to the documents, please contact your Program Administrator.
- For questions about a specific Policy or SOP, please contact the owner listed on the document.

Signature of Investigator / Scientist _____ Date (dd/mm/yy) _____

Signature of Scientific Program Leader _____ Date (dd/mm/yy) _____

Signature of Site Director, if applicable _____ Date (dd/mm/yy) _____

CEO Approval _____ Date (dd/mm/yy) _____

Privacy Office Approval _____ Date (dd/mm/yy) _____

This section is for the use of Ontario Cancer Registry

Signature _____ Date (dd/mm/yy) _____

on behalf of
- ☐ CCO
- ☐ Cancer Research Program

***Reference:**

For more information, please refer to the *Personal Health Information Protection Act* (PHIPA) which is found at: http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm

The Regulation to the Act (Reg. 329/04) can be found at: http://www.e-laws.gov.on.ca/html/regs/english/elaws_regs_040329_e.htm

Appendix 5: Project activation worksheet (PAW)

Project Activation Worksheet (PAW)

Updated on September 8, 2010

Instructions: Input data into the spaces provided. A completed Project Activation Worksheet is required in addition to a PIA form approved by the ICES President and CEO. All data is required before a project number can be assigned.
If you need detailed help, click on the section heading.

ICES PI:	Muhammad Mamdani	**NON-ICES Co-PI:**	Anne Holbrook
ICES SUPERVISOR: (if PI is a student)			

Project Title:

Hemorrhages associated with concomitant warfarin and amiodarone use: a population-based cohort study

Project Description:

According to the Institute for Safe Medication Practices Canada, anticoagulants are always amongst the top 10 drugs cited as patient safety concerns. Warfarin, an oral vitamin K antagonist, has been the near-exclusive anticoagulant used in the North American community-setting for patients, with occasional use of low-molecular-weight heparins. It is commonly indicated for the prevention and treatment of venous thromboembolism and pulmonary embolism in patients with atrial fibrillation (AF), prosthetic heart valves, and as adjunct prophylaxis therapy in patients after an acute myocardial infarction or stroke. Yet due to its narrow therapeutic window, the most common adverse effect of warfarin is bleeding. The annual risks of major and intracranial bleeding are conservatively estimated to be between 0.8-6.6% and 0.3-0.5%, respectively. Yet the bleeding risk can potentially be compounded due to the

In particular, the interaction between amiodarone and warfarin has not been fully elucidated. Amiodarone likely inhibits the hepatic elimination of warfarin via CYP 1A2 and 2C9 and thereby potentiates the anticoagulant effects of warfarin. Previous small studies have focused on the pharmacodynamic effects of the drug interaction. It has been shown that there is an increase in the international normalized ratio (INR) or prothrombin time (PT) as a result of the dose-dependent interaction which consequently requires warfarin dose adjustment. Yet few studies have looked at more clinically relevant outcomes such as bleeding. Our objective is to examine whether exposure to concomitant warfarin and amiodarone leads to a higher risk of major bleeding and death in-hospitalization at 14 days and at 30 days compared with warfarin therapy alone.

Program Group: **Drug, Diabetes & Kidney (DDK)**
(Click on the box)

Research Methodology:

Study design: Retrospective cohort

Population: Ontario residents 66 years or older previously on warfarin from linked Ontario administrative databases between July 1, 1994 to March 31, 2009 and followed up to March 31, 2010.

Exclusion Criteria: No warfarin prescription within 90 days prior to cohort entry date

Exposed group: New ODB claim for amiodarone

Unexposed group: No ODB claim for amiodarone

Outcomes: Primary endpoint is major bleeding at 14 days. Secondary endpoints include major bleeding at 30 days, and death in-hospitalization.

Statistical Analysis: 1:4 matching based on a high dimensional propensity model will be done. Conditional logistic regression will be performed which incorporates the paired nature of the data.

Content Key Words:

Select up to 4 key words from the drop down lists below:

1 Drugs

2 Adverse Drug Event

3

4

Project Management:

Type the name of the person who will provide updates on the project.

Chelsea Hellings/ Tara Gomes

If the person's name is not known, please indicate the role.

- [ ] PI
- [x] Research Coordinator
- [ ] Other Staff
- [ ] Senior P&B
- [ ] Administrative

Please list any other special project management needs:

Funding Data:

(if applicable)

Grant/Contract ID#:

(this is the number assigned by the funding agency)

Grant/Project Title: Ontario Drug Policy Research Network

Funding Agency: MOHLTC

Financial Administration: Li Ka Shing Knowledge Institute

(Name of institution administering funding)

Billing Information:

Bill To:	Karen Hood, Li Ka Shing Knowledge Institute
Contact Person:	
Street:	80 Bond Street
City, Country, Postal Code:	Toronto M5B 1W8
E-Mail Address:	hoodk@smh.ca
PO# / Billing# / Grant Cost Centre #:	
Any other information to print of invoices:	

Budget Information:

1. A copy of the grant award letter must be attatched to this PAW
2. If the pre-grant budget submitted to the granting agency is adjusted by the agency, a revised budget reflecting the changes should be submitted so it will be aligned with the new amount from granting agency.
3. PAWs that are missing a budget will not be issued a TRIM #.

Budget Option 1

Click on this link to enter your budget.

When you are done click on the "Return to Project Activation Worksheet"

Budget Option 2

Project budget is part of a larger blanket project. Project not budgeted but links to the blanket budget identified.

Blanket Project containing the total budget is:

Project Title: Ontario Drug Policy Research Network (2009 0760 000 000)

Grant / Project Title:

(If different from above)

Grant / Contract ID#

Once you have finished please save the file in the following format and email it to Conrad Pow and Sue Powell:

Notes:

Last Name____ Activation__Date (mmddyy)

Appendix 6: Non-disclosure agreement

ICES Institute for Clinical Evaluative Sciences

ICES COLLABORATING RESEARCHER NON-DISCLOSURE AGREEMENT

This document is intended for signature by non-ICES scientists collaborating on ICES projects, either with access to aggregated study results and/or participating in drafting manuscripts.

ICES is named as a **prescribed entity** in Ontario's privacy law – Section 45(1) of the *Personal Health Information Protection Act*, 2004 (*PHIPA*). ICES' access to data without consent for purposes of analyses or statistical compilation related to the management, evaluation, monitoring of, allocation to, planning for all or part of the Ontario health care system requires rigorous privacy protection.

- ☐ I AGREE that I will protect the privacy interests of persons whose confidential information* I have access to in the process of the current project, and agree that I will notify the ICES Principal Investigator should I have or become aware of concerns related to that confidential information;
- ☐ I AGREE that all confidential information relating to the current project should be kept in strict privacy;
- ☐ I AM RESPONSIBLE for use or misuse of confidential information entrusted to me;
- ☐ I WILL NOT DIVULGE confidential information nor allow access by unauthorized persons;
- ☐ I AGREE to shred all confidential documents, reports and statistical outputs on site as per ICES policy. This will be done using approved and provided ICES tools and receptacles;
- ☐ I AGREE that no attempt will be made to identify individuals from any aggregate and small cell size situations to which I have access;
- ☐ I AGREE that I will follow any collaboration principles or documentation put in place related to the project, including legal contracts and data-sharing agreements.

By signing this, I agree that I have read, understand and will comply with this agreement:

Name: _____

Signature: _____ Date: _____

Name of Project _____

ICES Scientist / Project Lead _____ Project End Date: _____

* For the purposes of this agreement, "confidential information" is defined as any information provided to or collected or used by ICES including (but not limited to) Financial Information and Personal Information.

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