Prevalence of Aspirin Receipt and Discontinuation Amongst Veterans Health Administration Community Living Center Residents with Indications for Secondary Prevention of Cardiovascular Events

by

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Doctorate of Pharmacy, University of Rhode Island College of Pharmacy, 2015

Submitted to the Graduate Faculty of

The School of Pharmacy in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2019

UNIVERSITY OF PITTSBURGH

SCHOOL OF PHARMACY

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March 20, 2019

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Prevalence of Aspirin Receipt and Discontinuation Amongst Veterans Health Administration Community Living Center Residents with Indications for Secondary Prevention of Cardiovascular Events

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Background: Continuation of aspirin for secondary prevention (ASP) in patients with limited life expectancy and/or advanced dementia (LLE/AD) is controversial, given increased risks and unclear evidence about continued benefits; yet little is known about patterns of use of ASP in this population. This study aimed to 1) describe prevalence and predictors of ASP amongst Veterans at admission to Veterans Affairs (VA) Community Living Centers (CLCs) and 2) assess cumulative incidence and factors predicting aspirin discontinuation within 90 days after admission to a VA CLC.

Methods: We performed a retrospective cohort study in Veterans with LLE/AD admitted to a VA CLC for ≥7 days in fiscal years 2009-15, who had history of coronary artery disease and/or stroke. ASP was defined as receipt of a preventive dose (25-325 mg daily) on ≥1 day in the first 7 days of the stay. Resident, caregiver, and facility level characteristics were extracted from admission Minimum Dataset (MDS) assessments, VA Corporate Data Warehouse, and Medicare claims. Multivariable logistic regression was used to determine factors associated with ASP at CLC admission. Fine and Gray subdistribution hazard models with death as a competing risk were used to identify predictors of aspirin discontinuation.

Results: The sample (n=37,165 CLC episodes) was 98% male, 78% white, and 35% aged ≥ 85 year; 48% received aspirin in the first week of the CLC stay. The strongest predictor of higher

odds of ASP was having a myocardial infarct in the last year (aOR=1.99, 95% CI=1.79-2.22). A total of 13,844 episodes qualified for the discontinuation analysis; cumulative incidence of ASP discontinuation was 33% by day 91 of the CLC stay. Strong predictors of aspirin discontinuation were documentation of limited prognosis or hospice use (aSDHR 1.90, 95% CI 1.67-2.14) and greater ADL dependency.

Conclusion: Just under half of older adults with LLE/AD used ASP at CLC admission, and a third of those discontinued ASP in the first 91 days. Wide variability in aspirin prescribing may reflect the unclear role of aspirin in end-of-life amongst prescribers. Given the controversy of continuing ASP at end-of-life, future research should assess outcomes of ASP discontinuation in this population.

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Preface

I would like to acknowledge the guidance of my mentor, Dr. Carolyn T. Thorpe, PhD, MPH, for her support over the last two years. I would like to acknowledge the funding support provided through Carolyn Thorpe's Health Services Research and Development Merit Award through the U.S. Department of Veterans Affairs (IIR 14-306), and the Veterans Affairs Office of Academic Affiliations' Medication Safety and Pharmacy Outcomes fellowship. I would also like to acknowledge members of my team who worked on this project alongside me: Maria K. Mor, PhD; Song Zhang, PhD; Florentina E Sileanu, MS; Xinhua Zhao, PhD; Sherrie L. Aspinall, PharmD, MSc; Mary Ersek, PhD, RN; Joseph T Hanlon, PharmD, MS; Jake Hunnicutt, PhD; Joshua D. Niznik, PharmD; Walid F. Gellad, MD, MPH; Loren J Schleiden, MS; Bryan Ketterer, MS; Meiqi He, MS; and Joshua M. Thorpe, PhD, MPH. I would also like to acknowledge the support and helpful feedback from Sam Poloyac, PhD, PharmD, as a member of my Masters Thesis committee. The views expressed in this paper are those of the authors, and no official endorsement by the Department of Veterans Affairs or the United States Government is intended or should be inferred.

1.0 Introduction

1.1 Burden of Cardiovascular Disease

It is estimated that over 92 million American adults have a diagnosis of cardiovascular disease (CVD), and CVD is the number one cause of death globally and in the United States (U.S).[1, 2] CVD consists of a constellation of diagnoses, including cerebrovascular disease and coronary artery disease (CAD).[2] An estimated $200 billion is spent on heart disease alone annually in the U.S.[1]

1.2 Recommendations for Initiation of Aspirin to Reduce Cardiovascular Events

A major focus in reducing morbidity and mortality related to CVD is on the prevention of secondary cardiovascular events. Aspirin is a first-line agent for the prevention of a secondary CVD event, including stroke, transient ischemic attack (TIA), and myocardial infarction, although the percentage of people with CVD who are actually prescribed aspirin ranges from 57-71%.[3-6] A number of guidelines strongly recommend aspirin for secondary prevention in those with or without diabetes and a history of CVD when the perceived benefit outweighs potential risk.[7, 8] The American Heart Association (AHA) and the American Stroke Association recommend aspirin at

doses of 50-325 mg daily, over warfarin, in patients with a history of stroke or TIA (Grade IB recommendation), and for patients unable to take anticoagulation in those with paroxysmal or permanent atrial fibrillation (Grade IA).[4] Aspirin combined with extended-release dipyridamole is also recommended in those with a history of stroke or TIA and cardiomyopathy (Grade IIB).[4] The American College of Chest Physicians recommends aspirin in those with a history of non-cardioembolic stroke or TIA at doses of 75-100 mg daily or aspirin combined with extended release dipyridamole (Grade 1A), and aspirin in those with a history of ischemic stroke or TIA and atrial fibrillation (Grade IB).[6] The AHA and the American College of Cardiology Foundation (ACCF) recommend aspirin at doses of 75-162 mg daily for patients with coronary artery disease (CAD) (Grade IA), daily doses of 100-325 mg daily for 1 year after undergoing coronary artery bypass grafting (CABG) (Grade IA), 75-325 mg of aspirin daily for those with a history of stroke or TIA or in combination with extended release dipyridamole twice daily (Grade IA), and aspirin 81 mg daily after a percutaneous intervention (Grade IB).[5] Only the AHA/ASA and the Chest guidelines recommend individualizing antiplatelet choices, with the Chest physicians only recommending against aspirin in the setting of weak evidence and high bleeding risk – noting lack of validated tools for bleed risk assessment outside of atrial fibrillation.[4, 6] Overall, current guidelines report strong evidence to initiate and continue aspirin in the setting of secondary CVD prevention, and avoid recommendations addressing the optimal duration of use, except in the context of after a CABG.

1.3 Benefits of Aspirin for Secondary Prevention

The evidence supporting aspirin's benefit in the secondary prevention of CVD events is fairly clear in the short-term.[9-12] Aspirin administered shortly after an ischemic stroke or a coronary revascularization is associated with reduced mortality, better functional outcomes and reduced recurrence of stroke or myocardial infarction in studies following patients for 4-24 weeks after an ischemic stroke.[6, 13] A meta-analysis of randomized controlled trials of aspirin for the secondary prevention of CVD showed reduced risk of major coronary events (non-fatal myocardial infarctions, coronary heart disease mortality), stroke (ischemic and stroke due to unknown cause), vascular death, and any serious vascular events by about 20% compared to those not receiving aspirin.[14] Additionally, studies have reported a prothrombotic state shortly after aspirin discontinuation[15], which has been supported by a number of case-reports (n=2-13 patients), and several retrospective and case-control studies.[16-20] This prothrombotic window appears to range from 8-25 days, in which patients are at highest risk of subsequent CVD events after aspirin discontinuation.[21] While case-reports offer low-quality evidence to support this risk after aspirin discontinuation, one meta-analysis included 2 retrospective studies assessing aspirin receipt prior to myocardial infarctions or acute coronary syndromes, and found that 2.3-10.2% of these patients had recently discontinued aspirin (mean duration of aspirin use prior to event was about 4 years).[21] The combination of strong evidence to prescribe aspirin upon a CVD event, and risk of a potential prothrombotic state upon discontinuation, likely contributes to the continued use of aspirin in the long-term for many patients, despite a lack of direct evidence to support long-term benefit beyond 5 years.[22]

The benefit-to-risk ratio of long-term aspirin use is not as clear, especially in older adults.[14, 22, 23] Most studies providing evidence for reduced cardiovascular and cerebrovascular events as a result of use of aspirin for secondary CVD prevention had a short duration of follow-up, only following patients for a mean duration of 3 weeks to 29 months[23] and lack evidence to support long-term benefit in older adults beyond 5 years.[22] Thus, it is unclear if the benefit from aspirin for secondary prevention continues beyond the duration of these trials and justifies the continued use of aspirin as patients age and approach the end-of-life.

1.4 Risks of Aspirin for Secondary Prevention

In addition to questions regarding continued benefit as adults age, a major consideration for continued aspirin use includes the risks of bleeding events. In a systematic review of 16 studies (N=17,000) assessing risk of bleeding in adults on aspirin for secondary prevention, the risk of extracranial bleeding was actually higher than in those on aspirin for primary prevention. There was an almost 3-fold risk of major extracranial bleeding (RR 2.69, 95% CI 1.25-5.76) in secondary prevention trials, and a 1.5-fold increased risk of bleeding in primary prevention studies (RR 1.54, 95% CI 1.30-1.82). Hemorrhagic strokes were elevated in those on aspirin for secondary prevention, though this was not statically significant (RR 1.67, 95% CI 0.97-2.90). Importantly, hemorrhagic strokes are considered more dangerous than ischemic strokes, especially in older adults.[14] In a population-based cohort study, amongst 3,166 aspirin-user on therapy for secondary prevention, risk of major bleeding was associated with increased age, especially amongst fatal bleeds (HR 5.53, 95% CI 2.65-11.54). Additionally, those 75 years of age and older were at higher risk for major upper gastrointestinal bleeding (HR 4.13, 95% CI 2.60-6.57), and fatal or disabling

gastrointestinal bleeding (HR 10.26, 95% CI 4.37-24.13).[24] Despite the bleeding risk, guidelines do not explicitly indicate what to do in those who are already at high risk of a bleeding event, such as older adults, except to consider individualizing therapy if the evidence to support use is weak.[6]

1.5 Potential for Increased Risks of Aspirin for Secondary Prevention in Older Adults with Limited Life Expectancy

The risk-to-benefit ratio is even more complicated by the physiological changes that affect the pharmacokinetics and pharmacodynamics of medications in older adults.[25] These physiological changes, such as decreased metabolism, elimination, hepatic blood flow, increased body fat, and reduced lean muscle mass and total body water, place older adults at a higher risk of adverse drug reactions due to higher bioavailability at typical adult medication doses and reduced first pass metabolism.[25] When patients are co-prescribed aspirin with warfarin, for example, they are at a higher risk of bleeding events than their younger counterparts due to a reduction in cytochrome P450 metabolizing enzyme activity with age.[25, 26] Pharmacokinetic changes could contribute to higher bioavailability of aspirin, which is metabolized to an inactive component in the gastric mucosa and in liver.[27] Slower gastric emptying time in older adults could partially explain the higher risk of gastrointestinal bleeding amongst older adults.[28] Additionally, as patients near the end-of-life (EOL), there are major physiological changes which occur that can increase the risk of adverse drug reactions, such as reduced gastric motility, delayed gastric emptying, decreased hepatic blood flow, and fluid deficits – all of which can increase the bioavailability of aspirin. The adverse events can occur even if they have been on that drug for a long period of time.[29-31]

Two notable trials of aspirin were also published recently, which suggest decreased CVD benefits and increased bleeding risk associated with aspirin use in older adults. The ASPirin in Reducing Events in the Elderly (ASPREE) trial was a RCT of 19,114 community-dwelling older adults who did not have cardiovascular disease. The researchers found no significant benefit in reducing cardiovascular disease and an increased risk of major hemorrhage.[32] The ASCEND (A Study of Cardiovascular Events in Diabetes) study group found a benefit of reducing cardiovascular events in a cohort of older adults with diabetes and no prior cardiovascular disease, but an excess risk of major bleeding.[33] Such a long-term study of aspirin for secondary prevention has not been conducted, though these two studies will likely prompt the re-assessment of aspirin use in older adults generally, as aspirin had previously been considered a safe and effective agent for primary prevention in this population.

1.6 Potential for Lack of Continued Benefit in Older Adults with Limited Life Expectancy

In older adults with limited life expectancy, another consideration as to whether aspirin should be used for secondary prevention is the expected time to benefit in relation to the patient's remaining estimated life expectancy. The time to benefit (TTB) for a medication can often only be ascertained by randomized clinical trials (RCTs)– using the time at which a statistically significant difference is seen between those on the medication and those on the control. Going one step further, the effect size at this TTB should be considered as well by using number needed to treat (NNT) compared to the number needed to harm (NNH) in an effort to weigh the benefits and risks. In those with a

limited life expectancy (LLE), the TTB of a new agent may exceed the patient's estimated life expectancy, putting into question whether or not a patient will realize the full benefit of the medication. Alternatively, patients who are on a medication for a long period of time often surpass the TTB of a medication that was determined in the RCT. Often the TTB is shorter, or as long, in duration as the clinical trial, which is a major limitation given that many medications, especially those for chronic conditions, are taken for life.[34]

1.7 Rationale for Considering the Discontinuation of Aspirin for Secondary Prevention in Older Adults with Limited Life Expectancy

Because of these physiological changes and potential changes in the benefit-to-risk ratio, the time when the provider becomes aware that a patient has LLE poses an excellent time to consider evaluating the utility, including TTB and TTH, of all medications the patient is taking. [34] Holmes and colleagues suggested a framework for prescribing medications at end of life, in which she notes the number of appropriate medications is reduced as the goal of care moves from curative to palliative, and life expectancy reduces.[35] Holmes recommends optimizing prescribing at EOL by focusing on medications which reduce burden, avoid harms, and improve quality of life, while reducing or deprescribing medications and focusing on the goals of care of the older adult with LLE, which often shift from curative/preventive to palliative.[29] In a setting where the goal is palliative versus curative or preventive, several medications are expected to be initiated to alleviate symptoms, thus it is important to consider discontinuing medications with increased short-term risks and/or reduced benefits, to reduce pill burden.[29]

Unfortunately, there is almost no literature to directly support or refute the safety of discontinuing aspirin in patients near the EOL, and very few studies which assess patterns of use of aspirin or antiplatelet therapy at EOL.[36] A recent systematic review found that while 10 RCTs, 2 case-control studies and 7 cohort studies assessed the discontinuation of preventive medications at EOL, only one of these studies assessed the discontinuation of aspirin specifically.[37] The study consisted of a small observational study (n=60) assessing medication discontinuation in the last months of life (n=60). The outcomes of aspirin discontinuation in this patient was not reported.[38]

The absence of data on outcomes of aspirin discontinuation in older adults with limited life expectancy likely explains the lack of guidance in CVD treatment guidelines and other geriatric prescribing guidelines, regarding the optimal duration of aspirin therapy and whether it should be discontinued in patients approaching the EOL. For example, the STOPPFrail criteria were recently published and specified that all anti-platelets for the indication of primary prevention should be considered for deprescribing in the LLE setting. This consensus group rejected the criteria to include anticoagulation, noting that while the risk of bleeding was high, in a *minority* of patients discontinuing anticoagulation may be inappropriate. While many agreed that anticoagulation should likely be discontinued at EOL, the lack of evidence describing the risk of deprescribing or discontinuing these agents prevented them from recommending it.[36] In addition, Holmes and colleagues assessed the feasibility of creating a deprescribing consensus guideline for palliative care patients with advanced dementia. Twelve geriatricians who were board certified in Palliative Medicine were involved in a modified Delphi consensus panel, where 34 resident medication lists were reviewed. Of the 81 medications included, consensus was reached on 69 of these medications (always appropriate, sometimes appropriate, rarely appropriate, or never appropriate). Aspirin was

one of 12 medications in which no consensus was reached regarding whether or not it should be continued in this population.[35] The authors noted a need for future research to assess the effects of aspirin discontinuation in patients with advanced dementia, especially considering its widespread use in this population.

1.8 Lack of Evidence Regarding Continued Use of Aspirin Near EOL Likely Contributes to Treatment Variation

Despite a lack of research evaluating the outcomes of aspirin discontinuation in older adults with LLE, a survey of 134 physicians who were given clinical vignettes of an older adult with CVD and progressively worsening cognitive function and dependency found that aspirin in the context of secondary prevention was the most common medication recommended for discontinuation.[39] Across all medications, the most common reason for deprescribing medications was dementia severity and pill burden. They also found that older physicians were less likely than younger physicians to rank LLE and cognitive impairment as important in considering deprescribing, and trainees were more likely to discontinue medications for secondary prevention.[39] Given this survey came after the assessment by Holmes, it is possible that discontinuation of aspirin is becoming less controversial in practice. However, the unclear risk-to-benefit ratio for continuation of aspirin in EOL, and lack of clinical consensus of best practices around aspirin prescribing near EOL, likely contribute to ambiguity for prescribers and the need to better understand prescribing practices amongst those with LLE.

There have been a handful of studies examining patterns of aspirin use and discontinuation in patients near the EOL. In one study of chronic medication use in the weeks just prior to death, one-third of patients remained on aspirin one week prior to their death.[40] In a study of patients discharged to hospice care, over 57% remained on aspirin, 26% remained on the anticoagulant enoxaparin, and 21% remained on warfarin; furthermore, 22% of these patients were newly initiated on these medications prior to hospice admission.[41] Common amongst these studies was the lack of reporting of additional factors which can often increase or decrease the odds of prescribing or discontinuing aspirin, including facility level factors of the nursing home or hospice care unit they are discharge to, comorbid cardiovascular risk factors, or information regarding next of kin (NOK). Additionally, these were fairly small, single-site hospice studies, limiting generalizability to the broader nursing home population at EOL, not explicitly on hospice care. Thus, further research on rates of aspirin use and discontinuation in large, generalizable samples of older adults near the end of life are needed, along with studies examining the impact of aspirin discontinuation on CV events and other patient-centered outcomes.

The VHA CLC is a nursing home setting, which providers Veterans with rehabilitation, skilled nursing care, assisted living, respite, hospice and other care for older or previously hospitalized Veterans. The VHA CLC population provides a unique opportunity to study aspirin prescribing patterns in patients near the EOL because of the availability of daily medication records for capturing detailed information on daily aspirin use and the ability to link these data to information on resident prognosis and health status, as well as facility characteristics that may affect discontinuation. In non-VHA claims data it can be increasingly difficult to assess aspirin use, given that the medication is available over the counter (OTC) and often not prescribed. Even

in non-VHA nursing home settings it is not uncommon for residents to bring in their own OTC agents, including aspirin. Thus, this setting provided the ideal dataset for assessing prescribing and discontinuation patterns in patients with LLE and AD, which could be generalizable to older adults at EOL. We included patients with AD, because the mortality risks have been estimated at over 50% over 6-18 months[16, 42], consistent with other terminal diseases.[43]

1.9 Objectives

The first aim of this study is to describe prevalence of and factors associated with aspirin receipt for secondary prevention of cardiovascular disease (those with a history of CAD and/or TIA/stroke) at the time of CLC admission. The second aim of this study is to assess, among CLC residents who received aspirin for secondary prevention at admission, the cumulative incidence of subsequent aspirin discontinuation during the first 90 days after CLC admission and identify resident and facility characteristics associated with discontinuation.

2.0 _Methods

A retrospective cohort study was conducted using administrative and clinical data collected from the Veterans Health Administration (VHA) from fiscal years (FY) 2009-2015. The Veterans Affairs Pittsburgh Healthcare System's Institutional Review Board approved this study.

2.1 Conceptual Model

To guide our investigation, we developed a conceptual model of factors which may influence prescribing and discontinuation of aspirin in nursing home residents with LLE/AD, based on a literature review. The model included the following factors: socio-demographics, environment of care, cardiovascular risk factors, markers of poor prognosis, facility characteristics, and bleeding risk factors. See Figure 1 below for the complete model.

Socio-demographics. Socio-demographics, including age, race/ethnicity, and sex, are included based on a study by Zullo and colleagues which found that the initiation of medications for secondary CVD prevention (i.e., beta-blockers and statins) in older adults admitted to a nursing home after a myocardial infarction (MI) was less likely in adults aged 85 years or older, as well as females.[44] In a study assessing receipt of anti-platelets or anticoagulant therapy in those with a history of stroke, the researchers found similar results and also noted a racial disparity, with lower odds of prescribing amongst Black compared to White patients.[45] Racial, ethnic and sex-based

disparities have also been reported in a systematic review of studies assessing the frequency of differences in these variables in medication treatment; they found that 73% of studies demonstrated disparities related to receipt of a evidence-based medication for chronic diseases.[46]

Environment of Care Factors. Several contextual factors surrounding the nursing home admission may also influence whether the resident is admitted on aspirin or is discontinued going forward. For example, residents admitted in more recent years may be more likely to have already been deprescribed aspirin or may discontinue aspirin after admission, as attention to deprescribing has gained traction in the literature. In addition, as medications are often initiated or restarted in the hospital setting, residents who are admitted from hospital rather than community settings or who were recently hospitalized may be more likely to enter the nursing home taking aspirin.[44, 47] In addition, the involvement of a caregiver may influence the prescribing of aspirin, as often in older adults with LLE or AD, the NOK and/or caregivers are responsible for healthcare related decision making. Pruskowski and colleagues surveyed conference attendees during The Society for Post-Acute and Long-Term Care Medicine Annual Conference, and found that deprescribing was more likely when either the patient, or their family/caregiver, indicate the deprescribing would improve quality of life.[48] While quality of life is difficult to assess in administration data, assessing who is listed as the NOK, their relationship to the Veteran, and their geographic distance to the CLC, could be important to whether a patient is continued on or discontinued from their chronic medications.

Cardiovascular Risk Factors. Specific risk factors for cardiovascular events may reduce the prescriber's propensity to consider discontinuation of aspirin, an idea which is supported by

several previous studies. In one study, recent hospitalization for a stroke resulted in significant changes to the odds of receipt of preventive CV medications – reducing the effect size of factors that were previously associated with higher odds of prescribing (such as atrial fibrillation, hypertension, CAD, peripheral vascular disease).[45] Risk factors for CVD have also been shown to be implicated in prescribing of chronic medications for secondary prevention, with higher odds of prescribing amongst those with CHF and recent coronary revascularization or angioplasty; lower odds of prescribing occurred in those with atrial fibrillation, and stable and unstable angina.[44] These studies also found that a history of stroke, atrial fibrillation, hypertension, CAD, and peripheral vascular disease predicted higher odds of prescribing.[44, 45]

Markers of Poor Prognosis. It is possible that when residents present with specific markers of poor prognosis (e.g., cancer, poor appetite, dehydration, advanced dementia) or signs and symptoms that may make taking medications more difficult (e.g., intravenous (IV) feeding tube placement, swallowing problems), prescribers may be prompted to review the medication list and discontinue those that are least likely to benefit or most likely to harm a patient. In the previous studies examining the use of chronic medications for secondary CV prevention, use of these medications was less likely in those with an Alzheimer's disease diagnosis, moderate to severe cognitive impairment compared to those with no cognitive impairment, and in those with more extensive dependence in ADLs.[44, 45]

Facility Characteristics. A survey of Vancouver family physicians found that common barriers to deprescribing include organizational factors, poor records in nursing home facilities, and lack of training of staff on the role of deprescribing, suggesting that facility level factors may

impact whether or not a patient is deprescribed or discontinued from their aspirin.[49] As such, specific factors such as region of the country[44], rural/urban location, bed size, complexity (i.e., academic affiliation and range of specialty services offered)) of the VHA parent station with which the CLC is affiliated, and staff turnover rates could contribute to the environment of a patient's care, but have yet to be fully explored in this population.

Bleeding Risk Factors. There is significant literature which supports the premise that proton pump inhibitors reduce the incidence of gastrointestinal bleeding in those on aspirin therapy[24], and some data supporting similar protection with H2 receptor antagonists (H2RAs).[50] Concomitant use of aspirin with medications such as non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX2) inhibitors, anti-platelets and anti-coagulants has also been associated with increased risk of bleeding, and these interactions are guidelines for appropriate prescribing in older adults (Beers Criteria, 2015, 2019). Thus, use of these medications may be potential predictors of aspirin use and discontinuation in this study.

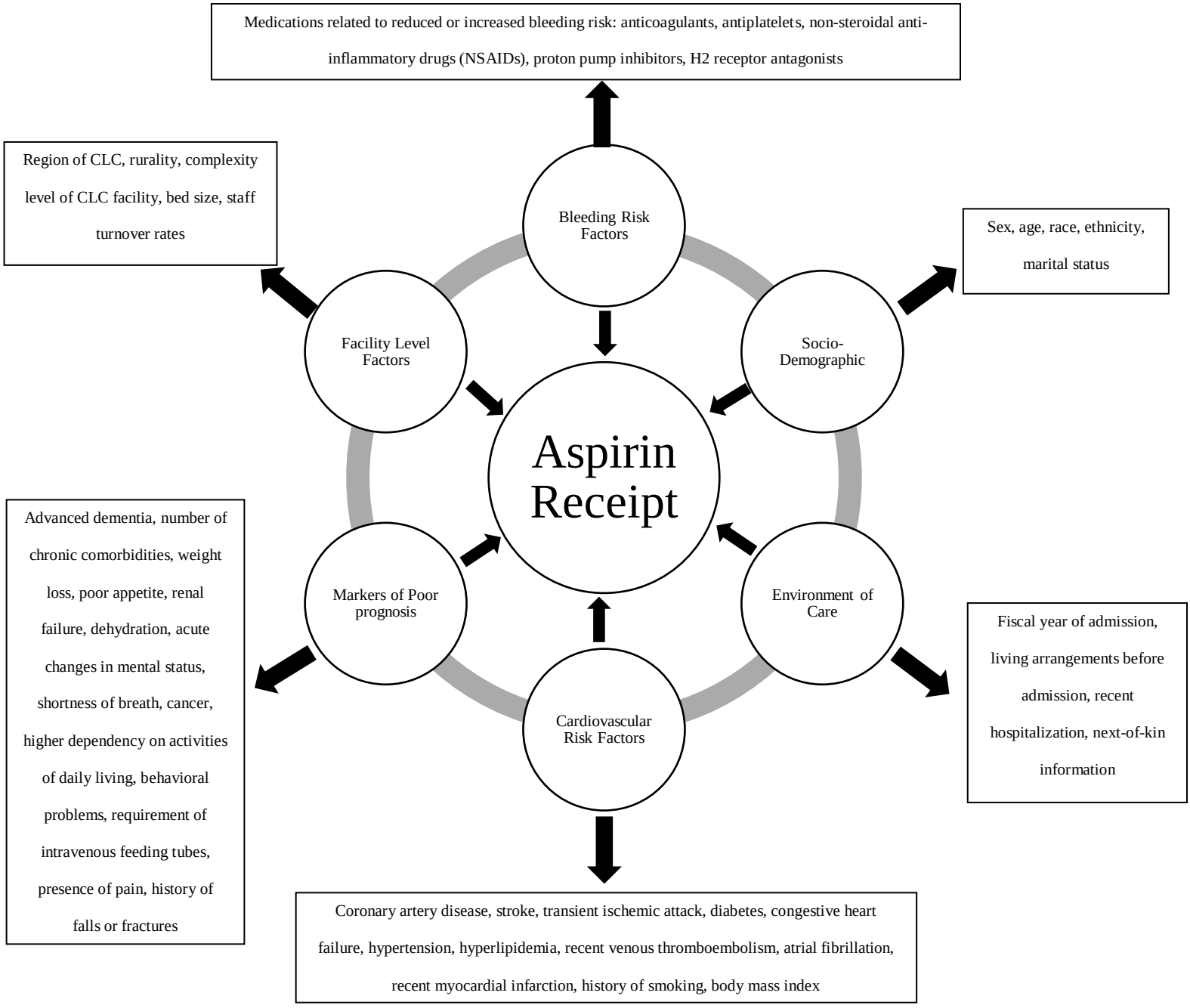

Figure 1: Conceptual Model for Aspirin Receipt

2.2 Data Sources

Data for this study was obtained from several administrative healthcare and clinical databases available for Veterans receiving healthcare in the VHA, and was used to construct an analytic dataset consisting of new CLC admissions over fiscal years 2009-2015 for Veterans with LLE/AD. The VA Residential History file, which uses VA and Medicare utilization data to track the location of Veterans as they transition through different settings of VA and non-VA care, was used to identify VHA CLC episodes. The Veterans Affairs (VA) Corporate Data Warehouse (CDW) was used to obtain information about VA utilization of care. Medicare fee-for-service claims were used to obtain information on non-VHA utilization of care, as all Veterans aged 65 and older are eligible to enroll in Medicare to cover the use of non-VHA health services in addition to VHA. The Minimum Dataset (MDS) contained comprehensive clinical assessment data on all Veterans at admission to VA CLCs over the study time frame. The MDS is a mandatory assessment tool which comprehensively assesses nursing home resident upon admission. The assessment is to be completed within 14 days of the admission, then quarterly and upon major changes in health status of the resident. Domains include demographics, behavior, diagnoses/conditions, functional status, cognitive status, nutrition/dental status, mood, continence, and discharge potential. Items containing in this dataset can be combined to create validated scales or indices use to measure health-related factors. Thus, this dataset was used to identify CLC residents with limited life expectancy/advanced dementia at admission, and define a set of covariates on resident prognosis and health status. During this study period, there were two available version of the MDS: v2.0 and v3.0. Version 3.0 became available in July of 2012 in the VHA. Bar-coded medication administration (BCMA) records provided detailed information regarding medication exposure. Using BCMA records, we could determine daily medication name and doses, which was useful in

determining medication covariates (described in section 2.6), and defining aspirin utilization and aspirin discontinuation (described in section 2.4 and 2.5). Data from the VHA Support Service Center (VSSC) were utilized to obtain facility-level factors.

2.3 Participants

These data sources were used to identify all Veterans aged 65 years or older who were admitted to a VHA CLC for at least 7 days over fiscal year (FY) 2009-2015 with evidence of limited life expectancy and/or advanced dementia at admission. CLC episode start and end dates were first determined using the RHF. The RHF creates a calendar which describes a patient's location, provider type and service type on any given day within a calendar year. The algorithm used by the RHF is hierarchical, first populating this calendar with information regarding inpatient claims, then emergency department and observation days, then skilled nursing facility claims, then additional NH claims, and finally home health claims. Hospice days are added last, because they are not location-specific, such as the other claims listed previously. Instead, hospice can be administered either at home or in a facility. Days spent consecutively in one of the above settings create an "episodelet" with the RHF for that patient, and the joining of episodelets creates an "episode" such as in the case where a patient may transition from a skilled nursing facility to less skilled care, while remaining in the same NH.[51] For the purpose of this study, an episode was created by concatenating adjacent episodelets as long as gaps between episodelets were <7 days. Episodes begin when a patient enters the CLC to the time they were discharged (either to home or to a hospital for > 7 days, as determined by gaps in episodelets), or died. Death was determined by using the VA vital status file. All CLC episodes with a linked MDS admission assessment

occurring within the first 30 days of the episode were included (n= 200,333). It was possible for multiple episodes to be included over this time frame for a single Veteran.

These CLC episodes were further limited to include only residents who met at least one of three possible criteria for exhibiting LLE/AD at admission. The first criterion for LLE was endorsement of the single item available in both v2.0 (item J5c) and v3.0 (item J1400) of the MDS which asks providers to state whether or not they believe the nursing home resident has a life expectancy of six months or less. This indicator alone has been shown to accurately identify those who have poor prognosis and LLE, with sensitivity of 53.2%, and specificity of 88.4%.[52]

The second criterion for LLE was a score of ≥36 on the MDS Mortality Risk Index – Revised (MMRI-R). The MMRI-R is a tool which predicts the likelihood of 6-month mortality amongst nursing home residents, and was originally created from measures in the MDS version 2.0.[53] Possible scores range 0-85 points, based on a weighted total of the following MDS items: male sex (5 points), admission to a nursing home in the past 3 months (8 points), shortness of breath, poor appetite (4 points), weight loss unintentionally in the last 3 months (5 points), heart failure (4 points), renal failure (6 points), dehydrated (4 points), cancer (ranging from 2 to 20 point based on age at admission), and a short-form ADL scale (with higher scores indicating greater dependency). Higher scores on the MMRI-R indicate poorer prognosis and greater likelihood of death, with scores ≥36 showing sensitivity of 34.4% and specificity of 92.2% for predicting 6-month mortality in non-VA MDS v2.0 assessments.[53] Recently, the MMRI-R was adapted to be used with MDS version 3.0, as the newer version of the MDS form had revised the phrasing of several items used to calculate the MMRI-R score.[52] Although most item revisions were minor and did not change their intended meaning, two items were subject to more substantive revisions. In

version 2.0 the item used for change in mental status included "recent deterioration in cognitive status," while version 3.0 read "acute change in mental status." The item for poor appetite in version 2.0 read "leaves food uneaten" while in version 3.0 it read "poor appetite or overeating." However, recent research showed that using these revised MDS v3.0 items to calculate the MMRI-R score did not negatively impact the measure's predictive ability with regard to 6-month mortality, with the overall model using the continuous MMRI-R version 3.0 score showing good prediction with a c-statistic of 0.81.[52] In addition, sensitivity and specificity of the ≥36 cutoff for predicting 6-month mortality were 70.5% and 77.1%, respectively.[52]

The third criterion for LLE/AD consisted of a score on a cognitive assessment scale included in the MDS indicating advanced dementia. Both versions 2.0 and 3.0 of the MDS use different assessments of cognition. The MDS version 2.0 uses the Cognitive Performance Scale (CPS) with all residents. However, MDS version 3.0 uses the Brief Interview for Mental Status (BIMS) with residents who can complete an interview, and the CPS with residents who are unable to complete an interview. Both tools have been validated against the Mini-Mental Status Examination for identifying severe cognitive impairment indicative of advanced dementia in nursing home residents.[54-56] The CPS ranges from 0 to 6, with higher scores representing worse cognition, and conducted by a trained observer. For the current study, a CPS value of ≥4 was considered indicative of advanced dementia, based on prior evidence suggesting good sensitivity (84%) and specificity (67%) of this cutoff for identifying severe impairment.[56] The BIMS ranges from 0 to 15 with lower values representing worse cognition, and is conducted via a patient interview. For the current study, a value of 7 or less on the BIMS was considered indicative of advanced dementia, based on prior evidence suggesting 83% sensitivity and 92% specificity of this cutoff for identifying severe impairment.[54, 56]

Applying these criteria for LLE/AD resulted in identification of 81,273 residents with at least one of the three LLE/AD criteria at CLC admission. We then further limited the sample to episodes in which the Veteran was aged 65 or older at admission (n=61,137, 75%). Further restricting the sample to CLC episodes with a minimum length of stay of at least 7 days resulted in 58,782 (96%) episodes.

The last step in sample construction was to limit to episodes for Veterans with a history of coronary artery disease (CAD) and/or stroke/transient ischemic attack (TIA), and thus were considered eligible for use of aspirin for secondary prevention. The history of CAD and/or stroke/TIA was determined by searching the VA CDW utilization records and Medicare claims for ICD-9 diagnosis codes for these conditions, using validated algorithms from the Chronic Condition Data Warehouse, as well as MDS indicators for these conditions (CCW Ischemic Heart Disease; CCW Stroke/Transient Ischemic Attack). See table 1 for a complete list of codes used to determine history of CAD, stroke and TIA. The final sample for Aim 1 consisted of 37,165 newly admitted CLC residents aged ≥65 years with LLE/AD and history of CAD or stroke/TIA at admission.

Aim 2 analyses were further restricted to Veterans meeting the above criteria who had at least 14 days of follow-up available in the CLC after the first date on which aspirin use was observed, to assess for aspirin discontinuation (n=13,844). See Figure 2 for a summary of the sample construction process.

Table 1: Diagnostic Codes Used to Identify the Primary Cohort

	Diagnosis Code Algorithm		**MDS indicators**
Conditions	*Number/type of claims*	*ICD-9 Codes*	

Coronary Artery Disease	At least 1 of the following claim/encounter type in the 2 years prior to admission: • Medicare inpatient • Medicare SNF • Medicare home health • Medicare outpatient • Medicare carrier • VHA inpatient • VHA outpatient • VHA outpatient fee	DX 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.4, 414.8, 414.9 **(**any DX on the claim)	V2.0: I1d V3.0: I0400
Stroke/TIA	At least 1 of the following during the 1 year prior to admission date: • Medicare inpatient • VHA inpatient ***OR*** At least 2 of the following (on different dates) during the 1 year prior to admission date: • Medicare outpatient • Medicare carrier • VHA outpatient • VHA outpatient fee	DX 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02 (any DX on the claim)	V2.0: I1t or I1bb V3.0: I4500

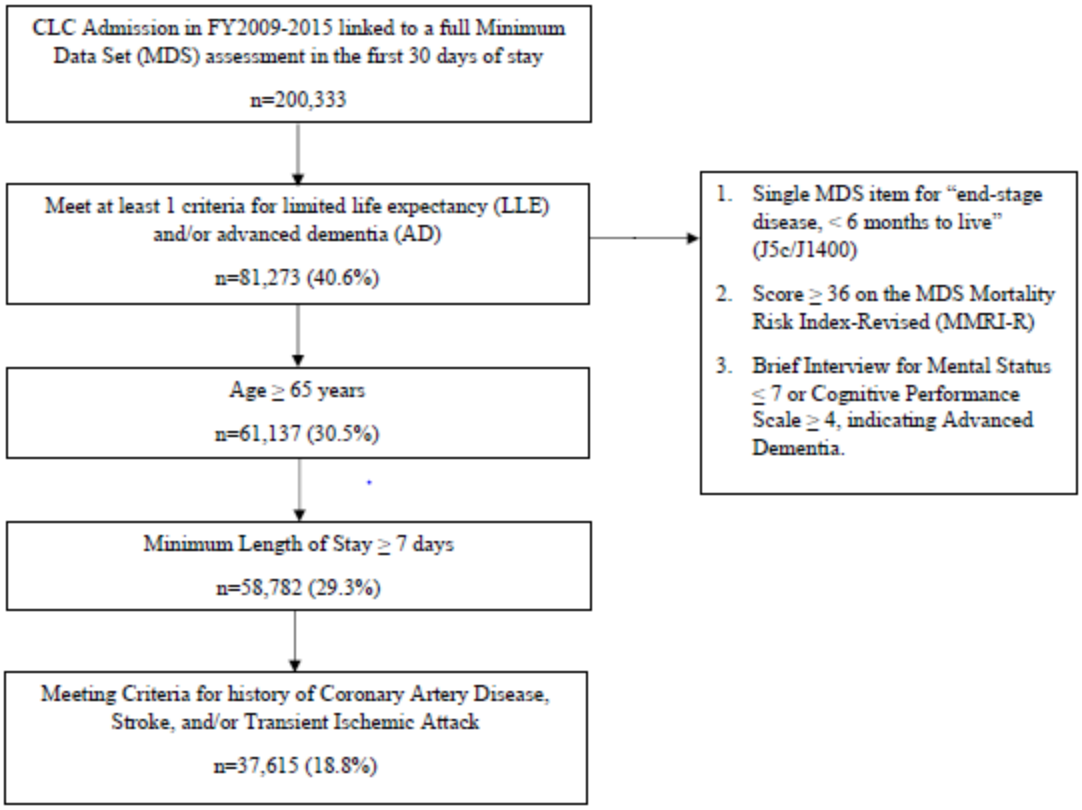

Figure 2: Cohort Construction for Aspirin Receipt

2.4 Aspirin User Definition

Aspirin use at admission was determined from BCMA records and was defined as having at least 1 day of aspirin use in the first 7 days of CLC episode with a total daily dose of 25-325 mg. We recognize that the recommended dose of aspirin is 50-325 mg in those with a history of stroke or TIA, and a total daily dose of 75-325 mg in those with a history of CAD.[4, 5] However, we ultimately decided to include those who received 25 mg of aspirin daily as aspirin users because of small numbers with this dosing, and to allow for missed or held dosages. The lower end of the

dose range of 25 mg was included to account for the use of aspirin/dipyridamole which contained 25 mg of aspirin per capsule and is dosed twice daily.[6, 57] The total daily dose of aspirin was calculated by adding all aspirin doses throughout the day that were administered. If a medication was not administered on that day (even if an order existed but no doses were actually recorded as given), the resident was not considered to be exposed to aspirin.

2.5 Aspirin Discontinuation

The aspirin discontinuation analysis was limited to the subgroup of Veterans who met criteria for initial aspirin use for secondary prevention in the first week of the CLC stay. Discontinuation of aspirin was defined as ≥14 consecutive days without aspirin use after the first day aspirin use was observed during the first week of the CLC stay. Veterans were followed for discontinuation until death, discharge, or day 91 of the CLC stay. Because the last 14 days of follow-up during this window consisted of "immortal time" in which it was not possible to observe a gap in aspirin use of 14 days, all Veterans were assigned either a censoring date equal to 14 days prior to death, discharge, or day 91 of the stay or a discontinuation date defined as the first day of the 14-day gap which qualified them for having discontinued therapy.

2.6 Covariates

A number of covariates were included to evaluate the patient-level and facility-level characteristics which were hypothesized according to our conceptual model as potential predictors

of use of aspirin for secondary prevention at CLC admission, and discontinuation of aspirin after CLC admission, respectively.

Socio-demographic factors:

Age at admission was calculated from the date of birth and admission date. Date of birth was pulled from MDS item AA3 from version 2.0 and A0900 from version 3.0. We subsequently categorized age into 3 categories for analysis: 65-74, 75-84 and ≥ 85 years. Sex was coded as a binary variable as either male or female, captured using MDS item AA2 and A0800 from version 2.0 and 3.0, respectively. Race and ethnicity were obtained from MDS items AA4 (v2.0) and A1000A-F (v3.0) and categorized into the following categories: white non-Hispanic, Black non-Hispanic, Hispanic, or other (consisting of American Indian, Alaska Native, Native Hawaiian, Pacific Islander or Asian). Marital status was obtained from MDS items A4 (v2.0) and A1200 (v3.0) and was categorized as married or not married (consisting of never married, widowed, separated, and divorced).

Environment of care factors:

Living arrangement before admission was determined using MDS items AB2 and A1800, from versions 2.0 and 3.0 respectively, and categorized as acute hospital, community (private home, board/care, assisted living, group home), nursing home, or other (psychiatric hospital, inpatient rehabilitation hospital, hospice, or other). Fiscal year of admission was based on the date of admission documented in the MDS, as noted above. Recent hospitalization was determined using Medicare claims data and VA claims data to determine a hospitalization that occurred within 90 days of the CLC admission. To capture caregiver factors, next-of-kin (NOK) information recorded in the VA electronic health record was abstracted from the VA CDW. This included the

relationship of the NOK to the Veteran (spouse, adult child, sibling, other relative, friend or other), as well the ZIP code for the NOK's home address. This ZIP code was then used to calculate the distance from the centroid of the NOK's ZIP code to the CLC, which was ascertained from the VA CDW. This continuous variable for distance was then categorized into quartiles of the distribution, first for the full study sample and then for the subsample of aspirin users at admission.

Cardiovascular risk factors:

These risk factors include chronic comorbidities which are associated with CVD, which include: diabetes, congestive heart failure, hypertension, hyperlipidemia, recent stroke, recent myocardial infarction (MI), recent venous thromboembolism (VTE), atrial fibrillation.[58-65] Comorbidities were obtained from CDW using ICD9/CPT4 codes as well as in the MDS. A full list of these comorbidities is included in table 2. For the purposes of this analysis, 1 year prior to CLC admission was used for the following variables as guidelines typically recommend continuation of aspirin for a least one year post-event, if aspirin is prescribed for these events: recent stroke, MI, VTE, hyperlipidemia, and atrial fibrillation.[5] Body mass index (BMI) was calculated using height and weight as recorded on the MDS, and was categorized as underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obese (>30 kg/m^2) based on World Health organization BMI categories.[66] Smoking status was obtained the MDS. In version 2.0, item AC1g asks if in the year prior to the date of entry to this nursing home, use of tobacco products was at least daily. In version 3.0, item J1300 asks if the resident is currently using tobacco. Both questions offered binary responses of yes or no.

Table 2: Diagnostic Codes and Algorithms for Cardiovascular Risk factors and History of Falls and Fractures

	Diagnosis Code Algorithm		**MDS indicators**
Conditions	*Number/type of claims*	*ICD-9/CPT4/HCPCS Codes*	
Diabetes	At least 1 of the following during the 2 years prior to admission date: • Medicare inpatient • Medicare SNF • Medicare home health • VHA inpatient ***OR*** At least 2 of the following (on different dates) during the 2 years prior to admission date: • Medicare outpatient • Medicare carrier • VHA outpatient • VHA outpatient fee	DX 249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41 **(any DX on the claim)**	V2.0: I1a V3.0: I2900
Hypertension	At least 1 of the following during the 1 year prior to admission date: • Medicare inpatient • Medicare SNF • Medicare home health • VHA inpatient ***OR*** At least 2 of the following (on different dates) during the 1 year prior to admission date: • Medicare outpatient • Medicare carrier • VHA outpatient • VHA outpatient fee	DX 362.11, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2 **(any DX on the claim)**	V2.0: I1h V3.0: I0700
Hyperlipidemia	**From CCW:**		

	272.0, 272.1, 272.2, 272.3, 272.4; any DX on the claim; at least 1 from the following: Medicare inpatient Medicare SNF Medicare home health VHA inpatient (including fee) OR At least 2 of the following: Medicare outpatient Medicare carrier VHA outpatient (including fee) Lookback period is 1 year prior to episode start		
Atrial fibrillation	**From CCW:** 427.31 (only 1st or 2nd DX on the claim) At least 1 from the following: Medicare inpatient VHA inpatient (including fee) OR At least 2 of the following: Medicare outpatient Medicare carrier VHA outpatient (including fee) Lookback period is 1 year prior to episode start		
History of Venous thromboembolism	Patient has the condition if they have at least one code in any position in any of the following files: Medicare inpatient VHA inpatient Medicare outpatient Medicare carrier VHA outpatient (including fee) Lookback period is 1 year prior to episode start	415.x (for PE, would include 415, 415.0, 415.1, 451.11, 415.12, 415.13, 415.19), 451.x and 453.x (DVT, would include: 415, 451.0, 451.1, 451.11, 451.19, 451.2, 451.8, 451.81, 451.82, 451.83, 451.84, 451.89, 451.9, 453, 453.0, 453.1, 453.2, 453.3, 453.4, 453.40, 453.41, 453.42, 453.5, 453.50, 453.51, 453.52, 453.6, 453.7, 453.71, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 453.8, 453.81, 453.82, 453.83, 453.84,	

		453.85, 453.86, 453.87, 453.89, 453.9)	
History of Falls, hip fractures or other fractures	A) Has one of the following ICD-9 diagnosis codes (E880-888, 820) or ICD-9 procedure codes (7855, 7905, 7915, 7925, 7935, 7965) or CPT codes (27227, 27228, 27230, 27232, 27234,-27236, 27238, 27240, 27242, 27244-27246, 27248. These codes must be in emergency room visits and/or hospitalizations in Medicare Part A and B claims or VHA CDW in the year prior to admission		J4a=1 or J4b=1 or J4c = 1 on MDS 2.0 OR J1700A=1 or J1700B=1 or J1700C=1 or J1800=1 on MDS 3.0
Recent myocardial infarction	At least 1 inpatient claim in VHA or Medicare in year prior to admission with DX 410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91 **(ONLY first or second DX on the claim)**		
Recent stroke/TIA	At least 1 inpatient or 2 outpatient/carrier claims in VHA or Medicare in year prior to admission with DX 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02 **(any DX on the claim)** ***EXCLUSION:*** *If any of the qualifying claims have: 800 <= DX Code <= 804.9, 850 <= DX Code <= 854.1 in any DX position* ***OR*** *DX V57xx* ***as the principal DX Code, then EXCLUDE.***		

Markers of poor prognosis:

Fall history was determine by indicators on the MDS or available in CDW and Medicare utilization data in the last 180 days prior to CLC admission. In MDS version 2.0, the item was J4a-

c, while version 3.0 utilized item J1700A-C and item J1800. ICD9 codes are included in table 2, along-side ICD9 and MDS codes for cardiovascular risk factors.[67, 68] Variables that can be indicative of poor prognosis were determined using MDS (in version 2.0 and version 3.0, respectively) and include: history of cancer (I1PP and I0100), swallowing problems (K1B and K0100A-D), IV tube feeding (K5B and K0500A), mechanical diets (K5C and K0500C), food left uneaten or poor appetite (K4C and D0200E2), recent weight loss (K3A and K0300), shortness of breath (J1L and J1100A-C), recent changes in cognitive status (B6 and C1600), dehydration (J1C and J1550C), renal insufficiency (I1QQ and I1500), and pain at admission (J2A and J0300).

Behavioral problems were assessed using the Aggressive Behavior Scale[69], which is based on the sum of 4 MDS items (verbally abusive [E4Ab/E0200B]; physically abusive [E4Ac/E0200A]; socially inappropriate/disruptive behavior [E4Ad/E0200C]; resists care [E4Ae/E0800]). Possible scores can range from 0 to 12 and are categorized into 4 categories: 0 (no behavioral problems), 1-2 (moderate problems), 3-5 (severe problems), >5 (very severe problems). Dependency in activities of daily living (ADLs) was assessed using the ADL-short form[70] and was scored by using the mean value of four ADLs item included on the MDS (toilet use, personal hygiene, eating and locomotion on unit), with higher scores indicating higher level of dependence. Continuous scores were categorized as 0 to < 1, ≥1 to <2 , ≥ 2 to <3 , ≥ 3 to < 4, and 4 for analysis.

At admission to the CLC, whether or not a patient is documented as being near the end of life may be documented in several ways: 1) endorsement on the admission MDS of item J5c/J1400 for “end-stage disease, less than 6 months to live”; 2) indication on the admission MDS of hospice use within the past 14 days (endorsement of item P1Ao in MDS 2.0 and either item O0100K1 or O0100K2 in MDS 3.0), and/or 3) admission to a hospice bed within the CLC, as indicated in the

VA CDW treating specialty movement files. As such, we created one summary variable that was coded as yes if any of these criteria were met and no if no criteria were met. Finally, total comorbidity burden was assessed using the Elixhauser comorbidity index which assesses the presence/absence of 30 conditions.[71] We created a variable representing the total number of Elixhauser conditions, excluding diabetes and diabetes with complications, and hypertension and hypertension with complications, as diabetes and hypertension were already captured using established claims-based algorithms, as described above. We then categorized this count into the following categories: 0-1, 2-3, 4-5, or $\geq$ 6 comorbid conditions.

Facility level characteristics:

Facility level factors included staff turnover rates, facility bed size, facility complexity, U.S census region, and rurality of the CLC. Facility bed size, health care provider turnover rates, and facility complexity were all obtained from VSSC website and linked to CLC episodes using VHA parent station identifiers and FY of admission. VSSC data is captured at the VHA parent station level, and there can be more than one CLC per parent station. Thus, patients at two different CLCs, with the same parent station, could have the same values available, even though they were in two different CLCs. Bed size and facility complexity level was available for FY11 and FY14 only, so CLC episodes were assigned a bed size and complexity level using the closest value available in time (i.e., residents admitted in FY09-11 were assigned the bed size and complexity level of the facility as determined at FY11, and residents in FY12-15 were assigned the bed size and complexity level of the facility in FY14). Turnover rates were available for FY11-15, thus turnover rates for FY09-11 were assumed to be the same as the FY11 value; and FY11-15 were matched to their appropriate turnover rate. This continuous variable for turnover rate was categorized by

quartiles of the distribution, first for the full study sample and then for the subsample of aspirin users at admission.

Bed size was transformed from a continuous variable to a categorical variable (<60 beds, 60-120 beds, >120 beds per facility) for analysis. Facility complexity level range from 1a to 3 by level of complexity. Complexity level 1a includes facilities with the largest levels of volume, patient risk, teaching and research, number and breadth of physician specialists, and level 5 intensive care units (ICUs). ICU levels range from 1 to 5, where high levels represent more complex ICUs. Complexity level 1b include facilities with large levels of volume, patient risk, teaching and research, and level 4 and 5 ICUs. Complexity level 1c facilities are similar to level 1b, however they only have level 4 ICUs. Complexity level 2 facilities have medium level volumes, patient risk, teaching and research activities, and level 3 and 4 ICUs. Complexity level 3 facilities include the lowest level of patient complexity, smallest level of volume, little or no teaching or research activities, lowest numbers and breadth of physician specialists, and level 1 or 2 ICUs. Census region from which the CLC was located, and urban influence code, which is a measure of rurality, were obtained by linking the zip code from the CLC to external data from the US census and the Area Health Resource File, respectively.[72, 73]

Bleeding risk factors

For this study, variables for use of medications which increase or decrease the risk of bleeding outcomes are included. Medications which were prescribed on the first or second day of the CLC admission were included and obtained from BCMA data. Medications include: anti-thrombotic agents, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and H2-receptor antagonists. Originally, we had planned to assess use of COX-2 inhibitors and

gastrointestinal protective agents at baseline (due to possible effects on bleeding risk) but too few individuals were observed to be taking these medications to include in the final analysis. With such small numbers, it is very difficult to assess the effect of a variable on an outcome where the variation is incredibly small, and there is also concern for privacy when values are <11.

2.7 Statistical Analysis

Descriptive statistics were used to determine the frequency of aspirin use and frequencies of covariates amongst the entire cohort. Descriptive statistics were also used to describe the frequency of covariates amongst those taking aspirin at admission who were followed for subsequent aspirin discontinuation. For all covariates with missing values, hotdeck imputation was used to impute values for those missing variable values.[74] Those imputed variable values were used as covariates in all analysis moving forward, and differences in variable distributions can be seen on table 1.

For Aim 1, the dependent variable is aspirin use at admission, which is defined as a binary outcome (yes/no) indicating any receipt of aspirin in the dosing range in the first 7 days of CLC visit. Univariable and multivariable logistic regression models were estimated to determine the variables significantly associated with higher or lower odds of aspirin use in the first week of the CLC, providing unadjusted and adjusted estimates, respectively. In all cases, clustering at the facility level was accounted for; this adjusted the standard error to account for intragroup correlation at the parent station (facility) level.

For Aim 2, the dependent variable was aspirin discontinuation, as previously described above. A cumulative incidence competing risk (CICR) method was used to determine the probability of an event (i.e., deprescribing) prior to censoring. First this was done to determine the overall incidence of aspirin discontinuation, and secondarily was performed using an indicator for "documentation of limited prognosis at admission" (as described previously) as the primary independent variable, to determine if the hazard of discontinuing was different between those with positive indicator of limited prognosis versus those without this indicator, adjusting for all other variables in the model. This was done to determine if the knowledge that one has limited life expectancy or the treating specialty of hospice modifies the relationship of patient and facility factors to deprescribing. Palliative care and hospice care is significantly different than non-hospice/palliative care. Most guidelines which recommend against potentially inappropriate medication (i.e., Beers Criteria, STOPP/START) explicitly indicate that the guidelines do not pertain to those on hospice or palliative care given differences in goals of care.[75-77] It is thus plausible that the likelihood of aspirin discontinuation may vary amongst those who have explicit documentation of limited prognosis versus those who do not.

Survival analysis allowing for the competing risk of death was chosen due to the high risk of death in these population (n=2,524, 18% of the qualifying cohort for discontinuation were censored due to death prior to CLC discharge), given that everyone in this cohort qualified as having LLE and/or advanced dementia (AD). Death is thus a competing risk, and using the CICR method has been shown to be more robust to differences in the outcome of interest over time than the Kaplan Meier approach. Death was the only censoring point used as a competing risk, because once someone has died, they are no longer eligible to be discontinued, and no longer have the same

probability of discontinuation as someone who remained in the study. Alternatively, being discharged from the CLC or reaching the end of the allotted study period does not compete with discontinuation, as discontinuation can occur after the discharge or at the end of the study period.[78] Standard survival analysis assumes that once a patient has been censored, they otherwise would still be at the same risk of the event (in this case deprescribing of aspirin), had they not been censored. Noordzij, et al recommend that in the event of a prognostic research aims (i.e., that you are predicting the probability of an outcome at a given time), such as in the case of this research, one should not conduct unadjusted analysis using Kaplan-Meier approach when competing risks occur because the independent censoring assumption is violated (patients will not be at the same risk of deprescribing if they die versus those who do not die and experience another competing event such as discharge from the CLC). Instead, one should use the CICR method to determine the probability of discontinuation before time, t. The rationale here is that Kaplan-Meier methods can often overestimate both the event of interest (discontinuation) and the competing risk while event-free survival (i.e. probability of not being discontinued) remains unbiased.

The CICR method was thus used to determine the cumulative incidence of discontinuation, with and without stratification by hospice status. The program was set to indicate discontinuation as the event of interest, and the competing risk was death. We subsequently modeled the unadjusted and adjusted associations of each covariate described above using Fine and Gray competing risk subdistribution hazard models.[79] All standard errors were adjusted for intragroup correlation at the parent station level by adding the parent station as a cluster variable. The outcome of a CICR method is not a hazard ratio, as is the output for Cox proportional hazard models, but instead subdistribution hazard ratios (SDHR). An interaction term of time was used to test the assumption of proportional hazards. This test is determining if the effect of the variable of interest

changes over time. In the event of violations of proportional hazards, the reporting of SDHRs will indicate an average effect of that variable on the hazard of discontinuation, as opposed to an instantaneous incidence of the event. Below, we report both unadjusted SDHRs as well as SDHRs adjusted for all other variables in the model, first for the entire discontinuation sample and then after stratifying this sample by the indicator of documentation of limited prognosis/hospice at admission, as described previously.

2.8 Sensitivity Analysis

We conducted a supplemental analysis to determine the sensitivity of our results to the length of the gap in aspirin use chosen to define discontinuation of therapy. Specifically, we conducted sensitivity analysis using a longer gap in therapy to define discontinuation, that is, ≥ 30 consecutive days without aspirin therapy rather than ≥14 days. In the sensitivity analysis, the Veterans were censored at either the new definition of aspirin discontinuation, 30 days before discharge from CLC, 30 days before death, and at day 91 of the CLC episode. The same statistical analysis approach was completed for the sensitivity analysis. Thirty days was chosen as the alternative gap length because this is commonly used when measuring discontinuation to medications when prescription refill records are available rather than daily BCMA data.[80-82]

3.0 Results

3.1 Demographics of Overall Sample

A total of 37,165 older Veterans qualified for this sample by having LLE/AD and either CAD or a history of stroke/TIA. Descriptive characteristics of the sample are shown in Table 1, before and after imputation of missing values. The cohort was predominantly male (98%), white, non-Hispanic (78%), and ≥75 years of age (73%). A majority of the cohort came from an acute hospital prior to their CLC admission (68%), and qualified as having LLE by a MMRI score of ≥36 (77%). A majority of the cohort had only one qualifying physical condition (CAD/Stroke/TIA) (78%) – of which CAD was the predominant qualifying condition (88%). Approximately 44% had some documentation of limited prognosis or hospice use at admission. This included 39% of the sample had an endorsement on the admission MDS of "end-stage disease, less than 6 months to live", and 32% of the sample were admitted to a hospice treating specialty in the 14 days prior to admission (data not shown in table). In addition, about 37% had received palliative care or a hospice consult in the year prior to their CLC admission. The most common comorbidities included diabetes (50%), congestive heart failure (46%), hypertension (92%), hyperlipidemia (67%), and cancer (38%), and over a third (38%) had >5 Elixhauser conditions. A majority of the cohort had no history of smoking (90%), and 43% had a normal BMI. Falls and fractures in the 180 days prior to admission were common, occurring in 46% of the sample. About 13% were prescribed an additional anti-platelet (other than aspirin), 42% were prescribed an anti-thrombotic agent, and almost half were prescribed a proton pump inhibitor at CLC admission (48%).

Table 3. Baseline Characteristics of Older Adult Veterans in the Community Living Center.

	Full Sample (N= 37,165)	Full Sample with Imputed Variables (N=37,165)
Demographics	**n (%)**	**n (%)**
Age at admission		
65-74	10,138 (27.3)	10,138 (27.3)
75-84	14,116 (38.0)	14,116 (38.0)
≥85	12,911 (34.7)	12,911 (34.7)
Sex		
Male	36,610 (98.5)	36,610 (98.5)
Female	555 (1.5)	555 (1.5)
Race/ethnicity		
White	29,117 (78.4)	29,314 (78.9)
Black	5,362 (14.4)	5,395 (14.5)
Hispanic	1,801 (4.9)	1,814 (4.9)
Other	636 (1.7)	642 (1.7)
Missing	249 (0.7)	-
Marital status		
Married	18,155 (48.9)	18,167 (48.9)
Not married	18,986 (51.1)	18,998 (51.1)
Missing	24 (0.06)	-
Environment of Care Factors		
Fiscal year of admission		
2009	4,755 (12.8)	4,755 (12.8)
2010	4,904 (13.2)	4,904 (13.2)
2011	5,162 (13.9)	5,162 (13.9)
2012	5,286 (14.2)	5,286 (14.2)
2013	5,724 (15.4)	5,724 (15.4)
2014	5,742 (15.5)	5,742 (15.5)
2015	5,592 (15.0)	5,592 (15.0)
Living arrangement before admission		
Acute hospital	25,143 (67.7)	25,144 (67.7)
Community	9,074 (24.4)	9,075 (24.4)
Nursing home	1,932 (5.2)	1,932 (5.2)
Other	1,014 (2.7)	1,014 (2.7)
Missing	2 (0.01)	-
Hospitalization in 90 days prior to admission	21,728 (58.5)	21,728 (58.5)
Next of kin relationship to the Veteran		
Spouse	15,031 (40.4)	15,038 (40.5)
Child	15,296 (41.1)	15,302 (41.2)
Sibling	3,290 (8.9)	3,290 (8.9)
Other relative	1,594 (4.3)	1,596 (4.3)

Friend or other specified person of unknown relation	1,939 (5.2)	1,939 (5.2)
Missing	15 0.04)	-
Distance from next of kin ZIP code centroid to the CLC		
Quartile 1	8,969 (24.1)	9,288 (25.0)
Quartile 2	8,969 (24.1)	9,317 (25.1)
Quartile 3	8,967 (24.1)	9,265 (24.9)
Quartile 4	8, 968 (24.1)	9,295 (25.0)
Missing	1,292 (3.5)	-
Cardiovascular Risk Factors		
Number of qualifying conditions (CAD, stroke/TIA)		
1	28,942 (77.9)	28,942 (77.9)
2	8,223 (22.1)	8,223 (22.1)
Diabetes	18,530 (49.9)	18,530 (49.9)
Congestive heart failure	17,245 (46.4)	17,245 (46.4)
Hypertension	34,068 (91.7)	34,068 (91.7)
Hyperlipidemia	24,706 (66.5)	24,706 (66.5)
Venous thromboembolism	5,087 (13.7)	5,087 (13.7)
Atrial fibrillation last year	7,012 (18.9)	7,012 (18.9)
Recent Myocardial Infarction in the last year	2,120 (5.7)	2,120 (5.7)
Recent Stroke in the last year	9,845 (26.5)	9,845 (26.5)
Current Smoker		
No	33,459 (90.0)	34,148 (91.9)
Yes	2,950 (7.9)	3,017 (8.1)
Missing	756 (2.0)	-
Body Mass Index (kg/m^2)		
Normal or healthy weight (18.5 to <25.0)	16,135 (43.4)	16,718 (45.0)
Underweight (<18.5)	3,595 (9.7)	3,712 (10.0)
Overweight (25.0 to <30.0)	9,843 (26.5)	10,221 (27.5)
Obese (≥30)	6,285 (16.9)	6,514 (17.5)
Missing	1,307 (3.5)	-
Markers of Poor Prognosis		
Advanced dementia	13,155 (35.4)	13,155 (35.4)
Documentation of limited prognosis or hospice use at admission	16,394 (44.1)	16,516 (44.4)
Number of Elixhauser conditions		
0-1	2,986 (8.0)	2,986 (8.0)
2-3	8,746 (23.5)	8,746 (23.5)
4-5	11,184 (30.1)	11,184 (30.1)
>5	14,249 (38.3)	14,249 (38.3)
Recent weight loss	14,571 (39.2)	14,571 (39.2)
Leaves food uneaten	16,296 (43.8)	16,296 (43.8)
Renal failure	6,679 (18.0)	6,679 (18.0)

Dehydration	559 (1.5)	559 (1.5)
Acute change in mental status	4,600 (12.4)	4,600 (12.4)
Shortness of breath	14,398 (38.7)	14,398 (38.7)
Cancer	14,371 (38.7)	14,371 (38.7)
Activities of Daily Living (ADL) score		
0 - <1	3,630 (9.8)	3,630 (9.8)
1 to <2	7,387 (19.9)	7,387 (19.9)
2 to <3	11,236 (30.2)	11,236 (30.2)
3 to <4	9, 488 (25.5)	9, 488 (25.5)
4	5,424 (14.6)	5,424 (14.6)
Aggressive Behavior		
None	30,518 (82.1)	30,872 (83.1)
Moderate	4,031 (10.9)	4,077 (11.0)
Severe	1,640 (4.4)	1,652 (4.5)
Very severe	560 (1.5)	564 (1.5)
Missing	416 (1.1)	-
IV feeding tube in place	3,572 (9.6)	3,572 (9.6)
On Mechanical Diet	16,036 (43.2)	16,036 (43.2)
Swallowing Problems	7,773 (20.9)	7,773 (20.9)
Presence of any pain (n, % yes)		
Yes	24,573 (66.1)	26, 275 (70.7)
No	10,204 (27.5)	10,890 (29.3)
Missing	2,388 (6.4)	-
History of falls, hip fracture, and other fractures in past 180 days		
Yes	17,216 (46.3)	17,709 (47.7)
No	18,981 (51.1)	19,456 (52.4)
Missing	968 (2.6)	-
Facility Factors		
US Census region of the CLC		
Northeast	6,381 (17.2)	6,381 (17.2)
Midwest	10,762 (29.0)	10,762 (29.0)
South	13,024 (35.0)	13,024 (35.0)
West	6,998 (18.8)	6,998 (18.8)
Urban Influence Code for the CLC		
Large metro	16,935 (45.6)	16,935 (45.6)
Small metro	13,269 (35.7)	13,269 (35.7)
Micropolitan	2,938 (7.9)	2,938 (7.9)
Noncore rural	4,023 (10.8)	4,023 (10.8)
Complexity Level of the parent station		
1a (Highest)	14,003 (37.8)	14,042 (37.8)
1b	4,553 (12.3)	4,560 (12.3)
1c	6,934 (18.7)	6,933 (18.7)
2	5,039 (13.6)	5,049 (13.6)
3 (Least Complex)	6,564 (17.7)	6,581 (17.7)
Missing	82	-

Bed Size of CLC		
<60 beds	15,715 (15.4)	15,715 (15.4)
60-120 beds	13,495 (36.3)	13,495 (36.3)
>/= 120 beds	17,955 (48.3)	17,955 (48.3)
Physician turnover rate		
Quartile 1	9,306 (25.0)	9,306 (25.0)
Quartile 2	9,652 (26.0)	9,652 (26.0)
Quartile 3	8,952 (24.1)	8,952 (24.1)
Quartile 4	9,255 (24.9)	9,255 (24.9)
Nurse turnover rate		
Quartile 1	9,427 (25.4)	9,427 (25.4)
Quartile 2	9,165 (24.7)	9,165 (24.7)
Quartile 3	9,427 (25.4)	9,427 (25.4)
Quartile 4	9,146 (24.6)	9,146 (24.6)
Pharmacist turnover rate		
Quartile 1	9,337 (25.1)	9,337 (25.1)
Quartile 2	9,350 (25.2)	9,350 (25.2)
Quartile 3	9,193 (24.7)	9,193 (24.7)
Quartile 4	9,285 (25.0)	9,285 (25.0)
Practical nurse turnover		
Quartile 1	9,316 (25.1)	9,316 (25.1)
Quartile 2	9,270 (24.9)	9,270 (24.9)
Quartile 3	9,325 (25.1)	9,325 (25.1)
Quartile 4	9,254 (24.9)	9,254 (24.9)
Psychology Turnover		
Quartile 1	9,443 (25.4)	9,443 (25.4)
Quartile 2	9,225 (24.8)	9,225 (24.8)
Quartile 3	9,239 (24.9)	9,239 (24.9)
Quartile 4	9,258 (24.9)	9,258 (24.9)
Medications Prescribed Which May Impact Aspirin Prescribing		
Anti-platelet	4,750 (12.8)	4,750 (12.8)
Anti-thrombotic Agents	15,690 (42.2)	15,690 (42.2)
H2- Receptor Antagonists	3,461 (9.3)	3,461 (9.3)
Proton Pump Inhibitors	17,993 (48.4)	17,993 (48.4)
NSAIDs	1,251 (3.4)	1,251 (3.4)

3.2 Aspirin Use in the Overall Sample

Aspirin was received by 48% of the sample during the first week of the CLC stay (N=17,973). A majority of the sample who met criteria for initial aspirin use did so on day 1 (54%)

or day 2 (38%) of the CLC stay (Table 4). The most commonly prescribed dose of aspirin for secondary prevention in the first 7 days of CLC admission was 81 milligrams, prescribed in 72% of the overall sample, including 77% of those with CAD only, 58% of those with stroke/TIA only, and 65% of those with both CAD and stroke/TIA (Table 5).

Table 4: Date of Community Living Center (CLC) Stay When Aspirin was Prescribed and Met Criteria for Secondary Prevention

CLC day	N = 17,973 (%)
1	9,762 (54.3)
2	6,770 (37.7)
3	965 (5.4)
4	179 (1.0)
5	129 (0.7)
6	87 (0.5)
7	81 (0.5)

Table 5: Aspirin Dosing on the Index Date by Diagnosis Amongst Aspirin User

Aspirin Dose (mg)	Total Cohort N= 17,973 (%)	CAD only N = 11,751 (%)	Stroke/TIA only N= 1,856 (%)	CAD and Stroke/TIA N= 4,366 (%)
25 to < 81	704 (3.9)	114 (1.0)	232 (12.5)	358 (8.2)
81	12,932 (72.0)	9,013 (76.7)	1,073 (57.8)	2,846 (65.2)
>81 to <162	113 (0.6)	20 (0.2)	27 (1.5)	66 (1.5)
162	384 (2.1)	254 (2.2)	36 (1.9)	94 (2.2)
>162 to <325	123 (0.7)	58 (0.5)	20 (1.1)	45 (1.0)
325	3717 (20.7)	2,292 (19.5)	468 (25.2)	957 (21.9)

3.3 Factors Predicting Receipt of Aspirin for Secondary Prevention of Cardiovascular Disease

Results of the univariable and multivariable logistic regression models are shown in Table 6. As the goal of this analysis is to identify factors significantly associated with initial aspirin use at admission, independent of all other factors, we highlight the results from the fully adjusted multivariable model here. Amongst the demographic factors associated with aspirin receipt, age ≥85 years was associated with higher odds of aspirin receipt (aOR 1.11, 95% CI 1.03-1.19), and female sex (aOR 0.73, 95% CI 0.60-0.89) and Hispanic ethnicity (aOR 0.75, 95% CI 0.61-0.92) were associated with lower odds of aspirin receipt. The only environment of care factor associated with higher odds of aspirin receipt included having a friend or other specified person of unknown relation as the NOK opposed to a spouse as the NOK (aOR, 1.16, 95% CI 1.01-1.34). A number of cardiovascular risk factors were associated with higher odds of aspirin receipt, including having both qualifying conditions (CAD and stroke/TIA) (aOR 1.17, 95% CI 1.09-1.26), diabetes (aOR 1.10, 95% CI 1.05-1.16), congestive heart failure (aOR 1.36, 95% CI 1.27-1.45), hypertension (aOR 1.24, 95% CI 1.13-1.36), hyperlipidemia (aOR 1.21, 95% CI 1.14-1.28), a recent myocardial infarction (aOR 1.99, 95% CI 1.79-2.22), and being a current smoker (aOR 1.17, 95% CI 1.08-1.26). Cardiovascular risk factors associated with lower odds of aspirin receipt included having a VTE in the year prior to CLC admission (aOR 0.67, 95% CI 0.62-0.72), having a diagnosis of atrial fibrillation (aOR 0.84, 95% CI 0.78-0.90), and being underweight versus normal or health weight (aOR 0.90, 95% CI 0.83-0.98).

Several markers of poor prognosis were associated with lower odds of aspirin receipt at admission, including documentation of limited prognosis or hospice use at admission (aOR 0.51, 95% CI 0.48-0.55), receipt of palliative care consult or hospice care in year prior to admission

(aOR 0.83, 95% CI 0.78-0.88), having 5 or more Elixhauser comorbidities versus 0-1 comorbidities (aOR 0.88, 95% CI 0.79-0.97), recent weight loss (aOR0.94, 95% CI 0.89-0.99), leaving food uneaten (aOR, 0.93, 95% CI 0.87-0.99), dehydration noted on MDS (aOR 0.80, 95% CI 0.68-0.95), cancer (aOR 0.75, 95% CI 0.71-0.79), requiring an intravenous feeding tube (aOR 0.88, 95% CI 0.81-0.95), ADL score of 3 to <4 (aOR 0.85, 95% CI 0.78-0.92) or 4 (aOR 0.71, 95% CI 0.64-0.79) versus 0 to <1, and pain documented on admission (aOR 0.92, 95% CI 0.87-0.97). Shortness of breath documented on admission (aOR 1.07, 95% CI 1.02-1.13) and having severe behavioral issues (aOR 1.20, 95% CI 1.09-1.31) or very severe behavioral issues (aOR 1.23, 95% CI 1.03-1.47) versus no aggressive behaviors documented at admission were associated with higher odds of aspirin receipt

Amongst facility level factors, receiving care the West (aOR 0.80, 95% CI 0.68-0.93) versus the Northeast, and residing in a complexity level 2 versus 1a facility (aOR 0.88, 95% CI, 0.77-1.00) were facility level factors associated with lower odds of receipt of aspirin. Facility factors associated with higher odds of aspirin receipt included being cared for in a small metropolitan area (aOR 1.13, 95% CI 1.02-1.25) or a micropolitan area (aOR 1.16, 95% CI 1.05-1.29) versus a large metropolitan area.

In addition, current use of other medications at admission that might modify the effectiveness or safety of aspirin use was also associated with higher odds of aspirin use, including being prescribed another anti-platelet agent (aOR 1.92, 95% CI 1.77-2.09), anti-thrombotic agent (aOR 1.35, 95% CI 1.25-1.46), H2-Receptor agonist (aOR 1.27, 95% CI 1.17-1.38), proton pump inhibitor (aOR 1.23, 95% CI 1.17-1.29) or NSAID (aOR 1.15, 95% CI 1.01-1.31). See table 6 below for all results, and figures 3 and 4 for tornado plots which display factors predicting higher and lower odds of aspirin receipt, respectively.

Table 6: Unadjusted and Adjusted Odds of Aspirin Receipt for Secondary Prevention of Cardiovascular Disease

	Unadjusted	Adjusted
Demographics	**OR (95% CI)**	**OR (95% CI)**
Age at admission		
65-74	Ref	Ref
75-84	1.03 (0.97-1.09)	1.05 (0.99-1.11)
≥85	1.04 (0.98-1.11)	1.11 (1.03-1.19)**
Sex		
Female	0.65 (0.54-0.78)**	0.73 (0.60-0.89)**
Race/ethnicity		
White	Ref	Ref
Black	1.00 (0.91-1.10)	1.02 (0.93-1.11)
Hispanic	0.68 (0.51-0.91)**	0.75 (0.61-0.92)**
Other	1.02 (0.81-1.28)	1.11 (0.90-1.37)
Marital status		
Married	1.00 (0.95-1.05)	0.98 (0.91-1.07)
Environment of Care Factors		
Fiscal year of admission		
2009	Ref	Ref
2010	0.99 (0.91-1.07)	1.02 (0.94-1.11)
2011	0.97 (0.90-1.04)	0.99 (0.91-1.06)
2012	1.00 (0.91-1.10)	0.98 (0.89-1.09)
2013	0.98 (0.89-1.08)	0.91 (0.82-1.01)
2014	1.01 (0.93-1.11)	0.95 (0.85-1.06)
2015	0.93 (0.86-1.01)	0.86 (0.77-0.96)*
Living arrangement before admission		
Acute hospital	Ref	Ref
Community	0.95 (0.88-1.02)	1.02 (0.95-1.08)
Nursing home	0.89 (0.78-1.00)	1.05 (0.95-1.16)
Other	0.71 (0.60-0.84)**	0.93 (0.81-1.06)
Hospitalization in 90 days prior to admission	1.00 (0.96-1.05)	1.00 (0.95-1.05)
Next of kin relationship to the Veteran¥		
Spouse	Ref	Ref
Child	1.04 (0.99-1.10)	1.05 (0.97-1.13)
Sibling	0.98 (0.89-1.07)	1.03 (0.92-1.15)
Other relative	1.00 (0.90-1.12)	1.06 (0.93-1.20)
Friend or other specified person of unknown relation	1.14 (1.02-1.28)*	1.16 (1.01-1.34)*
Distance from next of kin ZIP code centroid to the CLC¥		

Quartile 1	Ref	Ref
Quartile 2	1.02 (0.95-1.09)	1.01 (0.94-1.07)
Quartile 3	1.03 (0.96-1.10)	0.95 (0.90-1.02)
Quartile 4	1.17 (1.09-1.26)**	1.06 (0.99-1.13)
Cardiovascular Risk Factors		
Number of qualifying conditions (CAD, stroke/TIA, and/or diabetes)		
1	Ref	Ref
2	1.28 (1.21-1.35)**	1.17 (1.09-1.26)**
Diabetes	1.31 (1.24-1.38)**	1.10 (1.05-1.16)**
Congestive heart failure	1.51 (1.43-1.60)**	1.36 (1.27-1.45)**
Hypertension	1.59 (1.45-1.74)**	1.24 (1.13-1.36)**
Hyperlipidemia	1.39 (1.32-1.47)**	1.21 (1.14-1.28)**
Venous Thromboembolism	0.70 (0.66-0.75)**	0.67 (0.62-0.72)**
Atrial Fibrillation	0.97 (0.90-1.04)	0.84 (0.78-0.90)**
Recent stroke	1.07 (1.01-1.14)*	0.94 (0.87-1.01)
Recent MI	2.38 (2.15-2.62)**	1.99 (1.79-2.22)**
Current Smoker	1.10 (1.02-1.19)*	1.17 (1.08-1.26)**
Body Mass Index		
Normal or healthy weight (18.5 to <25.0)	Ref	Ref
Underweight (<18.5)	0.74 (0.68-0.80)**	0.90 (0.83-0.98)*
Overweight (25.0 to <30.0)	1.15 (1.10-1.21)**	1.00 (0.95-1.06)
Obese (≥30)	1.37 (1.28-1.47)**	1.03 (0.97-1.10)
Factors indicating limited prognosis		
Documentation of limited prognosis or hospice use at admission	0.36 (0.34-0.39)**	0.51 (0.48-0.55)**
Receipt of a palliative care consult or hospice care in year prior to admission	0.50 (0.47-0.53)**	0.83 (0.78-0.88)**
Number of Elixhauser conditions		
0-1	Ref	Ref
2-3	1.01 (0.93-1.10)	1.00 (0.91-1.09)
4-5	0.99 (0.89-1.09)	0.91 (0.82-1.02)
>5	1.04 (0.95-1.14)	0.88 (0.79-0.97)*
Advanced dementia	0.89 (0.84-0.95)**	0.99 (0.93-1.06)
Recent weight loss	0.92 (0.88-0.97)**	0.94 (0.89-0.99)**
Leaves food uneaten	0.74 (0.68-0.80)**	0.93 (0.87-0.99)*
Renal failure	1.30 (1.22-1.38)**	0.99 (0.93-1.05)
Dehydration	0.64 (0.54-0.76)**	0.80 (0.68-0.95)**
Acute change in mental status	0.73 (0.67-0.80)**	0.95 (0.87-1.03)
Shortness of breath	1.11 (1.04-1.18)**	1.07 (1.02-1.13)**
Cancer	0.63 (0.59-0.67)**	0.75 (0.71-0.79)**
Swallowing Problems	0.78 (0.75-0.82)**	0.96 (0.90-1.02)
IV feeding tube	0.83 (0.76-0.91)**	0.88 (0.81-0.95)**
Mechanical diet	0.88 (0.83-0.92)**	1.05 (1.00-1.10)

ADL short form score		
0 - <1	Ref	Ref
1 to <2	1.17 (1.10-1.26)**	1.03 (0.95-1.12)
2 to <3	1.04 (0.97-1.12)	0.96 (0.88-1.04)
3 to <4	0.76 (0.69-0.83)**	0.85 (0.78-0.92)**
4	0.53 (0.48-0.59)**	0.71 (0.64-0.79)**
Aggressive Behavior		
None	Ref	Ref
Moderate	1.08 (1.00-1.16)	1.05 (0.97-1.13)
Severe	1.15 (1.04-1.26)**	1.20 (1.09-1.31)**
Very severe	1.13 (0.94-1.36)	1.23 (1.03-1.47)
Presence of any pain	0.81 (0.76-0.87)**	0.92 (0.87-0.97)**
History of falls, hip fracture, and other fractures in past 180 days	1.06 (1.01-1.11)*	1.01 (0.97-1.05)
Facility Factors		
US Census region of the CLC		
Northeast	Ref	Ref
Midwest	1.27 (1.09-1.49)**	1.06 (0.93-1.19)
South	0.97 (0.81-1.16)	0.93 (0.82-1.06)
West	0.87 (0.70-1.07)	0.80 (0.68-0.93)**
Urban Influence Code for the CLC		
Large metro	Ref	Ref
Small metro	1.08 (0.95-1.23)	1.13 (1.02-1.25)*
Micropolitan	1.02 (0.82-1.26)	1.16 (1.05-1.29)**
Noncore rural	0.94 (0.68-1.29)	1.06 (0.91-1.24)
Complexity Level of the parent station		
1a (Highest)	Ref	Ref
1b	1.01 (0.82-1.24)	1.00 (0.88-1.14)
1c	0.99 (0.83-1.18)	0.94 (0.84-1.06)
2	0.99 (0.82-1.18)	0.88 (0.77-1.00)*
3 (Least Complex)	1.06 (0.89-1.28)	0.92 (0.80-1.06)
Bed Size of CLC		
>120 beds	Ref	Ref
60-120 beds	1.05 (0.90-1.22)	1.03 (0.92-1.16)
<60 beds	1.06 (0.91-1.23)	1.03 (0.93-1.14)
MD turnover rate		
Quartile 1	Ref	Ref
Quartile 2	1.13 (0.98-1.31)	1.01 (0.93-1.10)
Quartile 3	1.11 (0.96-1.30)	0.99 (0.90-1.09)
Quartile 4	1.16 (1.00-1.36)	1.00 (0.92-1.08)
Nurse turnover rate		
Quartile 1	Ref	Ref
Quartile 2	1.07 (0.91-1.25)	1.08 (0.98-1.18)
Quartile 3	1.08 (0.92-1.27)	1.10 (0.99-1.23)
Quartile 4	1.05 (0.89-1.22)	1.10 (0.98-1.24)
Pharmacist turnover rate		
Quartile 1	Ref	Ref

Quartile 2	1.08 (0.96-1.21)	0.99 (0.90-1.09)
Quartile 3	0.98 (0.87-1.11)	0.95 (0.86-1.05)
Quartile 4	1.07 (0.94-1.21)	1.05 (0.96-1.15)
Practical nurse turnover		
Quartile 1	Ref	Ref
Quartile 2	1.02 (0.87-1.20)	0.95 (0.87-1.04)
Quartile 3	1.11 (0.95-1.30)	0.99 (0.91-1.08)
Quartile 4	1.02 (0.87-1.20)	1.01 (0.91-1.11)
Psychology Turnover		
Quartile 1	Ref	Ref
Quartile 2	0.89 (0.78-1.01)	0.97 (0.88-1.07)
Quartile 3	0.97 (0.86-1.09)	1.01 (0.93-1.10)
Quartile 4	1.00 (0.89-1.13)	1.03 (0.94-1.14)
Medications prescribed (which may impact Aspirin Rx)		
Anti-platelet agents	2.59 (2.40-2.80)**	1.92 (1.77-2.09)**
Anti-thrombotic agents	1.62 (1.50-1.76)**	1.35 (1.25-1.46)**
H2RAs	1.34 (1.23-1.46)**	1.27 (1.17-1.38)**
PPIs	1.28 (1.21-1.36)**	1.23 (1.17-1.29)**
NSAIDs	1.18 (1.04-1.34)**	1.15 (1.01-1.31)*
*p<0.05, **p<0.01		

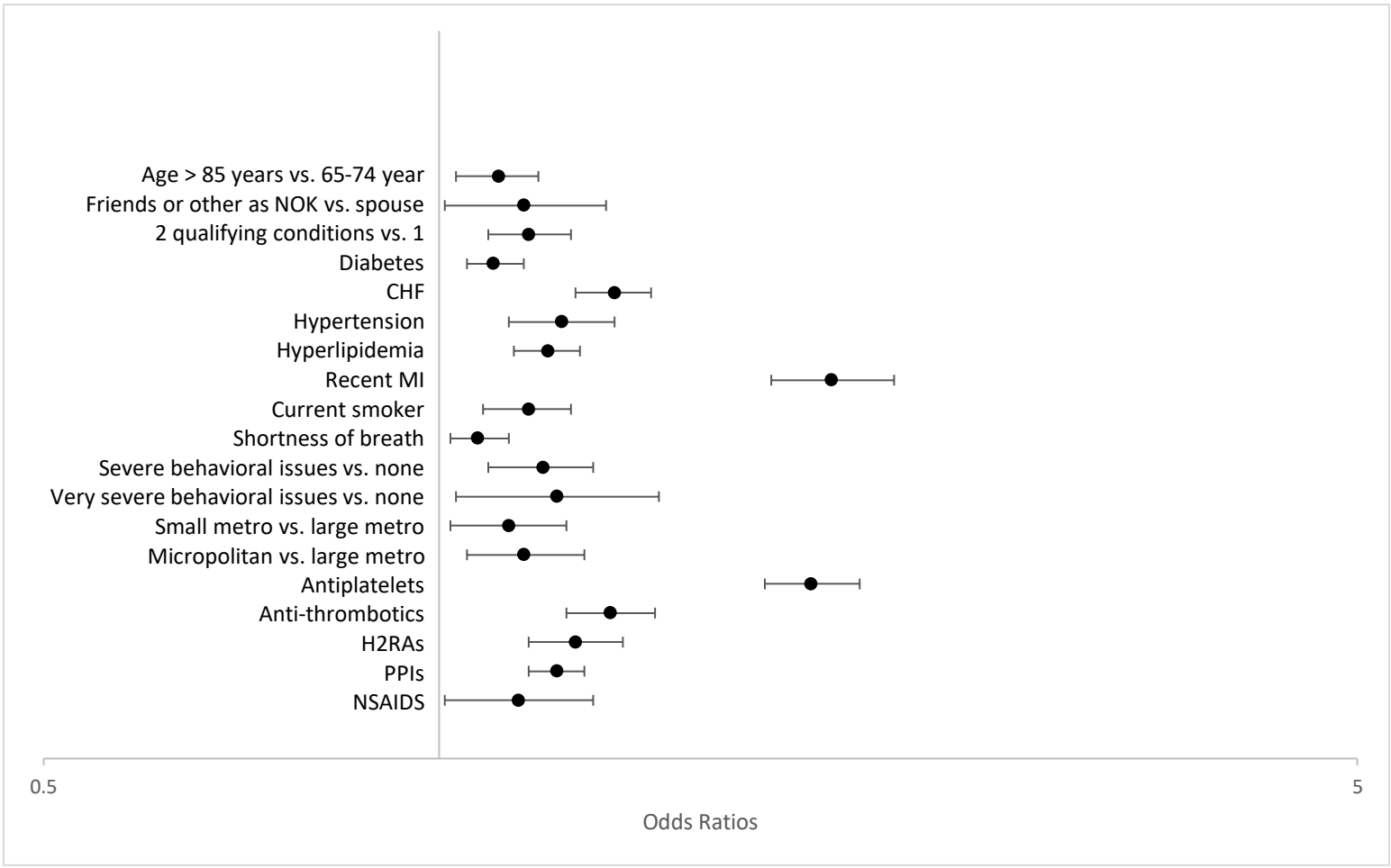

Figure 3: Factor Predicting Higher Odds of Aspirin Receipt

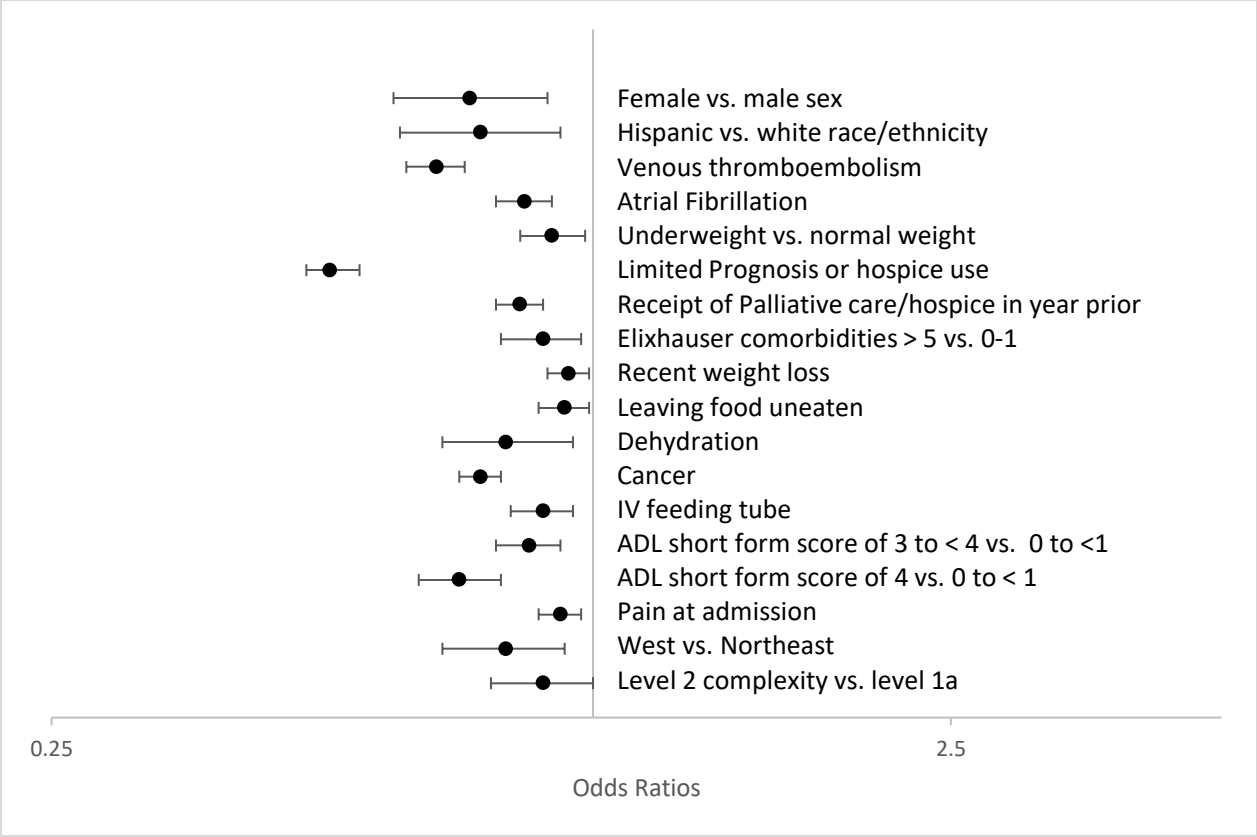

Figure 4: Factor Predicting Lower Odds of Aspirin Receipt

3.4 Demographics of Sample Qualifying for Discontinuation

A total of 13,844 residents received aspirin in the first week of the CLC stay and had at least 14 days of available follow-up in the CLC, and thus were included in the analysis of aspirin discontinuation. The sub-group was very similar to the overall sample, in that a majority of residents were ≥75 years of age (72%), male (99%), married (52%), non-Hispanic white (80%), and presented from an acute hospital setting prior to CLC admission (72.1%). The most common comorbidities included hypertension (94%), hyperlipidemia (70%), diabetes (54%), and congestive heart failure (53%); all comorbidities were slightly more prevalent in this subgroup

compared to the overall cohort. Comorbidities were common, with 40% of the population having more than five Elixhauser comorbidities. Markers of poor prognosis were common, including recent weight loss (40%), leaving food uneaten (40%), and cancer (34%). A majority of residents had no aggressive behavior (82%) but did have pain on admission (69%), and 50% had a history of falls, hip fractures or other fractures in the 180 days prior to admission. Co-administration of aspirin and antithrombotic therapy (51%) and proton pump inhibitors (53%) were common in this subgroup of initial aspirin users. Please refer to table 7 for full review of baseline characteristics in initial aspirin users.

Table 7: Baseline Characteristics of the Cohort Qualifying for Discontinuation of Aspirin

	Discontinuation Cohort (N= 13,844)	**Limited prognosis or hospice Indicator (N=4,092)**	**No Limited Prognosis or Hospice Use Indicator (N=9.752)**
Demographics	**n (%)**		
Age at admission**			
65-74	3,839 (27.7)	1,030 (25.2)	2,809 (28.8)
75-84	5,260 (38.0)	1,557 (38.1)	3,703 (38.0)
≥85	4,745 (34.3)	1,505 (36.8)	3,240 (33.2)
Sex**			
Male	13,686 (98.9)	4,020 (98.2)	9,666 (99.1)
Female	158 (1.1)	72 (1.8)	86 (0.9)
Race/ethnicity*			
White	11,121 (80.3)	3,323 (81.2)	7,798 (80.0)
Black	1,926 (13.9)	513 (12.5)	1,413 (14.5)
Hispanic	547 (4.0)	178 (4.4)	369 (3.8)
Other	250 (1.8)	78 (1.9)	172 (1.8)
Marital status			
Married	7,199 (52.0)	2,272 (55.5)	4,927 (50.5)
Not married	6,645 (48.0)	1,820 (44.5)	4,825 (49.5)
Environment of Care Factors			
Fiscal year of admission			
2009	1,864 (13.5)	514 (12.6)	1,350 (13.8)
2010	1,852 (13.4)	572 (14.0)	1,280 (13.1)
2011	1,960 (14.2)	596 (14.6)	1,364 (14.0)
2012	1,986 (14.4)	578 (14.1)	1,408 (14.4)
2013	2,124 (15.2)	612 (15.0)	1,512 (15.5)

2014	2,118 (15.3)	654 (16.0)	1,464 (15.0)
2015	1,940 (14.0)	566 (13.8)	1,374 (14.1)
Living arrangement before admission**			
Acute hospital	25,143 (67.7)	2,889 (70.6)	7,090 (72.7)
Community	9,074 (24.4)	826 (20.2)	1,918 (19.7)
Nursing home	1,932 (5.2)	251 (6.1)	537 (5.5)
Other	1,014 (2.7)	126 (3.1)	207 (2.1)
Hospitalization in 90 days prior to admission**	21,728 (58.5)	2,584 (63.2)	5,772 (59.2)
Next of kin relationship to the Veteran**			
Spouse	15,031 (40.4)	1,506 (36.8)	3,909 (40.1)
Child	15,296 (41.1)	1,799 (44.0)	3,940 (40.4)
Sibling	3,290 (8.9)	362 (8.9)	889 (9.1)
Other relative	1,594 (4.3)	192 (4.7)	421 (4.3)
Friend or other specified person of unknown relation	1,939 (5.2)	233 (5.7)	593 (6.1)
Distance from next of kin ZIP code centroid to the CLC**			
Quartile 1	9,979 (72.1)	1,176 (28.7)	2,285 (23.4)
Quartile 2	2,744 (19.8)	1,069 (26.1)	2,392 (24.5)
Quartile 3	788 (97.6)	997 (24.4)	2,464 (25.3)
Quartile 4	333 (2.4)	850 (20.8)	2,611 (26.8)
<u>Cardiovascular Risk Factors</u>			
Number of qualifying conditions (CAD, stroke/TIA)**			
1	10.451 (75.5)	3,270 (79.9)	7,181 (73.6)
2	3,393 (24.5)	822 (20.1)	2,571 (26.4)
Diabetes**	7,466 (53.9)	1,933 (47.2)	5,533 (56.7)
Congestive heart failure*	7,317 (52.9)	2,228 (54.5)	5,089 (52.2)
Hypertension**	12,982 (93.8)	3,777 (92.3)	9,205 (94.4)
Hyperlipidemia**	9,742 (70.4)	2,792 (68.2)	6,950 (71.3)
Venous thromboembolism	1,643 (11.9)	509 (12.4)	1,134 (11.6)
Atrial fibrillation last year	2,648 (19.1)	816 (19.9)	1,832 (18.8)
Recent Myocardial Infarction in the last year**	1,161 (8.4)	403 (9.9)	758 (7.8)
Recent Stroke in the last year**	3,733 (27.0)	897 (21.9)	2,836 (29.1)
Current Smoker			
No	12,611 (91.1)	3,693 (90.3)	8,918 (91.5)
Yes	1,233 (8.9)	399 (9.8)	834 (8.6)
Body Mass Index (kg/m^2)**			
Normal or healthy weight (18.5 to <25.0)	5,968 (43.1)	1,962 (48.0)	4,006 (41.1)
Underweight (<18.5)	1,107 (8.0)	472 (11.5)	635 (6.5)
Overweight (25.0 to <30.0)	3,970 (28.7)	1,084 (26.5)	2,886 (29.6)
Obese (≥30)	2,799 (20.2)	574 (14.0)	2,225 (22.8)

Markers of Poor Prognosis			
Advanced dementia**	4,211 (30.4)	1,075 (26.3)	3,136 (32.2)
Documentation of limited prognosis or hospice use at admission	4,094 (29.6)		
Number of Elixhauser conditions**			
0-1	1,019 (7.4)	221 (5.4)	798 (8.2)
2-3	3,144 (22.7)	846 (20.7)	2,298 (23.6)
4-5	4,145 (29.9)	1,264 (30.9)	2,881 (29.5)
>5	5,536 (40.0)	1,761 (43.0)	3,775 (38.7)
Recent weight loss**	5,555 (40.1)	1,568 (38.3)	3,987
Leaves food uneaten**	5,478 (39.6)	2,025 (49.5)	3,453 (35.4)
Renal failure**	2,830 (20.4)	681 (16.6)	2,149 (22.0)
Dehydration	138 (1.0)	43 (1.1)	95 (1.0)
Acute change in mental status**	1,365 (9.9)	496 (12.1)	869 (8.9)
Shortness of breath**	5,586 (40.4)	1,883 (46.0)	3,703 (38.0)
Cancer**	4,633 (33.5)	1,740 (42.5)	2,893 (29.7)
Activities of Daily Living (ADL) score**			
0 - <1	1,438 (10.4)	464 (11.3)	974 (10.0)
1 to <2	3,218 (23.2)	733 (17.9)	2,485 (25.5)
2 to <3	4,714 (34.1)	1,203 (29.4)	3,511 (36.0)
3 to <4	3,185 (23.0)	1,127 (27.5)	2,085 (21.1)
4	1,289 (9.3)	565 (13.8)	724 (7.4)
Aggressive Behavior**			
None	11,405 (82.4)	3,469 (84.8)	7,936 (81.4)
Moderate	1,552 (11.2)	378 (9.2)	1,174 (12.0)
Severe	669 (4.8)	193 (4.7)	476 (4.9)
Very severe	218 (1.6)	52 (1.3)	166 (1.7)
IV feeding tube in place**	1,282 (9.3)	275 (6.7)	1,007 (10.3)
On Mechanical Diet**	5,643 (40.8)	1,869 (45.7)	3,774 (38.7)
Swallowing Problems**	2,538 (18.3)	849 (20.8)	1,689 (17.3)
Presence of any pain (n, % yes)**			
Yes	9,563 (69.1)	3,005 (73.4)	6,558 (67.3)
No	4,281 (30.9)	1,087 (26.6)	3,194 (32.8)
History of falls, hip fracture, and other fractures in past 180 days**			
Yes	6,870 (49.6)	1,929 (47.1)	4,941 (50.7)
No	6,974 (50.4)	2,163 (52.9)	4,811 (49.3)
Facility Factors			
US Census region of the CLC**			
Northeast	2,355 (17.0)	821 (20.1)	1,534 (15.7)
Midwest	4,528 (32.7)	1,070 (26.2)	3,458 (35.5)
South	4,604 (33.3)	1,466 (35.8)	3,138(32.2)
West	2,357 (17.0)	735 (18.0)	1,622 (16.6)
Urban Influence Code for the CLC**			
Large metro	6,201 (44.8)	1,648 (40.3)	4,553 (46.7)
Small metro	5,078 (36.7)	1,593 (38.9)	3,485 (35.7)
Micropolitan	1,110 (8.0)	390 (9.5)	720 (7.4)

Noncore rural	1,455 (10.5)	461 (11.3)	994 (10.2)
Complexity Level of the parent station**			
1a (Highest)	5, 236 (37.8)	1,430 (35.0)	3,806 (39.0)
1b	1,583 (11.4)	452 (11.1)	1,131 (11.6)
1c	2,517 (18.2)	829 (20.3)	1,688 (17.3)
2	1,949 (14.1)	612 (15.0)	1,337 (13.7)
3 (Least Complex)	2,559 (18.5)	769 (18.8)	1,790 (18.4)
Bed Size of CLC**			
<60 beds	2,034 (14.7)	773 (18.9)	1,261 (12.9)
60-120 beds	4,934 (35.6)	1,399 (34.2)	3,535 (36.3)
>/= 120 beds	6,876 (49.7)	1,920 (46.9)	4,956 (50.8)
Physician turnover rate**			
Quartile 1	3,479 (25.1)	1,095 (26.8)	2,384 (24.5)
Quartile 2	3,492 (25.2)	958 (23.4)	2,534 (26.0)
Quartile 3	3,463 (25.0)	1,066 (26.1)	2,397 (24.6)
Quartile 4	3,410 (24.6)	973 (23.8)	2,437 (25.0)
Nurse turnover rate			
Quartile 1	3,532 (25.5)	1,007 (24.6)	2,525 (25.9)
Quartile 2	3,422 (24.7)	987 (24.1)	2,435 (25.0)
Quartile 3	3,447 (24.9)	1,036 (25.3)	2,411 (24.7)
Quartile 4	3,443 (24.9)	1,062 (26.0)	2,381 (24.4)
Pharmacist turnover rate**			
Quartile 1	3,476 (25.1)	1,158 (28.3)	2,318 (23.8)
Quartile 2	3,516 (25.4)	898 (22.0)	2,618 (26.9)
Quartile 3	3,397 (24.5)	957 (23.4)	2,440 (25.0)
Quartile 4	3,455 (25.0)	1,079 (26.4)	2,376 (24.4)
Practical nurse turnover**			
Quartile 1	3,477 (25.1)	1,087 (26.6)	2,390 (24.5)
Quartile 2	3,461 (25.0)	998 (24.4)	2,463 (25.3)
Quartile 3	3,467 (25.0)	962 (23.5)	2,505 (25.7)
Quartile 4	3,439 (24.8)	1,045 (25.5)	2,394 (24.6)
Psychology Turnover*			
Quartile 1	3,505 (25.3)	1,033 (25.2)	2,472 (25.4)
Quartile 2	3,435 (24.8)	1,046 (25.6)	2,389 (24.5)
Quartile 3	3,493 (25.2)	965 (23.6)	2,528 (25.9)
Quartile 4	3,411 (24.6)	1,048 (25.6)	2,363 (24.2)
Medications Prescribed Which May Impact Aspirin Prescribing			
Anti-platelet**	2,558 (18.5)	666 (16.3)	1,892 (19.4)
Anti-thrombotic Agents**	7,057 (51.0)	1,707 (41.7)	5,250 (54.9)
H2-Receptor Antagonists*	1,547 (11.2)	421 (10.3)	1,126 (11.6)
Proton Pump Inhibitors	7,290 (52.7)	2,119 (51.8)	5,171 (53.0)
NSAIDs**	514 (3.7)	124 (3.0)	390 (4.0)
*p<0.05, **p<0.01 for differences by limited prognosis or hospice use stratification			

3.5 Incidence and Factors Predicting Discontinuation of Aspirin for Secondary Prevention of Cardiovascular Disease

The cumulative incidence of aspirin discontinuation by day 91 of the CLC stay in this cohort was 33% (95% CI, 0.32-0.34). See figure 5 below for the cumulative incidence of aspirin discontinuation from day 0 to 91.

Results of the bivariable and multivariable competing risk models are shown in Table 8. As the goal of this analysis is to identify factors significantly associated with aspirin discontinuation in the first 91 days of CLC admission, independent of all other factors, we highlight the results from the fully adjusted multivariable model here.

Demographics factors associated with lower hazards of discontinuation include being 75-84 years of age (aSDHR 0.91, 95% CI 0.83-1.00), and being greater than 85 years old (aOR 0.89, 95% CI 0.80-0.99) versus 65-74 years. Hispanic ethnicity (aSDHR 1.43, 95% CI 1.13-1.81) and other non-White, non-Hispanic race/ethnicity (aSDHR 1.30, 95% CI 1.03-1.64) versus White, non-Hispanic race/ethnicity was associated with higher hazards of discontinuation.

Amongst environment of care factors associated with discontinuation, treatment in fiscal year 2012 was associated with higher hazards of discontinuation (aSDHR 1.23, 95% CI 1.04-1.46) versus year 2009. Factors predicting lower hazards of discontinuation of aspirin included those coming from the community (aSDHR 0.73, 95% CI 0.65-0.83) or from a nursing home (aSDHR 0.66, 95% CI 0.55-0.80) compared to coming from an acute hospital.

A few cardiovascular risk factors were associated with lower hazards of aspirin discontinuation, including diabetes (aSDHR 0.87, 95% CI 0.81-0.93) and having had an MI in the year prior to CLC admission (aSDHR 0.76, 95% CI 0.65-0.89).

A number of factors indicating limited prognosis were implicated in aspirin discontinuation. Having 2-3 Elixhuaser comorbidities (aSDHR 1.26, 95% CI 1.08-1.47), 4-5 Elizhauser comorbidities (aSDHR 1.20, 95% CI 1.02-1.41), and > 5 Elixhauser comorbidities (aSDHR 1.32, 95% CI 1.11-1.57) versus 0-1 comorbidities was associated with higher hazards of aspirin discontinuation. Those with a documented limited prognosis or hospice use at admission had the highest hazards of aspirin discontinuation (aSDHR 1.89, 95% CI 1.67-2.14). Other factors associated with higher hazards of discontinuation include: recent weight loss (aSDHR 1.11, 95% CI 1.03-1.19), leaving food uneaten (aSDHR 1.14, 95% CI 1.05-1.23), renal failure (aSDHR 1.16, 95% CI, 1.04-1.29), cancer (aSDHR 1.13, 95% CI 1.04-1.22), IV feeding tube requirement (aSDHR 1.21, 95% CI 1.06-1.38), those with dependence on 3 to < 4 ADLs (aSDHR 1.24, 95% CI 1.07-1.45), and all 4 ADLs versus those dependent on <1 ADL (aSDHR 1.37, 95% CI 1.15-1.63).

Amongst facility level factors, having a bed size at the CLC of < 60 versus ≥ 120 (aSDHR 0.81, 95% CI 0.68-0.97), having a nursing turnover rate in quartile 4 versus quartile 1 (aSDHR 0.80, 95% CI 0.66-0.98) and having a psychology turnover rate in quartile 4 versus quartile 1 (aSDHR 0.84, 95% CI 0.72-0.98) are associated with lower hazards of aspirin discontinuation. Having practical nursing turnover rates in quartile 3 versus 1 (aSDHR 1.18, 95% CI 1.02-1.36) and being cared for in a CLC in the South versus Northeast (aSDHR 1.24, 95% CI 1.01-1.52) was associated with higher hazards of discontinuation.

No medications which impact the risk of bleeding when combined with aspirin were associated with aspirin discontinuation.

In stratified analyses, in those with hospice or limited prognosis documented at admission, the following variables were no longer significantly associated with aspirin discontinuation: the

age category of 75-84 years, other or Hispanic race/ethnicity, recent MI, recent weight loss, cancer, IV feeding tube requirement, ADL short form score of 4 versus 0 to <1, being cared for in the South vs. Northeast, less than 60 beds versus > 120 beds in the CLC facility, nursing turnover rate quartile 4, psychology turnover rate quartile 4. However, in all cases the direction and magnitude of the aSDHR was similar to that observed in the non-stratified analyses. Variables which became significant in the limited prognosis and hospice use group, which were not previously associated with discontinuation in the adjusted model included: being care for in fiscal year 2015 versus 2009 (aSDHR 1.37, 95% CI 1.01-1.85), having a child as a NOK versus a spouse (aSDHR 1.21, 95% CI 1.02-1.44), congestive heart failure (aSDHR 0.88, 95% CI 0.78-0.99), being overweight versus normal weight (aSDHR 1.17, 95% CI 1.03-1.34), shortness of breath (aSDHR 0.86, 95% CI 0.76-0.97), ADL short form score of 2 to < 3 (aSDHR 1.27, 95% CI 1.00-1.61), being cared for in the West U.S. region versus the Northeast (aSDHR 1.38, 95% CI 1.02-1.88), facility complexity levels 1b (aSDHR 0.70, 95% CI 0.53-0.93), and 1c (aSDHR 0.75, 95% CI 0.57-0.99) versus complexity level 1a, quartiles 3 (aSDHR 1.25, 95% CI 1.03-1.50) and quartile 4 (aSDHR 1.23, 95% CI 1.01-1.50) of the pharmacist turnover rates categories compared to quartile 1, quartile 2 versus 1 of the practical nurse turnover rates (aSDHR 1.26, 95% CI 1.01-1.56), quartile 2 versus 1 of the psychology turnover category (aSDHR 1.26, 95% CI 1.02-1.56), and proton pump inhibitors (aSDHR 1.15, 95% CI 1.02-1.30).

Amongst those not in the limited prognosis or hospice use group, the following variables were no longer significantly associated with aspirin discontinuation, age categories 75-84 and ≥ 85 years, other race or ethnicity, admission during fiscal year 2012, any of the Elixhauser comorbidity categories, leaving food uneaten, ADL short form scores of 3 to <4 and 4, residing in a CLC in the South, and practical nurse turnover rates in quartile 3. Again, in all cases the direction

and magnitude of the aSDHR was similar to that observed in the non-stratified analyses. The following variables were significant in the group without limited prognosis or hospice use at admission, which were not previously significant in the adjusted model: congestive heart failure (aSDHR 1.13, 95% CI 1.01-1.26), venous thromboembolism (aSDHR 1.23, 95% CI 1.07-1.41), current smoking status (aSDHR 1.21, 95% CI 1.01-1.45), shortness of breath (aSDHR 1.12, 95% CI 1.00-1.25, psychology turnover rates in quartile 3 versus quartile 1 (aSDHR 0.80, 95% CI 0.68-0.93), and the use of anti-thrombotic agents (aSDHR 1.13, 95% CI 1.01-1.26).

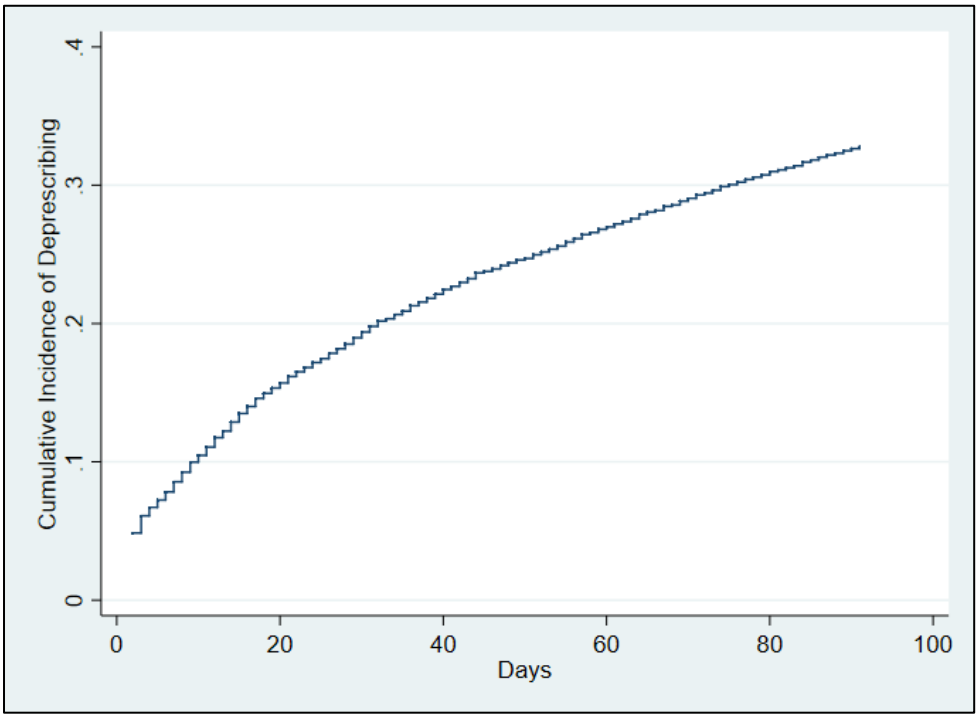

Figure 5: Cumulative Incidence of Discontinuation of Aspirin for Secondary Prevention of Cardiovascular Disease

Table 8: Univariable and Adjusted Subdistribution Hazard Ratios (SDHRs) for the Hazard of Discontinuation of Aspirin, Competing Risk Survival Analysis

	Unadjusted SDHR N=13,844	Adjusted SDHR N=13,844	Limited Prognosis Indicator Documented N=4,092	No Indication of Limited Prognosis Documented N=9,752
Demographics	**SDHR (95% CI)**	**aSDHR (95% CI)**	**aSDHR (95% CI)**	**aSDHR (95% CI)**
Age at admission				
65-74	Ref	Ref	Ref	Ref
75-84	1.04 (0.92-1.17)	0.91 (0.83-1.00)*	0.87 (0.75-1.02)	0.95 (0.84-1.07)
≥85	1.05 (0.93-1.18)	0.89 (0.80-0.99)*	0.80 (0.69-0.94)**	0.99 (0.87-1.13)
Sex				
Female	1.43 (1.02-2.02)*	0.98 (0.68-1.40)	1.02 (0.68-1.51)	0.93 (0.53-1.64)
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.03 (0.89-1.20)	1.00 (0.91-1.11)	1.17 (0.98-1.41)	0.92 (0.80-1.05)
Hispanic	1.53 (1.12-2.09)**	1.43 (1.13-1.81)**	1.36 (0.97-1.91)	1.51 (1.16-1.98)**
Other	1.23 (0.85-1.77)	1.30 (1.03-1.64)*	1.30 (0.91-1.87)	1.30 (0.97-1.73)
Marital status				
Married	0.98 (0.89-1.08)	1.08 (0.96-1.21)	1.13 (0.95-1.34)	1.05 (0.90-1.23)
Environment of Care Factors				
Fiscal year of admission				
2009	Ref	Ref	Ref	Ref
2010	1.07 (0.91-1.26)	1.04 (0.91-1.18)	1.17 (0.95-1.43)	1.02 (0.84-1.23)
2011	1.11 (0.91-1.36)	0.95 (0.83-1.09)	1.16 (0.92-1.47)	0.86 (0.73-1.03)
2012	1.18 (0.96-1.45)	1.23 (1.04-1.46)**	1.60 (1.22-2.08)**	1.06 (0.88-1.28)
2013	0.95 (0.76-1.18)	1.07 (0.90-1.27)	1.25 (0.96-1.63)	0.97 (0.80-1.18)
2014	1.05 (0.85-1.31)	1.15 (0.96-1.37)	1.24 (0.93-1.66)	1.09 (0.88-1.34)
2015	1.17 (0.96-1.43)	1.17 (0.97-1.41)	1.37 (1.01-1.85)*	1.07 (0.87-1.33)
Living arrangement before admission				
Acute hospital	Ref	Ref	Ref	Ref
Community	0.56 (0.47-0.68)**	0.73 (0.65-0.83)**	0.69 (0.58-0.82)**	0.80 (0.69-0.93)**
Nursing home	0.54 (0.39-0.73)**	0.66 (0.55-0.80)**	0.70 (0.52-0.94)*	0.65 (0.49-0.86)**
Other	0.63 (0.44-0.91)*	0.83 (0.66-1.04)	0.75 (0.55-1.02)	0.90 (0.62-1.32)
Hospitalization in 90 days prior to admission	1.09 (0.98-1.21)	1.03 (0.94-1.11)	1.05 (0.93-1.19)	0.99 (0.90-1.10)
Next of kin relationship to the Veteran¥				
Spouse	Ref	Ref	Ref	Ref
Child	1.06 (0.95-1.18)	1.11 (0.99-1.25)	1.21 (1.02-1.44)*	1.04 (0.88-1.22)
Sibling	0.90 (0.76-1.08)	0.98 (0.84-1.16)	0.92 (0.71-1.19)	1.00 (0.81-1.24)

Other relative	1.12 (0.89-1.41)	1.04 (0.84-1.28)	1.18 (0.91-1.53)	0.97 (0.70-1.35)
Friend or other specified person of unknown relation	0.94 (0.75-1.18)	1.04 (0.85-1.27)	1.09 (0.82-1.46)	0.98 (0.76-1.26)
Distance from next of kin ZIP code centroid to the CLC¥				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	1.00 (0.86-1.15)	1.02 (0.93-1.12)	1.06 (0.93-1.22)	0.97 (0.85-1.09)
Quartile 3	0.97 (0.82-1.14)	1.02 (0.93-1.12)	1.00 (0.86-1.18)	1.03 (0.91-1.17)
Quartile 4	0.86 (0.74-1.01)	0.94 (0.83-1.06)	0.97 (0.83-1.15)	0.90 (0.78-1.04)
Cardiovascular Risk Factors				
Number of qualifying conditions (CAD, stroke/TIA, and/or diabetes)				
1	Ref	Ref	Ref	Ref
2	0.79 (0.71-0.88)**	0.91 (0.81-1.02)	0.89 (0.74-1.07)	0.92 (0.79-1.06)
Diabetes	0.80 (0.73-0.87)**	0.87 (0.81-0.93)**	0.87 (0.78-0.97)*	0.86 (0.77-0.95)**
Congestive heart failure	1.06 (0.95-1.17)	1.01 (0.93-1.10)	0.88 (0.78-0.99)*	1.13 (1.01-1.26)*
Hypertension	0.90 (0.73-1.12)	0.98 (0.83-1.16)	1.14 (0.90-1.43)	0.85 (0.69-1.05)
Hyperlipidemia	0.90 (0.81-0.99)*	0.97 (0.90-1.06)	0.99 (0.88-1.12)	0.95 (0.86-1.05)
Venous Thromboembolism	1.21 (1.06-1.39)**	1.10 (0.99-1.22)	0.95 (0.79-1.15)	1.23 (1.07-1.41)**
Atrial Fibrillation	1.07 (0.95-1.21)	1.01 (0.92-1.11)	0.93 (0.81-1.05)	1.09 (0.94-1.27)
Recent stroke	0.90 (0.79-1.03)	0.99 (0.88-1.12)	0.93 (0.77-1.11)	1.05 (0.89-1.23)
Recent MI	0.87 (0.70-1.07)	0.76 (0.65-0.89)**	0.90 (0.73-1.12)	0.63 (0.51-0.77)**
Current Smoker	0.95 (0.80-1.13)	1.08 (0.95-1.23)	0.98 (0.81-1.20)	1.21 (1.01-1.45)*
Body Mass Index				
Normal or healthy weight (18.5 to <25.0)	Ref	Ref	Ref	Ref
Underweight (<18.5)	1.42 (1.20-1.69)**	1.10 (0.95-1.27)	1.05 (0.88-1.26)	1.14 (0.95-1.36)
Overweight (25.0 to <30.0)	0.95 (0.84-1.08)	1.09 (0.99-1.19)	1.17 (1.03-1.34)*	1.05 (0.92-1.19)
Obese (≥30)	0.82 (0.69-0.96)*	1.04 (0.92-1.17)	1.10 (0.92-1.32)	0.98 (0.86-1.13)
Factors indicating limited prognosis				
Documentation of limited prognosis	3.37 (2.89-3.93)**	1.89 (1.67-2.14)**		

or hospice use at admission				
Number of Elixhauser conditions				
0-1	Ref	Ref	Ref	Ref
2-3	1.51 (1.21-1.87)**	1.26 (1.08-1.47)**	1.38 (1.06-1.80)*	1.20 (0.95-1.52)
4-5	1.52 (1.20-1.93)**	1.20 (1.02-1.41)*	1.40 (1.06-1.84)*	1.06 (0.85-1.32)
>5	1.65 (1.29-2.11)**	1.32 (1.11-1.57)**	1.48 (1.12-1.96)**	1.20 (0.94-1.53)
Advanced dementia	1.00 (0.84-1.19)	1.00 (0.91-1.10)	1.14 (0.99-1.30)	0.91 (0.80-1.05)
Recent weight loss	1.15 (1.04-1.28)**	1.11 (1.03-1.19)**	1.08 (0.96-1.21)	1.14 (1.02-1.27)*
Leaves food uneaten	1.64 (1.46-1.85)**	1.14 (1.05-1.23)**	1.17 (1.03-1.32)*	1.08 (0.96-1.21)
Renal failure	0.96 (0.84-1.10)	1.16 (1.04-1.29)**	1.16 (1.00-1.36)*	1.16 (1.02-1.33)*
Dehydration	1.19 (0.66-2.16)	1.06 (0.73-1.54)	1.20 (0.78-1.86)	0.94 (0.56-1.58)
Acute change in mental status	1.43 (1.20-1.72)**	1.12 (0.99-1.27)	1.06 (0.87-1.30)	1.15 (1.00-1.34)
Shortness of breath	1.09 (0.97-1.23)	0.98 (0.90-1.07)	0.86 (0.76-0.97)*	1.12 (1.00-1.25)*
Cancer	1.16 (1.04-1.30)*	1.13 (1.04-1.22)**	1.04 (0.92-1.17)	1.18 (1.05-1.33)**
Swallowing Problems	1.44 (1.27-1.64)**	1.04 (0.94-1.15)	1.09 (0.95-1.24)	0.95 (0.83-1.08)
IV feeding tube	1.14 (0.96-1.36)	1.21 (1.06-1.38)**	0.99 (0.80-1.24)	1.37 (1.15-1.62)**
Mechanical diet	1.30 (1.18-1.43)**	1.03 (0.96-1.12)	1.03 (0.92-1.16)	1.03 (0.91-1.17)
ADL score				
0 - <1	Ref	Ref	Ref	Ref
1 to <2	0.96 (0.79-1.17)	0.98 (0.84-1.13)	1.09 (0.88-1.35)	0.88 (0.73-1.05)
2 to <3	1.20 (1.00-1.43)*	1.11 (0.95-1.29)	1.27 (1.00-1.61)*	0.95 (0.78-1.15)
3 to <4	1.64 (1.36-1.97)**	1.24 (1.07-1.45)**	1.29 (1.02-1.63)*	1.11 (0.92-1.35)
4	2.39 (1.92-2.98)**	1.37 (1.15-1.63)**	1.31 (1.00-1.73)	1.26 (0.99-1.60)
Aggressive Behavior				
None	Ref	Ref	Ref	Ref
Moderate	1.04 (0.88-1.24)	1.10 (0.99-1.22)	1.06 (0.89-1.27)	1.09 (0.94-1.26)
Severe	0.99 (0.76-1.27)	1.06 (0.90-1.24)	1.14 (0.91-1.43)	0.96 (0.75-1.23)
Very severe	0.77 (0.49-1.21)	1.08 (0.81-1.44)	0.96 (0.58-1.57)	1.20 (0.84-1.71)
Presence of any pain	1.33 (1.16-1.51)**	1.02 (0.94-1.10)	1.05 (0.93-1.18)	1.00 (0.89-1.10)
History of falls, hip fracture, and other fractures in past 180 days	0.94 (0.85-1.05)	1.01 (0.94-1.09)	1.02 (0.92-1.12)	1.00 (0.90-1.10)
<u>Facility Factors</u>				
US Census region of the CLC				
Northeast	Ref	Ref	Ref	Ref

Midwest	1.02 (0.74-1.43)	1.10 (0.89-1.34)	1.16 (0.88-1.54)	1.02 (0.82-1.28)
South	1.19 (0.82-1.74)	1.24 (1.01-1.52)*	1.20 (0.92-1.56)	1.19 (0.96-1.48)
West	1.40 (0.95-2.07)	1.30 (1.00-1.70)	1.38 (1.02-1.88)*	1.25 (0.91-1.70)
Urban Influence Code for the CLC				
Large metro	Ref	Ref	Ref	Ref
Small metro	0.93 (0.74-1.18)	0.89 (0.77-1.03)	0.91 (0.75-1.10)	0.86 (0.74-1.01)
Micropolitan	1.50 (1.02-2.21)*	1.14 (0.92-1.41)	1.13 (0.77-1.66)	1.12 (0.92-1.35)
Noncore rural	0.86 (0.51-1.47)	0.84 (0.66-1.07)	0.88 (0.64-1.21)	0.79 (0.61-1.02)
Complexity Level of the parent station				
1a (Highest)	Ref	Ref	Ref	Ref
1b	0.77 (0.51-1.15)	0.88 (0.72-1.08)	0.70 (0.53-0.93)*	1.08 (0.86-1.34)
1c	0.78 (0.59-1.04)	0.85 (0.71-1.01)	0.75 (0.57-0.99)*	0.92 (0.77-1.09)
2	0.83 (0.64-1.08)	0.98 (0.81-1.19)	0.88 (0.66-1.19)	1.02 (0.81-1.29)
3 (Least Complex)	0.71 (0.53-0.96)	1.01 (0.82-1.24)	0.88 (0.66-1.17)	1.12 (0.89-1.40)
Bed Size of CLC				
>120 beds	Ref	Ref	Ref	Ref
60-120 beds	0.78 (0.58-1.03)	0.87 (0.72-1.04)	0.87 (0.67-1.12)	0.89 (0.72-1.10)
<60 beds	0.67 (0.51-0.89)**	0.81 (0.68-0.97)*	0.83 (0.67-1.04)	0.82 (0.66-1.01)*
MD turnover rate				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	0.96 (0.75-1.22)	0.96 (0.82-1.11)	1.02 (0.82-1.26)	0.91 (0.77-1.08)
Quartile 3	1.07 (0.85-1.35)	1.04 (0.90-1.21)	1.11 (0.89-1.39)	0.99 (0.84-1.17)
Quartile 4	0.87 (0.70-1.07)	0.96 (0.83-1.10)	1.05 (0.82-1.35)	0.91 (0.77-1.08)
Nurse turnover rate				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	0.98 (0.78-1.22)	0.91 (0.78-1.06)	0.92 (0.73-1.17)	0.92 (0.77-1.09)
Quartile 3	0.88 (0.70-1.10)	0.84 (0.70-1.00)	0.85 (0.64-1.13)	0.84 (0.69-1.02)
Quartile 4	0.89 (0.69-1.13)	0.80 (0.66-0.98)*	0.84 (0.63-1.11)	0.77 (0.61-0.97)*
Pharmacist turnover rate				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	0.89 (0.72-1.09)	0.97 (0.83-1.13)	1.07 (0.87-1.32)	0.90 (0.75-1.09)
Quartile 3	1.11 (0.93-1.33)	1.04 (0.91-1.19)	1.25 (1.03-1.50)*	0.90 (0.75-1.07)
Quartile 4	0.99 (0.79-1.24)	1.07 (0.93-1.23)	1.23 (1.01-1.50)*	0.96 (0.81-1.14)
Practical nurse turnover				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	1.21 (0.91-1.60)	1.13 (0.99-1.30)	1.26 (1.01-1.56)*	1.00 (0.85-1.19)
Quartile 3	1.09 (0.85-1.39)	1.18 (1.02-1.36)*	1.23 (0.99-1.54)*	1.07 (0.90-1.26)
Quartile 4	1.23 (0.93-1.62)	1.12 (0.95-1.33)	1.13 (0.89-1.45)	1.11 (0.93-1.33)
Psychology Turnover				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	1.31 (1.06-1.61)*	1.11 (0.98-1.27)	1.26 (1.02-1.56)*	0.97 (0.83-1.13)

Quartile 3	0.98 (0.81-1.18)	0.94 (0.81-1.08)	1.11 (0.89-1.38)	0.80 (0.68-0.93)**
Quartile 4	1.00 (0.81-1.22)	0.84 (0.72-0.98)*	0.91 (0.73-1.15)	0.75 (0.62-0.91)**
Medications prescribed (which may impact Aspirin Rx)				
Anti-platelet agents	0.82 (0.72-0.93)**	0.93 (0.84-1.03)	0.85 (0.72-1.01)	1.01 (0.88-1.15)
Anti-thrombotic agents	1.14 (1.00-1.29)*	1.08 (0.98-1.19)	1.04 (0.91-1.19)	1.13 (1.01-1.26)*
H2RAs	0.94 (0.80-1.12)	0.89 (0.78-1.00)	0.95 (0.79-1.15)	0.87 (0.73-1.04)
PPIs	1.09 (0.98-1.21)	1.05 (0.98-1.13)	1.15 (1.02-1.30)*	0.97 (0.87-1.08)
NSAIDs	1.04 (0.82-1.32)	0.96 (0.80-1.15)	1.03 (0.79-1.34)	0.92 (0.73-1.15)
*p<0.05, **p<0.01, ¥ indicates the variable was imputed				

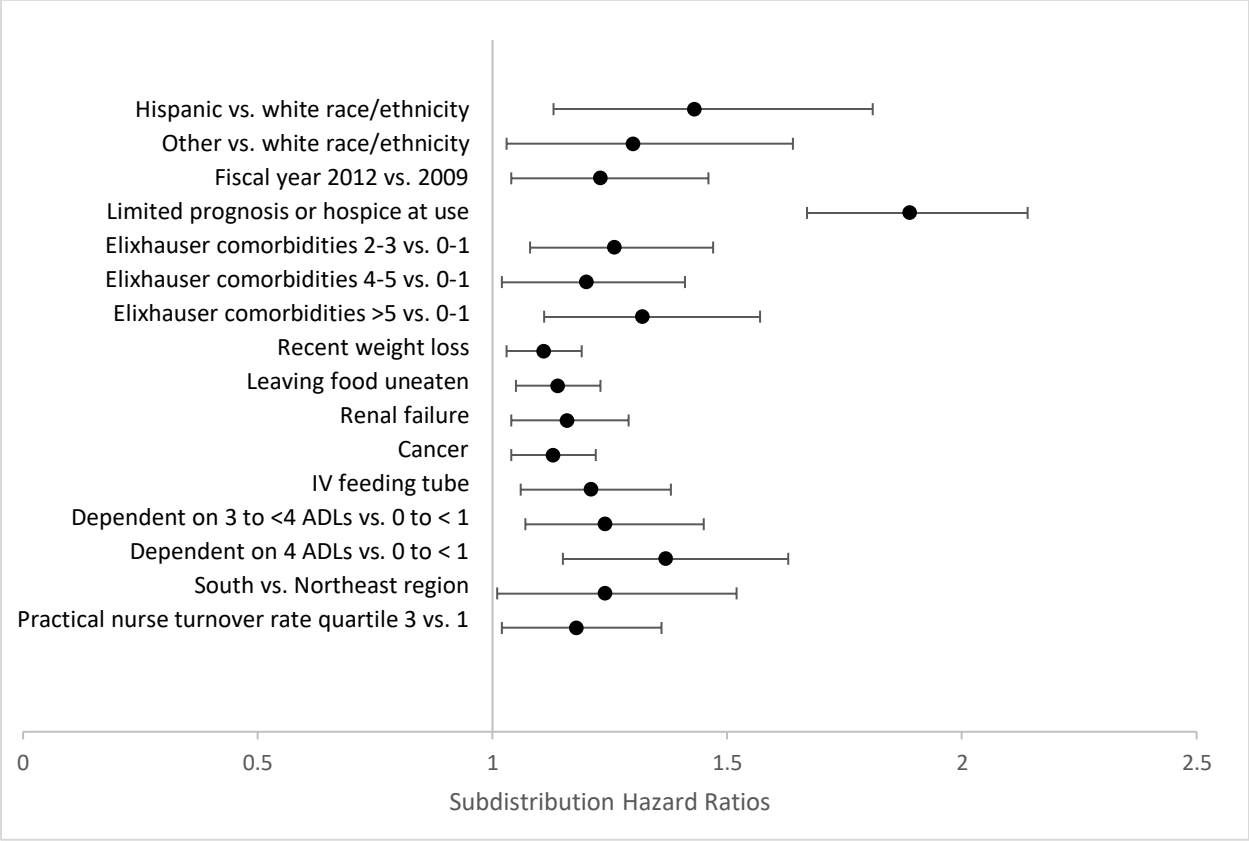

Figure 6: Factors Predicting Higher Hazards of Aspirin Discontinuation

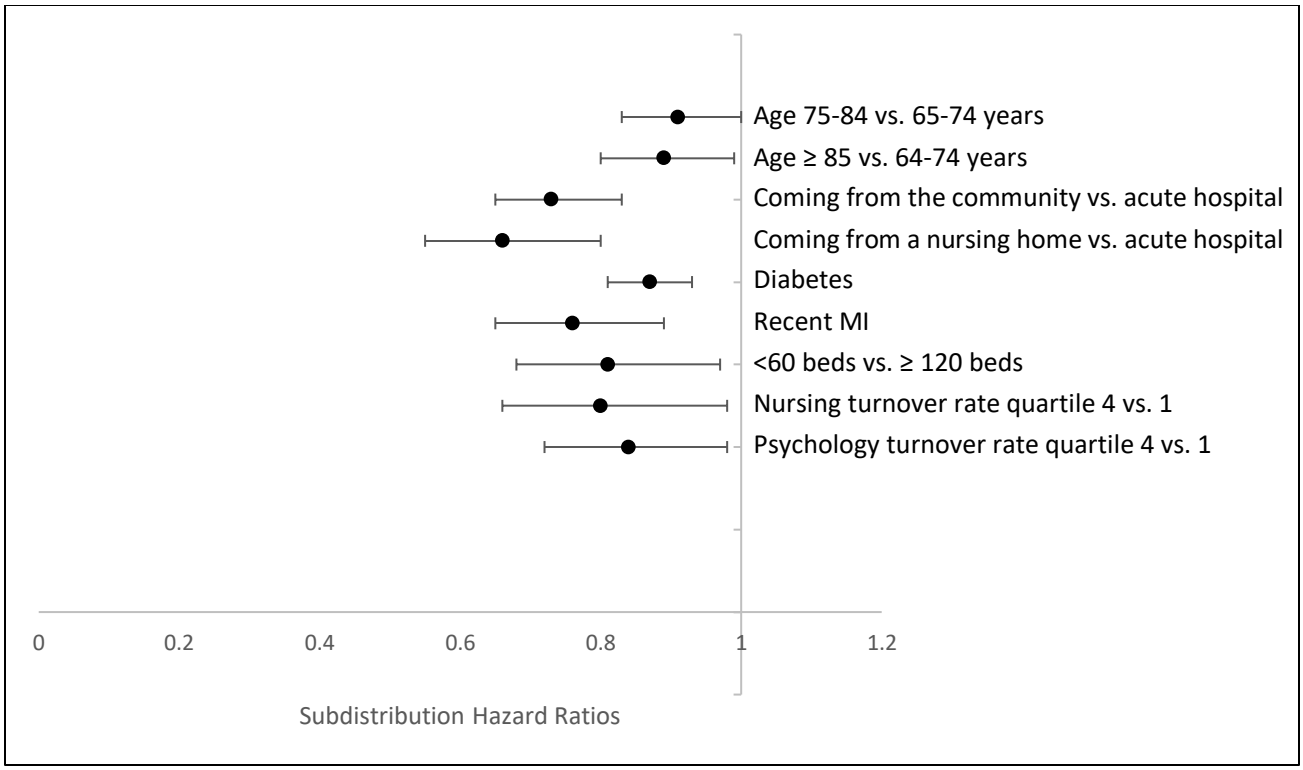

Figure 7: Factors Predicting Lower Hazards of Aspirin Discontinuation

3.6 Results of Sensitivity Analysis Using a 30-day Gap to Define Discontinuation

A total of 9,430 residents qualified for the discontinuation sample for the sensitivity analysis, in that they received aspirin during the first week of the CLC stay and remained in the CLC for at least 30 days thereafter. Consistent with the discontinuation subgroup from the primary analysis, a majority of these residents were 75 years of age or older (71.7%), male (98.8%), non-Hispanic white (79.9%), and married (52.7%). Most residents came from an acute hospital setting prior to CLC admission (71.2%). The most common comorbidities included diabetes (54.7%), congestive heart failure (52.1%), and hypertension (93.9%). Rates of concomitant medications and other indicators of poor prognosis were very similar to the primary analysis discontinuation

subgroup as well as the overall cohort for this study. See table 9 for the frequency of all covariates amongst the sensitivity analysis subgroup.

The cumulative incidence of discontinuation by day 91 of the CLC stay in this sample was 26% (CIF 0.26, 95% CI 0.25-0.27). See Figure 8 below for the cumulative incidence of discontinuation displayed over time (0-91 days).

Results of the univariable and multivariable competing risk models are shown in Table 10. As the goal of this analysis is to identify factors significantly associated with aspirin discontinuation in the first 91 days of CLC admission, independent of all other factors, we highlight the results from the fully adjusted multivariable model here.

Factors predicting hazards of discontinuation were consistent with the primary discontinuation analysis including: having other non-White/non-Hispanic race/ethnicity (aSDHR 1.43, 95% CI 1.05-1.95), Hispanic ethnicity (aSDHR 1.59, 95% CI 1.19-2.14), admission from the community (aSDHR 0.83, 95% CI 0.72-0.96) or from a nursing home (aSDHR 0.69, 95% CI 0.55-0.86) compared to an acute hospital, a diagnosis of diabetes (aSDHR 0.90, 95% CI 0.82-0.99), those with a recent MI in the year prior to CLC admission (aSDHR 0.78, 95% CI 0.62-0.98), having > 5 Elixhauser comorbidities (aSDHR 1.30, 95% CI 1.00-1.69) versus 0-1 comorbidities, documentation of limited prognosis or hospice use at admission (aSDHR 2.00, 95% CI 1.71-2.34), leaving food uneaten (aSDHR 1.24, 95% CI 1.13-1.37), cancer (aSDHR 1.13, 95% CI 1.03-1.24), IV feeding tube requirement (aSDHR 1.20, 95% CI 1.01-1.43), those with dependence on 3 to < 4 ADLs (aSDHR 1.38, 95% CI 1.11-1.73), and all 4 ADLs versus those dependent on <1 ADL (aSDHR 1.65, 95% CI 1.28-2.13), nursing turnover rate in quartile 4 (aSDHR 0.80, 95% CI 0.65-0.98), practical nursing turnover rates in quartile 3 (aSDHR 1.28, 95% CI 1.08-1.51) versus quartile 1.

Factors no longer associated with discontinuation of aspirin in the sensitivity analysis included: being in the age category 75-84 years and being greater than 85 years versus 65-74 years, treatment in fiscal year 2012 versus year 2009, having 2-3 Elixhuaser comorbidities or 4-5 Elizhauser comorbidities versus 0-1, recent weight loss, renal failure, being care for in the South versus the Northeast, bed sizes at the CLC of < 60 versus ≥ 120and a psychology turnover rate in quartile 4 versus quartile 1. The only factors which were significant in the sensitivity analysis but not significant in the primary analysis included: venous thromboembolism in the year prior (aSDHR 1.25, 95% CI 1.08-1.44) and having an ADL short form score of 2 to < 3 (aSDHR 1.38, 95% CI 1.11-1.73).

When stratified by receiving hospice or having a limited prognosis, the following variables were no longer significantly associated with aspirin discontinuation: hispanic ethnicity, other race and ethnicity category, coming from a nursing home versus an acute hospital, diagnosis of diabetes, venous thromboembolism is the last year, recent MI, cancer diagnosis, and IV feeding tube requirement. Variables which became significant in the limited prognosis and hospice use group, which were not previously associated with discontinuation in the adjusted sensitivity analysis model include: those in quartile 2 versus quartile 1 in distance from NOK (aSDHR 1.25, 95% CI 1.05-1.48), congestive heart failure (aSDHR 0.85, 95% CI 0.72-1.00), Elixhauser comorbidity categories 2-3 (aSDHR 1.55, 95% CI 1.02-2.34), and 4-5 (aSDHR 1.59, 95% CI 1.08-2.32) versus 0-1, renal failure (aSDHR 1.20, 95% CI 1.01-1.43), ADL short form score of 1 to < 2 (aSDHR 1.38, 95% CI 1.03-1.84) versus 0 to < 1, pharmacist turnover rate in quartile 3 versus 4 (aSDHR 1.34, 95% CI 1.03-1.75), practical nurse turnover rate in quartile 2 versus 1 (aSDHR 1.41,

95% CI 1.07-1.87), and quartile 2 versus 1 of the psychology turnover category (aSDHR 1.50, 95% CI 1.14-1.97).

Amongst those not in the limited prognosis or hospice use group, the following variables were no longer significantly associated with aspirin discontinuation: coming from the community or nursing home prior to admission versus an acute hospital, diabetes diagnosis, Elixhauser comorbidity category of > 5 versus 0-1, leaving food uneaten, cancer, all categories in the ADL short form scores, nursing turnover rate in quartile 4 versus 1, and quartile 3 of practical nurse turnover rates. The following variables were significant in the group without limited prognosis or hospice use at admission, which were not previously significant in the sensitivity analysis adjusted model: being cared for in fiscal year 2011 versus 2009 (aSDHR 0.77, 95% CI 0.62-0.96), current smoking status (aSDHR 1.37, 95% CI, 1.07-1.75), advanced dementia (aSDHR 0.82, 95% CI 0.68-0.98), and quartiles 3 (aSDHR 0.78, 95% CI, 0.63-0.98) or quartile 4 (aSDHR 0.69, 95% CI, 0.53-0.89) versus quartile 1 of the psychology turn over rate category.

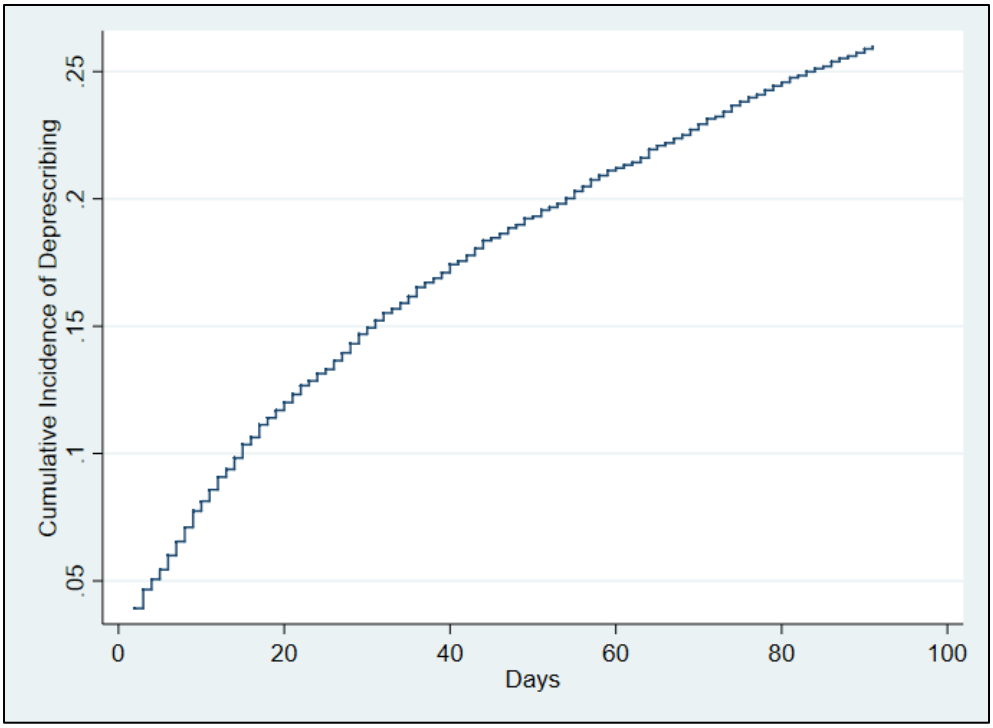

Figure 8: Cumulative Incidence of Discontinuation: Sensitivity Analysis

Table 9: Baseline Characteristics of the Cohort Qualifying for Discontinuation of Aspirin: Sensitivity Analysis

	Discontinuation Cohort (N= 9.430)	Limited Prognosis and Hospice Indicator (n=2,593)	No Limited Prognosis or Hospice indicator (N=6,837)
Demographics	**n (%)**	**n (%)**	**n (%)**
Age at admission**			
65-74	2,670 (28.3)	638 (24.6)	2,032 (29.7)
75-84	3,581 (38.0)	976 (37.6)	2,605 (38.1)
≥85	3,179 (33.7)	979 (37.8)	2,200 (32.2)
Sex**			
Male	9,321 (98.8)	2,548 (98.3)	6,773 (99.1)
Female	109 (1.2)	45 (1.7)	64 (0.9)
Race/ethnicity*			
White	7.533 (79.9)	2,114 (81.5)	5,419 (79.3)
Black	1,345 (14.3)	326 (12.6)	1,019 (14.9)
Hispanic	379 (4.0)	100 (3.9)	279 (4.1)
Other	173 (1.8)	53 (2.0)	120 (1.8)
Marital status**			
Married	4,972 (52.7)	1,448 (55.8)	3,524 (51.5)
Not married	4,458 (47.3)	1,145 (44.2)	3,313 (48.5)
Environment of Care Factors			

Fiscal year of admission			
2009	1,313 (13.9)	327 (12.6)	986 (14.4)
2010	1,280 (13.6)	362 (14.0)	918 (13.4)
2011	1,368 (14.5)	386 (14.9)	982 (14.4)
2012	1,313 (13.9)	363 (14.0)	950 (13.9)
2013	1,441 (15.3)	386 (14.9)	1,055 (15.4)
2014	1,435 (15.2)	404 (15.6)	1,031 (15.1)
2015	1,280 (13.6)	365 (14.1)	915 (13.4)
Living arrangement before admission**			
Acute hospital	6,717 (71.2)	1,739 (67.1)	4,978 (72.8)
Community	1,799 (19.1)	581 (22.4)	1,218 (17.8)
Nursing home	651 (6.9)	184 (7.1)	467 (6.8)
Other	263 (2.8)	89 (3.4)	174 (2.5)
Hospitalization in 90 days prior to admission*	5,808 (61.6)	1,651 (63.7)	4,157 (60.8)
Next of kin relationship to the Veteran*			
Spouse	3,570 (37.9)	931 (35.9)	2,639 (38.6)
Child	3,964 (42.0)	1,157 (44.6)	2,807 (41.1)
Sibling	892 (9.5)	234 (9.0)	658 (9.6)
Other relative	434 (4.6)	124 (4.8)	310 (4.5)
Friend or other specified person of unknown relation	570 (6.0)	147 (5.7)	423 (6.2)
Distance from next of kin ZIP code centroid to the CLC			
Quartile 1	2,360 (25.0)	755 (29.1)	1,605 (23.5)
Quartile 2	2,355 (25.0)	677 (26.1)	1,678 (24.5)
Quartile 3	2,358 (25.0)	627 (24.2)	1,731 (25.3)
Quartile 4	2,357 (25.0)	534 (20.6)	1,823 (26.7)
Cardiovascular Risk Factors			
Number of qualifying conditions (CAD, stroke/TIA)**			
1	7,009 (74.3)	2,051 (79.1)	4,958 (72.5)
2	2,421 (25.7)	542 (20.9)	1,879 (27.5)
Diabetes**	5,162 (54.7)	1,206 (46.5)	3,956 (57.9)
Congestive heart failure	4,916 (52.1)	1,386 (53.5)	3,530 (51.6)
Hypertension**	8.855 (93.9)	2,395 (92.4)	6,460 (94.5)
Hyperlipidemia**	6,626 (70.3)	1,753 (67.6)	4,837 (71.3)
Venous thromboembolism	1,144 (12.1)	309 (11.9)	835 (12.2)
Atrial fibrillation last year	1,823 (19.3)	499 (19.2)	1,324 (19.4)
Recent Myocardial Infarction in the last year**	757 (8.0)	247 (9.5)	510 (7.5)
Recent Stroke in the last year**	2,646 (28.1)	575 (22.2)	2,071 (30.3)
Current Smoker*			
No	8,589 (91.1)	2,331 (89.9)	6,258 (91.5)
Yes	841 (8.9)	262 (10.1)	579 (8.5)
Body Mass Index (kg/m^2)**			

Normal or healthy weight (18.5 to <25.0)	4,065 (43.1)	1,239 (47.8)	2,826 (41.3)
Underweight (<18.5)	757 (8.0)	300 (11.6)	457 (6.7)
Overweight (25.0 to <30.0)	2,688 (28.5)	697 (26.9)	1,991 (29.1)
Obese (≥30)	1,920 (20.4)	357 (13.8)	1,563 (22.9)
Markers of Poor Prognosis			
Advanced dementia**	2,906 (30.8)	652 (25.1)	2,254 (33.0)
Documentation of limited prognosis or hospice use at admission	2,593 (27.5)	-	-
Number of Elixhauser conditions**			
0-1	694 (7.4)	144 (5.6)	550 (8.0)
2-3	2,151 (22.8)	561 (21.6)	1,590 (23.3)
4-5	2,771 (29.4)	781 (30.1)	1,990 (29.1)
>5	3,814 (40.5)	1,107 (42.7)	2,707 (39.6)
Recent weight loss**	3,804 (40.3)	979 (37.8)	2,825 (41.3)
Leaves food uneaten**	3,619 (38.4)	1,176 (45.4)	2,443 (35.7)
Renal failure**	1,941 (20.6)	424 (16.4)	1,517 (22.2)
Dehydration	75 (0.8)	15 (0.6)	60 (0.9)
Acute change in mental status	915 (9.7)	261 (10.1)	654 (9.6)
Shortness of breath **	3,574 (37.9)	1,148 (44.3)	2,426 (35.5)
Cancer**	3,072 (32.6)	1,082 (41.7)	1,990 (29.1)
Activities of Daily Living (ADL) score**			
0 - <1	956 (10.1)	325 (12.5)	631 (9.2)
1 to <2	2,128 (22.6)	498 (19.2)	1,630 (23.8)
2 to <3	3,286 (34.9)	796 (30.7)	2,490 (36.4)
3 to <4	2,217 (23.5)	674 (26.0)	1,543 (22.6)
4	843 (8.9)	300 (11.6)	543 (7.9)
Aggressive Behavior**			
None	7,682 (81.5)	2,209 (85.2)	5,473 (80.1)
Moderate	1,110 (11.8)	229 (8.8)	881 (12.9)
Severe	477 (5.1)	122 (4.7)	355 (5.2)
Very severe	161 (1.7)	33 (1.3)	128 (1.9)
IV feeding tube in place**	924 (9.8)	164 (6.3)	760 (11.1)
On Mechanical Diet**	3,856 (40.9)	1,156 (44.6)	2,700 (39.5)
Swallowing Problems	1,736 (18.4)	505 (19.5)	1,231 (18.0)
Presence of any pain (n, % yes)**			
Yes	6,398 (67.9)	1,847 (71.2)	4,551 (66.6)
No	3,032 (32.2)	746 (28.8)	2,286 (33.4)
History of falls, hip fracture, and other fractures in past 180 days**			
Yes	4,738 (50.3)	1,244 (48.0)	3,494 (51.1)
No	4,692 (49.8)	1,349 (52.0)	3,343 (48.9)
Facility Factors			
US Census region of the CLC**			
Northeast	1,654 (17.5)	531 (20.5)	1,123 (16.4)
Midwest	2,946 (31.2)	686 (26.5)	2,260 (33.1)

South	3,263 (34.6)	902 (34.8)	2,361 (34.5)
West	1,567 (16.6)	474 (18.3)	1,093 (16.0)
Urban Influence Code for the CLC**			
Large metro	4,180 (44.3)	1,039 (40.1)	3,141 (45.9)
Small metro	3,509 (37.2)	1,041 (40.2)	2,468 (36.1)
Micropolitan	684 (7.3)	214 (8.3)	470 (6.9)
Noncore rural	1,057 (11.2)	299 (11.5)	758 (11.1)
Complexity Level of the parent station**			
1a (Highest)	3,474 (36.8)	818 (31.6)	2,656 (38.9)
1b	1,071 (1.14)	307 (11.8)	764 (11.2)
1c	1,707 (18.1)	518 (20.0)	1,189 (17.4)
2	1,369 (14.5)	418 (16.1)	951 (13.9)
3 (Least Complex)	1,809 (19.2)	532 (20.5)	1,277 (18.7)
Bed Size of CLC**			
<60 beds	1,288 (13.7)	470 (18.1)	818 (12.0)
60-120 beds	3,175 (33.7)	868 (33.5)	2,307 (33.7)
>/= 120 beds	4,967 (52.7)	1,255 (48.4)	3,712 (54.3)
Physician turnover rate			
Quartile 1	2,370 (25.1)	667 (25.7)	1,703 (24.9)
Quartile 2	2,481 (26.3)	647 (25.0)	1,834 (26.8)
Quartile 3	2,235 (23.7)	638 (24.6)	1,597 (23.4)
Quartile 4	2,344 (24.9)	641 (24.7)	1,703 (24.9)
Nurse turnover rate*			
Quartile 1	2,405 (25.5)	627 (24.2)	1,778 (26.0)
Quartile 2	2,349 (24.9)	620 (23.9)	1,729 (25.3)
Quartile 3	2,328 (24.7)	666 (25.7)	1,662 (24.3)
Quartile 4	2,348 (24.9)	680 (26.2)	1,668 (24.4)
Pharmacist turnover rate**			
Quartile 1	2,374 (25.2)	721 (27.8)	1,653 (24.2)
Quartile 2	2,347 (24.9)	592 (22.8)	1,755 (25.7)
Quartile 3	2,359 (25.0)	579 (22.3)	1,780 (26.0)
Quartile 4	2,350 (24.9)	701 (27.0)	1,649 (24.1)
Practical nurse turnover*			
Quartile 1	2,358 (25.0)	684 (26.4)	1,674 (24.5)
Quartile 2	2,403 (25.5)	628 (24.2)	1,775 (26.0)
Quartile 3	2,402 (25.5)	625 (24.1)	1,777 (26.0)
Quartile 4	2,267 (24.0)	656 (25.3)	1,611 (23.6)
Psychology Turnover**			
Quartile 1	2,367 (25.1)	674 (26.0)	1,693 (24.8)
Quartile 2	2,351 (24.9)	625 (24.1)	1,726 (25.2)
Quartile 3	2,355 (25.0)	596 (23.0)	1,759 (25.7)
Quartile 4	2,357 (25.0)	698 (26.9)	1,659 (24.3)
Medications Prescribed Which May Impact Aspirin Prescribing			
Anti-platelet*	1,749 (18.6)	435 (16.8)	1,314 (19.2)
Anti-thrombotic Agents**	4,729 (50.2)	1,026 (39.6)	3,703 (54.2)

H2- Receptor Antagonists	1,020 (10.8)	259 (10.0)	761 (11.1)
Proton Pump Inhibitors	4,962 (52.6)	1,329 (51.3)	3,633 (53.1)
NSAIDs**	361 (3.8)	77 (3.0)	284 (4.2)
*p<0.05, **p<0.01 for differences by limited prognosis or hospice use stratification			

Table 10: Univariable and Adjusted Subdistribution Hazard Ratios (SDHRs) for the Hazard of Discontinuation of Aspirin, Competing Risk Survival Analysis for Sensitivity Analysis

	Unadjusted SDHR N=9,430	**Adjusted SDHR N=9,430**	**Limited Prognosis Indicator Documented N=2,593**	**No Indication of Limited Prognosis Documented N=6,837**
Demographics	**SDHR (95% CI)**	**SDHR (95% CI)**	**SDHR (95% CI)**	**SDHR (95% CI)**
Age at admission				
65-74	Ref	Ref	Ref	Ref
75-84	1.09 (0.98-1.28)	0.94 (0.81-1.07)	0.96 (0.76-1.19)	0.92 (0.78-1.09)
≥85	1.06 (0.90-1.25)	0.89 (0.77-1.04)	0.82 (0.65-1.03)	0.95 (0.80-1.14)
Sex				
Female	1.46 (0.90-2.36)	0.97 (0.61-1.56)	0.81 (0.47-1.40)	1.07 (0.54-2.13)
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.05 (0.84-1.30)	1.05 (0.93-1.20)	1.12 (0.88-1.42)	1.02 (0.87-1.21)
Hispanic	1.58 (1.06-2.33)*	1.59 (1.19-2.14)**	1.40 (0.88-2.24)	1.70 (1.25-2.32)**
Other	1.13 (0.76-1.67)	1.43 (1.05-1.95)*	1.24 (0.76-.202)	1.55 (1.12-2.13)**
Marital status				
Married	1.00 (0.88-1.14)	1.04 (0.90-1.20)	1.07 (0.86-1.33)	1.01 (0.83-1.22)
Environment of Care Factors				
Fiscal year of admission				
2009	Ref	Ref	Ref	Ref
2010	1.08 (0.85-1.37)	1.07 (0.89-1.27)	1.06 (0.78-1.44)	1.14 (0.92-1.40)
2011	0.96 (0.73-1.27)	0.88 (0.73-1.05)	1.10 (0.85-1.43)	0.77 (0.62-0.96)*
2012	1.13 (0.88-1.45)	1.20 (0.97-1.50)	1.27 (0.91-1.78)	1.21 (0.94-1.55)
2013	0.84 (0.61-1.15)	0.95 (0.75-1.21)	0.90 (0.65-1.26)	1.00 (0.76-1.32)
2014	0.99 (0.73-1.31)	1.12 (0.90-1.39)	1.13 (0.78-1.62)	1.12 (0.85-1.47)
2015	1.10 (0.85-1.43)	1.05 (0.84-1.31)	1.14 (0.80-1.63)	0.99 (0.75-1.31)
Living arrangement before admission				
Acute hospital	Ref	Ref	Ref	Ref
Community	0.64 (0.52-0.78)**	0.83 (0.72-0.96)*	0.74 (0.60-0.90)**	0.94 (0.78-1.13)
Nursing home	0.47 (0.32-0.70)**	0.69 (0.55-0.86)**	0.71 (0.51-1.00)	0.69 (0.49-0.99)*
Other	0.64 (0.38-1.08)	0.85 (0.63-1.14)	0.74 (0.51-1.09)	0.97 (0.61-1.54)

Hospitalization in 90 days prior to admission	1.12 (0.97-1.29)	1.05 (0.93-1.18)	1.07 (0.89-1.29)	1.01 (0.88-1.16)
Next of kin relationship to the Veteran¥				
Spouse	Ref	Ref	Ref	Ref
Child	1.05 (0.89-1.25)	1.09 (0.94-1.26)	1.27 (1.00-1.63)	0.96 (0.79-1.17)
Sibling	0.89 (0.70-1.14)	0.97 (0.78-1.20)	1.09 (0.78-1.54)	0.87 (0.66-1.13)
Other relative	1.05 (0.74-1.49)	0.89 (0.66-1.19)	0.99 (0.65-1.49)	0.88 (0.58-1.34)
Friend or other specified person of unknown relation	0.79 (0.61-1.03)	0.92 (0.72-1.18)	1.11 (0.77-1.61)	0.77 (0.54-1.11)
Distance from next of kin ZIP code centroid to the CLC¥				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	1.01 (0.84-1.22)	1.07 (0.97-1.20)	1.25 (1.05-1.48)*	0.94 (0.80-1.10)
Quartile 3	0.93 (0.74-1.16)	1.02 (0.89-1.16)	1.19 (0.97-1.46)	0.92 (0.78-1.08)
Quartile 4	0.85 (0.69-1.05)	0.91 (0.79-1.05)	0.93 (0.74-1.17)	0.89 (0.74-1.07)
Cardiovascular Risk Factors				
Number of qualifying conditions (CAD, stroke/TIA, and/or diabetes)				
1	Ref	Ref	Ref	Ref
2	0.76 (0.67-0.90)**	0.98 (0.83-1.15)	0.80 (0.63-1.02)	1.07 (0.88-1.30)
Diabetes	0.83 (0.73-0.95)**	0.90 (0.82-0.99)*	0.90 (0.78-1.03)	0.90 (0.79-1.02)
Congestive heart failure	1.07 (0.94-1.22)	1.00 (0.91-1.09)	0.85 (0.72-1.00)*	1.12 (0.98-1.29)
Hypertension	0.88 (0.67-1.17)	0.94 (0.74-1.19)	1.16 (0.82-1.66)	0.78 (0.58-1.05)
Hyperlipidemia	0.89 (0.79-1.02)	0.98 (0.87-1.10)	1.03 (0.88-1.21)	0.92 (0.79-1.07)
Venous Thromboembolism	1.38 (1.16-1.65)**	1.25 (1.08-1.44)**	1.16 (0.93-1.44)	1.35 (1.12-1.63)**
Atrial Fibrillation	1.08 (0.90-1.30)	1.04 (0.92-1.17)	0.93 (0.75-1.14)	1.15 (0.97-1.38)
Recent stroke	0.82 (0.69-0.98)*	0.90 (0.76-1.08)	0.92 (0.71-1.19)	0.89 (0.72-1.11)
Recent MI	0.88 (0.65-1.19)	0.78 (0.62-0.98)*	0.91 (0.69-1.19)	0.63 (0.46-0.85)**
Current Smoker	1.01 (0.80-1.30)	1.12 (0.94-1.33)	0.89 (0.69-1.15)	1.37 (1.07-1.75)*
Body Mass Index				
Normal or healthy	Ref	Ref	Ref	Ref

weight (18.5 to <25.0)				
Underweight (<18.5)	1.26 (1.00-1.59)*	1.05 (0.87-1.26)	0.94 (0.75-1.18)	1.17 (0.93-1.48)
Overweight (25.0 to <30.0)	0.90 (0.76-1.07)	1.03 (0.90-1.18)	1.08 (0.89-1.32)	1.01 (0.86-1.19)
Obese (≥30)	0.86 (0.71-1.05)	1.09 (0.96-1.25)	1.13 (0.88-1.45)	1.05 (0.90-1.23)
Factors indicating limited prognosis				
Documentation of limited prognosis or hospice use at admission	3.40 (2.78-4.16)**	2.00 (1.71-2.34)**		
Number of Elixhauser conditions				
0-1	Ref	Ref	Ref	Ref
2-3	1.59 (1.14-2.21)**	1.25 (0.99-1.58)	1.55 (1.02-2.34)*	1.13 (0.82-1.55)
4-5	1.57 (1.11-2.22)*	1.24 (0.98-1.57)	1.59 (1.08-2.32)*	1.09 (0.80-1.48)
>5	1.68 (1.20-2.35)**	1.30 (1.00-1.69)*	1.62 (1.07-2.44)*	1.15 (0.82-1.60)
Advanced dementia	0.89 (0.73-1.10)	0.98 (0.88-1.11)	1.16 (0.98-1.37)	0.82 (0.68-0.98)*
Recent weight loss	1.16 (0.99-1.35)	1.07 (0.96-1.19)	1.07 (0.91-1.27)	1.04 (0.90-1.21)
Leaves food uneaten	1.73 (1.49-2.00)**	1.24 (1.13-1.37)**	1.41 (1.20-1.64)**	1.08 (0.95-1.24)
Renal failure	0.95 (0.79-1.15)	1.12 (1.00-1.26)	1.20 (1.01-1.43)*	1.04 (0.88-1.22)
Dehydration	0.68 (0.25-1.83)	0.79 (0.44-1.43)	0.87 (0.33-2.30)	0.62 (0.28-1.40)
Acute change in mental status	1.28 (0.99-1.65)	1.15 (0.97-1.37)	1.16 (0.87-1.55)	1.12 (0.88-1.42)
Shortness of breath	1.18 (1.00-1.39)*	1.00 (0.88-1.13)	0.94 (0.80-1.11)	1.02 (0.86-1.21)
Cancer	1.16 (0.99-1.36)	1.13 (1.03-1.24)**	1.13 (0.97-1.31)	1.07 (0.90-1.26)
Swallowing Problems	1.32 (1.12-1.55)**	1.07 (0.96-1.20)	1.13 (0.94-1.35)	0.98 (0.82-1.17)
IV feeding tube	1.14 (0.91-1.42)	1.20 (1.01-1.43)*	1.01 (0.73-1.38)	1.36 (1.10-1.68)**
Mechanical diet	1.20 (1.05-1.37)**	0.97 (0.87-1.08)	0.99 (0.85-1.16)	0.96 (0.81-1.13)
ADL score				
0 - <1	Ref	Ref	Ref	Ref
1 to <2	1.00 (0.76-1.32)	1.15 (0.94-1.41)	1.38 (1.03-1.84)*	0.95 (0.73-1.24)
2 to <3	1.17 (0.90-1.53)	1.38 (1.11-1.73)**	1.66 (1.23-2.24)**	1.09 (0.83-1.44)
3 to <4	1.44 (1.08-1.91)*	1.40 (1.11-1.76)**	1.43 (1.02-2.00)*	1.17 (0.87-1.56)
4	2.14 (1.53-2.99)**	1.65 (1.28-2.13)**	1.75 (1.17-2.63)*	1.30 (0.93-1.84)
Aggressive Behavior				
None	Ref	Ref	Ref	Ref
Moderate	0.82 (0.63-1.07)	0.92 (0.79-1.07)	0.89 (0.69-1.15)	0.92 (0.77-1.10)

Severe	1.03 (0.74-1.44)	1.08 (0.89-1.32)	1.16 (0.85-1.58)	0.99 (0.73-1.32)
Very severe	0.59 (0.33-1.06)	0.86 (0.58-1.28)	0.68 (0.29-1.59)	1.00 (0.61-1.63)
Presence of any pain	1.33 (1.11-1.60)**	1.02 (0.91-1.13)	1.07 (0.90-1.26)	0.98 (0.84-1.14)
History of falls, hip fracture, and other fractures in past 180 days	0.94 (0.82-1.08)	1.02 (0.91-1.14)	0.99 (0.85-1.15)	1.04 (0.90-1.20)
Facility Factors				
US Census region of the CLC				
Northeast	Ref	Ref	Ref	Ref
Midwest	0.98 (0.67-1.42)	0.97 (0.79-1.20)	1.09 (0.79-1.49)	0.89 (0.67-1.16)
South	1.15 (0.77-1.73)	1.16 (0.96-1.41)	1.18 (0.88-1.56)	1.09 (0.86-1.38)
West	1.50 (0.96-2.35)	1.20 (0.89-1.63)	1.33 (0.92-1.93)	1.15 (0.81-1.63)
Urban Influence Code for the CLC				
Large metro	Ref	Ref	Ref	Ref
Small metro	1.03 (0.80-1.33)	0.90 (0.77-1.06)	0.89 (0.69-1.14)	0.90 (0.76-1.07)
Micropolitan	1.44 (0.90-2.30)	1.15 (0.88-1.50)	1.19 (0.73-1.96)	1.07 (0.83-1.37)
Noncore rural	0.79 (0.42-1.50)	0.79 (0.59-1.05)	0.84 (0.58-1.21)	0.75 (0.54-1.02)
Complexity Level of the parent station				
1a (Highest)	Ref	Ref	Ref	Ref
1b	0.87 (0.53-1.44)	0.84 (0.65-1.09)	0.70 (0.48-1.00)	0.99 (0.76-1.30)
1c	0.82 (0.61-1.11)	0.82 (0.67-1.01)	0.75 (0.53-1.05)	0.89 (0.71-1.12)
2	0.97 (0.71-1.33)	1.01 (0.81-1.26)	1.02 (0.70-1.47)	0.95 (0.71-1.27)
3 (Least Complex)	0.72 (0.50-1.03)	0.97 (0.77-1.23)	0.89 (0.63-1.25)	1.02 (0.76-1.39)
Bed Size of CLC				
>120 beds	Ref	Ref	Ref	Ref
60-120 beds	0.80 (0.57-1.10)	0.90 (0.73-1.11)	0.94 (0.68-1.29)	0.88 (0.68-1.15)
<60 beds	0.66 (0.48-0.91)**	0.85 (0.70-1.03)	0.91 (0.69-1.21)	0.81 (0.64-1.03)
MD turnover rate				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	0.98 (0.73-1.32)	1.00 (0.83-1.20)	1.11 (0.89-1.40)	0.91 (0.73-1.14)
Quartile 3	1.03 (0.77-1.39)	1.11 (0.92-1.35)	1.13 (0.84-1.50)	1.07 (0.88-1.32)
Quartile 4	0.92 (0.73-1.16)	1.05 (0.89-1.25)	1.20 (0.91-1.57)	0.98 (0.79-1.22)
Nurse turnover rate				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	0.94 (0.70-1.27)	0.86 (0.71-1.04)	0.84 (0.62-1.14)	0.85 (0.67-1.09)
Quartile 3	0.93 (0.69-1.25)	0.85 (0.69-1.05)	0.84 (0.60-1.17)	0.86 (0.68-1.09)
Quartile 4	0.90 (0.67-1.21)	0.80 (0.65-0.98)*	0.82 (0.60-1.14)	0.78 (0.61-1.00)
Pharmacist turnover rate				
Quartile 1	Ref	Ref	Ref	Ref

Quartile 2	0.95 (0.74-1.21)	0.98 (0.81-1.18)	1.13 (0.88-1.45)	0.92 (0.70-1.19)
Quartile 3	1.14 (0.91-1.42)	1.04 (0.88-1.24)	1.34 (1.03-1.75)*	0.90 (0.71-1.15)
Quartile 4	1.00 (0.77-1.30)	1.01 (0.84-1.22)	1.12 (0.86-1.47)	0.99 (0.72-1.28)
Practical nurse turnover				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	1.27 (0.94-1.73)	1.19 (0.98-1.43)	1.41 (1.07-1.87)*	1.02 (0.80-1.31)
Quartile 3	1.19 (0.89-1.58)	1.28 (1.08-1.51)**	1.44 (1.10-1.88)**	1.09 (0.89-1.35)
Quartile 4	1.38 (0.99-1.94)	1.18 (0.96-1.46)	1.19 (0.86-1.67)	1.18 (0.94-1.47)
Psychology Turnover				
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	1.23 (0.95-1.58)	1.15 (0.97-1.37)	1.50 (1.14-1.97)**	0.93 (0.76-1.15)
Quartile 3	0.89 (0.71-1.12)	0.95 (0.79-1.15)	1.22 (0.94-1.60)	0.78 (0.63-0.98)*
Quartile 4	0.94 (0.73-1.20)	0.84 (0.69-1.02)	1.03 (0.78-1.36)	0.69 (0.53-0.89)**
Medications prescribed (which may impact Aspirin Rx)				
Anti-platelet agents	0.84 (0.70-1.00)	0.93 (0.82-1.07)	0.90 (0.72-1.12)	1.00 (0.85-1.18)
Anti-thrombotic agents	1.19 (1.02-1.39)*	1.13 (1.00-1.29)	1.17 (0.98-1.39)	1.10 (0.95-1.28)
H2RAs	0.97 (0.76-1.22)	0.94 (0.80-1.10)	0.91 (0.72-1.15)	1.00 (0.79-1.28)
PPIs	1.08 (0.95-1.23)	0.99 (0.89-1.09)	1.04 (0.91-1.20)	0.97 (0.85-1.12)
NSAIDs	1.10 (0.83-1.44)	1.04 (0.83-1.29)	1.03 (0.70-1.52)	1.06 (0.80-1.42)
*p<0.05, **p<0.01, ¥ indicates the variable was imputed				

4.0 Discussion

Continuation of aspirin for secondary prevention at end-of-life is controversial, given increased risks and unclear evidence about continued benefits; yet little is known about real-world patterns of aspirin use in patients near the end of life. In this large, national study of Veteran with LLE/AD who were admitted to VA CLCs over FY2009-2015, we found considerable variation in both aspirin use at CLC admission and subsequent aspirin discontinuation in those taking aspirin at admission. Specifically, only 48% used aspirin at admission, and one-third of initial users discontinued aspirin by day 91 of the CLC stay. We identified a number of resident and facility factors significantly associated with both aspirin use at admission and subsequent aspirin discontinuation. The factors most strongly associated with increased odds of aspirin use at CLC admission included a diagnosis of congestive heart failure, an MI in the year prior to admission, and concomitant anti-platelet therapy. In addition, individuals with limited prognosis or hospice use documented at admission had both greatly reduced odds of aspirin use and greatly increased hazard of subsequent discontinuation of aspirin. Finally, a number of individual markers of poor prognosis also predicted increased hazard of aspirin discontinuation after admission.

Current treatment guidelines recommend aspirin for secondary prevention indefinitely and do not address whether aspirin should be discontinued in the context of limited life expectancy, due to a lack of evidence on the risks and benefits of continuing aspirin in patients near the EOL. Therefore, it is difficult to judge whether or not the rate of receipt and discontinuation of aspirin observed in VA CLCs is reflective of “good” or “bad” care. The almost 50% split use of aspirin at CLC admission in this sample is not surprising, given this ambiguity. Our results highlight the need for future comparative effectiveness and safety studies of aspirin withdrawal in this

population. As randomized controlled trials of medication withdrawal in patients nearing the end of life face considerable feasibility barriers, further research using epidemiologic designs and existing healthcare data amongst large cohorts of older adults at EOL will be integral in our understanding of the risks and benefits of aspirin discontinuation. The data available within the VHA CLCs, which includes utilization data from both the VHA and Medicare, as well as a rich supply of clinical and facility level characteristics, would be an excellent resource for conducting such studies and allow for control of a large number of potential factors that could confound the relationship between aspirin discontinuation and outcomes. In recent commentary by Hilmer and Gnjidic, literature supports the deprescribing of medication such as central-nervous system acting medications to reduce outcomes such as falls, but falls short regarding literature pertaining to deprescribing in the setting of polypharmacy – and how this impacts the patient in terms of successful aging and quality of life. They go on to also discuss the critical need to move beyond the crutch of a clinical trial for these outcomes, demanding further research by observational studies, something which can certainly be conducted in the VHA setting.[83] In addition, the variation in aspirin discontinuation we observed across this population in the VHA CLC would be a strength for future epidemiologic studies, in that this variation can be harnessed to examine the effect of aspirin discontinuation on health outcomes in patients with LLE and/or AD.

We identified a number of factors in this study that were statistically significantly associated with higher and lower odds of aspirin receipt and hazard of aspirin discontinuation. Although it important to consider the exploratory nature of this study, our results generally lend to support to our conceptual model, which proposed that cardiovascular risk factors may encourage continuation of aspirin in this population, while markers of poor prognosis – and particularly explicit documentation of a new CLC resident as having limited prognosis or as a hospice patient

– may discourage its continuation. Our model was also supported in that several socio-demographic, environment of care factors, and facility characteristics were significantly associated with aspirin use and discontinuation. By including so many variables in these models, some of these variables will be statistically significant by chance alone; and, given the large sample, we were highly powered to see small differences between those who did and did not receive aspirin and those who did and did not discontinue aspirin. Notably, those factors which were more strongly associated with greater odds of aspirin receipt at admission and pose clinical implications included having had a recent myocardial infarction, concomitant treatment with antiplatelets (which is common pharmacological management post-MI), hypertension, and hypertension. We also found an increased odds of aspirin receipt associated with each class of medications we assessed, which may be reflective of a propensity toward polypharmacy. In addition to those with documentation of limited prognosis or hospice use at admission, receipt of aspirin was also markedly lower amongst females, those with a prior venous thromboembolism, those with cancer, those with greater ADL dependence, and patients of Hispanic ethnicity. With the exception of female sex, many of these same factors were also associated with aspirin discontinuation after admission, along with additional markers of poor prognosis.

In the absence of evidence regarding outcomes of aspirin discontinuation in older adults with LLE, managing aspirin will remain difficult in this population. Currently, it is unclear if older adults at EOL would benefit from discontinuation of aspirin for secondary prevention. The variability of aspirin prescribing for secondary prevention we observed in this study is directly at odds with treatment guidelines which strongly recommend initiating and indefinitely continuing use of aspirin, but in line with the predominant model that is used in geriatrics and palliative care when considering candidate medications for deprescribing.[29] Importantly, factors which predict

poor prognosis, such as cancer, high dependency on ADLs, and renal failure were associated with lower odds of aspirin receipt and higher hazards of aspirin discontinuation. This may indicate that prescribers are considering these factors heavily when considering the role of aspirin in these patients. While guidelines rarely recommend against the use of aspirin in this population, it is important to consider factors that increase one's risk of bleeding, such as being of older age, renal insufficiency, and concomitant use of other medications such as NSAIDs, anti-platelets and anti-thrombotic agents. The risk of major bleeding events is almost 3-fold higher in those on aspirin for secondary prevention versus placebo, while aspirin use reduces the risk of stroke and other cardiovascular disease by about 20%.[14] Without consensus amongst the geriatric and palliative care experts, the continuation of aspirin should be weighed against the risk of bleeding – of which gastrointestinal bleedings are significantly higher in older adults, and such bleeds are often more fatal and disabling in this population versus younger adults. The risk of a potential prothrombotic window shortly after aspirin discontinuation should be discussed with the patient as well. In the absence of withdrawal studies, this must be an individualized approach, which includes incorporating the patient and their caregivers' goals of care, and should be a shared decision making process.

Our results are generally consistent with a recent cross-sectional study of US adults with CAD surveyed by the 2015 Behavioral Risk Factor Surveillance System. Aspirin use was significantly associated with male sex, hypertension, diabetes, and "less than excellent general health" as reported by the patient. Lower reporting of aspirin use was associated with female sex, having less than a high school education, and self-reporting "excellent" health.[3] "Excellent-health" may be an indicator for lower rates of chronic comorbidities or concomitant medications, though it is unclear from this survey if this is true. Additionally, consistent with other studies looking at

chronic CVD medications in older adults, prescribing of aspirin was less likely amongst females.[44] However, older age was associated with higher odds of aspirin receipt and lower hazards of aspirin discontinuation in our study, contrary to our hypothesis that older age would predict lower odds of aspirin receipt and higher hazards of aspirin discontinuation. Regional differences in prescribing were also seen, though only in the West compared to the Northeast.[44] High odds of prescribing chronic CVD medication for secondary prevention was seen amongst those with CHF, and hypertension; lower odds of prescribing these medications occurred in those with atrial fibrillation, and in those with more extensive dependence in ADLs.[44, 45] As there are few studies which assess discontinuation of cardiovascular medications and factors predicting discontinuation in patients near the EOL, and none focusing on aspirin, there is little prior evidence to which we can compare our findings regarding predictors of discontinuation specifically.

4.1 Strengths

To our knowledge, this is the first national study examining prevalence and predictors of aspirin use and discontinuation in an end-of-life nursing home population. In addition, the use of BCMA data increases the novelty of this study. By using this data set, we can capture the total daily dose of all medications. In this study, it was highly important to be able to find those who were on a specific daily dose which is recommended for secondary prevention of CVD. This data is also important for determining exactly when a medication is initiated, discontinued, and re-started. For this study, it was imperative that proof of administration was available to determine if a patient met criteria for deprescribing, as well. Because most claims data only allow you to observe if a

patient was prescribed a medication every 30-90 days, typically a gap of at least 30 days is required to determine if a patient was potentially deprescribed on that medication. In this case, using BCMA data which provides information on daily administration of aspirin, we could theoretically rely on a shorter gap (e.g., 14 days) to confidently conclude discontinuation. This short gap period for discontinuation may reduce selection bias due to excluding or censoring potentially sicker patients who do not have this follow-up time available. Further, sensitivity analysis was performed using the traditional 30 day window; however in this case, we have much greater certainty than in studies relying on outpatient prescription drug claims or dispensing records that the patient truly not ingest the medication during those 30 days. This is especially important with regard to studying aspirin use and discontinuation, given that aspirin can be obtained over-the-counter and may not be reliably captured in claims or outpatient pharmacy dispensing records.

Another strength of this study was the incorporation of many chronic medications and chronic diseases which are either associated with aspirin use or CVD. This allowed us to explore more completely the predictors of receipt of aspirin and discontinuation of aspirin for secondary prevention in this population. Specifically, the inclusion of MDS variables allows us to evaluate more clinical prognostic factors than prior studies have included.[44-46] Additionally, using competing risk survival analysis is a major strength of this study, as it does not bias upward the cumulative incidence of deprescribing.

4.2 Limitations

A key limitation of our study is the unknown generalizability of our findings in non-Veteran end-of-life populations residing in non-VHA nursing homes (who, in contract to this

study's sample, are typically majority female), as well as to individuals near the EOL who remain in the community and are managed in outpatient settings. However, given that VHA and non-VHA guidelines do not differ with regard to recommendations for aspirin use in end-of-life populations, it is likely that similar care patterns would exist outside of VHA CLCs.

Another limitation of this study was our assumption of proportional hazards; i.e., that the effect of a given predictor variable on hazard of aspirin discontinuation does not vary over time. In cases where this assumption is violated and not addressed by altering the modeling approach, the reported hazard ratios must be interpreted as the average hazard over the 91 days of inclusion in the study, as opposed to an instantaneous hazard of deprescribing. There are several ways to address violations of the proportional hazards assumption, although all have difficulties. One approach is to split the model at different time periods and acquire different hazards of the event for each time period chosen. However, this method can introduce selection bias.[84] Alternatively, interaction terms can be introduced to the model by creating new variables that interact time with each variable that violates the assumption. However, this greatly increases the complexity of the modeling and can introduce variables which have SDHRs which are inherently difficult to interpret. In the discontinuation analysis for this study, we did test for violations of the proportional hazards assumption by interacting each variable in the bivariable competing risk models with follow-up time measured in days. In interpreting the p-values on these interaction terms to identify variables with significant interactions with time, we used a Bonferroni correction to account for the fact that with over 50 predictor variables ($p<0.00098$ indicates significant difference using a model with 51 total variables), some of these variables would violate the assumption by chance alone.[85] Using the Bonferroni correction, the following variables violated the assumption: the indicator for limited prognosis and hospice, leaving food uneaten, and dependency on ADLs. Thus,

for those variables, the reported SDHR must be interpreted as the average hazard of discontinuation over the 91 days of inclusion in the study, rather than the instantaneous hazard of deprescribing. Finally, a third limitation of our approach is the potential for measurement error in covariates that are defined based on past healthcare utilization (e.g., comorbidities). In cases where a resident had non-VHA health insurance other than Medicare fee-for-service, these conditions may be under-captured. However, the concomitant use of MDS assessments along with past healthcare utilization records to define most of the comorbidities likely minimized these errors.

5.0 Conclusion

Aspirin use for secondary prevention in Veteran nursing home residents with LLE and/or AD varied across patients, with just under 50% taking aspirin at CLC admission and only one-third subsequently having aspirin discontinued in the first 91 days of the CLC stay. Further qualitative studies may be useful in evaluating the decision-making process of continuing and discontinuing aspirin in those with LLE in this population. Next steps may include assessing effects of continuing versus discontinuing aspirin on negative cardiovascular outcomes (non-fatal MI, stroke, TIA, death due to cardiovascular disease, all-cause mortality) and negative bleeding outcomes (hospitalization due to bleeding events, death due to bleeding event, hemorrhagic stroke, major extracranial bleeding) among users of aspirin for secondary CVD prevention, which may better inform prescribers about the risk of discontinuing aspirin in this vulnerable population in the setting of lack of expert consensus and guideline recommendations.

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