Comparative risk of cardiac arrhythmias associated with acetylcholinesterase inhibitor use

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

Yichang Huang was the sole author for Chapter 3 and onwards, which were written under the supervision of Dr. Wasem Alsabbagh and were not written for publication at the time of uploading to UWSpace.

This thesis consists in part of two manuscripts written for publication. Exceptions to sole authorship of material are as follows:

Literature review presented in Chapters 1 and 2:

The first two chapters of the thesis, comprising the introduction and literature review of the thesis, have been published in peer-reviewed scientific journals. Dr. Wasem Alsabbagh, the supervisor of myself, Yichang Huang, is the senior author for these publications. He contributed content, style, and grammatical edits to these publications, as well as provided answers and feedback to any questions I may have had during the writing process.

As the lead author of these two chapters, I conceptualized the content, conducted the literature searches, conducted the overall writing of the literature review (introduction), re-drafting, and submitting the manuscripts.

Chapter 2 was published in an open-access journal under the CC BY-NC license, and as such, modifications were made relative to the published version to improve thesis flow. These modifications were made by me, Yichang Huang. Chapter 1 is included in the thesis as-is; although slight differences may be seen to the final published version as only the "accepted" (non-typeset) version is included in the thesis.

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These are the peer-reviewed versions of the articles in Chapters 1 and 2 respectively:

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Abstract

Background: Acquired long-QT syndrome (ALQTS) and its associated condition, torsades de pointes (TdP – a malignant cardiac arrhythmia), are associated with the use of certain medications. Case reports and pharmacodynamic studies suggest donepezil, one of the three acetylcholinesterase inhibitors (AChEIs) used in the treatment of Alzheimer's Disease (AD) and related dementias, may be associated with a greater risk of ALQTS and malignant arrhythmias. Only a limited number of studies have generated relevant information, and no population-based epidemiologic studies have directly examined comparative risk between AChEIs.

Methods: Using Canadian hospitalization and prescription medication administrative databases – the Discharge Abstract Database (DAD) and National Prescription Drug Utilization Information System (NPDUIS) respectively – I included individuals in seven jurisdictions (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island, Newfoundland and Labrador) between April 1st 2011 and January 31st 2019. Included adults were aged 66 and over, and either initiated the use of donepezil, galantamine, oral rivastigmine, or transdermal rivastigmine (defined as no previous dispensation of AChEI recorded in NPDUIS in 365 days prior). The outcome of a hospitalization for malignant arrhythmia was identified by ICD-10-CA codes I47.2 and I49.00. The hospitalization date set as the 15th of the month in primary analysis (with adjustment to first or end of month in sensitivity analyses) and a multivariable Cox regression model was fitted to estimate the hazard of a hospitalization for malignant arrhythmia, dependent upon AChEI use. The primary analysis assessed the time to hospitalization for malignant arrhythmia using the primary DAD diagnostic field and a maximum available follow-up of eight years. In secondary analyses, I included malignant arrhythmia codes from any diagnostic field and limited follow-up to 365 days. Variables adjusted for include demographic covariates and comorbidities identified from previous hospitalizations and prescription medication use.

Results: The cohort included 162,527 patients (mean age 82, 40% male; median days follow-up 386). Most subjects (n = 127,038; 78%) were treated with donepezil, while 25,582 (16%) received galantamine and 9,907 (6%) received rivastigmine. During a median follow up of 1.06 years, I identified 90 hospitalizations for a malignant arrhythmia – including 58 in the donepezil group (23 per 100,000 person-years) and 32 for other AChEIs (44 per 100,000 person-years). After adjustment for confounding, initiation of donepezil was associated with a 45% lower hazard of hospitalization (adjusted HR 0.55, 95% CI 0.36 to 0.85) relative to other AChEIs as a group. When assessing for malignant arrhythmias occurring in any diagnosis field, I identified 336 events (258 in the donepezil group and 78 in other AChEIs group); however, donepezil initiation was no longer significantly associated with hospitalizations (adjusted HR 1.01, 95% CI 0.78 to 1.30). My findings were similar in an analysis limited to 365 days of follow-up, and in sensitivity analyses modifying the hospitalization date definition (since only month/year of hospitalization was provided).

Conclusion: In this large, population-based cohort study, initiation of donepezil was not associated with an increased risk of hospitalization for malignant arrhythmias in comparison to other AChEIs. This was not consistent with case reports and pharmacodynamic studies. Given that adjustment for confounders moved the HR towards the null, residual confounding, caused by uncaptured comorbidities may have caused the lower risk in the donepezil group (e.g., since donepezil is a first line AChEI for treatment of Alzheimer's). Further research is warranted.

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Author's Disclosure

Parts of this material are based on data and information provided by the Canadian Institute for Health Information. However, the analyses, conclusions, opinions, and statements expressed herein are those of the author and not those of the Canadian Institute for Health Information.

All inferences, opinions, and conclusions drawn in this Thesis are those of the author, and do not reflect the opinions or policies of the Data Steward(s) in the Province of British Columbia.

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List of Abbreviations

AB	Alberta
ACh	Acetylcholine
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's Disease
aHR	Adjusted hazard ratio
AIC	Akaike Information Criterion
ALQTS	Acquired long-QT syndrome
AZCERT	Arizona Center for Education and Research
BC	British Columbia
CDSS	Clinical Decision Support System
CIHI	Canadian Institute for Health Information
CIHI-DAD	Canadian Institute for Health Information – Discharge Abstract Database
CIHI-NPDUIS	Canadian Institute for Health Information – National Prescription Drug Utilization Information System
CKD	Chronic kidney disease
CLQTS	Congenital long-QT syndrome
ECG	Electrocardiogram
FDA	Food and Drug Administration
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LQTS	Long-QT syndrome
MB	Manitoba
NL	Newfoundland and Labrador
ON	Ontario
PEI	Prince Edward Island
PPV	Positive predictive value
QT_C	Corrected QT interval
SK	Saskatchewan
TdP	Torsades de pointes

Chapter 1: Estimates of Population-Based Incidence of Malignant Arrhythmias Associated with Medication Use – a Narrative Review

1.1 Introduction

1.1.1 Overview of long-QT syndrome and its associated malignant arrhythmia, torsades de pointes

On an electrocardiogram (ECG), the QT interval is an important cardiac marker that represents ventricular depolarization as well as ventricular repolarization in its entirety.[1] Deviations from normal interval duration may have significant clinical implications, and in recommendations sent from the Council on Clinical Cardiology by the American Heart Association in 2009, a Bazett-corrected QT interval (commonly abbreviated to QT_CBZT[2] or QT_CB[3]) of ≥ 450 milliseconds (ms) in males and ≥ 460 ms in females should be considered prolonged.[4] In this article, the abbreviation QT_C will be used to specifically refer to QT_CB, as QT_CB is considered the current clinical standard and also most commonly used in pharmaceutical studies[3,5] in spite of its potential flaws.[3] Other corrected-QT calculations that exist include Fridericia (QTcFRD), Hodges (QTcHDG), Dmitrienko (QTcDMT), Rautaharju (QTcRTHa) and Framingham (QTcFRM) corrections.[2]

Long-QT syndrome present in both acquired (abbreviated ALQTS[6]) and congenital (abbreviated CLQTS[7]) forms, with medications being the most common cause of ALQTS;[8] many other determinants, including (but not limited to) electrolyte disturbances[9,10] structural heart disease,[11] cardiomyopathies,[10] bradycardia,[12] and female gender[4,9,10,13] can also contribute to its occurrence. The acquired form of LQTS is more common over the congenital form,[14] though mutations may predispose individuals towards ALQTS: one review states it is estimated that 40% of patients with medication-associated ALQTS have genetic mutations reported in CLQTS;[15] a different review states 5-20% of patients with medication-associated torsades de

pointes (TdP) have gene mutations which cause CLQTS.[16] For example, a recent study in 2019 found an association between QT_C duration and a particular single nucleotide polymorphism (rs11911509) in the *KCNE1* gene amongst methadone users; mutations in the *KCNE1* gene are known to cause CLQTS, although it was not stated if this particular single nucleotide polymorphism is associated with QT_C prolongation in the absence of medication use.[17] Nonetheless, silent mutations in CLQTS are known as "formes frustes" of CLQTS, which can then be aggravated by medications.[18,19]

The prolongation of the QT_C interval indicates an abnormally long delay in repolarization.[20] This can result in a type of ventricular tachycardia known as TdP, which can further degenerate into ventricular fibrillation (occurs in approximately 15-20% of TdP cases[21]) and cause cardiac arrest.[1,9,18] TdP is an unique ventricular tachycardia (and is also considered a malignant ventricular arrhythmia more generally[22]) – on the ECG, the ventricular tachycardia associated with TdP has a noticeable "twisting of the points" pattern[18] (which is also the English translation of the French term "torsades de pointes"). TdP is specifically described as a polymorphic arrhythmia, as the QRS complexes on the ECG are not constant, unlike other types of ventricular tachycardias.[1] Risk of TdP is especially high when QT_C interval > 500 ms or a medication increases QT_C by 60 ms or more.[1] The overall mortality of TdP is approximately 10-20%;[21] in most non-fatal cases, TdP is transient and asymptomatic.[18,23] However, symptomatic TdP is characterized by palpitations, syncope, dizziness, light-headedness, shortness of breath, and convulsions,[1,23] which can be associated with the rapid heart rate between 160-240 beats per minute.[1]

1.1.2 Cellular mechanism of long-QT syndrome and torsades de pointes associated with medications

At the cellular level, outward movement of potassium ions is the primary driver of repolarization of cardiomyocytes.[8] It is shown that the blockade of the "rapid" potassium current (I_{Kr}) is, at the very least, partly responsible for the pro-arrhythmic effect of medications,[8] as almost all QT_C-prolonging medications act on I_{Kr};[24] pharmacological inhibition studies have also specifically shown block of I_{Kr} predisposes individuals to TdP.[25] I_{Kr} goes through a specific protein channel that is known as the human Ether-à-go-go-Related-Gene channel (hERG),[24] otherwise known under the nomenclature $K_V11.1$.[26,27] As such, $K_V11.1$ blockage is proposed as the base of the arrhythmogenic substrate, as it is an important "pre-existing condition that forms [the] prerequisite for the induction of an arrhythmia."[28]

Generally, the QT interval reflects the duration of all action potentials for all ventricular cardiomyocytes.[19] Some heterogeneity in cardiomyocyte conduction, such as during the refractory period, is normal.[29] With the block of $K_V11.1$, TdP may result due to a combination of the following: a prolongation of repolarization,[18] increased heterogeneity of repolarization,[8] and early afterdepolarizations (defined as a premature inward depolarization current during the abnormally prolonged repolarization phase).[1,8] The inhomogeneous, spatial dispersion of cardiac repolarization resulting from the block of $K_V11.1$ is especially paramount as it is what may induce the early afterdepolarizations leading to TdP;[25,30] furthermore, a stable dispersion of cardiac repolarization has actually been found to prevent proarrhythmia even in the presence of a substantially prolonged QT interval.[30] Nevertheless, if sustained, TdP degenerates into ventricular fibrillation and cardiac arrest[8] as previously described.

Reduced serum potassium (hypokalemia) further increases the loss of function of $K_V11.1$,[31] although this may *appear* paradoxical[32,33] given that extracellular potassium levels are

lower than intracellular potassium levels,[34] and that I_{Kr} is an outward potassium current.[8] This observation is not actually a paradox; in a study of rabbit hearts, it was found that lowered extracellular potassium resulted in an acceleration of $K_V11.1$ internalization and degradation.[35] It has also been suggested that lowered extracellular potassium impairs the ability of the $K_V11.1$ to protect against premature excitation.[33]

In spite of the importance of $K_V11.1$ and its importance on cardiac repolarization, the ability of a particular medication to merely block $K_V11.1$ channels (and thus I_{Kr}) has not been found to be correlated with actual TdP risk.[18] This lack of $K_V11.1$ channel block/TdP risk correlation could be due to the effect of medications on other currents in cardiomyocytes. These effects can weaken the $K_V11.1$ channel blockage effect; an illustration of this is the medication verapamil – which is a potent $K_V11.1$ blocker that has its $K_V11.1$ block effect nullified through its additional blockage of the depolarizing calcium current.[24] On the other hand, additional effects may in fact potentiate $K_V11.1$-related pro-arrhythmic effects of medications. For example, some medications that affect I_{Kr} (including d-sotalol, thioridazine, and erythromycin) also increase the sodium current $I_{Na\text{-}L}$.[18,36,37] Increased $I_{Na\text{-}L}$ is known to cause QT_C prolongation in CLQTS, by being a persistent depolarizing force that opposes the repolarizing current and increasing the cardiac action potential duration.[38] Likewise, based on the pioneering work of Vaughan Williams, it has been known that certain (Class Ib) sodium channel *blockers* decreases action potential and QT interval duration;[39] supporting this, in a study of 28 antipsychotic medications by Silvestre et al., it was found that greater $Na_V1.5$ inhibition (the channel through which the current $I_{Na\text{-}L}$ flows) predicted a lower QT_C duration.[40] Further supporting the lack of $K_V11.1$ block/TdP risk correlation, the ratio of $K_V11.1$ to $Na_V1.5$ block explained 57% of QT_C variability; $K_V11.1$ block on its own only explained 33% of QT_C variability.[40] It must be noted

that not all sodium channel blockers will decrease action potential duration or QT_C; the Class Ia sodium channel blockers (as per the Vaughan Williams classification) also block potassium channels and increases QT interval instead.[39] However, this lends further evidence why a ratio of $K_V11.1$ to $Na_V1.5$ block explains more QT_C variability than just $K_V11.1$ block on its own (and why there is a lack of $K_V11.1$/TdP risk correlation). Regarding potassium channels and currents, I_{Ks}, the "slow" potassium current having some redundancy with I_{Kr}, may also be an important target for medications[26,41] as it is likewise shown to be dysfunctional in at least one form of CLQTS.[42]

Another relevant mechanism in the impairment of $K_V11.1$ is the inhibition of ion channel trafficking to the cell membrane.[42] Ways ion channel trafficking may be affected include increased proteasomal activity, defective chaperone proteins, retention of the channel protein at the endoplasmic reticulum, or improper channel folding.[42] For example, arsenic trioxide is known to cause QT_C-prolongation via inhibition of $K_V11.1$ channel trafficking, and not via direct $K_V11.1$ block;[43] pentamidine and fluoxetine (of which pentamidine is known to prolong the QT_C interval[44]) are also associated with disruption of protein trafficking.[16]

A concept known as the "repolarization reserve" was developed, which in essence attempts to explain "the complexity of [cardiac] repolarization"[45] – and also links the congenital and acquired forms of LQTS together[18] through some of the aforementioned mechanisms – thus helping to explain the different susceptibility to ALQTS amongst individuals. Certainly (and as described previously), not all individuals with medication-associated ALQTS or TdP will have mutations reported in CLQTS,[15,16] hence the term "medication-associated" ALQTS. As well, it is difficult to quantify how much individual mechanisms may contribute to the repolarization reserve;[46] it is stated that I_{Kr} and I_{Ks} are the major currents with regards to the repolarization

reserve.[41,46,47] Yet, the relevance of I_{Ks} towards medication use is debatable; multiple medications which block I_{Ks} also block I_{Kr}[41] (for example, azimilide[41,48] and terfenadine[41,49] – although terfenadine is no longer approved for use). As well, sodium, calcium, other potassium currents, [46,47] and ion pumps[46] all contribute towards cardiac repolarization.

1.1.3 Torsades de pointes is a malignant arrhythmia – so what is a malignant arrhythmia defined as?

Bigger (1983) defines out-of-hospital ventricular fibrillation, recurrent sustained ventricular tachycardia, and the TdP form of ventricular tachycardia all under the umbrella term "malignant ventricular arrhythmia," with the important feature of a *sustained* ventricular arrhythmia being required for the definition of "malignant."[22] Importantly, it is noted that "malignant arrhythmias" include non-TdP ventricular arrhythmias as well. Further, QT_C prolongation alone is not considered a malignant arrhythmia. Although QT_C prolongation can degenerate into TdP malignant arrhythmia as described previously, medication-associated TdP can occur in the absence of prolonged QT_C intervals as well.[50]

It may be argued that the term "malignant arrhythmia" is very general, as it insinuates any form of cardiac arrhythmia leading to severe or fatal patient outcomes should be considered "malignant." For example, premature ventricular contractions are generally not considered a concerning arrhythmia unless it is frequent.[51] However, a study found that usage of the medication nicorandil suppressed premature ventricular contractions in patients with a low heart rate[52] – which suggest their possible origin from trigger early afterdepolarizations, and erasure by augmenting outward potassium conductance. Certainly, whether premature ventricular contractions during bradycardia should then be considered a "malignant" arrhythmia would require an updated definition of malignant arrhythmia. Notably, in addition to already being a

risk factor for medication-associated ALQTS, bradycardia is a risk factor for TdP (which is for sure a malignant arrhythmia[22]) in patients with prolonged QT.[52]

The definition of malignant arrhythmia is paramount when attempts are made to assess TdP that may be associated with medication use. As it will be proposed in this article, *population-scale* epidemiological studies need to be conducted to assess this potentially devastating adverse medication event. In an epidemiological study, we argue that using the terminology medication-associated "malignant arrhythmia" to refer to medication-associated TdP is appropriate, as TdP is of "no doubt" that it is a malignant arrhythmia.[22] The rationale for using the general term "malignant arrhythmia" to refer to TdP is that it is not always practical to assess TdP specifically – it is likely that a diagnosis of TdP can only be confirmed through the use of an ECG, given that tachycardia is a non-specific symptom and TdP has unique ECG findings.[18] Thus, distinction between TdP or non-TdP ventricular tachycardia is not always possible (e.g., when using administrative databases); however, given the seriousness of arrhythmias associated with medication use, distinction is not likely important for medication-associated malignant arrhythmia – any association with medications of interest is of particular importance.[53]

Arguably, when TdP can be explicitly described, the umbrella term malignant arrhythmia should not be used. In this review, the term TdP will be used when used in source literature.

1.1.4 Categorization of the propensity of medications to be associated with long-QT syndrome and torsades de pointes

One of the first medications to be associated with ALQTS and TdP was quinidine, a medication used to treat atrial fibrillation, with the first report of quinidine-induced syncope dating back almost a century.[18] Over the years, several other antiarrhythmic medications were identified to cause ALQTS, but it was not until 1990 when it was known that many noncardiac

medications can prolong the QT_C interval and have proarrhythmic effects.[18] This discovery resulted in the withdrawal of multiple medications from several jurisdictions.[18,24] In 2005, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) released two guidelines (ICH S7B and ICH E14) regarding proarrhythmic cardiac safety assessments.[24] These ICH guidelines have since been adopted in Europe, the United States, Canada, and Japan,[24] with Canada adopting the guidelines in November 2006.[54]

CredibleMeds.org, a website maintained by the Arizona Center for Education and Research (AZCERT), lists medications that have a risk of causing ALQTS and/or TdP.[18] CredibleMeds was originally focused on medications marketed in the United States. The CredibleMeds lists are provided for free, and despite the initial US-centric focus, these lists have been used by many research studies around the world.[31,53,55–58] Studies using the CredibleMeds list of medications have supplemented the lists with additional medications of interest (i.e. medications marketed outside the US); starting in 2012, medications marketed only in Europe or Canada have been reviewed by AZCERT,[18] limiting the need for supplementation.

AZCERT developed the Adverse Drug Event Causality Analysis (ADECA) method, which uses 16 data types from four robust sources.[7] Analyzed medications are then placed into one of three primary categories of TdP risk: “known”, “possible” and “conditional” with medications in each category being constantly updated (every 30-45 days) based upon new evidence available.[7] The classification of medications is conducted through the use of the Bradford-Hill criteria for causality[7,18] on systematic analyses of cases reported to AZCERT, medical literature reports, and newly approved medication labels or medication label changes at the US Food and Drug Administration (FDA).[7] The known-risk category lists medications that

prolong the QT_C interval and are associated with TdP, even when used as directed on the medication label; this differs from the possible-risk category, which lists medications that can prolong the QT_C interval but without enough evidence to say that the medications are associated with TdP (when taken as recommended).[7] The conditional-risk category lists medications that are associated with TdP but only under certain conditions, such as overdose, electrolyte abnormalities, or drug-drug interactions.[7]

The CredibleMeds classification of known-risk is robust. A retrospective study by Meid et al. found that medications in the known-risk category were associated with hospital admission due to ventricular arrhythmias (including but not limited to TdP), whereas medications in the possible- and conditional-risk categories were not associated with aforementioned hospital admissions.[53] In a different study by Meid et al., it was found that known-risk medications resulted in the largest changes in QT_C; this association was "less pronounced" and absent for medications in the conditional- and possible-risk categories respectively.[11] A study by Jardin et al. found that medications on the CredibleMeds known-risk list (either alone or in combination with other QT_C-prolonging medications) were the only pharmacological risk factors for QT_C prolongation (known-risk alone, $p < .0001$).[59] Possible- or conditional-risk medications were not associated with QT_C prolongation when not in combination with known-risk medications (possible-risk alone, $p = 0.50$; conditional-risk alone, $p = 0.77$).[59] Likewise, a hospital study conducted by Pasquier et al. found that odds of QT_C interval prolongation was higher in patients (adjusted odds ratio, aOR 1.7, 95% CI 1.1-2.6) with at least one QT_C-prolonging medication at baseline (as determined from taking a medication on any of the three CredibleMeds lists).[60] Odds of QT_C prolongation further increased when the CredibleMeds known-risk list was considered independently (without possible- and conditional-risk medications in the logistic regression

model, aOR 2.1, 95% CI 1.1-3.8).[60] A 2016 systematic review found that the use of QT_C-prolonging medications from the AZCERT known-risk list was "clearly associated" with longer QT_C intervals when the list is considered as a whole; medications from the other risk classifications were not associated with prolonged QT_C when the lists were considered as a whole, although individual medications from the possible- or conditional-risk classifications were found to prolong QT_C.[10]

1.1.5 Additional major risk factors for QT_C-prolongation and torsades de pointes

The adoption of guidelines for cardiac safety assessments during drug development, and the creation of the CredibleMeds lists of QT_C-prolonging medications epitomize the health concerns resulting from ALQTS and TdP. Clinical Decision Support Systems (CDSS) have been designed to scan patients' electronic health records to warn physicians and pharmacists when a medication with a risk of ALQTS/TdP is prescribed, in an effort to reduce the potentially fatal occurrence of TdP.[18]

Published in 2013, a unique quantitative risk score for the development of ALQTS was developed by Tisdale et al.[9] and was implemented into a CDSS that was effective in reducing the risk for QT_C prolongation.[61] Risk factors include age ≥ 68 years, female sex, use of a loop diuretic, hypokalemia (defined as serum potassium ≤ 3.5 mEq/L), hospital admission QT_C ≥ 450 ms, acute myocardial infarct (MI), use of ≥ 2 QT_C-prolonging medications (22 of 26 identified medications on CredibleMeds known-risk list), sepsis, heart failure, and the use of only one QT_C-prolonging medication.[9] Given that a prolonged QT_C interval increases risk for TdP [9], Tisdale et al. cited a 2003 paper which identified similar risk factors (but for TdP instead of ALQTS).[62] It is estimated that 71% of patients that specifically develop TdP have ≥ 2 risk factors whereas > 90% of patients that develop TdP have ≥ 1 risk factor.[9,62] What is interesting to note is

that Tisdale's risk score determined that the use of only one, and the use of ≥ 2 QT_C-prolonging medications resulted in similar odds of inducing QT_C-interval prolongation, which contradicts previous studies.[9] However, a more recent (2017) study by Meid et al. also concludes that combinations of medications which prolong the QT_C interval (as separated by AZCERT risk categories) does not result in additional QT_C prolongation; rather, it seems that individual patient factors and specific combinations of medications are considerably more important than "mere drug numbers".[11] A systematic review by Vandael et al.,[10] which also identified risk factors for QT_C prolongation, was published after the paper by Tisdale et al. and identified additional risk factors including smoking, thyroid disturbances, and hypertension.[9,10] Interestingly, neither the Tisdale et al. nor Vandael et al. study found bradycardia as a risk factor for QT_C prolongation despite it being known to be associated with increased risk.[10,12]

Regarding the risk factor of female gender, it has been well known that females are more likely to develop TdP than men.[13] Most mechanisms as to why are unknown,[25] but potential explanations that have been studied or proposed include differing drug pharmacokinetics, a relative lack of protective effects from androgens, estrogens facilitating early after depolarizations, lowered I_{Kr} density, and other effects caused by sex hormones (such as on membrane transporters or metabolic enzymes).[13,25]

1.2 Previous epidemiological literature

1.2.1 The utility of epidemiology in the assessment of medication-associated long-QT syndrome and torsades de pointes

Given many identified risk factors (including but not limited to genetics – such as asymptomatic CLQTS; and all risk factors described previously) in the development of acquired QT_C prolongation and/or TdP, it can be clearly seen this medication-associated adverse event is not as simple as just looking at the risk of a particular medication. Certainly, when prescribing

medications, one must look at the entire body of risk factors for individual patients. At-risk patients need to be distinguished prior to administration of medications, although this may be difficult to do in routine clinical practice.

An important study that can illustrate the difficulty of identifying at-risk patients is a study published by Kääb et al. in 2003. Amongst a group of 20 patients that had previously experienced TdP deemed to be associated with QT-prolonging medications, treatment with sotalol (predominantly an I_{Kr} blocker[63] that is on the CredibleMeds known-risk list[44]), caused QT_C to increase beyond 480 ms in all patients.[63] However, only three of the patients were observed to develop TdP.[63] In comparison, in the group of 20 age- and sex-matched controls, no patients had a QT_C in excess of 480 ms after administration of sotalol, nor did any patient develop TdP.[63] Because patients with impaired renal or hepatic function were excluded from the study, in the absence of differences in other major risk factors – such as gender or age – it can be concluded that myocardial electrical properties make certain patients predisposed to medication-associated ALQTS resulting from I_{Kr} block.[63]

However, for the Kääb et al. study, thoroughly distinguishing the patients at higher risk of developing the medication-associated adverse event cannot be done without genetic testing. Thus, the study can *only* be considered a proof-of-concept for the existence of differences in myocardial electrical properties (in other words, the existence of the repolarization reserve).[63] Furthermore, although the control group was matched for age and sex, a much wider body of potential risk factors (i.e., those identified by Vandael et al.[10]) were not accounted for – when considered with the small sample size, the results by Kääb et al. would not be generalizable. As such, to better assist with clinical decision making, epidemiological studies should be conducted as further research to describe patients whom develop either medication-associated QT_C

prolongation or TdP. Epidemiological methodology can involve electronic databases, which may be large datasets that encompass diverse groups of patients.[64] A key advantage, then, would be broader generalizability without necessarily providing overlapping information to clinical trials.[64]

One of the key pieces of information that is relevant towards medication-associated adverse events is the rate at which it occurs in a population; as previously described, only three of 20 patients developed TdP despite every patient developing significantly prolonged QT_C in the Kääb et al. study.[63] Incidence rate, which is studied through epidemiology, is particularly important – as new occurrences of medication-associated adverse events are of concern. Epidemiological research is also especially relevant, since it can quickly add to the current body of knowledge – epidemiology using real-world data does not always require primary data collection.[64] And to emphasize generalizability, not only can an epidemiological study give information on the rate of occurrence, it can provide a fuller picture of patient demographics for those individuals that develop the adverse event – with large datasets,[64] epidemiological studies allow for easier analysis of *entire* populations.

It is already well known that certain medications prolong the QT_C interval and are associated with TdP, so notably, perhaps not many medications will keep being added to the CredibleMeds known-risk list – given that ICH guidelines will likely prevent such medications from reaching advanced stages of drug development. However, rate of occurrence in individuals taking current known-risk medications is still important. As well, for other medications (such as those listed on the conditional-risk list), the occurrence rate, and circumstances under which QT_C prolongation or TdP develop (especially relevant for medications typically not associated with much risk) should still be described through an epidemiological study.

1.2.2 A lack of estimations of incidence of medication-associated long-QT syndrome and torsades de pointes

Despite the recognition of the importance of medication-associated TdP, our knowledge of the epidemiology of this phenomenon is still limited. We performed a broad literature search of several scientific databases, including PubMed, Scopus, and Embase, using several keywords and search terms (Appendix A); few studies are found in the current literature, with regards to the estimation of the incidence of medication-associated ALQTS or TdP (summarized in Table 1). One of the earliest estimations of incidence was provided in a 2001 Swedish review by Darpö, which focused on reviewing medications that prolong the QT_C interval and are associated with TdP.[65] In the review, Darpö cited a specific study conducted over one month in 32 hospitals; importantly in the study, TdP cases were verified by ECG that was reviewed by three cardiologists, and the estimated incidence of all TdP cases was 4 per 100,000 per year in Sweden.[65] However, not all these cases were deemed medication-related; thus, the incidence of medication-associated TdP is likely lower. This estimation is notable, as the 2018 update of the Heart Disease and Stroke Statistics by the American Heart Association extrapolated the estimation to predict that there are 12,000 cases of medication-associated TdP annually in the United States.[66] Similarly, in Canada, a 2016 review paper by Tisdale also extrapolated Darpö's estimation and predicted that the number of TdP cases in Canada to be 1,400 annually, with 2% to 12% of these cases being associated with QT_C prolonging medications.[1] However, the extrapolation of estimates developed by Darpö should be carried with caution, considering its small sample size, limited timeframe, and a potential to be outdated (the article by Darpö was published in 2001).

Table 1: Summary of selected studies in the estimation of medication-associated ALQTS and/or malignant arrhythmias such as TdP [20,31,71,55–57,65,67–70]

Study	Methodology and study setting	Key results
Tahavori et al. 2016	Searches in the ISMP Canada CPhIR Program.	A total of 92 cases of QT_C prolongation or TdP between April 2010 and June 2016 identified.
Coughtrie et al. 2017	Cardiologists recruited across England, to refer cases of suspected proarrhythmia between 2003 and 2011. Prospective study.	95 of 124 analyzed cases had QT_C prolongation. 42 medications that are culpable in prolonging QT_C interval identified by 165 patient medication exposures. Most culpable medications found on "known risk" list of CredibleMeds.
Molokhia et al. 2008	Administrative data searches for the years 1999 to 2005 in an administrative area of Southwest France, which specifically contained three cities with a population of approximately 614,000.	*Drug-induced*[1] ALQTS (includes but not limited towards drug-induced TdP) incidence of **10.9 per million per year** in France.
Vandael et al. 2017	Belgian cases of TdP using the EudraVigilance database (pharmacovigilance) between 2001 and 2015.	31 cases specifically diagnosed as TdP identified. 11 of 21 implicated medications are from "known risk" list of CredibleMeds.
Michels et al. 2016	Hospital administrative records from one hospital in Cologne, Germany looked at over a period from 2007 to 2013.	33 patients with *drug-induced* ALQTS were identified, of which 55% also had TdP. Incidence estimated to be 0.1%. No whole-population estimation of incidence was done.
Darpö 2001	Review paper that described a prospective Swedish Medical Products Agency one-month pilot study conducted in 1999 (obtained through a personal communication with the Swedish Medical Products Agency). 32 hospitals covering a reference population of 4.2 million were studied for ventricular arrythmias and TdP, and classified based on the high- or	14 cases described as high- or medium-confidence TdP were found; this corresponded to an incidence of **3.3 cases per million over 28 days.** Annual incidence calculated to be **4 per 100,000 per year** in Sweden. However, of the 14 cases, only 11 cases had concomitant medication use, so incidence of medication-associated TdP is lower than 4 per

[1] Some authors refer to drug-associated ALQTS/TdP as "drug-induced" ALQTS/TdP. This implies that 1) LQTS is the outcome being measured, which may not be the case dependent upon methodology, and that 2) causality between the drug exposure and the outcome is present, which may not necessarily be the case. Nevertheless, the term "drug-induced" is used in this table if it is used in the original source literature.

Study	Methodology and study setting	Key results
	medium-confidence diagnosis criteria by Barbey et al.	100,000 per year. Validity of cases described should be high; all cases were evaluated by three cardiologists.
Sarganas et al. 2014	Physicians recruited to identify patients from 51 hospitals in Berlin between 2008 and 2011, as a part of the Berlin Pharmacovigilance Centre project. Prospective study.	Combined incidence of *drug-induced* ALQTS/TdP was estimated to be 3.2 per million person-years in Berlin. Stratified by sex, incidence is **2.5 per million person-years in males and 4.0 per million person-years in females**.
Barbey et al. 2002	Spontaneous adverse event reports received by the manufacturer for cisapride between 1990 and 1999 were looked at.	391 cases of ALQTS or QT_C prolongation (not reaching threshold for LQTS) out of 574 adverse event reports for cisapride worldwide. 145 cases were high-confidence ALQTS diagnoses, 92 cases were of medium-confidence diagnoses.
Trac et al. 2016	ODB Program database for prescription medication use, CIHI-DAD and CIHI-NACRS for hospital visits, as well as other databases. Study conducted on data between 2002 and 2013.	Use of macrolide antibiotics was not associated with higher risk of ventricular arrhythmia when compared to use of non-macrolide antibiotics (RR 1.06, 95% CI 0.83-1.36).
Qirjazi et al. 2016	ODB Program database for prescription medication use, CIHI-DAD, CIHI-NACRS, Ontario Mental Health Reporting System for hospitalizations, emergency room visits, and psychiatric facility visits. Other databases also used. Study conducted on data between 2002 and 2012.	Citalopram (but not escitalopram) was associated with a higher risk of a hospitalization for ventricular arrhythmia, relative to sertraline/paroxetine (RR 1.53, 95% CI 1.03-2.29).
Johannes et al. 2010	Saskatchewan Health database. Study conducted on data between 1990 and 2005.	Domperidone use was associated with a higher risk of serious ventricular arrhythmia and sudden cardiac death when compared to non-use (adjusted OR 1.59, 95% CI 1.28-1.98) or when compared to use of other proton pump inhibitors (adjusted OR 1.44, 95% CI 1.12-1.86).

Abbreviations: ALQTS (acquired long-QT syndrome); CIHI (Canadian Institute for Health Information); CPhIR (Community Pharmacy Incident Reporting); DAD (discharge abstract database); ISMP (Institute for Safe Medication Practices); LQTS (long-QT syndrome); NACRS (national ambulatory care reporting system); ODB (Ontario Drug Benefit); TdP (torsades de pointes)

Other studies regarding the estimation of the population incidence of medication-associated ALQTS or TdP include retrospective studies by Vandael et al., Molokhia et al., and Michels et al. (Table 1). However, all of these studies would share the same key limitation of the underestimation of the incidence of medication-associated ALQTS or TdP (if one were even provided),[55–57] either due to the case-reporting-dependent design (i.e. pharmacovigilance),[56] cases being limited to one hospital,[57] or small geographic region.[55] The estimated incidence of medication-associated ALQTS by Molokhia et al. was estimated to be even lower than Darpö's (1.09 per 100,000 per year);[55] the two retrospective studies by Vandael et al. and Michels et al. did not provide a population-based incidence estimation.[56,57]

Prospective studies conducted either did not provide a population-based estimation[31] or still provided an underestimate of the population-based incidence of ALQTS/TdP.[67] For example, a prospective study from 51 hospitals from Berlin, Germany estimated the incidence of drug-induced ALQTS/TdP to be 0.25 per 100,000 person-years in males and 0.40 per 100,000 person-years in females.[67]

Some studies examined malignant arrhythmia related to specific drug or medication class. For example, a study conducted in the United States by Barbey et al.[68] analyzed spontaneous adverse event reports received by the manufacturer for cisapride – which was removed from US and UK markets due to proarrhythmic concerns in 2000.[24] Similarly, some Canadian studies assessed arrhythmia associated with specific medications – such as retrospective studies by Trac et al.,[69] Qirjazi et al.,[70] and Johannes et al.[71] All of these studies cannot provide population-based

incidence estimates as they were limited in scope, since only some medications were studied (macrolide antibiotics; citalopram/escitalopram versus other antidepressants; domperidone versus other proton pump inhibitors respectively).[69–71]

1.2.3 Methodology of previous assessments of the outcome of acquired long-QT syndrome or torsades de pointes

The gold standard in the identification of QT_C prolongation is physician review of ECG results;[72] likely, identification of malignant arrhythmias such as TdP is also most accurately identified through ECG. However, the use of medical records to identify occurrence of clinical outcomes such as arrhythmias is probably impractical in population-based studies.[73] ECG readings and medical records are also likely to be underpowered in the quantification of exposure-outcome relationships,[72] with the insinuation that one cannot causally associate the use of a medication (exposure) with QT_C-prolongation (the outcome) – thus making it all the more difficult to rationalize the use of ECG readings in a study. Likewise, using a prospective study design requires a long duration to identify occurrences of medication-associated arrhythmia.[31]

Studies dependent on voluntary reporting data – such as the Community Pharmacy Incident Reporting Program used by Tahavori et al.,[20] or the European pharmacovigilance reporting systems[55] – are limited by reporter bias and accuracy of reported incidents.[20] An estimation (if one were to be provided) – using voluntary reporting data – would not be an accurate reflection of the true incidence of medication-associated ALQTS or TdP in any way. For example, based upon European pharmacovigilance databases, the reporting rate of TdP in Sweden was estimated to be to be 12 per 10 million total population,[55] or 0.12 per 100,000 – which is considerably lower than the 4 per 100,000 estimated through verified cases.[65] As such, the calculated population-based incidence of ALQTS will be an underestimation of the true incidence[55] if a voluntary reporting database is used.

Administrative databases, such as those coded using the International Classification of Diseases (ICD),[74] can be used as an alternate to medical record review or voluntary reporting studies, although administrative data oftentimes does not contain ECG data.[72] The use of administrative databases does avoid the biases and low reporting rates found in a voluntary reporting database; use of administrative databases also avoids having to conduct a study over a long period of time. Thus, administrative databases are very likely to be superior to reporting databases,[55] and more practical that prospective medical-records-based studies.[31] Clinical conditions are coded in administrative databases (such as hospitalization records) using standard coding systems (such as the International Coding of Diseases – ICD). The key element in the robustness of population-based estimations of ALQTS and other arrhythmia hospitalizations (using administrative databases) is the validity of the case definition using ICD codes. From studies we've reviewed, a summary of definitions of ventricular arrhythmias (or QT_C-prolongation) in databases is shown in Table 2; other definitions have been analyzed in the systematic review by Ye et al.[72] Some modifications of ICD provide a specific definition of LQTS; for example, the German modification of ICD-10 (ICD-10-GM) used by some authors,[57] define I45.8 as the specific code for LQTS.[57] However, this is not universal – the Canadian version of ICD-10 code I45.8, for instance, excludes "prolongation of QT interval".[75]

Table 2: Summary of selected code definitions used to identify arrhythmias or QTC-prolongation in administrative data [55–57,69,70,72,76]

Study	Code definition used	Commentary
Molokhia et al. 2008	ICD-10 codes of I47.2 (ventricular tachycardia), I49.0 (ventricular fibrillation), and I46.1 (sudden cardiac death). Discharge summaries of hospital medical information system was looked at;	Final confirmation of cases only yielded a PPV of 60%, as only 24 of the 40 identified cases could be ascertained via ECG. However, codes I47.2 and I49.0 were validated by other studies.

Study	Code definition used	Commentary
	was not stated if codes were primary diagnoses or not.	
Vandael et al. 2017	Cases coded with MedDRA narrow preferred terms "Torsade de Pointes" and "Ventricular tachycardia," extracted from the EudraVigilance European pharmacovigilance database maintained by the European Medicines Agency.	MedDRA is not related to ICD-10 and does not appear to be used in Canada.
Michels et al. 2016	ICD-10 German modification codes I45.8 (LQTS), I47.2, and I49.0 in ICU medical records. Was not stated if codes were primary diagnoses or not.	Conflicting information is provided about the code for LQTS (I45.8).
Trac et al. 2016; Qirjazi et al. 2016	ICD-10 codes used were I47.2 and I49.0 as a measure of the ventricular arrhythmia outcome. Database used was CIHI-DAD. Study by Qirjazi et al. specify that outcome codes may occur in any diagnostic position (i.e., most responsible *or* secondary diagnosis); the systematic review by Ye et al. specify that any hospitalization discharge diagnoses were used in the study by Trac et al.	Validation through manual review of 202 medical charts determined that the codes produced a PPV of 92% (95% CI of 87-95%).
Ye et al. 2018	Systematic review identified that ICD-9 codes 427.1, 427.4, 427.41, 427.42, 427.5, 427.9, 798, 798.1, 798.2 is valid for identifying ventricular arrhythmia and sudden cardiac death in medical data. Does not specify if code algorithm generated should be used in primary diagnosis field only, or also used in secondary/other diagnoses fields to identify cases. However, studies reviewed by Ye et al. used both primary/principal diagnosis only and principal/non-	ICD-9 no longer used in Canada.

Study	Code definition used	Commentary
	principal diagnoses combined to achieve a high PPV.	
Singh and Cleveland 2017	ICD-9 clinical modification codes 427.1, 427.2, 427.4x, 427.5, 427.60, or 427.69 in Medicare insurance claims data (specifically, Centers for Medicare and Medicaid Services Chronic Condition Data Warehouse). Was not stated of codes were primary diagnoses or not.	Authors stated that this set of codes was modified based upon another validated approach with a PPV of 92-100%. These set of codes were not used to identify ALQTS specifically. ICD-9 is no longer used in Canada.

Abbreviations: ALQTS (acquired long-QT syndrome); CIHI (Canadian Institute for Health Information); DAD (discharge abstract database); ECG (electrocardiogram); ICD (International statistical classification of diseases and related health problems; ICU (intensive care unit); LQTS (long-QT syndrome)

1.3 A valid operational definition, using Canadian hospital administrative data, and potential limitations

The Discharge Abstract Database from the Canadian Institute for Health Information (CIHI-DAD) is a pan-Canadian (though excluding the province of Québec) hospitalization database – and has been coded using ICD-10 in *all* provinces since 2006. ICD-10 is an updated coding system to ICD-9 and was introduced by the WHO in 1992; the ICD-10 Canadian version (ICD-10-CA) has been used in Canadian provinces starting in 2002.[77] ICD-10-CA only differs from ICD-10 in the extension of code character levels, and no codes are relocated nor deleted;[77] likely, ICD-10-CA and ICD-10 are rather interchangeable.

The codes used in a study by Singh and Cleveland a PPV of 92-100% were ICD-9 codes in Medicare claims data[76] and would thus not be appropriate for use as an outcome definition in a Canadian database (see Table 2). The study by Trac et al. used ICD-10 codes of I47.2 (ventricular tachycardia) and I49.0 (ventricular fibrillation) as a measure of the ventricular arrhythmia outcome in an administrative database;[69] the same author also conducted an

antidepressant study that used the same code definition for the ventricular arrhythmia outcome.[70] Although the PPV for the ICD-10 codes was validated to be high (92%, 95% CI 87-95%; although not as high as 92-100%),[69] cardiac arrythmia ICD-10 codes are limited by a low sensitivity[69] (of around 39% as determined by a study of ICD coding conducted in Alberta[77]). Notably, the ICD-10 code definition is also non-specific to TdP malignant arrhythmias, but as mentioned previously, distinction for TdP or non-TdP is not particularly important – and the term "malignant arrhythmia" to describe the coding by Trac et al. is valid.

In spite low sensitivity, the ICD-10 code definition used by Trac et al.[72] is still a reasonable option for the assessment of medication-associated malignant arrhythmia in Canadian databases – given Canadian hospital administrative databases are coded using ICD-10, and a high PPV illustrates that the codes will accurately capture cases in administrative databases.[72] Specificity and negative predictive value for cardiac arrhythmias coded in administrative data using ICD-10 is also expected to be high; the study conducted in Alberta found that specificity and negative predictive value were 99.2% and 85.3% respectively.[77] Furthermore, low sensitivity is to be expected with any ICD coding for cardiac conditions given that ECG is required for diagnosis – and patients may not always be hooked up onto an ECG.

Another crucial component required for population-based estimations of medication-related malignant arrhythmia hospitalizations is the availability of data pertaining to medications used by hospitalized patients. A pan-Canadian prescription drug database exists in the National Prescription Drug Utilization Information System (NPDUIS) maintained by CIHI, which captures all prescription medications received by public drug plans beneficiaries in Canada. Key information contained in NPDUIS include drug product information – such as drug identification number (DIN) or active ingredient(s) – as well as days supplied of the drug.[78] To study

medication-associated malignant arrhythmia, NPDUIS may be linked to CIHI-DAD; however, the linkage of the database is available only for the study of eight jurisdictions, accounting for two-thirds of the Canadian population (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island, Newfoundland and Labrador, and Yukon Territory). Although CIHI-NPDUIS covers prescription claims data for Ontario, Ontario also has a separate prescription medication database not accessed through CIHI.[79]

Nevertheless, using the linked data from CIHI is robust with regards to the study of medication-associated malignant arrhythmia hospitalizations on a population level. Data from DAD is received directly from either active care facilities, or from provincial health/regional authorities or ministries/departments of health.[80] NPDUIS collects claims data from individual provincial/territorial public drug programs through the ministries of health.[81] For the linkage between DAD and NPDUIS, CIHI is able to link databases using the encrypted health care number given by a particular province or territory, combined with the year of birth.[81] The accuracy of this data linkage process is estimated to be optimal as health care number is a unique identifier.

Coupled with the valid "known-risk" CredibleMeds categorization, using linked hospitalization and prescription databases (i.e. DAD and NPDUIS) would provide a robust estimation of medication-associated malignant arrhythmia hospitalizations on a population level. They are collected routinely from a large population over an extended period, and they are not prone to the bias pertaining to underreporting.

However, some limitations may still exist. First, the low sensitivity of proposed ICD-10 coding may still cause an underestimation of the true incidence. Nevertheless, using valid definition with optimal PPV ensures that these estimations are closer to the true incidence of any

other available data source. Second, prescription medication administrative databases would only capture prescriptions paid for by the public payer. In Canada, only those aged 65 and over are covered by public medication plans; those aged under 65 are usually not publicly covered – unless they are receivers of social assistance. However, the denominator for the incidence can be determined to be people at risk (i.e. individuals who are 65 and older); in fact, individuals aged 65 and over are those most at risk for malignant arrhythmia (whether or not it be associated with medication use).[9,10] Any study using administrative data to look at medication-associated malignant arrhythmia may reasonably exclude individuals under the age of 65. Although significant competing comorbidities are to be expected in individuals of advanced age, incident cases identified through this proposed methodology should be described by existing comorbidities – with these comorbidities making up part of the important whole-population-based patient demographic information and risk factors. Third, it is known that not all public drug plans are encompassed in NPDUIS, although it is believed that most public drug plans are; likely, only minimal public drug plan beneficiaries are not included in NPDUIS. Fourth, over-the-counter medications are also not captured via a *prescription* medication database. However, the vast majority of concerning medications (those on the CredibleMeds known-risk list) are prescribed. Lastly, use of administrative databases coded by ICD-10, such as the Canadian DAD, would only capture occurrences of malignant arrhythmia within hospitals. Nevertheless, hospitalization incidence can be considered a proxy of the overall risk of malignant arrhythmias. As such, awareness of this risk may lead to changes with the aim to reduce number of hospitalizations, and this will have a positive spillover effect in the community – a reduction of hospitalizations through decreased use of culpable medications should also reduce occurrences of medication-associated malignant arrhythmia outside of the hospital.

1.4 Conclusion

Despite the recognition of importance of malignant arrhythmias (specifically, TdP) associated with medication use, clinicians are not sure how widespread this condition is, even with CDSS alerts that inform clinicians of potentially troublesome medications. Certain medications associated with TdP have alternatives which do not prolong the QT_C interval.[9] Many of these QT_C-prolonging medications are used in the community; changing prescribing patterns to reduce hospitalizations will also reduce cases that do not reach the hospital, which are cases that may be fatal.

All epidemiological studies reviewed are tied together by one theme – limitations of methodology and/or scope. Limitations include the use of unreliable, voluntary databases;[20,68] a lack of coverage of a large portion of the population;[55,57,67] a relatively unfeasible prospective study design;[31,67] underestimations of the outcome if an estimation was even provided;[55,57,67] or only a focus on a limited number of medications.[69–71] Use of administrative databases (that are internationally recognized for quality[82]), such as the Canadian hospitalization database (DAD) linked to prescription databases (NPDUIS), can provide a far superior estimation relative to the use of voluntary reporting databases. Furthermore, use of administrative databases obviates the need of a prospective study design, which is not only time-consuming but may also not be feasible to provide the answer sought.

Despite some limitations, using comprehensive administrative databases such as those from the universal Canadian health care system – coupled with a validated case definition of malignant arrhythmia – would provide a generalizable, robust estimation of the incidence of medication-associated malignant arrhythmia in the large elderly population. As well, through the estimation of incidence, other descriptive statistics involving patient demographics can be

analyzed. As such, the results of this estimation have potentially the ability to change prescribing patterns to avoid QT_C-prolonging medications[9] – and provide a fuller picture of patients at particular risk of this adverse medication event.

Chapter 2: Comparative risk of cardiac arrhythmias associated with acetylcholinesterase inhibitors used in treatment of dementias – a narrative review

2.1 Introduction

2.1.1 Alzheimer's Disease and related dementias

Dementia is defined as the "acquired progressive cognitive impairment sufficient to impact [the] activities of daily living;" Alzheimer's Disease (AD) accounts for the vast majority of dementia cases.[83] Other types of dementia include Lewy body dementia, frontotemporal dementia, and vascular cognitive impairment.[83] Clinical features of dementias include loss of episodic memory, difficulties multitasking, and loss of confidence, with later disease stages of disease presenting through behavioural changes, impaired mobility, and possibly hallucinations and seizures.[83] With regards to AD specifically, main features of AD pathology are neurofibrillary tangles and amyloid plaques; the amyloid hypothesis (which is the primary theory with regards to how AD occurs) suggests that the accumulation of pathological forms of amyloid-beta is the primary pathological process in AD.[83]

Current approved treatments for AD are limited: in the United States and Canada, three AChEIs are approved for the treatment of AD symptoms (generic names: donepezil, galantamine, rivastigmine) and one NMDA receptor (a type of ionotropic glutamate receptor) antagonist (generic name: memantine) is approved.[84,85] None of the medications are disease-modifying (i.e. reducing amyloid-beta deposition); disease-modifying treatments are not yet available[83] (although new AD drugs are in the development pipeline).[86] The mechanism of action for AChEIs is the compensation for the loss of central cholinergic neurons in AD (and thus loss of the neurotransmitter acetylcholine (ACh))[87] through decreased breakdown of ACh. Tacrine, an older AChEI, has largely been abandoned from use[88] although it is still available in countries such as the United States.

2.1.2 Efficacy and safety differences between the three acetylcholinesterase inhibitors

Overall, it is considered that there are no profound differences between AChEIs with regards to efficacy or safety, and the selection of a specific agent to prescribe a patient is mainly based upon ease of use, patient tolerability, cost, and clinician/patient preference.[89] A 2008 systematic review of randomized controlled trials showed that evidence is unclear with regards to saying if one of the three AChEIs are more efficacious.[90] Active treatment of any of the three AChEIs found that cognition, functional, global assessment of change, and behavioural improvement is similar amongst patients treated.[90]

Regarding safety, rivastigmine appeared to have the highest incidence of common adverse events (such as vomiting, nausea, dizziness, diarrhea, weight loss) and donepezil appeared to have the lowest incidence.[90] Likewise, the frequency of withdrawals (in general) and withdrawals due to adverse events is highest in rivastigmine trials and lowest in donepezil trials.[90] However, a more recent (2017) review reported that the odds of adverse events was higher in galantamine trials, although donepezil still had the lowest odds of adverse events.[91] Still, all three AChEIs are considered to provide significant improvements compared to placebo, without any indication as to which AChEI is better safety- or efficacy-wise.[91]

Contrasting the common adverse events of AChEIs, there are some potential differences in uncommon/rare adverse effects. Fleet et al. in 2019, for example, found that "donepezil was associated with a higher risk of hospital admission [for] rhabdomyolysis compared [to] rivastigmine or galantamine," with the rationale of the study being based upon a Health Canada alert for donepezil.[92] Post-marketing surveillance may indicate there are important differences within AChEIs with regards to safety. Among other emerging adverse effects that have arisen in recent years is the potentially fatal arrhythmia that can result from donepezil.[93]

2.1.3 CredibleMeds and other regulatory agency updates regarding acetylcholinesterase inhibitors

In spite of review articles finding minimal safety differences between AChEIs, one key and perhaps concerning addition to the CredibleMeds known-risk (of ALQTS/TdP) list was donepezil – which was added to the known-risk list in March 2015.[93] On the other hand, galantamine is only on the conditional-risk list of CredibleMeds[44] whereas rivastigmine is not listed on CredibleMeds.

All three AChEIs were originally approved for use prior to the introduction of pre-clinical cardiac safety assessments in 2005. Donepezil was originally marketed in Canada in 1997 (initial approval in the United States in 1996), and rivastigmine and galantamine were initially marketed in Canada (and approved in the United States) in 2000 and 2001 respectively. In July 2015, coinciding with the CredibleMeds addition for donepezil, the FDA submitted a letter to Eisai Inc. (the manufacturer of Aricept – brand name for donepezil) accepting a revision to the Aricept medication label – with the addition of QT_C prolongation and TdP to the postmarketing experience section.[94] Notably, Health Canada did not create any alerts regarding Aricept and its potential association with QT_C prolongation or TdP. However, alerts were issued in January 2015 regarding the risk of rhabdomyolysis and neuroleptic malignant syndrome.[95]

Neither the labels for Aricept, Razadyne (brand name of galantamine manufactured by Janssen Pharmaceuticals Inc.), nor Exelon (brand name of rivastigmine manufactured by Novartis Pharmaceuticals Corp.) list QT_C prolongation under contraindications, warnings and precautions, nor adverse reactions (other than in the postmarketing subsection for Aricept); there are also no relevant studies regarding cardiac function described under non-clinical toxicology either.[96–98] However, the label for Exelon does list tachycardia under postmarketing experience for cardiac disorders,[98] of which TdP is a type of tachycardia as previously described. The label

for Razadyne additionally lists complete atrioventricular block under postmarketing experience,[97] which is a disorder which may result in QT_C prolongation or TdP.[99] It also lists one postmarketing report of QT_C prolongation and TdP, although it was attributed to a massive overdose.[97]

Donepezil is the most prescribed of the three AChEIs; thus, addition of donepezil to the known-risk list of CredibleMeds is of concern. Studies conducted in two Canadian provinces found that about two-thirds of new users of AChEIs were prescribed donepezil (66% in British Columbia[100] and 69% in Ontario[92]). CredibleMeds utilizes case reports in risk assessment[7], but the Bradford Hill causality analysis is used to determine possible causality between usage of a certain medication and potential of QT_C prolongation and/or TdP.[7] As such, although there may be more case reports for donepezil given increased donepezil use, the additional utilization of pharmacological literature for causality analysis[7] may support that there is in fact an elevated risk with donepezil – and increased case reports are not simply due to increased use.

2.2 Mechanistic differences between the three acetylcholinesterase inhibitors that may lead to donepezil being a higher-risk medication

Patients whom are prescribed donepezil usually have other risk factors for TdP/ALQTS, including female sex and advanced age,[9,10] as dementias such as AD are more prevalent in individuals of advanced age and in females.[101] To illustrate, amongst the British Columbia cohort of new AChEI users, 95% were over age 65 and 60% of the cohort were female.[100] Nonetheless, these characteristics are expected to be common among all AChEI users. In spite of similar efficacy and safety profiles between the three AChEIs, there are still some pharmacological differences (summarized in Table 3 alongside regulatory agency information) between the three AChEIs – differences which may theoretically provide an explanation as to why only donepezil

has been identified as a medication with "known risk" to prolong the QT_C interval and be associated with TdP – which in turn gives credence to the CredibleMeds classification.

Table 3: Summary of mechanisms of QT_C prolongation and TdP malignant arrhythmia by AChEI medications, as well as summary of regulatory agency information [7]

	Donepezil	**Galantamine**	**Rivastigmine**
CredibleMeds classification	Known-risk (prolongs QT_C interval and associated with TdP even when used as directed on medication label)	Conditional-risk (associated with TdP but only under certain conditions, such as overdose, electrolyte abnormalities, or drug interactions)	Not listed on CredibleMeds
Regulatory agency information, postmarketing	QT_C prolongation and TdP added to postmarketing section of FDA medication label for Aricept in 2015. However, no alert for Health Canada.	Mention of occurrence of QT_C prolongation and TdP in singular postmarketing report for Razadyne, but QT_C prolongation and TdP not specifically listed under postmarketing section of FDA medication label. Complete atrioventricular block listed under postmarketing.	Only tachycardia listed under postmarketing section of FDA medication label.
Common mechanisms of QT_C prolongation and TdP malignant arrhythmia	• Increased intracellular calcium as a result of cardiac ACh receptor action • Bradycardia-associated QT_C prolongation • Drug-drug interaction due to metabolism by CYP3A4 and 2D6 (donepezil and galantamine only) • Increases spatial dispersion of repolarization (donepezil and galantamine only)		
Unique mechanisms of QT_C prolongation and TdP malignant arrhythmia	• Potent inhibitor of I_{Kr} (tail current inhibited at IC_{50} of 1.3 μM with metabolites inhibiting at similar IC_{50}); concentration of donepezil during	• Weak inhibitor of I_{Kr} (IC_{50} of 760.2 μM) • No studies found regarding other effects, such as $K_V11.1$ channel	• No relevant drug-drug interactions • No studies found regarding inhibition of I_{Kr} or other effects on $K_V11.1$ channel protein

	Donepezil	Galantamine	Rivastigmine
	regular and prolonged use may reach IC_{50} • Inhibits the $K_V11.1$ channel protein expression and channel protein trafficking to the plasma membrane • σ_1 receptor agonist at therapeutic doses	protein expression and trafficking	• Does not increase spatial dispersion of repolarization

Abbreviations: FDA (Food and Drug Administration); QT_C (corrected QT interval); TdP (torsades de pointes)

2.2.1 Two important similarities that may be associated with risk of arrhythmia – but do not result in differences in risk between acetylcholinesterase inhibitors

Prior to listing pharmacological differences between the three AChEIs, it is important to note two similarities that are associated with risk – although these similarities should not result in *differing* risk between AChEIs. First, all AChEIs are associated with bradycardia; one mechanism is through the blockage of cholinesterase (associated with the vagal nerve) causing atrioventricular[102,103] or sinoatrial block.[96] Blockage of cholinesterase associated with the vagal nerve can also cause prolonged QT;[102] atrioventricular block is known to be associated with increased risk of QT_C prolongation and TdP in certain patients.[99]

Notably, as previously stated, bradycardia is also known to increase the risk of medication-associated ALQTS[12] and bradycardia is a risk factor for TdP in patients with prolonged QT;[52] certain mutations occurring in congenital LQTS are also associated with bradycardia.[104] Contrasting this, other studies have not found bradycardia to be a risk factor for QT_C prolongation,[9,10] although this may be due to study methodology.[10]

Between AChEIs, it has been shown that bradycardia occurs at a similar frequency.[91] As such, although bradycardia may contribute to an increased risk of QT_C prolongation and TdP in general, when the similar frequency of bradycardia is considered concurrently with the mechanism through which bradycardia (or atrioventricular block) may occur, increased risk of QT_C prolongation and TdP for an individual AChEI (i.e., donepezil) cannot be attributed to bradycardia.

It has also been found that activation of cardiac ACh receptors will open voltage-gated calcium channels; this in turn leads to the conclusion that intracellular calcium levels increase, prolonging the cardiac action potential cycle, and hence increasing risk of ventricular arrhythmias.[105] However, it is unlikely that differences in risk of arrhythmia would occur on the basis of ACh activation of cardiac ACh receptors – as all AChEIs increase ACh levels. As well, there is no evidence that one AChEI results in drastically different levels of ACh in comparison to other AChEIs; otherwise, significant efficacy or safety differences should be seen.

2.2.2 Mechanistic differences that may not be associated with differences in risk

There are some pharmacological differences between the three AChEIs that are likely *not* associated with QT_C interval prolongation and TdP – including the positive allosteric modulator activity of galantamine on the nicotinic ACh receptor, and the inhibition of butyrylcholinesterase by rivastigmine.[106] Donepezil and rivastigmine are reported to not have allosteric modulator activity on the nicotinic ACh receptor,[107] although one study on rat brains found that donepezil desensitizes the nicotinic ACh receptor on substantia nigra dopaminergic neurons by being a non-competitive *antagonist*.[108]

Nicotinic ACh receptor allosteric effects by galantamine, towards QT_C prolongation or TdP, are not known – and it may be that there are no relevant effects towards cardiac

arrhythmias. This may be due to several reasons: there is a massive diversity and wide distribution of nicotinic ACh receptors,[109] all AChEIs increase ACh – which act on nicotinic ACh receptors regardless, and maximum levels of receptor activation remain unchanged in the presence of positive allosteric modulators.[110] However, one study found that galantamine increases dopamine output in the prefrontal cortex of rat brains, suggesting that this effect is due to the allosteric potentiation of nicotinic ACh receptors.[111] Dopamine is known to induce ventricular arrhythmias in animals and it may be associated with sinus tachycardia in humans as well.[112] On the other hand, it is not known if the particular increased release of dopamine *specifically* in the brain (caused by the potentiation of nicotinic ACh receptors by galantamine) would affect the heart.

Butyrylcholinesterase is dominant enzyme in the periphery and metabolises many different exogenous compounds.[106] For example, suxamethonium (an analogue of ACh) may cause arrhythmia when there is low butyrylcholinesterase activity.[113] A study also found that administration of butyrylcholinsterase with a lethal dose of sarin vapour in minipigs increased survivability and also prevented cardiac abnormalities.[114] However, no definitive conclusions regarding overall cardiac function in humans and the inhibition of butyrylcholinsterase by rivastigmine can be drawn.

2.2.3 Drug-drug interactions and acetylcholinesterase inhibitors

When considering differences between AChEIs that may affect risk of QT_C prolongation or TdP, donepezil and galantamine may have significant pharmacokinetic drug interactions;[115] this is explained by donepezil and galantamine being metabolized by the cytochrome enzymes CYP3A4 and CYP2D6.[91] These are two hepatic cytochrome enzymes associated with clinically significant drug-drug interactions,[1,14] or in other words, these cytochrome metabolic pathways

are often shared by concomitantly prescribed medications.[91] Meanwhile, rivastigmine bypasses the hepatic metabolism pathways and relevant drug-drug interactions are not expected.[116]

However, hepatic metabolism (or lack thereof) by cytochrome enzymes would *only* explain a greater risk of QT_C-interval prolongation due to pharmacokinetic drug-drug interactions; donepezil is on the known-risk list of CredibleMeds, which is not necessarily "conditional" upon drug-drug interactions.[7] In contrast, though, these drug-drug interactions by galantamine *would* explain why galantamine is on the *conditional-risk* list.[44]

2.2.4 Mechanistic differences that are associated with differences in risk

It can be speculated that the significant blockage of I_{Kr}[117] is a potential explanation as to why donepezil is on the known-risk list of CredibleMeds – and is associated with both QT_C prolongation and TdP during routine use. Other mechanisms that can also contribute to this increase in risk are: the effect of donepezil on $K_V11.1$ trafficking,[42] donepezil increasing spatial dispersion of repolarization[30] and, potentially to a lesser degree, the σ_1 receptor agonist activity of donepezil.[118]

2.2.5 Potency of I_{Kr} inhibition by donepezil

A crucial difference in risk may lie in the potency of I_{Kr} inhibition; pharmacological research studies pertaining to I_{Kr} inhibition by donepezil and galantamine are found in the literature. Regarding rivastigmine, no literature is available regarding I_{Kr} inhibition; only a study on rivastigmine block of two hippocampal neuronal potassium channels was reported.[119]

Although the ability of a medication to block I_{Kr} cannot fully explain TdP risk,[18] it can explain the relative difference in risk. A study by Chae et al. found that donepezil inhibits the tail current of I_{Kr} with an IC_{50} of 1.3 μM, with the metabolites of donepezil inhibiting the tail current at a similar concentration.[117] On the other hand, a study by Vigneault et al. found that

galantamine inhibits I_{Kr} with an IC_{50} of 760.2 μM.[120] In comparison, a study by Kamiya et al. looked at terfenadine and cisapride (two medications withdrawn from market over proarrhythmic concerns about 20 years ago)[24] and found that IC_{50} of I_{Kr} block by terfenadine and cisapride was 0.35 μM and 0.63 μM respectively.[49]

Because the external potassium concentrations used by Chae et al. and Vigneault et al. is not entirely identical (5 mM versus 4 mM respectively[117,120]), methodology differences could explain some variance but would not result in major differences (700 fold) in the IC_{50} values estimated. Still, the two studies were not head-to-head comparisons, and head-to-head studies would provide much stronger evidence with regards to the potency of inhibition of I_{Kr}. IC_{50} is defined as the concentration of an inhibitor in which a response is lowered by half, and it is considered as a measure of potency of an antagonist.[121] In lieu of a head-to-head comparison, using the two studies by Chae et al. and Vigneault et al., donepezil is a far more potent inhibitor of I_{Kr} than galantamine (and an relatively potent I_{Kr} blocker overall when compared to cisapride) – the concentration of donepezil required to inhibit the I_{Kr} current (by half) is considerably lower than the concentration of galantamine required.

It must be noted that the IC_{50} experimentally determined (1.3 μM) is much higher than the therapeutic plasma concentration of donepezil used in the treatment of AD (Cmax of 60.5 μg/L or 0.16 μM for the 10 mg dose in healthy patients).[122] However, donepezil has been shown to accumulate in humans after multiple doses (in which the accumulated concentration is enough to block I_{Kr} according to Chae et al.).[117] Indeed, donepezil has an elimination half-life of over 100 hours in the elderly – where reduced clearance is expected,[123] so repeated dosing will very likely cause clinically significant medication accumulation. As well, donepezil has a large volume of distribution which signifies a large proportion of the medication is distributed into the

tissue; the heart-to-plasma partition coefficient of donepezil is 6.32 ± 0.79 in rat heart tissue.[124] With the 10 mg dose of donepezil having a Cmax of 60.5 μg/L (0.16 μM);[122] when multiplied by the heart-to-plasma partition coefficient, the concentration in the heart would be approximately 1.01 μM, which is not much lower than the IC_{50} of I_{Kr} block by donepezil (1.3 μM). Importantly, although the aforementioned partition coefficient pharmacokinetic data is interesting to note, it is unknown if the 1.01 μM heart concentration calculated through the rat heart tissue plasma partition coefficient would accurately represent the concentration in human heart tissue during routine clinical use.

2.2.6 Other relevant mechanisms which may contribute to the increased risk seen in donepezil

There are other differences between AChEIs – including donepezil inhibiting $K_V11.1$ channel protein expression and channel protein trafficking to the plasma membrane.[42] This characteristic is similar to inhibition of $K_V11.1$ protein channel trafficking by escitalopram[117] – an antidepressant also on the known-risk list of CredibleMeds.[44] Donepezil, escitalopram and citalopram (the racemic mixture of escitalopram and of known-risk as well)[44] all inhibit $K_V11.1$ channel trafficking.[42] Similarly, arsenic trioxide (yet another medication on the CredibleMeds known-risk list[44]) is known to prolong the QT_C interval by inhibition of $K_V11.1$ trafficking, and not via direct I_{Kr} block.[43] Importantly, lowered $K_V11.1$ density (such as during hypokalemia) contributes to loss of function of $K_V11.1$.[31,35] No studies reported any interactions with galantamine or rivastigmine and $K_V11.1$ channel trafficking.

Another finding that may support the increased risk for donepezil and QT_C prolongation or TdP is a recently published (2020) study by Ellermann et al. Female rabbit hearts were treated with one of the three AChEIs in rising concentrations – donepezil was found to prolong the QT interval and action potential duration, induce early afterdepolarizations and TdP, and augment

spatial dispersion of repolarization; galantamine induced early afterdepolarizations and TdP, and augmented spatial dispersion of repolarization, but *decreased* QT interval and action potential duration; rivastigmine prolonged the QT interval and action potential duration, but did not augment spatial dispersion of repolarization and TdP was not observed.[30] In other words, of the three AChEIs, *only* donepezil prolonged QT interval and action potential duration, triggered early afterdepolarizations and TdP, *and* augmented spatial dispersion of repolarization.

Lastly, a mechanism that may be involved in the risk of QT_C prolongation/TdP by donepezil is the σ_1 receptor agonist activity of donepezil. σ_1 receptor activity of galantamine or rivastigmine is less researched and have conflicting results.[125–127] Donepezil binds to σ_1 receptors in the human brain at therapeutic doses, possibly contributing to the mechanism of pharmacological action of donepezil, as σ_1 receptors play a role in the pathophysiology of several neuropsychiatric diseases.[126]

Although σ_1 receptors are known to have high importance in the nervous system, σ_1 receptors are widely found.[128] Limited studies have shown that nanomolar concentrations of σ_1 receptor ligands increase contractility, contraction frequency, and cause irregular contractions in newborn rat cardiomyocytes; as well, various σ receptor ligands have been found to inhibit potassium currents in the central nervous system, which may also translate to inhibition of cardiac potassium channels – thus increasing QT_C duration and causing TdP.[118] Indeed, it has also been found that σ_1 receptor antagonists have antiarrhythmic effects against epinephrine-induced arrhythmias in rats, and σ_1 agonists had proarrhythmic effects; it was hypothesized that these particular results are dependent upon cardiac and not central nervous system σ receptors[129] and it is known that σ_1 receptors are found in the membranes of adult rat ventricular cardiomyocytes.[130] However, a recently published (2020) systematic review puts doubt upon the

negative effects of σ_1 activation; it was found that activation of σ_1 receptors have a role in cardioprotection against hypertrophy, cellular toxicity/apoptosis, and maladaptive endoplasmic reticulum stress responses; as well, σ_1 receptors promote $K_V11.1$ expression (although results are conflicting on this matter).[130]

2.3 Clinical and epidemiological literature regarding potential increased risk associated with donepezil

Studies have examined the association between AChEIs and bradycardia, likely due to the peripheral parasympathomimetic effects of AChEIs resulting in increased risk of bradycardia as already described. As previously mentioned, bradycardia has been determined to occur at similar frequency between AChEIs.[91] However, it is important to review studies of AChEI use and bradycardia – despite bradycardia being associated with risk for QT_C prolongation and TdP,[12,52] assessment of all adverse cardiac events at once may be difficult to do.

To illustrate, two relevant studies are cohort studies conducted using administrative databases by Gill et al. and Hernandez et al., both published in 2009. Gill et al. looked at Ontario data between 2002 and 2004; it was found that AChEI use in comparison to non-use was associated with increased frequency of hospital visits for syncope (adjusted hazard ratio (aHR) 1.76, 95% CI 1.57-1.98), bradycardia (aHR 1.69, 95% CI 1.32-2.15), permanent pacemaker insertion (aHR 1.49, 95% CI 1.12-2.00), and hip fracture (aHR 1.18, 95% CI 1.04-1.34).[131,132] However, using the comparison group of "non-use" may be confounded by indication and heathy user bias.[133] Nevertheless, both AChEI use and non-use cohorts were defined from patients with diagnoses of dementia.[131] Notably, though, a different study also conducted using Ontario administrative data found that AChEI use *reduced* risk of pacemaker insertion (unadjusted HR 0.58, 95% CI 0.55-0.61) with adjustment for covariates not notably changing results.[134]

Hernandez et al. looked at a different population (New England Veterans Affairs Healthcare System between 1999 and 2007) and found a similar result to Gill et al.; a greater risk for bradycardia in the patients taking AChEIs (in comparison to non-use, aHR 1.4, 95% CI 1.1-1.6) was seen.[132,135] It was also found that patients with bradycardia are more likely to experience falls, syncope, or have a pacemaker implantation.[135]

With regards to the studies by Gill et al. and Hernandez et al., it must be noted that bradycardia can lead to syncope, and this can lead to falls and likewise fall-related injuries (such as hip fracture).[131] Notably, syncope (as a symptom by itself) is associated with malignant tachycardic arrhythmias such as TdP.[1] Neither the methodology of the Gill et al. nor the Hernandez et al. study allowed for the investigation of tachycardias; the methodology used only included administrative data coding specifically for bradycardia or low heart rate.[131,135] As such, on a population scale, it was not determined how exactly AChEIs may be associated with QT_C prolongation or tachycardias such as TdP, despite AChEIs being strongly associated with bradycardia. Proxy measures such as syncope would not be valid, and a separate methodology is required.

Two studies that specifically analyzed donepezil treatment on a variety of ECG parameters are a study by Igeta et al., published in 2014, and a study by Wang et al., published in 2018.[102,136] The study by Igeta et al. was retrospective in design with the analysis of medical records, whereas the study by Wang et al. was prospective in design with the recruitment of patients. Both studies found that administration of donepezil reduced heart rate, supporting the findings by Gill et al. and Hernandez et al where an increased risk of bradycardia was observed. Importantly, neither study found that QT_C was prolonged subsequently to the administration of donepezil.[102,136] However, both studies do note case reports involving donepezil, prolonged QT

interval, and TdP. Limitations of both studies include small sample size (Igeta et al., n = 18; Wang et al., n = 60) and a lack of comparisons against the other AChEIs; furthermore, the study by Wang et al. involved stringent inclusion and exclusion criteria, limiting generalizability. Importantly though, both studies were conducted in elderly patients.

Another study that assessed only donepezil was a population-based case-control study that analyzed co-prescribing of donepezil with antibiotics and associated bradycardia/syncope; it noted no significant differences with regards to risks and co-prescription of donepezil with different antibiotics.[137]

2.3.1 A review of case reports

Despite AChEI use being associated with increased risk of bradycardia, changes in ECG or cardiovascular function reported in empirical data have been inconsistent, as demonstrated between studies showing no change in QT_C contrasting case reports demonstrating QT_C prolongation and TdP.[91,102,136] Furthermore, only minimal studies even report on QT_C. A recent 2019 abstract for a systematic review pertaining to all AChEI effects on cardiac conduction (including QT_C intervals and occurrence of TdP) found only four randomized-controlled trials and five cohort studies which reported on QT_C interval – of which only one randomized-controlled trial and one cohort study reported clinically significant results.[138] Additionally, no population-based studies examined the *comparative* impact of the different AChEIs on malignant arrhythmias such as TdP. Given this, it would be prudent to review case reports that are published in the literature.

Table 4: Summary of selected case reports regarding acetylcholinesterase inhibitors and QT_C prolongation/malignant arrhythmia, chronologically ordered [123,139–143]

Case report	Culpable medication	Patient age/sex	Relevant details
Walsh et al. 2002	Rivastigmine	78M	• Polypharmacy (also receiving diltiazem, citalopram, furosemide, aspirin, ranitidine) • Low-normal serum potassium (3.4 mM) • Prior to initiation of rivastigmine, normal QT_C (397 ms) • Seven days after initiation of rivastigmine, QT_C measured to be prolonged (477 ms) • One-week post-discontinuation, QT_C measured to be normal at 399 ms; QT_C remained normal two-months post-discontinuation
Suleyman et al. 2006	Donepezil	82M	• Patient admitted to ED for dizziness and syncope • Patient used 10 mg/day donepezil for past month; no history of other drug use • No history of cardiac disease • ECG revealed complete AV block and ventricular tachyarrhythmia; heart rate at admission was extremely low at 35 beats per minute • Patient treated via stoppage of donepezil and temporary pacemaker; discharged after six days
Fisher et al. 2008	Galantamine	85M	• Patient treated with extended release galantamine 8 mg/day for 1.5 years • History of CAD, hypertension, and other comorbidities; prior occurrence of syncope and bradycardia • At time of admission, patient had syncope, prolonged QT_C, serious cardiac arrhythmias (including premature ventricular contractions), vomiting, and diarrhea • At time of admission, use of multiple medications (irbesartan; clopidogrel; simvastatin; pantoprazole, ergocalciferol; calcium carbonate; acetaminophen) • After admission, galantamine and irbesartan was ceased (the second cessation of galantamine for the patient) and QT_C normalized from 503 ms to 443 ms after four days

Case report	Culpable medication	Patient age/sex	Relevant details
Takaya et al. 2009	Donepezil	83F	• History of MI and multiple other comorbidities • Admitted for diarrhea, vomiting, syncope; no previous history of syncope • Lower than normal heart rate at admission at 54 beats per minute • Use of 5 mg/day of donepezil for at least two years and bisoprolol • Lab work showed low plasma potassium and ECG showed QT_C of 645 ms • Ventricular premature contractions frequently recorded on ECG monitoring • Confirmed TdP on continuous ECG monitoring • Donepezil washed out; QT_C still prolonged (485 ms) on 14th day after admission, but patient discharged in stable condition
Gurbuz et al. 2016	Donepezil	84F	• Patient admitted to ED due to recurrent syncope • Concomitant drugs include donepezil 10 mg (used for one year at time of admission), ramipril, and ASA • No history of antiarrhythmic drug use nor family history of LQTS or sudden cardiac death; prior occurrence of syncope (three years prior to current admission) • Lab work showed normal electrolytes • QT_C interval extremely prolonged (624 ms) at admission; TdP episode occurred during follow-up in coronary care unit • Donepezil removed from drug regimen and QT_C interval normalized within 10 days (to 430 ms) • One-year follow-up resulted in no further complaints of palpitations and syncope
Vogel et al. 2019	Donepezil	26F	• Patient admitted to impatient psychiatric hospital for suicide attempt not from overdose • Medical history of major depression, traumatic brain injury, seizures, hemiplegia, gastroesophageal reflux disease, tachycardia • At time of admission, patient was taking quetiapine, divalproex sodium, metoprolol, montelukast, polyethylene glycol-3350, calcium with vitamin D, pantoprazole, and cephalexin • Donepezil initiated several weeks after admission, starting at 5 mg/once daily, titrated

Case report	Culpable medication	Patient age/sex	Relevant details
			up to 20 mg after three weeks (10 mg/twice daily) • ECG after last dose change shows QT_C of 463 ms and follow-up ECG showed QT_C of 528 ms • At last dose change, patient was also taking pantoprazole and quetiapine • Laboratory results were normal during hospital stay; discontinuation of donepezil normalized QT_C

Abbreviations: ASA (acetylsalicylic acid); AV (atrioventricular); CAD (coronary artery disease); ECG (electrocardiogram); ED (emergency department); LQTS (long-QT syndrome); MI (myocardial infarction); QT_C (corrected QT interval)

We identified and reviewed six individual case reports (summarized in Table 4). Four of them involved patients taking donepezil, while one case involved galantamine and one involved rivastigmine. Five identified cases occurred in very old individuals (one case age 78, other cases aged > 80); most cases had prolonged QT_C intervals (some extremely prolonged; > 600 ms), with QT_C interval normalizing after discontinuation of the AChEI. Three cases occurred in males and three in females. Four of six identified cases also had occurrences of arrhythmia. However, not all patients were on multiple medications, nor did all patients have comorbidities.[123,139–143] Of the four donepezil cases, two cases had minimal comorbidity or polypharmacy relative to other cases,[123,141] perhaps making donepezil more likely to be causally associated with the QT_C prolongation and arrhythmia (relative to the other cases). For the Vogel et al. case,[142] donepezil was also considered the likely cause of the observed QT_C prolongation, in spite of the existing comorbidities and polypharmacy. Importantly, the Vogel et al. case was the only one we found occurring in a young individual.[142] Findings also worth highlighting include one case having observations of complete atrioventricular block, bradycardia, and ventricular tachyarrhythmia,[123] as well as a case with findings of low heart rate concurrently with premature ventricular

contractions[140] (premature ventricular contractions are concerning when in combination with bradycardia[52]).

Four of the six case reports we reviewed also provided summaries of other case reports in literature. Gurbuz et al. [141] noted that they found five reported cases of QT_C prolongation associated with donepezil use, with three cases experiencing TdP. Vogel et al. reported two additional case reports (not previously described by us or by Gurbuz et al.) of QT_C prolongation associated with donepezil use.[142] Most other cases had significant comorbidities and/or polypharmacy; all cases occurred in individuals aged 80 and over.[142] Another case report primarily summarized cases of bradycardia and atrioventricular block with donepezil use,[123] while the fourth case report[143] provided a summary of reports to the Australian Adverse Drug Reaction Advisory Committee prior to June 2007, and found that galantamine had the highest rate of reporting for arrhythmia.

Malik et al. published a series of seven cases involving donepezil use, QT_C prolongation, and TdP. We reviewed this case series in detail as it was a more in-depth description of cases (relative to aforementioned case reports which only provided short summaries of other cases), it was more recent (published in December 2019), and only one case was previously reviewed by us (Takaya et al.).[105] This case series focused on donepezil and did not examine galantamine or rivastigmine.[105,144] Two additional cases from this series (not previously described by us, by Gurbuz et al., or by Vogel et al.) occurred in female patients over the age of 80 who were on multiple medications and had hypertension.[105] One of these cases is of exceptional significance as the patient developed asymptomatic TdP multiple times without a finding of prolonged QT_C.[105,145] Findings of TdP in the absence of prolonged QT_C have also occurred in other patients; for example, a 72 year old female patient on sotalol and dofetilide.[50]

In the seven cases reviewed by Malik et al.,[105] six cases occurred in females and one occurred in a male; all cases occurred in patients over age 80. Of six cases that had findings of prolonged QT_C, three developed TdP (including the Takaya et al. case we described). Donepezil was withdrawn in five of the six cases with prolonged QT_C (and also withdrawn for the case without prolonged QT_C); findings of normalized QT_C were seen in four of the five cases. The Takaya et al. case did not result in a normalization of QT_C (as described in Table 4) although withdrawal of donepezil did reduce QT_C from 645 ms to 485 ms. For the case where donepezil was not withdrawn, benidipine was switched to amlodipine which resulted in normalized QT_C. Two other cases specifically worth noting from the case series are the cases published by Tanaka et al. in 2009 – both cases (90-year-old male, 87-year old female) had bradycardia, atrioventricular block, and QT_C prolongation, with the 87-year-old female also developing TdP followed by ventricular fibrillation.[105]

2.4 Conclusion

Donepezil is the only agent – among all AChEIs used to treat dementias such as AD – that is deemed to be associated with a known-risk of QTc prolongation and TdP malignant arrhythmia.[44] This narrative review found that the evidence for QT_C prolongation and associated TdP regarding donepezil consists only of case reports[105,123,140–142,145] and pharmacological studies with potential explanations for increased risk.[30,42,117] Table 3 shows several mechanisms may explain the QT_C prolongation and TdP by donepezil and contrasts it against galantamine and rivastigmine. Still, the current knowledge on this topic is limited – no population-based epidemiological studies have examined the comparative risk of malignant arrhythmias associated with use of the three different AChEIs.[132]

A comparative study between AChEIs is needed, as case reports or pharmacological literature is not conclusive evidence of increased risk for donepezil. It is expected that observational epidemiological studies, such as a population-based retrospective cohort (in the same vein as studies regarding AChEIs and bradycardia[131,135]) be conducted to confirm if the increased risk with donepezil use is in fact appearing in the real-life practice. If results show that there are differences in risk of malignant arrhythmias such as TdP between the AChEIs, then changes in prescribing patterns should be made.

Chapter 3: The Literature Gap and Study Objectives

As expressed in the conclusion of Chapter 2, a comparative study for the risk of malignant arrhythmia is needed – such a study does not exist, and it appears that donepezil is associated with a higher risk. Because with the aging population of Canada, I would expect an increase in the incidence of AD and related dementias; clinicians should have as much information as they can to make evidence-based decisions in the safest choice of AChEI. As such, this literature gap ought to be filled, and it is the objective of this study to do so. The choice of one of the three AChEIs for treatment of AD symptoms is primarily dependent upon clinician and patient preference; a more evidence-based approach is expected should differences in risk be found to exist.

As expressed in Chapter 1, valid methodology exists which allows for the measurement (and thus comparison) of malignant arrhythmias using Canadian administrative databases. Potential limitations, as noted in Chapter 1 (i.e., not all age groups present in databases; low sensitivity for outcome measure; competing comorbidities) will not hamper the validity of such a study – AChEIs are overwhelmingly prescribed to older individuals (which are covered by CIHI databases); a low sensitivity is not expected to impact a comparative study – as it is non differential; and competing comorbidities can be used as covariates in analysis. The most important limitations may be that many occurrences of malignant arrhythmia occur outside the confines of a hospital, as well as an inability to assess mortality data with regards to AChEI use; however, from the conclusion of Chapter 1, changing prescribing patterns to reduce hospitalizations will also reduce cases that do not reach the hospital – which are cases that may also be fatal.

Chapter 4: Methodology

4.1 Study Design

Retrospective population-based cohort study design.

4.2 Study aim/objective

Amongst elderly individuals (those aged 66 and over) in Canada, the study aims to determine if new initiation of donepezil is associated with a higher risk of hospitalization for a malignant arrhythmia, in comparison to new initiation of galantamine or rivastigmine.

4.3 Hypothesis

Amongst elderly individuals (those aged 66 and over) in Canada, the hazard of hospitalization for malignant arrhythmia is higher in individuals who newly initiated donepezil, than in individuals who newly initiated galantamine or rivastigmine.

4.4 Data source

DAD and NPDUIS, a hospitalization discharge and prescription medication database maintained by CIHI respectively, are the two sources of data for this study. A CIHI data fiscal year starts on April 1st and ends March 31st of the subsequent year;[146] this study utilizes DAD data between 2006-2007 to 2018-2019 fiscal years and NPDUIS data between 2010-2011 to 2018-2019 fiscal years for the jurisdictions of British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB), Ontario (ON), Prince Edward Island (PEI), and Newfoundland and Labrador (NL).

An online data request is sent to CIHI in which a data requestor gives an initial set of data specifications for CIHI to provide. For the DAD portion of my given data, I was provided the

following variables: meaningless but unique patient identifier; month and year of admission to hospital; birth year; income quintile of individual; province of patient's health card; hospital admission category; diagnosis code, cluster, prefix, and type of up to 25 diagnosis fields; hospital discharge disposition; gender; up to 20 fields of hospital interventions; and length of hospital stay. However, 20 fields of hospital interventions, hospital discharge disposition, and length of hospital stay were not provided for all observations in the dataset. For the NPDUIS portion of my given data, I was provided the following variables: meaningless but unique patient identifier; province of patient's health card; sex; age; unique identifier for medication claim; service date of dispensation; income quintile of individual; Anatomical Therapeutic Chemical (ATC) classification; DIN/PDIN and PDIN flag; active ingredient; route of administration of medication; days' supply of medication; and quantity accepted of medication.

The 25 DAD diagnosis fields correspond to the primary diagnosis field (most responsible for hospital admission) as well as 24 diagnosis fields that can correspond to other diagnosis types; including pre-admit comorbidity or subsequent diagnoses due to hospital intervention. Individuals' income quintiles are determined by CIHI using Statistics Canada's Postal Code Conversion File Plus (PCCF+), which links 6-character postal codes to census geographic areas – of which income information (for geographic areas) can then be extracted and assigned to patients.[147] DINs (drug identification numbers) are assigned by Health Canada to uniquely identify medication products, and are specific towards a manufacturer, product name, active ingredient(s), strength(s), and pharmaceutical form. PDINs (pseudo-drug identification numbers) are used when a benefit has not been assigned a DIN by Health Canada.[148] A list of medications provided in the NPDUIS dataset is found in Appendix B (Tables 5 and 6).

NPDUIS only captures accepted medication claims where at least part of the claim was accepted by a provincial public plan or program, either toward a deductible (if applicable) or for payment. As such, not all medication use will be captured through NPDUIS. NPDUIS also does not capture prescriptions that were written but not dispensed, the unit of dispensed quantities, nor diagnoses for dispensed prescriptions. In the timeframe of NPDUIS data (2010-2011 to 2018-2019 fiscal years), NPDUIS captures the following medication plans and programs:

Table 7: Public medication plans and programs captured by NPDUIS between 2010-2011 to 2018-2019 fiscal years

Jurisdiction	Plan/program captured; description	Plans/programs not captured
Newfoundland and Labrador	• Foundation Plan • 65 Plus Plan • Access Plan • Select Needs/Cystic Fibrosis Plan • Select Needs/Growth Hormone Plan • Assurance Plan • Personal Care Home • Child Youth and Family Services • Home Support Services • Long Term Care	
Prince Edward Island	• Diabetes Control Program • Generic Drug Program • Opioid Replacement Therapy Drug Program • Immunization Program • Family Health Benefit Program • High-Cost Drug Program • Nursing Home • Seniors' Drug Cost Assistance Program • Catastrophic Drug Program • Children in Care Financial Assistance • Sexually Transmitted Diseases	• Residents of privately owned nursing homes whose care is not publicly subsidized are not covered through the Nursing Home Program but may be covered through other plans • Residents of government manors (publicly owned nursing homes) are covered through the Institutional Pharmacy Program but these claims are not captured in NPDUIS

Jurisdiction	Plan/program captured; description	Plans/programs not captured
	• Quit Smoking Program/Smoking Cessation Program	• All other PEI provincial medication plans not listed to the left are not captured in NPDUIS
Manitoba	• Employment and Income Assistance Program • Palliative Care • Pharmacare • Personal Health Care/Nursing Homes	
Saskatchewan	• Universal Program	
Ontario	• Ministry of Community Services (MCSS) • MOHLTC (Ministry of Health and Long-Term Care) Ontario Drug Benefit Program (ODB)	
Alberta	• Non-Group • Seniors • Palliative Care	• Income Support • Alberta Adult Health Benefit • Assured Income for the Severely Handicapped • Alberta Child Benefit • Any claim financed to residents of long-term care facilities
British Columbia	• Fair PharmaCare • Permanent Residents of Licensed Residential Care Facilities • Recipients of British Columbia Income Assistance • Cystic Fibrosis • Children in the At Home Program • No-Chare Psychiatric Medication Program • BC Palliative Care Drug Plan • Smoking Cessation	

Individuals covered by federal medication programs, or individuals covered by provincial workers' compensation boards are not eligible for provincial public coverage and are also not

captured in NPDUIS. Federal medication programs include those delivered by the Correctional Service of Canada, Veterans Affairs Canada, and First Nations and Inuit Health Branch (except for Ontario where individuals may be covered both through the Ontario Drug Benefit program as well as the First Nations and Inuit Health Branch).

4.5 Validity and linkage of CIHI databases

As described in Chapter 1, data from DAD is received directly from either active care facilities, or from provincial health/regional authorities or ministries/departments of health.[80] NPDUIS collects claims data from individual provincial/territorial public drug programs through the ministries of health.[81] As such, the error rate is expected to be low. For the linkage between DAD and NPDUIS, I linked the databases using a meaningless, unique encrypted patient identifier given to each individual in the dataset by CIHI. This encrypted patient identifier is generated based upon the province or territory of the individual's health card information, combined with the year of birth.[81] The accuracy of this data linkage process is estimated to be optimal, as can be seen below.

A previous report[149] has found that demographic variables were coded extremely well in DAD (>99.8% agreement between original coder and re-abstractor on data such as gender, birthdate, health card number, admission date, and discharge date). Most responsible diagnosis (the first diagnosis field in DAD) was also determined to be well coded; and it is stated that "inferences derived from the [most responsible diagnosis] … are reaffirmed by this [report]." Detailed information pertaining to the accuracy of the data in NPDUIS could not be found; however, given submission of data to the database by government ministries (as previously stated),[81] it is assumed that NPDUIS data is highly accurate. An older 2003 study conducted on the Ontario ODB (of which NPDUIS pulls from) found an error rate of 0.7% (95% CI 0.5%,

0.9%).[150] However, assessment of the accuracy of other jurisdictions may be difficult, given that only the plans covered by NPDUIS were listed, and not the provincial databases themselves. For example, the BC database used to record community pharmacy dispensations is called PharmaNet, and previous studies have assessed accuracy of particular indicators such as adherence;[151] it is unknown if NPDUIS pulls BC prescription medication data from PharmaNet, or how the plans covered by NPDUIS in BC may reflect PharmaNet or NPDUIS accuracy for BC.

4.6 Study participants

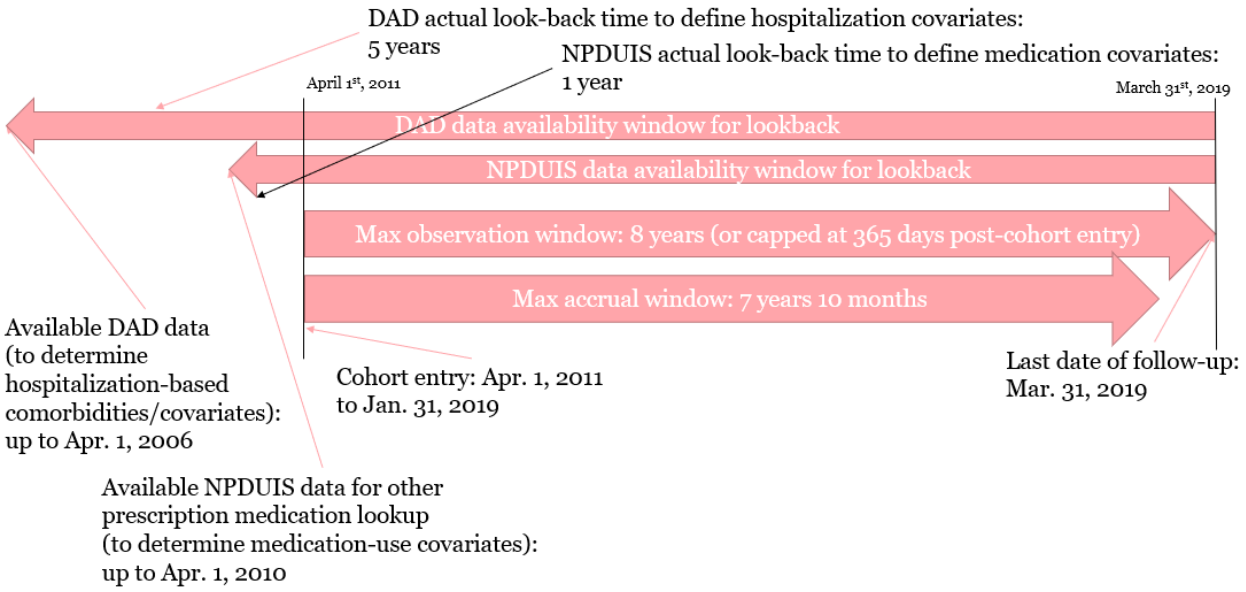

Figure 1: visualization of project time-frame definition.

For the source population, the cohort of individuals to be analyzed was assessed through NPDUIS. In the NPDUIS dataset directly provided by CIHI, individuals were included if they were aged 66 and over and dispensed either donepezil, galantamine, or rivastigmine between the fiscal years and jurisdictions listed in Section 4.4. For my data request, CIHI excluded patients who were dispensed donepezil, galantamine, or rivastigmine in the 365 days prior to cohort entry

date (index date); patients that had no dispensations of prescription medications in the 365 days prior to the first dispensation of donepezil, galantamine, or rivastigmine; patients dispensed a combination of donepezil, galantamine, or rivastigmine on the first dispensation date of any of those medications; or patients whose sex was missing or unknown. Regarding exclusions due to unknown sex, CIHI estimates that 0.04% of individuals were excluded based on unknown sex.

The first dispensation of donepezil, galantamine, or rivastigmine was considered the index date, or T_0 with regards to follow-up time. Additional exclusion criteria, administered after the data specifications provided by CIHI, were the following:

- Patients who entered the cohort in February or March 2019. Due to the lack of "date" data provided regarding the occurrence time of the event of interest (only month/year of hospitalization provided), patients who entered the cohort in February or March 2019 were excluded from the study to ensure enough follow-up time.
- Patients dispensed neostigmine or pyridostigmine (ATC codes N07AA01, N07AA02 respectively) at any time were excluded from the study.
- Patients who have a record for the definition of event (outlined in Section 4.10 below) in the 365 days *prior* to index date were excluded from the study.

4.7 Exposure assessment

After administration of exclusion criteria as described in Section 4.6, any individual aged 66 and over that was dispensed donepezil for the first time in NPDUIS was included in the exposure group. Following an intention-to-treat methodology, this individual was followed-up until an occurrence of an event or until an individual met censoring criteria outlined in Section 4.11. Gaps in donepezil coverage, as would be determined by days' supply variable, are not

considered in the assessment of the exposure. The exposure group will be referred to as the donepezil group in the thesis.

4.8 Assessment of control group

After administration of exclusion criteria as described in Section 4.6, any individual aged 66 and over that were dispensed galantamine, oral rivastigmine, or transdermal rivastigmine for the first time in NPDUIS was included in the control group. Following an intention-to-treat methodology, this individual was followed-up until an occurrence of an event or until an individual met censoring criteria outlined in Section 4.11. Gaps in galantamine, transdermal rivastigmine, or oral rivastigmine coverage, as would be determined by days' supply variable, are not considered in the assessment of the control group.

In the main analysis, the "other" AChEI group, which contains galantamine, oral rivastigmine, and transdermal rivastigmine, will be considered the main control group. In the secondary analysis, the control group(s) will be referred to separately as the galantamine group, oral rivastigmine group, or transdermal rivastigmine group (except for in Cox regression which still combined the two rivastigmine groups as one) – as they were assessed separately.

4.9 Follow-up period

Two follow-up periods were established. First, as the primary analysis, patients were followed-up from the index date until the occurrence of the outcome, or the end of the study period (March 31st, 2019). As such, the maximum possible follow-up period was eight years following the index date (refer to Figure 1). Secondly, patients were followed-up for up to 365 days following the index date (as a secondary analysis). Follow-up ended if an event of interest occurred, or if the patient met censoring criteria should an event of interest not occur.

The rationale for two separate follow-up periods was that it has been found that the development of LQTS in antipsychotic drugs had a median of 11 days (interquartile range of 3 to 31.3 days).[58] A study also reviewed that onset of TdP following administration of a QT_C prolonging days was within 72 hours for 18% of people; between 3 and 30 days, onset occurred for 42% of people; the remaining 40% of people had onset after 30 days.[152] A study on terfenadine, a medication removed due to QT_C prolongation risk,[24] found that median time-to-onset of TdP was 10 days.[153] It is more likely that capping follow-up at 365 days increases the likelihood that an occurrence of a hospitalization of malignant arrhythmia is associated with the initiation of AChEI. On the other hand, capping follow-up may result in outcomes that are missed, which are outcomes that may still be associated with constant AChEI use. Nevertheless, it was expected that results of a time-to-event analysis between an unlimited follow-up, and capping follow-up at one year, would not significantly differ.

4.10 Definition of event

Per previous studies reviewed in Chapter 1 Sections 1.1.3 and 1.3, a malignant arrhythmia was defined as a hospitalization with an ICD-10-CA diagnosis of I47.2 (ventricular tachycardia) or I49.00 (ventricular fibrillation).[69,70] DAD has up to 25 separate diagnosis fields, and separate analyses were conducted – as the main analysis, the definition of event was I47.2 or I49.00 in the primary diagnosis field only (identified as the first DAD diagnosis field – all labeled diagnosis type M); as the secondary analysis, the definition of event was I47.2 or I49.00 in any of the 25 diagnosis fields. The type of diagnosis was ignored for non-primary diagnoses.

Due to data limitations, whereby the date of hospitalization admission was not provided in DAD (only month and year provided), the event of interest was coded as the 15th day of the month, with sensitivity analyses coding the event of interest as the 1st and 30th day of the month

(28th of the month if event occurred in February). As described previously, this hospitalization date adjustment was also conducted when considering exclusions due to previous malignant arrhythmia in 365 days pre-index date of AChEI.

4.11 Censoring

Individuals were censored at the end of follow-up time if an event of interest did not occur. Individuals were censored prior to the end of follow-up time (either March 31st, 2019 or 365 days post index) at the earliest of the following criteria:

1. If an individual switched between donepezil, galantamine, transdermal rivastigmine, or oral rivastigmine, individual was censored at switch date.
2. The last AChEI fill days' supply +50% grace period.

The criteria of not filling any prescription was not considered as censoring criteria, as if an individual was censored at the last AChEI fill days' supply +50% grace period, even if they filled no other prescriptions before that (which is unlikely), they'd still be alive at the last AChEI fill date (unless some sort of data error occurred).

4.12 Statistical methodology

The analysis for this study was conducted as a survival (time-to-event) analysis. Regression was conducted using the Cox proportional hazards regression model.

4.13 Covariates

Factors that were considered important confounding variables were chosen based upon known risk factors for LQTS and/or malignant arrhythmia (such as those identified by Tisdale et al. or Vandael et al.).[9,10] In the Cox regression model, in addition to exposure to AChEI medication group, 42 variables were considered for inclusion in the model as confounders.

Demographic covariates, including age, sex, income quintile, and index year were determined using the NPDUIS data record for the index AChEI dispensation. Comorbidities were determined based upon hospitalization data in the five years prior to index medication date, while medication use was determined based upon prescription medication data in the 365 days prior to index date (as per Figure 1).

With regards to comorbidities based upon prescription medication data, additional definitions were generated using the data sets given by CIHI, although not all comorbidity definitions were considered in descriptive statistics or Cox regression analysis – covariates based upon medications' effects on cytochrome P450 enzymes were ignored since utilization of such a broad range of medications at baseline is not an accurate indicator of a pharmacokinetic drug-drug interaction that may be present at the occurrence of an outcome of malignant arrhythmia. Table 8, below, shows the variables considered for inclusion into the Cox model, in addition to AChEI medication group. Exact definitions of medication use based upon prescription medication data is found in Appendix B (Table 9), and exact definitions of comorbidities based upon hospitalization data (using all 25 DAD diagnosis fields) is found in Appendix C (Table 10).

Table 8: Covariates considered for inclusion in the Cox regression model

Demographic factors
Age group (expanded into five quintiles based on age distribution: 66-75, 76-80, 81-84, 85-87, 88-100+)
Patient sex
Patient jurisdiction
Patient income quintile depending on area of residence – computed by CIHI
Index year (of donepezil or other AChEI medication)
Comorbidities determined based upon hospitalization data (determined using DAD) in the five years prior to index medication date
Previous malignant arrhythmia (*between one and five years prior to index medication date only*)

Previous diagnosis of myocardial infarct

Previous diagnosis of angina

Previous diagnosis of cardiomyopathy

Previous diagnosis of heart failure

Previous diagnosis of conduction disorders

Previous diagnosis of liver disease

Previous diagnosis of hypothyroidism

Previous occurrence of sepsis

Previous hypertension

Previous chronic kidney disease (CKD)

Previously determined use of pacemaker

Previous coronary revascularization procedure

Medication-use variables determined based upon prescription medication data (determined using NPDUIS) in the 365 days prior to index medication date

Antithrombotic agent use

Cardiac glycoside use

Class I and III antiarrhythmic agent use

Use of cardiac stimulants, excluding glycosides

Use of vasodilators in cardiac disease

Use of centrally acting antiadrenergics

Use of peripherally acting antiadrenergics

Use of agents acting on arteriolar smooth muscle

Use of thiazides

Use of low ceiling diuretics (excluding thiazides)

Use of loop diuretics

Use of potassium sparing agents

Use of diuretics and potassium sparing agents in combination

Use of peripheral vasodilators

Use of beta blockers, excluding sympathomimetics

Use of beta blockers with sympathomimetic activity

Use of beta blocking agents and other diuretics

Use of dihydropyridines

Use of selective calcium channel blockers (CCBs) with direct cardiac effects

Use of CredibleMeds known-risk medications
Use of "female" hormones
Use of "male" hormones
Use of thyroid hormones
Use of antithyroid preparations

4.14 Detailed statistical analyses

Descriptive statistics of covariates were assessed using frequency tables and Chi-square tests between donepezil and other AChEI medication groups (except for the continuous age variable which was compared through a Student's t-test or one-way ANOVA). The continuous age variable was converted into a categorical age group based on quintiles (66-75, 76-80, 81-84, 85-87, 88-100+). The maximum recorded age in the cohort was 100 as the exact age of any individuals older than 100 was not reported by CIHI. All variables considered for analysis in the study were categorical.

Initial survival analysis consisted of graphing probability distribution functions (of event occurrence versus time), cumulative incidence curves (separated by exposure vs. control medication group), and computing incidence rates of the outcome through a Poisson regression. Cumulative incidence (failure) curves were preferred over survival curves given the outcome of interest (malignant arrhythmia) being extremely rare. Both the Log-Rank and Wilcoxon tests were assessed for the cumulative incidence curves, given that earlier occurrences of the outcome may have greater importance than later occurrences. A p-value of less than 0.05 was considered statistically significant in the analysis, both for assessment of the cumulative incidence curves, and for Cox regression as described below.

Prior to building the Cox regression model, all combinations of predictor variables were assessed through the Phi Coefficient (for any 2x2 comparison) or Cramer's V (for any

comparison bigger than a 2x2 comparison) statistic, to determine correlations between predictor variables. Correlations between predictor variables provided an important determining factor as to whether certain predictor variables (or combinations of predictor variables) were to not be used together in the final Cox model. The cut-off I used for a significant correlation between predictor variables was the absolute value of Phi Coefficient or Cramer's V being greater than 0.15.[154]

Variables significant in the univariate analysis tests were entered in the final Cox model if they were not significantly correlated with other covariates already included in the Cox model. Variables deemed to be unstable (i.e., variables suffering an extreme departure from the proportional hazards assumptions due to low event rate in one group of a binary variable) were also not considered for inclusion. Variables forced into the Cox regression model were age, patient sex, occurrence of previous malignant arrhythmia, and loop diuretic use; age, patient sex, and loop diuretic use have been previously found to be important predictors for ALQTS and arrhythmias,[9,10] and it was also expected that previous malignant arrhythmias could be predictive of future occurrences. After determination of variables to force into the Cox regression model, I assessed AIC for inclusion of additional variables. Model building was conducted using a manual forward method, and covariates were retained in the Cox model if they decreased AIC. However, variables were not included in the Cox regression model even if inclusion AIC (or if they were significant at the univariate model), if strong correlations with predictors already in the Cox regression model was observed (as per Phi Coefficients/Cramer's V above).

After the full Cox regression model was built, proportional hazards assumption was assessed through the plotting of Martingale residuals. As well, to test for potential effect modifiers, interaction terms were introduced into the Cox model after proportional hazards was

verified. Age group and patient sex were tested for effect modification through interaction terms, as well as age group by hospitalization/medication comorbidity covariates, patient sex by hospitalization/medication comorbidity covariates, and AChEI medication group by all other covariates in the model. A p-value of less than 0.05 was considered significant with regards to the interaction terms.

SAS® version 9.4 (SAS Institute Inc., Cary, NC) was used to perform the statistical analysis. Figures were also generated in SAS® version 9.4 and underwent modifications by photo editing software if key figure elements (e.g., axis labels) were not generated correctly. If applicable, additional calculations were also done with Microsoft Excel.

4.15 Sensitivity and secondary analyses

As described in Sections 4.7 and 4.9, CIHI did not provide exact date of hospitalization in DAD (only month/year provided). Sensitivity analyses will consider if the hospitalization date is set as the 1st, 15th, or 30th (28th for February) of the month with regards to exclusion based on 365 days prior to AChEI index date, as well as a separate analysis excluding *all* patients who had a record for the definition of an event prior to index date (instead of just those with a record within 365 days prior to index date). As described in Section 4.10, the adjustments for hospitalization date was also used when looking at the occurrence of the outcome. As previously stated, hospitalization dates assigned as the 15th of the month (for both exclusions and outcomes) is the primary hospitalization date definition.

For probability distribution functions and Cox regression, as described previously, secondary analyses involved using all 25 DAD diagnosis fields (instead of just the primary diagnosis field), capping follow-up at 365 days (instead of using the maximum possible available follow-up), and separating out the "other" AChEI group into individual galantamine, oral

rivastigmine, and transdermal rivastigmine initiators. For probability distribution functions and Cox regression, I repeated all analyses and generated all tables/figures for using the sensitivity and secondary definitions of hospitalization.

Importantly, application of hospitalization date sensitivity criteria may result in certain patients being excluded from the cohort, or censored. The application of sensitivity was used to assess if changing the hospitalization date definition criteria would change conclusions drawn with regards to the medication group and outcome). An exclusion based on hospitalization date definition took priority over the hospitalization date definition for outcome, for individuals that had an I47.2/I49.00 hospitalization that would vary between exclusion or outcome dependent upon hospitalization date definition (e.g. noted I47.2/I49.00 in the same month as AChEI index).

4.16 Missingness in data

Outside of patient income quintile, no variables contained missing information. However, patient income quintile was not "missing" in the SAS coding sense; rather, CIHI assigned missing patient income quintile to an actual value that represented "missing" or "N/A." Patient income quintile was not included in the Cox regression model due to non-significance with the outcome of interest (hospitalization for malignant arrhythmia), and as such missingness was ignored. No patients were excluded from the cohort on the basis of missing income quintile information.

Chapter 5: Results

5.1 Study sample

From April 1st, 2011 to March 31st, 2019, and for individuals aged 66 and older, the specifications of the dataset provided by CIHI resulted in 9,021,532 dispensations of donepezil, galantamine, or rivastigmine, corresponding to 165,604 unique individuals. Although I requested CIHI to provide prescription claims data of AChEI dispensations in the jurisdictions AB, BC, SK, MB, ON, NL, and PEI, users of AChEIs in these jurisdictions were excluded from the dataset provided by CIHI: if sex was unknown, if they had a dispensation of an AChEI at age 65, if they had dispensations for multiple AChEIs at index date (the date at which an individual was first dispensed an AChEI in the claims data), or if they had no claims for *any* medications in the 365 days prior to the first dispensation of an AChEI. The number of exclusions based on the above criteria was not provided by CIHI. Additionally, as described in the methods, NPDUIS only includes accepted medication claims, "where at least part of the claim was accepted by the public plan/program, either toward a deductible (if applicable) or for payment." In numbers provided by CIHI, the proportion of donepezil claims accepted by public drug programs are 23.1%, 66.7%, and 77.8% in SK, BC, and MB respectively.

From the initial dataset provided by CIHI, n = 165,604 (number of individuals dispensed donepezil, galantamine, or rivastigmine according to the criteria I provided CIHI), n = 2,721 were excluded on the basis of index date being in February or March 2019, and n = 197 were excluded on the basis of a neostigmine or pyridostigmine dispensation at any time. As hospitalization data lacked the exact date of admission to hospital, exclusions due to the definition of event being found on record in the 365 days *prior* to index date was completed in two stages: first, n = 150 were excluded from the remaining cohort. Three criteria were then

applied with regards to hospitalization date; either hospitalization date was considered the 1st, 15th (primary definition), or 30th (28th for February) of the month, and further exclusions were conducted on the basis described above during the analysis. For the primary definition of hospitalization, an additional n = 9 were excluded (so total of 159 exclusions due to previous malignant arrhythmia), leading to a final cohort size of 162,527.

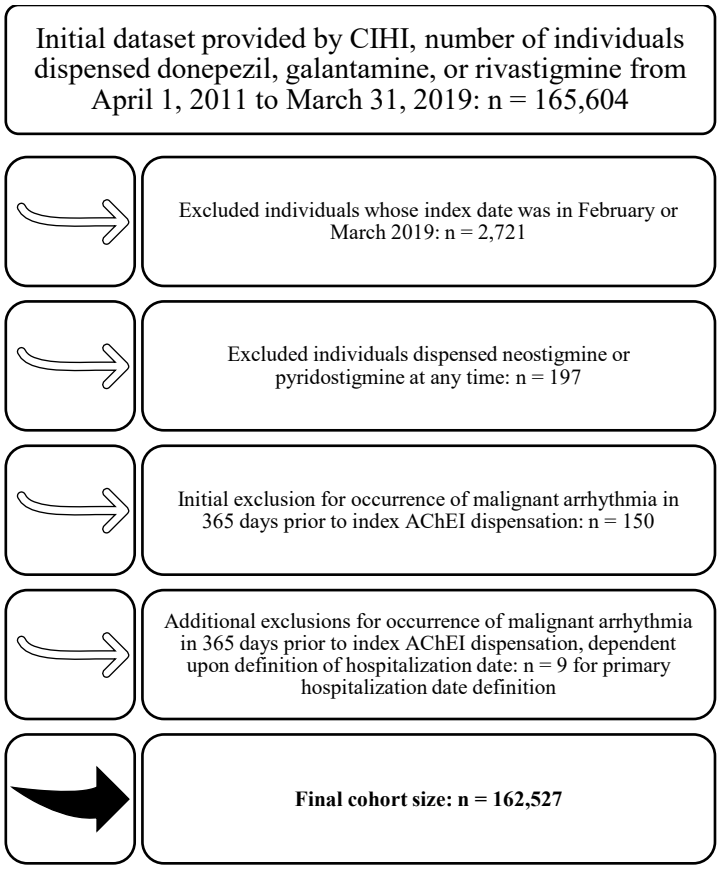

Figure 2: cohort selection, primary definition for hospitalization date used

As previously described in the methods, assigning the hospitalization date as the 15th of the month (for both exclusions due to malignant arrhythmia in 365 days prior to AChEI index date and for occurrence of event post-index) is the primary analysis conducted; unless stated otherwise, all analyses follow this date definition.

5.2 Descriptive statistics between AChEI medication groups

Tables 11 and 12 describe the characteristics amongst the different groups of AChEI initiators (donepezil, galantamine, oral rivastigmine, transdermal rivastigmine). Donepezil initiators account for a little over 78% of the total cohort of 162,527. Among other AChEIs, galantamine was the most common agent (n = 25,582 or 15.7% of all initiators), while transdermal rivastigmine was the least common AChEI (n = 3,371 or 2.1% of all initiators). The mean age of the sample was 81.5 (SD 6.75), median age was 82, and there was a higher proportion of females (59.8% of cohort). A little over 36% of the cohort also have noted dispensations for CredibleMeds known-risk medications.

There were significant differences between donepezil and other AChEIs initiators. Of the 18 hospitalization or prescription covariates which differed (when comparing donepezil against other AChEIs together), in 16 of those did the "other" AChEIs have the higher proportion (the two in which the other group was not higher were thiazide use and use of low ceiling diuretics excluding thiazides). Of the 23 hospitalization or prescription covariates where at least one AChEI group differed (when comparing donepezil against other AChEIs separately), galantamine initiators had the higher proportion (in comparison to donepezil initiators) in up to 18 of these covariates (with only one covariate – thiazide use – where galantamine initiators had a lower proportion than donepezil initiators). In two of these covariates (antithrombotic medication use and use of CredibleMeds known-risk medications) this difference was greater than 3%. In up to seven of the 23 differing covariates (most notably previous myocardial infarct, antithrombotic medication use, and use of dihydropyridine calcium channel blockers), galantamine initiators have greater comorbidity burden than both oral and transdermal rivastigmine initiators, although this trend was not consistent amongst the other covariates whose

proportions significantly differed between AChEI groups – for some covariates it was rivastigmine initiators that had the highest comorbidity burden (most notably conduction disorders, hypertension, and loop diuretic use).

Table 11: Comparison between donepezil and combined galantamine, oral rivastigmine, and transdermal rivastigmine ("other")

	Initiators of donepezil (n, % of total donepezil initiators) Total n = 127,038 Total % = 78.2%		**Initiators of other AChEIs (n, % of total initiators of other AChEIs)** Total n = 35,489 Total % = 21.8%		**Total N = 162,527 (n, % of entire cohort)**	**p-value (chi-square test)**
Age						
Mean (SD)	81.4 (6.8)		81.5 (6.8)		81.5 (6.8)	0.0283
Median (IQR)	82.0 (77.0-86.0)		82.0 (77.0-86.0)		82.0 (77.0-86.0)	(T-test)
Age group						0.1841
66-75	25,543	20.1%	7,191	20.3%	32,734 (20.1%)	
76-80	28,349	22.3%	8,068	22.7%	36,417 (22.4%)	
81-84	28,652	22.6%	7,954	22.4%	36,606 (22.5%)	
85-87	19,762	15.6%	5,540	15.6%	25,302 (15.6%)	
88-100+	24,732	19.5%	6,736	19.0%	31,468 (19.4%)	
Sex						<0.0001
Male	50,343	39.6%	14,950	42.1%	65,293 (40.2%)	
Female	76,695	60.4%	20,539	57.9%	97,234 (59.8%)	
Jurisdiction						<0.0001
British Columbia	17,045	13.4%	6,125	17.3%	23,170 (14.3%)	
Alberta	10,829	8.5%	3,519	9.9%	14,348 (8.8%)	
Saskatchewan	2,648	2.1%	381	1.1%	3,029 (1.9%)	
Manitoba	4,181	3.3%	653	1.8%	4,834 (3.0%)	
Ontario	89,632	70.6%	24,139	68.0%	113,771 (70.0%)	
Prince Edward Island	887	0.7%	385	1.1%	1,272 (7.8%)	
Newfoundland and Labrador	1,816	1.4%	287	0.8%	2,103 (1.3%)	
Income quintile						<0.0001
Lowest	27,889	22.0%	8,263	23.3%	36,162 (22.3%)	
Medium-low	27,490	21.6%	7,691	21.7%	35,181 (21.7%)	
Medium	24,088	19.0%	6,708	18.9%	30,796 (19.0%)	
Medium-high	21,573	17.0%	5,758	16.2%	27,331 (16.8%)	
Highest	22,516	17.7%	6,459	18.2%	28,975 (17.8%)	
N/A, missing, or out of province	3,742	2.7%	610	1.7%	4,352 (2.7%)	
Index year						<0.0001

	Initiators of donepezil (n, % of total donepezil initiators) Total n = 127,038 Total % = 78.2%		Initiators of other AChEIs (n, % of total initiators of other AChEIs) Total n = 35,489 Total % = 21.8%		Total N = 162,527 (n, % of entire cohort)	p-value (chi-square test)
2011	13,838	10.9%	5,572	15.7%	19,410 (11.9%)	
2012	19,233	15.1%	6,338	17.9%	25,571 (15.7%)	
2013	17,107	13.5%	5,066	14.3%	22,173 (13.6%)	
2014	15,393	12.1%	4,505	12.7%	19,898 (12.2%)	
2015	15,382	12.1%	4,273	12.0%	19,655 (12.1%)	
2016	15,416	12.1%	3,568	10.1%	18,984 (11.7%)	
2017	14,826	11.7%	3,069	8.7%	17,895 (11.0%)	
2018	14,658	11.5%	2,854	8.0%	17,512 (10.8%)	
2019	1,185	0.9%	244	0.7%	1,429 (0.9%)	
Previous malignant arrhythmia between 1- and 5-years pre-index						
Yes	281	0.2%	73	0.2%	354 (0.2%)	0.5798
Previous myocardial infarct						
Yes	10,628	8.4%	3,191	9.0%	13,819 (8.5%)	0.0002
Angina						
Yes	2,304	1.8%	637	1.8%	2,941 (1.8%)	0.8152
Cardiomyopathy						
Yes	440	0.4%	131	0.4%	571 (0.4%)	0.5215
Heart failure						
Yes	6,199	4.9%	1,947	5.5%	8,146 (5.0%)	<0.0001
Conduction disorders						
Yes	13,658	10.8%	4,097	11.5%	17,755 (10.9%)	<0.0001
Liver disease						
Yes	872	0.7%	234	0.7%	1,106 (0.7%)	0.5837
Hypothyroidism						
Yes	3,002	2.4%	846	2.4%	3,848 (2.4%)	0.8201
Sepsis						
Yes	1,908	1.5%	595	1.7%	2,503 (1.5%)	0.0182
Hypertension						
Yes	28,328	22.3%	8,298	23.4%	36,626 (22.5%)	<0.0001
Chronic kidney disease						
Yes	5,677	4.5%	1,700	4.8%	7,377 (4.5%)	0.0101
Pacemaker use						
Yes	1,743	1.4%	482	1.4%	2,225 (1.4%)	0.8425
Coronary revascularization procedure						
Yes	3,133	2.4%	931	2.6%	4,064 (2.5%)	0.0937
Antithrombotic agent use						
Yes	27,449	21.6%	8,596	24.2%	36,045 (22.2%)	<0.0001
Use of Vitamin K and other hemostatics						

	Initiators of donepezil (n, % of total donepezil initiators) Total n = 127,038 Total % = 78.2%		Initiators of other AChEIs (n, % of total initiators of other AChEIs) Total n = 35,489 Total % = 21.8%		Total N = 162,527 (n, % of entire cohort)	p-value (chi-square test)
Yes	35	0.03%	12	0.03%	47 (0.03%)	0.5396
Cardiac glycoside use						
Yes	4,134	3.3%	1,256	3.5%	5,390 (3.3%)	0.0080
Class I and III antiarrhythmic use						
Yes	1,348	1.1%	541	1.5%	1,889 (1.2%)	<0.0001
Use of cardiac stimulants, excluding glycosides						
Yes	545	0.4%	230	0.7%	775 (0.5%)	<0.0001
Use of vasodilators in cardiac disease						
Yes	10,106	8.0%	3,039	8.6%	13,145 (8.1%)	0.0002
Use of other cardiac preparations						
Yes	<6	Suppressed	<6	Suppressed	<6	N/A
Use of centrally acting antiadrenergics						
Yes	520	0.4%	150	0.4%	670 (0.4%)	0.7288
Use of peripherally acting antiadrenergics						
Yes	961	0.8%	304	0.9%	1,265 (0.8%)	0.0577
Use of agents acting on arteriolar smooth muscle						
Yes	621	0.5%	181	0.5%	802 (0.5%)	0.6146
Use of other antihypertensives						
Yes	11	0.01%	<6	Suppressed	Supp.	N/A
Use of thiazides						
Yes	17,821	14.0%	4,761	13.4%	22,582 (13.9%)	0.0032
Use of low ceiling diuretics, excluding thiazides						
Yes	3,664	2.9%	946	2.7%	4,610 (2.8%)	0.0283
Use of loop diuretics						
Yes	17,467	13.8%	5,287	14.9%	22,754 (14.0%)	<0.0001
Use of potassium sparing agents						
Yes	3,069	2.4%	936	2.6%	4,005 (2.5%)	0.0173
Use of diuretics and potassium sparing agents in combination						
Yes	2,593	2.0%	697	2.0%	3,290 (2.0%)	0.3617
Use of peripheral vasodilators						
Yes	456	0.4%	127	0.4%	583 (0.4%)	0.9758
Use of beta blocking agents, excluding sympathomimetics						
Yes	36,111	28.4%	10,391	29.3%	46,502 (28.6%)	0.0016
Use of beta blockers with sympathomimetic activity						
Yes	994	0.8%	283	0.8%	1,277 (0.8%)	0.7774
Use of beta blocking agents and other diuretics						
Yes	309	0.2%	76	0.2%	385 (0.2%)	0.3190
Use of dihydropyridine derivatives (CCBs)						

	Initiators of donepezil (n, % of total donepezil initiators) Total n = 127,038 Total % = 78.2%		Initiators of other AChEIs (n, % of total initiators of other AChEIs) Total n = 35,489 Total % = 21.8%		Total N = 162,527 (n, % of entire cohort)	p-value (chi-square test)
Yes	31,726	25.0%	8,868	25.0%	40,594 (25.0%)	0.9558
Use of selective CCBs with direct cardiac effects						
Yes	7,308	5.8%	2,163	6.1%	9,471 (5.8%)	0.0150
Use of CredibleMeds known-risk medications						
Yes	44,663	35.2%	14,055	39.6%	58,718 (36.1%)	<0.0001
Use of "female hormones"						
Yes	4,475	3.5%	1,218	3.4%	5,693 (3.5%)	0.4122
Use of "male hormones"						
Yes	345	0.3%	108	0.3%	453 (0.3%)	0.3009
Use of thyroid hormones						
Yes	25,933	20.4%	7,228	20.4%	33,161 (20.4%)	0.8469
Use of antithyroid preparations						
Yes	198	0.2%	63	0.2%	261 (0.2%)	0.3676

Table 12: Comparison between donepezil, galantamine, oral rivastigmine, and transdermal rivastigmine

	Initiators of donepezil (n, % of total donepezil initiators) Total n=127,038 Total %=78.2%		Initiators of galantamine (n, % of total galantamine initiators) Total n=25,582 Total %=15.7%		Initiators of oral rivastigmine (n, % of total oral rivastigmine initiators) Total n=6,536 Total %=4.0%		Initiators of transdermal rivastigmine (n, % of total transdermal rivastigmine initiators) Total n=3,371 Total %=2.1%		Initiators of rivastigmine combined (n, % of total rivastigmine initiators) Total n=9,907 Total %=6.1%		p-value (when considering rivastigmine initiators separately, chi-square test)
Age											
Mean (SD)	81.4 (6.8)		81.6 (6.7)		80.3 (7.0)		81.6 (6.5)		[redacted]		<0.0001
Median (IQR)	82.0 (77.0-86.0)		82.0 (77.0-86.0)		80.0 (75.0-85.0)		82.0 (77.0-86.0)				(ANOVA)
Age group											<0.0001
66-75	25,543	20.1%	4,849	19.0%	1,710	26.2%	632	18.8%	2,342	23.6%	
76-80	28,349	22.3%	5,740	22.4%	1,568	24.0%	760	22.6%	2,328	23.5%	
81-84	28,652	22.6%	5,780	22.6%	1,335	20.4%	839	24.9%	2,174	21.9%	
85-87	19,762	15.6%	4,144	16.2%	877	13.4%	519	15.4%	1,396	14.1%	
88-100+	24,732	19.5%	5,069	19.8%	1,046	16.0%	621	18.4%	1,667	16.8%	
Sex											<0.0001
Male	50,343	39.6%	10,213	39.9%	3,308	50.6%	1,429	42.4%	4,737	47.8%	
Female	76,695	60.4%	15,369	60.1%	3,228	49.4%	1,942	57.6%	5,170	52.2%	
Jurisdiction											<0.0001
British Columbia	17,045	13.4%	2,362	9.2%	394	6.0%	3,369	100.0 %	3,763	38.0%	
Alberta	10,829	8.5%	2,764	10.8%	755	11.6%	<6	Supp.	Supp.	Supp.	

	Initiators of donepezil (n, % of total donepezil initiators) Total n=127,038 Total %=78.2%		**Initiators of galantamine (n, % of total galantamine initiators)** Total n=25,582 Total %=15.7%		**Initiators of oral rivastigmine (n, % of total oral rivastigmine initiators)** Total n=6,536 Total %=4.0%		**Initiators of transdermal rivastigmine (n, % of total transdermal rivastigmine initiators)** Total n=3,371 Total %=2.1%		**Initiators of rivastigmine combined (n, % of total rivastigmine initiators)** Total n=9,907 Total %=6.1%		**p-value (when considering rivastigmine initiators separately, chi-square test)**
Saskatchewan	2,648	2.1%	318	1.2%	63	1.0%	<6	Supp.	Supp.	Supp.	
Manitoba	4,181	3.3%	453	1.8%	198	3.0%	<6	Supp.	Supp.	Supp.	
Ontario	89,632	70.6%	19,079	74.6%	5,060	77.4%	<6	Supp.	Supp.	Supp.	
Prince Edward Island	887	0.7%	370	1.5%	15	0.2%	<6	Supp.	Supp.	Supp.	
Newfoundland and Labrador	1,816	1.4%	236	0.9%	51	0.8%	<6	Supp.	Supp.	Supp.	
Income quintile											<0.0001
Lowest	27,889	22.0%	6,042	23.6%	1,345	20.6%	876	26.0%	2,221	22.4%	
Medium-low	27,490	21.6%	5,605	21.9%	1,390	21.3%	696	20.7%	2,086	21.1%	
Medium	24,088	19.0%	4,879	19.1%	1,189	18.2%	640	19.0%	1,829	18.5%	
Medium-high	21,573	17.0%	4,051	15.8%	1,163	17.8%	544	16.1%	1,707	17.2%	
Highest	22,516	17.7%	4,527	17.7%	1,340	20.50%	592	17.6%	1,932	19.5%	
N/A, missing, or out of province	3,742	2.7%	478	1.9%	109	1.7%	23	0.7%	132	1.3%	
Index year											<0.0001
2011	13,838	10.9%	4,076	15.9%	872	13.3%	624	18.5%	1,496	15.1%	
2012	19,233	15.1%	4,454	17.4%	1,023	15.7%	861	25.5%	1,884	19.0%	
2013	17,107	13.5%	3,532	13.8%	838	12.8%	696	20.7%	1,534	15.5%	
2014	15,393	12.1%	3,184	12.5%	780	11.9%	541	16.1%	1,321	13.3%	
2015	15,382	12.1%	3,018	11.8%	746	11.4%	509	15.1%	1,255	12.7%	
2016	15,416	12.1%	2,681	10.2%	752	11.5%	135	4.0%	887	9.0%	
2017	14,826	11.7%	2,341	9.2%	723	11.1%	<6	Supp.	Supp.	Supp.	
2018	14,658	11.5%	2,119	8.3%	735	11.3%	<6	Supp.	Supp.	Supp.	
2019	1,185	0.9%	177	0.7%	67	1.0%	<6	Supp.	Supp.	Supp.	
Previous malignant arrhythmia between 1- and 5-years pre-index											
Yes	281	0.2%	52	0.2%	18	0.3%	<6	Supp.	Supp.	Supp.	0.2739
Previous myocardial infarct											
Yes	10,628	8.4%	2,366	9.3%	598	9.2%	227	6.7%	825	8.3%	<0.0001
Angina											
Yes	2,304	1.8%	458	1.8%	126	1.9%	53	1.6%	179	1.8%	0.6486
Cardiomyopathy											
Yes	440	0.4%	97	0.5%	27	0.4%	7	0.2%	34	0.3%	0.3399
Heart failure											
Yes	6,199	4.9%	1,405	5.5%	372	5.7%	170	5.0%	542	5.5%	<0.0001
Conduction disorders											
Yes	13,658	10.8%	2,942	11.5%	831	12.7%	324	9.6%	1,155	11.7%	<0.0001
Liver disease											
Yes	872	0.7%	182	0.7%	36	0.6%	16	0.5%	52	0.5%	0.2438
Hypothyroidism											
Yes	3,002	2.4%	648	2.5%	164	2.5%	34	1.0%	198	2.0%	<0.0001

	Initiators of donepezil (n, % of total donepezil initiators) Total n=127,038 Total %=78.2%		Initiators of galantamine (n, % of total galantamine initiators) Total n=25,582 Total %=15.7%		Initiators of oral rivastigmine (n, % of total oral rivastigmine initiators) Total n=6,536 Total %=4.0%		Initiators of transdermal rivastigmine (n, % of total transdermal rivastigmine initiators) Total n=3,371 Total %=2.1%		Initiators of rivastigmine combined (n, % of total rivastigmine initiators) Total n=9,907 Total %=6.1%		p-value (when considering rivastigmine initiators separately, chi-square test)
Sepsis											
Yes	1,908	1.5%	392	1.5%	140	2.1%	63	1.9%	203	2.0%	0.0002
Hypertension											
Yes	28,328	22.3%	5,973	23.4%	1,681	25.7%	644	19.1%	2,325	23.5%	<0.0001
Chronic kidney disease											
Yes	5,677	4.5%	1,152	4.5%	392	6.0%	156	4.6%	548	5.5%	<0.0001
Pacemaker use											
Yes	1,743	1.4%	342	1.3%	112	1.7%	28	0.8%	140	1.4%	0.0042
Coronary revascularization procedure											
Yes	3,133	2.4%	713	2.8%	191	2.9%	27	0.8%	218	2.2%	<0.0001
Antithrombotic agent use											
Yes	27,449	21.6%	6,440	25.2%	1,597	24.4%	559	16.6%	2,156	21.8%	<0.0001
Use of Vitamin K and other hemostatics											
Yes	35	0.03%	6	0.02%	<6	Supp.	<6	Supp.	Supp.	Supp.	N/A
Cardiac glycoside use											
Yes	4,134	3.3%	907	3.6%	223	3.4%	126	3.7%	349	3.5%	0.0509
Class I and III antiarrhythmic use											
Yes	1,348	1.1%	376	1.5%	112	1.7%	53	1.6%	165	1.7%	<0.0001
Use of cardiac stimulants, excluding glycosides											
Yes	545	0.4%	116	0.5%	82	1.3%	32	1.0%	114	1.2%	<0.0001
Use of vasodilators in cardiac disease											
Yes	10,106	8.0%	2,152	8.4%	584	8.9%	303	9.0%	887	9.0%	0.0008
Use of other cardiac preparations											
Yes	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	Supp.	Supp.	N/A
Use of centrally acting antiadrenergics											
Yes	520	0.4%	102	0.4%	28	0.4%	20	0.6%	48	0.5%	0.4115
Use of peripherally acting antiadrenergics											
Yes	961	0.8%	231	0.9%	62	1.0%	11	0.3%	73	0.7%	0.0006
Use of agents acting on arteriolar smooth muscle											
Yes	621	0.5%	120	0.47%	39	0.6%	22	0.7%	61	0.6%	0.3178
Use of other antihypertensives											
Yes	11	0.01%	<6	Supp.	<6	Supp.	<6	Supp.	Supp.	Supp.	N/A
Use of thiazides											
Yes	17,821	14.0%	3,554	13.9%	716	11.0%	491	14.6%	1,207	12.2%	<0.0001
Use of low ceiling diuretics, excluding thiazides											
Yes	3,664	2.9%	751	2.9%	178	2.7%	17	0.5%	195	2.0%	<0.0001
Use of loop diuretics											
Yes	17,467	13.8%	3,777	14.8%	1,031	15.8%	479	14.2%	1,510	15.2%	<0.0001
Use of potassium sparing agents											
Yes	3,069	2.4%	675	2.6%	163	2.5%	98	2.9%	261	2.6%	0.0644
Use of diuretics and potassium sparing agents in combination											

	Initiators of donepezil (n, % of total donepezil initiators) Total n=127,038 Total %=78.2%		**Initiators of galantamine (n, % of total galantamine initiators)** Total n=25,582 Total %=15.7%		**Initiators of oral rivastigmine (n, % of total oral rivastigmine initiators)** Total n=6,536 Total %=4.0%		**Initiators of transdermal rivastigmine (n, % of total transdermal rivastigmine initiators)** Total n=3,371 Total %=2.1%		**Initiators of rivastigmine combined (n, % of total rivastigmine initiators)** Total n=9,907 Total %=6.1%		**p-value (when considering rivastigmine initiators separately, chi-square test)**
Yes	2,593	2.0%	517	2.0%	111	1.7%	69	2.1%	180	1.8%	0.2965
Use of peripheral vasodilators											
Yes	456	0.4%	93	0.4%	26	0.4%	8	0.2%	34	0.3%	0.6400
Use of beta blocking agents, excluding sympathomimetics											
Yes	36,111	28.4%	7,603	29.7%	1,925	29.5%	863	25.6%	2,788	28.1%	<0.0001
Use of beta blockers with sympathomimetic activity											
Yes	994	0.8%	209	0.8%	40	0.6%	34	1.0%	74	0.7%	0.1706
Use of beta blocking agents and other diuretics											
Yes	309	0.2%	55	0.2%	13	0.2%	8	0.2%	21	0.2%	0.7687
Use of dihydropyridine derivatives (CCBs)											
Yes	31,726	25.0%	6,642	26.0%	1,492	22.8%	734	21.8%	2,226	22.5%	<0.0001
Use of selective CCBs with direct cardiac effects											
Yes	7,308	5.8%	1,582	6.2%	368	5.6%	213	6.3%	581	5.9%	0.0271
Use of CredibleMeds known-risk medications											
Yes	44,663	35.2%	9,856	38.5%	2,808	43.0%	1,391	41.3%	4,199	42.4%	<0.0001
Use of "female hormones"											
Yes	4,475	3.5%	920	3.6%	219	3.4%	79	2.3%	298	3.0%	0.0021
Use of "male hormones"											
Yes	345	0.3%	88	0.3%	18	0.3%	<6	Supp.	Supp.	Supp.	0.0186
Use of thyroid hormones											
Yes	25,933	20.4%	5,339	20.9%	1,204	18.4%	685	20.3%	1,889	19.1%	0.0002
Use of antithyroid preparations											
Yes	198	0.2%	44	0.2%	12	0.2%	7	0.2%	19	0.2%	0.7852

5.3 Correlation coefficients between all variables of interest

Appendix D (Tables 14-20) shows the correlation coefficients (either Phi Coefficient for a 2x2 comparison or Cramer's V for a comparison bigger than 2x2) for all covariates generated for the cohort (when assigning the hospitalization date as the 15th of the month). As described in Section 4.15 in the Methods, correlation coefficients were a key determinant in the building of the Cox regression model.

Table 13: List of correlated variables and action taken with regards to Cox regression model building

Covariate	Details and actions taken
Jurisdiction	Correlated with AChEI medication group; correlation found to be due to transdermal rivastigmine only being used in BC. Jurisdiction not used in Cox model due to non-significance.
Patient income quintile	Correlated with jurisdiction because income quintiles not captured for patients for SK. Patient income quintile not used in Cox model due to non-significance. Correlation not present if SK excluded (Cramer's V = 0.0348).
Use of thyroid hormones	Correlated with patient sex and hypothyroidism. Covariate not used in Cox model due to non-significance.
Previous myocardial infarct	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
Previous heart failure	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
Conduction disorders	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
Hypothyroidism	Correlated with thyroid hormone use. Hypothyroidism not used in Cox model due to non-significance.
Hypertension	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
CKD	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use. CKD also not used in Cox model due to non-significance.
Pacemaker use	Many correlations with other hospitalization or prescription medication determined comorbidities. Used in final Cox model due to no correlations with other variables already in model.
Coronary revascularization procedure	Many correlations with other hospitalization or prescription medication determined comorbidities. Used in final Cox model due to no correlations with other variables already in model.
Antithrombotic agent use	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.

Covariate	Details and actions taken
Cardiac glycosides use	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
Vasodilator use (in cardiac disease)	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
Use of loop diuretics	Variable forced into Cox regression model as described previously. Many correlations with other hospitalization or prescription medication determined comorbidities.
Use of potassium sparing agents	Correlated with loop diuretic use. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
Use of beta blockers, excluding sympathomimetics	Many correlations with other hospitalization or prescription medication determined comorbidities. Not used in Cox model due to correlation with the forced variable of loop diuretic use.
Use of dihydropyridine derivatives	Correlated with hypertension. Variable not used in Cox model due to non-significance.
Use of thyroid hormones	Correlated with hypothyroidism. Variable not used in Cox model due to non-significance.
Use of "female" hormones	Correlated with use of "male" hormones. Variable not used in Cox model due to non-significance.

5.4 Descriptive survival analysis (without Cox regression) and other trends on the occurrence of malignant arrhythmia

Figure 3 shows the probability density function amongst all individuals in the cohort with the event of interest in the primary DAD diagnosis field only (uncapped follow-up). A total of 90 events occur (total incidence rate of 27.7 per 100,000 person-years, 95% CI 22.5, 34.0); the probability density function is heavily right skewed, with 50% of events occurring at or prior to 386 days, and the maximum follow-up duration being 2,616 days. Figures 4 and 5 show the associated cumulative incidence (failure) curve. Both the Log-Rank and Wilcoxon tests show an association between the AChEI group and the outcome, and it can be seen that there is a limited number of events occurring in initiators of both transdermal and oral rivastigmine.

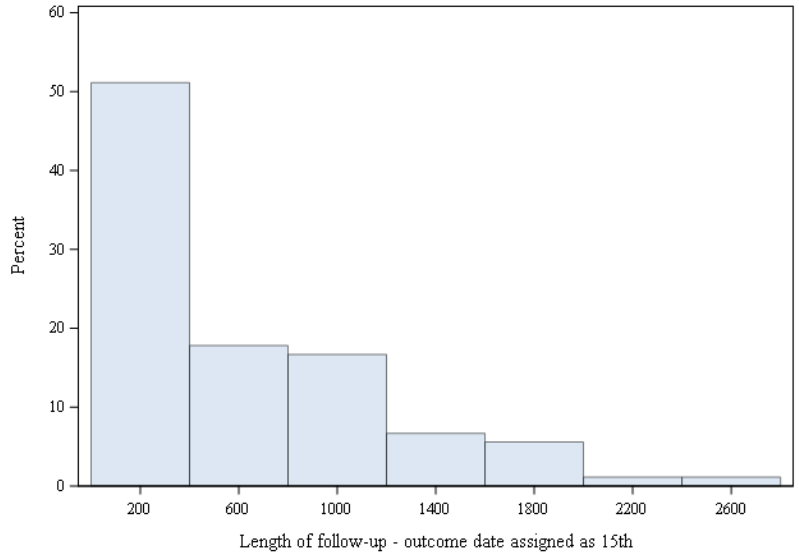

Figure 3: Probability distribution function of occurrence of malignant arrhythmia in primary DAD diagnosis field only, when hospitalization dates for exclusions and outcomes are assigned as the 15th of the month

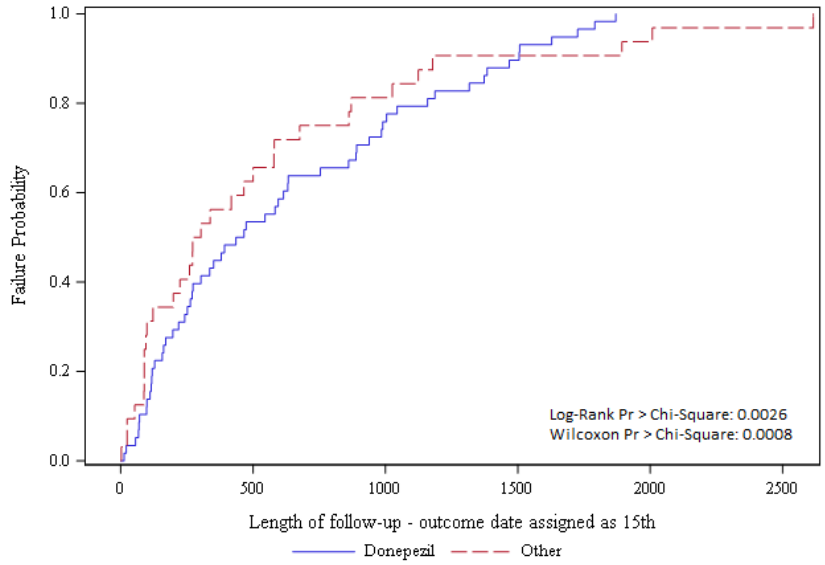

Figure 4: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in primary DAD diagnosis field only, comparing donepezil to the other AChEIs together with uncapped follow-up. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

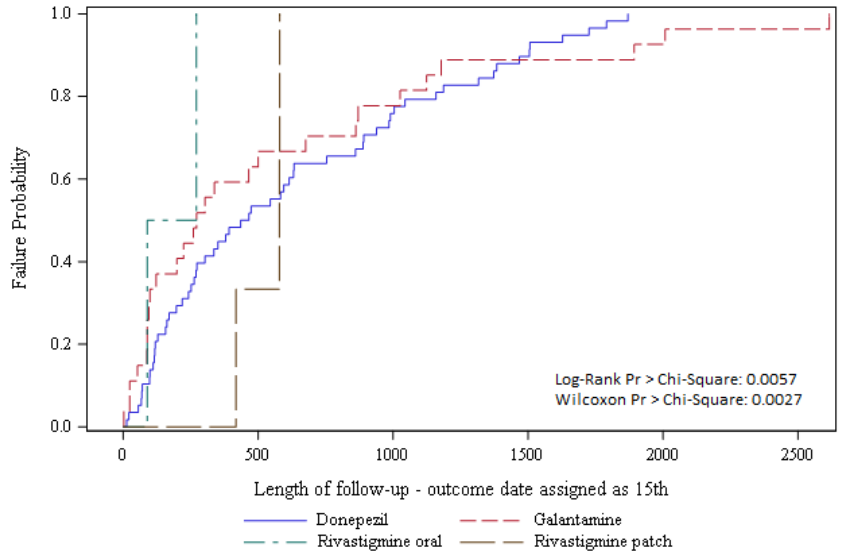

Figure 5: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in primary DAD diagnosis field only, comparing donepezil to the other AChEIs separately with uncapped follow-up. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

Notably, it is donepezil that has a lower incidence of hospitalization for malignant arrhythmia. Amongst donepezil initiators, the incidence rate is 23.0 per 100,000 person-years (95% CI 17.8, 29.7). Non-donepezil initiators (as a whole) have an incidence rate of 43.9 per 100,000 person-years (95% CI 31.1, 62.1), which from Figure 4 it can be seen that this is significantly higher than donepezil initiators. When assessed individually, galantamine initiators had an incidence rate of 48.7 per 100,000 person-years (95% CI 33.4, 71.0), transdermal rivastigmine had an incidence rate of 48.5 per 100,000 person-years (95% CI 15.7, 150.5), and oral rivastigmine had an incidence rate of 17.8 per 100,000 person-years (95% CI 4.5, 71.2). Given a wide confidence interval for the incidence rate for both transdermal and oral rivastigmine initiators, without Cox regression, it cannot be ascertained if that is significantly different than the incidence amongst donepezil initiators.

5.5 Cox regression model building

Using malignant arrhythmia outcomes occurring in the primary DAD diagnosis field only and using the comparison of donepezil versus all other AChEIs combined, a crude Cox regression model (containing only AChEI group) found that donepezil was associated with a lower incidence of (i.e., protective against) occurrence of malignant arrhythmias (HR 0.521, 95% CI 0.338, 0.802), confirming the crude, initial survival analysis in Section 5.4. 17 additional variables were significantly associated with occurrence of malignant arrhythmias when it was included in the Cox model alongside AChEI group; not considering patient sex, all were associated with greater risk if present in the patient. Six variables could not be assessed through Cox regression as not enough data was present (extreme number of patients were coded as not having the comorbidity present, or very few individuals had an outcome in the group coded as having the comorbidity present, which caused a departure from the proportional hazards assumption). The other 19 variables were non-significant in the univariate analysis, including patient income quintile even when considering those that had patient income quintile coded to "N/A, missing, or out of province." No variables changed the association between donepezil and outcome of malignant arrhythmia. See Table 22 in Appendix E for an additional breakdown of univariate Cox regression.

Table 21: Summary of univariate Cox regression, when considered alongside AChEI group (donepezil vs. other AChEI)

Significant association	Non-significant	Not enough data/PH violation
Patient sex (female protective)	Patient age group	Previous diagnosed sepsis
Previous malignant arrhythmia	Patient jurisdiction	Use of centrally acting antiadrenergics

Significant association	Non-significant	Not enough data/PH violation
Previous myocardial infarct	Patient income quintile	Use of peripherally acting antiadrenergics
Angina	Index year of AChEI	Use of peripheral vasodilators
Previous diagnosed cardiomyopathy	Previous diagnosed liver disease	Use of "male" hormones
Previous diagnosed heart failure	Previous diagnosed hypothyroidism	Use of antithyroid preparations
Previous diagnosed conduction disorders	Previous diagnosed CKD	
Previous diagnosed hypertension	Cardiac stimulant use, excluding glycosides	
Previous pacemaker use	Use of agents acting on arteriolar smooth muscle	
Previous coronary revascularization procedure	Use of thiazides	
Antithrombotic agent use	Use of low ceiling diuretics, excluding thiazides	
Cardiac glycoside use	Use of diuretics and potassium sparing agents in combination	
Class I/III antiarrhythmic agent use	Use of beta blockers with sympathomimetic activity	
Vasodilator use in cardiac disease	Use of beta blockers and other diuretics	
Use of loop diuretics	Use of dihydropyridine derivatives	
Use of potassium sparing agents	Use of selective CCBs with direct cardiac effects	
Use of beta blockers, excluding sympathomimetics	Use of CredibleMeds known-risk medications	
	Use of "female" hormones	
	Use of thyroid hormones	

The final number of confounding variables was eight: patient sex, patient age group, occurrence of previous malignant arrhythmia (between 1- and 5-years pre-AChEI index), loop

diuretic use, previous diagnosed cardiomyopathy, pacemaker use, previous coronary revascularization procedure, and class I/III antiarrhythmic agent use. Inclusion of additional variables (namely, previous diagnosed heart failure and antithrombotic agent use) decreased the AIC of the model but were ultimately not included due to correlations with other variables included earlier in the model (especially since AIC decrease was negligible). All other variables were not included in the model due to statistical non-significance at the univariate level and/or no reduction of AIC through a forward model building methodology.

The final Cox regression model still showed donepezil to be associated with a lower incidence of malignant arrhythmias (aHR 0.551, 95% CI 0.358, 0.849). A full breakdown of the model building process can be seen in Appendix E, and Table 23 below shows the effects of all predictors included in the model. Notably, pacemaker use, and previous coronary revascularization procedure no longer meet the threshold for significance, although they were retained in the model due to reductions in AIC. Furthermore, the 95% confidence intervals for occurrence of previous malignant arrhythmia and previous diagnosed cardiomyopathy are far narrower than in univariate analysis. No major violations of proportional hazards were present in the full Cox regression model (see Table 27 in Appendix E).

Table 23: Effects of all predictors in full Cox regression model

	Variable	Hazard ratio estimate	95% confidence interval	
			Lower limit	Upper limit
Uncapped follow-up, malignant arrhythmia outcome in primary diagnosis field only, hospitalization date for exclusions (for malignant arrhythmia in 365 days prior to AChEI index) and for outcome set as 15th of the month	AChEI medication group, crude (reference: other AChEIs together)	0.521	0.338	0.802
	AChEI medication group, adjusted (reference: other AChEIs together)	**0.551**	**0.358**	**0.849**
	Patient sex (reference: male)	0.268	0.168	0.429
	Patient age quintile (reference: age 66-75)	76-80: 1.258 81-84: 0.846 85-87: 0.853 88-100+: 1.294	76-80: 0.691 81-84: 0.435 85-87: 0.400 88-100+: 0.657	76-80: 2.291 81-84: 1.645 85-87: 1.818 88-100+: 2.546
	Occurrence of previous malignant arrhythmia (1- and 5-years pre-index)	4.821	1.525	15.238

Loop diuretic use	3.145	1.975	5.008
Previous diagnosed cardiomyopathy	3.716	1.127	12.255
Pacemaker use	1.708	0.684	4.266
Previous coronary revascularization procedure	1.920	0.927	3.979
Class I and III antiarrhythmic agent use	4.525	2.146	9.539

5.6 Assessment of effect modification in full Cox regression model

As can be seen in Table 28 in Appendix E, introduction of patient age by patient sex, patient age by comorbidity, or patient sex by comorbidity effect modification did not result in notable increases in model fitness; none of the effect modification terms were significant. Furthermore, AChEI medication group did not have any significant interactions with other covariates.

5.7 Sensitivity and secondary analyses for crude survival analysis and Cox regression models

Given an extremely wide confidence interval at the univariate level for occurrence of previous malignant arrhythmia (HR 26.385, 95% CI 9.677, 71.946), a separate Cox analysis excluded the 354 patients with previous malignant arrhythmia. Model fit was significantly better (AIC decreased from 1915.726 to 1850.283). However, results on AChEI medication group remain largely unchanged. On the other hand, the effects of the confounding variables of previous diagnosed cardiomyopathy and pacemaker use were stronger and weaker respectively. A fuller breakdown of the exclusion of all previous malignant arrhythmia patients is provided in Section 5.7.4; further sensitivity and secondary analyses retained patients with previous malignant arrhythmia.

Table 29: Effects of all predictors in full Cox regression model, with all previous malignant arrhythmia patients excluded

	Variable	Hazard ratio estimate	95% confidence interval	
			Lower limit	Upper limit
Uncapped follow-up, malignant arrhythmia outcome in primary diagnosis field only, hospitalization date for exclusions (for malignant arrhythmia in 365 days prior to AChEI index) and for outcome set as 15th of the month	AChEI medication group, crude (reference: other AChEIs together)	0.521	0.338	0.802
	AChEI medication group, adjusted (reference: other AChEIs together)	**0.548**	**0.352**	**0.851**
	Patient sex (reference: male)	0.273	0.170	0.438
	Patient age quintile (reference: age 66-75)	76-80: 1.324 81-84: 0.853 85-87: 0.843 88-100+: 1.397	76-80: 0.717 81-84: 0.430 85-87: 0.384 88-100+: 0.702	76-80: 2.445 81-84: 1.694 85-87: 1.854 88-100+: 2.780
	Loop diuretic use	3.168	1.970	5.095
	Previous diagnosed cardiomyopathy	5.195	1.553	17.372
	Pacemaker use	0.982	0.289	3.342
	Previous coronary revascularization procedure	2.034	0.943	4.386
	Class I and III antiarrhythmic agent use	4.432	1.974	9.950

As described in Section 4.15, sensitivity and secondary analyses was also carried out by:

1) modifying the date of hospitalization (when considering exclusions due to malignant arrhythmia in 365 days prior to AChEI index date) and modifying the date of hospitalization for the event of malignant arrhythmia post-index,
2) modifying the malignant arrhythmia outcome definition (to use all 25 DAD diagnosis fields),
3) modifying the follow-up duration (to cap at 365 days maximum),
4) and separating out the "other" AChEI group into individual galantamine, oral rivastigmine, and transdermal rivastigmine groups.

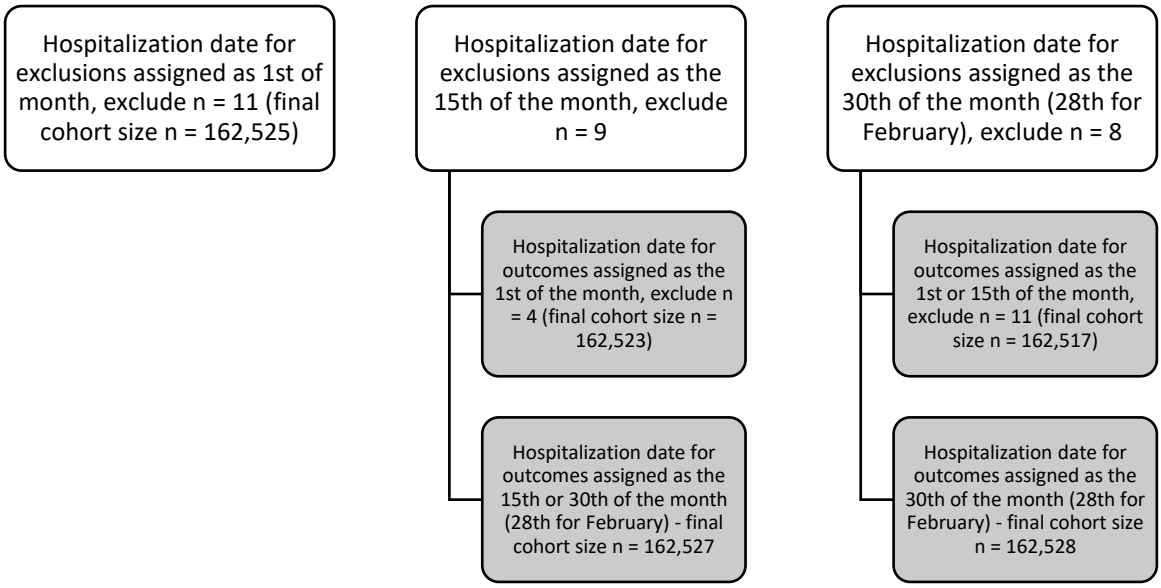

Figure 6: Expanded cohort selection breakdown given modification of hospitalization dates for either exclusions due to malignant arrhythmias in 365 days prior to AChEI index, or for outcomes of malignant arrhythmia post AChEI index. Initial cohort selection breakdown can be seen in Figure 2.

5.7.1 Sensitivity and secondary analyses on probability distribution functions

When considering sensitivity analyses 1) and 2) and only looking at the probability distribution function of event occurrence, it was noted that:

- Amongst all individuals in the cohort with the event of interest in any DAD diagnosis field (uncapped follow-up), using the different date definitions when considering the exclusions or outcome does not notably change the probability density function (figures not shown). However, the total number of events does change somewhat; for example, the range stretches from 348 events (if the definition of the 1st of the month is used when considering exclusions and the 1st of the month is used when considering the outcome) to 308 events (if the definition of the 1st of the month is used when considering exclusions, and the 30th (28th for February) of the month is

used when considering outcome). See Table 30 for a breakdown of the number of events dependent upon hospitalization date definition.

- Same as above, amongst all individuals in the cohort with the event of interest in any DAD diagnosis field and capping follow-up at 365 days, using the different date definitions when considering the exclusions or outcome does not notably change the probability density function, although additional emphasis (i.e. a lesser concentration of events) may be seen on the lack of events early or near the end of follow-up (see Figures 14 and 15 in Section 5.7.3). Again, the total number of events does change somewhat; for example, the range stretches from 137 events (if the definition of the 1st or 15th of the month is used when considering exclusions, and the 1st of the month is used when considering the outcome) to 109 events (if the definition of the 1st of the month is used when considering exclusions, and the 30th (28th for February) of the month is used when considering outcome).
- Amongst all individuals in the cohort with the event of interest in the primary DAD diagnosis field only (uncapped follow-up), using the different date definitions when considering the exclusions or outcome does not notably change the probability density function (figures not shown). The range stretches from 90 to 81 events (if the definition of the 1st of the month is used when considering exclusions, and the 30th (28th for February) of the month is used when considering outcome).
- Similar as above, amongst all individuals in the cohort with the event of interest in the primary DAD diagnosis field only and capping follow-up at 365 days, using the different date definitions when considering the exclusions or outcome does not notably change the probability density function (results not shown). The range

stretches from 44 to 38 events (if the definition of the 1st of the month is used when considering exclusions, and the 30th (28th for February) of the month is used when considering outcome).

As it will be described in Section 5.7.4, modifying hospitalization date definitions does not affect conclusions made through hazard ratios computed through Cox regression either.

Table 30: Summary of number of occurrences of malignant arrhythmia, per follow-up length and DAD diagnosis fields

Follow-up length and definition in DAD		**Exclusion date set as 1st of the month (for previous malignant arrhythmia in 365 days pre-AChEI index)**	**Exclusion date set as 15th of the month**	**Exclusion date set as 30th of the month (28th for February)**
Maximum follow-up, all diagnosis fields	Outcome date set as 1st of the month	348	348	347
	Outcome date set as 15th of the month	332	336	331
	Outcome date set as 30th of the month (28th for February)	308	312	318
Follow-up capped at 365 days, all diagnosis fields	Outcome date set as 1st of the month	137	137	136
	Outcome date set as 15th of the month	125	129	124
	Outcome date set as 30th of the month (28th for February)	109	113	120
Maximum follow-up, primary diagnosis field only	Outcome date set as 1st of the month	89	89	89
	Outcome date set as 15th of the month	88	90	88
	Outcome date set as 30th of the month (28th for February)	81	83	85
Follow-up capped at 365 days, primary diagnosis field only	Outcome date set as 1st of the month	43	43	43
	Outcome date set as 15th of the month	42	44	42
	Outcome date set as 30th of the month (28th for February)	38	40	42

5.7.2 Analyses on probability distribution functions and cumulative incidence curves, using the primary DAD diagnosis field but capping follow-up to 365 days as a secondary analysis

Using the primary hospitalization date definition, Figure 7 shows the probability density function amongst all individuals in the cohort while capping follow-up at 365 days. A total of 44 events occurred (total incidence rate of 36.3 per 100,000 person-years, 95% CI 27.0, 48.7), and the probability density function does not have any particular distribution shape. However, there is a noticeable spike in events occurring around the 90-day follow-up time, with the other follow-up times within 365 days remaining relatively consistent. 50% of events occur prior to 121 days; however, the probability density function is not heavily right skewed and most of the events occurring prior the half-year mark can be accounted for in the spike occurring around the 90-day follow-up time. Figures 8 and 9 show the associated cumulative incidence (failure) curves. Similar to an uncapped follow-up, there is an association between AChEI group and the outcome using either the Log-Rank or Wilcoxon tests. From Figure 9, it is also apparent that there are no events in the transdermal rivastigmine group.

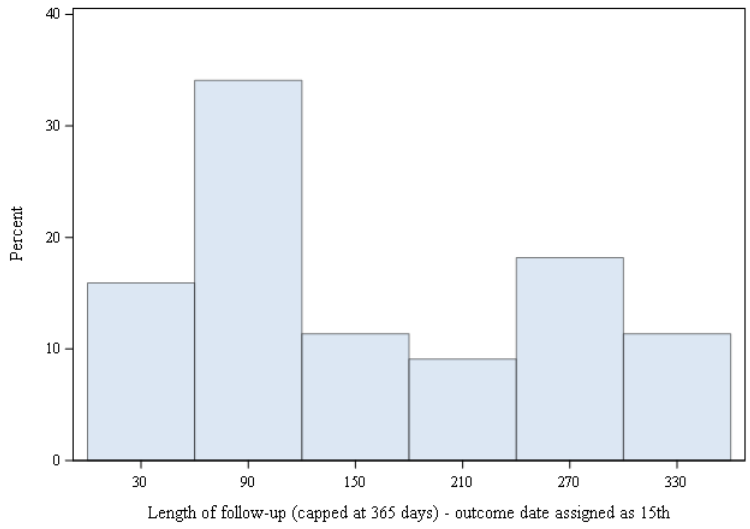

Figure 7: Probability distribution function of occurrence of malignant arrhythmia in primary DAD diagnosis field only, when hospitalization dates for exclusions and outcomes are assigned as the 15th of the month, and follow-up is capped at 365 days

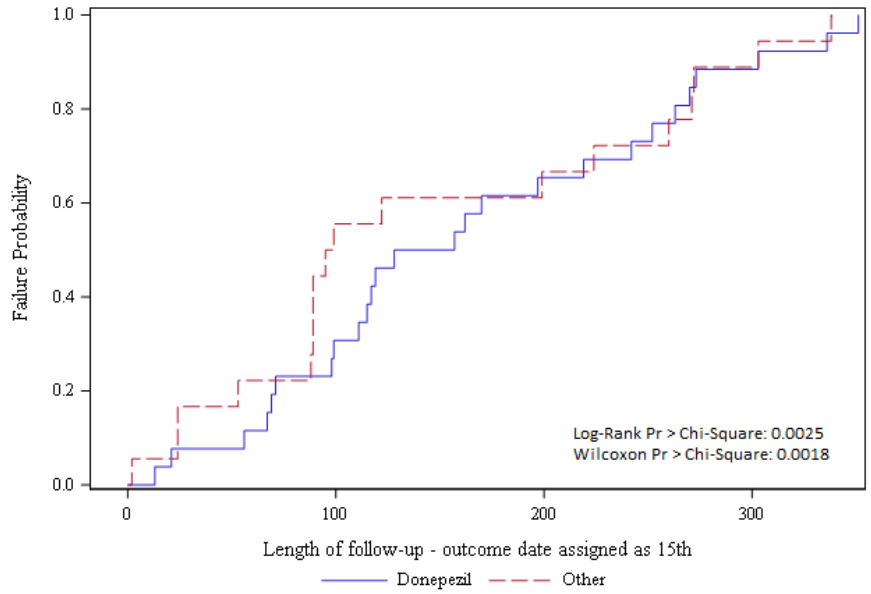

Figure 8: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in primary DAD diagnosis field only, comparing donepezil to the other AChEIs together with follow-up capped at 365 days. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

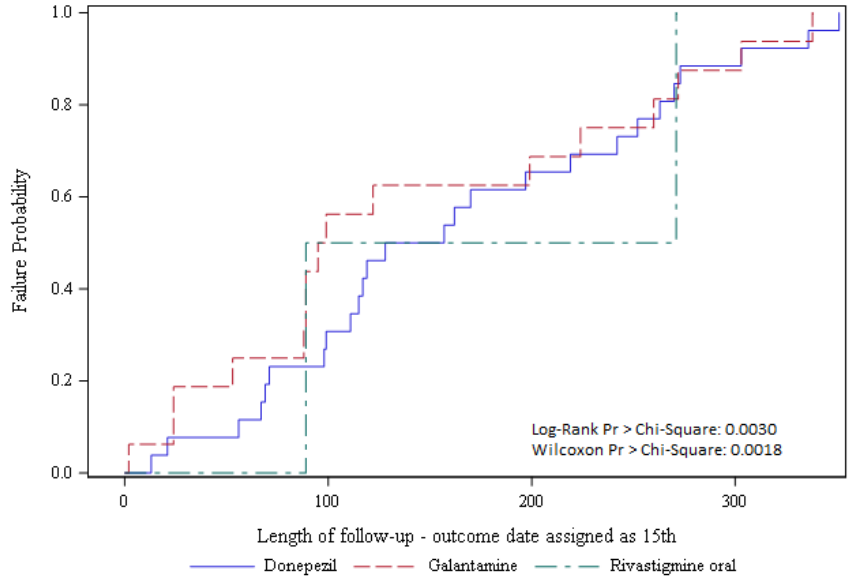

Figure 9: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in primary DAD diagnosis field only, comparing donepezil to the other AChEIs separately with follow-up capped at 365 days. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

The associated incidence rates for the 365-day capped follow-up are 27.5 per 100,000 person-years amongst donepezil initiators (95% CI 18.7, 40.4); 81.2 per 100,000 person-years amongst galantamine initiators (95% CI 49.7, 132.5); and 43.3 per 100,000 person-years amongst oral rivastigmine initiators (95% CI 10.8, 173.3). Amongst all non-donepezil initiators, the incidence rate is 67.3 per 100,000 person-years (95% CI 42.4, 106.9). Overall, these incidence rates are higher than that of an uncapped follow-up, but with wider confidence intervals. Otherwise, the same trends are present.

5.7.3 Analyses on probability distribution functions and cumulative incidence curves, using all 25 DAD diagnosis fields as a secondary analysis

With regards to assessing occurrences of malignant arrhythmia in any of the 25 DAD diagnosis fields, Figure 10 shows the probability density function amongst all individuals in the cohort using an uncapped follow-up. A total of 336 events occur (total incidence rate of 103.4 per 100,000 person-years, 95% CI 92.9, 115.0); the probability density function is heavily right skewed, with 50% of events occurring prior to 516 days, and the maximum duration of follow-up being 2,649 days. This result is similar to that of using the primary DAD diagnosis field only. However, Figure 11 shows the associated cumulative incidence (failure) curve; different from when assessing the outcome in the primary DAD diagnosis field, neither the Log-Rank tests nor the Wilcoxon tests show any significant differences between donepezil and the other AChEIs with regards to time trends and incidence. Figure 12 shows the same cumulative incidence curve, with other AChEIs separated out individually. Conclusions drawn from Log-Rank or Wilcoxon tests would remain unchanged. The incidence rates of individual AChEI initiators are all near the total incidence rate of 103.4 per 100,000 person-years.

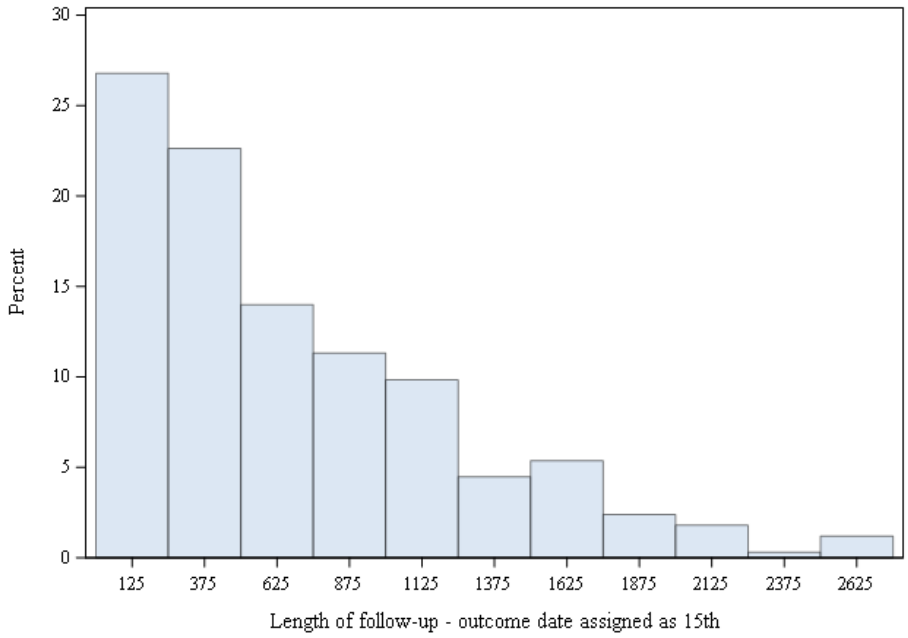

Figure 10: Probability distribution function of occurrence of malignant arrhythmia in any 25 DAD diagnosis fields using uncapped follow-up, when hospitalization dates for exclusions and outcomes are assigned as the 15th of the month

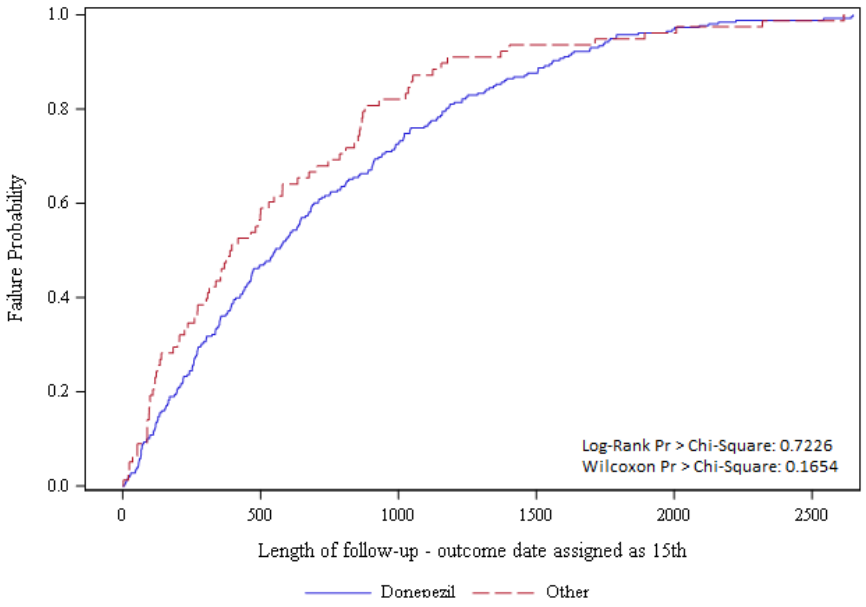

Figure 11: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in all 25 DAD diagnosis fields, comparing donepezil to the other AChEIs together with maximum possible follow-up time. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

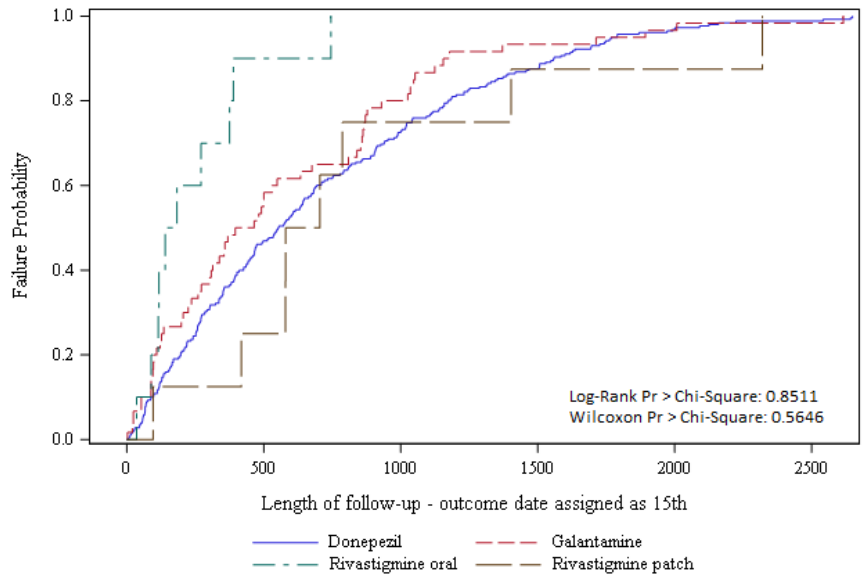

Figure 12: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in all 25 DAD diagnosis fields, comparing donepezil to the other AChEIs separately with maximum possible follow-up time. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

Figure 13 shows the probability density function amongst all individuals and capping follow-up at 365 days (using all 25 DAD diagnosis fields). A total of 129 events occur (total incidence rate of 106.4 per 100,000 person-years, 95% CI 89.5, 126.4); the probability density function does not have any particular distribution shape, although the probability density function is not entirely uniform either, as less events appear to occur very early, or near the end of follow-up. 50% of events occur at or prior to 155 days; although most events occur prior to the half-year mark (specifically peaking around the three months mark), the histogram is not noticeably right skewed. Again, this is similar to the results if only the primary DAD diagnosis field was used. Figures 16 and 17 show the associated cumulative incidence (failure) curve; similar to the uncapped follow-up using all 25 DAD diagnosis fields, neither the Log-Rank nor the Wilcoxon test show any significant differences between donepezil and the other AChEIs.

From Figure 17, it is still extremely apparent that there is a limited number of events occurring in initiators of transdermal rivastigmine.

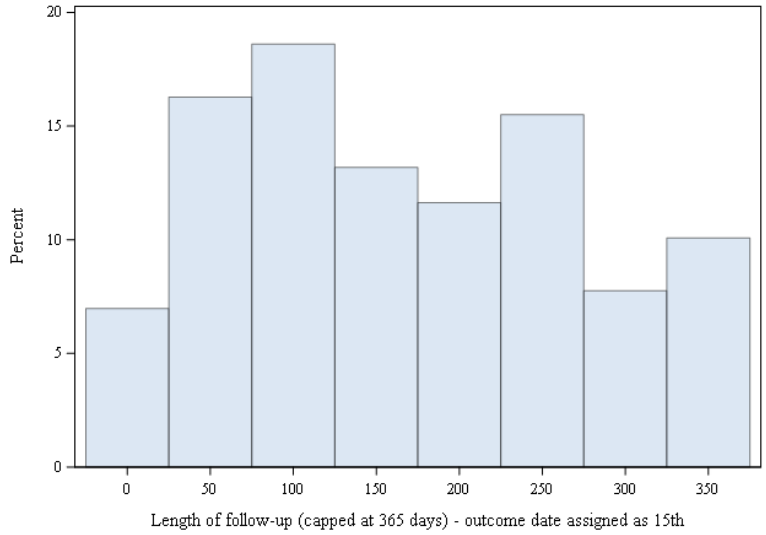

Figure 13: Probability distribution function of occurrence of malignant arrhythmia in any 25 DAD diagnosis fields, when hospitalization dates for exclusions and outcomes are assigned as the 15th of the month, and follow-up is capped at 365 days

As described previously, the shape of the probability density function will look *slightly* different dependent upon the hospitalization date definition used. Additional emphasis may be seen on the lack of events early or near the end of follow-up – although overall, the probability distribution function is still largely similar.

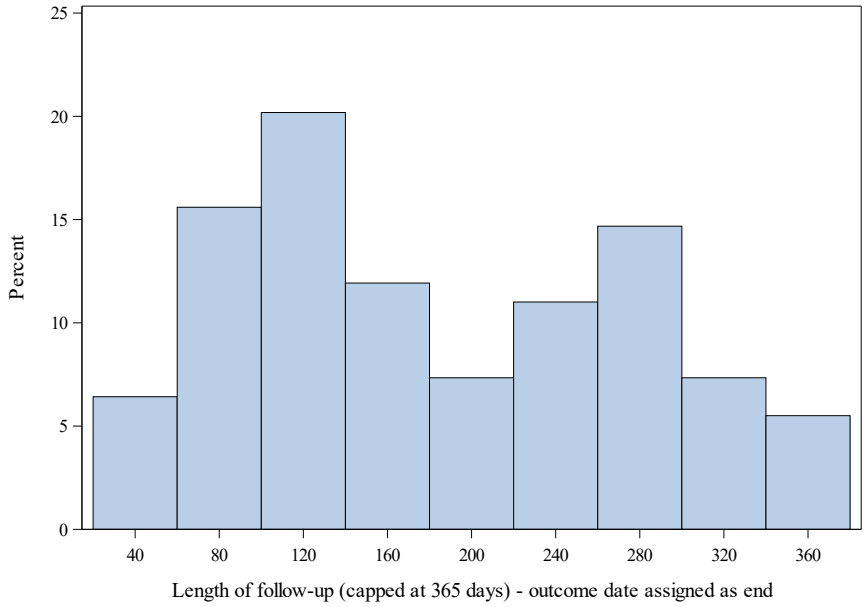

Figure 14: Probability distribution function of occurrence of malignant arrhythmia in any 25 DAD diagnosis fields, when hospitalization dates for exclusions is assigned as the 1st of the month, and outcomes are assigned as the 30th of the month (28th for February), and follow-up is capped at 365 days.

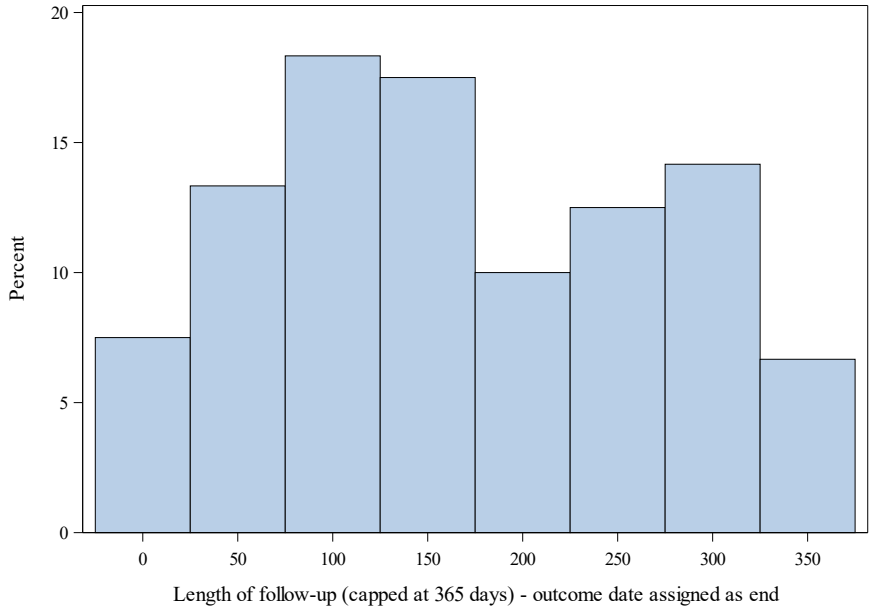

Figure 15: Probability distribution function of occurrence of malignant arrhythmia in any 25 DAD diagnosis fields, when hospitalization dates for exclusions and outcomes are assigned as the 30th of the month (28th for February), and follow-up is capped at 365 days.

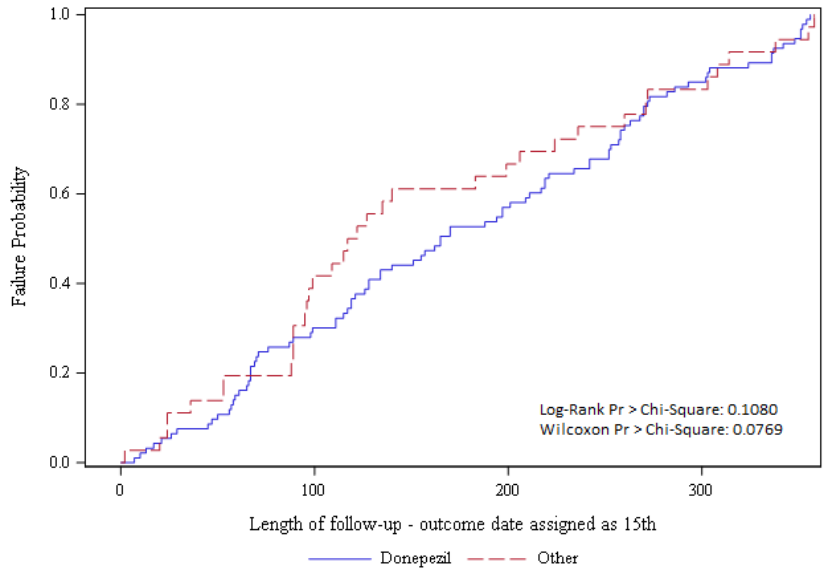

Figure 16: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in all 25 DAD diagnosis fields, comparing donepezil to the other AChEIs together with follow-up time capped at 365 days. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

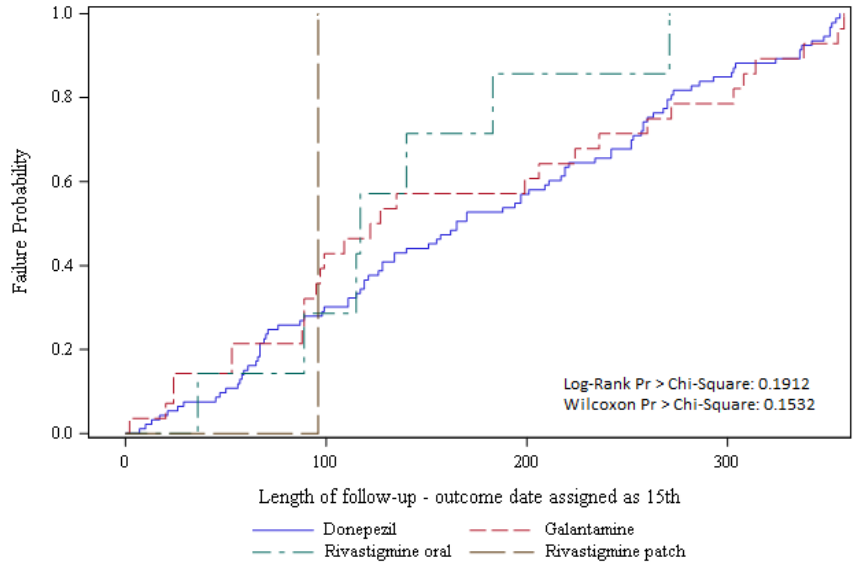

Figure 17: Cumulative incidence (failure) curve of occurrence of malignant arrhythmia in all 25 DAD diagnosis fields, comparing donepezil to the other AChEIs separately with follow-up time capped at 365 days. Censored individuals are not shown on this cumulative incidence curve, as given the extreme number of censored individuals, it would not be possible to display censoring. The Log-Rank and Wilcoxon tests are accurate for if censoring was considered.

Different from an uncapped follow-up with all 25 DAD diagnosis fields, the individual AChEI initiator incidence rates are not near the total incidence rate of 106.4 per 100,000 person-years, although the larger variability may be attributed to wider confidence intervals, a shorter follow-up time, and a lesser number of events. Cox regression would be required to see if rates are significantly different amongst different AChEI groups.

A breakdown of *all* cumulative incidence curves in table format is shown in Table 31, comparing and contrasting follow-up durations and using primary or all DAD diagnosis fields. Given the finding that sex is associated with the outcome of malignant arrhythmia (specifically with female sex being associated with lower risk), a breakdown of event occurrence by patient age quintile and patient sex (without incidence rate calculations) is also shown in Table 32.

Table 31: Breakdown of occurrence of malignant arrhythmia by AChEI medication group, diagnosis field use in DAD, and follow-up duration

		Donepezil n = 127,038		Galantamine n = 25,582		Rivastigmine oral n = 6,536		Other all n = 35,489 Rivastigmine patch n = 3,371		p-value (donepezil vs. galantamine vs. rivastigmine oral vs. rivastigmine patch)	Total (n events, %, p-value of donepezil vs. all other AChEIs together)			**Total n = 162,527**	
All period (n events, %)	All diagnosis fields	258	0.20%	60	0.23%	10	0.15%	8	0.24%	0.5503	78	0.22%	0.5404	**336**	**0.21%**
Cap at 365 days (n events, %)	All diagnosis fields	93	0.07%	28	0.11%	7	0.11%	<6	Supp.	0.1570	Supp.	Supp.	0.0950	Supp.	**0.08%**
All period (n events, %)	Primary diagnosis field only	58	0.05%	27	0.11%	<6	Supp.	<6	Supp.	0.0016	32	0.04%	0.0016	**90**	**0.06%**
Cap at 365 days (n events, %)	Primary diagnosis field only	26	0.02%	16	0.06%	<6	Supp.	<6	Supp.	0.0019	18	0.05%	0.0022	**44**	**0.03%**

Incidence rate (per 100,000 person-years) (95% CI)		Donepezil	Galantamine	Rivastigmine oral	Rivastigmine patch	All non-donepezil	Total
All period	All diagnosis fields	102.3 (90.5, 115.6)	108.3 (84.1, 139.4)	89.1 (47.9, 165.5)	129.4 (64.7, 258.8)	107.1 (85.8, 133.7)	103.4 (92.9, 115.0)
Cap at 365 days	All diagnosis fields	98.3 (80.3, 120.5)	142.0 (98.1, 205.7)	151.7 (72.3, 318.2)	41.7 (5.9, 296.1)	134.7 (97.2, 186.7)	106.4 (89.5, 126.4)
All period	Primary diagnosis field only	23.0 (17.8, 29.7)	48.7 (33.4, 71.0)	17.8 (4.5, 71.2)	48.5 (15.7, 150.5)	43.9 (31.1, 62.1)	27.7 (22.5, 34.0)
Cap at 365 days	Primary diagnosis field only	27.5 (18.7, 40.4)	81.2 (49.7, 132.5)	43.3 (10.8, 173.3)	0	67.3 (42.4, 106.9)	36.3 (27.0, 48.7)

Table 32: Breakdown of occurrence of malignant arrhythmia by AChEI medication group, diagnosis field use in DAD, follow-up duration, patient sex, and patient age quintile

			Age 66-75 n, % Total n=7,191 Total 20.1%		Ag 76-80 n, % Total n=8,068 Total 22.3%		Age 81-84 n, % Total n=7,954 Total 22.6%		Age 85-87 n, % Total n=5,540 Total 15.7%		Age 88-100+ n, % Total n=6,736 Total 19.5%		Patient sex | n, % F Total n=76,695 Total 60.4%		M Total n=50,343 Total 39.6%	
All period (n events, %)	All diagnosis fields	Donepezil n=258	52	20.2%	76	29.5%	50	19.4%	34	13.2%	46	17.8%	101	39.2%	157	60.9%
		Galantamine n=60	14	23.3%	14	23.3%	13	21.7%	10	16.7%	9	15.0%	16	26.7%	44	73.3%
		Rivastigmine Oral n=10	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	8	80.0%
		Rivastigmine Patch n=8	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.
		Total non-donepezil n=78	18	23.1%	22	28.2%	16	20.5%	12	15.4%	10	12.8%	21	26.9%	57	73.1%
		Total n=336	70	20.8%	98	29.2%	66	19.6%	46	13.7%	56	16.7%	122	36.3%	214	63.7%
Cap at 365 days (n events, %)	All diagnosis fields	Donepezil n=93	16	17.2%	27	29.0%	20	21.5%	12	12.9%	18	19.4%	35	37.6%	58	62.4%
		Galantamine n=28	6	21.4%	7	25.0%	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	23	82.1%
		Rivastigmine Oral n=7	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	6	85.7%
		Rivastigmine Patch n<6	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.
		Total non-donepezil n=36	7	19.4%	11	30.6%	6	16.7%	7	19.4%	<6	Supp.	7	19.4%	29	80.6%
		Total n=129	23	17.8%	38	29.5%	26	20.2%	19	14.7%	23	17.8%	42	32.6%	87	67.4%
All period (n events, %)	Primary diagnosis field only	Donepezil n=58	11	19.0%	17	29.3%	13	22.4%	<6	Supp.	12	20.7%	17	29.3%	41	70.7%
		Galantamine n=27	6	22.2%	8	29.6%	<6	Supp.	<6	Supp.	<6	Supp.	7	25.9%	20	74.1%
		Rivastigmine Oral n<6	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.
		Rivastigmine Patch n<6	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.
		Total non-donepezil n=32	7	21.9%	10	31.3%	<6	Supp.	6	18.8%	<6	Supp.	8	25.0%	24	75.0%
		Total n=90	18	20.0%	27	30.0%	17	18.9%	11	12.2%	17	18.9%	25	27.8%	65	72.2%
Cap at 365 days (n events, %)	Primary diagnosis field only	Donepezil n=26	<6	Supp.	<6	Supp.	10	38.5%	<6	Supp.	<6	Supp.	<6	Supp.	21	80.8%
		Galantamine n=16	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	14	87.5%
		Rivastigmine Oral n<6	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.
		Rivastigmine Patch n<6	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.
		Total non-donepezil n=18	<6	Supp.	6	33.3%	<6	Supp.	<6	Supp.	<6	Supp.	<6	Supp.	16	88.9%
		Total n=44	7	15.9%	11	25.0%	12	27.3%	6	13.6%	8	18.2%	7	15.9%	37	84.1%

5.7.4 Sensitivity and secondary analyses, Cox regression

Unlike the crude, initial survival analysis, in Cox regression, rivastigmine was not further separated into oral or transdermal rivastigmine groups, due to a departure from the proportional hazards assumption with a low event rate. Using the same Cox regression model built in Section 5.5, sensitivity and secondary analyses found that for all definitions of hospitalization date, donepezil was associated with lower risk for malignant arrhythmias and galantamine was

associated with greater risk, when considering the primary diagnosis field in DAD only. Likewise, this still confirms findings from the initial survival analysis, and this conclusion does not change if follow-up is limited to a 365-day maximum. Similarly confirming other secondary analyses above, when the outcome definition is changed to include all 25 DAD diagnosis fields, the association between AChEI medication group and the outcome of malignant arrhythmia is no longer significant (i.e., donepezil is no longer significantly associated with lower risk for malignant arrhythmias). Notably, this conclusion remains true with follow-up capped at 365 days.

Furthermore, no conclusions (regarding AChEI medication group) change if all patients with a previous malignant arrhythmia (at anytime pre-AChEI index) are excluded – although assessments of outcomes for rivastigmine initiators in the primary DAD diagnosis field while capping follow-up at 365 days find that the computed HR and lower limit of the 95% CI are decreased (upper limit of 95% CI remains largely unchanged and as such results are still non-significant at the 0.05 level). For example, using the primary hospitalization date definition, the computed HR on rivastigmine initiators while including those with previous malignant arrhythmia is 0.899 (95% CI 0.213, 3.799). Removing all of those with previous malignant arrhythmias changes the computed HR to 0.473 (95% CI 0.064, 3.503); this trend remains consistent across all hospitalization date definitions for rivastigmine initiators. No other patterns regarding major changes in computed HRs while excluding all of those with previous malignant arrhythmia are present.

A full breakdown of hazard ratios (assessing AChEI medication group) generated from sensitivity analysis can be seen in Table 33 and 34 and Figures 18-23 in Appendix F (results only shown for models retaining patients with previous malignant arrhythmia between 1- and 5-years

pre-AChEI index). Some sensitivity definitions resulted in a departure from the proportional hazards assumption for comorbidity covariates.

Chapter 6: Discussion, Strengths, and Limitations

6.1 Discussion

I used linked prescription medication and hospitalization discharge databases in a cohort of 162,527 patients who initiated AChEI use between April 1st, 2011, and January 31st, 2019, in seven Canadian provinces, to assess the association between specific AChEI agents and hospitalizations for malignant arrhythmia (defined as an occurrence of ICD-10-CA codes I47.2 or I49.00). Donepezil was specifically compared against the other AChEIs (galantamine and rivastigmine), and two different follow-ups were used, either a maximum available follow-up of eight years (up to March 31st, 2019), or a follow-up capped at 365 days (from AChEI initiation). Assessments of the outcome also occurred in both the DAD primary diagnosis field (only) and in any of the 25 DAD diagnosis fields.

Donepezil initiators account for a little over 78% of the total cohort, and females account for almost 60% of the total cohort. During a median follow up of 1.06 years, 90 hospitalizations for a malignant arrhythmia were identified. Of them, 58 hospitalizations were in the donepezil group (23 per 100,000 person-years) and 32 were in the other AChEIs group (44 per 100,000 person-years). After adjustment, initiation of donepezil was associated with a 45% lower hazard of hospitalization (adjusted HR 0.55, 95% CI 0.36 to 0.85) relative to other AChEIs as a group. When assessing malignant arrhythmia in any diagnosis field, donepezil initiation was no longer significantly associated with hospitalizations (adjusted HR 1.01, 95% CI 0.78 to 1.30). The limiting of follow up to 365 days as well as sensitivity analyses did not change the results.

6.1.1 Discussions on the cohort characteristics

The proportion of donepezil initiators (78%) is higher than previous studies, which have found that donepezil comprise 66% and 69% of new AChEI users in BC and ON

respectively.[92,100] Similarly, in a study among newly admitted long-term care residents in SK and ON, of dementia pharmacotherapy users, 67.7% and 62.2% were on donepezil in SK and ON respectively.[155] Amongst other AChEI initiators, in my cohort, galantamine use appears to decrease over time (17.4% of galantamine users initiated in 2012 calendar year to only 8.3% of galantamine users initiating in 2018 calendar year); this same trend may exist between transdermal rivastigmine patch use and index year (there was decreased use from 2011-2016, and from calendar year 2017 and onwards there were essentially no transdermal rivastigmine initiations – although this second observation would be explained by transdermal rivastigmine being delisted by BC – as explained later). Similar trends with regards to galantamine/rivastigmine use were observed in the ON study, which assessed a longer duration (2002-2017).[92] As such, my high proportion of donepezil initiators may not be entirely unexpected given these similar trends in other studies, with my study having a shorter study duration that is also more recent (2011-2019). My cohort sex breakdown of 60% of the cohort being female is on par with previous studies;[100] females are known to have a higher prevalence of dementias and AD in Canada,[101] and with the longer life expectancy of females, it would be expected that the incidence is higher in females as well.

One key finding outside the assessment of malignant arrhythmias in AChEI initiators was that almost all dispensations for transdermal rivastigmine during the study were in BC. Since NDPUIS only captures dispensations of prescription medications paid for by publicly funded medication plans, the coverage of transdermal rivastigmine would explain why only BC patients received transdermal rivastigmine (as of 2015, the only other jurisdictions providing some public coverage for transdermal rivastigmine are Québec and the Yukon Territory).[156] However, in the report published by BC PharmaCare in April 2016, it mentions that transdermal rivastigmine

ceased to be covered by BC PharmaCare.[157] Correspondingly, in my cohort, dispensations of transdermal rivastigmine ended in 2016. The report details how transdermal rivastigmine is almost 5.5 times the cost of the cheapest AChEI option, donepezil,[156,157] which perhaps explains why public drug plans do not cover transdermal rivastigmine anymore (or perhaps never covered it in the first place). Outside the scope of this study, given the unique delivery method of transdermal rivastigmine (which may lead to greater safety profiles and/or adherence), pharmacoeconomic studies may be called for to assess transdermal rivastigmine; the Ontario Drug Policy Research Network report has found that the rivastigmine patch can be cost-effective with a price reduction of approximately 55%.[156] Interestingly, in my cohort, rivastigmine patch initiation was associated with income quintile – with the higher the income quintile, the lower number of individuals who initiate the rivastigmine patch (26% of transdermal rivastigmine initiators were in the lowest quintile; this decreases to 17.5% of transdermal rivastigmine initiators being in the highest income quintile). However, it can be observed the association with income may not be limited to rivastigmine patch initiators in my cohort.

Other jurisdictional differences regarding AChEI use in Canada include the assessment of Ontario having a "[more] liberal listing for [cognitive enhancers] relative to all other provinces in Canada."[156] Corroborating information provided by CIHI regarding my particular cohort (i.e., only 23.1% of donepezil claims were accepted by public drug programs in SK), SK has the lowest rate of publicly funded cognitive enhancer use, at 10 per 1,000 elderly population.[156] These jurisdictional differences can also be seen in a study analyzing new admissions to long-term care in SK and ON, which found only 8.1% of SK residents were receiving dementia pharmacotherapy, contrasted by a much higher 33.2% in ON.[155] However, within each jurisdiction, coverage of *particular* AChEIs do not differ from each other (except for the

rivastigmine patch as mentioned previously);[158] utilization patterns or differences in risk cannot be attributed to prescription filling requirements in each jurisdiction.

In addition to costs, it may also be that the different approvals of AChEIs in Canada play a role in high donepezil usage. As mentioned, donepezil, rivastigmine, and galantamine were approved for use in Canada in 1997, 2000, and 2001 respectively. A three-year difference may have allowed for effective marketing of donepezil to take place (especially since donepezil would have been in a rather bare therapeutic area at the time of introduction), leading to more clinical experience among physicians. As such, this would have allowed for donepezil to hold a large market share even after approval of other AChEIs.[159] This is especially relevant as it has been previously found that all three AChEIs have similar efficacy and safety profiles – so there would be no real reason for prescribers to switch from donepezil if they were already prescribing it heavily.

Notably, initiators of other AChEIs (galantamine or rivastigmine) had consistently higher proportions of comorbidities (as determined through hospitalizations and higher prescription medication use) in comparison to initiators of donepezil, except for thiazide and non-thiazide low-ceiling diuretics. This finding is somewhat consistent with an Ontario Drug Policy Research Network report detailing how rivastigmine users had more comorbidities.[156] The Canadian guidelines do not recommend specific AChEI over others,[160] but interestingly, a BC PharmaCare report recommends donepezil be the first-line treatment for AD, with switching to galantamine or rivastigmine requiring reassessment of the patient's condition.[157] It was not explicitly stated why the report recommended donepezil as first line, but given the evidence presented and language used in the report, it is surmised that recommendations were made based upon the safety profile for donepezil – as well as a lower price.[157] Interestingly, switching to galantamine

or rivastigmine is only approved for donepezil intolerance and not ineffectiveness.[157] Nonetheless, given trends in my cohort and previous literature,[92,100,156] assuming the reason for high donepezil usage is similar recommendations across provinces (for donepezil being the first-line AD treatment), then it can be surmised that galantamine and rivastigmine users should have more comorbidities, as they will use them later in their course of treatment – though to counterpoint, it must be noted mean and median ages between AChEI groups were almost identical in my cohort, and my inclusion criteria should in theory only keep new initiators (but it is always possible previous AChEI dispensations occurred that were not captured by NPDUIS, either due to being outside the coverage of public plans or due to year of dispensation not captured). Whether donepezil being a first line AChEI being counterintuitive against FDA and CredibleMeds warnings (i.e., donepezil being a known-risk CredibleMeds medication for AQTLS) is debatable. On one hand, one would not want to initiate a higher-risk medication as a first-line option; on the other hand, given that users of AChEIs often switch from their initial AChEI, one does not want to switch a patient to a higher risk AChEI when they may already be more ill.

Correlations between hospitalization-determined comorbidities and prescription medication use covariates, several of which were found, were to be expected in this cohort given all individuals are over 66 years of age – polypharmacy and multiple chronic conditions are typical. For example, myocardial infarction was strongly correlated with several other heart conditions (Phi Coefficients > 0.25), use of heart medications were associated with heart conditions (Phi Coefficients > 0.25), and thyroid hormone use was strongly correlated with hypothyroidism (Phi Coefficient 0.2876). This assures me of the robustness of my definitions for hospitalization- and prescription medication-determined comorbidities. One finding with

regards to correlations was that income quintile was not captured for any individual in SK, resulting in a high value for Cramer's V (0.4098); excluding SK from the assessment between jurisdiction and patient income quintile reduced Cramer's V to 0.0348. It is unknown why income quintile was not captured amongst SK patients, although it is likely due to a lower population – which led to suppression of income information of areas' median income to maintain privacy in that province. Regarding different privacy legislation, for example, during the request for CIHI data, BC required an additional supplemental application piece due to privacy legislation; this was not needed for any of the other jurisdictions I requested.

6.1.2 Analyses of donepezil vs. other AChEIs on malignant arrhythmia risk

The initiation of donepezil was associated with lower hazard of malignant arrhythmia when patients were followed for both the maximum period and capped at 365 days. This may be explained by the observation of galantamine and rivastigmine initiators having greater proportions with regards to hospitalization comorbidities and medication use. However, adjustment for these potential confounding variables did not result in different conclusions with regards to donepezil being associated with a lower risk of hospitalization for malignant arrhythmia (when considering only the primary DAD diagnosis field). Adjustment for confounders did move the computed hazard ratio slightly towards the null (HR 0.521, 95% CI 0.338, 0.802; aHR 0.551, 95% CI 0.358, 0.849), although the result is still statistically significant at the 0.05 level. Comparing Figure 20 and Figure 21, it is clear that the finding of the lower risk for donepezil is entirely attributable to galantamine having a greater hazard of a hospitalization for malignant arrhythmia. Interestingly, this does agree with the one piece of literature which found (in a summary of reports to the Australian Adverse Drug Reaction Advisory Committee prior to June 2007) that galantamine had the highest rate of reporting for arrhythmia.[142]

Nevertheless, despite galantamine initiators generally having a greater burden of comorbidity, adjustment for confounders still only slightly moved the computed hazard ratio towards the null. As such, the impact of residual confounding on the statistics computed is likely to be present. As previously discussed, the BC PharmaCare report recommends donepezil be the first-line treatment for AD, with switching to galantamine or rivastigmine requiring reassessment of the patient's condition.[157] Given trends in my cohort and previous literature,[92,100] residual confounding pertaining to higher comorbidities among galantamine and rivastigmine initiators could perhaps explain the decreased hazard of hospitalization in donepezil initiators in my cohort even with adjustment for confounders. I have attempted to account for as many comorbid conditions through assessment of hospitalization discharges and other medication use as per previous studies;[69,70,92] however, it is possible that some comorbidities are still not captured in all patients. If patients have not been discharged from a hospital, but have comorbidities as diagnosed by general or specialist practitioners, they would not be captured in the assessment of comorbidities through DAD. In addition, health behaviours are not captured in my data – and the lack of association between AChEI initiation and malignant arrhythmias in all 25 DAD diagnosis fields may further support the notion that comorbidities diagnosed outside the hospital may account for a major portion of comorbidity diagnoses. Even *with* the use of all 25 DAD diagnosis fields in capturing some outside-hospital comorbidities, it cannot be that *everything* is accurately reflected in those 25 DAD diagnosis fields.

Since I found that donepezil initiation was associated with a *lower* risk of malignant arrhythmia, given the (limited) evidence I reviewed that showed donepezil should be associated with *higher* risk of malignant arrhythmia, the results are unexpected. Adjustment for confounders moved the HR towards the null, which again, supports that residual confounding

should be suspected as the main factor of the association between other AChEIs and malignant arrhythmia. However, this did not (nor would it be expected to) change the association direction. As such, my results support lack of association between donepezil and risk of malignant arrythmia.

Nevertheless, even if the association between other AChEIs and malignant arrhythmia is true, given the extremely low event rate considering the sample size (58 events amongst 127,038 donepezil initiators and 32 events amongst 35,489 other AChEI initiators – corresponding to an incidence rate of 23.0 per 100,000 person-years and 43.9 per 100,000 person-years respectively), there is likely no clinical significance to the greater risk of other AChEIs. The number needed to harm (assuming causation) would be calculated as approximately 2,246.5 individuals. Altogether, however, my hypothesis of the hazard of hospitalization for malignant arrhythmia being higher in individuals who newly initiated donepezil, than in individuals who newly initiated galantamine or rivastigmine, was proven to be untrue.

6.1.3 Discussion of sensitivity and secondary analyses, and other comparisons

Sensitivity and secondary analyses generally showed a consistency with the main analysis. As expected, capping follow-up to 365 days, and/or adjusting hospitalization dates did not affect any conclusions that would be drawn from the main analysis (although capping follow-up does lead to a higher strength of association – using the main hospitalization date definition (the 15th of the month), capped aHR 0.432, 95% CI 0.236, 0.791). This can also be seen when considering both Log-Rank and Wilcoxon statistical tests on the cumulative incidence curves. Furthermore, removing all individuals with previously diagnosed malignant arrhythmia at any time pre-AChEI index changed no conclusions. These lack of differences were to be expected, as if occurrences of malignant arrhythmia occurring closer to AChEI initiation are more likely

associated with AChEI initiation (or initiation of any medication for that matter),[58,152,153] the proportion of individuals whose occurrence of malignant arrhythmia after 365 days that are not associated with AChEI use, would *also* be expected to be equal between AChEI medication groups. However, this was the rationale for using the Wilcoxon test alongside the Log-Rank test when comparing crude cumulative incidence curves – earlier events are more likely associated with initiation of AChEI.

Further limiting follow-up to six and three months may be relevant for assessment of malignant arrhythmias post-AChEI initiation, since within 365 days, more than 50% of the events occurred prior to the half-year mark. However, for this cohort, the number of events would be too limited to perform such an analysis (capping follow-up at 365 days leaves 44 events if only the primary DAD diagnosis field is used, further reducing to 22 events would not give an accurate estimation). This same "lack of events" problem would be pertinent if I was to perform a subgroup analysis separating out those with previous malignant arrhythmias (or even *any* previously diagnosed cardiac conduction disorders – 11% of the cohort).

Changing definitions for hospitalization date can result in a difference of up to 40 events (when considering all 25 DAD diagnosis fields); this is up to almost a 13% difference in number of events. Even when considering only the primary DAD diagnosis field, the nine events is over a 11% difference. Regarding occurrence of malignant arrhythmias and follow-up time, the skewed follow-up time would be expected if malignant arrhythmias had some association with AChEI use (since occurrence would occur relatively soon after initiation as described). When using the main definition of hospitalization dates, 50% of outcomes (when considering only the primary DAD diagnosis field) occurred prior to 386 days. Capping follow-up to 365 days leaves

approximately 36% and 45% of the total outcomes captured for all 25 DAD diagnosis fields and the primary DAD diagnosis field respectively.

Though again, further supporting that my hypothesis was proven not to be true, changing the outcome definition from the primary DAD diagnosis field only, to considering all 25 DAD diagnosis fields *still* shows that donepezil is not at a higher risk for malignant arrhythmia. Notably, the *lower* risk of malignant arrhythmia for donepezil initiators (found in the analysis looking only at the primary DAD diagnosis field) was no longer present when all 25 DAD diagnosis fields are considered. Donepezil initiators may still be at a lower risk for hospitalizations for malignant arrhythmias; the result just does not reach statistical significance at the 0.05 level.

A couple of reasons might account for why. First, it was insinuated that only the primary DAD diagnosis field be used to conduct analyses, as only the primary DAD diagnosis field may accurately represent an outcome of interest (due to highly accurate encoding or otherwise).[149] One possibility for this recommendation is again, non-primary diagnoses may be from outside of the hospital admission – for example, one diagnosis type for any diagnosis from field 2 to 25 is "pre-admit comorbidity diagnosis". If an ECG (the gold standard for diagnosing cardiac conditions)[72] was not used to make a pre-admit diagnosis (as may be the case outside a hospital environment), it cannot be said for certain of its accuracy. It may also be that a malignant arrhythmia in fields 2 to 25 was associated with something else (such as the primary diagnosis that was not a malignant arrhythmia, or an intervention such as a medication causing a malignant arrhythmia after admission – which are diagnoses that may be identified through diagnosis type and/or prefix). It may have been more relevant to break down the diagnosis type for the malignant arrhythmia diagnosis in the non-primary diagnosis field, or to assess what the primary

diagnosis was in any non-primary diagnosis of malignant arrhythmia – and then subsequently compare to see if the same association were to be present as if I just used the primary DAD diagnosis field.

What is interesting is that capping follow-up to 365 days while using all 25 DAD diagnosis fields to identify malignant arrhythmia was what showed that donepezil initiators *may* still be at a lower risk for hospitalizations for malignant arrhythmias – the result just does not reach statistical significance at the 0.05 level. However, given that capping follow-up to 365 days led to a greater strength of association when using only the primary DAD diagnosis field, this finding may just be attributed to the primary diagnoses themselves (that are, of course, within any of the 25 diagnosis fields).

Nonetheless, despite a likely lack of clinical significance regarding the greater risk of hospitalizations for malignant arrhythmias for other AChEIs (in comparison to donepezil), the overall low event rate is reassuring regarding the safety of AChEIs – this reassurance is still important clinically. Previous studies have found (using the same definition of a hospitalization for malignant arrhythmia and a very similar elderly cohort) a malignant arrhythmia occurrence rate of 87 events per group of 137,701 citalopram users (versus 56 events per group of 135,746 paroxetine or sertraline users), and 134 events per group of 503,612 macrolide antibiotic users (versus 126 events per group of 503,612 non-macrolide antibiotic users).[69,70] In my cohort, the total event rate (primary diagnoses only, uncapped follow-up) was 90 events per 162,527 cohort size (corresponding to an incidence rate of 27.7 per 100,000 person-years). This is a lower event rate than that of citalopram users, which importantly is also a CredibleMeds known-risk medication[44] as reviewed previously. Notably, the study on antidepressants and the study on macrolide antibiotics (also of CredibleMeds known-risk)[44] only followed-up patients for 90 and

30 days respectively;[69,70] as such, their corresponding incidence rates of 256 per 100,000 person-years (for citalopram users) and 324 per 100,000 person-years (for macrolide antibiotic users) are considerably higher than any of the incidence rates calculated for my cohort (be it using all 25 DAD diagnosis fields to assess malignant arrhythmias and/or capping follow-up to 365 days). With further evidence from a systematic review stating that only one of four RCTs (on AChEIs) finding clinically significant changes on QT_C intervals, and only one of five cohort studies finding clinically significant changes on QT_C intervals,[138] as such, AChEIs are safe to be used in elderly individuals from a malignant arrhythmia point-of-view.

6.1.4 Specific analysis on patient sex and the association between AChEIs and arrythmia risk

Between sexes, oral rivastigmine users were more balanced, whereas other AChEIs followed the overall trend of having increased female users. Interestingly, a stark difference is seen in Table 32 with regards to patient sex and hospitalizations for malignant arrhythmia; despite female patients making up over 60% of the cohort, most occurrences in malignant arrhythmia occurred in males (for females: aHR 0.268; 95% CI 0.168, 0.429). This directly contrasts previous studies,[4,9,10,13] which have all found that females are at a higher risk for aLQTS and/or arrhythmias. As well, patient age quintile did not have a significant effect on hazard of malignant arrhythmia when AChEI medication group is considered together with age. In the full Cox model, together with patient sex and other comorbidities, age was also insignificant – nor was there effect modification between age and sex (in fact no effect modification between *any* variables in my Cox model).

This lack of effect modification (between age and sex) may be due to survivorship bias.[9,10] Given the high average age of my cohort, and that women live longer than men, it may be that my cohort captured females that tended to be healthier than males captured in the cohort.

Although this argument can also be made for the males in my cohort (the men captured in this cohort should be healthier than those not captured in the cohort – thus females should still be at higher risk), when the average cohort age is so high, combining that with the lower expectancy of males may cause more outcomes to be seen in men.

Contrasting the effect found for patient sex, after adjusting for AChEI medication group, it can be seen that many comorbidities result in a greater hazard of hospitalization for malignant arrhythmia, which is to be expected given previous literature.[9–11] It was not assessed for these comorbidities whether adjusting for sex would change the conclusions on particular comorbidities.

6.2 Advantages and strengths of study

My retrospective cohort study using survival analysis for answering the question of interest has advantages over other study designs. First, a cohort study provides a look into the real-world association between AChEI initiation and its potential association with malignant arrhythmia. Second, the use of survival analysis over other methodologies, such as logistic regression, allows for the use of the passage of time as a variable. Furthermore, using two different follow-up periods, an uncapped and a follow-up period capped at 365 days, allows for the assessment of events that may occur early after AChEI initiation. Finally, this study examines a relatively large sample of Canadians from several jurisdictions, that would be expected to be representative of the Canadian elderly population.

6.3 Limitations

Some specific limitations can be noted in my study. First, as previously mentioned, this cohort only captures individuals who are covered by provincial public drug plans. Although this

may cause a reduced sample size, individuals covered by private insurance may be categorically different than those only covered by public drug plans (which may be rather pertinent for SK given the low rate of publicly funded users of cognitive enhancers). Interestingly, in ON, there is said to be little galantamine or rivastigmine use outside of publicly funded drug programs.[156]

To counterpoint, it may also be that a patient covered by private insurance still has public insurance claims, as may be the case in Ontario where ODB is the primary insurance. Importantly, in Ontario, memantine is the most commonly dispensed cognitive enhancer through private insurance, because it is not covered by Ontario's public drug plans.[156] Another crucial thing to note that private insurance is usually provided through employment benefits, which is typically not applicable towards my cohort of elderly (and likely retired) individuals. As such, my study should still be an accurate representation of the Canadian elderly population, even without the ability to look at private insurance claims.

Furthermore, even with the limited number of claims accepted by public drug programs (in provinces such as SK), this should not affect a comparative assessment between AChEIs. Although CIHI explicitly stated the limited proportion of claims accepted was in donepezil claims, regulations do not appear to be different in any Canadian jurisdiction with regards to *differential* approval for AChEI use. Rather, criteria for use of *any* AChEI are similar or the exact same;[156,158] differences only exist when considering different formulations (e.g. an oral solution or the rivastigmine patch).

Secondly, the rationale for excluding patients who were dispensed donepezil, galantamine, or rivastigmine in the 365 days prior to cohort entry date (index date) is to capture "new" users of AChEIs (as initiator design is advantageous in comparative studies – since it eliminates prevalent user bias and bias due to covariates being affected by medication use

itself/reduces the confounding for intermediate characteristics in the causal path).[161,162] However, in the exclusion criteria defined by CIHI, *included* individuals may not be truly *new.* Some patients may have received AChEIs prior to the earliest fiscal year captured by my particular NPDUIS dataset; and also whether this affected comorbidity burden in my study is unknown, as previously discussed. Generally, though, this problem is not expected to be majorly differential between AChEIs, so results nor conclusions are not expected to be affected.

Third, a limitation occurs in the fact that I did not take medication adherence or gaps in AChEI use into consideration with the analysis of the cohort. However, given that capping follow-up to 365 days resulted in the same conclusions in comparison to an uncapped follow-up, any conclusions drawn would still be valid. Ideally, further limiting follow-up time to six or three months post-AChEI index would provide the highest likelihood that there are no AChEI usage gaps – but as previously described, there would not be enough events in this cohort to perform such an analysis. As mentioned, notably, capping follow-up to 365 days does result in a greater strength of association, when considering only the primary DAD diagnosis field. This same trend holds when all 25 DAD diagnosis fields are considered.

Fourth, a limitation occurs in the fact that dose of AChEI could not be considered in the analysis, as dose was not provided in the dataset. It would be expected that higher doses of AChEIs would result in an increased hazard of hospitalization for malignant arrhythmia. On the other hand, if dose were to be considered, comparisons between different AChEIs would be made more difficult, as attempting to assess for an equivalent dose between the AChEIs may not be possible.

Fifth, a limitation may be present in the fact that I did not consider diagnosis prefix (specifically Q for questionable/query diagnosis) in the assessment of the outcome of malignant

arrhythmia, or assessment of any comorbidities. To start, ignoring diagnosis prefix in the assessment of *comorbidities* is likely not to result in any invalidity – even if there were to be an unequal number of comorbidities labelled as Q between AChEI medication groups. As well, ignoring diagnosis prefix in the assessment of the outcome of malignant arrhythmia is likely not concerning for the primary DAD diagnosis field, given that the most responsible diagnosis in DAD is well coded and that any conclusions drawn from it are expected to be accurate.[149]

Importantly, only one event would be removed if I was to remove Q prefixes for outcomes in the primary diagnosis field. Seven events would be removed if I were to consider Q prefixes for outcomes in any DAD diagnosis field (when considering unlimited follow-up); capping follow-up to 365 days for any DAD diagnosis field again only removes one event.

As well, previous studies using the same code definition for assessment of malignant arrhythmia did not describe how Q diagnosis prefixes were handled.[69,70] The Q diagnosis prefix definition may have also been changed during the time period the cohort encompasses. According to CIHI, the Q prefix changed in 2018 to only be "query" diagnoses, instead of both "query" and "questionable" diagnoses. Although this is more likely to be change purely in semantics, I cannot be certain that Q diagnosis prefixes would mean the same thing during the entirety of the time period the cohort encompasses – and as such it may be better to consider any Q diagnosis prefixes alongside all other diagnoses.

Sixth, not all potential drug-drug interactions could be assessed – despite its potential importance with AChEIs. Although CYP3A4 and CYP2D6 inhibition/induction by medication use were determined through the dataset, a valid methodology to consider potential drug-drug interactions with AChEIs was not formulated (since adjusting for it after baseline would be a complex methodology fraught with problems such as event mediation). It was expected that

adjusting for CYP3A4/2D6 inhibition/induction at baseline would not be a particularly accurate method of assessment of potential pharmacokinetic disturbances on AChEI metabolism – since such drug-drug interactions may no longer be present at the occurrence of an outcome of malignant arrhythmia. Unlike adjustment for antiarrhythmic agent or loop diuretic use, which in spite of a similar invalidity that would be present with regards to adjusting for those medications at baseline, at least assessment of antiarrhythmic agent or loop diuretic use can be a proxy measure for other comorbidities (which was deemed to be the case given correlations with other comorbidity variables as determined through Phi Coefficients). Furthermore, adjusting for CredibleMeds known-risk medication use at baseline found that it was not a significant predictor for hospitalizations for malignant arrhythmia at the univariate level (but the more specific "antiarrhythmic medication use" was significant). As such, it is not likely that a catch-all predictor variable (i.e. CredibleMeds known-risk medications, CYP3A4 inhibitors, CYP3A4 inducers, CYP2D6 inhibitors) would be an accurate evaluation of any comorbidity or drug-drug interaction.

Specifically regarding CredibleMeds known-risk medications, CIHI could not provide the entirety of this list of medications, since additional medications were added onto the known-risk list after release of data.[163–166] Furthermore, as seen in Table 6b (the list of medications *that was* grouped as CredibleMeds known-risk by CIHI), certain antiarrhythmic medications were not grouped into the CredibleMeds known-risk medications (e.g. amiodarone). It was unknown why this happened, but it is believed to be a result of back and forth miscommunication between me and CIHI regarding exact data requirements. However, since CredibleMeds known-risk medications were ultimately not in the Cox regression model, this limitation is not that relevant;

antiarrhythmic medications on its own are far more pertinent towards malignant arrhythmias and this was able to be adjusted for separately in the analysis.

Seventh, mortality data could not be used with my cohort, and as such, any information regarding deaths cannot be assessed. However, part of the rationale of my study would be to change prescribing patterns to reduce hospitalizations; this will also reduce cases that do not reach the hospital – which are cases that may also be fatal. As well, a lack of mortality data would not invalidate my methodology given that I censored patients who stopped usage of AChEIs. On the other hand, assuming there is some truth towards patients using galantamine or rivastigmine being sicker than patients using donepezil (since it is surmised that donepezil is a first-line AChEI given provincial guidelines – as well as the high proportions of individuals in my cohort using donepezil), it would be interesting to see if all-cause mortality would differ between AChEI groups. Importantly, however, mortality due to arrhythmias would likely not be something that could be accurately assessed; codes for specific cause of death (in Ontario) are expected to be inaccurate.[69]

Finally, although the definition of malignant arrhythmia has been validated by previous studies for the use of comparative studies between medications,[69,70] any relationship with AChEI medication use (or any medication use for that matter) would be purely speculative. Assessment of a prolonged QT_C interval through ECG would be more ideal, although it would not be possible in an administrative database – and any QT_C interval would have to be measured prospectively soon after AChEI initiation.

Chapter 7: Implications and Conclusion

7.1 Implications and further research

This study examined the risk of hospitalization for malignant arrhythmia associated with the initiation of the different AChEIs in AD and related dementias, in the real-world environment using a large cohort of elderly Canadian individuals from several jurisdictions. The study assists in filling the knowledge gap of whether donepezil is associated with a greater risk, in comparison to galantamine or rivastigmine.

Further research is called for given the conclusion that for this cohort, donepezil was associated with a lower risk for hospitalizations for malignant arrhythmias, and galantamine results in greater risk – which (outside of some reports to the Australian Adverse Drug Reaction Advisory Committee) is opposite of the hypothesized result of donepezil initiators being at greater risk of hospitalization for malignant arrhythmia. Adjustment for confounding variables moved the computed hazard ratio towards the null, and it is possible that residual confounding is present given an extremely low event rate. This study provides evidence that AChEIs are safe for use, as the incidence rate of malignant arrythmia was very low (27.7 per 100,000 person-years when not capping follow-up and looking at primary diagnoses only) and the increased relative risk of other AChEIs has a very high "number needed to harm" (2246.5) assuming causality. Residual confounding from uncapturable comorbidities may be present in the computed hazard ratios. High-dimensional propensity-scoring may be called for to adjust for more residual confounding in future studies.

As such, this present research has raised the question of how comorbidity burden may affect risk of hospitalization for malignant arrhythmia. It would be interesting to see if alternate methods of comorbidity assessment (e.g., chronic disease score[167] or as mentioned, propensity

scores[69]) may affect conclusions. Ideally, any cohort should be considerably larger to hopefully capture more events. A larger cohort is also called for given the finding that capping follow-up duration to 365 days increases the strength of association (as can be seen through the computed hazard ratios). Capping follow-up makes the assessed events more likely to be associated with AChEI initiation; whether the associations found in my study are even stronger when further reducing follow-up duration ought to be investigated.

If a large enough cohort of individuals can be generated, it would also be interesting to compare AChEI use and occurrence of malignant arrhythmia in *generally* healthy elderly individuals. Certainly, given the extremely low event rate, and large comorbidity burden in many elderly individuals, such an analysis may not be possible. However, given the fact that for BC (and potentially for all Canadian jurisdictions given the high utilization rate of donepezil) that donepezil is the first-line AChEI (with other AChEIs being substitutes),[157] it is likely a patient's comorbidity burden is a greater determinant of hospitalization for malignant arrhythmia use amongst AChEI users, than the AChEI itself.

7.2 Conclusion

The purpose of this study was to assist in filling the knowledge gap of whether donepezil is associated with a greater risk of hospitalization for malignant arrhythmia, in comparison to galantamine or rivastigmine, through using real-world data. In this cohort, donepezil was associated with a 45%-57% lower hazard for hospitalization for malignant arrhythmia (when considering only the primary DAD diagnosis field) in comparison to initiation of other AChEIs for AD and related dementias (uncapped follow-up aHR 0.551, 95% CI 0.358, 0.849; capped follow-up aHR 0.432, 95% CI 0.236, 0.791). When all 25 DAD diagnosis fields are considered (and using the main definition for hospitalization dates), donepezil may still be associated with a

23% lower hazard for a hospitalization for malignant arrhythmia, although the result is no longer statistically significant (capped follow-up aHR 0.773, 95% CI 0.526, 1.137). The protective nature of donepezil is fully attributable to increased risk among galantamine initiators (primary DAD diagnosis field, capped follow-up aHR 2.877, 95% CI 1.538, 5.383). These results were not expected, although the likeliness of the conclusions being affected by uncapturable comorbidities necessitates the need for future studies.

Clinically, the results are important because they reassure patients and clinicians regarding the safety of AChEIs. For donepezil specifically, the CredibleMeds warning was not supported by empirical evidence; this is in spite of the robust evidence assessment methods utilized by CredibleMeds in the listing of medications – including (but not limited to) case reports, FDA label changes, and pharmacological literature.[7] On the other hand, some of the trends present in the cohort behooves the need for medical practitioners to continue to perform detailed patient assessments prior to prescribing and dispensing AChEI medications. If the first line AChEI (donepezil) needs to be changed, it may suggest closer monitoring may be required for other comorbid conditions. At present – and in the absence of additional studies – since the results find that donepezil is not associated with an *increased* risk of hospitalization for malignant arrhythmia (despite AChEI pharmacological mechanisms that may suggest otherwise), utilization of donepezil as a first-line treatment for AD or other related dementias should still be a safe choice.

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Appendices

Appendix A – search terms used in malignant arrhythmia literature searches

Pubmed search strategy:
("long QT syndrome" OR "prolonged QT" OR "QT prolongation" OR "QT interval" OR ventricular arrhythmia* OR Arrhythmias, Cardiac[Mesh:NoExp] OR Brugada Syndrome[Mesh:NoExp] OR Cardiac Complexes, Premature[Mesh] OR Commotio Cordis[Mesh:NoExp] OR Heart Block[Mesh] OR Long QT Syndrome[Mesh] OR Parasystole[Mesh] OR Pre-Excitation Syndromes[Mesh] OR Tachycardia[Mesh] OR Ventricular Fibrillation[Mesh] OR Ventricular Flutter[Mesh] OR Death, Sudden, Cardiac[Mesh] OR Torsades de Pointes[Mesh] OR Heart Arrest[Mesh] OR Tachycardia, Supraventricular[Mesh])

Embase search strategy:

1. operational definition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2. exp "International Classification of Diseases"/
3. exp long QT syndrome/
4. long qt syndrome.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5. prolonged qt.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6. qt prolongation.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7. qt interval.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8. exp heart ventricle arrhythmia/
9. ventricular arrhythmia.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
10. 3 or 4 or 5 or 6 or 7 or 8 or 9
11. 1 or 2
12. 10 and 11
13. exp drug surveillance program/
14. pharmacovigilance.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
15. 11 or 13 or 14
16. 1 and 2
17. 10 and 16
18. 11 or 15

19. 10 and 18

Scopus search strategy:
(TITLE-ABS-KEY ((“operational definition” OR algorithm OR “ICD-10 code” OR definition* OR icd-10 OR “administrative data” OR “pharmacovigilance” OR “international classification of diseases”)) AND TITLE-ABS-KEY ((“Long QT syndrome” OR “prolonged QT” OR “QT prolongation” OR “QT interval” OR “ventricular arrhythmia” OR tachycardia OR “ventricular fibrillation” OR “torsades de pointes”)))

Appendix B – medications captured by NPDUIS data set and definition of medication-use comorbidities based upon NPDUIS

Table 5: AChEI medication breakdown provided by CIHI

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
N06DA02	DONEPEZIL	02322358	PMS DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE (DONEPEZIL HYDROCHLORIDE MONOHYDRATE)	ORAL
N06DA02	DONEPEZIL	02400588	AURO DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02428482	SEPTA DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02381516	RAN DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02362260	APO DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE (DONEPEZIL HYDROCHLORIDE MONOHYDRATE)	ORAL
N06DA02	DONEPEZIL	02397595	ACT DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE (DONEPEZIL HYDROCHLORIDE MONOHYDRATE)	ORAL
N06DA03	RIVASTIGMINE	02311305	RATIO RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02332833	MYLAN RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
N06DA03	RIVASTIGMINE	02302845	EXELON 5 4.6mg/24HOUR Patch ER	RIVASTIGMINE	TRANSDERMAL
N06DA03	RIVASTIGMINE	02336723	APO RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02406985	MINT RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02324563	SANDOZ RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02245240	EXELON 2mg/mL sol	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02324601	SANDOZ RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA04	GALANTAMINE	02398397	PMS GALANTAMINE ER 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02425173	AURO GALANTAMINE ER 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02316951	PAT GALANTAMINE ER 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA02	DONEPEZIL	02404427	JAMP DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA03	RIVASTIGMINE	02306050	PMS RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02306026	NOVO RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02332817	MYLAN RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02311291	RATIO RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE	ORAL

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
				HYDROGEN TARTRATE)	
N06DA03	RIVASTIGMINE	02332825	MYLAN RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02336731	APO RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA04	GALANTAMINE	02420848	MAR GALANTAMINE ER 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02244298	REMINYL 4mg tab	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02316978	PAT GALANTAMINE ER 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02339439	MYLAN GALANTAMINE 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02316943	PAT GALANTAMINE ER 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA02	DONEPEZIL	02269457	ARICEPT RDT 5mg Tab OD	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02359480	MYLAN DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02328666	SANDOZ DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02439557	NAT DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02425343	ECL DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02420600	DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02232043	ARICEPT 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA03	RIVASTIGMINE	02242116	EXELON 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02311313	RATIO RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE	ORAL

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
				HYDROGEN TARTRATE)	
N06DA03	RIVASTIGMINE	02332809	MYLAN RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02302853	EXELON 10 9.5mg/24HOUR Patch ER	RIVASTIGMINE	TRANSDERMAL
N06DA03	RIVASTIGMINE	02324598	SANDOZ RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02336715	APO RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02401649	MED RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02432803	EXELON 15 13.3mg/24HOUR Patch ER	RIVASTIGMINE	TRANSDERMAL
N06DA03	RIVASTIGMINE	02336758	APO RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02305984	NOVO RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02306018	NOVO RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA04	GALANTAMINE	02443023	GALANTAMINE ER 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02425157	AURO GALANTAMINE ER 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02443031	GALANTAMINE ER 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02244299	REMINYL 8mg tab	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
N06DA02	DONEPEZIL	02400561	AURO DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02439565	NAT DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02340607	TEVA DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02419874	ACCEL DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA03	RIVASTIGMINE	02306042	PMS RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02305992	NOVO RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02401614	MED RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02401630	MED RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA04	GALANTAMINE	02420821	MAR GALANTAMINE ER 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02420856	MAR GALANTAMINE ER 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02425165	AURO GALANTAMINE ER 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02339447	MYLAN GALANTAMINE 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA02	DONEPEZIL	02322331	PMS DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE (DONEPEZIL HYDROCHLORIDE MONOHYDRATE)	ORAL
N06DA02	DONEPEZIL	02426854	DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02425351	ECL DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
N06DA02	DONEPEZIL	02419866	ACCEL DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02232044	ARICEPT 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02426943	VAN DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA03	RIVASTIGMINE	02324571	SANDOZ RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02407019	MINT RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02242117	EXELON 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA02	DONEPEZIL	02359472	MYLAN DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02381508	RAN DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02402645	DONEPEZIL HYDROCHLORIDE 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02402653	DONEPEZIL HYDROCHLORIDE 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02412853	BIO DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02412861	BIO DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02416948	JAMP DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02340615	TEVA DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02426951	VAN DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02416956	JAMP DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02402106	MAR DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA04	GALANTAMINE	02266717	REMINYL ER 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
N06DA04	GALANTAMINE	02266725	REMINYL ER 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02398370	PMS GALANTAMINE ER 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02339455	MYLAN GALANTAMINE 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA02	DONEPEZIL	02428490	SEPTA DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02420597	DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02362279	APO DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE (DONEPEZIL HYDROCHLORIDE MONOHYDRATE)	ORAL
N06DA02	DONEPEZIL	02328682	SANDOZ DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02269465	ARICEPT RDT 10mg Tab OD	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02397609	ACT DONEPEZIL 10mg tab	DONEPEZIL HYDROCHLORIDE (DONEPEZIL HYDROCHLORIDE MONOHYDRATE)	ORAL
N06DA02	DONEPEZIL	02402092	MAR DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA02	DONEPEZIL	02404419	JAMP DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA03	RIVASTIGMINE	02407000	MINT RIVASTIGMINE 4.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02306069	PMS RIVASTIGMINE 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02401622	MED RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02306034	PMS RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL

ATC Level 5 Code	ATC Level 5 Description	DIN	CIHI Uniform Description	Active ingredient description	Route
N06DA03	RIVASTIGMINE	02406993	MINT RIVASTIGMINE 3mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA04	GALANTAMINE	02266733	REMINYL ER 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02398389	PMS GALANTAMINE ER 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA02	DONEPEZIL	02426846	DONEPEZIL 5mg tab	DONEPEZIL HYDROCHLORIDE	ORAL
N06DA03	RIVASTIGMINE	02242118	EXELON 6mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02311283	RATIO RIVASTIGMINE 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA03	RIVASTIGMINE	02242115	EXELON 1.5mg cap	RIVASTIGMINE (RIVASTIGMINE HYDROGEN TARTRATE)	ORAL
N06DA04	GALANTAMINE	02244300	REMINYL 12mg tab	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02377950	TEVA GALANTAMINE 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02377969	TEVA GALANTAMINE 16mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02377977	TEVA GALANTAMINE 24mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL
N06DA04	GALANTAMINE	02443015	GALANTAMINE ER 8mg Cap ER	GALANTAMINE (GALANTAMINE HYDROBROMIDE)	ORAL

Table 6: breakdown of non-AChEI (covariate) medications, to be provided by CIHI

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	ACENOCOUMAROL	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	ACETYLSALICYLIC ACID	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	APIXABAN	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	CLOPIDOGREL (CLOPIDOGREL BISULFATE)	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	DABIGATRAN ETEXILATE (DABIGATRAN ETEXILATE MESILATE)	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	DALTEPARIN SODIUM	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	DIPYRIDAMOLE	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	DIPYRIDAMOLE, ACETYLSALICYLIC ACID	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	EDOXABAN (EDOXABAN TOSYLATE MONOHYDRATE)	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	ENOXAPARIN SODIUM	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	EPOPROSTENOL (EPOPROSTENOL SODIUM)	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	FONDAPARINUX SODIUM	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	HEPARIN SODIUM	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	NADROPARIN CALCIUM	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	PRASUGREL (PRASUGREL HYDROCHLORIDE)	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	RIVAROXABAN	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	SELEXIPAG	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	TICAGRELOR	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	TICLOPIDINE HYDROCHLORIDE	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	TINZAPARIN SODIUM	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	TREPROSTINIL (TREPROSTINIL SODIUM)	OTHER
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	WARFARIN SODIUM	ORAL
Blood And Blood Forming Organs	Antithrombotic Agents	B01A	N	WARFARIN SODIUM	
Blood And Blood Forming Organs	Antifibrinolytics	B02A	N	ALFA 1-PROTEINASE INHIBITOR (HUMAN)	OTHER
Blood And Blood Forming Organs	Antifibrinolytics	B02A	N	TRANEXAMIC ACID	ORAL
Blood And Blood Forming Organs	Antifibrinolytics	B02A	N	TRANEXAMIC ACID	OTHER
Blood And Blood Forming Organs	Vitamin K And Other Hemostatics	B02B	N	ELTROMBOPAG (ELTROMBOPAG OLAMINE)	ORAL
Blood And Blood Forming Organs	Vitamin K And Other Hemostatics	B02B	N	ROMIPLOSTIM	OTHER

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Blood And Blood Forming Organs	Vitamin K And Other Hemostatics	B02B	N	VITAMIN K1	OTHER
Cardiovascular System	Cardiac Glycosides)	C01A	N	DIGOXIN	ORAL
Cardiovascular System	Cardiac Glycosides)	C01A	N	DIGOXIN	OTHER
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	AMIODARONE HYDROCHLORIDE	ORAL
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	DISOPYRAMIDE	ORAL
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	DRONEDARONE (DRONEDARONE HYDROCHLORIDE)	ORAL
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	FLECAINIDE ACETATE	ORAL
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	LIDOCAINE HYDROCHLORIDE	OTHER
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	MEXILETINE HYDROCHLORIDE	ORAL
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	PROCAINAMIDE HYDROCHLORIDE	ORAL
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	PROPAFENONE HYDROCHLORIDE	ORAL
Cardiovascular System	Antiarrhythmics, Class I And Iii	C01B	N	QUINIDINE SULFATE	ORAL
Cardiovascular System	Cardiac Stimulants (Excl. Cardiac Glycosides)	C01C	N	EPINEPHRINE	OTHER
Cardiovascular System	Cardiac Stimulants (Excl. Cardiac Glycosides)	C01C	N	EPINEPHRINE (EPINEPHRINE HYDROCHLORIDE)	OTHER
Cardiovascular System	Cardiac Stimulants (Excl. Cardiac Glycosides)	C01C	N	MIDODRINE HYDROCHLORIDE	ORAL
Cardiovascular System	Vasodilators Used In Cardiac Diseases	C01D	N	ISOSORBIDE DINITRATE	ORAL
Cardiovascular System	Vasodilators Used In Cardiac Diseases	C01D	N	ISOSORBIDE DINITRATE	OTHER
Cardiovascular System	Vasodilators Used In Cardiac Diseases	C01D	N	ISOSORBIDE-5-MONONITRATE	ORAL
Cardiovascular System	Vasodilators Used In Cardiac Diseases	C01D	N	NITROGLYCERIN	OTHER
Cardiovascular System	Other Cardiac Preparations	C01E	N	ALPROSTADIL	OTHER
Cardiovascular System	Other Cardiac Preparations	C01E	N	INDOMETHACIN	OTHER
Cardiovascular System	Other Cardiac Preparations	C01E	N	IVABRADINE (IVABRADINE HYDROCHLORIDE)	ORAL
Cardiovascular System	Other Cardiac Preparations	C01E	N	UBIDECARENONE	ORAL
Cardiovascular System	Antiadrenergic Agents, Centrally Acting	C02A	N	CLONIDINE HYDROCHLORIDE	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Cardiovascular System	Antiadrenergic Agents, Centrally Acting	C02A	N	METHYLDOPA	ORAL
Cardiovascular System	Antiadrenergic Agents, Peripherally Acting	C02C	N	DOXAZOSIN (DOXAZOSIN MESYLATE)	ORAL
Cardiovascular System	Antiadrenergic Agents, Peripherally Acting	C02C	N	PRAZOSIN (PRAZOSIN HYDROCHLORIDE)	ORAL
Cardiovascular System	Antiadrenergic Agents, Peripherally Acting	C02C	N	PRAZOSIN HYDROCHLORIDE	ORAL
Cardiovascular System	Arteriolar Smooth Muscle, Agents Acting On	C02D	N	HYDRALAZINE HYDROCHLORIDE	ORAL
Cardiovascular System	Arteriolar Smooth Muscle, Agents Acting On	C02D	N	HYDRALAZINE HYDROCHLORIDE	OTHER
Cardiovascular System	Arteriolar Smooth Muscle, Agents Acting On	C02D	N	MINOXIDIL	ORAL
Cardiovascular System	Other Antihypertensives	C02K	N	AMBRISENTAN	ORAL
Cardiovascular System	Other Antihypertensives	C02K	N	BOSENTAN (BOSENTAN MONOHYDRATE)	ORAL
Cardiovascular System	Other Antihypertensives	C02K	N	MACITENTAN	ORAL
Cardiovascular System	Other Antihypertensives	C02K	N	RIOCIGUAT	ORAL
Cardiovascular System	Other Antihypertensives	C02K	N	SILDENAFIL (SILDENAFIL CITRATE)	ORAL
Cardiovascular System	Low-Ceiling Diuretics, Thiazides	C03A	N	HYDROCHLOROTHIAZIDE	ORAL
Cardiovascular System	Low-Ceiling Diuretics, Excl. Thiazides	C03B	N	CHLORTHALIDONE	ORAL
Cardiovascular System	Low-Ceiling Diuretics, Excl. Thiazides	C03B	N	INDAPAMIDE	ORAL
Cardiovascular System	Low-Ceiling Diuretics, Excl. Thiazides	C03B	N	METOLAZONE	ORAL
Cardiovascular System	High-Ceiling Diuretics	C03C	N	BUMETANIDE	ORAL
Cardiovascular System	High-Ceiling Diuretics	C03C	N	ETHACRYNIC ACID	ORAL
Cardiovascular System	High-Ceiling Diuretics	C03C	N	FUROSEMIDE	ORAL
Cardiovascular System	High-Ceiling Diuretics	C03C	N	FUROSEMIDE	OTHER
Cardiovascular System	Potassium-Sparing Agents	C03D	N	AMILORIDE HYDROCHLORIDE	ORAL
Cardiovascular System	Potassium-Sparing Agents	C03D	N	EPLERENONE	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Cardiovascular System	Potassium-Sparing Agents	C03D	N	SPIRONOLACTONE	ORAL
Cardiovascular System	Diuretics And Potassium-Sparing Agents In Combination	C03E	N	HYDROCHLOROTHIAZIDE, AMILORIDE HYDROCHLORIDE	ORAL
Cardiovascular System	Diuretics And Potassium-Sparing Agents In Combination	C03E	N	HYDROCHLOROTHIAZIDE, SPIRONOLACTONE	ORAL
Cardiovascular System	Diuretics And Potassium-Sparing Agents In Combination	C03E	N	HYDROCHLOROTHIAZIDE, TRIAMTERENE	ORAL
Cardiovascular System	Other Diuretics	C03X	N	TOLVAPTAN	ORAL
Cardiovascular System	Peripheral Vasodilators	C04A	N	ERGOLOID MESYLATES	ORAL
Cardiovascular System	Peripheral Vasodilators	C04A	N	NICOTINIC ACID	ORAL
Cardiovascular System	Peripheral Vasodilators	C04A	N	NYLIDRIN HYDROCHLORIDE	ORAL
Cardiovascular System	Peripheral Vasodilators	C04A	N	PENTOXIFYLLINE	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	ACEBUTOLOL (ACEBUTOLOL HYDROCHLORIDE)	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	ACEBUTOLOL HYDROCHLORIDE	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	ATENOLOL	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	ATENOLOL	
Cardiovascular System	Beta Blocking Agents	C07A	N	BISOPROLOL FUMARATE	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	CARVEDILOL	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	LABETALOL HYDROCHLORIDE	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	LABETALOL HYDROCHLORIDE	
Cardiovascular System	Beta Blocking Agents	C07A	N	METOPROLOL TARTRATE	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	METOPROLOL TARTRATE	OTHER
Cardiovascular System	Beta Blocking Agents	C07A	N	NADOLOL	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	PINDOLOL	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	PROPRANOLOL HYDROCHLORIDE	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	PROPRANOLOL HYDROCHLORIDE	

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Cardiovascular System	Beta Blocking Agents	C07A	N	SOTALOL HYDROCHLORIDE	ORAL
Cardiovascular System	Beta Blocking Agents	C07A	N	TIMOLOL MALEATE	ORAL
Cardiovascular System	Pindolol	C07AA03	N	PINDOLOL	ORAL
Cardiovascular System	Acebutolol	C07AB04	N	ACEBUTOLOL (ACEBUTOLOL HYDROCHLORIDE)	ORAL
Cardiovascular System	Acebutolol	C07AB04	N	ACEBUTOLOL HYDROCHLORIDE	ORAL
Cardiovascular System	Labetalol	C07AG01	N	LABETALOL HYDROCHLORIDE	ORAL
Cardiovascular System	Labetalol	C07AG01	N	LABETALOL HYDROCHLORIDE	
Cardiovascular System	Beta Blocking Agents And Other Diuretics	C07C	N	ATENOLOL	
Cardiovascular System	Beta Blocking Agents And Other Diuretics	C07C	N	ATENOLOL, CHLORTHALIDONE	ORAL
Cardiovascular System	Beta Blocking Agents And Other Diuretics	C07C	N	PINDOLOL, HYDROCHLOROTHIAZIDE	ORAL
Cardiovascular System	Pindolol	C07CA03	N	PINDOLOL, HYDROCHLOROTHIAZIDE	ORAL
Cardiovascular System	Selective Calcium Channel Blockers With Mainly Vascular Effects	C08C	N	AMLODIPINE (AMLODIPINE BESYLATE)	ORAL
Cardiovascular System	Selective Calcium Channel Blockers With Mainly Vascular Effects	C08C	N	FELODIPINE	ORAL
Cardiovascular System	Selective Calcium Channel Blockers With Mainly Vascular Effects	C08C	N	NIFEDIPINE	ORAL
Cardiovascular System	Selective Calcium Channel Blockers With Mainly Vascular Effects	C08C	N	NIMODIPINE	ORAL
Cardiovascular System	Dihydropyridine Derivatives	C08CA	N	AMLODIPINE (AMLODIPINE BESYLATE)	ORAL
Cardiovascular System	Dihydropyridine Derivatives	C08CA	N	FELODIPINE	ORAL
Cardiovascular System	Dihydropyridine Derivatives	C08CA	N	NIFEDIPINE	ORAL
Cardiovascular System	Dihydropyridine Derivatives	C08CA	N	NIMODIPINE	ORAL
Cardiovascular System	Selective Calcium Channel Blockers With Direct Cardiac Effects	C08D	N	DILTIAZEM HYDROCHLORIDE	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Cardiovascular System	Selective Calcium Channel Blockers With Direct Cardiac Effects	C08D	N	DILTIAZEM HYDROCHLORIDE	
Cardiovascular System	Selective Calcium Channel Blockers With Direct Cardiac Effects	C08D	N	VERAPAMIL HYDROCHLORIDE	ORAL
Cardiovascular System	Selective Calcium Channel Blockers With Direct Cardiac Effects	C08D	N	VERAPAMIL HYDROCHLORIDE	OTHER
CredibleMeds	Papaverine	A03AD01	N	PAPAVERINE HYDROCHLORIDE	OTHER
CredibleMeds	Domperidone	A03FA03	N	DOMPERIDONE (DOMPERIDONE MALEATE)	ORAL
CredibleMeds	Domperidone	A03FA03	Y		
CredibleMeds	Ondansetron	A04AA01	N	ONDANSETRON	ORAL
CredibleMeds	Ondansetron	A04AA01	N	ONDANSETRON (ONDANSETRON HYDROCHLORIDE DIHYDRATE)	ORAL
CredibleMeds	Ondansetron	A04AA01	N	ONDANSETRON (ONDANSETRON HYDROCHLORIDE DIHYDRATE)	OTHER
CredibleMeds	Ondansetron	A04AA01	N	ONDANSETRON (ONDANSETRON HYDROCHLORIDE)	ORAL
CredibleMeds	Ondansetron	A04AA01	Y		
CredibleMeds	Procainamide	C01BA02	N	PROCAINAMIDE HYDROCHLORIDE	ORAL
CredibleMeds	Disopyramide	C01BA03	N	DISOPYRAMIDE	ORAL
CredibleMeds	Flecainide	C01BC04	N	FLECAINIDE ACETATE	ORAL
CredibleMeds	Amiodarone	C01BD01	N	AMIODARONE HYDROCHLORIDE	ORAL
CredibleMeds	Amiodarone	C01BD01	Y		
CredibleMeds	Dronedarone	C01BD07	N	DRONEDARONE (DRONEDARONE HYDROCHLORIDE)	ORAL
CredibleMeds	Sotalol	C07AA07	N	SOTALOL HYDROCHLORIDE	ORAL
CredibleMeds	Sotalol	C07AA07	Y		
CredibleMeds	Erythromycin	D10AF02	Y		
CredibleMeds	Erythromycin	J01FA01	N	ERYTHROMYCIN	ORAL
CredibleMeds	Erythromycin	J01FA01	N	ERYTHROMYCIN (ERYTHROMYCIN ESTOLATE)	ORAL
CredibleMeds	Erythromycin	J01FA01	N	ERYTHROMYCIN (ERYTHROMYCIN ETHYLSUCCINATE)	ORAL
CredibleMeds	Erythromycin	J01FA01	N	ERYTHROMYCIN (ERYTHROMYCIN STEARATE)	ORAL
CredibleMeds	Erythromycin	J01FA01	N	ERYTHROMYCIN LACTOBIONATE	OTHER
CredibleMeds	Azithromycin	J01FA10	N	AZITHROMYCIN	ORAL
CredibleMeds	Azithromycin	J01FA10	N	AZITHROMYCIN	OTHER

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
CredibleMeds	Azithromycin	J01FA10	N	AZITHROMYCIN (AZITHROMYCIN DIHYDRATE)	ORAL
CredibleMeds	Azithromycin	J01FA10	N	AZITHROMYCIN (AZITHROMYCIN ISOPROPANOLATE MONOHYDRATE)	ORAL
CredibleMeds	Azithromycin	J01FA10	N	AZITHROMYCIN (AZITHROMYCIN MONOHYDRATE HEMIETHANOLATE)	ORAL
CredibleMeds	Azithromycin	J01FA10	N	AZITHROMYCIN (AZITHROMYCIN MONOHYDRATE)	ORAL
CredibleMeds	Azithromycin	J01FA10	Y		
CredibleMeds	Ciprofloxacin	J01MA02	N	CIPROFLOXACIN	ORAL
CredibleMeds	Ciprofloxacin	J01MA02	N	CIPROFLOXACIN (CIPROFLOXACIN HYDROCHLORIDE)	ORAL
CredibleMeds	Ciprofloxacin	J01MA02	N	CIPROFLOXACIN (CIPROFLOXACIN HYDROCHLORIDE, CIPROFLOXACIN)	ORAL
CredibleMeds	Ciprofloxacin	J01MA02	Y		
CredibleMeds	Levofloxacin	J01MA12	N	LEVOFLOXACIN	ORAL
CredibleMeds	Levofloxacin	J01MA12	N	LEVOFLOXACIN (LEVOFLOXACIN HEMIHYDRATE)	ORAL
CredibleMeds	Moxifloxacin	J01MA14	N	MOXIFLOXACIN (MOXIFLOXACIN HYDROCHLORIDE)	ORAL
CredibleMeds	Moxifloxacin	J01MA14	N	MOXIFLOXACIN (MOXIFLOXACIN HYDROCHLORIDE)	OTHER
CredibleMeds	Fluconazole	J02AC01	N	FLUCONAZOLE	ORAL
CredibleMeds	Fluconazole	J02AC01	N	FLUCONAZOLE	OTHER
CredibleMeds	Fluconazole	J02AC01	N	FLUCONAZOLE, CLOTRIMAZOLE	ORAL
CredibleMeds	Fluconazole	J02AC01	N	FLUCONAZOLE, CLOTRIMAZOLE	OTHER
CredibleMeds	Fluconazole	J02AC01	Y		
CredibleMeds	Vandetanib	L01XE12	N	VANDETANIB	ORAL
CredibleMeds	Anagrelide	L01XX35	N	ANAGRELIDE (ANAGRELIDE HYDROCHLORIDE MONOHYDRATE)	ORAL
CredibleMeds	Anagrelide	L01XX35	N	ANAGRELIDE (ANAGRELIDE HYDROCHLORIDE)	ORAL
CredibleMeds	Anagrelide	L01XX35	Y		
CredibleMeds	Chlorpromazine	N05AA01	N	CHLORPROMAZINE (CHLORPROMAZINE HYDROCHLORIDE)	ORAL
CredibleMeds	Chlorpromazine	N05AA01	N	CHLORPROMAZINE (CHLORPROMAZINE HYDROCHLORIDE)	OTHER
CredibleMeds	Chlorpromazine	N05AA01	Y		
CredibleMeds	Thioridazine	N05AC02	Y		

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
CredibleMeds	Haloperidol	N05AD01	N	HALOPERIDOL	ORAL
CredibleMeds	Haloperidol	N05AD01	N	HALOPERIDOL	OTHER
CredibleMeds	Haloperidol	N05AD01	N	HALOPERIDOL (HALOPERIDOL DECANOATE)	OTHER
CredibleMeds	Haloperidol	N05AD01	Y		
CredibleMeds	Droperidol	N05AD08	N	DROPERIDOL	OTHER
CredibleMeds	Pimozide	N05AG02	N	PIMOZIDE	ORAL
CredibleMeds	Citalopram	N06AB04	N	CITALOPRAM (CITALOPRAM HYDROBROMIDE)	ORAL
CredibleMeds	Citalopram	N06AB04	Y		
CredibleMeds	Escitalopram	N06AB10	N	ESCITALOPRAM	ORAL
CredibleMeds	Escitalopram	N06AB10	N	ESCITALOPRAM (ESCITALOPRAM OXALATE)	ORAL
CredibleMeds	Escitalopram	N06AB10	Y		
CredibleMeds	Methadone	N07BC02	N	METHADONE HYDROCHLORIDE	ORAL
CredibleMeds	Methadone	N07BC02	Y		
CredibleMeds	Chloroquine	P01BA01	N	CHLOROQUINE DIPHOSPHATE	ORAL
CredibleMeds	Erythromycin	S01AA17	N	ERYTHROMYCIN	OTHER
CredibleMeds	Ciprofloxacin	S01AE03	N	CIPROFLOXACIN (CIPROFLOXACIN HYDROCHLORIDE)	OTHER
CredibleMeds	Gatifloxacin	S01AE06	N	GATIFLOXACIN	OTHER
CredibleMeds	Moxifloxacin	S01AE07	N	MOXIFLOXACIN (MOXIFLOXACIN HYDROCHLORIDE)	OTHER
CredibleMeds	Ciprofloxacin	S03AA07	N	CIPROFLOXACIN (CIPROFLOXACIN HYDROCHLORIDE)	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	DESOGESTREL, DESOGESTREL, DESOGESTREL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	DESOGESTREL, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	DROSPIRENONE, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	ETHINYL ESTRADIOL, DESOGESTREL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	ETHINYL ESTRADIOL, DROSPIRENONE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	ETHINYL ESTRADIOL, ETHINYL ESTRADIOL, LEVONORGESTREL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	ETHINYL ESTRADIOL, ETHYNODIOL DIACETATE	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	ETHINYL ESTRADIOL, LEVONORGESTREL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	ETHINYL ESTRADIOL, NORGESTREL (NORGESTREL)	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	LEVONORGESTREL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	LEVONORGESTREL, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	MEDROXYPROGESTERONE ACETATE	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	NORETHINDRONE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	NORETHINDRONE ACETATE, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	NORETHINDRONE, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	NORETHINDRONE, NORETHINDRONE, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	NORETHINDRONE, NORETHINDRONE, NORETHINDRONE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	NORGESTIMATE, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03A	N	NORGESTIMATE, NORGESTIMATE, NORGESTIMATE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	CONJUGATED ESTROGENS	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	CONJUGATED ESTROGENS	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTRADIOL	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTRADIOL (ESTRADIOL HEMIHYDRATE)	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTRADIOL (ESTRADIOL HEMIHYDRATE)	OTHER

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTRADIOL VALERATE	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTRONE	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTROPIPATE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03C	N	ESTROPIPATE	
Female hormones	Sex Hormones And Modulators Of The Genital System	G03D	N	DIENOGEST	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03D	N	MEDROXYPROGESTERONE ACETATE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03D	N	NORETHINDRONE ACETATE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03D	N	PROGESTERONE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03D	N	PROGESTERONE	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03F	N	MEDROXYPROGESTERONE ACETATE, CONJUGATED ESTROGENS	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03F	N	NORETHINDRONE ACETATE, ESTRADIOL	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03F	N	NORETHINDRONE ACETATE, ETHINYL ESTRADIOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03F	N	PROGESTERONE, ESTRADIOL (ESTRADIOL HEMIHYDRATE)	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03F	N	PROGESTERONE, ESTRADIOL (ESTRADIOL HEMIHYDRATE)	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03G	N	CHORIONIC GONADOTROPIN, WATER	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03G	N	CLOMIPHENE CITRATE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03H	N	CYPROTERONE ACETATE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03H	N	CYPROTERONE ACETATE	OTHER

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Female hormones	Sex Hormones And Modulators Of The Genital System	G03X	N	DANAZOL	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03X	N	DANAZOL	
Female hormones	Sex Hormones And Modulators Of The Genital System	G03X	N	MIFEPRISTONE, MISOPROSTOL	OTHER
Female hormones	Sex Hormones And Modulators Of The Genital System	G03X	N	RALOXIFENE HYDROCHLORIDE	ORAL
Female hormones	Sex Hormones And Modulators Of The Genital System	G03X	N	ULIPRISTAL ACETATE	ORAL
Loop diuretics	Furosemide	C03CA01	N	FUROSEMIDE	ORAL
Loop diuretics	Furosemide	C03CA01	N	FUROSEMIDE	OTHER
Loop diuretics	Bumetanide	C03CA02	N	BUMETANIDE	ORAL
Male hormones	Sex Hormones And Modulators Of The Genital System	G03B	N	TESTOSTERONE	OTHER
Male hormones	Sex Hormones And Modulators Of The Genital System	G03B	N	TESTOSTERONE CYPIONATE	OTHER
Male hormones	Sex Hormones And Modulators Of The Genital System	G03B	N	TESTOSTERONE ENANTHATE	OTHER
Male hormones	Sex Hormones And Modulators Of The Genital System	G03B	N	TESTOSTERONE UNDECANOATE	ORAL
non-AD AChEIs*	Neostigmine	N07AA01	N	NEOSTIGMINE BROMIDE	ORAL
non-AD AChEIs*	Neostigmine	N07AA01	N	NEOSTIGMINE METHYLSULFATE	OTHER
non-AD AChEIs*	Pyridostigmine	N07AA02	N	PYRIDOSTIGMINE BROMIDE	ORAL
Strong inducers of CYP3A4	Rifaximin	A07AA11	N	RIFAXIMIN	ORAL
Strong inducers of CYP3A4	Dexamethasone	H02AB02	N	DEXAMETHASONE	ORAL
Strong inducers of CYP3A4	Dexamethasone	H02AB02	N	DEXAMETHASONE (DEXAMETHASONE SODIUM PHOSPHATE)	OTHER
Strong inducers of CYP3A4	Dexamethasone	H02AB02	N	DEXAMETHASONE PHOSPHATE (DEXAMETHASONE SODIUM PHOSPHATE)	OTHER
Strong inducers of CYP3A4	Rifampicin	J04AB02	N	RIFAMPIN	ORAL
Strong inducers of CYP3A4	Rifampicin	J04AB02	N	RIFAMPIN	
Strong inducers of CYP3A4	Midostaurin	L01XE39	N	MIDOSTAURIN	ORAL
Strong inducers of CYP3A4	Mitotane	L01XX23	N	MITOTANE	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Strong inducers of CYP3A4	Enzalutamide	L02BB04	N	ENZALUTAMIDE	ORAL
Strong inducers of CYP3A4	Phenobarbital	N03AA02	N	PHENOBARBITAL	ORAL
Strong inducers of CYP3A4	Phenobarbital	N03AA02	N	PHENOBARBITAL SODIUM	OTHER
Strong inducers of CYP3A4	Primidone	N03AA03	N	PRIMIDONE	ORAL
Strong inducers of CYP3A4	Phenytoin	N03AB02	N	PHENYTOIN	ORAL
Strong inducers of CYP3A4	Phenytoin	N03AB02	N	PHENYTOIN SODIUM	ORAL
Strong inducers of CYP3A4	Phenytoin	N03AB02	N	PHENYTOIN SODIUM	OTHER
Strong inducers of CYP3A4	Carbamazepine	N03AF01	N	CARBAMAZEPINE	ORAL
Strong inducers of CYP3A4	Pentobarbital	N05CA01	N	PENTOBARBITAL SODIUM	ORAL
Strong inducers of CYP3A4	Pentobarbital	N05CA01	N	PENTOBARBITAL SODIUM	OTHER
Strong inducers of CYP3A4	Dexamethasone	S01BA01	N	DEXAMETHASONE	OTHER
Strong inducers of CYP3A4	Rimexolone	S01BA13	N	RIMEXOLONE	OTHER
Strong inducers of CYP3A4	Dexamethasone	S01CA01	N	DEXAMETHASONE, POLYMYXIN B SULFATE, NEOMYCIN (NEOMYCIN SULFATE)	OTHER
Strong inducers of CYP3A4	Dexamethasone	S01CA01	N	DEXAMETHASONE, TOBRAMYCIN	OTHER
Strong inducers of CYP3A4	Dexamethasone	S02CA06	N	DEXAMETHASONE, CIPROFLOXACIN (CIPROFLOXACIN HYDROCHLORIDE)	OTHER
Strong inducers of CYP3A4	Dexamethasone	S03BA01	N	DEXAMETHASONE PHOSPHATE (DEXAMETHASONE SODIUM PHOSPHATE)	OTHER
Strong inducers of CYP3A4	Dexamethasone	S03CA01	N	DEXAMETHASONE (DEXAMETHASONE SODIUM METASULPHOBENZOATE), FRAMYCETIN SULFATE, GRAMICIDIN	OTHER
Strong inducers of CYP3A4	Dexamethasone	S03CA01	N	DEXAMETHASONE SODIUM METASULPHOBENZOATE, FRAMYCETIN SULFATE, GRAMICIDIN	OTHER
Strong inducers of CYP3A4	Dexamethasone	S03CA01	N	DEXAMETHASONE, FRAMYCETIN SULFATE, GRAMICIDIN	OTHER
Strong inhibitors of CYP2D6	Propafenone	C01BC03	N	PROPAFENONE HYDROCHLORIDE	ORAL
Strong inhibitors of CYP2D6	Cinacalcet	H05BX01	N	CINACALCET (CINACALCET HYDROCHLORIDE)	ORAL
Strong inhibitors of CYP2D6	Midostaurin	L01XE39	N	MIDOSTAURIN	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Strong inhibitors of CYP2D6	Orphenadrine	M03BC01	N	ORPHENADRINE CITRATE	ORAL
Strong inhibitors of CYP2D6	Fluoxetine	N06AB03	N	FLUOXETINE (FLUOXETINE HYDROCHLORIDE)	ORAL
Strong inhibitors of CYP2D6	Paroxetine	N06AB05	N	PAROXETINE (PAROXETINE HYDROCHLORIDE ACETONE SOLVATE)	ORAL
Strong inhibitors of CYP2D6	Paroxetine	N06AB05	N	PAROXETINE (PAROXETINE HYDROCHLORIDE HEMIHYDRATE)	ORAL
Strong inhibitors of CYP2D6	Paroxetine	N06AB05	N	PAROXETINE (PAROXETINE HYDROCHLORIDE)	ORAL
Strong inhibitors of CYP2D6	Paroxetine	N06AB05	N	PAROXETINE (PAROXETINE HYDROCHLORIDE, ISOPROPYL SOLVATE)	ORAL
Strong inhibitors of CYP2D6	Bupropion	N06AX12	N	BUPROPION HYDROCHLORIDE	ORAL
Strong inhibitors of CYP2D6 and CredibleMeds	Quinidine	C01BA01	N	QUINIDINE SULFATE	ORAL
Strong inhibitors of CYP2D6 and CredibleMeds	Methotrimeprazine (Levomepromazine)	N05AA02	N	METHOTRIMEPRAZINE (METHOTRIMEPRAZINE HYDROCHLORIDE)	ORAL
Strong inhibitors of CYP2D6 and CredibleMeds	Methotrimeprazine (Levomepromazine)	N05AA02	N	METHOTRIMEPRAZINE (METHOTRIMEPRAZINE HYDROCHLORIDE)	OTHER
Strong inhibitors of CYP2D6 and CredibleMeds	Methotrimeprazine (Levomepromazine)	N05AA02	N	METHOTRIMEPRAZINE (METHOTRIMEPRAZINE MALEATE)	ORAL
Strong inhibitors of CYP2D6 and CredibleMeds	Methotrimeprazine (Levomepromazine)	N05AA02	Y		
Strong inhibitors of CYP3A4	Clarithromycin	A02BD07	N	LANSOPRAZOLE, AMOXICILLIN, CLARITHROMYCIN	ORAL
Strong inhibitors of CYP3A4	Loperamide	A07DA03	N	LOPERAMIDE HYDROCHLORIDE	ORAL
Strong inhibitors of CYP3A4	Loperamide	A07DA53	N	LOPERAMIDE HYDROCHLORIDE, SIMETHICONE	ORAL
Strong inhibitors of CYP3A4	Econazole	D01AC03	N	ECONAZOLE NITRATE	OTHER
Strong inhibitors of CYP3A4	Ketoconazole	D01AC08	N	KETOCONAZOLE	OTHER
Strong inhibitors of CYP3A4	Methimazole (Thiamazole)	H03BB02	N	METHIMAZOLE	ORAL
Strong inhibitors of CYP3A4	Ketoconazole	J02AB02	N	KETOCONAZOLE	ORAL
Strong inhibitors of CYP3A4	Itraconazole	J02AC02	N	ITRACONAZOLE	ORAL
Strong inhibitors of CYP3A4	Voriconazole	J02AC03	N	VORICONAZOLE	ORAL
Strong inhibitors of CYP3A4	Voriconazole	J02AC03	N	VORICONAZOLE	OTHER

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Strong inhibitors of CYP3A4	Posaconazole	J02AC04	N	POSACONAZOLE	ORAL
Strong inhibitors of CYP3A4	Saquinavir	J05AE01	N	SAQUINAVIR (SAQUINAVIR MESYLATE)	ORAL
Strong inhibitors of CYP3A4	Indinavir	J05AE02	N	INDINAVIR (INDINAVIR SULFATE)	ORAL
Strong inhibitors of CYP3A4	Ritonavir	J05AE03	N	RITONAVIR	ORAL
Strong inhibitors of CYP3A4	Nelfinavir	J05AE04	N	NELFINAVIR (NELFINAVIR MESYLATE)	ORAL
Strong inhibitors of CYP3A4	Atazanavir	J05AE08	N	ATAZANAVIR (ATAZANAVIR SULFATE)	ORAL
Strong inhibitors of CYP3A4	Tipranavir	J05AE09	N	TIPRANAVIR	ORAL
Strong inhibitors of CYP3A4	Darunavir	J05AE10	N	DARUNAVIR (DARUNAVIR ETHANOLATE)	ORAL
Strong inhibitors of CYP3A4	Delavirdine	J05AG02	N	DELAVIRDINE MESYLATE	ORAL
Strong inhibitors of CYP3A4	Efavirenz	J05AG03	N	EFAVIRENZ	ORAL
Strong inhibitors of CYP3A4	Telaprevir	J05AP02	N	TELAPREVIR	ORAL
Strong inhibitors of CYP3A4	Boceprevir	J05AP03	N	BOCEPREVIR	ORAL
Strong inhibitors of CYP3A4	Ritonavir	J05AP52	N	DASABUVIR (DASABUVIR SODIUM MONOHYDRATE), PARITAPREVIR, RITONAVIR	ORAL
Strong inhibitors of CYP3A4	Efavirenz	J05AR06	N	EMTRICITABINE, TENOFOVIR DISOPROXIL FUMARATE, EFAVIRENZ	ORAL
Strong inhibitors of CYP3A4	Cobicistat	J05AR09	N	TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE, ELVITEGRAVIR	ORAL
Strong inhibitors of CYP3A4	Elvitegravir	J05AR09	N	TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE, ELVITEGRAVIR	ORAL
Strong inhibitors of CYP3A4	Lopinavir	J05AR10	N	LOPINAVIR, RITONAVIR	ORAL
Strong inhibitors of CYP3A4	Ritonavir	J05AR10	N	LOPINAVIR, RITONAVIR	ORAL
Strong inhibitors of CYP3A4	Lopinavir	J05AR10	N	RITONAVIR, LOPINAVIR	ORAL
Strong inhibitors of CYP3A4	Ritonavir	J05AR10	N	RITONAVIR, LOPINAVIR	ORAL
Strong inhibitors of CYP3A4	Cobicistat	J05AR14	N	DARUNAVIR (DARUNAVIR ETHANOLATE), COBICISTAT	ORAL
Strong inhibitors of CYP3A4	Darunavir	J05AR14	N	DARUNAVIR (DARUNAVIR ETHANOLATE), COBICISTAT	ORAL
Strong inhibitors of CYP3A4	Cobicistat	J05AR18	N	EMTRICITABINE, ELVITEGRAVIR, COBICISTAT	ORAL
Strong inhibitors of CYP3A4	Elvitegravir	J05AR18	N	EMTRICITABINE, ELVITEGRAVIR, COBICISTAT	ORAL

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Strong inhibitors of CYP3A4	Nilotinib	L01XE08	N	NILOTINIB (NILOTINIB HYDROCHLORIDE MONOHYDRATE)	ORAL
Strong inhibitors of CYP3A4	Midostaurin	L01XE39	N	MIDOSTAURIN	ORAL
Strong inhibitors of CYP3A4	Idelalisib	L01XX47	N	IDELALISIB	ORAL
Strong inhibitors of CYP3A4	Naloxone	N02AA55	N	OXYCODONE HYDROCHLORIDE, NALOXONE HYDROCHLORIDE	ORAL
Strong inhibitors of CYP3A4	Ergotamine	N02CA52	N	ERGOTAMINE TARTRATE, CAFFEINE	ORAL
Strong inhibitors of CYP3A4	Ergotamine	N02CA52	N	ERGOTAMINE TARTRATE, CAFFEINE	OTHER
Strong inhibitors of CYP3A4	Ergotamine	N02CA52	N	ERGOTAMINE TARTRATE, CAFFEINE CITRATE, DIPHENHYDRAMINE HYDROCHLORIDE	ORAL
Strong inhibitors of CYP3A4	Ergotamine	N02CA52	N	ERGOTAMINE TARTRATE, CAFFEINE, DIMENHYDRINATE	ORAL
Strong inhibitors of CYP3A4	Naloxone	V03AB15	N	NALOXONE HYDROCHLORIDE	OTHER
Strong inhibitors of CYP3A4 and CredibleMeds	Clarithromycin	J01FA09	N	CLARITHROMYCIN	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Preparations	H03A	N	LEVOTHYROXINE SODIUM	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Preparations	H03A	N	LEVOTHYROXINE SODIUM	OTHER
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Preparations	H03A	N	LEVOTHYROXINE SODIUM	
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Preparations	H03A	N	LIOTHYRONINE (LIOTHYRONINE SODIUM)	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Preparations	H03A	N	THYROID	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Hormones	H03AA	N	LEVOTHYROXINE SODIUM	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Hormones	H03AA	N	LEVOTHYROXINE SODIUM	OTHER
Systemic Hormonal Preparations, Excl.	Thyroid Hormones	H03AA	N	LEVOTHYROXINE SODIUM	

Category	Covariate description	ATC code	PDIN flag	Active ingredient description	Route
Sex Hormones And Insulins					
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Hormones	H03AA	N	LIOTHYRONINE (LIOTHYRONINE SODIUM)	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Thyroid Hormones	H03AA	N	THYROID	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Antithyroid Preparations	H03B	N	METHIMAZOLE	ORAL
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Antithyroid Preparations	H03B	N	PROPYLTHIOURACIL	ORAL

Table 6b: Covariate medications specifically listed as CredibleMeds known-risk on actual SAS dataset provided by CIHI

A03BA03 – domperidone
A04AA01 – ondansetron
D10FA02 – erythromycin
J01FA01 – erythromycin
J01FA09 – clarithromycin
J01FA10 – azithromycin
J01MA02 – ciprofloxacin
J01MA12 – levofloxacin
J01MA14 – moxifloxacin
J02AC01 – fluconazole
L01XX35 – anagrelide
N05AA01 – chlorpromazine
N05AA02 – methotrimeprazine (levomepromazine)
N05AD01 – haloperidol
N05AG02 – pimozide
N06AB04 – citalopram
N06AB10 – escitalopram
N07BC02 – methadone
P01BA01 – chloroquine
S01AA17 – erythromycin
S01AE03 – ciprofloxacin
S01AE06 – gatifloxacin
S01AE07 – moxifloxacin
S02CA06 – dexamethasone (dexamethasone, ciprofloxacin)
S03AA07 – ciprofloxacin

Note how there are no ATC codes starting with C in the actual provided medications.

Table 9: Definition of covariate medications that were to be considered for use in analysis

ATC Code or other definition	Covariate Description
B01A	Antithrombotic agents
B02A	Antifibrinolytics – *not used in analysis*
B02B	Vitamin K and other hemostatics – *not considered in Cox regression model due to low dispensations*

ATC Code or other definition	Covariate Description
C01A	Cardiac glycosides
C01B	Class I and III antiarrhymics
C01C	Cardiac stimulants, excluding glycosides
C01D	Vasodilators used in cardiac disease
C01E	Other cardiac preparations – *not considered in Cox regression model due to low dispensations*
C02A	Centrally acting antiadrenergic agents
C02C	Peripherally acting antiadrenergic agents
C02D	Agents acting on arteriolar smooth muscle
C02K	Other antihypertensives
C03A	Low-ceiling diuretics/thiazides
C03B	Low ceiling diuretics excluding thiazides
C03C	Loop diuretics
C03D	Potassium sparing agents
C03E	Diuretics and potassium sparing agents in combination
C03X	Other diuretics – *no dispensations in NPDUIS data*
C04A	Peripheral vasodilators
C07A, except for: C07AA03 C07AB04 C07AG01 C07AG03	Beta blocking agents, excluding sympathomimetics
C07AA03 C07AB04 C07AG01 C07AG03	Beta blockers with sympathomimetic activity
C07C	Beta blocking agents and other diuretics
C08CA	Dihydropyridine derivatives/selective CCBs with mainly vascular effects
C08D	Selective CCBs with direct cardiac effects
Any medication containing "CredibleMeds" in description	CredibleMeds known-risk list medications

ATC Code or other definition	Covariate Description
G03A G03C G03D G03F G03G G03H G03X	"Female" hormones
G03B	"Male" hormones
N07AA01 N07AA02	Neostigmine and pyridostigmine, *used as exclusion criteria*
Any medication stated as a strong CYP3A4 inducer	Strong CYP3A4 inducers – *not used in analysis*
Any medication stated as a strong CYP3A4 inhibitor	Strong CYP3A4 inhibitors – *not used in analysis*
Any medication stated as a strong CYP2D6 inhibitor	Strong CYP2D6 inhibitors – *not used in analysis*
H03A/H03AA	Thyroid hormones
H03B	Antithyroid preparations

Appendix C – definition of hospitalization-determined comorbidities

Table 10: Definition of hospitalization-determined comorbidities that were to be considered for use in analysis

Comorbidity	Codes (ICD-10-CA)

MI/ischemic heart disease/CAD	• I21 Acute myocardial infarction *& also coded as acute MI by Trac
	  o I21.0 Acute transmural myocardial infarction of anterior wall
	  o I21.1 Acute transmural myocardial infarction of inferior wall
	  o I21.2 Acute transmural myocardial infarction of other sites
	  o I21.3 Acute transmural myocardial infarction of unspecified site
	  o I21.4 Acute subendocardial myocardial infarction
	  o I21.9 Acute myocardial infarction, unspecified
	• I22 Subsequent myocardial infarction *& also coded as acute MI by Trac

Comorbidity	Codes (ICD-10-CA)
	○ I22.0 Subsequent myocardial infarction of anterior wall ○ I22.1 Subsequent myocardial infarction of inferior wall ○ I22.8 Subsequent myocardial infarction of other sites ○ I22.9 Subsequent myocardial infarction of unspecified site • I24 Other acute ischaemic heart diseases & ○ I24.0 Coronary thrombosis not resulting in myocardial infarction ○ I24.1 Dressler's syndrome ○ I24.8 Other forms of acute ischaemic heart disease ○ I24.9 Acute ischaemic heart disease, unspecified • I25 Chronic ischaemic heart disease & ○ I25.0 Atherosclerotic cardiovascular disease, so described ○ I25.1 Atherosclerotic heart disease ▪ I25.10 Atherosclerotic heart disease of native coronary artery ▪ I25.11 Atherosclerotic heart disease of autologous vein bypass graft ▪ I25.12 Atherosclerotic heart disease of nonautologous biological bypass graft ▪ I25.13 Atherosclerotic heart disease of artery bypass graft ▪ I25.14 Atherosclerotic heart disease of unspecified type of bypass graft ▪ I25.15 Atherosclerotic heart disease of coronary artery of transplanted heart ▪ I25.19 Atherosclerotic heart disease of unspecified type of vessel, native or graft ○ I25.2 Old myocardial infarction ○ I25.3 Aneurysm of heart ○ I25.4 Coronary artery aneurysm and dissection ○ I25.5 Ischaemic cardiomyopathy *& coded as heart failure by Fleet and by Trac ○ I25.6 Silent myocardial ischaemia ○ I25.8 Other forms of chronic ischaemic heart disease ○ I25.9 Chronic ischaemic heart disease, unspecified ○ R93.1 Abnormal findings on diagnostic imaging of heart and coronary circulation &
Angina	• I20 Angina pectoris *& ○ I20.0 Unstable angina ○ I20.1 Angina pectoris with documented spasm ○ I20.8 Other forms of angina pectoris ▪ I20.80 Atypical angina ▪ I20.88 Other forms of angina pectoris

Comorbidity	Codes (ICD-10-CA)
	○ I20.9 Angina pectoris, unspecified • I23 Certain current complications following acute myocardial infarction * ○ I23.0 Haemopericardium as current complication following acute myocardial infarction ○ I23.1 Atrial septal defect as current complication following acute myocardial infarction ○ I23.2 Ventricular septal defect as current complication following acute myocardial infarction ○ I23.3 Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction ○ I23.4 Rupture of chordae tendineae as current complication following acute myocardial infarction ○ I23.5 Rupture of papillary muscle as current complication following acute myocardial infarction ○ I23.6 Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction ○ I23.8 Other current complications following acute myocardial infarction ▪ I23.80 Papillary muscle dysfunction as current complication following acute myocardial infarction ▪ I23.81 Pericarditis as current complication following acute myocardial infarction ▪ I23.82 Postmyocardial infarction angina as current complication following acute myocardial infarction ▪ I23.88 Other current complications following acute myocardial infarction
Cardiomyopathy	• I42 Cardiomyopathy ○ I42.0 Dilated cardiomyopathy ○ I42.1 Obstructive hypertrophic cardiomyopathy ○ I42.2 Other hypertrophic cardiomyopathy ○ I42.3 Endomyocardial (eosinophilic) disease ○ I42.4 Endocardial fibroelastosis ○ I42.5 Other restrictive cardiomyopathy ○ I42.6 Alcoholic cardiomyopathy *coded as alcoholism by Fleet ○ I42.7 Cardiomyopathy due to drugs and other external agents ○ I42.8 Other cardiomyopathies ○ I42.9 Cardiomyopathy, unspecified • I43 Cardiomyopathy in diseases classified elsewhere (the ICD-10-CA tabular list marks all I43 codes with an asterisk) ○ I43.0 Cardiomyopathy in infectious and parasitic diseases classified elsewhere

Comorbidity	Codes (ICD-10-CA)
	○ I43.1 Cardiomyopathy in metabolic diseases ○ I43.2 Cardiomyopathy in nutritional diseases ○ I43.8 Cardiomyopathy in other diseases classified elsewhere
Heart failure	• I50 Heart failure ○ I50.0 Congestive heart failure *& ○ I50.1 Left ventricular failure *& ○ I50.9 Heart failure, unspecified *& • J81 Pulmonary oedema *&
Previous malignant arrhythmia	○ I47.2 Ventricular tachycardia ▪ I49.00 Ventricular fibrillation
Conduction disorders	• I44 Atrioventricular and left bundle-branch block ○ I44.0 Atrioventricular block, first degree ○ I44.1 Atrioventricular block, second degree ○ I44.2 Atrioventricular block, complete ○ I44.3 Other and unspecified atrioventricular block ○ I44.4 Left anterior fascicular block ○ I44.5 Left posterior fascicular block ○ I44.6 Other and unspecified fascicular block ○ I44.7 Left bundle-branch block, unspecified • I45 Other conduction disorders ○ I45.0 Right fascicular block ○ I45.1 Other and unspecified right bundle-branch block ○ I45.2 Bifascicular block ○ I45.3 Trifascicular block ○ I45.4 Nonspecific intraventricular block ○ I45.5 Other specified heart block ○ I45.6 Pre-excitation syndrome ○ I45.8 Other specified conduction disorders ○ I45.9 Conduction disorder, unspecified • I47 Paroxysmal tachycardia ○ I47.0 Re-entry ventricular arrhythmia ○ I47.1 Supraventricular tachycardia ○ I47.2 Ventricular tachycardia (*also under previous malignant arrhythmia*) ○ I47.9 Paroxysmal tachycardia, unspecified • I48 Atrial fibrillation and flutter *& coded as atrial fibrillation/flutter by both Fleet and Trac ○ I48.0 Atrial fibrillation ▪ I48.00 Paroxysmal atrial fibrillation ▪ I48.01 Persistent atrial fibrillation ▪ I48.02 Chronic atrial fibrillation ○ I48.3 Typical atrial flutter ○ I48.4 Atypical atrial flutter

Comorbidity	Codes (ICD-10-CA)
	○ I48.9 Atrial fibrillation and atrial flutter, unspecified ▪ I48.90 Atrial fibrillation, unspecified ▪ I48.91 Atrial flutter, unspecified • I49 Other cardiac arrhythmias ○ I49.0 Ventricular fibrillation and flutter ▪ I49.00 Ventricular fibrillation (*also under previous malignant arrhythmia*) ▪ I49.01 Ventricular flutter ○ I49.1 Atrial premature depolarization ○ I49.2 Junctional premature depolarization ○ I49.3 Ventricular premature depolarization ○ I49.4 Other and unspecified premature depolarization ○ I49.5 Sick sinus syndrome ○ I49.8 Other specified cardiac arrhythmias ○ I49.9 Cardiac arrhythmia, unspecified ○ G52.2 Disorders of vagus nerve • R00 Abnormalities of heart beat ○ R00.0 Tachycardia, unspecified ○ R00.1 Bradycardia, unspecified ○ R00.2 Palpitations ○ R00.8 Other and unspecified abnormalities of heart beat
Liver disease/non-specific liver disease (defined by Fleet et al.)/Trac et al. defines this as chronic liver disease	• K70 Alcoholic liver disease *& ○ K70.0 Alcoholic fatty liver ○ K70.1 Alcoholic hepatitis ○ K70.2 Alcoholic fibrosis and sclerosis of liver ○ K70.3 Alcoholic cirrhosis of liver ○ K70.4 Alcoholic hepatic failure ○ K70.9 Alcoholic liver disease, unspecified • K71 Toxic liver disease ○ K71.0 Toxic liver disease with cholestasis ○ K71.1 Toxic liver disease with hepatic necrosis ○ K71.2 Toxic liver disease with acute hepatitis ○ K71.3 Toxic liver disease with chronic persistent hepatitis *& ○ K71.4 Toxic liver disease with chronic lobular hepatitis *& ○ K71.5 Toxic liver disease with chronic active hepatitis *& ○ K71.6 Toxic liver disease with hepatitis, not elsewhere classified ○ K71.7 Toxic liver disease with fibrosis and cirrhosis of liver *& ○ K71.8 Toxic liver disease with other disorders of liver ○ K71.9 Toxic liver disease, unspecified • K72 Hepatic failure, not elsewhere classified ○ K72.0 Acute and subacute hepatic failure

Comorbidity	Codes (ICD-10-CA)
	○ K72.1 Chronic hepatic failure *& ○ K72.9 Hepatic failure, unspecified *& • K73 Chronic hepatitis, not elsewhere classified *& ○ K73.0 Chronic persistent hepatitis, not elsewhere classified ○ K73.1 Chronic lobular hepatitis, not elsewhere classified ○ K73.2 Chronic active hepatitis, not elsewhere classified ○ K73.8 Other chronic hepatitis, not elsewhere classified ○ K73.9 Chronic hepatitis, unspecified • K74 Fibrosis and cirrhosis of liver *& ○ K74.0 Hepatic fibrosis ○ K74.1 Hepatic sclerosis ○ K74.2 Hepatic fibrosis with hepatic sclerosis ○ K74.3 Primary biliary cirrhosis ○ K74.4 Secondary biliary cirrhosis ○ K74.5 Biliary cirrhosis, unspecified ○ K74.6 Other and unspecified cirrhosis of liver • K75 Other inflammatory liver diseases ○ K75.0 Abscess of liver ○ K75.1 Phlebitis of portal vein ○ K75.2 Nonspecific reactive hepatitis ○ K75.3 Granulomatous hepatitis, not elsewhere classified *& ○ K75.4 Autoimmune hepatitis *& ○ K75.8 Other specified inflammatory liver diseases *& ○ K75.9 Inflammatory liver disease, unspecified *& • K76 Other diseases of liver *& ○ K76.0 Fatty (change of) liver, not elsewhere classified ○ K76.1 Chronic passive congestion of liver ○ K76.2 Central haemorrhagic necrosis of liver ○ K76.3 Infarction of liver ○ K76.4 Peliosis hepatis ○ K76.5 Hepatic veno-occlusive disease ○ K76.6 Portal hypertension ○ K76.7 Hepatorenal syndrome ○ K76.8 Other specified diseases of liver ○ K76.9 Liver disease, unspecified • K77 Liver disorders in diseases classified elsewhere (all K77 codes are marked with an asterisk in the tabular list) *& ○ K77.0 Liver disorders in infectious and parasitic diseases classified elsewhere ○ K77.8 Liver disorders in other diseases classified elsewhere • B16 Acute hepatitis B *& ○ B16.0 Acute hepatitis B with delta-agent (coinfection) with hepatic coma

Comorbidity	Codes (ICD-10-CA)
	○ B16.1 Acute hepatitis B with delta-agent (coinfection) without hepatic coma ○ B16.2 Acute hepatitis B without delta-agent with hepatic coma ○ B16.9 Acute hepatitis B without delta-agent and without hepatic coma • B17 Other acute viral hepatitis *& ○ B17.0 Acute delta-(super)infection of hepatitis B carrier ○ B17.1 Acute hepatitis C ○ B17.2 Acute hepatitis E ○ B17.8 Other specified acute viral hepatitis ○ B17.9 Acute viral hepatitis, unspecified • B18 Chronic viral hepatitis *& ○ B18.0 Chronic viral hepatitis B with delta-agent ○ B18.1 Chronic viral hepatitis B without delta-agent ○ B18.2 Chronic viral hepatitis C ○ B18.8 Other chronic viral hepatitis ○ B18.9 Chronic viral hepatitis, unspecified • B19 Unspecified viral hepatitis *& ○ B19.0 Unspecified viral hepatitis with hepatic coma ○ B19.9 Unspecified viral hepatitis without hepatic coma • I85 Oesophageal varices *& ○ I85.0 Oesophageal varices with bleeding ○ I85.9 Oesophageal varices without bleeding • R16 Hepatomegaly and splenomegaly, not elsewhere classified. Only use the next level codes below. ○ R16.0 Hepatomegaly, not elsewhere classified *& ○ R16.2 Splenomegaly, not elsewhere classified *& • R17 Unspecified jaundice *& • R18 Ascites *& ○ B94.2 Sequelae of viral hepatitis *& ○ Z22.5 Carrier of viral hepatitis *& ▪ Z22.50 Carrier of viral hepatitis B ○ E83.0 Disorders of copper metabolism *& ○ E83.1 Disorders of iron metabolism *&
Hypothyroidism	• E02 Subclinical iodine-deficiency hypothyroidism * • E03 Other hypothyroidism * ○ E03.0 Congenital hypothyroidism with diffuse goitre ○ E03.1 Congenital hypothyroidism without goitre ○ E03.2 Hypothyroidism due to medicaments and other exogenous substances ○ E03.3 Postinfectious hypothyroidism ○ E03.4 Atrophy of thyroid (acquired) ○ E03.5 Myxoedema coma

Comorbidity	Codes (ICD-10-CA)
	○ E03.8 Other specified hypothyroidism ○ E03.9 Hypothyroidism, unspecified
Sepsis	• A26.7 Erysipelothrix sepsis * • A40 Streptococcal sepsis ○ A40.0 Sepsis due to streptococcus, group A * ○ A40.1 Sepsis due to streptococcus, group B ○ A40.2 Sepsis due to streptococcus, group D ○ A40.3 Sepsis due to Streptococcus pneumoniae ○ A40.8 Other streptococcal sepsis ○ A40.9 Streptococcal sepsis, unspecified • A41 Other sepsis ○ A41.0 Sepsis due to Staphylococcus aureus * ○ A41.1 Sepsis due to other specified staphylococcus * ○ A41.2 Sepsis due to unspecified staphylococcus * ○ A41.3 Sepsis due to unspecified staphylococcus * ○ A41.4 Sepsis due to anaerobes ○ A41.5 Sepsis due to other Gram-negative organisms * ▪ A41.50 Sepsis due to Escherichia coli [E.coli] ▪ A41.51 Sepsis due to Pseudomonas ▪ A41.52 Sepsis due to Serratia ▪ A41.58 Sepsis due to other gram-negative organisms ○ A41.8 Other specified sepsis ▪ A41.80 Sepsis due to enterococcus ▪ A41.88 Other specified sepsis * ○ A41.9 Sepsis, unspecified * ○ A02.1 Salmonella sepsis ○ A22.7 Anthrax sepsis ○ A24.1 Acute and fulminating melioidosis – includes sepsis ○ A32.7 Listerial sepsis ○ A42.7 Actinomycotic sepsis ▪ A54.86 Gonococcal sepsis ○ B00.7 Disseminated herpesviral disease – includes herpesviral sepsis ○ B37.7 Candidal sepsis ○ R57.2 Septic shock I did not include sepsis codes due to procedures (i.e. infection after surgery) as those codes were not very specific.
Hypertension	• I10 Essential (primary) hypertension % ○ I10.0 Benign hypertension ○ I10.1 Malignant hypertension • I11 Hypertensive heart disease %

Comorbidity	Codes (ICD-10-CA)
	• I12 Hypertensive renal disease % • I13 Hypertensive heart and renal disease % *& I12 and I13 also includes kidney diseases as coded by Fleet and Trac
CKD	o E10.2 Type 1 diabetes mellitus with kidney complications *& ▪ E10.20 Type 1 diabetes mellitus with incipient diabetic nephropathy (N08.3-*) (marked with cross in tabular list) ▪ E10.23 Type 1 diabetes mellitus with established or advanced kidney disease (N08.3-*) (marked with cross in tabular list) ▪ E10.28 Type 1 diabetes mellitus with other specified kidney complication not elsewhere classified o E11.2 Type 2 diabetes mellitus with kidney complications *& ▪ E11.20 Type 2 diabetes mellitus with incipient diabetic nephropathy (N08.3-*) (marked with cross in tabular list) ▪ E11.23 Type 2 diabetes mellitus with established or advanced kidney disease (N08.3-*) (marked with cross in tabular list) ▪ E11.28 Type 2 diabetes mellitus with other specified kidney complication not elsewhere classified o E13.2 Other specified diabetes mellitus with kidney complications *& ▪ E13.20 other specified diabetes mellitus with incipient diabetic nephropathy (N08.3-*) (marked with cross in tabular list) ▪ E13.23 Other specified diabetes mellitus with established or advanced kidney disease (N08.3-*) (marked with cross in tabular list) ▪ E13.28 Other specified diabetes mellitus with other specified kidney complication not elsewhere classified o E14.2 Unspecified diabetes mellitus with kidney complications *& ▪ E14.20 Unspecified diabetes mellitus with incipient diabetic nephropathy (N08.3-*) (marked with cross in tabular list) ▪ E14.23 Unspecified diabetes mellitus with established or advanced kidney disease (N08.3-*) (marked with cross in tabular list) ▪ E14.28 Unspecified diabetes mellitus with other specified kidney complication not elsewhere classified o N16.5 Renal tubulo-interstitial disorders in transplant rejection (marked with asterisk in tabular list) &

Comorbidity	Codes (ICD-10-CA)

	• N08 Glomerular disorders in diseases classified elsewhere (marked with asterisk in tabular list) *&
	  o N08.0 Glomerular disorders in infectious and parasitic diseases classified elsewhere (marked with asterisk in tabular list)
	  o N08.1 Glomerular disorders in neoplastic diseases (marked with asterisk in tabular list)
	  o N08.2 Glomerular disorders in blood diseases and disorders involving the immune mechanism (marked with asterisk in tabular list)
	  o N08.3 Glomerular disorders in diabetes mellitus (E10-E14† with common fourth character .2) (marked with asterisk in tabular list)
	  ▪ N08.31 Glomerular disorders in diabetes mellitus, chronic kidney disease, stage 1 (marked with asterisk in tabular list)
	  ▪ N08.32 Glomerular disorders in diabetes mellitus, chronic kidney disease, stage 2 (marked with asterisk in tabular list)
	  ▪ N08.33 Glomerular disorders in diabetes mellitus, chronic kidney disease, stage 3 (marked with asterisk in tabular list)
	  ▪ N08.34 Glomerular disorders in diabetes mellitus, chronic kidney disease, stage 4 (marked with asterisk in tabular list)
	  ▪ N08.35 Glomerular disorders in diabetes mellitus, chronic kidney disease, stage 5 (marked with asterisk in tabular list)
	  ▪ N08.38 Other glomerular disorders in diabetes mellitus (marked with asterisk in tabular list)
	  ▪ N08.39 Unspecified glomerular disorders in diabetes mellitus (marked with asterisk in tabular list)
	  o N08.4 Glomerular disorders in other endocrine, nutritional and metabolic diseases (marked with asterisk in tabular list)
	  o N08.5 Glomerular disorders in systemic connective tissue disorders (marked with asterisk in tabular list)
	  o N08.8 Glomerular disorders in other diseases classified elsewhere (marked with asterisk in tabular list)
	• N18 Chronic kidney disease *&
	  o N18.1 Chronic kidney disease, stage 1
	  o N18.2 Chronic kidney disease, stage 2
	  o N18.3 Chronic kidney disease, stage 3
	  o N18.4 Chronic kidney disease, stage 4
	  o N18.5 Chronic kidney disease, stage 5
	  o N18.9 Chronic kidney disease, unspecified

Comorbidity	Codes (ICD-10-CA)
	• N19 Unspecified kidney failure *& o T86.1 Kidney transplant failure and rejection & ▪ T86.100 Kidney transplant rejection ▪ T86.101 Kidney transplant failure o Z94.0 Kidney transplant status &
Pacemaker use	o Z45.0 Adjustment and management of cardiac devices ▪ Z45.00 Adjustment and management of cardiac pacemaker ▪ Z45.01 Adjustment and management of cardioverter/defibrillator ▪ Z45.02 Adjustment and management of cardiac resynchronization therapy device ▪ Z45.08 Adjustment and management of other and unspecified cardiac devices o Z95.0 Presence of electronic cardiac devices ▪ Z95.00 Presence of cardiac pacemaker ▪ Z95.01 Presence of cardioverter/defibrillator ▪ Z95.02 Presence of cardiac resynchronization therapy device ▪ Z95.08 Presence of other and unspecified electronic cardiac devices o Z99.4 Dependence on artificial heart
Coronary revascularization procedure	o Z95.1 Presence of aortocoronary bypass graft o Z95.5 Presence of coronary angioplasty implant and graft *& coded as CAD by Fleet et al. and Trac et al. o Z95.8 Presence of other cardiac and vascular implants and grafts & coded as CAD by Trac et al. o Z95.9 Presence of cardiac and vascular implant and graft, unspecified & coded as CAD by Trac et al. o T82.2 Mechanical complication of coronary artery bypass and valve grafts *& coded as CAD by Trac et al.

Notes:

- In the tabular list, a cross (actually defined as a dagger by the tabular list) "is used to indicate a code that represents the etiology or underlying cause of a disease. A code representing the manifestation of the disease should also be recorded. The dagger code should be sequenced before the manifestation code."

- In the tabular list, an asterisk "is used to indicate a code that represents the manifestation of a disease. This code should be paired with a dagger (etiology) code and should follow this in sequence."
- Comorbidities used by Risk of rhabdomyolysis with donepezil compared with rivastigmine or galantamine: a population-based cohort study published in CMAJ by Fleet et al. in 2019 are marked with an *.
- Comorbidities used by Macrolide antibiotics and the risk of ventricular arrhythmia in older adults published in CMAJ by Trac et al. in 2016 are marked with an &.
- Comorbidities defined by Validity of Canadian discharge abstract data for hypertension and diabetes from 2002 to 2013 by Jiang et al. in CMAJ Open in 2016 are marked with a %.
    - http://cmajopen.ca/content/4/4/E646.full
- The second and last authors of the Fleet and Trac articles in CMAJ are the same, which explains common comorbidity coding.

Appendix D – correlation tables between all variables

The absolute value of the Cramer's V or Phi Coefficient is displayed in the tables below. Bolded values show that the correlation coefficient is greater than 0.15.

Table 14: Correlation coefficients between AChEI medication group and all other variables

	Donepezil versus other combined	Donepezil versus other separated
Age quintile	0.0062	0.0220
Patient sex	0.0210	0.0443
Jurisdiction	0.0726	**0.2120**
Patient income quintile	0.0340	0.0243

	Donepezil versus other combined	Donepezil versus other separated
AChEI index year	0.0943	0.0704
Previous malignant arrhythmia between 1- and 5-years pre-index	0.0014	0.0049
Previous myocardial infarct	0.0093	0.0154
Angina	0.0006	0.0032
Cardiomyopathy	0.0016	0.0045
Heart failure	0.0115	0.0120
Conduction disorders	0.0105	0.0157
Liver disease	0.0014	0.0051
Hypothyroidism	0.0006	0.0137
Sepsis	0.0059	0.0109
Hypertension	0.0107	0.0214
Chronic kidney disease	0.0064	0.0144
Pacemaker use	0.0005	0.0090
Coronary revascularization procedure	0.0042	0.0182
Antithrombotic agent use	0.0260	0.0382
Cardiac glycoside use	0.0066	0.0069
Class I and III antiarrhythmic use	0.0179	0.0183
Use of cardiac stimulants, excluding glycosides	0.0131	0.0255
Use of vasodilators in cardiac disease	0.0092	0.0101
Use of centrally acting antiadrenergics	0.0009	0.0042
Use of peripherally acting antiadrenergics	0.0047	0.0103
Use of agents acting on arteriolar smooth muscle	0.0012	0.0047
Use of thiazides	0.0073	0.0176
Use of low ceiling diuretics, excluding thiazides	0.0054	0.0206

	Donepezil versus other combined	Donepezil versus other separated
Use of loop diuretics	0.0137	0.0149
Use of potassium sparing agents	0.0059	0.0067
Use of diuretics and potassium sparing agents in combination	0.0023	0.0048
Use of peripheral vasodilators	0.0001	0.0032
Use of beta blocking agents, excluding sympathomimetics	0.0078	0.0146
Use of beta blockers with sympathomimetic activity	0.0007	0.0056
Use of beta blocking agents and other diuretics	0.0025	0.0026
Use of dihydropyridine derivatives (CCBs)	0.0001	0.0172
Use of selective CCBs with direct cardiac effects	0.0060	0.0075
Use of CredibleMeds known-risk medications	0.0382	0.0420
Use of “female hormones”	0.0020	0.0095
Use of “male hormones”	0.0026	0.0078
Use of thyroid hormones	0.0005	0.0109
Use of antithyroid preparations	0.0022	0.0026

Table 15: Correlation coefficients between demographic variables

	Patient sex	Jurisdiction	Patient income quintile	AChEI Index Year
Patient age quintile	0.1038	0.0207	0.0188	0.0222
Patient sex		0.0176	0.0496	0.0234
Jurisdiction			**0.40948**	0.0258

Patient income quintile	[redacted]	0.0135

Table 16: Correlation coefficients between demographic variables and hospitalization covariates

	Patient age quintile	Patient sex	Jurisdiction	Patient income quintile	AChEI index year
Previous malignant arrhythmia	0.0049	0.0223	0.0088	0.0076	0.0063
Myocardial infarct	0.0492	0.0816	0.0424	0.0102	0.0458
Angina	0.0147	0.0292	0.0171	0.0130	0.0281
Cardiomyopathy	0.0083	0.0056	0.0127	0.0033	0.0072
Heart failure	0.0854	0.0102	0.0198	0.0140	0.0307
Conduction disorders	0.1082	0.0485	0.0336	0.0058	0.0259
Liver disease	0.0145	0.0129	0.0137	0.0089	0.0081
Hypothyroidism	0.0445	0.0500	0.0764	0.0124	0.0219
Sepsis	0.0134	0.0310	0.0211	0.0121	0.0072
Hypertension	0.0998	0.0096	0.0668	0.0331	0.0423
CKD	0.0495	0.0431	0.0209	0.0250	0.0062
Pacemaker use	0.0540	0.0326	0.0270	0.0072	0.0164
Coronary revascularization procedure	0.0204	0.0823	0.0452	0.0066	0.0268

Table 17: Correlation coefficients between demographic variables and medication-use-covariates

	Patient age quintile	Patient sex	Jurisdiction	Patient income quintile	AChEI index year
Antithrombotic agent use	0.1004	0.0831	0.0723	0.0146	0.0124

	Patient age quintile	Patient sex	Jurisdiction	Patient income quintile	AChEI index year
Cardiac glycosides use	0.0609	0.0047	0.0208	0.0052	0.0494
Class I and III antiarrhythmic use	0.0156	0.0149	0.0171	0.0072	0.0194
Cardiac stimulants (excluding glycosides) use	0.0205	0.0083	0.0099	0.0124	0.0196
Vasodilator use (in cardiac disease)	0.0687	0.0320	0.0305	0.0240	0.0546
Centrally acting antiadrenergics use	0.0048	0.0188	0.0226	0.0207	0.0116
Peripherally acting antiadrenergics use	0.0062	0.0618	0.0321	0.0149	0.0123
Use of agents acting on arteriolar smooth muscle	0.0066	0.0006	0.0195	0.0097	0.0139
Thiazide use	0.0344	0.0661	0.0424	0.0099	0.0639
Use of low ceiling diuretics, excluding thiazides	0.0149	0.0153	0.0591	0.0110	0.0047
Use of loop diuretics	0.1455	0.0060	0.0262	0.0258	0.0407
Use of potassium sparing agents	0.0275	0.0019	0.0167	0.0101	0.0105
Use of diuretics and potassium sparing agents in combination	0.0270	0.0451	0.0239	0.0152	0.0394
Use of peripheral vasodilators	0.0093	0.0147	0.0058	0.0083	0.0152

	Patient age quintile	Patient sex	Jurisdiction	Patient income quintile	AChEI index year
Use of beta blockers, excluding sympathomimetics	0.0685	0.0287	0.0477	0.0125	0.0219
Use of beta blockers with sympathomimetic activity	0.0212	0.0007	0.0110	0.0067	0.0226
Use of beta blocking agents and other diuretics	0.0060	0.0095	0.0119	0.0077	0.0133
Use of dihydropyridine derivatives (CCBs)	0.0708	0.0493	0.0457	0.0297	0.0086
Use of selective CCBs with direct cardiac effects	0.0404	0.0317	0.0174	0.0097	0.0351
Use of CredibleMeds known-risk medications	0.0203	0.0492	0.0491	0.0443	0.0555
Use of “female hormones”	0.0201	0.1169	0.0437	0.0091	0.0061
Use of “male hormones”	0.0240	0.0640	0.0179	0.0113	0.0068
Use of thyroid hormones	0.0754	**0.1621**	0.0667	0.0096	0.0042
Use of antithyroid preparations	0.0058	0.0144	0.0151	0.0104	0.0169

Table 18: Correlation coefficients between hospitalization-determined covariates

	Myocardial infarct	Angina	Cardiomyopathy	Heart failure	Conduction disorders	Liver disease	Hypothyroidism	Sepsis	Hypertension	CKD	Pacemaker use	Coronary revascularization procedure
Previous malignant arrhythmia	0.0539	0.0184	0.0329	0.0437	0.0450	0.0090	0.0101	0.0059	0.0288	0.0202	0.0717	0.0466
Myocardial infarct		**0.3060**	0.0837	**0.2762**	**0.2577**	0.0483	0.0880	0.0803	**0.3496**	**0.1708**	0.1370	**0.4122**
Angina			0.0263	0.1042	0.1127	0.0180	0.0396	0.0235	**0.1569**	0.0697	0.0690	**0.2298**
Cardiomyopathy				0.1346	0.0855	0.0318	0.0263	0.0154	0.0633	0.0520	0.0762	0.0271
Heart failure					**0.3383**	0.0709	0.0861	0.0949	**0.2449**	**0.2360**	**0.1617**	**0.1563**

	Myocardial infarct	Angina	Cardiomyopathy	Heart failure	Conduction disorders	Liver disease	Hypothyroidism	Sepsis	Hypertension	CKD	Pacemaker use	Coronary revascularization procedure
Conduction disorders						0.0540	0.1032	0.0890	**0.3270**	**0.1744**	**0.2191**	**0.1521**
Liver disease							0.0373	0.0632	0.0736	0.0621	0.0225	0.0284
Hypothyroidism								0.0321	**0.1801**	0.0800	0.0496	0.0453
Sepsis									0.1026	0.1177	0.0351	0.0373
Hypertension										**0.2399**	0.1316	**0.2011**
CKD											0.0862	0.1076
Pacemaker use												0.1310

Table 19: Correlation coefficients between hospitalization and medication-use- covariates

	Previous malignant arrhythmia	Myocardial infarct	Angina	Cardiomyopathy	Heart failure	Conduction disorders	Liver disease	Hypothyroidism	Sepsis	Hypertension	CKD	Pacemaker use	Coronary revascularization procedure
Antithrombotic agent use	0.0357	**0.2245**	0.1017	0.0431	**0.2094**	**0.3510**	0.0210	0.0471	0.0513	**0.2088**	0.1098	0.1155	0.1366
Cardiac glycosides use	0.0164	0.0653	0.0262	0.0569	**0.1930**	**0.2590**	0.0194	0.0272	0.0206	0.0678	0.0522	0.0766	0.0377
Class I and III antiarrhythmic use	0.0861	0.0637	0.0279	0.0518	0.0814	0.1473	0.0043	0.0269	0.0135	0.0474	0.0401	0.0589	0.0396
Cardiac stimulants (excluding glycosides) use	0.0025	0.0048	0.0067	0.0034	0.0074	0.0101	0.0084	0.0045	0.0044	0.0058	0.0128	0.0103	0.0032
Vasodilator use (in cardiac disease)	0.0157	**0.2849**	**0.1937**	0.0327	**0.1706**	0.1173	0.0161	0.0305	0.0280	0.1366	0.1022	0.0639	**0.1569**
Centrally acting antiadrenergic use	0.0011	0.0100	0.0064	0.0027	0.0151	0.0076	0.0030	0.0051	0.0021	0.0264	0.0349	0.0015	0.0075
Peripherally acting antiadrenergic use	0.0011	0.0124	0.0022	0.0017	0.0137	0.0123	0.0020	0.0032	0.0105	0.0193	0.0342	0.0070	0.0064
Use of agents acting on arteriolar smooth muscle	0.0042	0.0374	0.0201	0.0181	0.0716	0.0418	0.0049	0.0144	0.0154	0.0663	0.1112	0.0151	0.0275
Thiazide use	0.0043	0.0176	0.0066	0.0112	0.0288	0.0113	0.0086	0.0078	0.0135	0.0459	0.0096	0.0132	0.0096
Use of low ceiling diuretics, excluding thiazides	0.0055	0.0134	0.0066	0.0105	0.0401	0.0299	0.0070	0.0097	0.0051	0.0430	0.0493	0.0169	0.0099
Use of loop diuretics	0.0344	**0.1785**	0.0711	0.0734	**0.3857**	**0.2438**	0.0535	0.0604	0.0604	**0.1806**	**0.1853**	0.1110	0.1016
Use of potassium sparing agents	0.0351	0.0900	0.0299	0.0912	**0.2123**	0.1085	0.0689	0.0269	0.0246	0.0746	0.0767	0.0667	0.0526
Use of diuretics and potassium sparing agents in combination	0.0058	0.0128	0.0048	0.0041	0.0146	0.0068	0.0002	0.0020	0.0073	0.0061	0.0003	0.0011	0.0135
Use of peripheral vasodilators	0.0104	0.0245	0.0112	0.0001	0.0164	0.0126	0.0076	0.0042	0.0042	0.0255	0.0205	0.0071	0.0220
Use of beta blockers, excluding sympathomimetics	0.0437	**0.2554**	0.1201	0.0632	**0.1929**	**0.2361**	0.0316	0.0365	0.0445	**0.1966**	0.1198	0.0764	0.1421
Use of beta blockers with sympathomimetic activity	0.0042	0.0074	0.0041	0.0006	0.0019	0.0073	0.0006	0.0033	0.0004	0.0074	0.0000	0.0039	0.0085
Use of beta blocking agents and other diuretics	0.0023	0.0067	0.0019	0.0008	0.0054	0.0065	0.0006	0.0043	0.0051	0.0017	0.0021	0.0014	0.0054
Use of dihydropyridine derivatives (CCBs)	0.0038	0.0408	0.0293	0.0030	0.0287	0.0206	0.0089	0.0158	0.0104	**0.1624**	0.0814	0.0046	0.0303
Use of selective CCBs with direct cardiac effects	0.0026	0.0234	0.0135	0.0012	0.0469	0.1115	0.0011	0.0091	0.0083	0.0550	0.0276	0.0150	0.0068
Use of CredibleMeds known-risk medications	0.0011	0.0547	0.0292	0.0125	0.0654	0.0520	0.0195	0.0390	0.0473	0.0969	0.0628	0.0228	0.0248
Use of "female hormones"	0.0046	0.0148	0.0033	0.0011	0.0097	0.0120	0.0023	0.0179	0.0018	0.0022	0.0087	0.0040	0.0101
Use of "male hormones"	0.0000	0.0044	0.0007	0.0028	0.0041	0.0017	0.0013	0.0040	0.0009	0.0025	0.0047	0.0022	0.0072
Use of thyroid hormones	0.0101	0.0168	0.0069	0.0079	0.0319	0.0270	0.0067	**0.2876**	0.0051	0.0262	0.0232	0.0117	0.0034
Use of antithyroid preparations	0.0014	0.0012	0.0003	0.0028	0.0056	0.0101	0.0033	0.0059	0.0037	0.0048	0.0045	0.0032	0.0025

Table 20: Correlation coefficients between medication-use-determined covariates

	Cardiac glycosides use	Class I and III antiarrhythmic use	Cardiac stimulants (excluding glycosides) use	Vasodilator use (in cardiac disease)	Centrally acting antiadrenergic use	Peripherally acting antiadrenergic use	Use of agents acting on arteriolar smooth muscle	Thiazide use	Use of low ceiling diuretics, excluding thiazides	Use of loop diuretics	Use of potassium sparing agents	Use of diuretics and potassium sparing agents in combination	Use of peripheral vasodilators	Use of beta blockers, excluding sympathomimetics	Use of beta blockers with sympathomimetic activity	Use of beta blocking agents and other diuretics	Use of dihydropyridine derivatives (CCBs)	Use of selective CCBs with direct cardiac effects	Use of CredibleMeds known-risk medications	Use of "female hormones"	Use of "male hormones"	Use of thyroid hormones	Use of antithyroid preparations
Antithrombotic agent use	**0.2431**	0.1227	0.0082	**0.1698**	0.0038	0.0198	0.0281	0.0050	0.0304	**0.2360**	0.1030	0.0105	0.0262	**0.2842**	0.0015	0.0062	0.0403	0.1171	0.0193	0.0179	0.0046	0.0181	0.0052
Cardiac glycosides use		0.0562	0.0051	0.0676	0.0012	0.0024	0.0125	0.0168	0.0085	**0.1969**	0.1109	0.0012	0.0061	0.1435	0.0036	0.0055	0.0224	0.1041	0.0180	0.0073	0.0033	0.0207	0.0063
Class I and III antiarrhythmic use			0.0050	0.0464	0.0002	0.0100	0.0120	0.0067	0.0098	0.0805	0.0379	0.0030	0.0050	0.0670	0.0031	0.0018	0.0019	0.0223	0.0017	0.0032	0.0003	0.0494	0.0086
Cardiac stimulants (excluding glycosides) use				0.0086	0.0025	0.0000	0.0079	0.0113	0.0005	0.0022	0.0040	0.0036	0.0027	0.0055	0.0051	0.0003	0.0115	0.0030	0.0145	0.0053	0.0014	0.0004	0.0039
Vasodilator use (in cardiac disease)					0.0172	0.0156	0.0690	0.0030	0.0224	**0.1746**	0.0808	0.0045	0.0271	**0.2303**	0.0247	0.0047	0.0710	0.0622	0.0524	0.0051	0.0007	0.0236	0.0039
Centrally acting antiadrenergic use						0.0249	0.0750	0.0152	0.0185	0.0299	0.0189	0.0058	0.0026	0.0217	0.0084	0.0008	0.0194	0.0197	0.0086	0.0092	0.0002	0.0048	0.0094
Peripherally acting antiadrenergic use							0.0287	0.0092	0.0224	0.0284	0.0144	0.0027	0.0017	0.0260	0.0056	0.0029	0.0358	0.0165	0.0023	0.0043	0.0139	0.0087	0.0001
Use of agents acting on arteriolar smooth muscle								0.0103	0.0287	0.0670	0.0420	0.0039	0.0105	0.0559	0.0096	0.0016	0.0659	0.0230	0.0152	0.0020	0.0013	0.0068	0.0081
Thiazide use									0.0378	0.0518	0.0073	0.0294	0.0057	0.0377	0.0227	0.0126	0.0996	0.0313	0.0094	0.0011	0.0047	0.0059	0.0041
Use of low ceiling diuretics, excluding thiazides										0.0314	0.0391	0.0151	0.0003	0.0418	0.0121	0.0107	0.0598	0.0252	0.0059	0.0025	0.0020	0.0066	0.0043
Use of loop diuretics											**0.2389**	0.0100	0.0197	**0.2215**	0.0065	0.0109	0.0588	0.0785	0.0850	0.0052	0.0042	0.0523	0.0060
Use of potassium sparing agents												0.0251	0.0057	0.1125	0.0061	0.0045	0.0150	0.0287	0.0267	0.0003	0.0046	0.0217	0.0006
Use of diuretics and potassium sparing agents in combination													0.0013	0.0098	0.0105	0.0052	0.0146	0.0157	0.0017	0.0090	0.0051	0.0064	0.0041
Use of peripheral vasodilators														0.0246	0.0028	0.0034	0.0189	0.0031	0.0082	0.0014	0.0007	0.0028	0.0024
Use of beta blockers, excluding sympathomimetics															0.0397	0.0037	0.1280	0.0085	0.0284	0.0127	0.0043	0.0173	0.0144
Use of beta blockers with																0.0029	0.0382	0.0025	0.0060	0.0037	0.0007	0.0008	0.0001

Appendix E – details of full Cox regression model building process

Table 22: Breakdown of univariate analysis on outcomes of malignant arrhythmias, when variables considered alongside AChEI medication group

Significant association with outcome		**Non-significant association with outcome**	
Variable	**HR (95% CI)**	**Variable**	**HR (95% CI)**
Patient sex (female protective)	0.252 (0.159, 0.401)	Patient age quintile	Reference: 66-75 76-80: 1.358 (0.784, 2.466) 81-84: 0.894 (0.461, 1.734) 85-87: 0.892 (0.421, 1.890) 88-100+: 1.278 (0.658, 2.485)
Previous malignant arrhythmia	26.385 (9.677, 71.946)	Patient jurisdiction	Reference: ON BC: 0.570 (0.274, 1.184) AB: 0.456 (0.167, 1.250) SK: 2.724 (0.855. 8.683) MB: 0.411 (0.057, 2.956) PEI: not enough data NL: 0.910 (0.126, 6.556)
Previous myocardial infarct	4.218 (2.643, 6.732)	Patient income quintile	Reference: medium quintile (3) Lowest quintile (1): 1.208 (0.610, 2.392) Medium-low quintile (2): 0.992 (0.484, 2.033)

Significant association with outcome		Non-significant association with outcome	
Variable	**HR (95% CI)**	**Variable**	**HR (95% CI)**
			Medium-high quintile (4): 1.477 (0.734, 2.969) Highest quintile (5): 1.426 (0.715, 2.844)
Previous diagnosed angina	3.270 (1.327, 8.055)	Index year of AChEI	Reference: 2011 2012: 1.110 (0.533, 2.312) 2013: 1.862 (0.934, 3.713) 2014: 1.037 (0.457, 2.351) 2015: 1.173 (0.515, 2.671) 2016: 0.802 (0.298, 2.158) 2017: 0.558 (0.155, 2.004) 2018: 1.607 (0.547, 4.717) 2019: not enough data
Previous diagnosed cardiomyopathy	12.519 (3.957, 39.606)	Previous diagnosed liver disease	1.856 (0.259, 13.319)
Previous diagnosed heart failure	8.815 (5.514, 14.092)	Previous diagnosed hypothyroidism	2.004 (0.736, 5.460)
Previous diagnosed conduction disorders	3.712 (2.352, 5.858)	Previous diagnosed CKD	1.839 (0.803, 4.213)
Previous diagnosed hypertension	1.915 (1.240, 2.959)	Cardiac stimulant use, excluding glycosides	2.485 (0.346, 17.847)
Previous pacemaker use	7.084 (3.273, 15.331)	Use of agents acting on arteriolar smooth muscle	2.804 (0.391, 20.128)
Previous coronary revascularization procedure	5.113 (2.650, 9.868)	Use of thiazides	0.719 (0.373, 1.388)
Antithrombotic agent use	4.282 (2.828, 6.482)	Use of low ceiling diuretics, excluding thiazides	1.615 (0.593, 4.402)

Significant association with outcome		Non-significant association with outcome	
Variable	**HR (95% CI)**	**Variable**	**HR (95% CI)**
Cardiac glycoside use	4.997 (2.720, 9.178)	Use of diuretics and potassium sparing agents in combination	1.001 (0.246, 4.065)
Class I/III antiarrhythmic agent use	11.368 (5.885, 21.959)	Use of beta blockers with sympathomimetic activity	2.683 (0.661, 10.899)
Vasodilator use in cardiac disease	2.400 (1.379, 4.179)	Use of beta blockers and other diuretics	4.242 (0.591, 30.439)
Use of loop diuretics	4.118 (2.680, 6.329)	Use of dihydropyridine derivatives	0.919 (0.564, 1.498)
Use of potassium sparing agents	8.003 (4.443, 14.416)	Use of selective CCBs with direct cardiac effects	1.142 (0.499, 2.615)
Use of beta blockers, excluding sympathomimetics	2.746 (1.816, 4.152)	Use of CredibleMeds known-risk medications	1.237 (0.813, 1.883)
		Use of “female” hormones	0.611 (0.150, 2.481)
		Use of thyroid hormones	1.065 (0.642, 1.767)

Table 24: Effect of variable inclusion on AIC, only hospitalization-determined or prescription medication-determined variables (non-correlated) and forced variables considered

Model	AIC
Crude (AChEI medication group only, donepezil vs. other AChEIs combined)	2008.752
+ Patient sex	1971.596
+ Patient sex, age quintile, previous malignant arrhythmia	1961.373
+ Patient sex, age, previous malignant arrhythmia, loop diuretic use (all forced variables)	1930.926
Forced variables + previous diagnosed angina	1931.225

Model	AIC
Forced variables + previous diagnosed cardiomyopathy	1928.498
Forced variables + previous pacemaker use	1928.754
Forced variables + previous coronary revascularization procedure	1928.086
Forced variables + class I and III antiarrhythmic use	1918.242

Table 25: Effect of variable inclusion on AIC, assessment of including all combinations of previous diagnosed cardiomyopathy, previous pacemaker use, previous coronary revascularization procedure, class I and III antiarrhythmic use

Model	AIC
Forced variables only	1930.926
+ cardiomyopathy, pacemaker	1927.004
+ cardiomyopathy, coronary revascularization	1925.588
+ cardiomyopathy, class I and III antiarrhythmics	1916.796
+ pacemaker, coronary revascularization	1927.562
+ pacemaker, class I and III antiarrhythmics	1917.567
+ coronary revascularization, class I and III antiarrhythmics	1916.528
+ cardiomyopathy, pacemaker, coronary revascularization	1925.606
+ cardiomyopathy, pacemaker, class I and III antiarrhythmics	1916.438
+ cardiomyopathy, coronary revascularization, class I and III antiarrhythmics	1914.929
+ pacemaker, coronary revascularization, class I and III antiarrhythmics	1917.043
+ cardiomyopathy, pacemaker, coronary revascularization, class I and III antiarrhythmics	1915.726

Table 26: Assessment of AIC with the inclusion of additional significant univariate predictors that are correlated to variables in full model

Model	AIC
AChEI medication group, patient sex, age quintile, previous malignant arrhythmia, loop diuretic use, previous diagnosed cardiomyopathy, previous pacemaker use, previous coronary revascularization, class I and III antiarrhythmic use (full model, no correlated predictors)	1915.726
+ previous diagnosed conduction disorders	1913.878
+ previous myocardial infarct	1912.918
+ previous diagnosed heart failure	1900.461
+ previous diagnosed hypertension	1917.162
+ antithrombotic agent use	1902.299
+ cardiac glycoside use	1910.711
+ vasodilator use in cardiac disease	1916.910
+ use of potassium sparing agents	1907.846
+ use of beta blockers (excluding sympathomimetics)	1911.739
+ antithrombotic agent use, previous diagnosed heart failure	1890.342

Table 27: Assessment of proportional hazards for built Cox regression model through plotted Martingale residuals (1,000 simulations)

Variable	Pr > MaxAbsVal
AChEI medication group	0.3660
Age 76-80	0.6220
Age 81-84	0.0720
Age 85-87	0.8050
Age 88-100+	0.6140
Patient Sex	0.0460
Previous malignant arrhythmia (1- 5-years pre-AChEI index)	0.6680
Loop diuretic use	0.2560

Variable	Pr > MaxAbsVal
Previous cardiomyopathy	0.2470
Previous coronary revascularization procedure	0.7260
Pacemaker use	0.7840
Class I/III antiarrhythmic agent use	0.1230

Table 28: Effect modification breakdown for model fit and significance

	Interaction term	AIC	p-value of interaction term
Uncapped follow-up, malignant arrhythmia outcome in primary diagnosis field only, hospitalization date for exclusions (for malignant arrhythmia in 365 days prior to AChEI index) and for outcome set as 15th of the month	No interaction terms	1915.726	
	+ patient age quintile*patient sex	1916.878	0.1659
	+ patient age quintile*previous malignant arrhythmia	1921.403	0.9215
	+ patient age quintile*loop diuretic use	1917.324	0.2031
	+ patient age quintile*cardiomyopathy	1921.727	0.9945
	+ patient age quintile*coronary revascularization	1915.132	0.1772
	+ patient age quintile*pacemaker	1923.309	0.9813
	+ patient age quintile*antiarrhythmic agents	1922.545	0.8905
	+ patient sex*previous malignant arrhythmia	1916.670	0.9750
	+ patient sex*loop diuretic use	1917.455	0.6052
	+ patient sex*cardiomyopathy	1915.964	0.2006
	+ patient sex*coronary revascularization	1917.685	0.8431
	+ patient sex*pacemaker	1917.722	0.9460
	+ patient sex*antiarrhythmic agents	1915.384	0.1122
	+ AChEI medication group*patient sex	1917.651	0.7836
	+ AChEI medication group*patient age quintile	1920.765	0.5822
	+ AChEI medication group*previous malignant arrhythmia	1917.724	0.9638
	+ AChEI medication group*loop diuretic use	1917.507	0.6393
	+ AChEI medication group*cardiomyopathy	1915.120	0.9785
	+ AChEI medication group*coronary revascularization	1917.679	0.8292

+ AChEI medication group*pacemaker	1916.789	0.3787
+ AChEI medication group*antiarrhythmic agent use	1917.659	0.7946

Appendix F – sensitivity analysis of Cox regression

Table 33: Breakdown of adjusted hazard ratios (assessing AChEI medication group) determined through sensitivity analysis (comparison: Donepezil versus galantamine/rivastigmine oral/patch combined; REFERENCE: galantamine/rivastigmine oral/rivastigmine patch combined ("other" AChEI medication group))

Event definition	Follow-up duration	Exclusion date for malignant arrythmia diagnosis (in 365 days pre-AChEI index)	Event date definition	Hazard ratio	95% CI	
					Lower bound	Upper bound
I47.2 or I49.00 only in main diagnosis field	Maximum possible	Exclusion coded as 1st of month	Event coded as 1st of month	0.567	0.366	0.877
			Event coded as 15th of the month	0.558	0.360	0.865
			Event coded as 30th of month (28th for February)	0.575	0.363	0.910
		Exclusion coded as 15th of the month	Event coded as 1st of month	0.567	0.366	0.878
			Event coded as 15th of the month	**0.551**	**0.358**	**0.849**
			Event coded as 30th of month (28th for February)	0.567	0.361	0.892
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	0.567	0.366	0.878
			Event coded as 15th of the month	0.558	0.360	0.865
			Event coded as 30th of month (28th for February)	0.590	0.376	0.924
	Capped at 365 days	Exclusion coded as 1st of month	Event coded as 1st of month	0.453	0.245	0.837
			Event coded as 15th of the month	0.436	0.235	0.810
			Event coded as 30th of month (28th for February)	0.404	0.211	0.773
		Exclusion coded as 15th of the month	Event coded as 1st of month	0.454	0.245	0.838
			Event coded as 15th of the month	0.432	0.236	0.791
			Event coded as 30th of month (28th for February)	0.401	0.213	0.755
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	0.454	0.245	0.838
			Event coded as 15th of the month	0.437	0.235	0.812

			Event coded as 30th of month (28th for February)	0.440	0.237	0.818
Occurrence of I47.2 or I49.00 in any of the 25 DAD diagnosis fields	Maximum possible	Exclusion coded as 1st of month	Event coded as 1st of month	0.969	0.757	1.241
			Event coded as 15th of the month	1.008	0.781	1.301
			Event coded as 30th of month (28th for February)	0.963	0.742	1.252
		Exclusion coded as 15th of the month	Event coded as 1st of month	0.970	0.757	1.241
			Event coded as 15th of the month	1.007	0.782	1.298
			Event coded as 30th of month (28th for February)	0.964	0.743	1.250
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	0.967	0.755	1.238
			Event coded as 15th of the month	1.005	0.779	1.297
			Event coded as 30th of month (28th for February)	0.990	0.764	1.283
	Capped at 365 days	Exclusion coded as 1st of month	Event coded as 1st of month	0.723	0.500	1.045
			Event coded as 15th of the month	0.766	0.518	1.133
			Event coded as 30th of month (28th for February)	0.718	0.475	1.086
		Exclusion coded as 15th of the month	Event coded as 1st of month	0.723	0.500	1.046
			Event coded as 15th of the month	0.773	0.526	1.137
			Event coded as 30th of month (28th for February)	0.727	0.484	1.092
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	0.718	0.496	1.039
			Event coded as 15th of the month	0.761	0.515	1.126
			Event coded as 30th of month (28th for February)	0.796	0.533	1.189

Table 34: Breakdown of adjusted hazard ratios (assessing AChEI medication group) determined through sensitivity analysis (Donepezil versus galantamine versus rivastigmine (oral and patch combined; REFERENCE: Donepezil group; G = galantamine, R = rivastigmine))

Event definition	**Follow-up duration**	**Exclusion date for malignant arrythmia diagnosis (in 365 days pre-AChEI index)**	**Event date definition**	**Hazard ratio**	**95% CI**	
					Lower Bound	**Upper Bound**
I47.2 or I49.00 only in main	Maximum possible	Exclusion coded as 1st of month	Event coded as 1st of month	G: 1.986	1.249	3.157
				R: 1.115	0.446	2.785

diagnosis field			Event coded as 15th of the month	G: 2.018	1.268	3.211
				R: 1.133	0.453	2.834
			Event coded as 30th of month (28th for February)	G: 1.926	1.179	3.145
				R: 1.200	0.478	3.009
		Exclusion coded as 15th of the month	Event coded as 1st of month	G: 1.985	1.249	3.155
				R: 1.114	0.446	2.784
			Event coded as 15th of the month	**G: 2.059**	**1.303**	**3.253**
				R: 1.105	**0.442**	**2.761**
			Event coded as 30th of month (28th for February)	G: 1.972	1.218	3.194
				R: 1.168	0.466	2.926
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	G: 1.985	1.249	3.155
				R: 1.114	0.446	2.784
			Event coded as 15th of the month	G: 2.016	1.267	3.209
				R: 1.133	0.453	2.833
			Event coded as 30th of month (28th for February)	G: 1.900	1.176	3.068
				R: 1.119	0.447	2.800
	Capped at 365 days	Exclusion coded as 1st of month	Event coded as 1st of month	G: 2.714	1.433	5.142
				R: 0.922	0.218	3.896
			Event coded as 15th of the month	G: 2.821	1.482	5.370
				R: 0.953	0.225	4.037
			Event coded as 30th of month (28th for February)	G: 3.060	1.558	6.011
				R: 1.059	0.248	4.520
		Exclusion coded as 15th of the month	Event coded as 1st of month	G: 2.708	1.430	5.129
				R: 0.920	0.218	3.889
			Event coded as 15th of the month	G: 2.877	1.538	5.383
				R: 0.899	0.213	3.799
			Event coded as 30th of month (28th for February)	G: 3.119	1.619	6.007
				R: 0.993	0.233	4.226
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	G: 2.708	1.430	5.128
				R: 0.920	0.218	3.889
			Event coded as 15th of the month	G: 2.814	1.479	5.356
				R: 0.951	0.225	4.028
			Event coded as 30th of month (28th for February)	G: 2.847	1.494	5.427
				R: 0.904	0.213	3.829
			Event coded as 1st of month	G: 1.063	0.809	1.397

Occurrence of I47.2 or I49.00 in any of the 25 DAD diagnosis fields	Maximum possible	Exclusion coded as 1st of month	Event coded as 15th of the month	R: 0.937	0.588	1.494
				G: 1.015	0.765	1.348
			Event coded as 30th of month (28th for February)	R: 0.923	0.572	1.491
				G: 1.049	0.784	1.405
		Exclusion coded as 15th of the month	Event coded as 1st of month	R: 1.004	0.621	1.624
				G: 1.063	0.809	1.397
			Event coded as 15th of the month	R: 0.937	0.588	1.494
				G: 1.020	0.770	1.352
			Event coded as 30th of month (28th for February)	R: 0.911	0.564	1.470
				G: 1.054	0.789	1.408
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	R: 0.989	0.612	1.599
				G: 1.066	0.811	1.402
			Event coded as 15th of the month	R: 0.939	0.589	1.497
				G: 1.019	0.767	1.352
			Event coded as 30th of month (28th for February)	R: 0.925	0.573	1.493
				G: 1.028	0.770	1.372
	Capped at 365 days	Exclusion coded as 1st of month	Event coded as 1st of month	R: 0.959	0.593	1.549
				G: 1.430	0.949	2.155
			Event coded as 15th of the month	R: 1.261	0.657	2.421
				G: 1.391	0.904	2.140
			Event coded as 30th of month (28th for February)	R: 1.078	0.522	2.225
				G: 1.443	0.912	2.283
		Exclusion coded as 15th of the month	Event coded as 1st of month	R: 1.258	0.606	2.609
				G: 1.429	0.949	2.153
			Event coded as 15th of the month	R: 1.260	0.656	2.419
				G: 1.391	0.911	2.124
			Event coded as 30th of month (28th for February)	R: 1.037	0.503	2.138
				G: 1.442	0.920	2.261
		Exclusion coded as 30th of month (28th for February)	Event coded as 1st of month	R: 1.201	0.580	2.489
				G: 1.440	0.955	2.171
			Event coded as 15th of the month	R: 1.266	0.659	2.432
				G: 1.401	0.911	2.157
			Event coded as 30th of month (28th for February)	R: 1.083	0.525	2.237
				G: 1.318	0.844	2.057
				R: 1.097	0.531	2.268

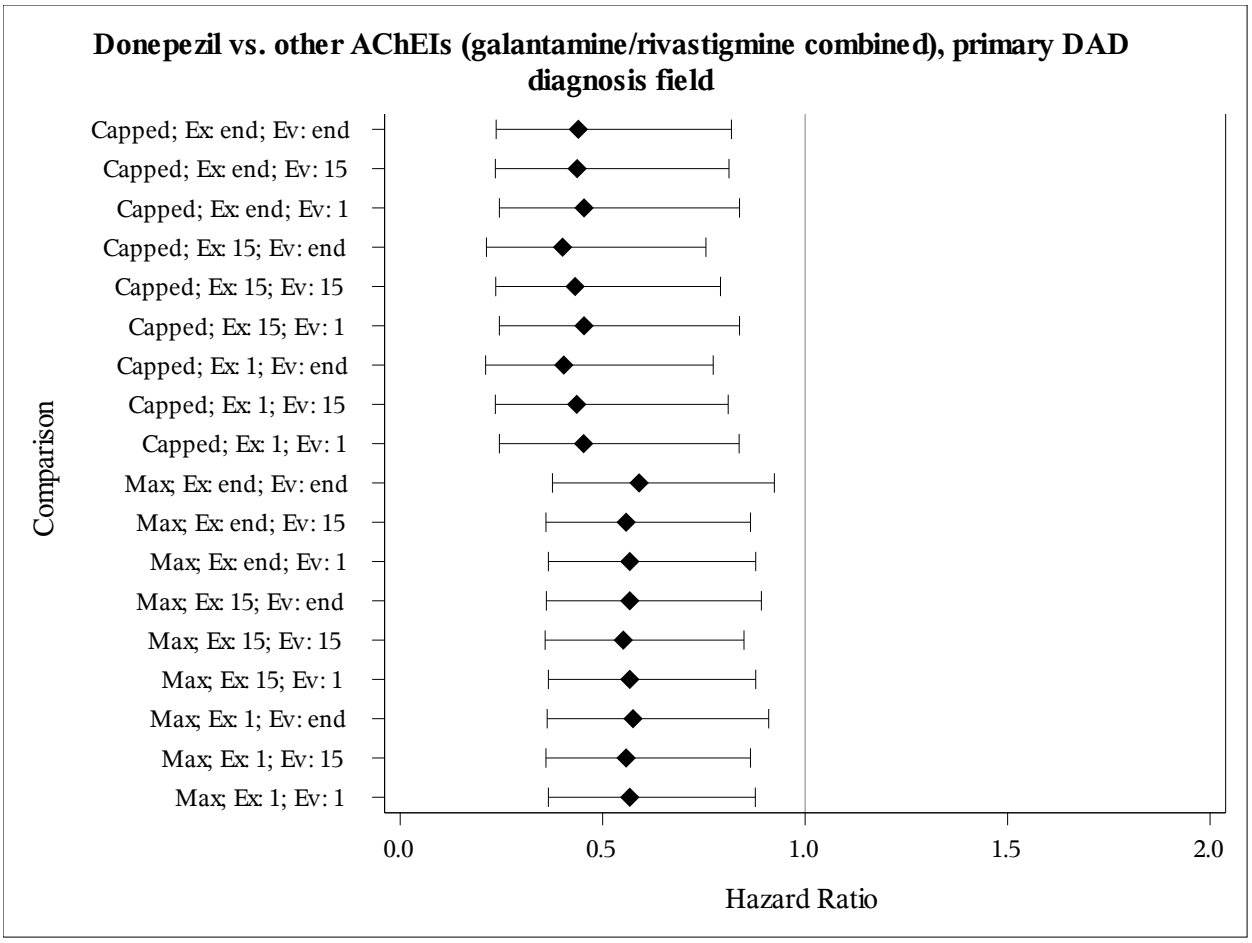

Figure 18: sensitivity of analysis of donepezil versus other AChEI medication groups (galantamine/rivastigmine combined) assessing events in primary DAD diagnosis field only. Legend: capped = follow-up limited to 365 days; max = unlimited follow-up duration; ex. = exclusion date definition (for assessment of malignant arrhythmias between 0- and 365-days pre-index – 1st, 15th, or end (30th, or 28th of month for February)); ev. = event date definition (1st, 15th, or end (30th, or 28th of month for February)).

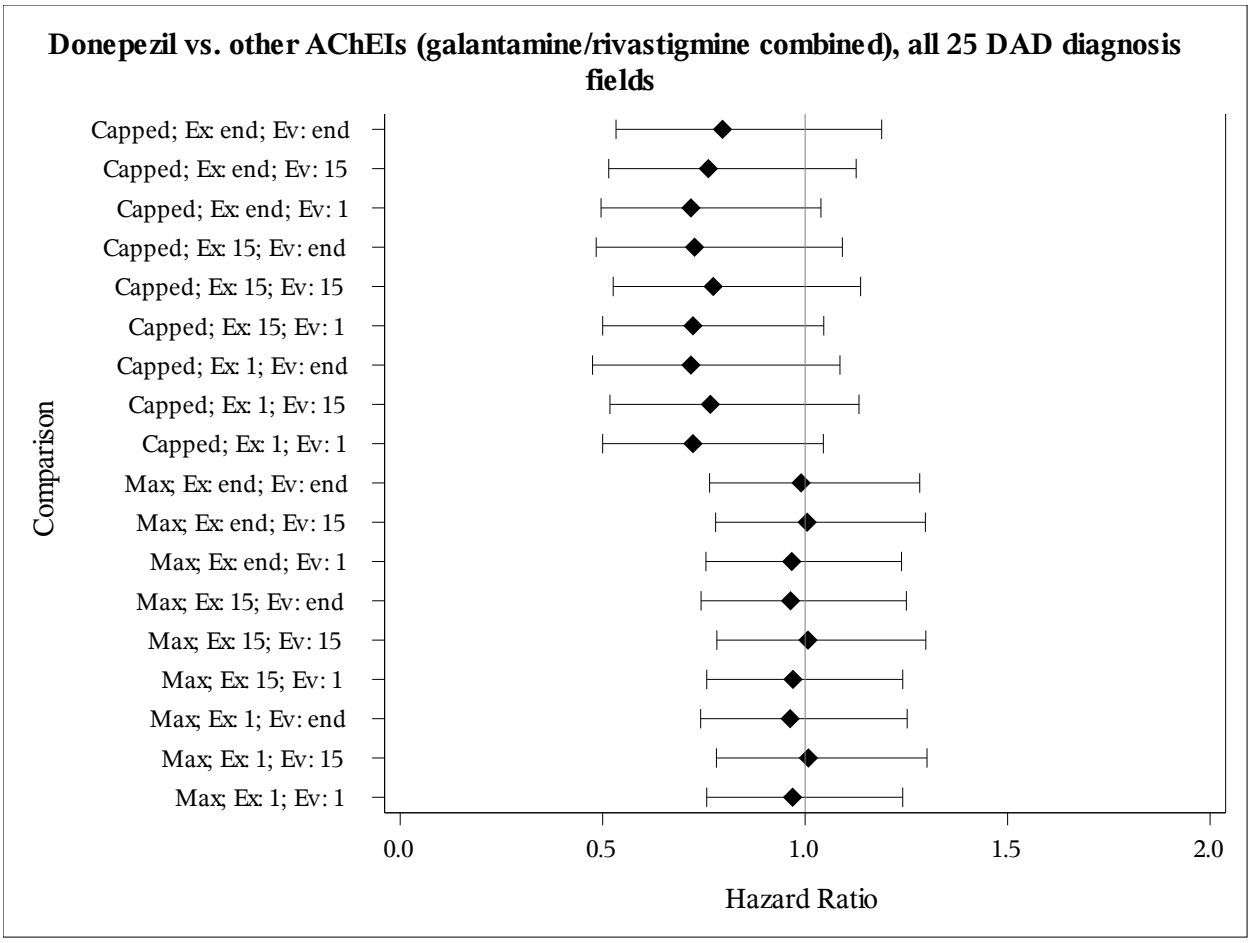

Figure 19: sensitivity of analysis of donepezil versus other AChEI medication groups (galantamine/rivastigmine combined) assessing events in all 25 DAD diagnosis fields. Legend: capped = follow-up limited to 365 days; max = unlimited follow-up duration; ex. = exclusion date definition (for assessment of malignant arrhythmias between 0- and 365-days pre-index – 1st, 15th, or end (30th, or 28th of month for February)); ev. = event date definition (1st, 15th, or end (30th, or 28th of month for February)).

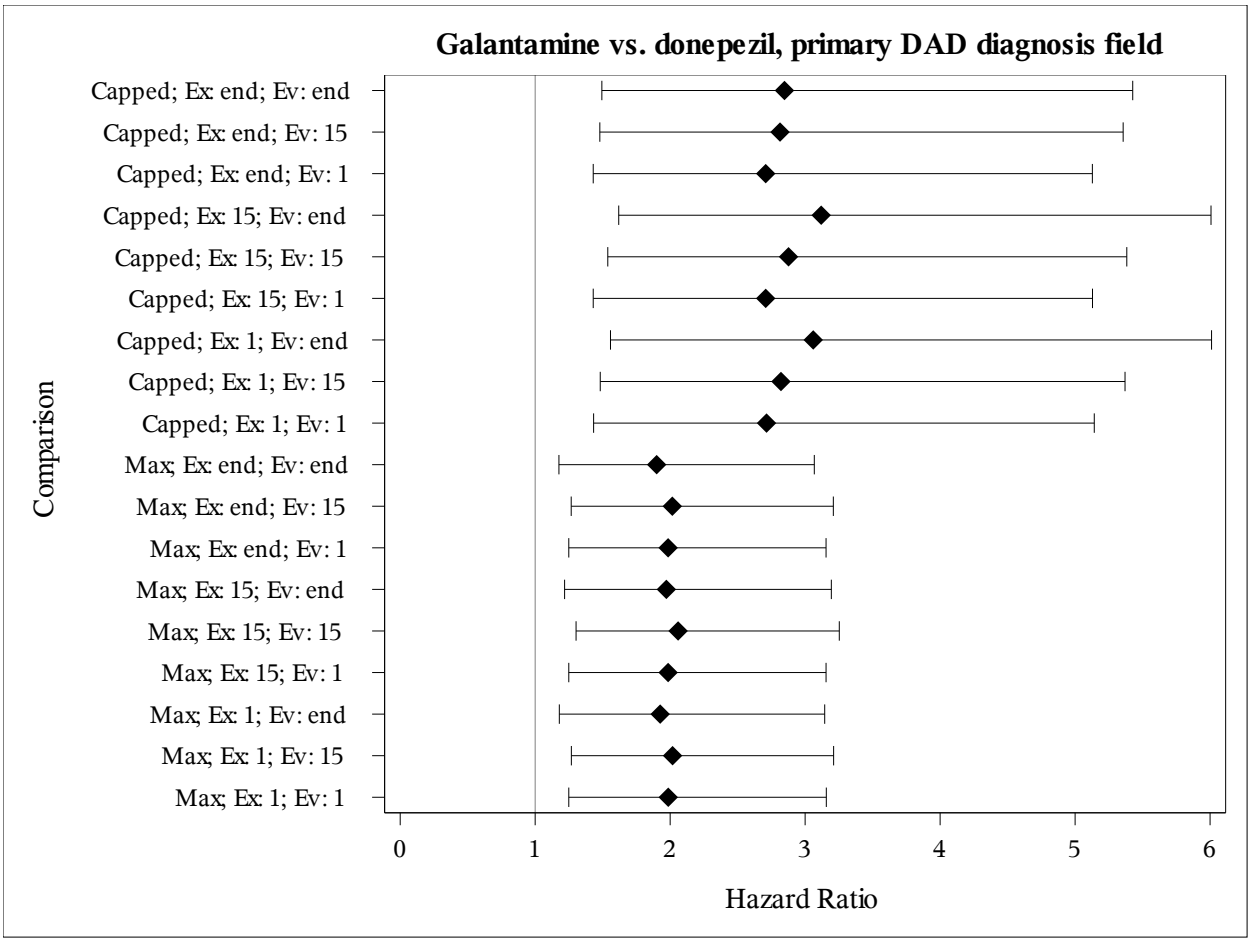

Figure 20: sensitivity of analysis of galantamine versus donepezil, assessing events in primary DAD diagnosis field only. Legend: capped = follow-up limited to 365 days; max = unlimited follow-up duration; ex. = exclusion date definition (for assessment of malignant arrhythmias between 0- and 365-days pre-index – 1st, 15th, or end (30th, or 28th of month for February)); ev. = event date definition (1st, 15th, or end (30th, or 28th of month for February)).

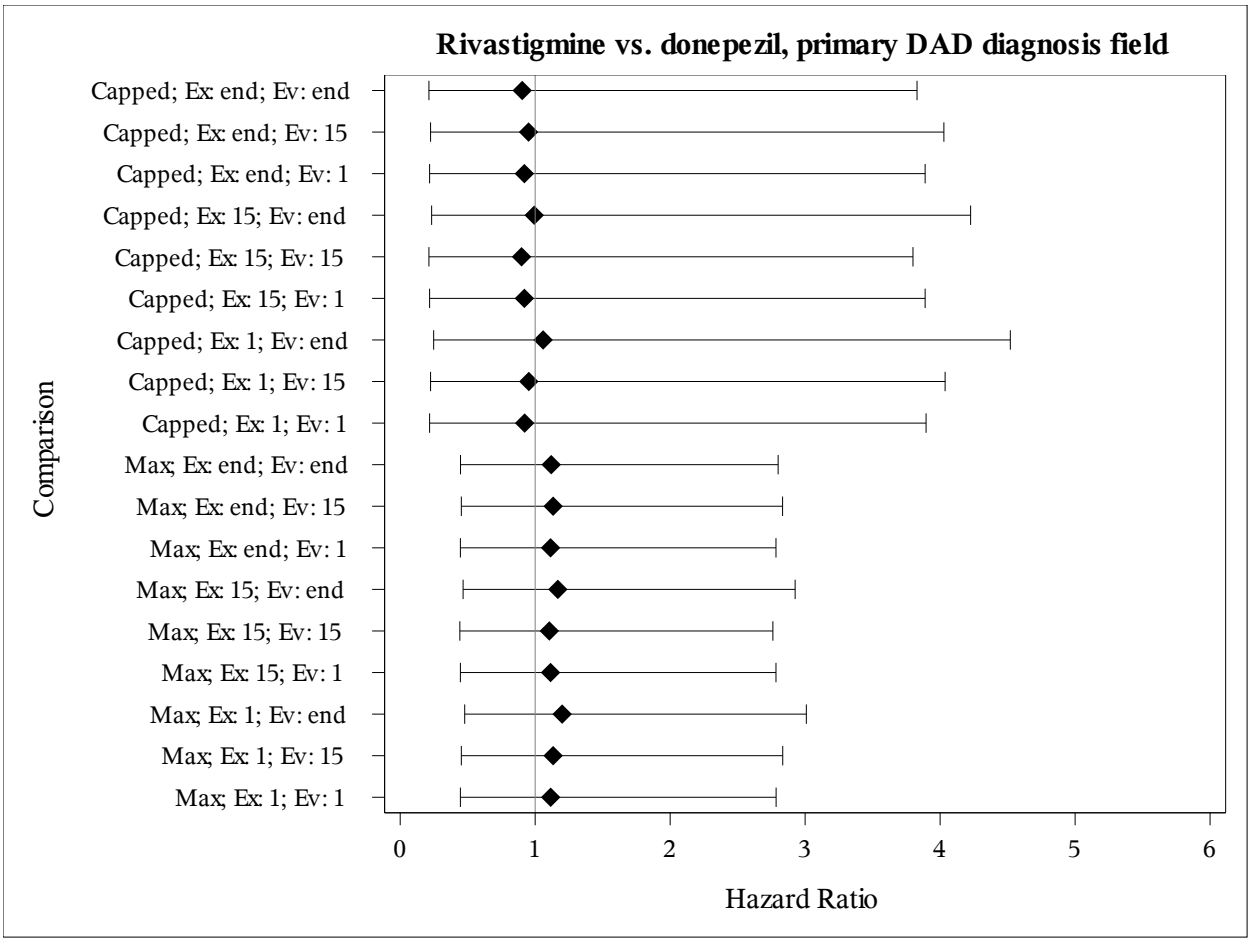

Figure 21: sensitivity of analysis of rivastigmine versus donepezil, assessing events in primary DAD diagnosis field only. Legend: capped = follow-up limited to 365 days; max = unlimited follow-up duration; ex. = exclusion date definition (for assessment of malignant arrhythmias between 0- and 365-days pre-index – 1st, 15th, or end (30th, or 28th of month for February)); ev. = event date definition (1st, 15th, or end (30th, or 28th of month for February)).

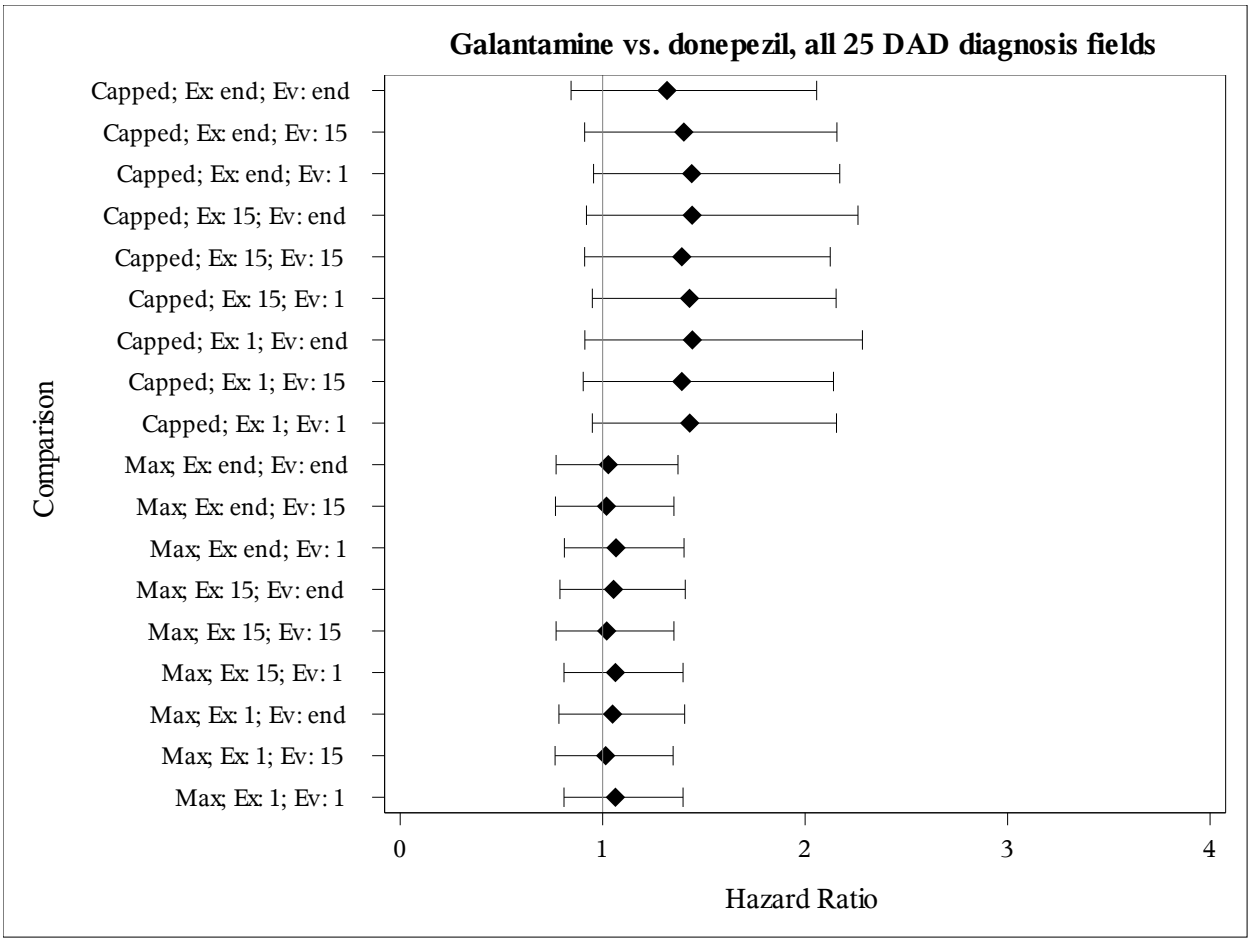

Figure 22: sensitivity of analysis of galantamine versus donepezil, assessing events in all 25 DAD diagnosis fields. Legend: capped = follow-up limited to 365 days; max = unlimited follow-up duration; ex. = exclusion date definition (for assessment of malignant arrhythmias between 0- and 365-days pre-index – 1st, 15th, or end (30th, or 28th of month for February)); ev. = event date definition (1st, 15th, or end (30th, or 28th of month for February)).

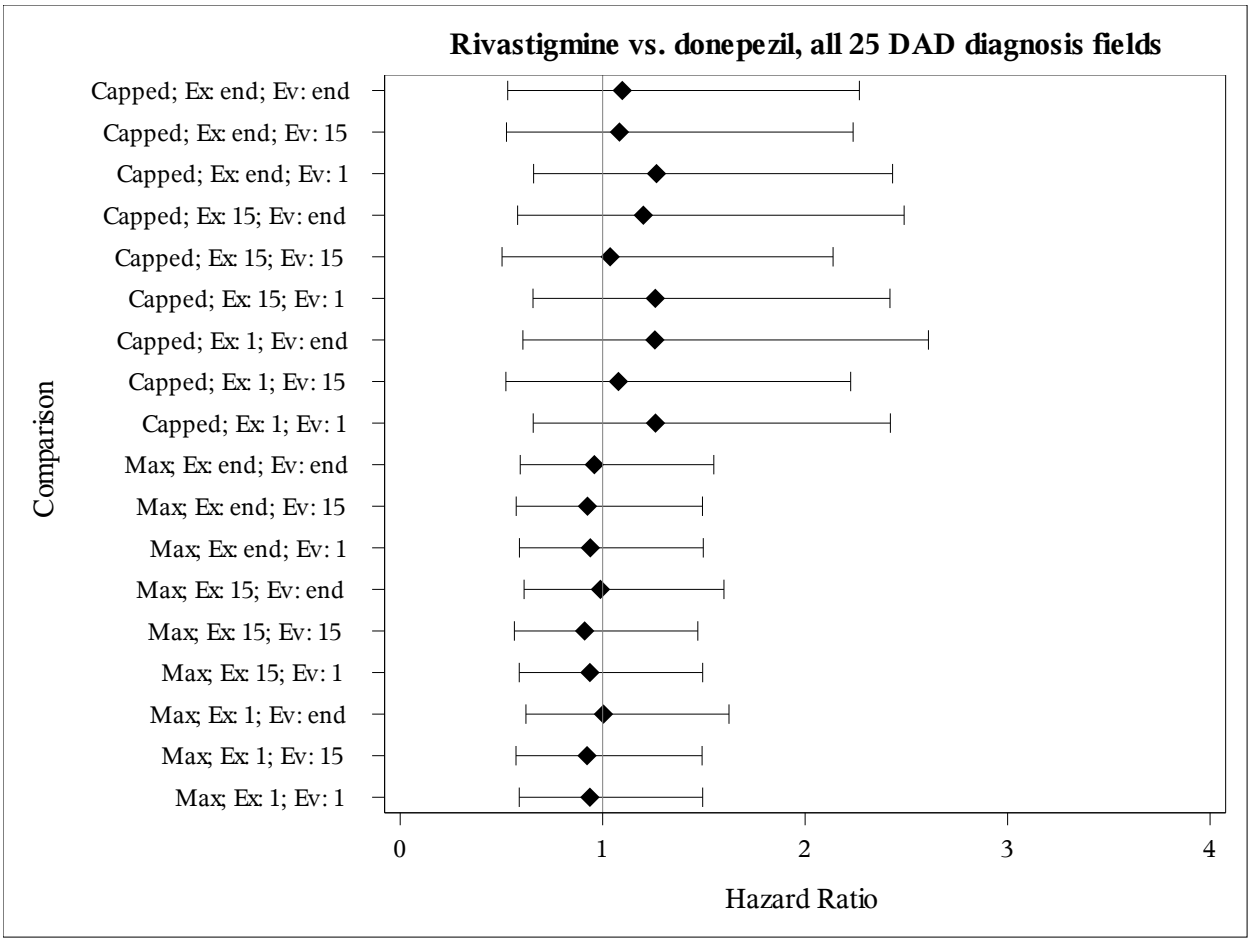

Figure 23: sensitivity of analysis of rivastigmine versus donepezil, assessing events in all 25 DAD diagnosis fields. Legend: capped = follow-up limited to 365 days; max = unlimited follow-up duration; ex. = exclusion date definition (for assessment of malignant arrhythmias between 0- and 365-days pre-index – 1st, 15th, or end (30th, or 28th of month for February)); ev. = event date definition (1st, 15th, or end (30th, or 28th of month for February)).