Long-Term Use of Cardiovascular Medications: Identifying and Encouraging Optimal Duration

LONG-TERM USE OF CARDIOVASCULAR MEDICATIONS: IDENTIFYING AND ENCOURAGING OPTIMAL DURATION

ALEXIS A. KRUMME

A Dissertation Submitted to the Faculty of

The Harvard T.H. Chan School of Public Health

in Partial Fulfillment of the Requirements

for the Degree of *Doctor of Science*

in the *Department of Epidemiology*

Harvard University

Boston, Massachusetts

November, 2017

Dissertation Advisor: Dr. Joshua J. Gagne Alexis A. Krumme

Long-term Use of Cardiovascular Medications: Identifying and Encouraging Optimal Duration

Abstract

In the face of increasingly widespread availability and uptake of medications to treat and prevent cardiovascular disease, this dissertation is motivated by two broad research questions regarding the duration of cardiovascular therapy. First: how long should patients continue therapy when there are risks and benefits that may change over time? Second: how can continuation be encouraged when therapies are known to be safe and effective?

In Aim 1, we compared exposure definitions of antiplatelet discontinuation versus continuation at 12 months after a drug-eluting coronary stent and associations with ischemic and bleeding events. We found that increasing restrictions on the definition of therapy continuation yielded results consistent with those from the Dual Antiplatelet Therapy trial, in particular through greater compliance with assigned exposure status during follow-up. Our results also suggest the potential for residual confounding by unmeasured characteristics, which for ischemic events may exaggerate effects of continuation, while for bleeding events may attenuate such effects, particularly if providers are monitoring and appropriately discontinuing therapy among patients at higher risk of bleeding.

In Aim 2, we compared the long-term effectiveness and safety of prasugrel and clopidogrel. Among patients with acute coronary syndrome at the time of the coronary stent procedure, prasugrel use suggested ischemic benefit without increased risk of bleeding. In contrast, in patients with stable ischemic heart disease only, prasugrel use was not associated with ischemic benefit but was associated with increased risk of bleeding. For both groups, ischemic endpoint results are

consistent with trial findings; for the bleeding endpoint, results may reflect differences in baseline bleeding risk.

In Aim 3, we evaluated the impact of a pharmacy-based adherence improvement program on cardiovascular and healthcare outcomes. We found that adherence to cardiovascular medications improved by a small but significant amount among synchronized patients, with the largest improvements observed among patients with lowest baseline adherence level. Healthcare resource use decreased significantly, however cardiovascular clinical outcome rates did not differ between synchronized and control patients.

Table of Contents

List of Figures with Captions

List of Tables with Captions

Acknowledgements

I would first like to thank my research committee, to whom I am indebted for the tremendous intellectual support I've received throughout the dissertation process. Josh Gagne, Niteesh Choudhry, Bob Glynn, and Sebastian Schneeweiss have given me their time and thoughtful feedback, and engaged in lively discussions during our committee meetings. Their mentorship has been extraordinary and has made my experience as a young researcher at Harvard and in the Division of Pharmacoepidemiology so positive.

I would like to thank Josh Gagne in particular, who was my first link to DoPE over 4 years ago, for taking me on first as a research scientist and then as a student. Over two and a half years, he has helped me become a more rigorous thinker and researcher, always with an open ear and open mind. I could not have asked for a better advisor and mentor, and I hope I can one day bring the same generosity and support to someone else's education. I would also like to thank Niteesh Choudhry, my first boss at DoPE, who has consistently advocated for me and challenged me to take on new opportunities. He has taught me, often by example, to think and write like a researcher, and to be creative in my questions and thoughtful in my answers to them.

I would like to thank my family for their endless encouragement and support of my academic journey. In particular, I would like to acknowledge the strong women in my family, from my grandmother who studied for a PhD in Romania later in life, to my mom who came to the US from Romania at age 20 to go to college and graduate school, to my sister who set a high bar by obtaining a PhD from another school in Cambridge. Finally, to my husband, Alex: You are truly everything to me. You light up my day, every day.

Alexis A. Krumme

Chapter 1 DEFINING EXPOSURE IN OBSERVATIONAL STUDIES COMPARING OUTCOMES OF TREATMENT DISCONTINUATION

Alexis A. Krumme, MS[1,2]; Robert J. Glynn, PhD, ScD[1]; Sebastian Schneeweiss, MD, ScD[1,2]; Niteesh K. Choudhry, MD, PhD[1]; Angela Y. Tong, MS[1]; Joshua J. Gagne, ScD, PharmD[1,2]

Affiliations

[1] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120

[2] Harvard TH Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115

ABSTRACT

Background: Continuation of antiplatelet therapy beyond 12 months after a drug-eluting stent (DES) procedure reduced the risk of a major cardiovascular and cerebrovascular event (MACCE) in the Dual Antiplatelet Therapy (DAPT) trial. Observational studies have evaluated outcomes related to different durations of therapy but are susceptible to bias.

Methods and Results: Using de-identified claims from commercially insured and Medicare populations in the US, we compared how increasingly stringent definitions of exposure affect associations between antiplatelet continuation vs. discontinuation and MACCE, myocardial infarction, and intracerebral hemorrhage or gastrointestinal bleeding in patients meeting DAPT trial inclusion criteria between 2004 and 2013. Therapy continuation at 12 months was defined as: (1) having antiplatelet supply on hand vs. not (landmark time); (2) refilling within 30 days vs. not among individuals with antiplatelet supply; (3) criteria 2 plus continuous prior antiplatelet use; and (4) criteria 2 and 3 plus a cardiologist visit in months 10–12. Propensity score-adjusted hazard ratios were compared. Cohort sizes were 53,679, 27,524, 16,971, and 7,948, respectively, of which 20% were discontinuers on average. Increasing restriction led to progressively larger associations with continued treatment: Cohort 1 MACCE HR=0.79 (0.73, 0.87), MI 0.74 (0.65, 0.83), bleed 1.03 (0.96, 1.11), vs. Cohort 4 MACCE HR=0.66 (0.48, 0.91), MI 0.56 (0.37, 0.86), bleed 1.24 (0.95, 1.61). Estimates trended towards DAPT trial estimates and were associated with reduced levels of exposure misclassification.

Conclusions: In an example of long-term antiplatelet use, increasing restrictions on the definition of therapy continuation yielded results consistent with trial estimates by reducing exposure misclassification.

INTRODUCTION

Randomized trials are the gold standard for evaluating drug effectiveness, including longer-term therapy continuation compared to earlier discontinuation.(1–4) In one such example, the Dual Antiplatelet Therapy (DAPT) trial, subjects were randomized to either discontinue their antiplatelet regimen at 12 months after a drug-eluting stent (DES) procedure or continue for another 18 months, while maintaining continuous aspirin use.(5) The investigators found that continuation beyond 12 months reduced the risk of a major adverse cardiovascular or cerebrovascular event (MACCE) and elevated risk of a major bleeding event, prompting changes in the 2016 ACC-AHA guidelines for antiplatelet therapy duration.(6) At the same time, randomized trial designs pose particular challenges for studying optimal duration of longer-term therapy, such as high cost and long study duration due to extended follow up, which may explain why they are rarely conducted.

Observational data have also been used to evaluate outcomes related to different durations of therapy and may confer certain advantages over randomized designs, notably the ability to efficiently evaluate a wide range of therapy durations in large populations of real-world patients. Such studies have had to address two issues: (1) lack of complete information on reasons for therapy discontinuation after initiation, leading to residual confounding through a phenomenon known as the 'healthy adherer' or 'sick stopper' effect, which has been documented to differing degrees in administrative claims-based studies;(7,8) (2) imprecise assignment of therapy discontinuation, resulting in misclassification bias. The 'landmark time' method, which classifies patients into exposure groups solely based on whether they are on treatment at a given point in time, has been used in many studies exploring the optimal duration of antiplatelet therapy but may be particularly vulnerable to bias due to confounding and exposure misclassification.(9–17) Nonetheless, several observational studies of antiplatelet use beyond 12 months have been

directionally consistent with the DAPT Trial, suggesting that observational data sources could provide valid and useful results.(9,12)

We sought to evaluate the ability of a large administrative claims dataset to replicate the results from the DAPT trial. Starting with the landmark time method, we use a structured approach of increasing levels of cohort restriction to more accurately assign exposure to therapy discontinuation versus continuation to illustrate how these criteria affect the strength of an association between antiplatelet therapy duration and ischemic and bleeding events in relation to the DAPT trial results.(18)

METHODS

Study population and setting

We used data from the Clinformatics Data Mart (OptumInsight, Eden Prairie, MN) from January 1, 2004 to September 30, 2015 which includes medical and pharmacy claims data on patients with commercial insurance plans as well as patients with a Medicare supplement plan administered by a large national insurer.

To identify the initial cohort, we followed the inclusion and exclusion criteria of the DAPT trial, wherever possible.(19) Patients 18 years and older were included if they had a percutaneous coronary intervention (PCI) with DES placement and at least 180 days of continuous insurance eligibility prior and one year after. Patients were required to have filled a prescription for clopidogrel 75 mg or prasugrel 5 mg or 10 mg within 7 days of DES, and had to be free of stroke, coronary artery bypass graft (CABG), moderate or severe bleed, and any anticoagulant dispensing during the first year after. Patients additionally had to be free of PCI and myocardial infarction (MI) during days 42-365 after DES. A complete CONSORT diagram is available in Table 1.3.

Antiplatelet discontinuation at 12 months

We constructed four nested cohorts with increasingly stringent exposure definitions (Figure 1.1). Antiplatelet use and timing was measured using pharmacy claims data, which have been shown to be a valid proxy for actual medication taking.(20) For each definition, patients were required to be outcome-free between the 365-day mark post-DES placement date and the assigned exposure date, and were allowed to switch between the two antiplatelet therapies at most once during the one-year run-in period, as in the DAPT Trial.

Cohort 1 – Landmark time: We observed whether or not a patient had medication supply available on the day after the one-year mark after the DES procedure (i.e. at day 366), meaning the patient had a prescription dispensation prior to and had supply remaining from that prescription on that date based on the days supply. Patients with medication available were classified as continuers, those without as discontinuers, and follow-up began on day 367.

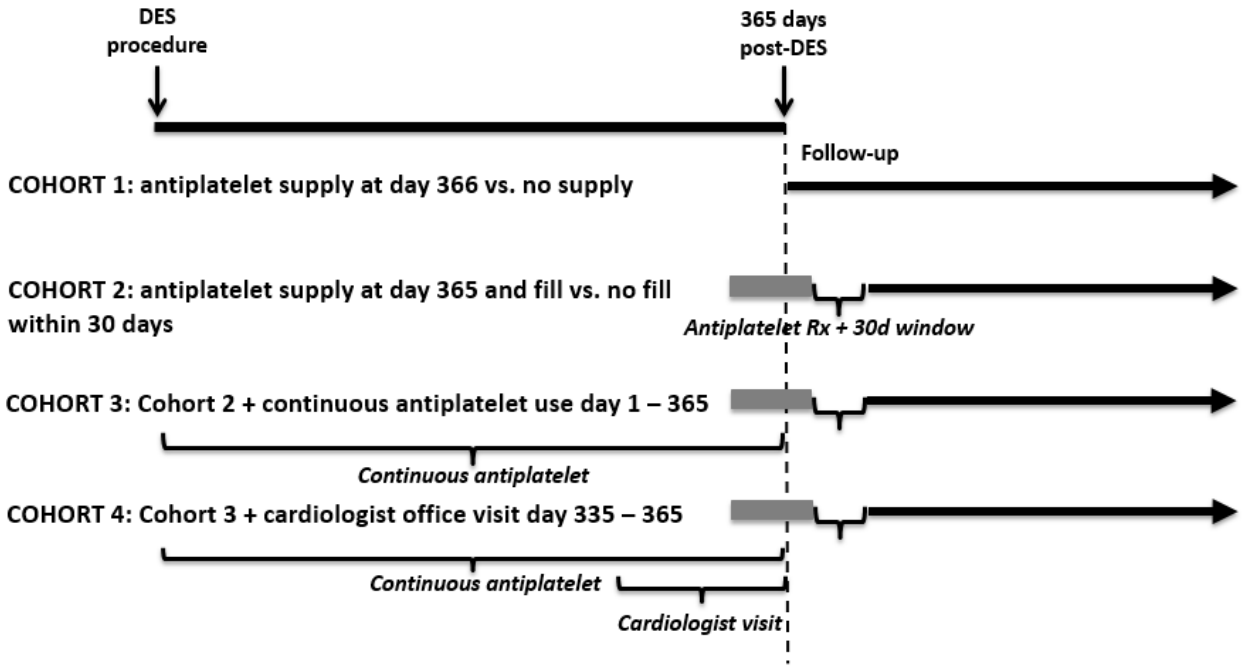
Cohort 2 – Refill vs. no refill after day 365: First restricting to patients with medication supply available at the one-year mark after DES procedure, we observed whether or not the patient refilled their antiplatelet medication within 30 days after the end of days supply of the fill spanning day 365. Patients with a refill within this period were classified as continuers, those without as discontinuers, and follow-up began after these 30 days had elapsed. For example, a patient with a 30-day antiplatelet fill on day 350 would have 15 pills remaining on day 365; for this patient, exposure status would be assigned based on the presence or absence of another fill within 30 days of day 380 post-DES. So as to maintain a population with exposure dates as close to the one-year mark as possible, we calculated the number of days between day 365 and the exposure date and included only patients below the median.

Cohort 3 – Continuous use prior to day 365: Cohort 3 additionally required members of Cohort 2 to be continuously taking their antiplatelet therapy in the year after stent placement. We observed whether a patient had medication supply available on each day in the year following DES placement

and calculated a proportion of days covered (PDC) for each patient. Following the same criteria as the DAPT trial, we restricted to patients with PDC≥0.80 and no interruption of therapy longer than 14 days. Exposure classification and date of start of follow-up were the same as in Cohort 2.

Cohort 4 – Cardiology office visit in months 10 – 12: We restricted to patients who met criteria for Cohort 3 and had an outpatient visit with a cardiologist in months 10 – 12 after DES. Exposure classification and start of follow-up date were the same as in Cohort 2.

The landmark time approach (Cohort 1) provides a simple indexing mechanism that can be used in settings where complete medication use information in unavailable.(9–12) However, patients who are not on therapy at the one year mark may have discontinued long before the measurement is taken. Cohort 2 attempts to reduce this misclassification through restriction to patients with an active medication at one year. Additionally, the landmark time approach does not typically account for medication use patterns prior to the landmark time. As such, the continuer group is likely enriched with patients who adhere to their medications whereas many of the discontinuers are likely non-adherent. This can create confounding bias due to the so-called 'healthy adherer' and 'sick stopper' effects.(7,21,22) Cohort 3, by restricting to patients with continuous use prior to start of follow-up, attempts to reduce these effects. We additionally anticipate that restriction to consistent prior adherence will correlate with continuous use among continuers during follow-up, reducing exposure misclassification. Finally, with Cohort 4 we restrict to a population where the decision to discontinue may be more likely to have been influenced by clinical, guideline-driven recommendations from a prescriber. This population may be more likely to comply with their prescriber's recommendations, thus reducing exposure misclassification.



DES = drug-eluting stent

Figure 1.1: Levels of restriction in exposure definition

Outcome measurement

The primary outcome was time to major adverse cardiovascular or cerebrovascular event (MACCE), a composite of myocardial infarction, stroke, or all-cause mortality within 18 months after exposure date. Secondary outcomes were time-to-myocardial infarction, and time-to-bleeding episode, defined as GUSTO moderate and severe bleed, consisting of intracerebral hemorrhage, inpatient blood transfusion, endovascular or gastric embolization procedure, and gastrointestinal or urogenital bleed episode.(23) Outcomes were defined based on ICD-9 diagnosis and procedure codes for inpatient stays.(24–26) Patients were censored if they experienced a gap in continuous insurance coverage >1 month.

Covariates

For the 180 days prior to the DES procedure, we included demographic and health plan benefit characteristics, clinical covariates related to the index stenting procedure, and

characteristics of the index antiplatelet medication. For the 365 days after the DES procedures, we included medication use characteristics, such as individual and total number of cardiovascular medications, adherence to cardiovascular medications, and the total number of unique medications, a measure of medication burden, and non-cardiovascular clinical comorbidity and a combined comorbidity score, and several characteristics shown to correlated with health-seeking behaviors.(27,28) In both periods, we measured cardiovascular comorbidity and resource utilization, including total hospitalization duration, emergency room visits, and intensive care unit stays.

Statistical analysis

We constructed a propensity score for each cohort using a logistic regression model predicting antiplatelet discontinuation as a function of the covariates above. In each cohort, we estimated unadjusted associations between antiplatelet continuation and time-to-event using Cox proportional hazards models, and models with propensity score adjustment and restricted cubic spline modeling, comparing these to the results from the DAPT trial.

We conducted several analyses to evaluate exposure misclassification. First, we evaluated the extent to which patients were compliant with their exposure classification during follow-up. We evaluated change in exposure status, defined as the presence of an antiplatelet prescription fill among discontinuers and a gap in supply of 30 days among continuers, during 6-month intervals of follow-up. We also evaluated the proportion of days covered by antiplatelet medications during follow-up, which under perfect compliance should be 1 among continuers and 0 among discontinuers. Second we conducted a misclassification bias sensitivity analysis to estimate bias-adjusted measures of association for each outcome using estimated values of exposure sensitivity (proportion of correctly classified continuers) and specificity (proportion of correctly classified discontinuers), under the assumption that exposure misclassification would be non-differential

with respect to the outcome.(29) The institutional review board of Brigham and Women's Hospital approved this study.

RESULTS

Cohorts and covariates

Out of more than 110,000 patients receiving a DES procedure between 2004 and 2013, 53,679 were included in Cohort 1, 34% of whom were discontinuers (Table 1.3). After restricting to patients with a prescription dispensation covering day 365, Cohort 2 comprised 27,524 patients (16% discontinuers). Of these, 16,971 were retained after restriction to continuous antiplatelet use prior in the year following DES placement (13% discontinuers). Cohort 4 consisted of 7,948 with a cardiology office visit in months 10-12 (15% discontinuers).

Across cohorts, indications for the initial stent procedure were similar, with slightly elevated rates of prior PCI and MI in cohorts 2, 3, and 4 (Table 1.2). Around half of patients presented with acute ischemic heart disease, with a small increase seen in continuers (55.5% - 56.3% for discontinuers, 56.8% - 59.4% for continuers). Average age was consistently around 61 years old, and the proportion of female patients was between 27%-30% across cohorts, with discontinuers having higher proportions of females in cohorts 2 – 4; these rates were similar to those in the DAPT trial (average age 61.7 years, 25.4% female). Discontinuers were more likely to be enrolled in Medicare, less likely to have an index prescription of clopidogrel and more likely to have a higher copayment for this initial fill. Around 2% of patients switched between the two generics, consistent with the rates seen in the DAPT trial.

Table 1.1: Baseline characteristics by cohort

Characteristic	Cohort 1		Cohort 2		Cohort 3		Cohort 4	
	Discontinuer (N=18,252)	Continuer (N=35,427)	Discontinuer (N=4,367)	Continuer (N=23,157)	Discontinuer (N=2,177)	Continuer (N=14,794)	Discontinuer (N=1,191)	Continuer (N=6,757)
Pre-Drug-Eluting Stent[1]								
Demographic and health plan benefit								
Age, mean (SD)	61.54 (11.2)	61.58 (10.8)	61.53 (10.7)	61.15 (10.9)	62.03 (10.6)	61.11 (10.8)	62.49 (10.8)	61.59 (10.9)
Female sex	27.8%	28.6%	30.3%	28.7%	30.0%	27.9%	32.2%	29.0%
Region								
Midwest	32.2%	31.3%	33.4%	31.2%	35.2%	32.2%	33.2%	28.5%
Northeast	8.5%	9.7%	7.9%	9.2%	8.6%	9.6%	8.7%	10.9%
South	46.8%	47.1%	44.8%	48.9%	41.9%	47.8%	44.6%	49.6%
West	12.3%	11.9%	13.9%	10.5%	14.2%	10.4%	13.4%	11.0%
Medicare	34.7%	31.2%	33.4%	31.2%	33.5%	30.1%	36.1%	32.2%
Health plan type								
HMO	16.5%	13.4%	14.4%	13.5%	14.6%	12.7%	12.7%	12.3%
Point of Service	42.9%	46.0%	43.4%	47.2%	42.6%	48.2%	41.2%	46.8%
PPO	9.1%	8.4%	8.8%	7.7%	8.5%	7.7%	8.9%	8.2%
Other	31.5%	32.2%	33.3%	31.6%	34.4%	31.5%	37.2%	32.7%
Stent event								
Acute ischemic heart disease	55.6%	56.8%	55.5%	58.0%	56.3%	59.4%	56.0%	58.2%
Emergency Room visit	17.5%	15.7%	18.1%	15.8%	18.2%	15.4%	18.1%	14.7%
Length of episode (days), mean (SD)	2.5 (1.9)	2.5 (1.8)	2.4 (1.5)	2.5 (1.8)	2.3 (1.4)	2.4 (1.7)	2.3 (1.4)	2.4 (1.7)
Year								
2004	9.3%	4.1%	4.5%	4.0%	3.8%	3.6%	3.0%	3.6%
2005	15.3%	9.5%	9.4%	9.7%	8.9%	8.7%	8.1%	7.9%
2006	12.3%	13.1%	9.7%	13.9%	8.6%	13.8%	7.5%	13.9%
2007	7.7%	10.1%	7.9%	10.5%	7.4%	10.9%	7.2%	10.9%
2008	8.2%	10.9%	9.2%	11.1%	9.6%	11.2%	9.6%	11.4%
2009	9.4%	11.4%	10.5%	11.6%	9.7%	11.8%	9.6%	12.0%
2010	11.1%	11.5%	13.8%	11.3%	13.8%	11.7%	13.9%	11.6%
2011	11.2%	12.0%	14.7%	11.7%	15.0%	11.9%	16.4%	11.9%
2012	10.8%	12.6%	15.0%	11.7%	17.7%	11.8%	19.0%	12.2%
2013	4.6%	4.8%	5.2%	4.5%	5.6%	4.7%	5.9%	4.6%
Index antiplatelet prescription								
Clopidogrel	91.2%	91.7%	88.2%	92.3%	88.8%	93.2%	87.3%	93.0%
Brand name drug	86.0%	83.7%	83.3%	84.4%	80.8%	83.5%	79.8%	83.5%
Days supply ≤30	91.3%	91.5%	91.0%	94.6%	91.5%	95.1%	92.4%	95.5%
Patient out of pocket amount, mean (SD)	$33.82 ($31.20)	$30.40 ($26.90)	$32.22 ($28.70)	$29.35 ($24.40)	$30.32 ($29.00)	$28.28 ($22.80)	$30.67 ($29.50)	$28.34 ($22.10)
Total drug cost, mean (SD)	$163.40 ($95.30)	$167.96 ($107.50)	$169.78 ($90.00)	$161.02 ($80.10)	$167.86 ($90.90)	$160.82 ($84.10)	$166.08 ($91.50)	$158.63 ($65.00)
Initiator	94.1%	92.3%	94.1%	92.0%	95.9%	93.4%	96.0%	93.5%
Days between DES and antiplatelet fill	1.1 (1.6)	1.1 (1.6)	1.1 (1.5)	1.2 (1.6)	0.9 (1.4)	1.1 (1.6)	1.0 (1.4)	1.1 (1.6)
Switch in generic during follow-up	2.1%	2.4%	2.8%	2.2%	2.1%	1.6%	2.4%	1.8%

Cardiovascular comorbidity & procedures								
Myocardial infarction	3.8%	3.5%	3.2%	3.7%	2.9%	3.6%	3.0%	3.7%
Percutaneous coronary intervention	3.2%	3.1%	2.4%	3.2%	2.2%	3.0%	2.5%	3.1%
Gastrointestinal bleed	2.4%	2.3%	2.4%	2.3%	1.9%	2.0%	1.8%	2.3%
Embolism	1.0%	0.9%	0.9%	0.9%	0.7%	0.8%	0.7%	1.0%
Left heart catheterization	4.6%	4.2%	3.6%	4.3%	3.8%	3.8%	4.1%	4.3%
Stress test	23.4%	23.7%	22.4%	23.0%	22.9%	22.0%	23.4%	24.2%
Resource utilization								
Outpatient visits								
0-1	28.9%	27.1%	27.7%	28.3%	28.6%	29.5%	26.3%	26.9%
2-5	48.5%	49.9%	49.9%	49.4%	50.2%	49.9%	49.3%	49.7%
>5	22.6%	23.1%	22.5%	22.3%	21.3%	20.6%	24.4%	23.4%
Hospitalization length of stay (days)								
0	85.8%	87.3%	88.3%	86.9%	89.3%	87.9%	89.0%	87.3%
1-7	10.5%	9.7%	9.2%	9.9%	8.5%	9.5%	8.6%	10.1%
>7	3.7%	3.1%	2.5%	3.2%	2.1%	2.6%	2.4%	2.7%
Emergency Room visit	10.0%	9.4%	9.5%	9.4%	9.3%	8.8%	9.6%	9.2%
Intensive Care Unit stay	7.6%	6.9%	6.5%	7.1%	5.5%	6.6%	5.2%	7.1%
Post-Drug-Eluting Stent[2]								
Cardiovascular comorbidity & procedures								
Myocardial infarction[3]	0.4%	0.4%	0.3%	0.4%	0.2%	0.3%	0.3%	0.3%
Percutaneous coronary intervention[3]	24.9%	27.8%	24.5%	28.9%	22.9%	30.1%	23.4%	30.0%
Gastrointestinal bleed	6.6%	5.9%	7.1%	6.4%	6.8%	5.6%	7.4%	6.0%
Embolism	2.1%	1.9%	2.2%	2.0%	1.8%	1.8%	2.0%	2.0%
Left heart catheterization	21.2%	21.7%	20.0%	23.2%	18.9%	23.4%	19.6%	23.4%
Stress test	31.6%	34.1%	32.8%	37.7%	34.1%	38.2%	36.5%	44.5%
Resource utilization								
Outpatient visits								
0-1	3.3%	1.3%	1.6%	1.0%	1.1%	0.8%	0.3%	0.1%
2-5	26.1%	22.9%	19.6%	18.7%	19.3%	18.8%	13.8%	12.2%
>5	70.6%	75.8%	78.8%	80.3%	79.6%	80.3%	86.0%	87.8%
Hospitalization length of stay (days)								
0	65.0%	66.7%	65.7%	64.7%	69.4%	66.3%	68.7%	65.7%
1-7	27.3%	27.7%	27.8%	29.0%	26.0%	29.3%	26.5%	29.8%
>7	7.7%	5.7%	6.5%	6.3%	4.6%	4.4%	4.8%	4.5%
Emergency Room visit	18.7%	17.3%	19.6%	18.6%	18.7%	17.6%	20.2%	18.8%
Intensive Care Unit stay	28.4%	29.0%	27.4%	30.6%	23.7%	30.5%	24.6%	30.8%
Comorbid medications								
Statin	87.5%	93.8%	93.4%	94.1%	94.6%	94.6%	94.6%	94.9%
ACEi[4]	54.3%	58.0%	56.2%	59.2%	55.9%	59.2%	56.1%	58.7%
ARB[5]	18.9%	20.7%	20.9%	20.6%	21.2%	20.3%	22.7%	21.6%
Calcium channel blocker	21.7%	22.2%	22.1%	22.0%	21.1%	20.8%	21.2%	22.1%
Beta blocker	67.4%	71.0%	70.8%	71.4%	71.5%	72.0%	71.4%	71.8%
Cardiovascular medications, mean (SD)	2.95 (1.3)	3.12 (1.2)	3.10 (1.2)	3.14 (1.2)	3.08 (1.2)	3.11 (1.2)	3.12 (1.2)	3.15 (1.2)
PDC[6] cardiovascular medications, mean (SD)	0.67 (0.3)	0.80 (0.2)	0.73 (0.2)	0.78 (0.2)	0.80 (0.2)	0.81 (0.2)	0.81 (0.2)	0.82 (0.2)
Oral hypoglycemic	22.4%	22.9%	21.7%	23.4%	19.6%	22.0%	18.6%	21.1%
Insulin	10.3%	9.6%	9.0%	9.8%	6.9%	8.6%	5.6%	8.1%

Other non-selective NSAID	14.7%	14.8%	16.4%	16.3%	14.8%	15.4%	15.4%	15.6%
Antiulcer and acid suppressant	28.7%	30.7%	31.0%	30.9%	31.2%	29.7%	32.2%	31.3%
Total medications, mean (SD)	11.14 (6.0)	11.54 (5.9)	11.90 (6.2)	12.02 (6.2)	11.56 (6.0)	11.58 (5.8)	12.03 (6.3)	11.86 (5.9)
Monthly copayment, mean (SD)	$147.68 ($124.30)	$184.67 ($136.00)	$178.75 ($136.30)	$212.11 ($154.30)	$189.01 ($144.30)	$214.09 ($153.30)	$195.64 ($138.40)	$219.60 ($154.00)
Medical comorbidity and procedures								
Hypertension	84.0%	85.9%	86.3%	86.9%	85.8%	86.4%	86.6%	88.2%
Hyperlipidemia	91.7%	94.4%	94.6%	95.1%	95.4%	95.4%	96.3%	96.4%
Congestive heart failure	4.0%	3.4%	3.7%	3.7%	2.6%	2.8%	3.3%	3.3%
Diabetes mellitus	35.8%	34.4%	33.5%	35.3%	29.9%	33.6%	28.6%	33.4%
Peripheral artery disease	11.9%	12.1%	11.9%	12.9%	10.5%	12.0%	11.0%	13.2%
Abnormal renal function	9.8%	9.2%	9.7%	9.7%	8.3%	8.8%	7.9%	9.2%
Nephropathy, diabetic or hypertensive	6.1%	5.7%	6.1%	6.0%	4.9%	5.3%	3.7%	5.3%
Abnormal liver function	4.5%	3.9%	3.8%	4.3%	2.9%	4.1%	2.7%	4.3%
Asthma/COPD	19.6%	18.1%	19.3%	19.2%	17.5%	18.1%	19.1%	18.5%
Alzheimer's or dementia	1.9%	1.6%	2.0%	1.7%	1.6%	1.3%	1.6%	1.3%
Depression	9.3%	9.1%	10.4%	9.7%	9.6%	9.0%	10.4%	8.9%
Cancer	7.1%	6.8%	7.6%	7.1%	7.7%	6.8%	8.6%	7.6%
Osteoporosis	7.3%	7.0%	7.4%	7.6%	7.9%	7.3%	8.8%	7.8%
Combined comorbidity score, mean (SD)	0.94 (2.1)	0.83 (2.0)	0.88 (2.1)	0.90 (2.0)	0.71 (1.9)	0.77 (1.8)	0.81 (1.9)	0.88 (1.9)
Healthy user characteristics								
Flu shot	22.2%	24.2%	25.9%	25.9%	28.0%	26.0%	30.1%	27.2%
Fecal occult blood test	6.3%	6.9%	7.5%	7.4%	7.9%	7.3%	9.1%	8.3%
Mammogram or PSA test	31.2%	34.8%	36.5%	37.8%	37.7%	38.4%	39.3%	41.3%
Colonoscopy	6.7%	6.8%	8.5%	7.7%	8.0%	7.4%	8.1%	7.6%

[1] 180 days prior to drug-eluting stent through stent procedure discharge date; [2] through exposure date; [3] during days 1-42 after DES, per DAPT trial inclusion criteria; [4] Angiotensin-converting enzyme inhibitor; [5] Angiotensin II receptor blocker; [6] Proportion of days covered

After the initial DES procedure, continuers across all cohorts had higher rates of PCI within the first 42 days (27.8% vs. 24.9% in Cohort 1; 30.0% vs. 23.4% in Cohort 2). Resource utilization rates in the year following DES placement were similar across all cohorts, as were prevalences of individual comorbidities, however discontinuers had slightly lower combined comorbidity scores compared to continuers in Cohorts 2 – 4, whereas this was reversed in Cohort 1 (0.94 in discontinuers vs. 0.83 in continuers). Cardiovascular medication use tended to be higher in continuers as was adherence to these medications, a difference most pronounced in Cohort 1 (PDC=0.67 for discontinuers, 0.80 for continuers). Resource utilization and healthy user characteristics did not have any consistent trends between exposure groups or across cohorts.

Outcomes

More than 90% of patients maintained continuous insurance eligibility during the maximum 18 months of follow-up. In Cohorts 1-4, 4.4%, 4.0%, 3.4%, and 3.2% of patients experienced a MACCE outcome, respectively. Risks of MI were 2.2%, 1.8%, 1.6%, and 1.6%, and for bleeding were 6.7%, 6.5%, 6.3%, and 6.6%, respectively. Unadjusted Cox models are presented in Figure 1.4. Results adjusting for propensity score (presented in Figure 1.3) constructed from all covariates in Table 1.1 are presented in Figure 1.2. For all outcomes, measures of association became larger with increased cohort restriction. Hazard ratios for MACCE for each subsequent restriction were 0.79 (0.73, 0.87), 0.75 (0.64, 0.87), 0.70 (0.56, 0.88), and 0.67 (0.48, 0.92), respectively, compared to 0.71, (0.59, 0.85) in the DAPT trial. For secondary outcomes, hazard ratios trended towards the point estimates of the DAPT trial. In Cohort 4, the hazard ratio for MI was 0.57 (0.37, 0.87) compared to 0.47 (0.37, 0.61) in the DAPT trial; for bleeding, it was 1.24 (0.95,

1.61) versus 1.61 (1.21, 2.16) in the DAPT trial.

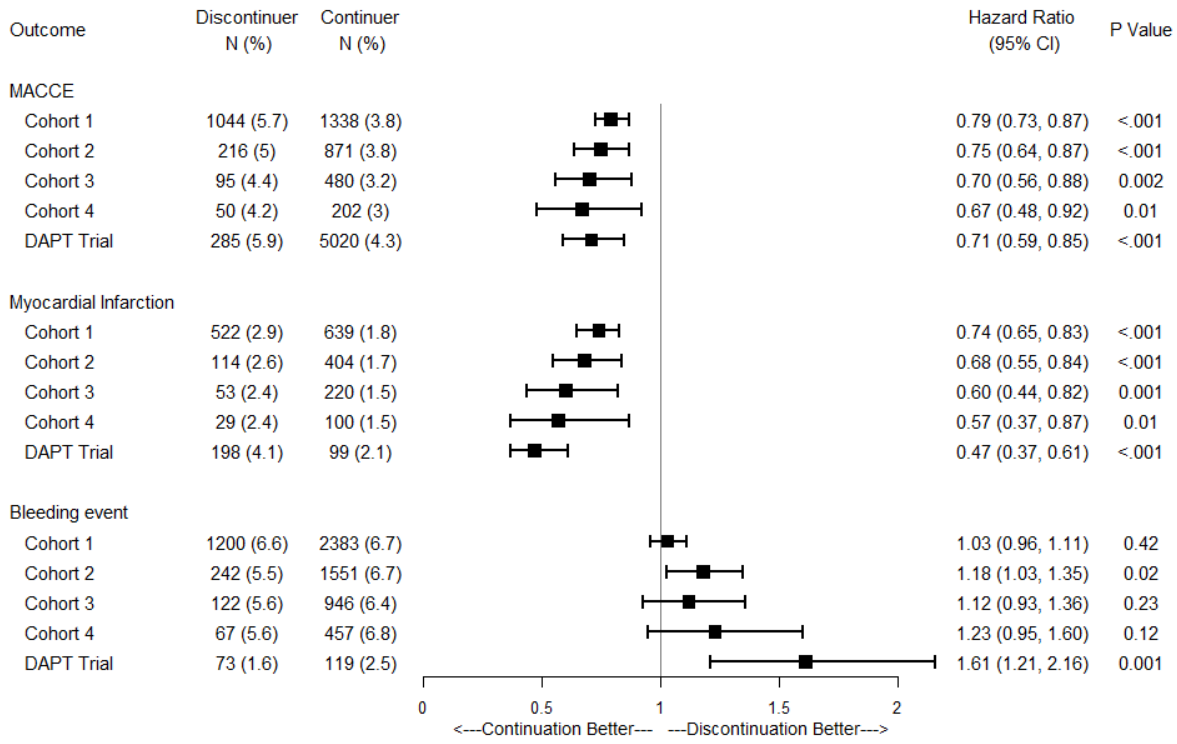


Figure 1.2: Adjusted hazard ratios, continuation versus discontinuation

Increasing cohort restriction led to reduced levels of exposure misclassification (Table 1.2). Of continuers in Cohort 1 at start of follow-up, 69% continued therapy in the first 6 months compared to 80% in Cohort 4. Of discontinuers in Cohort 1, 61% had no new fills within the first 6 months compared to 82% in Cohort 4. At 12 and 18 months of follow-up, continuers and discontinuers were similarly more compliant with their exposure classification in subsequent cohorts. Continuers had greater antiplatelet coverage in Cohort 4 versus Cohort 1 (PDC 0.75 vs. 0.68) while discontinuers had lower antiplatelet coverage (0.13 vs. 0.24), indicating greater consistency with assigned exposure status. We derived values of exposure sensitivity and specificity using the observed proportion of days covered from Table 1.2. With exposure sensitivity and specificity of 0.97 and 0.37, respectively, the corrected odds ratio of MACCE was 0.54 (0.30, 0.98), compared to 0.72 (0.60, 0.86) in the DAPT trial. For MI and bleeding outcomes, the corrected

odds ratios were 0.40 (0.17, 0.96) and 1.37 (0.90, 2.10), compared to 0.48 (0.38, 0.62) and 1.62 (1.21, 2.17) in the DAPT trial.

Table 1.2: Compliance with initial exposure classification during follow-up

Misclassification measure	Cohort 1		Cohort 2		Cohort 3		Cohort 4	
	Discontinuer	Continuer	Discontinuer	Continuer	Discontinuer	Continuer	Discontinuer	Continuer
Compliance with exposure classification:								
6 months of follow-up, N(%)	60.5%	68.6%	69.2%	75.6%	79.3%	79.5%	82.0%	79.8%
12 months of follow-up, N(%)	57.0%	56.1%	66.4%	62.8%	76.9%	67.6%	79.4%	68.4%
18 months of follow-up, N(%)	55.1%	47.7%	64.9%	54.9%	75.9%	59.6%	78.4%	60.5%
Days to change in exposure classification among patients with a change over 18 months, mean (med)	67 (22)	185 (134)	71 (26)	197 (162)	77 (29)	206 (178)	87 (29)	203 (177)
PDC with antiplatelet until censoring by MACCE outcome, insurance disenrollment, or death	0.24	0.68	0.18	0.72	0.14	0.74	0.13	0.75
PDC with antiplatelet until censoring by bleeding outcome, insurance disenrollment, or death	0.24	0.69	0.19	0.73	0.15	0.75	0.13	0.76

[1] Proportion of days covered; [2] Major adverse cardiovascular or cerebrovascular event

DISCUSSION

In a series of cohorts of long-term antiplatelet use after DES procedure, increasing restrictions on the definition of therapy continuation yielded results consistent with those from the DAPT trial. For ischemic events, results consistently trended downward, with each restriction having similar impact on the decreasing point estimates. Results for bleeding outcomes did not change monotonically across the levels of restriction and the final estimate was not as large as that from the DAPT trial, but were directionally consistent.

In parallel to these trends, increasing cohort restrictions led to greater compliance with assigned exposure status during follow-up. Reducing exposure misclassification that is non-differential with respect to the outcome would, in expectation, undo a bias towards the null, which may in part explain the trends in the point estimates observed in this study. Restrictions between cohorts 1, 2, and 3 led to the largest reductions in exposure misclassification, which in continuers at least is supported by research that has found prior adherence and medication taking patterns to be strong predictors of future use.(30) In contrast, patients with a visit to a cardiologist did not seem to have been significantly more compliant than other patients; this may reflect the cardiologist as having less influence on the decision to continue or discontinue therapy, or it is possible that prescriber-driven decisions regarding therapy duration are not necessarily coming from a cardiologist in an outpatient setting. Among discontinuers, the overall high level of new filling early in follow-up highlights challenges of assigning exposure status using prescription refill-based definitions; longer gaps between fills to define discontinuation may improve exposure misclassification but will also miss early events and further mismeasure exposure time of patients who discontinued long before their pill supply elapsed.

Our results also suggest the potential for residual confounding by unmeasured characteristics. Confounding by the 'healthy adherer' effect is generally expected to bias results

away from the null, exaggerating any differences between discontinuers and continuers.(7,31) For the MACCE outcome, point estimates from cohorts 3 and 4 surpassed the DAPT trial estimate, and a sensitivity analysis further adjusting for exposure misclassification bias suggested that corrected effects for MACCE and MI could be substantially larger than those from the trial. Differences in measured covariates, particularly in Cohort 1, suggest that continuers are healthier individuals than discontinuers, having for instance lower comorbidity and higher levels of adherence.

In contrast, for a safety outcome such as bleeding, we may expect residual confounding to attenuate rather than exaggerate the effect of continuation if prescribers are closely monitoring patients and discontinuing their therapy at 12 months based on perceived risk of bleeding. This may in part explain why bleeding estimates, even after correcting for exposure misclassification, fell short of the DAPT trial estimate. Small reductions in gastrointestinal bleed in the year after DES observed in our cohorts suggest as much, but the factors influencing prescriber decision-making are largely unmeasured in claims data. Evaluating important clinical and behavioral confounders, as well as the reason for discontinuation is critical for both confounding control and stratifying patients who may be 'sick stopper's from those who discontinue early due to treatment success or other clinical reasons.(9)

Few observational studies have evaluated outcomes of long-term antiplatelet use and most have done so using the landmark time approach. Nearly all have found improvements in ischemic events of varying magnitude and significance, with mixed results for bleeding.(10,12,32,33) Whereas the landmark time approach has the benefit of avoiding biases due to immortal time in assigning exposure after therapy initiation, it may not adequately guard against confounding or misclassification bias.(17) Moreover, the definition of how the landmark is assessed is rarely explicitly stated. Registry-based observational studies face the challenge of eliciting medication taking behaviors from patients, whereas claims-based studies must grapple with the issues we have

outlined here. This study explicitly describes these choices and compares their consequences. Future studies of optimal therapy duration may apply these findings in settings where exposure misclassification is a concern and relevant confounders are known and measured.

Our study has several limitations. We tried to mimic the DAPT trial as much as possible, but the use of administrative claims data limited our ascertainment of stent thrombosis and bleeding outcomes. The ICD-9 code for stent thrombosis covers all complications of cardiac devices, implants, and grafts and therefore was not used as an exclusion criterion due to low specificity. However, stent thrombosis is rare and would likely be captured in other exclusion criteria such as MI. Because codes for inpatient blood transfusions are typically not available in claims data, we likely did not capture all blood transfusions required for the GUSTO definition. However, we included gastrointestinal and urogenital bleed in our definition in an attempt to capture moderate bleeding episodes. This may have hindered our ability to directly compare our results to the DAPT trial. Aspirin use in our study could not accurately be measured because of the predominant use of over-the-counter medication, which typically does not generate a pharmacy claim. If discontinuation of antiplatelet therapy was highly correlated with discontinuation of aspirin, our results may have exaggerated the effects of continued antiplatelet use as compared to the DAPT trial in which participants were instructed to continue with aspirin therapy. In a systematic review of adherence to dual antiplatelet therapy after coronary stenting, aspirin adherence at 12 months was greater than 90%, despite a decline in antiplatelet use during this same period, suggesting that our assumption of continued aspirin may be tenable.(34)

One notable difference in baseline characteristics was the proportion of patients with prior MI (22% in DAPT vs. approximately 3.5% in our study). If disease severity or prior coronary stenting modifies the effect of continuation vs. discontinuation on outcomes, then our results may not be directly comparable without additional stratification. Reassuringly, the trial investigators

found consistent effects stratified on prior MI.(5) Finally, a period of increased risk immediately after discontinuation has been documented among clopidogrel users, which, in cohorts 2-4 would have attenuated our results relative to the DAPT trial.(20,35) However, the numbers of events during this period were small and are therefore unlikely to influence the results.

In an example of long-term antiplatelet use, results from this study demonstrate approaches for improved exposure definition when studying the effect of long-term medication use using large administrative databases.

ACKNOWLEDGEMENTS

AAK receives tuition support from Harvard TH Chan School of Public Health (partially supported by training grants from Pfizer, Takeda, Bayer, and Asisa)

REFERENCES

1. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med. 1993 Jul 1;329(1):1–7.

2. Kutner JS, Blatchford PJ, Taylor DH, Ritchie CS, Bull JH, Fairclough DL, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med. 2015 May;175(5):691–700.

3. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006 Dec 27;296(24):2927–38.

4. Moonen JEF, Foster-Dingley JC, de Ruijter W, van der Grond J, Bertens AS, van Buchem MA, et al. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning-the DANTE Study Leiden: A Randomized Clinical Trial. JAMA Intern Med. 2015 Oct 1;175(10):1622–30.

5. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014 Dec 4;371(23):2155–66.

6. Levine G. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease [Internet]. [cited 2016 Apr 5]. (American College of

Cardiology/American Heart Association Task Force on Clinical Practice Guidelines). Available from: http://content.onlinejacc.org/article.aspx?articleid=2507082

7. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med. 2011 May;26(5):546–50.

8. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA. 2007 Jan 10;297(2):177–86.

9. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet Lond Engl. 2013 Nov 23;382(9906):1714–22.

10. Tada T, Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Byrne RA, et al. Duration of dual antiplatelet therapy and long-term clinical outcome after coronary drug-eluting stent implantation: landmark analyses from the CREDO-Kyoto PCI/CABG Registry Cohort-2. Circ Cardiovasc Interv. 2012 Jun;5(3):381–91.

11. Tsai TT, Ho PM, Xu S, Powers JD, Carroll NM, Shetterly SM, et al. Increased risk of bleeding in patients on clopidogrel therapy after drug-eluting stents implantation: insights from the HMO Research Network-Stent Registry (HMORN-stent). Circ Cardiovasc Interv. 2010 Jun 1;3(3):230–5.

12. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. 2007 Jan 10;297(2):159–68.

13. Petersen JL, Barron JJ, Hammill BG, Cziraky MJ, Anstrom KJ, Wahl PM, et al. Clopidogrel use and clinical events after drug-eluting stent implantation: findings from the HealthCore Integrated Research Database. Am Heart J. 2010 Mar;159(3):462–470.e1.

14. Roy P, Bonello L, Torguson R, Okabe T, Pinto Slottow TL, Steinberg DH, et al. Temporal relation between Clopidogrel cessation and stent thrombosis after drug-eluting stent implantation. Am J Cardiol. 2009 Mar 15;103(6):801–5.

15. Thim T, Johansen MB, Chisholm GE, Schmidt M, Kaltoft A, Sørensen HT, et al. Clopidogrel discontinuation within the first year after coronary drug-eluting stent implantation: an observational study. BMC Cardiovasc Disord. 2014 Aug 13;14:100.

16. Shin D-H, Chae I-H, Youn T-J, Cho S-I, Kwon D-A, Suh J-W, et al. Reasonable duration of Clopidogrel use after drug-eluting stent implantation in Korean patients. Am J Cardiol. 2009 Dec 15;104(12):1668–73.

17. Mi X, Hammill BG, Curtis LH, Greiner MA, Setoguchi S. Impact of immortal person-time and time scale in comparative effectiveness research for medical devices: a case for implantable cardioverter-defibrillators. J Clin Epidemiol. 2013 Aug;66(8 Suppl):S138-144.

18. Schneeweiss S, Patrick AR, Stürmer T, Brookhart MA, Avorn J, Maclure M, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. Med Care. 2007 Oct;45(10 Supl 2):S131-142.

19. Mauri L, Kereiakes DJ, Normand S-LT, Wiviott SD, Cohen DJ, Holmes DR, et al. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. Am Heart J. 2010 Dec;160(6):1035–1041, 1041.e1.

20. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. Med Care. 2006 May;44(5):471–7.

21. Granger BB, Swedberg K, Ekman I, Granger CB, Olofsson B, McMurray JJV, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet Lond Engl. 2005 Dec 10;366(9502):2005–11.

22. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006 Jul 1;333(7557):15.

23. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med. 1993 Sep 2;329(10):673–82.

24. Wahl PM, Rodgers K, Schneeweiss S, Gage BF, Butler J, Wilmer C, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):596–603.

25. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:100–28.

26. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011 Jun;20(6):560–6.

27. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011 Jul;64(7):749–59.

28. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol. 2007 Aug 1;166(3):348–54.

29. Lash T, Fox M, Fink A. Applying quantitative bias analysis to epidemiologic data. New York: Springer; 2009.

30. Franklin JM, Shrank WH, Lii J, Krumme AK, Matlin OS, Brennan TA, et al. Observing versus Predicting: Initial Patterns of Filling Predict Long-Term Adherence More Accurately Than High-Dimensional Modeling Techniques. Health Serv Res. 2015 Apr 16;

31. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. Epidemiol Camb Mass. 2001 Nov;12(6):682–9.

32. Chang TI, Montez-Rath ME, Shen JI, Solomon MD, Chertow GM, Winkelmayer WC. Thienopyridine use after coronary stenting in low income patients enrolled in medicare part D receiving maintenance dialysis. J Am Heart Assoc. 2014 Oct 21;3(5):e001356.

33. Mulukutla SR, Marroquin OC, Vlachos HA, Selzer F, Toma C, Kip KE, et al. Benefit of long-term dual anti-platelet therapy in patients treated with drug-eluting stents: from the NHLBI dynamic registry. Am J Cardiol. 2013 Feb 15;111(4):486–92.

34. Czarny MJ, Nathan AS, Yeh RW, Mauri L. Adherence to dual antiplatelet therapy after coronary stenting: a systematic review. Clin Cardiol. 2014 Aug;37(8):505–13.

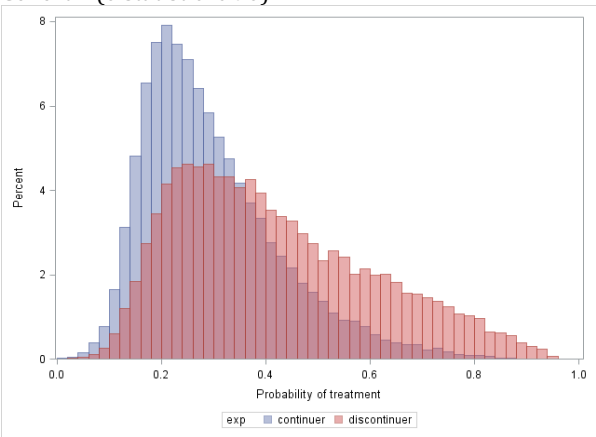
35. Ho PM, Tsai TT, Wang TY, Shetterly SM, Clarke CL, Go AS, et al. Adverse events after stopping clopidogrel in post-acute coronary syndrome patients: Insights from a large integrated healthcare delivery system. Circ Cardiovasc Qual Outcomes. 2010 May;3(3):303–8.

APPENDIX

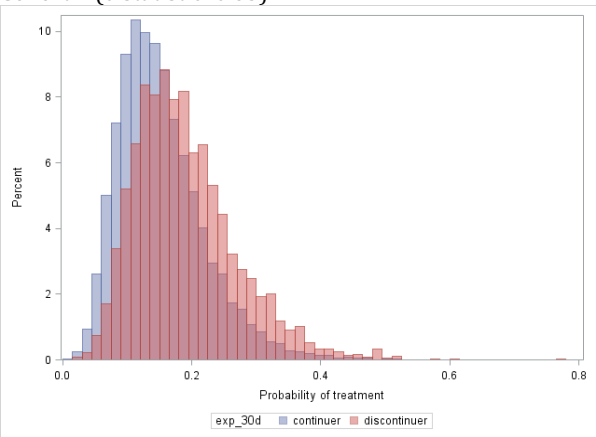
Table 1.3: Cohort inclusion criteria

Cohort flow	N
Drug-eluting stent (DES) procedure during study period with 180 days continuous eligibility prior	130,568
+ Clopidogrel or prasugrel dispensed within 7 days of DES	86,157
+ No missing or ambiguous sex or age information; over 18 years old	86,156
+ No percutaneous coronary intervention or myocardial infarction in days 42-365 after DES	79,801
+ No stroke, coronary artery bypass graft, GUSTO bleed, or anticoagulant dispensing during 365 days after DES	73,229
+ Continuous eligibility 365 days after DES	54,163
+ Once daily dosage on all antiplatelet prescription fills in 365 days after DES, no more than one switch between two generic antiplatelets	53,802
+ No MI, stroke, GUSTO bleed, PCI, CABG, or anticoagulant fill between DES+365 and exposure date	53,679 (Cohort 1)
+ On therapy at day 365 and remaining medication on hand ≤46 days; continuous medical and pharmacy insurance eligibility between DES+365 and exposure date; no MI, stroke, bleed, PCI, CABG, or anticoagulant fill between DES+365 and exposure date	27,524 (Cohort 2)
+ Proportion of days covered ≥0.8 prior to day 365; no 14-day gap prior to day 365	16,971 (Cohort 3)
+ Cardiology office visit during months 10 – 12 after DES	7,948 (Cohort 4)

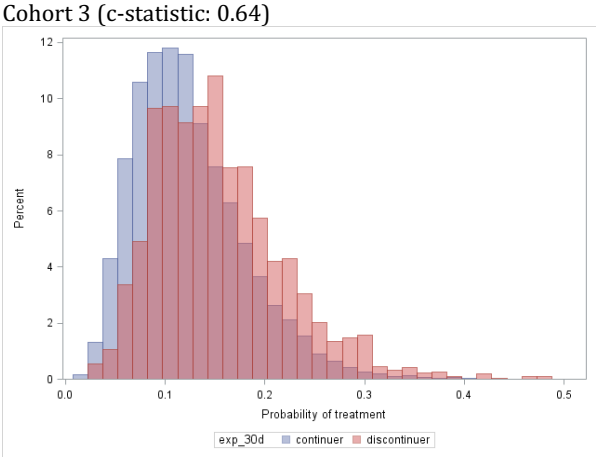
Cohort 1 (c-statistic: 0.70)



Cohort 2 (c-statistic: 0.65)



Cohort 3 (c-statistic: 0.64)



Cohort 4 (c-statistic: 0.65)

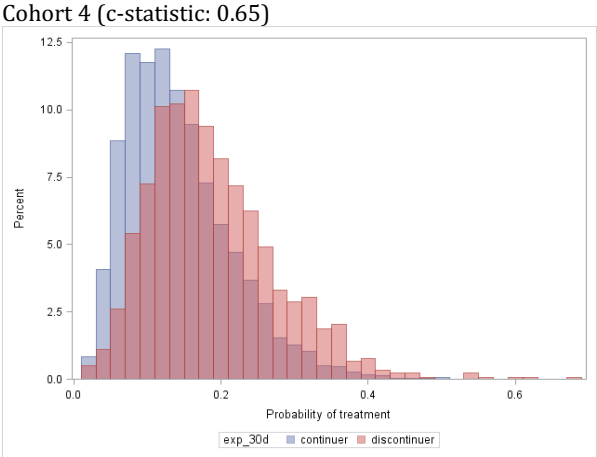


Figure 1.3: Propensity score distribution by cohort

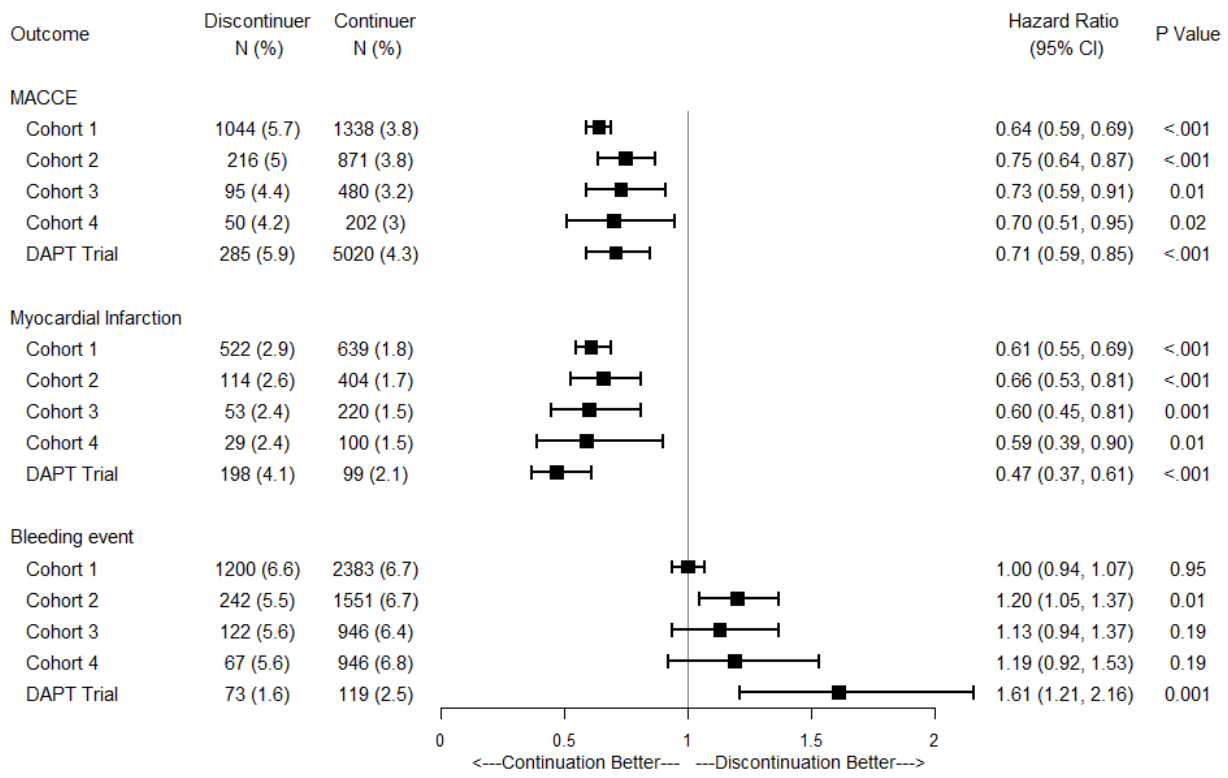


Figure 1.4: Unadjusted hazard ratios, continuation versus discontinuation

Chapter 2 COMPARATIVE EFFECTIVENESS AND SAFETY OF LONG-TERM PRASUGREL AND CLOPIDOGREL THERAPY AFTER DRUG-ELUTING STENT

Alexis A. Krumme[1,2]; Robert J. Glynn[1]; Sebastian Schneeweiss[1,2]; Niteesh K. Choudhry[1,2]; Jennifer Lewey[3]; Angela Y. Tong[1]; Joshua J. Gagne[1,2]

Affiliations

[1] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120

[2] Harvard TH Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115

ABSTRACT

Background: Prasugrel has been increasingly prescribed for the prevention of thrombotic events after acute coronary syndrome (ACS), however limited real-world data exist examining its long-term safety and effectiveness relative to clopidogrel. We sought to evaluate the long-term effectiveness and safety of treatment with prasugrel versus clopidogrel among patients with acute coronary syndrome and those with stable ischemic heart disease only.

Methods: We used data from 2009 – 2015 from two large US administrative claims databases which include patients with commercial insurance and those with a Medicare supplement plan. Patients with a drug-eluting stent (DES) and a prescription fill for clopidogrel or prasugrel within 7 days were included. The primary outcome was major adverse cardiovascular or cerebrovascular event (MACCE), a composite of myocardial infarction (MI), stroke, or all-cause mortality within 30 months. Secondary outcomes were MI alone and moderate or major bleeding episode. We followed patients until treatment discontinuation or switch, health plan disenrollment, or end of data. We evaluated outcomes using Cox proportional hazards models with propensity score matching weights, combining effects across databases using an inverse variance-weighted, fixed-effects model. In secondary analyses, we estimated hazard ratios among patients event-free and on-treatment at six and twelve months of therapy.

Results: The study included 83,896 patients in four cohorts defined by database and ACS status at the time of stenting; after propensity score matching weights were applied, the cohort consisted of 32,483 weighted patients. In weighted Cox proportional hazards models, the combined hazard ratios (HRs) suggested decreased risk of ischemic events with prasugrel among patients with ACS (HR=0.86, 95% CI=(0.73, 1.02) for MACCE; HR=0.83, 95% CI=(0.68, 1.01) for MI), and similar rates of bleeding (HR=1.05, 95% CI=(0.93, 1.18)). Among patients without ACS, HRs for ischemic events were similar in patients on prasugrel vs. clopidogrel (HR=1.08, 95% CI=(0.83, 1.41) for MACCE, and

HR=1.12, 95% CI=(0.78, 1.59) for MI), while bleeding rates were significantly higher in prasugrel patients (HR=1.18, 95% CI=(1.01, 1.38)). In subsequent 6- and 12-month cohorts, the HRs for MACCE, MI, and bleeding were consistent with those at baseline, but did not reach statistical significance. In all cohorts, prasugrel use was associated with earlier discontinuation relative to clopidogrel.

Conclusions: Evidence for antiplatelet use increasingly favors long-term therapy. Our study suggests that long-term treatment favors prasugrel use for the prevention of ischemic events without compensatory increases in bleeding events among patients with ACS; however the evidence is less clear for patients without ACS. Consideration of long-term compliance patterns of these two therapies is warranted in future research efforts to guide prescriber decision-making at the time of therapy initiation.

INTRODUCTION

Dual antiplatelet therapy with an adenosine diphosphate receptor (ADP) inhibitor plus aspirin has been the standard of care for reducing the risk of thrombotic events after acute coronary syndrome (ACS) for over 15 years. In 2009, the TRITON-TIMI 38 randomized trial demonstrated the superior efficacy of prasugrel plus aspirin compared to the older antiplatelet agent clopidogrel plus aspirin in reducing the risk of ischemic events over 15 months of treatment, with an accompanying increased risk of major bleeding events among patients with ACS undergoing percutaneous coronary intervention (PCI).(1) Prasugrel plus aspirin reduced the primary efficacy endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 2.3% on the absolute scale (19% on the relative scale) but increased risk of major bleeding by 0.6% on the absolute scale (34% on the relative scale). Since then, prasugrel, along with the newer agent ticagrelor, has been increasingly prescribed, however clopidogrel continues to account for approximately two thirds of new antiplatelet prescriptions after ACS and PCI.(2,3)

More recent studies have focused on whether longer-term antiplatelet therapy offers significant benefit for the prevention of late clinical events.(4,5) In 2014, results from the Dual Antiplatelet Therapy (DAPT) trial suggested that the beneficial effect of continuation of dual antiplatelet therapy beyond 12 months, versus discontinuation, in preventing major adverse cardiovascular and cerebrovascular events (MACCE) may be stronger in patients on prasugrel compared to those on clopidogrel, however the effectiveness of these two therapies was not formally compared because assignment to a particular therapy was not randomly allocated.(6) Meanwhile, only limited observational data exist to support the comparative effectiveness of these therapies in large populations in real-world settings, and whether any effects persist with duration

of treatment.(7–9) In contrast to randomized trial results, two recent registry-based studies found no significant difference in ischemic effects of the drugs in the first year of therapy.(7,8)

Establishing which therapy is more effective and safer is relevant to clinicians at the time of stenting procedure as well as over the course of post-procedure treatment. In this study, we used two large nationally-representative administrative claims databases to evaluate the long-term effectiveness and safety of treatment with clopidogrel versus prasugrel, specifically looking at effects after stenting procedure, and after 6 and 12 months of therapy. The study focuses on two groups of individuals, those with acute coronary syndrome and those with stable ischemic heart disease only, to evaluate whether there may be categorical differences in effects in these populations.

METHODS

Study population and setting

We used data from the Optum Research Database (ORD) and Truven Health Analytics MarketScan databases from July 1, 2009 to September 30, 2015 for ORD and to September 30, 2014 for MarketScan. These data include medical and pharmacy claims data on patients with commercial insurance plans as well as patients with a Medicare supplement plan.

We identified patients 18 years and older with a percutaneous coronary intervention (PCI) with drug-eluting stent (DES) placement and a prescription fill for clopidogrel 75 mg or prasugrel 5 mg or 10 mg within 7 days of DES, and at least 180 days of continuous insurance eligibility prior to the DES procedure. Patients additionally had to remain event-free and enrolled in benefits between the DES date and first antiplatelet prescription. We stratified our study population on database enrollment and the patient's indication for the DES: acute coronary syndrome vs. no acute coronary syndrome. These diagnoses were identified by ICD-9 codes (410.xx – 411.xx for acute coronary

syndrome; no ACS codes and 413.xx – 414.xx for no acute coronary syndrome) from the DES procedure episode.

Exposure definition

Patients were assigned to a treatment group (clopidogrel or prasugrel) based on their first prescription fill after DES and the index date was assigned as the prescription fill date. Antiplatelet use and timing was measured using pharmacy claims data, which have been shown to be a valid proxy for actual medication taking.(10)

Outcome measurement

The primary outcome was time to major adverse cardiovascular or cerebrovascular event (MACCE), a composite of myocardial infarction, stroke, or all-cause mortality within 30 months after index date. Secondary outcomes were time-to-myocardial infarction, and time-to-bleeding episode, defined as GUSTO moderate and severe bleed, consisting of intracerebral hemorrhage, inpatient blood transfusion, endovascular or gastric embolization procedure, and gastrointestinal or urogenital bleed episode.(11) Outcomes were defined based on ICD-9 diagnosis and procedure codes for inpatient stays.(12–14)

Covariates

We assessed covariates in the 180 days prior to and including the DES procedure and characteristics of the index antiplatelet prescription. We included demographic and health plan benefit characteristics, clinical covariates related to the stenting procedure, and select cardiovascular and resource utilization characteristics. We also included medication use characteristics, such as individual and total number of cardiovascular medications and the total number of unique medications, a measure of medication burden, and non-cardiovascular clinical comorbidity as well as a combined comorbidity score. Finally, we included several characteristics

shown to be correlated with health-seeking behaviors, such as receipt of influenza vaccination.(15,16)

Statistical analysis

Within cohorts (i.e. those with and without ACS and separately in each database), we compared the baseline characteristics of the patients in the prasugrel and clopidogrel groups. To account for factors associated with receipt of initial antiplatelet treatment and study outcomes, we constructed a propensity score using a logistic regression model predicting exposure treatment as a function of the covariates above. Continuous covariates were modeled with quadratic terms. The propensity score was used to construct matching weights for each patient based on the probabilities of receiving each of the comparator treatments for that database and indication.(17) Briefly, matching weights reweight treatment groups to emulate a propensity score matched population. To our knowledge, this is the first study to use matching weights in an applied setting. The result is a cohort that downweights patients with low propensity of treatment without trimming them from the cohort as in matching. The numerator of the matching weight is the minimum of the propensity score for receipt of prasugrel and receipt of clopidogrel; the denominator is the propensity score corresponding to the treatment received. Balance in the weighted cohorts was assessed using absolute standardized differences.(18)

To study the time-varying comparative effectiveness and safety of prasugrel and clopidogrel, we evaluated outcomes among the subsets of patients remaining uncensored for that outcome in the first 6 and 12 months after index antiplatelet prescription. For example, to study MACCE beyond 6 months, our cohort consisted of patients who did not experience MACCE in the first 180 days after DES, did not experience a gap of 30 days or more in treatment, did not switch treatment, and had continuous insurance eligibility up to that point. In cohorts beginning at index date (*Baseline Cohort*), patients were followed for a maximum of 900 days (30 months). The subset

of patients eligible for follow-up at 6 months (*6-Month Cohort*) was followed for up to 24 months and those eligible for follow-up at 12 months (*12-Month Cohort*) for up to 18 months. We constructed propensity score matching weights separately in each cohort defined by time period and outcome of interest. The study design is illustrated in Figure 2.1.

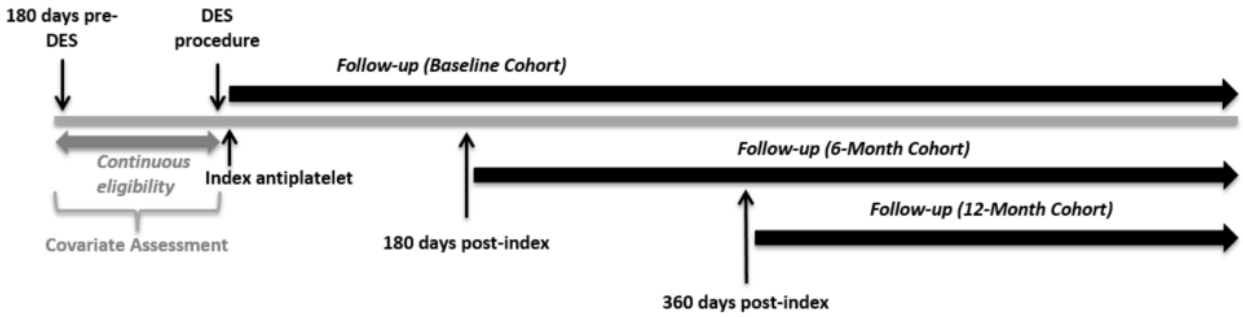


Figure 2.1: Study design

Our analysis was an 'as treated' analysis, with patients censored at treatment discontinuation or switch in treatment arm, defined as a gap in continuous antiplatelet use of 30 days or more. Gap in treatment was assessed as a count of the number of days with no new fill after supply of a prescription fill had elapsed; a switch in treatment was defined as a prescription fill for the other antiplatelet therapy. Patients were additionally censored if they experienced a gap in insurance coverage ≥1 month.

To evaluate adjusted incidence rates in the baseline cohort, we constructed weighted Kaplan-Meier plots. We estimated hazard ratios for associations between index antiplatelet treatment and time-to-each outcome using weighted Cox proportional hazards. The primary analysis used all follow-up time. In secondary analyses, we estimated hazard ratios following the first six months of therapy, and the first 12 months of therapy. Hazard ratios for the two databases were combined using an inverse variance-weighted, fixed-effects model. We conducted a further

analysis to correct the variance of the pooled estimates for potential overlaps in person-time between the databases by 10% or 20%.(19)

We conducted several pre-specified subgroup analyses to evaluate treatment effect heterogeneity in different populations by stratifying on the following covariates, each time constructing propensity score weights within the subgroup population: age, sex, diabetes diagnosis prior to DES, and DAPT score. The latter is a combined measure of ischemic and bleeding risk that incorporates 9 components and ranges from -2 to 10.(20) DAPT trial researchers found that a score of ≥2 was associated with decreased risk of ischemic events with no increase in bleeding, while a score of <2 was associated with increased bleeding with no significant differences in ischemic rates among continuers vs. discontinuers at 12 months. We used the following components of the DAPT score, available in administrative claims data: prior MI or PCI, diabetes diagnosis, congestive heart failure diagnosis, and age; "MI at time of stent" was a component of the main stratification factor of our analysis and so was not included in the score calculation, and the following variables could not be measured in claims data: stent diameter, stenting of vein graft, left ventricular ejection fraction, smoking status. We dichotomized the score at ≥0 vs. <0, which scales the score at the same threshold as the DAPT score based on the available components.

We conducted two sensitivity analyses to evaluate the robustness of our results. First, we restricted our cohorts to patients with indications for both prasugrel and clopidogrel, i.e. patients with equipoise for both treatments at the time of the DES procedure. Specifically, we restricted our cohorts to patients less than 75 years old and with no history of stroke. Second, we conducted a post hoc analysis using incidence of fracture, an outcome not known to be associated with antiplatelet use, as a negative control outcome. Deviations from the null would suggest the presence of residual confounding.(7,21) We restricted this analysis to patients with no evidence of fracture in the baseline period and followed them until they received a fracture diagnosis, lost

enrollment eligibility, or reached the end of the study, whichever occurred first. The institutional review board of Brigham and Women's Hospital approved this study.

RESULTS

Cohorts and covariates

After applying eligibility criteria, the study included 83,896 patients in four cohorts: ORD patients with ACS (N=21,710, 20.6% with index antiplatelet of prasugrel) and without ACS (N=16,594, 15.1% with prasugrel), and MarketScan patients with ACS (N=29,571, 22.0% with prasugrel) and without ACS (N=16,021, 17.4% with prasugrel)(Table 2.4). In all cohorts, the share of prasugrel prescriptions increased over time. Clopidogrel users tended to be older, were more likely to be female, and their index prescription was more likely to be a 90-day fill. Patients on clopidogrel had greater resource utilization, more cardiovascular and total number of medications, and greater comorbidity, although prevalences of individual comorbidities were generally well-balanced.

The propensity score-weighted study population consisted of 32,483 weighted patients (Table 2.1). All covariates were well-balanced between prasugrel and clopidogrel users (absolute standardized difference ≤ 0.01 for all covariates; propensity score distributions in Figure 2.3). Across study cohorts, patients without ACS tended to be older than patients with ACS, taking more medications, had a higher comorbidity score, and were more likely to have had a prior stress test. Patients in the MarketScan database were younger and with greater uptake of prasugrel relative to patients in the ORD. Across all cohorts, 90% of patients filled their index antiplatelet within 5 days of the DES procedure.

Table 2.1: Baseline characteristics of cohorts by database weighted by propensity score matching weights

Characteristic	Acute Coronary Syndrome at cohort entry						No Acute Coronary Syndrome at cohort entry					
	Optum Research Database			MarketScan			Optum Research Database			MarketScan		
	Pras. N=4,457	Clop. N=4,467	ASD[1]	Pras. N=6,471	Clop. N=6,484	ASD	Pras. N=2,506	Clop. N=2,512	ASD	Pras. N=2,790	Clop. N=2,796	ASD
Year												
2009	2%	2%	0.00	3.0%	3.0%	0.00	2.0%	2.0%	0.00	2.9%	2.9%	0.00
2010	18.8%	18.8%	0.00	26.3%	26.4%	0.00	20.4%	20.5%	0.00	23.3%	23.1%	0.00
2011	31.7%	31.6%	0.00	45.0%	45.0%	0.00	31.7%	31.6%	0.00	46.5%	46.7%	0.00
2012	34.3%	34.3%	0.00	25.6%	25.6%	0.00	32.7%	32.6%	0.00	27.3%	27.2%	0.00
2013	13.2%	13.3%	0.00	--	--		13.1%	13.3%	0.01	--	--	
Demographic and health plan benefit												
Age, mean (SD)	58.2 (9.8)	58.1 (4.9)	0.01	56.7 (8.7)	56.6 (4.6)	0.01	60.9 (9.2)	60.9 (3.9)	0.01	59.9 (8.7)	59.8 (4.0)	0.01
Female sex	22.9%	22.9%	0.00	21.5%	21.4%	0.00	22.3%	22.4%	0.00	24.3%	24.5%	0.00
Region												
Midwest	25.8%	26.1%	0.01	27.5%	27.8%	0.01	21.8%	21.7%	0.00	26.5%	26.7%	0.00
Northeast	9.6%	9.6%	0.00	18.8%	18.7%	0.00	7.9%	8.0%	0.00	17.4%	17.4%	0.00
South	49.7%	49.4%	0.01	36.1%	36.3%	0.00	57.7%	57.4%	0.01	41.4%	41.3%	0.00
West	14.8%	14.8%	0.00	15.9%	15.6%	0.01	12.5%	12.8%	0.01	13.0%	12.9%	0.00
Medicare	24.5%	24.4%	0.00	17.6%	17.3%	0.01	33.8%	33.7%	0.00	30.1%	30.1%	0.00
Health plan type												
Health Maintenance Org.	9.5%	9.4%	0.00	13.1%	12.9%	0.01	10.1%	10.1%	0.00	11.0%	11.0%	0.00
Other	26.8%	26.7%	0.00	21.9%	21.8%	0.00	32.5%	32.4%	0.00	24.5%	24.5%	0.00
Point of Care	6.3%	6.3%	0.00	4.0%	4.0%	0.00	8.1%	8.2%	0.00	4.3%	4.3%	0.00
Preferred Provider Org.	57.4%	57.5%	0.00	61.0%	61.4%	0.01	49.3%	49.4%	0.00	60.2%	60.3%	0.00
Resource utilization												
Outpatient visits												
0-1	40.9%	41.0%	0.00	42.9%	43.0%	0.00	13.4%	13.6%	0.01	11.4%	11.4%	0.00
2-5	43.2%	43.0%	0.00	42.1%	42.2%	0.00	54.2%	53.9%	0.01	55.9%	55.6%	0.01
>5	16.0%	16.0%	0.00	15.0%	14.8%	0.00	32.4%	32.5%	0.00	32.8%	33.0%	0.01
Hospitalization length of stay (days)												
0	90.1%	90.1%	0.00	91.5%	91.5%	0.00	85.0%	84.9%	0.00	88.1%	88.2%	0.01
1-7	7.6%	7.7%	0.00	6.4%	6.4%	0.00	11.3%	11.4%	0.00	9.5%	9.4%	0.01

>7	2.3%	2.2%	0.00	2.0%	2.1%	0.00	3.8%	3.7%	0.00	2.4%	2.4%	0.00
Emergency Room visit	8.5%	8.5%	0.00	12.6%	12.5%	0.00	12.7%	12.9%	0.01	19.7%	19.7%	0.00
Index antiplatelet prescription												
Days supply ≤30	95.7%	95.7%	0.00	93.5%	93.5%	0.00	93.0%	92.9%	0.00	89.1%	89.2%	0.00
Initiator	92.8%	92.7%	0.00	91.6%	91.4%	0.01	84.9%	84.4%	0.01	85.4%	85.4%	0.00
Comorbid medications												
Statin	36.5%	36.5%	0.00	35.5%	35.7%	0.00	57.3%	57.5%	0.00	60.7%	60.7%	0.00
ACEi[2]	23.2%	23.4%	0.01	23.6%	23.6%	0.00	34.4%	34.4%	0.00	36.7%	36.8%	0.00
ARB[3]	12.9%	12.9%	0.00	14.0%	13.9%	0.00	18.2%	18.3%	0.00	20.1%	20.1%	0.00
Calcium channel blocker	14.7%	14.7%	0.00	15.2%	15.3%	0.00	20.7%	20.8%	0.00	21.4%	21.5%	0.00
Beta blocker	22.3%	22.4%	0.00	23.1%	23.3%	0.01	40.8%	40.9%	0.00	44.3%	44.0%	0.01
Anticoagulant	1.4%	1.4%	0.00	1.3%	1.4%	0.00	2.6%	2.6%	0.00	2.9%	3.0%	0.01
Oral hypoglycemic	16.9%	16.9%	0.00	16.3%	16.3%	0.00	25.9%	26%	0.00	27.2%	27.5%	0.01
Insulin	8.3%	8.4%	0.00	7.8%	7.8%	0.00	12.3%	12.3%	0.00	12.8%	12.9%	0.00
Other non-selective NSAID	12.8%	12.9%	0.00	12.6%	12.6%	0.00	14.3%	14.2%	0.00	13.9%	14.0%	0.00
Antiulcer and acid suppressant	16.0%	16.1%	0.00	17.5%	17.6%	0.00	24.8%	24.8%	0.00	25.6%	25.6%	0.00
Number of cardiovascular medications, mean (SD)	1.3 (1.4)	1.3 (0.7)	0.00	1.4 (1.5)	1.4 (0.8)	0.00	2.1 (1.5)	2.1 (0.6)	0.00	2.3 (1.5)	2.3 (0.7)	0.00
Total number of medications, mean (SD)	5.1 (4.9)	5.1 (2.5)	0.00	5.0 (4.7)	5.0 (2.5)	0.00	7.4 (5.4)	7.4 (2.3)	0.00	7.7 (5.1)	7.7 (2.3)	0.00
Medical comorbidity and procedures												
Myocardial infarction	3.4%	3.4%	0.00	3.1%	3.1%	0.00	4.0%	4.1%	0.01	3.1%	3.0%	0.01
Percutaneous coronary intervention	3.2%	3.2%	0.00	3.5%	3.5%	0.00	7.1%	7.3%	0.01	5.2%	5.2%	0.00
Stroke	0.0%	0.0%	0.00	0.1%	0.1%	0.00	0.3%	0.3%	0.00	0.4%	0.4%	0.00
Gastrointestinal bleed	1.7%	1.7%	0.00	1.3%	1.4%	0.01	2.5%	2.4%	0.00	1.5%	1.6%	0.01
Embolism	0.9%	0.9%	0.00	0.7%	0.7%	0.00	1.6%	1.5%	0.00	1.3%	1.3%	0.00
Stress test	6.1%	6.1%	0.00	7.0%	7.1%	0.00	34.7%	34.6%	0.00	38.9%	39.0%	0.00
Hypertension	45.9%	46.0%	0.00	39.4%	39.5%	0.00	72.6%	72.7%	0.00	64.3%	64.3%	0.00
Hyperlipidemia	46.4%	46.3%	0.00	37.0%	37.1%	0.00	74.4%	74.5%	0.00	59.6%	59.4%	0.00

Congestive heart failure	1.0%	1.0%	0.01	1.1%	1.1%	0.00	2.2%	2.2%	0.00	2.2%	2.1%	0.00
Diabetes mellitus	25.5%	25.7%	0.00	23.1%	23.1%	0.00	38.3%	38.3%	0.00	36.2%	36.2%	0.00
Peripheral artery disease	2.8%	2.8%	0.00	2.7%	2.7%	0.00	7.4%	7.3%	0.00	5.9%	5.8%	0.00
Abnormal renal function	4.4%	4.4%	0.00	2.3%	2.3%	0.00	7.1%	7.1%	0.00	4.0%	4.0%	0.00
Nephropathy, diabetic or hypertensive	2.5%	2.5%	0.00	1.7%	1.7%	0.00	4.5%	4.6%	0.00	3.1%	3.1%	0.00
Abnormal liver function	1.9%	2.0%	0.00	1.7%	1.7%	0.00	3.3%	3.3%	0.00	3.1%	3.2%	0.01
Asthma/COPD	9.5%	9.3%	0.00	7.1%	7.1%	0.00	13.4%	13.4%	0.00	10.8%	10.9%	0.00
Alzheimer's or dementia	0.2%	0.2%	0.00	0.2%	0.3%	0.00	0.4%	0.4%	0.00	0.3%	0.2%	0.00
Depression	5.3%	5.3%	0.00	4.4%	4.4%	0.00	5.7%	5.7%	0.00	4.8%	4.8%	0.00
Cancer	2.9%	2.8%	0.00	2.0%	1.9%	0.01	3.8%	3.7%	0.00	2.6%	2.6%	0.00
Osteoporosis	3.3%	3.2%	0.00	2.1%	2.1%	0.00	4.5%	4.4%	0.00	3.3%	3.3%	0.00
Combined comorbidity score, mean (SD)	0.18 (1.21)	0.17 (0.61)	0.00	0.07 (1.03)	0.07 (0.55)	0.00	0.43 (1.62)	0.43 (0.69)	0.00	0.28 (1.37)	0.29 (0.63)	0.00
Healthy user characteristics												
Flu shot	9.6%	9.6%	0.00	6.7%	6.6%	0.00	11.3%	11.3%	0.00	10.5%	10.7%	0.01
Fecal occult blood test	97.1%	97.1%	0.00	2.5%	2.4%	0.00	4.6%	4.7%	0.00	3.7%	3.7%	0.00
Mammogram or PSA test	2.9%	2.9%	0.00	13.5%	13.6%	0.00	25.5%	25.5%	0.00	18.3%	18.3%	0.00
Colonoscopy	18.3%	18.2%	0.00	2.9%	2.9%	0.00	5.4%	5.4%	0.00	3.7%	3.8%	0.00

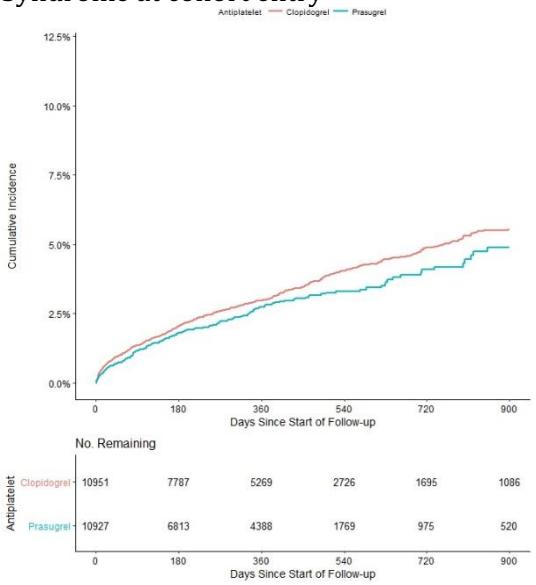
[1] Absolute standardized difference; [2] Angiotensin-converting enzyme inhibitor; [3] Angiotensin II receptor inhibitor

Outcomes

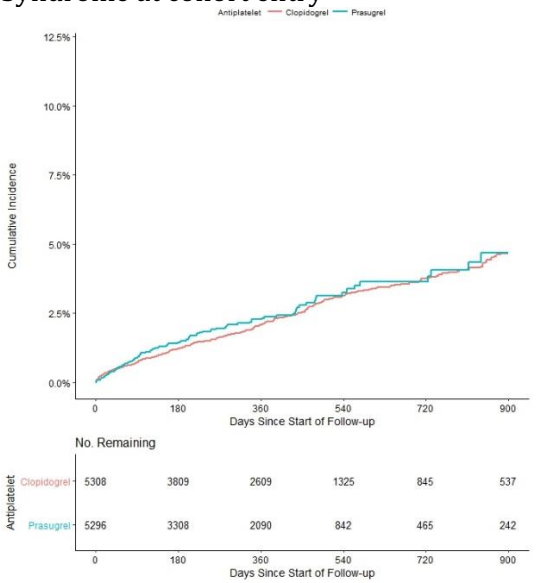
Patients remained continuously enrolled for a median of 900 days in the ORD and 669 days in the MarketScan database. Patients remained on their index treatment for a median of 339 days in the ACS cohort from the ORD, and 329 days in the MarketScan database; for patients with no ACS, these numbers were 333 and 352, respectively. In all cohorts, prasugrel use was associated with earlier discontinuation relative to clopidogrel, even after application of propensity-score matching weights (HR=1.21, 95% CI=(1.18, 1.24) in patients with ACS; HR=1.23, 95% CI=(1.19, 1.27) in patients without ACS). At 6 months, among patients with ACS, 71.1% of patients on clopidogrel and 62.4% on prasugrel remained on treatment and free of MACCE; among patients with no ACS, these percentages were 71.8% and 62.4%, respectively. At 12 months, among patients with ACS, 48.1% of patients on clopidogrel and 40.2% on prasugrel remained on treatment and free of MACCE; among patients with no ACS, these percentages were 49.2% and 39.5%, respectively.

Among patients with ACS, there were 3.1 major adverse cardiovascular and cerebrovascular events (MACCE) per 100 person-years in the prasugrel group versus 4.1 in the clopidogrel group in the ORD; in the MarketScan database, incidence rates were 2.4 events per 100 person-years and 3.6, respectively (unadjusted incidence rates presented in Table 2.5). Weighted Kaplan Meier cumulative incidence plots are presented in Figure 2.2 and show a protective effect for prasugrel use among patients with ACS for MACCE (PANEL A) and a null effect for bleeding (PANEL C). Among patients with no ACS, prasugrel and clopidogrel appear equivalent with respect to MACCE (PANEL B), while prasugrel patients have an increased risk of bleeding relative to clopidogrel patients (PANEL D). Cumulative incidence plots stratified by database are presented in Figure 2.4 and 2.5.

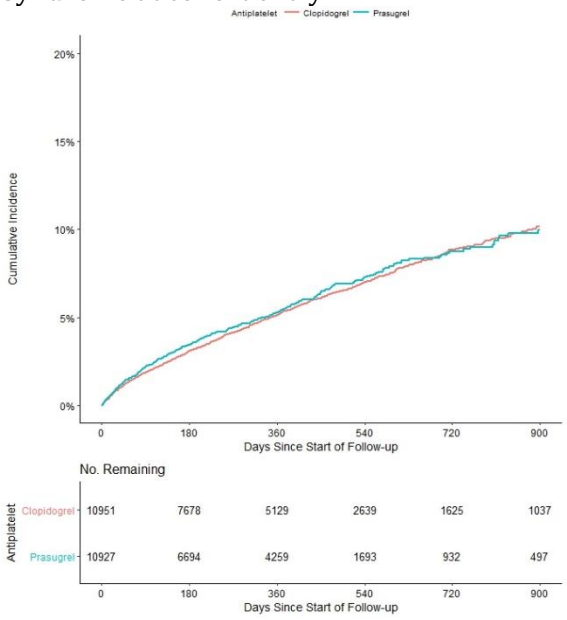
PANEL A: MACCE in patients with Acute Coronary Syndrome at cohort entry



PANEL B: MACCE in patients without Acute Coronary Syndrome at cohort entry



PANEL C: Bleeding in patients with Acute Coronary Syndrome at cohort entry



PANEL D: Bleeding in patients without Acute Coronary Syndrome at cohort entry

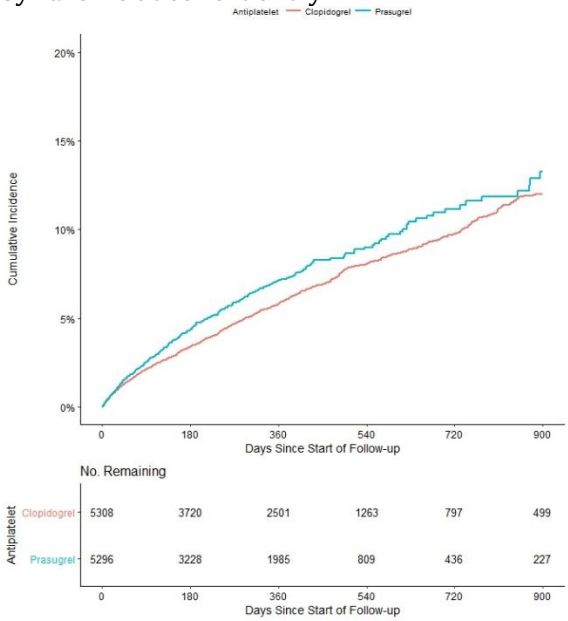


Figure 2.2: Kaplan Meier cumulative incidence, major adverse cardiovascular or cerebrovascular event and bleeding

In weighted Cox proportional hazards models, the combined hazard ratios suggested decreased risk of MACCE and MI with prasugrel among patients with ACS (HR=0.86, 95% CI=(0.73, 1.02) for MACCE; HR=0.83, 95% CI=(0.68, 1.01) for MI), and similar rates of bleeding (HR=1.05,

95% CI=(0.93, 1.18))(Table 2.2). Among patients without ACS, hazard ratios for MACCE and MI were similar in patients on prasugrel vs. clopidogrel (HR=1.08, 95% CI=(0.83, 1.41) for MACCE, and HR=1.12, 95% CI=(0.78, 1.59) for MI), while bleeding rates were significantly higher in prasugrel patients (HR=1.18, 95% CI=(1.01, 1.38)). In the 6-month cohort, the hazard ratio for MACCE, MI, and bleeding were (HR=0.86, 95% CI=(0.65, 1.15), HR=0.77, 95% CI=(0.54, 1.10), HR=0.96, 95% CI=(0.79, 1.16)), respectively, among patients with ACS. In the 12-month cohort, the hazard ratio for MACCE, MI, and bleeding were (HR=0.73, 95% CI=(0.47, 1.12), HR=0.67, 95% CI=(0.39, 1.14), HR=1.00, 95% CI=(0.76, 1.33)), respectively, among patients with ACS. In pooling databases, heterogeneity was typically very low (I^2=0), however 4 estimates demonstrated moderate heterogeneity.

Table 2.2: Adjusted Cox proportional hazards models comparing prasugrel to clopidogrel

Outcome	Acute Coronary Syndrome at cohort entry			No Acute Coronary Syndrome at cohort entry		
	Baseline cohort	6 month cohort	12 month cohort	Baseline cohort	6 month cohort	12 month cohort
MACCE[1]						
Optum Research Database	0.91 (0.71, 1.16)	1.02 (0.68, 1.55)	0.96 (0.51, 1.78)	0.89 (0.60, 1.33)	0.94 (0.52, 1.72)	1.10 (0.47, 2.57)
MarketScan	0.82 (0.66, 1.03)	0.75 (0.51, 1.10)	0.56 (0.31, 1.02)	1.26 (0.88, 1.79)	1.11 (0.63, 1.93)	0.82 (0.37, 1.84)
Combined	0.86 (0.73, 1.02)	0.86 (0.65, 1.15)	0.73 (0.47, 1.12)	1.08 (0.83, 1.41)	1.03 (0.68, 1.54)	0.94 (0.53, 1.69)
Heterogeneity (I^2)	0	16.4	30.4	37.6	0	0
Myocardial Infarction						
Optum Research Database	0.82 (0.61, 1.09)	0.83 (0.50, 1.38)	0.94 (0.45, 1.96)	1.03 (0.63, 1.69)	1.05 (0.49, 2.26)	1.30 (0.48, 3.48)
MarketScan	0.84 (0.64, 1.10)	0.72 (0.44, 1.17)	0.47 (0.22, 1.01)	1.22 (0.73, 2.03)	1.40 (0.63, 3.10)	1.38 (0.46, 4.11)
Combined	0.83 (0.68, 1.01)	0.77 (0.54, 1.10)	0.67 (0.39, 1.14)	1.12 (0.78, 1.59)	1.20 (0.69, 2.09)	1.33 (0.64, 2.77)
Heterogeneity (I^2)	0	0	38.3	0	0	0
Bleeding						
Optum Research Database	1.01 (0.84, 1.21)	0.94 (0.69, 1.26)	1.03 (0.67, 1.58)	1.15 (0.93, 1.43)	0.92 (0.65, 1.31)	0.84 (0.48, 1.45)
MarketScan	1.08 (0.92, 1.27)	0.97 (0.76, 1.25)	0.98 (0.68, 1.42)	1.22 (0.97, 1.53)	1.24 (0.89, 1.75)	1.16 (0.69, 1.95)
Combined	1.05 (0.93, 1.18)	0.96 (0.79, 1.16)	1.00 (0.76, 1.33)	1.18 (1.01, 1.38)	1.08 (0.84, 1.38)	0.99 (0.68, 1.45)
Heterogeneity (I^2)	0	0	0	0	30.5	0

[1] Major adverse cardiovascular or cerebrovascular event

In subgroup analyses, among patients with no ACS, bleeding outcomes were significantly increased prasugrel vs. clopidogrel users in younger patients (HR=1.32, 95% CI=(1.04, 1.68)), and patients with diabetes (HR=1.29, 95% CI=(1.00, 1.67))(Table 2.3). In contrast, bleeding outcomes were non-significant and highly consistent across subgroups of patients with ACS. Patients with lower DAPT score had reduced rates of ischemic events on prasugrel compared to patients with higher DAPT score in both patients with ACS and without, however all effects were non-significant.

Table 2.3: Subgroup analyses, baseline cohort comparing prasugrel to clopidogrel

Subgroup	Acute Coronary Syndrome at cohort entry		No Acute Coronary Syndrome at cohort entry	
	MACCE[1]	Bleeding	MACCE[1]	Bleeding
Age				
≤60	0.82 (0.66, 1.04)	1.06 (0.90, 1.24)	1.36 (0.92, 2.02)	1.32 (1.04, 1.68)
>60	0.89 (0.70, 1.13)	1.02 (0.86, 1.22)	0.90 (0.63, 1.29)	1.07 (0.87, 1.32)
Sex				
Female	0.90 (0.67, 1.23)	1.07 (0.84, 1.36)	1.22 (0.75, 1.99)	1.33 (0.99, 1.79)
Male	0.85 (0.70, 1.03)	1.05 (0.91, 1.20)	1.03 (0.75, 1.42)	1.13 (0.94, 1.36)
Diabetes				
Yes	1.05 (0.81, 1.36)	1.05 (0.83, 1.33)	1.15 (0.81, 1.65)	1.29 (1.00, 1.67)
No	0.76 (0.61, 0.94)	1.05 (0.91, 1.21)	1.00 (0.68, 1.47)	1.12 (0.92, 1.37)
DAPT score				
High	0.87 (0.73, 1.05)	1.04 (0.91, 1.18)	1.16 (0.86, 1.55)	1.20 (1.00, 1.43)
Low	0.80 (0.52, 1.22)	1.12 (0.85, 1.47)	0.89 (0.49, 1.64)	1.14 (0.82, 1.59)

[1] Major adverse cardiovascular or cerebrovascular event

In a sensitivity analysis restricting to patients with indications for prasugrel, results were similar to the main analysis, with the MACCE outcome in ACS patients achieving statistical significance (HR=0.83, 95% CI=(0.70, 0.98)). A negative control outcome of fracture yielded results consistent with the null hypothesis in ACS (HR=0.95, 95% CI=(0.80, 1.13)) and no ACS cohorts (HR=0.99, 95% CI=(0.79, 1.24)). Results from the variance adjustment for potential overlap across databases are presented in Table 2.6.

DISCUSSION

In a large, multidatabase study representative of real-world patterns of antiplatelet use after drug-eluting stent procedure, initiation of prasugrel versus clopidogrel appeared to confer benefit against ischemic events over up to 30 months of therapy without increased risk of moderate or major bleeding events among patients with acute coronary syndrome. In contrast, use of prasugrel was not associated with ischemic benefit but was associated with increased risk of moderate or major bleeding events among patients with stable coronary syndrome.

Our results among patients with ACS are consistent with evidence from the TRITON TIMI 38 trial, which found a similar reduction in ischemic risk with prasugrel versus clopidogrel that persisted over time, primarily driven by reductions in myocardial infarction.(1) The magnitude of this effect increased, though remained non-significant, among the subsets of patients who remained on therapy and event-free at 6 and 12 months. This continued long-term benefit of treatment with prasugrel is consistent with stratified results from the DAPT trial, which found larger benefits of continuing versus discontinuing prasugrel (HR=0.52, 95% CI (0.38, 0.71)) than with continuing versus discontinuing clopidogrel (HR=0.80, 95% CI (0.64, 1.01)).(6)

Patients without acute coronary syndrome at the time of stenting did not derive ischemic benefit from treatment with prasugrel, findings consistent with several trials of antiplatelet use in patients with stable ischemic heart disease.(22) In the CHARISMA trial, patients with stable ischemic heart disease did not benefit from dual antiplatelet therapy with clopidogrel, while studies of longer-term dual antiplatelet use have found mixed results.(6,23,24) The more recent TRILOGY-ACS trial in patients with ACS managed medically with prasugrel or clopidogrel, who could be considered lower risk than patients in our cohort with ACS, found no increased risk of ischemic events over 30 months of follow-up.(25)

Half of patients remained on their index antiplatelet therapy for at least 11 months after stent, however the majority of earlier discontinuation occurred within the first six months of therapy. These high levels of early discontinuation have been documented elsewhere and present an important public health concern, given the demonstrated benefit of treatment for at least 6 months in the majority of patients.(26,27) Prasugrel users had on average a shorter duration of treatment, which may have biased the bleeding results in favor of prasugrel if prescribers were monitoring prasugrel patients more closely for bleeding events or treating them cautiously. In the use of anticoagulants, prescribers have been shown to be more risk-averse with respect to bleeding

versus thrombotic outcomes.(28) While switching therapies after index was uncommon relative to discontinuation, switching to prasugrel occurred significantly more often than switching to clopidogrel. Such differential switching could have resulted in bias in favor of clopidogrel if patients on clopidogrel who developed signs or predictors of ischemia were more likely to be switched to the more potent antiplatelet agent. In a survey of reasons for switching antiplatelet therapy, while rates of switching were generally low, step-up in therapy accounted for nearly two thirds of switching from clopidogrel to prasugrel or ticagrelor.(29)

It is also possible that there is residual confounding by unmeasured patient or provider characteristics. Many factors influencing prescriber decision-making are often unmeasured in claims data, as are important patient characteristics such as smoking status and BMI. Given the fact that stable ischemic heart disease encompasses a diverse pathology, our cohort of patients without ACS may have been subject to greater residual bias.(22) Reassuringly, our study was able to measure many of the most important confounders identified in a recent registry-based study, and results from our negative control outcome of fracture suggest that there was not a large 'healthy user' effect influencing the initial prescribing decision.(8)

Several limitations relating to the capture of study variables should be noted. Dual antiplatelet therapy regimens include concomitant use of aspirin, which could not be accurately measured in our study because of the predominant use of over-the-counter medication, which typically does not generate a pharmacy claim. In a systematic review of adherence to dual antiplatelet therapy after coronary stenting, adherence to aspirin therapy remained high throughout the first year of therapy, despite a decline in antiplatelet use during this same period, suggesting that aspirin use is high and independent of antiplatelet use.(26) Second, because codes for inpatient blood transfusions are typically not available in claims data, we likely did not capture all blood transfusions required for the GUSTO definition. Our bleeding definition instead included

gastrointestinal and urogenital bleed in an attempt to capture moderate bleeding episodes, which may have hindered our ability to directly compare our results to trial results. Capture of only in-hospital myocardial infarction may similarly mean that MACCE and MI outcomes are underreported relative to randomized trials. Only in-hospital death information is available in the MarketScan database, which could lead to bias if one of the antiplatelet treatments was differentially associated with out-of-hospital death; however, prasugrel and clopidogrel are not known to differentially affect mortality other than through cardiovascular processes. Since 2008, newer "second generation" drug-eluting stents, which pose a lower risk of stent thrombosis, have increasingly become the standard of care for PCI. In our study, we could not measure DES stent type. If prescribers preferentially selected prasugrel for one type of DES over another, this may have biased our estimates, however the low overall prevalence of stent thrombosis suggests that the effect would be minimal. Finally, there was some observed heterogeneity across effect estimates in the two databases, which may in part be explained by the fact that the ORD comprises data from one national insurer whereas MarketScan combines data from multiple insurers; additionally there were differences in important outcome risk factors, such as age, which may modify the effect of the observed associations.

Our study did not include ticagrelor, a newer ADP receptor-inhibiting antiplatelet with similar efficacy profile as prasugrel compared to clopidogrel in randomized trials, due to small sample size in our study period.(31) Recent trends suggest uptake of ticagrelor has been rapid; in 2013, two years after its introduction, ticagrelor accounted for the same share of new antiplatelet prescriptions as prasugrel.(2,9) Ticagrelor may in part be increasingly prescribed due to fewer contraindications and perceived safety benefit relative to prasugrel, however the twice-a-day dosing and side effect of dyspnea have been noted as important factors related to early treatment discontinuation or switch.(31) Whereas one large randomized head-to-head trial suggested equivalent efficacy of prasugrel and ticagrelor, different prescribing patterns, indications, and

treatment discontinuation patterns may affect the real-world comparative effectiveness of these two therapies.(32)

Evidence for antiplatelet use increasingly favors long-term therapy.(33) A recent summary of evidence described the choice of which antiplatelet to prescribe given the intention to treat long-term as a "trilemma that is not easily solved".(5) Our large, nationally representative study suggests that long-term treatment may favor prasugrel use for the prevention of ischemic events without compensatory increases in bleeding events among patients with acute coronary syndrome, however the evidence is less clear for patients without ACS. Consideration of long-term compliance patterns of these two therapies is warranted in future research efforts to guide prescriber decision-making at the time of therapy initiation.

ACKNOWLEDGEMENTS

AAK receives tuition support from Harvard TH Chan School of Public Health (partially supported by training grants from Pfizer, Takeda, Bayer, and Asisa)

REFERENCES

1. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15;357(20):2001–15.

2. Kim K, Lee TA, Touchette DR, DiDomenico RJ, Ardati AK, Walton SM. Contemporary Trends in Oral Antiplatelet Agent Use in Patients Treated with Percutaneous Coronary Intervention for Acute Coronary Syndrome. J Manag Care Spec Pharm. 2017 Jan;23(1):57–63.

3. Sandhu A, Seth M, Dixon S, Share D, Wohns D, Lalonde T, et al. Contemporary use of prasugrel in clinical practice: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Circ Cardiovasc Qual Outcomes. 2013 May 1;6(3):293–8.

4. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006 Dec 19;48(12):2584–91.

5. Alexopoulos D, Xanthopoulou I, Moulias A, Lekakis J. Long-Term P2Y12-Receptor Antagonists in Post-Myocardial Infarction Patients: Facing a New Trilemma? J Am Coll Cardiol. 2016 Sep 13;68(11):1223–32.

6. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014 Dec 4;371(23):2155–66.

7. Federspiel JJ, Anstrom KJ, Xian Y, McCoy LA, Effron MB, Faries DE, et al. Comparing Inverse Probability of Treatment Weighting and Instrumental Variable Methods for the Evaluation of Adenosine Diphosphate Receptor Inhibitors After Percutaneous Coronary Intervention. JAMA Cardiol. 2016 Sep 1;1(6):655–65.

8. Vora AN, Peterson ED, McCoy LA, Effron MB, Anstrom KJ, Faries DE, et al. Factors Associated With Initial Prasugrel Versus Clopidogrel Selection for Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention: Insights From the Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment

Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) Study. J Am Heart Assoc. 2016 Sep 23;5(9).

9. Yudi MB, Clark DJ, Farouque O, Eccleston D, Andrianopoulos N, Duffy SJ, et al. Clopidogrel, prasugrel or ticagrelor in patients with acute coronary syndromes undergoing percutaneous coronary intervention. Intern Med J. 2016 May;46(5):559–65.

10. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. Med Care. 2006 May;44(5):471–7.

11. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med. 1993 Sep 2;329(10):673–82.

12. Wahl PM, Rodgers K, Schneeweiss S, Gage BF, Butler J, Wilmer C, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):596–603.

13. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:100–28.

14. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011 Jun;20(6):560–6.

15. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011 Jul;64(7):749–59.

16. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol. 2007 Aug 1;166(3):348–54.

17. Li L, Greene T. A weighting analogue to pair matching in propensity score analysis. Int J Biostat. 2013 Jul 31;9(2):215–34.

18. Austin PC, Stuart EA. Estimating the effect of treatment on binary outcomes using full matching on the propensity score. Stat Methods Med Res. 2015 Sep 1;

19. Munder T, Brütsch O, Leonhart R, Gerger H, Barth J. Researcher allegiance in psychotherapy outcome research: an overview of reviews. Clin Psychol Rev. 2013 Jun;33(4):501–11.

20. Yeh RW, Secemsky EA, Kereiakes DJ, Normand S-LT, Gershlick AH, Cohen DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. JAMA. 2016 Apr 26;315(16):1735–49.

21. Gagne JJ, Choudhry NK, Kesselheim AS, Polinski JM, Hutchins D, Matlin OS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014 Sep 16;161(6):400–7.

22. Sandhu A, Valle J, Maddox TM. Dual Anti-Platelet Therapy in Stable Ischemic Heart Disease: Striking a Delicate Balance. Am Coll Cardiol [Internet]. 2015 Oct 8 [cited 2017 Jul 15]; Available from: http://www.acc.org/latest-in-cardiology/articles/2015/10/08/09/50/dual-anti-platelet-therapy-in-stable-ischemic-heart-disease

23. Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006 Apr 20;354(16):1706–17.

24. Lemesle G, Lamblin N, Meurice T, Tricot O, Lallemant R, Nugue O, et al. Dual antiplatelet therapy in patients with stable coronary artery disease in modern practice: prevalence, correlates, and impact on prognosis (from the Suivi d'une cohorte de patients COROnariens stables en region NORd-Pas-de-Calais study). Am Heart J. 2014 Oct;168(4):479–86.

25. Roe MT, Armstrong PW, Fox KAA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med. 2012 Oct 4;367(14):1297–309.

26. Czarny MJ, Nathan AS, Yeh RW, Mauri L. Adherence to dual antiplatelet therapy after coronary stenting: a systematic review. Clin Cardiol. 2014 Aug;37(8):505–13.

27. Cutlip DE, Kereiakes DJ, Mauri L, Stoler R, Dauerman HL, EDUCATE Investigators. Thrombotic complications associated with early and late nonadherence to dual antiplatelet therapy. JACC Cardiovasc Interv. 2015 Mar;8(3):404–10.

28. Choudhry NK, Anderson GM, Laupacis A, Ross-Degnan D, Normand S-LT, Soumerai SB. Impact of adverse events on prescribing warfarin in patients with atrial fibrillation: matched pair analysis. BMJ. 2006 Jan 21;332(7534):141–5.

29. Zettler ME, Peterson ED, McCoy LA, Effron MB, Anstrom KJ, Henry TD, et al. Switching of adenosine diphosphate receptor inhibitor after hospital discharge among myocardial infarction patients: Insights from the Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) observational study. Am Heart J. 2017 Jan;183:62–8.

30. Gosling R, Yazdani M, Parviz Y, Hall IR, Grech ED, Gunn JP, et al. Comparison of P2Y12 inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: Single center study of 10 793 consecutive "real-world" patients. Platelets. 2017 Mar 7;1–7.

31. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep 10;361(11):1045–57.

32. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, et al. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circulation. 2016 Nov 22;134(21):1603–12.

33. Levine G. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease [Internet]. [cited 2016 Apr 5]. (American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines). Available from: http://content.onlinejacc.org/article.aspx?articleid=2507082

APPENDIX

Table 2.4: Baseline characteristics of cohorts by database

Characteristic	Acute Coronary Syndrome at cohort entry						No Acute Coronary Syndrome at cohort entry					
	Optum Research Database			MarketScan			Optum Research Database			MarketScan		
	Pras. N=4,466	Clop. N=17,244	ASD[1]	Pras. N=6,494	Clop. N=23,077	ASD	Pras. N=2,507	Clop. N=14,087	ASD	Pras. N=2,795	Clop. N=13,226	ASD
Year												
2009	87 (1.9)	2541 (14.7)	0.48	194 (3)	4669 (20.2)	0.56	51 (2)	2023 (14.4)	0.46	82 (2.9)	2674 (20.2)	0.56
2010	839 (18.8)	4267 (24.7)	0.15	1705 (26.3)	7562 (32.8)	0.14	512 (20.4)	3866 (27.4)	0.17	649 (23.2)	3952 (29.9)	0.15
2011	1413 (31.6)	4150 (24.1)	0.17	2922 (45)	7313 (31.7)	0.28	794 (31.7)	3303 (23.4)	0.19	1300 (46.5)	4547 (34.4)	0.25
2012	1537 (34.4)	4250 (24.6)	0.22	1673 (25.8)	3533 (15.3)	0.26	821 (32.7)	3257 (23.1)	0.22	764 (27.3)	2053 (15.5)	0.29
2013	590 (13.2)	2036 (11.8)	0.04	--	--		329 (13.1)	1638 (11.6)	0.05	--	--	
Demographic and health plan benefit												
Age, mean (SD)	58.2 (9.8)	63.2 (11.8)	0.47	56.6 (8.7)	60.6 (11.1)	0.40	60.9 (9.2)	66.1 (10.5)	0.52	59.9 (8.7)	64.1 (10.6)	0.43
Female sex	1020 (22.8)	5388 (31.2)	0.19	1391 (21.4)	6529 (28.3)	0.16	560 (22.3)	4486 (31.8)	0.22	680 (24.3)	3751 (28.4)	0.09
Region												
Midwest	1151 (25.8)	5284 (30.6)	0.11	1785 (27.5)	6905 (29.9)	0.05	546 (21.8)	4137 (29.4)	0.18	742 (26.5)	3906 (29.5)	0.07
Northeast	426 (9.5)	2001 (11.6)	0.07	1218 (18.8)	4563 (19.8)	0.03	198 (7.9)	1313 (9.3)	0.05	485 (17.4)	2520 (19.1)	0.04
South	2223 (49.8)	7695 (44.6)	0.10	2348 (36.2)	7262 (31.5)	0.10	1446 (57.7)	7045 (50)	0.15	1158 (41.4)	4698 (35.5)	0.12
West	662 (14.8)	2249 (13)	0.05	1032 (15.9)	4007 (17.4)	0.04	314 (12.5)	1576 (11.2)	0.04	362 (13)	1956 (14.8)	0.05
Medicare	1092 (24.5)	7094 (41.1)	0.36	1137 (17.5)	7317 (31.7)	0.33	848 (33.8)	7196 (51.1)	0.36	841 (30.1)	5843 (44.2)	0.30
Health plan type												
HMO[2]	422 (9.4)	2166 (12.6)	0.10	846 (13)	4050 (17.5)	0.13	253 (10.1)	1833 (13)	0.09	308 (11)	1898 (14.4)	0.10
Other	1197 (26.8)	6411 (37.2)	0.22	1422 (21.9)	5251 (22.8)	0.02	814 (32.5)	5971 (42.4)	0.21	686 (24.5)	3599 (27.2)	0.06
Point of Care	283 (6.3)	1414 (8.2)	0.07	261 (4)	772 (3.3)	0.04	204 (8.1)	1464 (10.4)	0.08	120 (4.3)	464 (3.5)	0.04
PPO[3]	2564 (57.4)	7253 (42.1)	0.31	3965 (61.1)	13004 (56.4)	0.10	1236 (49.3)	4819 (34.2)	0.31	1681 (60.1)	7265 (54.9)	0.11

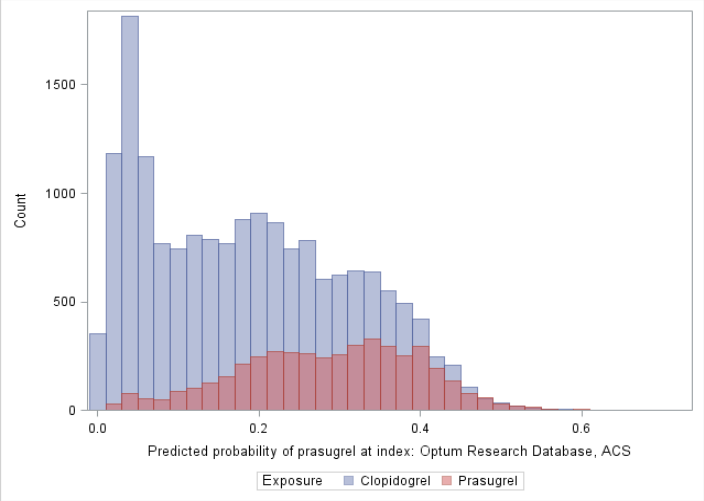
Resource utilization												
Outpatient visits												
0-1	1824 (40.8)	6213 (36)	0.10	2779 (42.8)	8819 (38.2)	0.09	337 (13.4)	1517 (10.8)	0.08	318 (11.4)	1410 (10.7)	0.02
2-5	1928 (43.2)	7669 (44.5)	0.03	2739 (42.2)	9977 (43.2)	0.02	1358 (54.2)	7167 (50.9)	0.07	1561 (55.8)	6945 (52.5)	0.07
>5	714 (16)	3362 (19.5)	0.09	976 (15)	4281 (18.6)	0.09	812 (32.4)	5403 (38.4)	0.13	916 (32.8)	4871 (36.8)	0.09
Hospitalization length of stay (days)												
0	4023 (90.1)	14977 (86.9)	0.10	5943 (91.5)	20455 (88.6)	0.10	2129 (84.9)	11805 (83.8)	0.03	2458 (87.9)	11378 (86)	0.06
1-7	342 (7.7)	1593 (9.2)	0.06	419 (6.5)	1976 (8.6)	0.08	284 (11.3)	1534 (10.9)	0.01	270 (9.7)	1420 (10.7)	0.04
>7	101 (2.3)	674 (3.9)	0.10	132 (2)	646 (2.8)	0.05	94 (3.7)	748 (5.3)	0.08	67 (2.4)	428 (3.2)	0.05
ER visit	377 (8.4)	1975 (11.5)	0.10	819 (12.6)	3487 (15.1)	0.07	318 (12.7)	2139 (15.2)	0.07	549 (19.6)	2622 (19.8)	0.01
Index antiplatelet prescription												
Days supply ≤30	4274 (95.7)	15653 (90.8)	0.20	6073 (93.5)	20318 (88)	0.19	2331 (93)	12307 (87.4)	0.19	2492 (89.2)	11074 (83.7)	0.16
Initiator	4137 (92.6)	16179 (93.8)	0.05	5928 (91.3)	21581 (93.5)	0.08	2127 (84.8)	12383 (87.9)	0.09	2385 (85.3)	11570 (87.5)	0.06
Comorbid medications												
Statin	1636 (36.6)	6569 (38.1)	0.03	2312 (35.6)	8969 (38.9)	0.07	1437 (57.3)	8382 (59.5)	0.04	1699 (60.8)	8144 (61.6)	0.02
ACEi[4]	1036 (23.2)	4659 (27)	0.09	1535 (23.6)	5810 (25.2)	0.04	862 (34.4)	5359 (38)	0.08	1026 (36.7)	4862 (36.8)	0.00
ARB[5]	578 (12.9)	2238 (13)	0.00	910 (14)	3280 (14.2)	0.01	457 (18.2)	2547 (18.1)	0.00	562 (20.1)	2645 (20)	0.00
Calcium channel blocker	656 (14.7)	3267 (18.9)	0.11	989 (15.2)	4064 (17.6)	0.06	520 (20.7)	3622 (25.7)	0.12	597 (21.4)	3216 (24.3)	0.07
Beta blocker	998 (22.3)	4760 (27.6)	0.12	1505 (23.2)	6583 (28.5)	0.12	1022 (40.8)	6298 (44.7)	0.08	1240 (44.4)	6191 (46.8)	0.05
Anticoagulant	64 (1.4)	635 (3.7)	0.14	86 (1.3)	738 (3.2)	0.13	66 (2.6)	1008 (7.2)	0.21	82 (2.9)	828 (6.3)	0.16
Oral hypoglycemic	755 (16.9)	3200 (18.6)	0.04	1058 (16.3)	4048 (17.5)	0.03	650 (25.9)	3456 (24.5)	0.03	761 (27.2)	3189 (24.1)	0.07
Insulin	372 (8.3)	1435 (8.3)	0.00	507 (7.8)	1794 (7.8)	0.00	308 (12.3)	1726 (12.3)	0.00	360 (12.9)	1482 (11.2)	0.05
Other non-	572 (12.8)	2272 (13.2)	0.01	817 (12.6)	2940 (12.7)	0.01	358 (14.3)	1985 (14.1)	0.01	389 (13.9)	1841 (13.9)	0.00

selective NSAID												
Antiulcer and acid suppressant	715 (16)	3349 (19.4)	0.09	1143 (17.6)	4369 (18.9)	0.03	622 (24.8)	3633 (25.8)	0.02	715 (25.6)	3417 (25.8)	0.01
Number of cardiovascular medications, mean (SD)	1.3 (1.4)	1.6 (1.5)	0.16	1.4 (1.5)	1.6 (1.5)	0.12	2.1 (1.5)	2.4 (1.5)	0.17	2.3 (1.5)	2.4 (1.5)	0.07
Total number of medications, mean (SD)	5.1 (4.9)	5.7 (5.0)	0.12	5.0 (4.7)	5.6 (4.9)	0.11	7.4 (5.4)	7.9 (5.3)	0.10	7.7 (5.1)	7.8 (4.9)	0.02
Medical comorbidity and procedures												
Myocardial infarction	155 (3.5)	746 (4.3)	0.04	200 (3.1)	899 (3.9)	0.04	100 (4)	399 (2.8)	0.06	89 (3.2)	280 (2.1)	0.07
Percutaneous coronary intervention	146 (3.3)	405 (2.3)	0.06	230 (3.5)	596 (2.6)	0.06	179 (7.1)	734 (5.2)	0.08	150 (5.4)	470 (3.6)	0.09
Stroke	1 (0)	62 (0.4)	0.08	8 (0.1)	111 (0.5)	0.07	7 (0.3)	86 (0.6)	0.05	10 (0.4)	118 (0.9)	0.07
Gastrointestinal bleed	74 (1.7)	318 (1.8)	0.01	85 (1.3)	392 (1.7)	0.03	62 (2.5)	389 (2.8)	0.02	42 (1.5)	266 (2)	0.04
Embolism	40 (0.9)	246 (1.4)	0.05	48 (0.7)	239 (1)	0.03	39 (1.6)	340 (2.4)	0.06	36 (1.3)	179 (1.4)	0.01
Stress test	276 (6.2)	1094 (6.3)	0.01	455 (7)	1790 (7.8)	0.03	869 (34.7)	4988 (35.4)	0.02	1086 (38.9)	5103 (38.6)	0.01
Hypertension	2051 (45.9)	9318 (54)	0.16	2560 (39.4)	10136 (43.9)	0.09	1819 (72.6)	10886 (77.3)	0.11	1797 (64.3)	8486 (64.2)	0.00
Hyperlipidemia	2074 (46.4)	8423 (48.8)	0.05	2409 (37.1)	8854 (38.4)	0.03	1865 (74.4)	10363 (73.6)	0.02	1666 (59.6)	7543 (57)	0.05
Congestive heart failure	46 (1)	332 (1.9)	0.07	76 (1.2)	368 (1.6)	0.04	56 (2.2)	518 (3.7)	0.09	60 (2.1)	390 (2.9)	0.05
Diabetes mellitus	1138 (25.5)	4894 (28.4)	0.07	1503 (23.1)	5636 (24.4)	0.03	960 (38.3)	5417 (38.5)	0.00	1012 (36.2)	4475 (33.8)	0.05

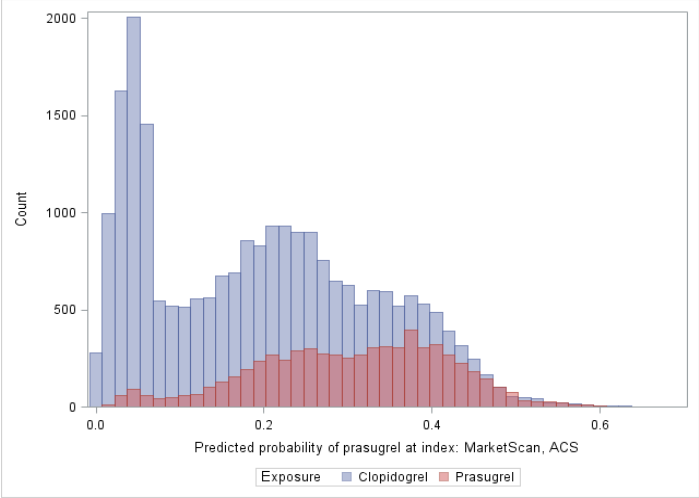
Peripheral artery disease	127 (2.8)	854 (5)	0.11	173 (2.7)	812 (3.5)	0.05	185 (7.4)	1468 (10.4)	0.11	166 (5.9)	1013 (7.7)	0.07
Abnormal renal function	196 (4.4)	1109 (6.4)	0.09	152 (2.3)	1071 (4.6)	0.13	179 (7.1)	1450 (10.3)	0.11	113 (4)	764 (5.8)	0.08
Nephropathy, diabetic or hypertensive	111 (2.5)	669 (3.9)	0.08	113 (1.7)	716 (3.1)	0.09	114 (4.5)	872 (6.2)	0.07	88 (3.1)	520 (3.9)	0.04
Abnormal liver function	85 (1.9)	337 (2)	0.00	109 (1.7)	393 (1.7)	0.00	83 (3.3)	482 (3.4)	0.01	88 (3.1)	324 (2.4)	0.04
Asthma/COPD	422 (9.4)	2178 (12.6)	0.10	461 (7.1)	2181 (9.5)	0.09	336 (13.4)	2491 (17.7)	0.12	302 (10.8)	1670 (12.6)	0.06
Alzheimer's or dementia	11 (0.2)	175 (1)	0.10	16 (0.2)	173 (0.7)	0.07	10 (0.4)	224 (1.6)	0.12	7 (0.3)	131 (1)	0.09
Depression	237 (5.3)	968 (5.6)	0.01	286 (4.4)	1063 (4.6)	0.01	143 (5.7)	903 (6.4)	0.03	135 (4.8)	634 (4.8)	0.00
Cancer	128 (2.9)	678 (3.9)	0.06	128 (2)	654 (2.8)	0.06	94 (3.7)	808 (5.7)	0.09	73 (2.6)	506 (3.8)	0.07
Osteoporosis	145 (3.2)	819 (4.7)	0.08	138 (2.1)	720 (3.1)	0.06	112 (4.5)	812 (5.8)	0.06	91 (3.3)	533 (4)	0.04
Combined comorbidity score, mean (SD)	0.18 (1.21)	0.38 (1.5)	0.15	0.07 (1.04)	0.24 (1.26)	0.15	0.43 (1.62)	0.84 (1.93)	0.23	0.28 (1.37)	0.5 (1.54)	0.15
Healthy user characteristics												
Flu shot	428 (9.6)	1896 (11)	0.05	435 (6.7)	1692 (7.3)	0.03	284 (11.3)	1933 (13.7)	0.07	293 (10.5)	1288 (9.7)	0.03
Fecal occult blood test	131 (2.9)	514 (3)	0.00	160 (2.5)	541 (2.3)	0.01	115 (4.6)	601 (4.3)	0.02	102 (3.6)	465 (3.5)	0.01
Mammogram or PSA test	818 (18.3)	2875 (16.7)	0.04	881 (13.6)	2845 (12.3)	0.04	639 (25.5)	3389 (24.1)	0.03	511 (18.3)	2330 (17.6)	0.02
Colonoscopy	179 (4)	639 (3.7)	0.02	191 (2.9)	642 (2.8)	0.01	136 (5.4)	686 (4.9)	0.03	104 (3.7)	502 (3.8)	0.00

[1] Absolute standardized difference; [2] Health maintenance organization; [3] Preferred provider organization; [4] Angiotensin-converting enzyme inhibitor; [5] Angiotensin II receptor inhibitor

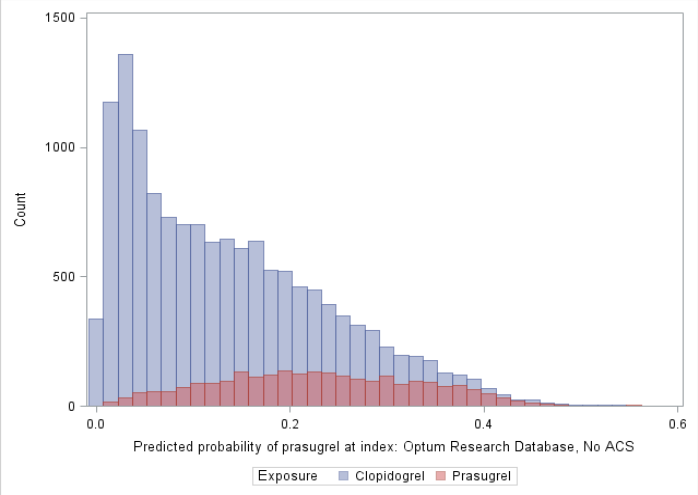
PANEL A: Patients with Acute Coronary Syndrome at cohort entry (Optum Research Database), c-stat: 0.73



PANEL B: Patients with Acute Coronary Syndrome at cohort entry (MarketScan), c-stat: 0.73



PANEL C: Patients without Acute Coronary Syndrome at cohort entry (Optum Research Database), c-stat: 0.74



PANEL D: Patients without Acute Coronary Syndrome at cohort entry (MarketScan), c-stat: 0.74

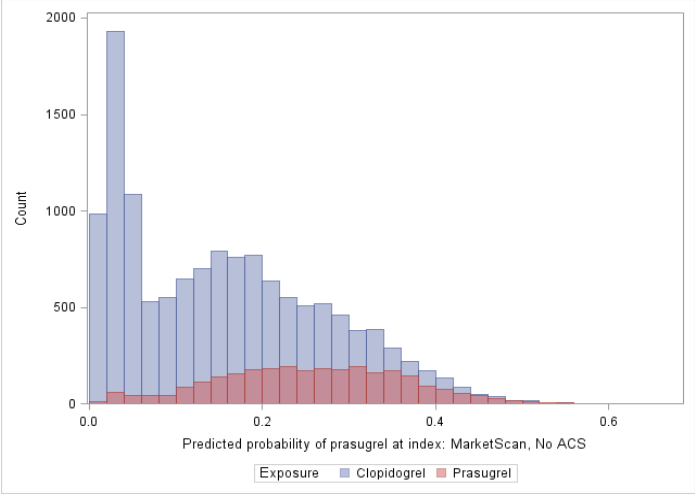


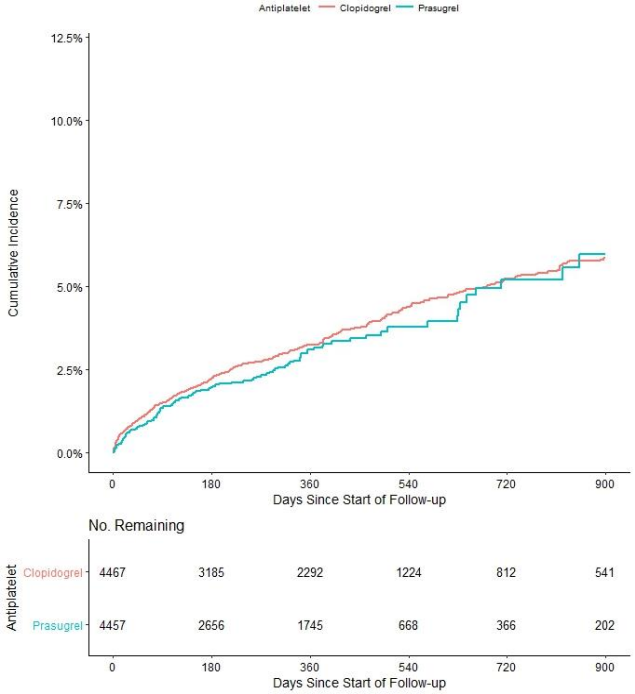
Figure 2.3: Propensity score distribution

Table 2.5: Crude event rates by cohort

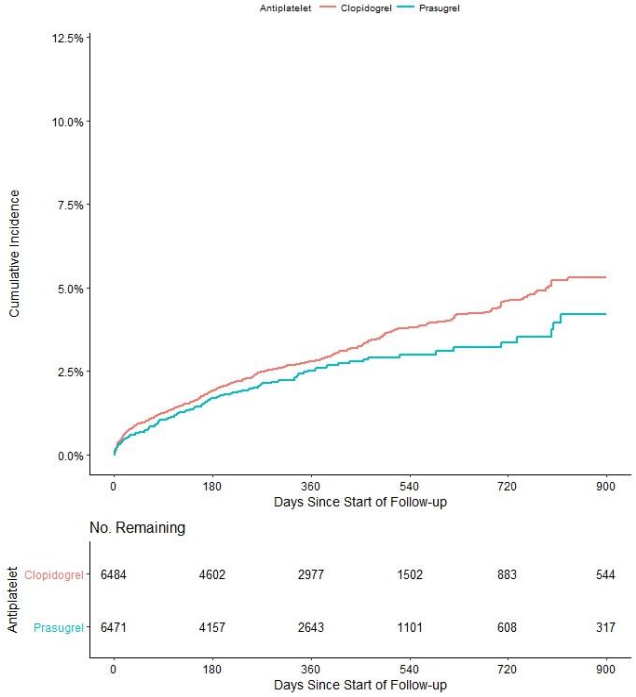
Outcome	Acute Coronary Syndrome at cohort entry							No Acute Coronary Syndrome at cohort entry						
	Prasugrel			Clopidogrel			Hazard Ratio	Prasugrel			Clopidogrel			Hazard Ratio
	Events	PY[1]	IR[2] (per 100 PY)	Events	PY	IR (per 100 PY)		Events	PY	IR (per 100 PY)	Events	PY	IR (per 100 PY)	
MACCE[3]														
Optum Research Database	114	3705	3.1	773	18783	4.1	0.69 (0.57, 0.84)	42	2062	2.0	495	5060	3.3	0.59 (0.43, 0.81)
MarketScan	138	5712	2.4	830	23306	3.6	0.65 (0.54, 0.78)	66	2456	2.7	374	3801	2.7	0.97 (0.75, 1.26)
Myocardial Infarction														
Optum Research Database	77	3709	2.1	505	18870	2.7	0.71 (0.56, 0.90)	29	2067	1.4	239	5141	1.6	0.85 (0.57, 1.24)
MarketScan	95	5729	1.7	508	23478	2.2	0.73 (0.58, 0.91)	31	2472	1.3	155	3922	1.1	1.09 (0.74, 1.60)
Bleed														
Optum Research Database	213	3628	5.9	1270	18253	7.0	0.79 (0.68, 0.91)	160	1989	8.0	1197	4437	8.3	0.92 (0.78, 1.09)
MarketScan	299	5593	5.3	1332	22865	5.8	0.89 (0.78, 1.01)	156	2396	6.5	867	3401	6.5	0.98 (0.83, 1.16)

[1] Person-years; [2] Incidence rate; [3] Major adverse cardiovascular or cerebrovascular event

PANEL A: Patients with Acute Coronary Syndrome at cohort entry (Optum Research Database)



PANEL B: Patients with Acute Coronary Syndrome at cohort (MarketScan)



PANEL C: Patients without Acute Coronary Syndrome at cohort entry (Optum Research Database)

PANEL D: Patients without Acute Coronary Syndrome at cohort entry (MarketScan)

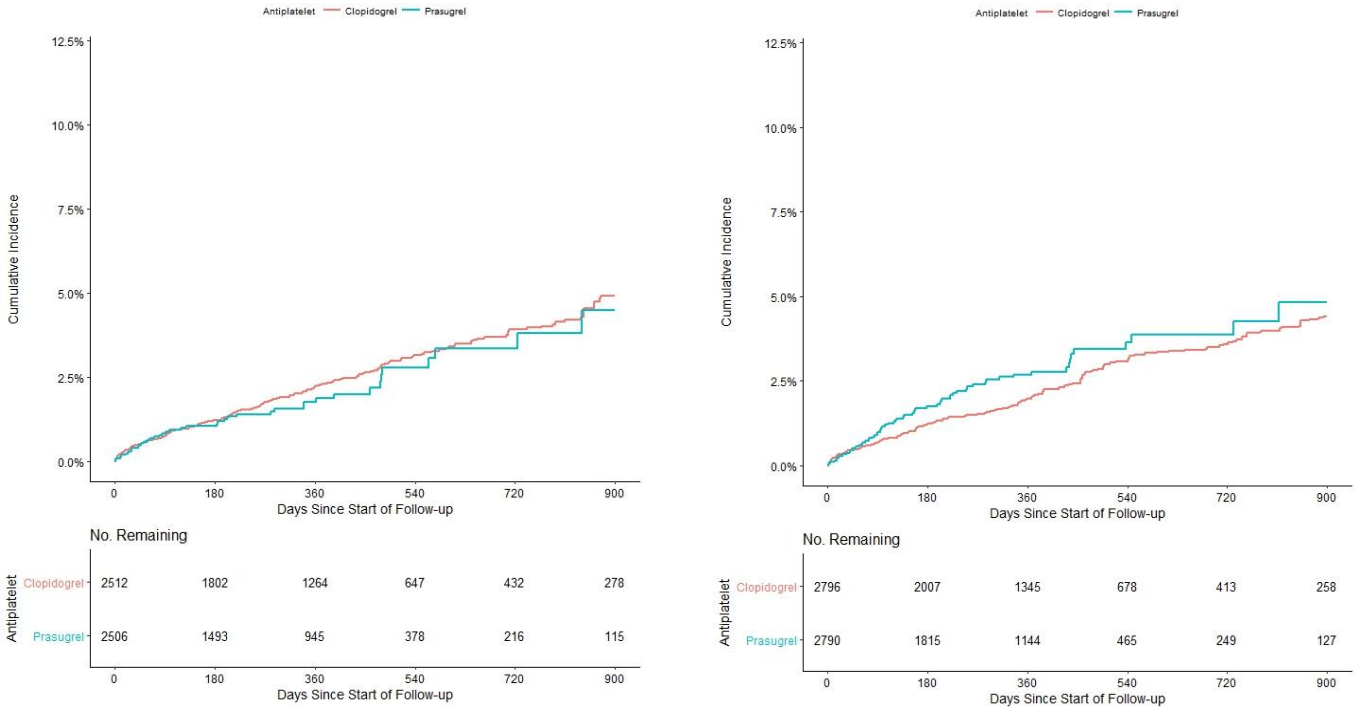
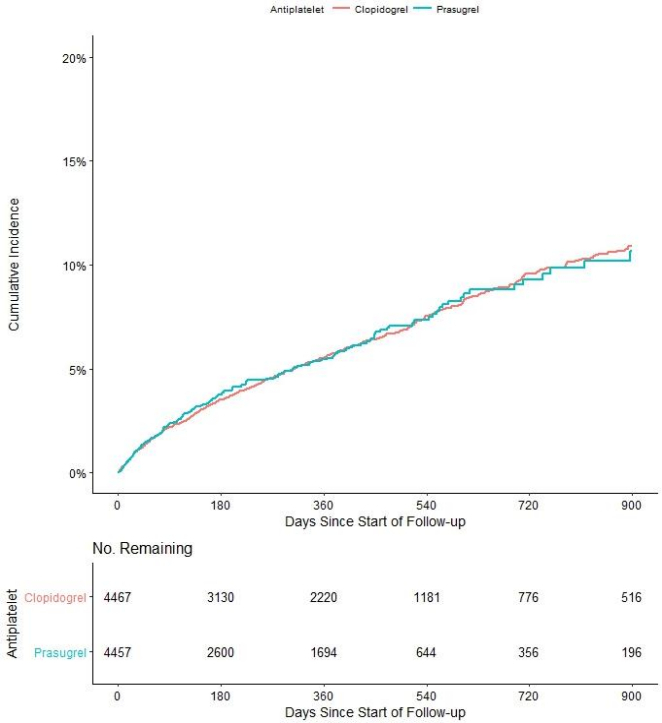
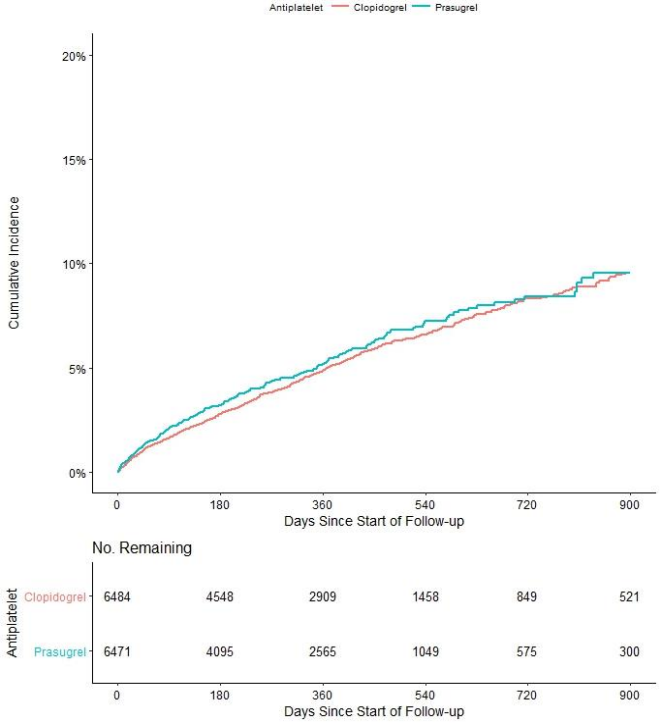


Figure 2.4: Kaplan Meier cumulative incidence, major adverse cardiovascular or cerebrovascular event

PANEL A: Patients with Acute Coronary Syndrome at cohort entry (Optum Research Database)



PANEL B: Patients with Acute Coronary Syndrome at cohort entry (MarketScan)



PANEL C: Patients without Acute Coronary Syndrome at cohort entry (Optum Research Database)

PANEL D: Patients without Acute Coronary Syndrome at cohort entry (MarketScan)

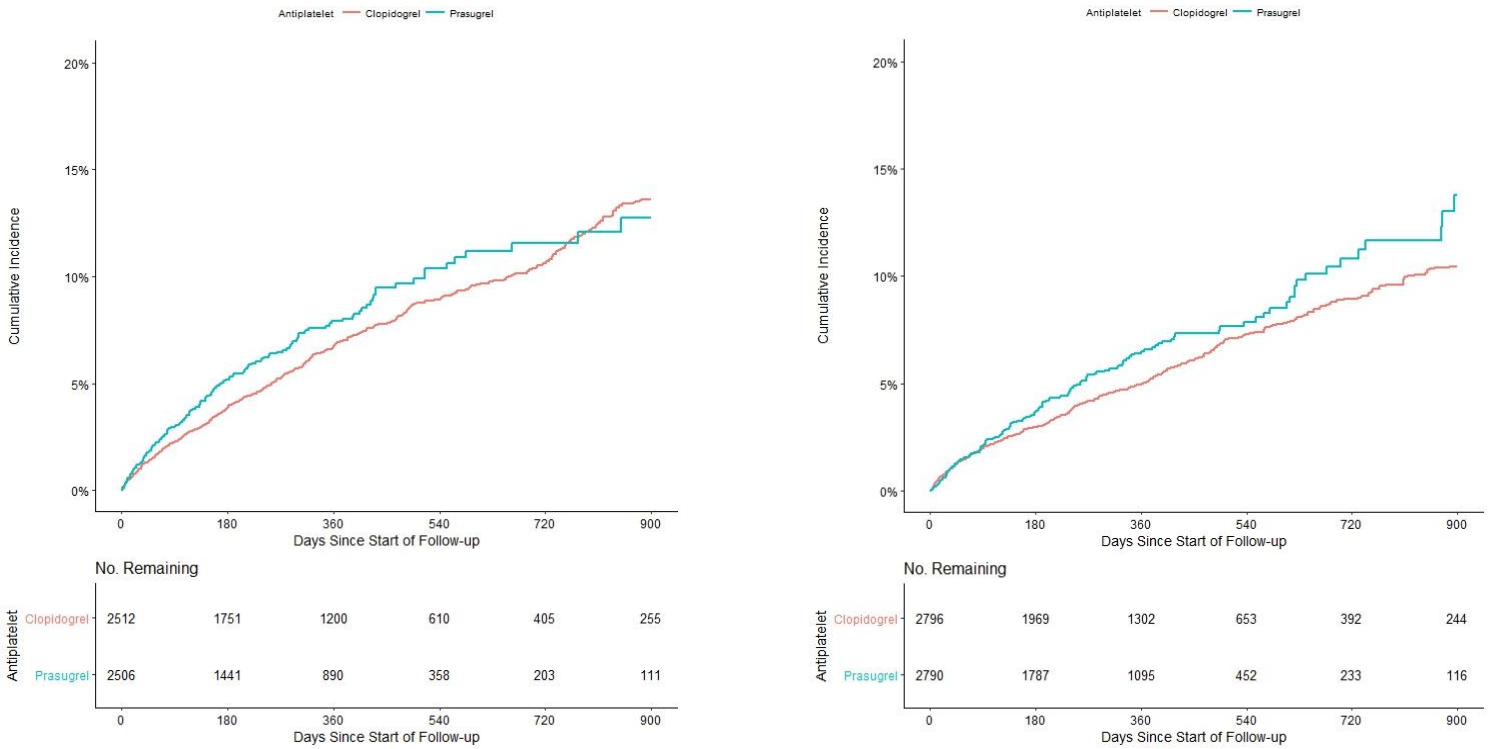


Figure 2.5: Kaplan Meier cumulative incidence, bleeding

Table 2.6: Variance adjustment for cohort overlap across databases

Amount of overlap	Acute Coronary Syndrome at cohort entry						No Acute Coronary Syndrome at cohort entry					
	Baseline cohort		6 month cohort		12 month cohort		Baseline cohort		6 month cohort		12 month cohort	
	MACCE	Bleeding	MACCE	Bleeding	MACCE	Bleeding	MACCE	Bleeding	MACCE	Bleeding	MACCE	Bleeding
10%	0.86 (0.68, 1.09)	1.05 (0.88, 1.25)	0.86 (0.58, 1.29)	0.96 (0.73, 1.26)	0.90 (0.49, 1.68)	1.00 (0.67, 1.50)	1.08 (0.74, 1.58)	1.18 (0.95, 1.48)	1.03 (0.57, 1.85)	1.08 (0.76, 1.53)	0.94 (0.41, 2.18)	0.94 (0.40, 2.20)
20%	0.86 (0.68, 1.09)	1.05 (0.88, 1.25)	0.86 (0.57, 1.30)	0.96 (0.73, 1.26)	0.90 (0.48, 1.69)	1.00 (0.67, 1.50)	1.08 (0.74, 1.58)	1.18 (0.94, 1.48)	1.03 (0.57, 1.86)	1.08 (0.76, 1.54)	0.99 (0.58, 1.71)	0.99 (0.57, 1.72)

Chapter 3 EVALUATION OF THE IMPACT OF MEDICATIONS SYNCHRONIZATION PROGRAMS ON ADHERENCE, CLINICAL OUTCOMES, AND HEALTHCARE RESOURCE UTILIZATION

Alexis A. Krumme[1,2]; Robert J. Glynn[1]; Sebastian Schneeweiss[1,2]; Joshua J. Gagne[1,2]; J. Samantha Dougherty[3]; Greg Brill[1]; Niteesh K. Choudhry[1]

Affiliations

[1] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120

[2] Harvard TH Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115

[3] Pharmaceutical Research and Manufacturers of America (PhRMA), 950 F St. NW #300, Washington, DC 20004

ABSTRACT

The burden of filling complex chronic disease medication regimens is an important barrier to adherence. Pharmacy-based medication synchronization programs simplify the refill process by enabling patients to pick up medications on a single visit; however, little about their effectiveness is known. We evaluated the impact of two synchronization programs on adherence, cardiovascular events, and resource utilization among Medicare beneficiaries treated for two or more chronic conditions between 2011 and 2014, at least one of which was hypertension, hyperlipidemia, or diabetes. Among 22,805 patients, mean percent of days covered (PDC) for controls was 84% and was 3.1 points higher among synchronized patients; adherence improvement was 3-fold higher in patients with low baseline adherence (PDC ≤70%). Rates of hospitalization or ED visits and outpatient visits were significantly lower in the synchronized group, while cardiovascular event rates were similar. Synchronization programs improved adherence for patients with cardiovascular disease, especially those with low adherence.

INTRODUCTION

Although highly evidenced-based, complex chronic disease regimens pose many challenges for patients, including the need for many trips to the pharmacy to fill their prescriptions. This can be particularly burdensome for older adults who are managing several chronic illnesses and can lead to medication non-adherence. For instance, patients with cardiovascular disease make an average of 20 pharmacy visits per year.(1) Ten percent of such patients make 44 or more visits annually and their adherence rates are 8% lower compared to patients with the lowest prescribing and filling complexity, an effect that can translate into meaningful differences in clinical outcomes.(1,2)

Programs offered by pharmacies to synchronize medication filling aim to simplify the refilling process by enabling patients to pick up all of their medications on a single visit.(3–5) Other standard components of medication synchronization programs, such as refill reminders and regular pharmacist appointments, are designed to maintain synchronization and reinforce adherence behaviors over time.

In 2014, an estimated 355,000 patients were enrolled in medication synchronization programs in 3,334 chain and retail store pharmacies across the US.(6) As of 2017, this number is estimated to be more than 3.5 million. While these programs have proliferated, they have been incompletely evaluated. In particular, while programs run by geographically-localized community pharmacy and mail-order pharmacies appear to improve adherence, their impact in settings where the majority of patients fill their medications – retail chains – remains unknown.(7–12) Further, the impact of synchronization programs on clinical outcomes and resource utilization remains unknown.

In this study, we evaluated the impact of two regional pharmacy-based medication synchronization programs on adherence to cardiovascular medications, cardiovascular clinical outcomes, and healthcare resource utilization for Medicare fee-for-service beneficiaries with hypertension, hyperlipidemia, and/or diabetes, three of the top five most prevalent conditions in Medicare enrollees.(13)

METHODS

Medication synchronization programs

Two medication synchronization programs were selected and agreed to participate in this research study: a mid-sized pharmacy chain with approximately 100 locations serving in 6 Midwestern states that began its program in 2011, and a large supermarket chain with approximately 1,000 stores in 6 Southeastern states that began its program in 2013. These were two of the earliest chain pharmacy medication synchronization programs available which makes it unlikely that any of the patients in our study would have knowledge of, have been offered, or been previously enrolled in a competing program.(6)

The first program served a predominantly rural population, and included individuals on at least two medications to treat a chronic condition. The second program included individuals on three or more chronic disease medications as well as Medicare beneficiaries taking a medication covered by Medicare adherence Star Ratings.(14) In both programs, monthly appointments with pharmacy staff were offered to patients, and recommended if there were any changes in their regimen. Programs were available to anyone wishing to enroll, offered at no cost, and provided a suite of monthly reminders and connection to other pharmacy-based services such as immunizations and medication therapy management.

Enrolled patients and pharmacy staff selected a future fill date of one of their medications the date when synchronization would begin. Typically, this 'anchor' fill was chosen to minimize copayments for the partial dispensings of all other medications that must have occurred to align all fill dates around the anchor fill date. In both programs, the majority of patients had their prescriptions fully synchronized within 30-days of enrollment.

Study population and data source

We included Medicare beneficiaries who enrolled in one of the two medication synchronization programs between July 2011 and June 2014. Patients had to have a prescription fill for the treatment of one of three chronic cardiovascular conditions – hypertension, diabetes, or hyperlipidemia – within 90 days of program enrollment at a retail pharmacy and 180 days of continuous Medicare Part A, B, and D eligibility prior to this prescription fill (Figure 3.1). The index date was defined as the first fill for an eligible medication on or after enrollment date. During the 180-day period preceding the index date, patients were required to have a prescription fill for a cardiovascular condition and one for either a different cardiovascular condition or another chronic condition identified by CMS as part of core Maintenance Therapy Management (complete list of conditions and medications classes in Table 3.4).(15)

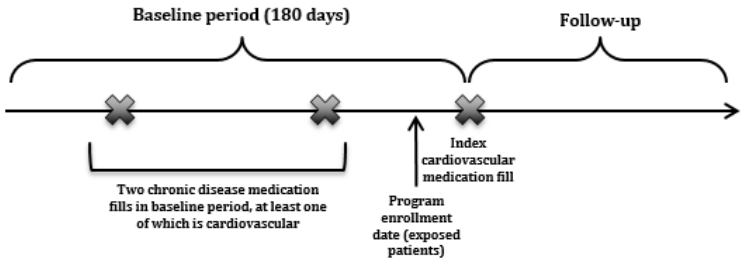


Figure 3.1: Study design

Eligible control patients were those living in one of the 11 US states in which the two participating programs operated pharmacies during the study period and with a prescription fill for

an oral cardiovascular medication between July 2011 and June 2014 occurring at a different pharmacy from any exposed patient; index date was defined as the prescription fill date for this medication. Thus, the control population consists of patients who could have enrolled in one of the two programs during the study period, yet with a low probability that they were in fact offered enrollment and declined since they went to non-participating pharmacies. Control patients had the same requirements for continuous Medicare eligibility and chronic medication use for at least two conditions as synchronized patients. Controls were eligible for cohort entry once in every 6-month interval but were matched only once (see Statistical analysis).

We conducted our study using Medicare pharmacy and medical claims data from 2011-2014 for patients enrolled in Medicare Part A and B and a Part D Plan (PDP). These data contain complete eligibility as well as paid claims for all procedures, physician encounters, hospitalizations, and filled prescriptions (including dose dispensed and amounts paid by Medicare and the patient) reimbursed by Medicare. Aggregate data on socioeconomic status, race/ethnicity, and educational attainment were obtained by linking zip code of residence with data from the 2010 US Census.

Covariates

We constructed covariates that could be associated with program enrollment as well as cardiovascular-related clinical and healthcare outcomes, notably clinical comorbidity profile, medication burden and use patterns, socio-demographic characteristics, prior resource utilization characteristics, and benefit and index pharmacy characteristics in the 180 days prior to index fill. Clinical comorbidity was defined as the presence of individual chronic conditions, with a focus on cardiovascular comorbidity, and also summarized using the Combined Comorbidity Score.(16) Medication burden was defined as the number of drugs for cardiovascular conditions (1-3), total number of chronic disease medication classes (up to 26), and adherence to cardiovascular medication classes and to all chronic disease medication classes; the latter was measured as the

mean proportion of days covered (PDC) across medication classes with at least one fill during the baseline period, beginning with the first fill in this period.

Socio-demographic characteristics included age, sex, race, and zip code-level education, race, and household income covariates. Resource utilization was assessed using the number of outpatient office visits, total days hospitalized, number of emergency department visits, and intensive care unit stay during the baseline period. Medicare Part D benefit characteristics included Part D Low-Income Subsidy eligibility, plan premium amount, and whether the plan was a Program of All-inclusive Care for the Elderly (PACE) plan. Finally, we measured 'healthy adherer' characteristics, behaviors that have been shown to be positively associated with medication adherence: receipt of influenza vaccine, fecal occult blood test, mammogram or PSA screening, colonoscopy screening.(17,18)

Outcomes

The primary study outcome was monthly adherence to cardiovascular medications during the year after the index date. Adherence was evaluated using the Proportion of Days Covered (PDC), defined as the ratio of the total number of days on which the patient had medications available (numerator) and the total number of days in the measurement period; it is a widely used measure that has been well-studied in several therapeutic classes.(19) All medications within a medication class were considered interchangeable. Follow-up for all outcomes began in the second month after index date to allow for an induction period before programs could potentially begin working. Further, as with all claims-based methods of adherence estimation, adherence was 100% for virtually all patients in the first month after the index date. Follow-up continued for the subsequent eleven 30-day intervals and patients were censored at the end of follow-up or loss of Medicare enrollment.

Patients were followed for as many cardiovascular medication classes they filled during follow-up. A monthly PDC was calculated for each eligible medication class, which was used to calculate an overall mean monthly PDC for a patient as the average PDC for all cardiovascular medication classes in a given 30-day interval. We additionally evaluated monthly optimal adherence, defined as a PDC≥0.80 to all medication classes which a patient was eligible for in a given month.

Secondary outcomes included 1) incidence of major adverse cardiovascular event and 2) monthly healthcare resource utilization. Major adverse cardiovascular event, evaluated using International Statistical Classification of Disease and Related Health Problems, 9th Revision (ICD-9) and Current Procedural Terminology (CPT) codes, was defined as a diagnosis of myocardial infarction, unstable angina, stroke, or congestive heart failure, an endpoint that has been used elsewhere over 24 months (definitions in Table 2.5).(20,21) We also evaluated this outcome including revascularization, by adding percutaneous coronary intervention (PCI) and coronary artery bypass graft procedures. Healthcare resource utilization was measured as the monthly number of inpatient hospitalization stays or emergency department visits, and number of physician office visits over eleven 30-day intervals.

Statistical analysis

We used a logistic regression model that predicted the probability of enrollment in a medication synchronization program as a function of the baseline covariates to construct propensity scores for synchronized and control patients. Propensity score construction and matching were conducted sequentially in each 6-month interval; once a control patient was matched, the patient could not be sampled as a control in future intervals, similar to the design of a prospective randomized trial. Synchronized patients were variable ratio matched to up to 3 control patients using nearest neighbor matching and a caliper of 0.025 on the propensity score scale

within each of the two geographic regions defined by the programs (Midwest or Southeast).(22) Weights were assigned to control patients in each matched set to account for the variable ratio matched sets and scaled to sum to the number of unique control patients included in the analysis.(23) After matching, we compared weighted baseline characteristics to ensure balance of measured covariates.

Adherence and resource utilization outcomes were evaluated using weighted generalized estimating equations with an autoregressive covariance structure to account for the correlation of repeated measures over time. Mean adherence was modeled with an identity link and normal distribution; optimal adherence was modeled with a log link and binomial distribution; resource utilization outcomes were modeled with a log link and negative binomial distribution. The cardiovascular clinical outcome was evaluated using a weighted Cox proportional hazards model. We performed several subgroup analyses, re-matching patients for each subgroup: 1) program region (Midwest vs. Southeast); 2) baseline PDC tertile (≤0.70, 0.70-0.85, >0.85); 3) receipt of the Part D low income subsidy at index; 4) primary versus secondary prevention, with secondary prevention defined as diagnosis of myocardial infarction, unstable angina, stroke, congestive heart failure, peripheral artery disease, bleed, diabetic or hypertensive nephropathy, or PCI procedure during baseline.

We conducted several sensitivity analyses. During the study period, the Southeastern US program offered three commonly prescribed generic cardiovascular medications free of charge to patients and insurers. To account for the possibility that these prescription fills were inconsistently submitted as Medicare claims prior to 2014, we removed patients from the Southeastern US region who filled these medications at index. Second, for the resource utilization outcomes we used a Poisson distribution. Third, we evaluated whether our results changed when the baseline period for prescription drug inclusion criteria and covariates was extended to 365 days prior to index.

Finally, we conducted an exploratory analysis of the average individual change in the number of prescriptions filled per unique fill date, with positive changes in synchronized compared to control patients indicating greater fill synchronization.

RESULTS

Study population and characteristics

After applying all cohort inclusion criteria, the final study population consisted of 7,744 synchronized and 200,047 eligible control patient-observations for 62,413 unique patients (Table 3.1). Before matching, synchronized patients tended to be older than control patients (mean age 74.7 vs. 70.8 years, absolute standardized difference (ASD)=0.37), and more often of white race (89.1% vs. 80.1%, ASD=0.25). Synchronized patients were less likely to receive the Part D low income subsidy (23.6% vs. 38.9%, ASD=0.33) and tended to be taking medications in more chronic disease classes (5.1 vs. 4.8, ASD=0.17). The prevalence of individual clinical comorbidities were relatively balanced between groups, with the exception of diabetes (56.0% in exposed vs. 42.0% in unexposed, ASD=0.28).

The final matched cohort consisted of 6,519 synchronized and 16,286 control patients; 84% of synchronized patients were matched to 2.5 control patients on average (comparison of matched and unmatched synchronized patients in Table 3.7). After matching, covariates were well-balanced between groups (ASD<0.10)(Table 3.1). Nearly half of patients were taking medications for two cardiovascular conditions, and had a mean adherence of 0.85 to their cardiovascular medications. Because program enrollment grew over time, we observed right-censoring of patients at the end of available data: 25.0% of the cohort was censored by 9 months of follow-up, and 57.0% by 12 months.

Table 3.1: Baseline characteristics, full and matched cohort

Characteristic	Full Cohort			Matched Cohort		
	Synchronized patients (N=7,744)	Control patient-observations (N=200,047)	ASD[1]	Synchronized patients (N=6,519)	Control patients (N=16,286)	ASD
Demographic						
Age, mean (SD)	74.7 (9.1)	70.8 (11.5)	0.37	74.0 (9.1)	74.3 (9.0)	0.03
Female sex	4,778 (61.7)	122,841 (61.4)	0.01	3,961 (60.8)	8,867 (61.2)	0.01
Race						
White	6,899 (89.1)	160,213 (80.1)	0.25	5,758 (88.3)	12,696 (87.6)	0.02
Black	263 (3.4)	25,798 (12.9)	0.35	249 (3.8)	604 (4.2)	0.02
Hispanic	394 (5.1)	10,045 (5)	0.00	348 (5.3)	855 (5.9)	0.02
Other/unknown	188 (2.4)	3,991 (2)	0.03	164 (2.5)	341 (2.4)	0.01
Median household income in zip code, mean (SD)	$50,603 ($14,933)	$49,197 ($15,791)	0.09	$51,701 ($15,257)	$51,801 ($14,000)	0.01
Percent black in zip code, mean (SD)	7.0 (12.6)	15.6 (19.2)	0.53	7.9 (13.3)	8.1 (11.9)	0.01
Percent with at least high school education in zip code, mean (SD)	87.8 (6.0)	84.3 (8.3)	0.49	87.8 (6.0)	87.9 (5.8)	0.02
Participating program region						
Southeastern	3,784 (48.9)	159,522 (79.7)	0.68	3,561 (54.6)	7,911 (54.6)	0.00
Midwestern	3,960 (51.1)	40,525 (20.3)	0.68	2,958 (45.4)	6,586 (45.4)	0.00
Calendar interval						
Jan 2012 - Jun 2012	47 (0.6)	38,317 (19.2)	0.65	47 (0.7)	110 (0.8)	0.00
Jul 2012 - Dec 2012	858 (11.1)	39,995 (20)	0.25	848 (13)	1,964 (13.6)	0.02
Jan 2013 - Jun 2013	858 (11.1)	39,713 (19.9)	0.24	709 (10.9)	1,549 (10.7)	0.01
Jul 2013 - Dec 2013	1,220 (15.8)	44,046 (22)	0.16	722 (11.1)	1,504 (10.4)	0.02
Jan 2014 - Jun 2014	4,761 (61.5)	37,976 (19)	0.96	4,193 (64.3)	9,369 (64.6)	0.01
Medicare benefits						
Years in Medicare, mean (SD)	12.5 (7.7)	11.7 (7.9)	0.09	12.1 (7.6)	12.5 (7.3)	0.06
Low income subsidy in 3 out of 6 months prior to index	1,828 (23.6)	77,728 (38.9)	0.33	1,615 (24.8)	3,719 (25.7)	0.02
At least one Part D fill in catastrophic phase	689 (8.9)	20,662 (10.3)	0.05	614 (9.4)	1,406 (9.7)	0.01
PACE plan[2]	812 (10.5)	15,874 (7.9)	0.09	710 (10.9)	1,569 (10.8)	0.00
Monthly plan premium, mean (SD)	$42.21 ($21.79)	$39.59 ($18.79)	0.13	$42.01 ($22.04)	$41.76 ($20.19)	0.01
Institutional stay prior to index	191 (2.5)	4,151 (2.1)	0.03	153 (2.3)	367 (2.5)	0.01
Index fill						
Patient cost index fill, mean (SD)	$10.51 ($24.02)	$11.11 ($25.65)	0.02	$10.51 ($25.20)	$10.63 ($20.28)	0.01
Total cost index fill, mean (SD)	$30.19 ($88.27)	$35.33 ($79.36)	0.06	$31.08 ($91.97)	$31.69 ($69.60)	0.01
Days supply index fill ≤30 days	5,018 (64.8)	127,097 (63.5)	0.03	4,225 (64.8)	9,172 (63.3)	0.03
Chronic disease medication usage						
Chronic disease medication classes, mean (SD)	5.1 (1.9)	4.8 (1.9)	0.17	5.1 (1.9)	5.1 (1.9)	0.00
PDC[3], chronic disease medication classes, mean (SD)	0.84 (0.15)	0.78 (0.18)	0.36	0.83 (0.15)	0.83 (0.14)	0.01
PDC[3], cardiovascular medication classes, mean (SD)	0.86 (0.16)	0.80 (0.20)	0.32	0.85 (0.16)	0.85 (0.15)	0.01
Cardiovascular conditions						
1	1,089 (14.1)	43,826 (21.9)	0.21	947 (14.5)	2,510 (17.3)	0.08

2	3,688 (47.6)	104,113 (52)	0.09	3,051 (46.8)	6,897 (47.6)	0.02
3	2,967 (38.3)	52,108 (26)	0.27	2,521 (38.7)	5,090 (35.1)	0.07
Distinct drugs, mean (SD)	9.5 (4.8)	9.6 (5.0)	0.04	9.6 (4.9)	9.7 (4.7)	0.02
Copayments, all prescriptions, mean (SD)	$392 ($471)	$299 ($410)	0.21	$385 ($457)	$377 ($479)	0.02
Clinical comorbidity						
Hyperlipidemia	5,514 (71.2)	138,897 (69.4)	0.04	4,678 (71.8)	10,355 (71.4)	0.01
Hypertension	6,111 (78.9)	159,641 (79.8)	0.02	5,166 (79.2)	11,469 (79.1)	0.00
Diabetes	4,334 (56)	83,940 (42)	0.28	3,773 (57.9)	8,192 (56.5)	0.03
Myocardial infarction	61 (0.8)	1,339 (0.7)	0.01	49 (0.8)	118 (0.8)	0.01
Unstable angina	65 (0.8)	1,887 (0.9)	0.01	56 (0.9)	128 (0.9)	0.00
Heart failure	221 (2.9)	5,947 (3)	0.01	192 (2.9)	421 (2.9)	0.00
Stroke	58 (0.7)	1,335 (0.7)	0.01	43 (0.7)	88 (0.6)	0.01
Peripheral artery disease	320 (4.1)	7,789 (3.9)	0.01	284 (4.4)	681 (4.7)	0.02
Bleed (cranial or GI)	239 (3.1)	7,090 (3.5)	0.03	221 (3.4)	497 (3.4)	0.00
Atrial fibrillation	225 (2.9)	5,426 (2.7)	0.01	194 (3)	450 (3.1)	0.01
Chronic renal insufficiency	1,148 (14.8)	25,017 (12.5)	0.07	965 (14.8)	2,180 (15)	0.01
Diabetic nephropathy	326 (4.2)	5,770 (2.9)	0.07	295 (4.5)	645 (4.4)	0.00
Hypertensive nephropathy	533 (6.9)	12,620 (6.3)	0.02	449 (6.9)	1,033 (7.1)	0.01
Dialysis	39 (0.5)	2,110 (1.1)	0.06	37 (0.6)	80 (0.6)	0.00
Abnormal liver function	269 (3.5)	8,106 (4.1)	0.03	238 (3.7)	533 (3.7)	0.00
Asthma/COPD	1,597 (20.6)	44,344 (22.2)	0.04	1,391 (21.3)	3,123 (21.5)	0.01
Alzheimer's or dementia	412 (5.3)	10,898 (5.4)	0.01	334 (5.1)	805 (5.6)	0.02
Depression	961 (12.4)	28,346 (14.2)	0.05	820 (12.6)	1,863 (12.9)	0.01
Osteoporosis	1,122 (14.5)	27,593 (13.8)	0.02	940 (14.4)	2,160 (14.9)	0.01
Cancer	709 (9.2)	16,208 (8.1)	0.04	599 (9.2)	1,331 (9.2)	0.00
Percutaneous coronary intervention	79 (1)	1,750 (0.9)	0.02	64 (1)	149 (1)	0.01
Stress test	254 (3.3)	7,125 (3.6)	0.02	227 (3.5)	521 (3.6)	0.01
Combined comorbidity score, mean (SD)	1.2 (2.2)	1.1 (2.2)	0.04	1.2 (2.3)	1.2 (2.1)	0.02
Resource utilization						
Outpatient visits						
0 to 2	2,473 (31.9)	56,856 (28.4)	0.08	1,968 (30.2)	4,319 (29.8)	0.01
2 to 4	1,712 (22.1)	46,449 (23.2)	0.03	1,442 (22.1)	3,181 (21.9)	0.00
4 to 7	1,686 (21.8)	47,618 (23.8)	0.05	1,445 (22.2)	3,217 (22.2)	0.00
>7	1,873 (24.2)	49,124 (24.6)	0.01	1,664 (25.5)	3,779 (26.1)	0.01
Hospitalization length of stay (days)						
0	6,817 (88)	174,275 (87.1)	0.03	5,724 (87.8)	12,690 (87.5)	0.01
1 to 4	425 (5.5)	11,279 (5.6)	0.01	361 (5.5)	818 (5.6)	0.00
>4	502 (6.5)	14,493 (7.2)	0.03	434 (6.7)	989 (6.8)	0.01
Emergency Room visits						
0	7,220 (93.2)	182,737 (91.3)	0.07	6,043 (92.7)	13,422 (92.6)	0.00
1	416 (5.4)	13,690 (6.8)	0.06	375 (5.8)	833 (5.7)	0.00
>1	108 (1.4)	3,620 (1.8)	0.03	101 (1.5)	241 (1.7)	0.01
Intensive Care Unit stay	952 (12.3)	26,090 (13)	0.02	812 (12.5)	1,843 (12.7)	0.01
Healthy adherer effect						
Flu shot	2,878 (37.2)	62,016 (31)	0.13	2,422 (37.2)	5,324 (36.7)	0.01
Fecal occult blood test	293 (3.8)	7,936 (4)	0.01	246 (3.8)	527 (3.6)	0.01
Mammogram or PSA	2,057 (26.6)	47,729 (23.9)	0.06	1,739 (26.7)	3,827 (26.4)	0.01
Colonoscopy	365 (4.7)	7,907 (4)	0.04	307 (4.7)	627 (4.3)	0.02

[1] Absolute standardized difference; [2] Program for All-inclusive Care in the Elderly; [3] Proportion of Days Covered

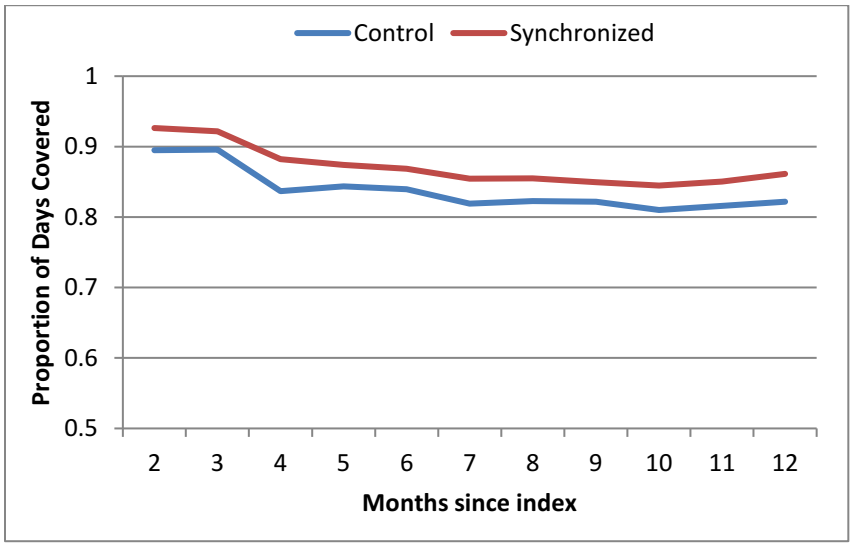
Adherence

Mean adherence declined over time in both groups, with the effect size between them remaining constant (Figure 3.2 Panel A, Figure 3.3). Monthly PDC during follow-up was 0.031 points higher in synchronized compared to matched control patients (PDC difference: 0.03 (0.03, 0.04); p<.0001) and synchronized patients had an 8% higher odds of being optimally adherent to all of their cardiovascular medications over time compared to control patients (OR: 1.08 (1.07, 1.10); p<.0001)(Table 3.2).

Cardiovascular outcomes

Monthly rates of hospitalization or ED visits and outpatient office visits were lower in synchronized versus control patients (RR=0.91 (0.84, 0.99), p=0.04; RR=0.97 (0.95, 0.99), p=0.02, respectively). Event rate for the cardiovascular clinical endpoint was 9.5 per 100 person-years in synchronized patients and 10.0 per 100 person-years in control patients. Synchronized patients had non-statistically significant lower rates of the cardiovascular clinical endpoint, with and without revascularization (HR=0.95 (0.86, 1.05); p=0.32). Kaplan Meier plots suggest an effect of intervention beyond year 1 of follow-up (Figure 3.2, Panel B), and test of an interaction term between the exposure and time at one year of follow-up was significant (p<.0001). Stratification of the Cox proportional hazards models on follow-up up to vs. after 1 year suggested an effect in later time periods, although confidence intervals were overlapping (HR=0.97 (0.87, 1.08), p=0.63 in year 1; HR=0.86 (0.65, 1.14), p=0.30 beyond year 1).

PANEL A



PANEL B

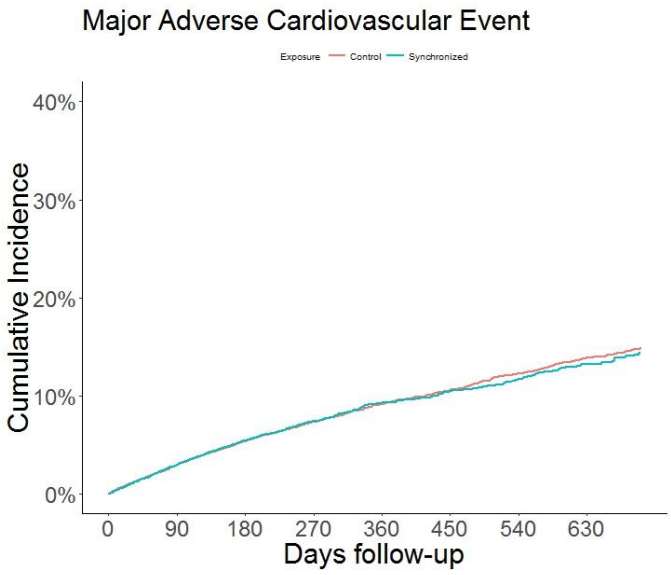


Figure 3.2: Monthly mean proportion of days covered for cardiovascular medications (Panel A) and Kaplan Meier cumulative incidence, major adverse cardiovascular event (Panel B)

Table 3.2: Model-based results for primary and secondary outcomes

Outcome	Estimates by exposure group			Model estimates	
	Measure	Synchronized	Control	Point estimate measure	Point estimate (95% CI): Synchronized vs. Control
Adherence to cardiovascular medications					
Proportion of days covered	Average monthly PDC	0.87	0.84	Monthly change in PDC	0.03 (0.03, 0.04)
Optimal adherence	Average proportion of patients optimally adherent	63.7%	57.6%	Odds ratio of monthly proportion optimally adherent	1.08 (1.07, 1.10)
Major adverse cardiovascular event	Event rate	9.5 per 100 person-years	10.0 per 100 person-years	Hazard ratio	0.95 (0.86, 1.05)
Resource utilization					
Hospitalizations and emergency department visits	Average monthly events	0.045	0.048	Rate ratio of monthly number of visits	0.91 (0.84, 0.99)
Physician office visits	Average monthly events	0.77	0.80	Rate ratio of monthly number of visits	0.97 (0.95, 0.99)

Subgroup analyses

Results in four key subgroups are presented in Table 3.3. The proportion of patients achieving optimal adherence was higher in the Midwestern program, though mean difference in PDC between groups was the same in the two regions. Individuals with the lowest baseline adherence (PDC≤0.70) had the largest gains in adherence associated with the intervention (PDC difference=0.06 (0.05, 0.08) vs. 0.02 (0.01, 0.03) in the other two groups). The corresponding odds of optimal adherence were 19% higher in synchronized vs. control patients with baseline PDC ≤0.70 (OR=1.19 (1.15, 1.24)) and 7% higher in synchronized vs. control patients with baseline PDC between 0.70 and 0.85 (OR=1.07 (1.04, 1.10)). Receipt of the Part D low income subsidy was associated with small increases in optimal adherence.

Table 3.3: Primary outcome results stratified by key subgroup

Subgroup	Matched subgroup population			Adherence outcomes			
	Synchronized	Control	Proportion synchronized matched	Proportion of Days Covered	p-value	Optimal Adherence	p-value
Program region							
Midwestern	2,958	7,390	0.75	0.03 (0.03, 0.04)	<.0001	1.11 (1.09, 1.13)	<.0001
Southeastern	3,561	8,896	0.94	0.03 (0.02, 0.03)	<.0001	1.05 (1.03, 1.07)	<.0001
Baseline adherence level							
PDC[1] ≤0.70	1,303	3,362	0.95	0.06 (0.05, 0.08)	<.0001	1.19 (1.15, 1.24)	<.0001
0.70<PDC[1]≤0.85	1,975	4,982	0.92	0.02 (0.01, 0.03)	<.0001	1.07 (1.04, 1.10)	<.0001
PDC[1]>0.85	3,654	8,954	0.87	0.02 (0.02, 0.03)	<.0001	1.04 (1.03, 1.06)	<.0001
Part D Low-income subsidy at index							
No LIS	4,909	12,028	0.83	0.03 (0.02, 0.03)	<.0001	1.08 (1.06, 1.09)	<.0001
Full or partial dual LIS eligibility	1,610	4,092	0.88	0.04 (0.03, 0.05)	<.0001	1.10 (1.07, 1.14)	<.0001
Primary prevention vs. secondary prevention or at high risk							
Primary	5,463	13,587	0.85	0.03 (0.03, 0.04)	<.0001	1.08 (1.07, 1.10)	<.0001
Secondary or at high risk	1,205	2,973	0.90	0.03 (0.02, 0.04)	<.0001	1.07 (1.03, 1.11)	0.0004

[1] Proportion of days covered

Sensitivity analyses

Results were robust to sensitivity analyses. In particular, the extension of the prescription drug baseline period to 365 days yielded a matched cohort and results similar to the main analysis (93% of synchronized patients from the main analysis were included) as a result of the similarities in baseline period adherence and medication use characteristics. In an exploratory analysis of the number of prescription fills per unique fill date, synchronized patients had 23% increase in the number of fills per visit, on average, compared to 3% increase among control patients.

DISCUSSION

In this study of Medicare beneficiaries, enrollment in a medication synchronization program was associated with a small but significant improvement in adherence to cardiovascular medications and statistically significant reductions in hospitalizations or ED visits and outpatient visits. Program enrollment was also associated with non-significant reductions in major adverse cardiovascular events that were larger in magnitude beginning

12 months after enrollment. The intervention had the largest effect on adherence among patients with lower baseline adherence.

Our results are similar to those from an evaluation of an at-mail refill synchronization program conducted in a population of Medicare managed care beneficiaries, suggesting that addressing logistical issues related to medication supply may be the principal mechanism by which these programs are successful.(9) That study was restricted to patients receiving all of their medications at mail and whose prescriptions did not include medications with atypical refill schedules. In contrast, our study provides nationally representative results for patients in the manner that the majority of patients fill their medications, and suggests that retail and at-mail populations may have similar responses to a medication synchronization intervention. While we were not able to determine which components of the pharmacy-based synchronization program are most effective, the moderate success of other pharmacist-led interventions to improve adherence may mean that further study of the long-term effects of pharmacist engagement in medication synchronization programs is warranted.(24)

Although statistically significant, the magnitude of the adherence improvement from medication synchronization was modest. There are several potential explanations for this. First, our cohort was defined by patients who filled prescriptions for at least two chronic conditions in the baseline period. This requirement was implemented to form a cohort of patients who were 'program-eligible' per the programs' targeting criteria and the definition of fill synchronization itself, which requires the presence of more than one medication. Patients who were inconsistent fillers (i.e. with a gap greater than 6 months) or for whom

index was their first cardiovascular fill would have been excluded from our cohort. Consistent prevalent users are more likely to have an established routine around medication filling and may be less likely to benefit from the reminders and logistical support provided by the program.(25) Synchronized patients moreover exhibited high levels of baseline adherence, with mean PDC exceeding 0.84. High adherence at baseline could lead to a ceiling effect, whereby these patients may only be able to achieve small additional gains. Indeed, larger associations were observed in those with lower baseline PDC.

Despite this, adherence improvements in our study were accompanied by small gains in healthcare resource utilization and major adverse cardiovascular event rates. These results are consistent with several studies of adherence-improving interventions that have found that even modest adherence differences translate into improved resource use outcomes over time.(2,26–28) In addition, medication synchronization may lead to more consistent medication use allowing patients to fully realize the benefits of prescribed therapy, averting healthcare encounters due to medication-related adverse events. Additionally, in medication synchronization programs, the pharmacist acts as an important patient resource and may help avoid unnecessary outpatient visits by addressing medication inconsistencies and possible medication errors, and smoothing out prescription refills. Improvement in major adverse cardiovascular event was seen predominantly beginning in the second year of follow-up, but was overall non-significant. Our study was likely underpowered to detect significant improvements in cardiovascular endpoints, which was exacerbated by significant right censoring of our cohort.

In subgroup analyses, patients with the lowest tertile of baseline adherence saw a three-fold increase in effect size compared to the other two, results that are aligned with findings from two other studies, and support the hypothesis that patients with erratic filling behaviors benefit more from the support provided by the program.(9,11) Future programs may consider targeting outreach enrollment specifically to patients with lower adherence who may benefit the most. Greater adherence gains among patients receiving the Part D low-income subsidy, although small, suggest that removing barriers of cost may work synergistically with the synchronization program. Interventions reducing or eliminating copayments have been effective in improving adherence in other settings.(2,26) Exploring partnerships or opportunities to offer lower priced medications may be an effective way of improving enrollment and retention in medication synchronization programs. Policy-oriented changes, such as CMS' 2014 requirement that Part D Plans offer pro-rated copayments for short fills, may also play an important role.(29)

Several limitations to our study should be acknowledged. The generalizability of our results may be limited by the fact that enrollees early in the existence of these two programs may be more health conscious than the general Medicare population. As these programs expand and recruit more patients, it will be important to re-evaluate the impact of the programs on adherence. Second, we were able to adjust for a large number of potential confounders, however patient characteristics determining the decision to enroll in a medication synchronization program may not be completely explained in administrative claims data. As with any intervention implemented under real-world conditions, there are several factors that may have influenced how the intervention was delivered during our study period, for example changes to how patients were targeted for

enrollment. Insofar as these changes are reflected in measured covariates, our propensity score constructed in different time periods would have controlled for any potentially confounding effects. Externally, Medicare star quality ratings for adherence were rolled out during our study period, which may have improved adherence over time as Part D Plans became more actively involved in adherence management; however we would not expect this to be differential by group. Finally, maintenance of synchronization over time in these two programs could not readily be evaluated in this study. Our exploratory analysis of the number of prescriptions filled per unique fill date reassuringly suggests greater consolidation of fills occurring during follow-up; however understanding the average duration of enrollment could inform important quality improvement priorities for these programs.

Few high quality studies have been conducted to evaluate the impact of pharmacy-based medication synchronization programs on medication adherence and, more importantly, downstream healthcare outcomes.(6) This study demonstrates the potential of such programs to have a lasting impact on patient outcomes. Future research will need to evaluate benefit in other populations, the duration of effects, and whether benefits translate into cost savings for patients and insurers.

ACKNOWLEDGEMENTS

AAK received tuition support from Harvard TH Chan School of Public Health (partially supported by training grants from Pfizer, Takeda, Bayer, and Asisa). This project was funded by a grant from Pharmaceutical Research and Manufacturers of America to Brigham and Women's Hospital.

REFERENCES

1. Choudhry NK, Fischer MA, Avorn J, Liberman JN, Schneeweiss S, Pakes J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. Arch Intern Med. 2011 May 9;171(9):814–22.

2. Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. N Engl J Med. 2011 Dec 1;365(22):2088–97.

3. Ross A, Jami H, Young HA, Katz R. Sync and swim: the impact of medication consolidation on adherence in Medicaid patients. J Prim Care Community Health. 2013 Oct;4(4):240–4.

4. Agarwal S, Tang SSK, Rosenberg N, Pettitt D, McLaughlin T, Joyce A, et al. Does synchronizing initiation of therapy affect adherence to concomitant use of antihypertensive and lipid-lowering therapy? Am J Ther. 2009 Apr;16(2):119–26.

5. Delate T, Fairman KA, Carey SM, Motheral BR. Randomized controlled trial of a dose consolidation program. J Manag Care Pharm JMCP. 2004 Oct;10(5):396–403.

6. Krumme AA, Isaman DL, Stolpe SF, Dougherty S, Choudhry NK. Prevalence, effectiveness, and characteristics of pharmacy-based medication synchronization programs. Am J Manag Care. 2016 Mar;22(3):179–86.

7. Holdford DA, Inocencio TJ. Adherence and persistence associated with an appointment-based medication synchronization program. J Am Pharm Assoc JAPhA. 2013 Dec;53(6):576–83.

8. Patterson JA, Holdford DA, Saxena K. Cost-benefit of appointment-based medication synchronization in community pharmacies. Am J Manag Care. 2016 Sep;22(9):587–93.

9. Doshi JA, Lim R, Li P, Young PP, Lawnicki VF, State JJ, et al. A Synchronized Prescription Refill Program Improved Medication Adherence. Health Aff Proj Hope. 2016 Aug 1;35(8):1504–12.

10. Duru OK, Schmittdiel JA, Dyer WT, Parker MM, Uratsu CS, Chan J, et al. Mail-order pharmacy use and adherence to diabetes-related medications. Am J Manag Care. 2010 Jan;16(1):33–40.

11. Blackburn DF, Tran D, Quiring C. Evaluation of a refill synchronization program in two community pharmacies. J Am Pharm Assoc JAPhA. 2016 Dec;56(6):656–9.

12. DiDonato K, Vetter K, Liu Y, May J, Hartwig DM. Examining the effect of a medication synchronization or an education program on health outcomes of hypertensive patients in a community pharmacy setting. Innov Pharm. 2014;5(3).

13. Chronic conditions among Medicare beneficiaries, chartbook, 2012 edition [Internet]. Centers for Medicare and Medicaid Services; 2012 [cited 2017 Apr 21]. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/

14. Medicare 2016 Part C & D Star Rating Technical Notes [Internet]. Centers for Medicare and Medicaid Services; [cited 2016 Apr 27]. Available from:

https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/Downloads/2016-Technical-Notes-Preview-1-v2015_08_05.pdf

15. 2012 Medicare Part D Medication Therapy Management (MTM) Programs [Internet]. [cited 2017 Feb 2]. Available from: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/CY2012-MTM-Fact-Sheet.pdf

16. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011 Jul;64(7):749–59.

17. Dormuth CR, Patrick AR, Shrank WH, Wright JM, Glynn RJ, Sutherland J, et al. Statin adherence and risk of accidents: a cautionary tale. Circulation. 2009 Apr 21;119(15):2051–7.

18. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol. 2007 Aug 1;166(3):348–54.

19. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. Med Care. 2008 Nov;46(11):1125–33.

20. Cannon CP, Sharis PJ, Schweiger MJ, McCabe CH, Diver DJ, Shah PK, et al. Prospective validation of a composite end point in thrombolytic trials of acute myocardial infarction (TIMI 4 and 5). Thrombosis In Myocardial Infarction. Am J Cardiol. 1997 Sep 15;80(6):696–9.

21. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet Lond Engl. 2002 Mar 23;359(9311):995–1003.

22. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med. 2014 Jun;275(6):570–80.

23. Austin PC, Stuart EA. Estimating the effect of treatment on binary outcomes using full matching on the propensity score. Stat Methods Med Res. 2015 Sep 1;

24. Cutrona SL, Choudhry NK, Fischer MA, Servi A, Liberman JN, Brennan TA, et al. Modes of delivery for interventions to improve cardiovascular medication adherence. Am J Manag Care. 2010;16(12):929–42.

25. Krumme AA, Franklin JM, Isaman DL, Matlin OS, Tong AY, Spettell CM, et al. Predicting 1-Year Statin Adherence Among Prevalent Users: A Retrospective Cohort Study. J Manag Care Spec Pharm. 2017 Apr;23(4):494–502.

26. Hsu J, Price M, Huang J, Brand R, Fung V, Hui R, et al. Unintended consequences of caps on Medicare drug benefits. N Engl J Med. 2006 Jun 1;354(22):2349–59.

27. Gagne JJ, Choudhry NK, Kesselheim AS, Polinski JM, Hutchins D, Matlin OS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014 Sep 16;161(6):400–7.

28. Choudhry NK, Fischer MA, Avorn JL, Lee JL, Schneeweiss S, Solomon DH, et al. The impact of reducing cardiovascular medication copayments on health spending and resource utilization. J Am Coll Cardiol. 2012 Oct 30;60(18):1817–24.

29. Advance Notice of Methodological Changes for Calendar Year (CY) 2014 for Medicare Advantage (MA) Capitation Rates, Part C and Part D Payment Policies and 2014 Call Letter [Internet]. Centers for Medicare and Medicaid Services; 2013 Feb [cited 2017 Apr 24]. Available from: https://www.cms.gov/medicare/health-plans/medicareadvtgspecratestats/downloads/advance2014.pdf

APPENDIX

Table 3.4: Chronic condition therapeutic areas and medication classes

Therapeutic Area	Medication Class
Lipid-lowering	Statin
	Non-statin lipid-lowering
Antihypertensive	Angiotensin-converting enzyme inhibitor
	Angiotensin receptor blocker
	Calcium channel blocker
	Beta blocker
	Diuretic
	Aldosterone
	Nitrate/vasodilator
Oral antidiabetic	Sulfonylurea
	Glucagon-like peptide 1 agonist
	Meglitinide
	Biguanide
	Thiazolidinedione
	Alpha glucosidase inhibitor
	Sodium glucose co-transporter 2 inhibitor
	Dipeptidyl peptidase-4 inhibitor
Anti-osteoporosis	Selective estrogen receptor modulator
	Calcitonin
	Bisphosphonate
Asthma/COPD	Inhaled anticholinergic
	Inhaled corticosteroid
	Leukotriene modulator
	Long-acting beta agonist
	Adrenergic combination
	Anti-inflammatory agent
	Xanthine
	Selective phosphodiesterase 4 inhibitor
Antidepressant	Selective serotonin reuptake inhibitor
	Aminoketone
	Selective serotonin and norepinephrine reuptake inhibitor
	Tetracyclic
	Selective noradrenaline reuptake inhibitor
	Tricyclic
	Monoamine oxidase inhibitor
Antipsychotic	Typical antipsychotic
	Atypical antipsychotic
Anti-rheumatic	Disease-modifying anti-rheumatic drug
	Biological disease-modifying anti-rheumatic drug
Heart failure	Digoxin

Table 3.5: Major adverse cardiovascular event component definitions

Condition	Criteria	Specificity	Reference
Acute myocardial infarction	ICD-9 410.x (except 410.x2) as the principal or secondary inpatient diagnosis and length of stay of >3 and <180 days	99	Petersen LA, Wright S, Normand SL, et al. Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. J Gen Intern Med 1999;14:555–8.
Unstable Angina	ICD-9 411 as principal inpatient or outpatient diagnosis	96	Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. Am Heart J 2002;144:290– 6.
Stroke	ICD-9 433.x1, 434 (excluding 434.x0), 435.xx, 436.xx, 437.1x or 437.9x inpatient diagnoses in any position	99	Birman-Deych E, Waterman AD, Yan Y, et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43:480–5.
Congestive heart failure	ICD-9 428.x as the principal inpatient diagnosis	97	Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. Am Heart J 2002;144:290– 6.

Table 3.6: Cohort inclusion criteria

Inclusion criteria	Synchronized	Control
In dataset received from CMS with at least one Part D claim	21,445	770,123
Medication synchronization program enrollment date: 07/11-06/14	19,533	N/A
Fill of a cardiovascular medication (on or after enrollment date for exposed)	11,462	624,827
Continuous Part A,B,D enrollment 180 days prior to index	10,450	339,587
Fill for two chronic disease medications, at least one of which is cardiovascular 180 days prior to index	8,730	288,361
No end-stage renal disease qualification in any year, no missing or ambiguous sex, resides in one of 11 states with a participating pharmacy	8,534	84,141
Index date prior to June 30, 2014 (ensuring minimum 6 months of follow-up); index date within 90 days of enrollment date	8,023	N/A
Index fill at a retail pharmacy	7,852	63,601
Clinical event free in the first 30 days (MI, stroke, angina, CHF, death) and enrolled	7,744	62,413

Table 3.7: Baseline characteristics, matched vs. unmatched synchronized patients

Characteristic	Matched (N=6,519)	Unmatched (N=1,225)	ASD
Demographic			
Age	74.0 (9.1)	78.0 (8.0)	0.47
Female	3961 (60.8)	817 (66.7)	0.12
Race			
White	5,758 (88.3)	1,141 (93.1)	0.17
Black	249 (3.8)	14 (1.1)	0.17
Hispanic	348 (5.3)	46 (3.8)	0.08
Other/unknown	164 (2.5)	24 (2)	0.04
Median household income in zip code, mean (SD)	$51,701 ($15,257)	$44,057 ($10,713)	0.58
Percent black in zip code, mean (SD)	7.9 (13.3)	1.5 (4.6)	0.65
Percent at least high school education in zip code, mean (SD)	87.8 (6.0)	87.8 (5.6)	0.01
Participating program region			
Southeastern	3,561 (54.6)	223 (18.2)	0.82
Midwestern	2,958 (45.4)	1,002 (81.8)	
Calendar interval			
Jan 2012 - Jun 2012	47 (0.7)	0 (0)	0.12
Jul 2012 - Dec 2012	848 (13)	10 (0.8)	0.50
Jan 2013 - Jun 2013	709 (10.9)	149 (12.2)	0.04
Jul 2013 - Dec 2013	722 (11.1)	498 (40.7)	0.72
Jan 2014 - Jun 2014	4,193 (64.3)	568 (46.4)	0.37
Medicare benefits			
Years in Medicare, mean (SD)	12.1 (7.6)	14.6 (7.6)	0.33
Low income subsidy 3 out of 6 months prior to index	1,615 (24.8)	213 (17.4)	0.18
At least one Part D fill in catastrophic phase	614 (9.4)	75 (6.1)	0.12
PACE plan	710 (10.9)	102 (8.3)	0.09
Monthly plan premium amount, mean (SD)	$42.01 ($22.04)	$43.30 ($20.39)	0.06
Institutional stay prior to index	153 (2.3)	38 (3.1)	0.05
Index fill			
Patient cost index fill, mean (SD)	$10.51 ($25.20)	$10.48 ($24.06)	0.00
Total cost index fill, mean (SD)	$31.08 ($91.97)	$25.42 ($64.93)	0.07
Days supply index fill ≤30 days	4,225 (64.8)	793 (64.7)	0.00
Chronic disease medication usage			
Number of chronic disease medication classes, mean (SD)	5.1 (1.9)	5.2 (1.9)	0.04
PDC, chronic disease medication classes, mean (SD)	0.83 (0.15)	0.88 (0.12)	0.33
PDC, cardiovascular medication classes, mean (SD)	0.85 (0.16)	0.90 (0.13)	0.31
Number of cardiovascular conditions			
1	947 (14.5)	142 (11.6)	0.09
2	3,051 (46.8)	637 (52)	0.10
3	2,521 (38.7)	446 (36.4)	0.05
Distinct drugs, mean (SD)	9.6 (4.9)	8.8 (4.2)	0.18
Total copayments, all prescriptions, mean (SD)	$384.79 ($457.18)	$430.06 ($538.28)	0.09
Clinical comorbidity			
Hyperlipidemia	4,678 (71.8)	836 (68.2)	0.08
Hypertension	5,166 (79.2)	945 (77.1)	0.05
Diabetes	3,773 (57.9)	561 (45.8)	0.24
Myocardial infarction	49 (0.8)	12 (1)	0.03
Unstable angina	56 (0.9)	9 (0.7)	0.01
Heart failure	192 (2.9)	29 (2.4)	0.04
Stroke	43 (0.7)	15 (1.2)	0.06
Peripheral artery disease	284 (4.4)	36 (2.9)	0.08

Bleed (cranial or GI)	221 (3.4)	18 (1.5)	0.13
Atrial fibrillation	194 (3)	31 (2.5)	0.03
Chronic renal insufficiency	965 (14.8)	183 (14.9)	0.00
Diabetic nephropathy	295 (4.5)	31 (2.5)	0.11
Hypertensive nephropathy	449 (6.9)	84 (6.9)	0.00
Dialysis	37 (0.6)	2 (0.2)	0.07
Abnormal liver function	238 (3.7)	31 (2.5)	0.07
Asthma/COPD	1,391 (21.3)	206 (16.8)	0.12
Alzheimer's or dementia	334 (5.1)	78 (6.4)	0.05
Depression	820 (12.6)	141 (11.5)	0.03
Osteoporosis	940 (14.4)	182 (14.9)	0.01
Cancer	599 (9.2)	110 (9)	0.01
Percutaneous coronary intervention	64 (1)	15 (1.2)	0.02
Stress test	227 (3.5)	27 (2.2)	0.08
Combined comorbidity score, mean (SD)	1.2 (2.3)	1.00 (2.1)	0.10
Resource utilization			
Outpatient visits			
0 to 2	1,968 (30.2)	505 (41.2)	0.23
2 to 4	1,442 (22.1)	270 (22)	0.00
4 to 7	1,445 (22.2)	241 (19.7)	0.06
>7	1,664 (25.5)	209 (17.1)	0.21
Hospitalization length of stay			
0	5,724 (87.8)	1,093 (89.2)	0.05
1 to 4	361 (5.5)	64 (5.2)	0.01
>4	434 (6.7)	68 (5.6)	0.05
Emergency Room visit			
0	6,043 (92.7)	1,177 (96.1)	0.15
1	375 (5.8)	41 (3.3)	0.12
>1	101 (1.5)	7 (0.6)	0.10
Intensive Care Unit stay	812 (12.5)	140 (11.4)	0.03
Healthy adherer effect			
Flu shot	2,422 (37.2)	456 (37.2)	0.00
Fecal occult blood test	246 (3.8)	47 (3.8)	0.00
Mammogram or PSA	1,739 (26.7)	318 (26)	0.02
Colonoscopy	307 (4.7)	58 (4.7)	0.00

[1] Absolute standardized difference; [2] Program for All-inclusive Care in the Elderly; [3] Proportion of Days Covered

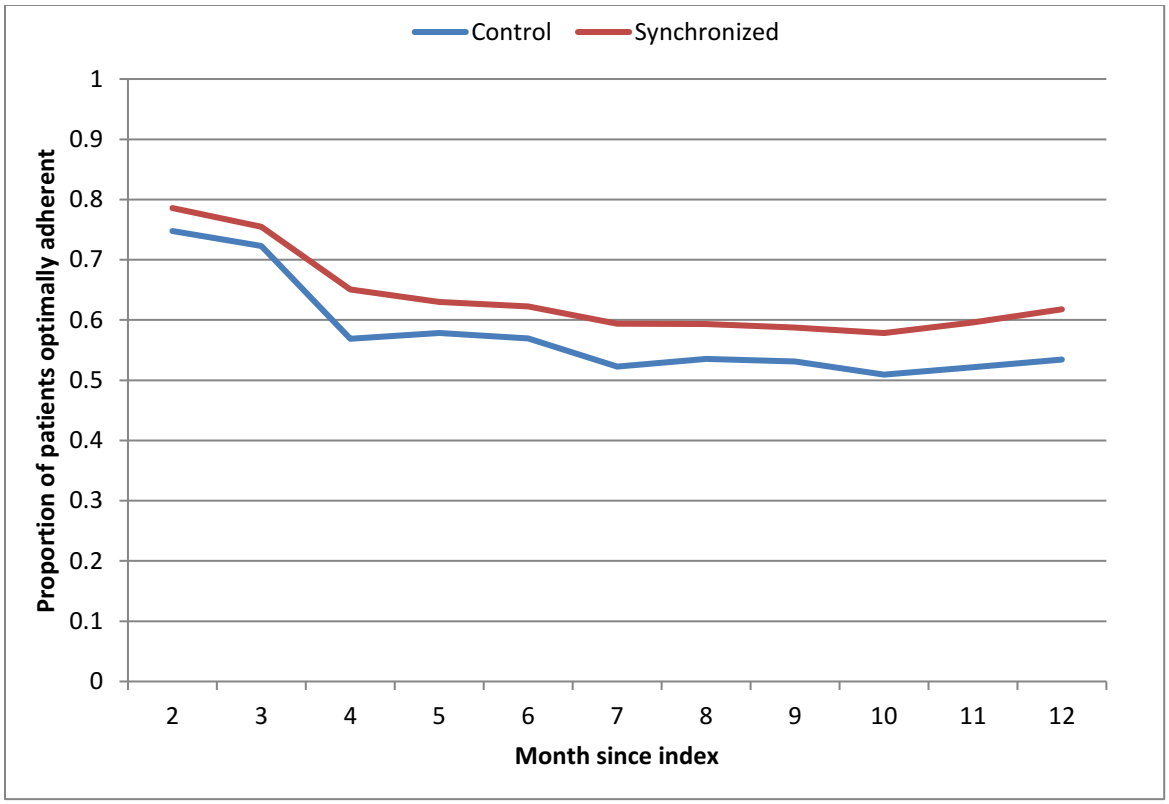


Figure 3.3: Proportion of patients optimally adherent during follow-up