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Economic outcomes with prasugrel versus clopidogrel in acute coronary syndrome patients: observations from prasugrel users and matched clopidogrel users

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Abstract

Objective: To compare healthcare costs between clopidogrel and prasugrel over 30-day and 365-day periods after discharge from the hospital or emergency room (ER) in patients treated with prasugrel who were hospitalized or had an ER visit for an acute coronary syndrome (ACS) event.

Methods: This retrospective observational study was based on claims from January 2009–July 2012 in the Truven Health Analytics MarketScan database. Clopidogrel patients were propensity-score matched 1:1 to prasugrel-treated patients. Lin's frequentist cost history method for censored data and Bayesian zeroinflated gamma regression models were used to analyze healthcare costs.

Results: The clopidogrel/prasugrel matched-cohort included 10,963 well-matched pairs of patients. Lin's frequentist analysis showed that outpatient visit costs were significantly lower for clopidogrel than prasugrel after 30 days of follow-up. At 30 days, Bayesian data analysis showed strong evidence that clopidogrel was superior to prasugrel for all-cause and ACS-related hospitalization costs and showed very strong evidence that clopidogrel was superior to prasugrel for all-cause and ACS-related outpatient visit costs. At 365 days, Bayesian data analysis showed strong evidence that clopidogrel was superior to prasugrel for all-cause outpatient visit costs and very strong evidence that clopidogrel was superior to prasugrel for ACS-related outpatient visit costs. Point estimates of the all-cause and ACS-related ER visit costs at 30 days and 365 days were similar, but statistical results were inconclusive because of the large variability in this outcome variable.

Conclusion: Based on retrospective observational data in a real-world setting, all-cause and ACS-related hospitalization and outpatient visit costs were lower for clopidogrel than prasugrel over 30 days after discharge from a hospitalization or ER visit associated with ACS in patients treated with prasugrel. At 365 days the difference in all-cause and ACS-related outpatient costs remained, but there was little evidence of a difference in either all-cause or ACS-related hospitalization costs.

Keywords

Acute coronary syndrome; Clopidogrel; Prasugrel; Healthcare utilization; Healthcare economics; Hospitalization; Bayes factor

Introduction

Acute coronary syndrome (ACS) encompasses a range of ischemic conditions, including ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina (UA). Every year, there are ~785,000 ACS events in the US, and ~470,000 patients will experience a recurrent event¹. Advanced treatments and improved control of risk factors have decreased mortality from cardiovascular disease². Despite this, hospital re-admissions for recurrent ACS events are frequent and associated with substantial costs^{2,3}.

ACS has a high economic impact; ACS patients account for costs to the American healthcare system of more than \$150 billion annually⁴, with ~60% of these costs related to ACS hospitalization³. Among 13,731 patients with ACS followed for a mean of 9.75 months after their initial event, healthcare costs were \$22,529 per patient (including the index event) and, of those costs, 71% were attributable to hospitalizations⁵. A number of studies have found that both short- and long-term re-admission rates are high among ACS patients and that a relatively important proportion of those readmissions could be preventable⁴⁻¹². Considering the sizeable costs of hospital re-admissions to the healthcare system, improved outcomes and treatments for ACS patients are of great interest.

Once patients have been clinically stabilized, standard therapy for ACS includes anti-ischemic and antithrombotic drugs. Aspirin decreases the short-term risk of cardiovascular death and non-fatal stroke. Dual antiplatelet therapy with a P2Y₁₂ antagonist and aspirin has been shown to be clinically beneficial and is the standard therapy for ACS¹³. As a central mediator of the hemostatic response, the P2Y₁₂ receptor, activated by adenosine diphosphate, plays a central role in platelet activation. Of note, P2Y₁₂ antagonist monotherapy is recommended when aspirin is contraindicated^{14,15}.

The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) placebo-controlled, double-blind trial showed the combination of clopidogrel and aspirin to be beneficial in ACS patients whether or not they undergo revascularization; based on CURE, clopidogrel was the first P2Y₁₂ antagonist to be approved for use in ACS¹⁶. Prasugrel was approved in 2009. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) trial, prasugrel had greater platelet inhibition and quicker onset of action than clopidogrel, but also was associated with increased bleeding¹⁷.

Following an acute coronary event, either clopidogrel or prasugrel is recommended in conjunction with aspirin¹⁸. According to most guidelines, clopidogrel and prasugrel should be administered for up to 12 months after an ACS event^{19–22}. There is a lack of real-world evidence comparing economic outcomes between prasugrel and clopidogrel. This study, thus, aimed to compare healthcare costs between prasugrel and clopidogrel for up to 1 year of treatment in patients receiving prasugrel using healthcare claims from the US.

Methods

Data source

The Truven Health Analytics MarketScan database was used, which combines two separate databases, the Commercial Claims and Encounters database and the Medicare Supplemental and Coordination of Benefits database, to cover all age groups. It includes medical and pharmacy claims from ~100 health plans, and government and public organizations, representing ~30 million covered lives. Claims from January 1, 2009–July 31, 2012 were used.

The data elements used in this study included health plan enrolment records, participant demographics, inpatient and outpatient medical services, and outpatient prescription drug dispensing records. The data included in the MarketScan database are de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality.

Study design

An observational matched-cohort design was used to compare all-cause and ACS-related costs of hospitalizations, emergency room (ER) visits, and outpatient visits for the 30-day and 1-year periods after initiation of treatment. Patients included in the analysis were 18 years of age, with one or more diagnosis claims of ACS (International Classification of Diseases, 9th Revision [ICD-9]: 410.xx [except 410.x2], 411.1x, and 411.8x) during a hospitalization or ER visit. The first such event in the study period for which the patient was continuously enrolled (with insurance coverage) for the previous 6 months was the index event (hospitalization or ER visit). Patients also had at least one dispensing for clopidogrel or prasugrel (the date of the first dispensing being defined as the index date) within 14 days of the date of index hospitalization discharge or ER discharge. The 14-day window was used since patients may already have received clopidogrel or prasugrel medication for a short period of time during the hospital stay or ER visit (e.g. medication samples), which would not have been observed in the current study since patients were identified with outpatient pharmacy data because inpatient pharmacy data was not available. The 14-day window thus allowed patients the time to fill their prescription at the pharmacy after their hospital or ER discharge. It is worth noting that patients with an ER admission were discharged the same day. The observation period spanned January 1, 2009–July 31, 2012; patients were followed from the index date to the earliest of the following events: (1) end of treatment compliance (i.e. the first day after which there was a gap of at least 30 days in therapy), (2) end of insurance coverage, (3) end of data availability, or (4) 12 months after the index date.

Demographic and baseline characteristics were based on data from the 6-month period before the index ACS event.

Study end-points

The main end-points of the study were actual paid healthcare costs (in \$US), including costs of hospitalization, ER visits, and outpatient visits summarized over the 30-day and 365-day periods after the index date. ACS-related costs were determined separately from all-cause costs, based on one or more diagnosis claims of ACS (ICD-9: 410 xx [except 410.x2], 411.1x, and 411.8x). Of note, pharmacy costs were excluded to allow a comparison between clopidogrel and prasugrel cohorts not confounded by pharmacy costs.

Statistical analysis

Patients were matched first by percutaneous coronary intervention (PCI) status (yes, no) and then by propensity scores. Propensity score matching was used to adjust for the differences in baseline characteristics and reduce confounding bias. Patient-level propensity scores were calculated using multivariable logistic regression. Within PCI strata, patients in the clopidogrel cohort were matched 1:1 to prasugrel patients based on propensity score calipers of 5% and all baseline characteristics listed in Table 1 to form the study populations. All analyses with propensity score modeling, matching, and assessment of the quality of matching were part of the design phase of the study before any analyses of outcomes were conducted. Descriptive statistics were used to summarize patient baseline characteristics evaluated during the 6 months before the index ACS event. Means ($\pm$ standard deviations [SDs]) are reported for continuous variables, and frequencies and percentages are reported for categorical variables. For each baseline variable, balance between treatment groups was assessed using the standardized difference in means; the balance for a particular variable was considered acceptable (good) if the standardized difference was at most 10%. The analysis methods for outcomes were prespecified before looking at the outcomes data.

Frequentist analysis of healthcare cost

Costs were calculated for each cohort using the method of Lin *et al.*²³ to account for different lengths of observation among studied patients. In our application of this analysis, we assumed that patients were censored at the end of follow-up and had no events that terminated cost accumulation (e.g., no deaths). Cost differences and 95% confidence intervals (CIs) based on 1000 bootstrap replications of the Lin *et al.*²³ analysis were used to compare costs between treatments. A difference in mean costs between treatments was declared statistically significant if the 95% CI did not include 0.

Bayesian data analysis of healthcare cost

For the Bayesian data analysis, only the subset of cases with complete data up to and including the period of interest were included. A zero-inflated gamma regression model with non-informative flat priors was used and parameters (mean costs) were simulated from the posterior distribution for the model using Markov chain Monte Carlo (MCMC). From the MCMC samples, means, SDs, medians, and 95% credible intervals of mean healthcare costs are reported for the posterior distribution of mean costs for each cohort. Based on the

MCMC for mean costs, the ratio of mean costs (clopidogrel mean/prasugrel mean) was simulated and its posterior distribution was summarized like those for mean costs. The probability that clopidogrel is superior to prasugrel (the posterior probability that the ratio of means is <1), and the probability that prasugrel is superior to clopidogrel (the posterior probability that the ratio of means is >1), were determined, and their ratio, the superiority Bayes factor, is presented. The scheme of Kass and Raftery²⁴ was used to assess the strength of evidence for or against the hypothesis that clopidogrel is superior relative to the hypothesis that prasugrel is superior (Table 2).

To better understand the magnitude of the differences between treatments, three additional probabilities were calculated at various non-inferiority/equivalence margins ($d = 0.05, 0.10, 0.15, 0.20$): (1) clopidogrel non-inferior to prasugrel, (2) prasugrel non-inferior to clopidogrel, and (3) clopidogrel equivalent to prasugrel (Figure 1)²⁵. The minimum equivalence margin or minimum non-inferiority margin at which the probability of equivalence or noninferiority were at least 0.95, $\text{Min}(d)$, was taken to be a measure of the degree of equivalence or non-inferiority; for the data to support a conclusion of equivalence or noninferiority, the margin would need to be at least $\text{Min}(d)$ (minimum margin for which the drugs would be declared equivalent or non-inferior).

Results

Among the 428,013 patients who had at least one ACS diagnosis, a total of 301,318 had at least 180 days of baseline eligibility prior to their index ACS event. Of those patients, 301,157 were at least 18 years, and 76,355 had at least one dispensing for clopidogrel ($n = 65,392$) or prasugrel ($n = 10,963$) between January 2009 and July 2012. In the clopidogrel/prasugrel matched-cohort ($n = 10,963/ n = 10,963$), patients were well matched demographically and by all other baseline characteristics. Among the baseline characteristics that were well matched in the matched-cohort, there were baseline ischemic or bleeding risk factors such as acute myocardial infarction, hypertension, anemia, and previous ischemic stroke/TIA which were unbalanced (i.e., standardized difference in means $>10\%$) in the pre-matched cohorts. The mean age of patients in the matched-cohort was 57.4 years in both arms, and 21.5% and 21.9% were female in the clopidogrel and prasugrel arms, respectively (Table 1).

Healthcare-associated costs

Frequentist analysis of costs—With the exception of both ACS-related and all-cause outpatient visit costs up to 30 days, there were no statistically significant differences in mean costs between clopidogrel and prasugrel based on Lin's method (Table 3). The differences in mean costs per patient up to 30 days were $-\$201$ in favor of clopidogrel for ACS-related outpatient costs ($\$1337$ and $\$1538$ for clopidogrel and prasugrel, 95% CI = $-\$337$ to $-\$67$) and $-\$153$ in favor of clopidogrel for all-cause outpatient costs ($\$1740$ and $\$1893$ for clopidogrel and prasugrel, 95% CI = $-\$305$ to $-\$8$).

Although not assessed statistically, some patterns are evident in the cost summaries (Table 3). Of the three cost sources, mean costs for ER visits were the lowest and showed relatively small apparent increases from 30 days to 365 days and from ACS-related costs to all-cause

costs. At up to 30 days, mean hospitalization costs and outpatient costs were intermediate in magnitude, with mean all-cause outpatient costs somewhat larger than mean ACS-related outpatient costs. Mean hospitalization and outpatient costs at 365 days were generally high; mean all-cause hospitalization costs were 5–10% higher than mean ACS-related hospitalization costs, while mean all-cause outpatient costs were 55–70% higher than mean ACS-related outpatient costs.

Bayesian analysis of costs—With the exception of the posterior means at 365 days for mean ACS-related hospitalization costs and for mean all-cause hospitalization costs, the posterior means for mean costs across outcome types (hospitalizations, ER visits, and outpatient visits) and causes (ACS-related and all-cause) were similar to those found in the frequentist analysis. The 95% credible intervals for the posterior distribution of the ratio of mean costs did not contain one (i.e., were statistically significant) for 30-day ACS-related hospitalization costs, 30-day and 365-day ACS-related outpatient visit costs, and 30-day all-cause outpatient costs (Table 4; Figure 2).

Tables 5 and 6 presents posterior probabilities of superiority and superiority Bayes factors for all-cause and ACS-related events at Days 30 and 365. At 30 days, there was strong evidence that clopidogrel was superior to prasugrel for both all-cause and ACS-related hospitalization costs and there was very strong evidence that clopidogrel was superior to prasugrel for all-cause and ACS-related outpatient costs. A similar pattern was seen at Day 365, except that there was no longer evidence of a difference in all-cause hospitalization costs and there was positive (in contrast to strong) evidence that clopidogrel was superior to prasugrel for ACS-related hospitalization costs.

Tables 7 and 8 present the posterior probabilities of equivalence and non-inferiority for all-cause and ACS-related events across a range of margins for 30 days and 365 days. At 30 days, the minimum margin at which clopidogrel would be declared equivalent to prasugrel (the Min(d)) was between 0.10–0.15 for all cost variables, except ACS-related ER costs and ACS-related outpatient costs, for which the Min(d) was between 0.15–0.20. At 365 days, the equivalence Min(d) was between 0.05 – 0.10 for all-cause outpatient costs, between 0.10–0.15 for all-cause hospitalization costs, and between 0.15–0.20 for all-cause ER costs, ACS-related hospitalization costs, ACS-related ER costs, and ACS-related outpatient costs. At 30 days, the Min(d) at which prasugrel would be declared non-inferior to clopidogrel was between 0.05 – 0.10 for all-cause ER costs, between 0.10–0.15 for all-cause hospitalization costs, all-cause outpatient costs, and ACS-related hospitalization costs, and between 0.15–0.20 for ACS-related ER costs and ACS-related outpatient costs. The Min(d) at 30 days at which clopidogrel would be declared non-inferior to prasugrel was between 0.00–0.05 for all-cause hospitalization costs, all-cause outpatient costs, ACS-related hospitalization costs, and ACS-related outpatient costs, and between 0.10–0.15 for all-cause ER costs and ACS-related ER costs. At 365 days, the Min(d) at which prasugrel would be declared noninferior to clopidogrel was between 0.05–0.10 for all-cause ER costs and all-cause outpatient costs, between 0.10–0.15 for all-cause hospitalization costs and ACS-related ER costs, and between 0.15–0.20 for ACS-related hospitalization costs and ACS-related outpatient costs. The Min(d) at 365 days at which clopidogrel would be declared noninferior to prasugrel was between 0.00–0.05 for all-cause outpatient costs and ACS-related outpatient costs, between

0.05–0.10 for all-cause hospitalization costs and ACS-related hospitalization costs, and between 0.15–0.20 for all-cause ER costs and ACS-related ER costs.

Discussion

Either clopidogrel or prasugrel may be used along with aspirin for long-term anti-thrombotic management of patients with ACS. This analysis of the Truven Health Analytics MarketScan database reports the real-world healthcare costs of patients with ACS using clopidogrel or prasugrel. Bayesian analysis revealed that clopidogrel was superior to prasugrel in hospitalization costs and outpatient costs at 30 days and in outpatient costs at 365 days.

A previous study by the present authors estimated healthcare resource utilization in the same matched-cohorts that were used in the present study²⁶. In that study there was positive evidence that the mean number of all-cause and ACS-related hospitalizations at 1 month were smaller for clopidogrel than for prasugrel, which is consistent with the cost findings at 30 days for these events of the present study. In the previous study, there was little evidence of a difference in these means (for mean number of all-cause and ACS-related hospitalizations) at 12 months, which is consistent with the reduced evidence for a difference in cost for these events over 365 days in this study. The cost findings of this study for ACS-related outpatient visits at 365 days are consistent with the number of such events at 12 months in the previous study. The finding of positive evidence for a difference in cost for all-cause outpatient visits at 30 days in this study is inconsistent with the finding of little evidence for a difference in the mean numbers of these events in the previous study. Finally, in both studies there was little evidence of differences between clopidogrel and prasugrel for the ER visit outcomes.

As noted below, a limitation of this study is that a Bayesian analysis that accounted for censoring of the cost data could not be implemented. This would not appreciably affect the 30-day cost results, but could affect the 365-day results. If the data that were missing because of censoring were missing completely at random, then an analysis based on the completers, as it was done in the Bayesian analyses, would be valid. An analysis not reported here supports the assumption that the missing data were missing completely at random for all outcomes except the ACS-related and all-cause hospitalization costs at 365 days. Because our findings for these outcomes are inconclusive, whether or not there is a difference remains an open question. So, the conclusions of the study were not affected by this limitation.

Well-designed observational studies with appropriate statistical techniques that adjust for potential confounding factors through matching techniques provide valuable information, with real-life scenarios and high generalizability. Since no equivalence/non-inferiority margins were pre-specified, we have assessed all of the hypotheses across a range of equivalence/non-inferiority margins.

Costs for clopidogrel have high probabilities to be superior (re-hospitalization, outpatient) or non-inferior/equivalent (ER) with the Bayesian approach, given reasonable choices of

margins. A cost-effectiveness study was based on data from the TRITON-TIMI 38 analyzed resource use data for 6705 ACS patients with planned PCI over almost 15 months²⁷. Based on event rates in the trial and diagnosis-related group (DRG)-related cost methodology, it was estimated that endpoint-related rehospitalization costs were \$218 more for clopidogrel than prasugrel in the initial 30 days of treatment and \$530 more for clopidogrel than prasugrel over the median duration of follow-up of 14.7 months in both groups, with neither difference being statistically significant. Two studies that developed economic models based on event rates from TRITON-TIMI 38 found unfavorable re-hospitalization cost-effectiveness ratios for clopidogrel relative to prasugrel^{28,29}. The results of these economic modeling studies, which assign costs based on event rates in the TRITON-TIMI 38 trial and other non-primary sources, and those of our study, which are based on primary cost data, suggest that further real-world studies based on primary cost data are warranted.

Our study is subject to a number of limitations. First, claims data, while extremely valuable in establishing treatment patterns and healthcare resource utilization, are not collected for research purposes and may contain billing inaccuracies or missing data for procedures, diagnoses, and costs. Second, retrospective, observational designs are inherently susceptible to various biases, such as classification bias and hidden confounders³⁰. False-positive or false-negative identification of an ACS event may be a factor. The effects of unmeasured variables are not known, and the results of this study may not be generalizable to other patient populations. Finally, for the frequentist analysis, Lin *et al.*'s²³ estimate was applied to adjust for censored count data. However, there is no censoring adjustment method available in the Bayesian analysis setting. Therefore, only complete patient data up to the analysis time point were used, although this should have only a minor impact, if any, on the 30-day results.

Conclusion

Based on retrospective observational data generated in a real-world setting, all-cause and ACS-related hospitalization costs and outpatient visit costs were lower for clopidogrel than for prasugrel over the 30 days after discharge from a hospitalization or ER visit associated with ACS in patients treated with prasugrel. At 365 days the difference in all-cause and ACS-related outpatient costs remained, but there was little evidence of a difference in either all-cause or ACS-related hospitalization costs. There was little evidence of a difference in all-cause and ACS-related ER visit costs at 30 and 365 days.

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Transparency

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Declaration of financial/other relationships

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Figure 1.

Illustration of the five key posterior probabilities. r , ratio of means; d , non-inferiority/equivalence margin. The posterior probabilities are the areas under the posterior density curve for the indicated intervals.

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Figure 2. Posterior densities for ratio of means of ACS-related hospitalization costs at 30 days and 365 days. *A ratio of 1 indicates that the mean cost of clopidogrel is lower than the mean cost of prasugrel.

Table 1.
Demographics and clinical characteristics of clopidogrel/prasugrel pre-matched and matched-cohorts.

Variable	Pre-matched cohorts			Matched cohorts*		
	Clopidogrel	Prasugrel	Std Diffy ^{†,‡}	Clopidogrel	Prasugrel	Std Diffy ^{†,‡}
Number of patients	65,392	10,963		10,963	10,963	
Demographics [§]						
Age, mean (SD)	63.8 (12.7)	57.4 (9.2)	57.6%	57.4 (10.6)	57.4 (9.2)	0.0%
Female, n (%)	20,836 (31.9)	2403 (21.9)	22.4%	2360 (21.5)	2403 (21.9)	1.0%
Region [§] , n (%)						
South	24,233 (37.1)	4415 (40.3)	6.6%	4440 (40.5)	4415 (40.3)	0.5%
Northeast	9284 (14.2)	1461 (13.3)	2.5%	1457 (13.3)	1461 (13.3)	0.1%
West	10,066 (15.4)	1717 (15.7)	0.7%	1680 (15.3)	1717 (15.7)	0.9%
North Central	21,297 (32.6)	3216 (29.3)	7.0%	3228 (29.4)	3216 (29.3)	0.2%
Unknown	512 (0.8)	154 (1.4)	6.0%	158 (1.4)	154 (1.4)	0.3%
Type of insurance [§] , n (%)						
Comprehensive	14,177 (21.7)	1262 (11.5)	27.3%	1209 (11.0)	1262 (11.5)	1.5%
HMO	9353 (14.3)	1455 (13.3)	3.0%	1437 (13.1)	1455 (13.3)	0.5%
POS	4145 (6.3)	833 (7.6)	4.9%	850 (7.8)	833 (7.6)	0.6%
PPO	33,015 (50.5)	6240 (56.9)	12.9%	6278 (57.3)	6240 (56.9)	0.7%
Other	3366 (5.1)	913 (8.3)	12.7%	915 (8.3)	913 (8.3)	0.1%
Unknown	1336 (2.0)	260 (2.4)	2.2%	274 (2.5)	260 (2.4)	0.8%
Year of index date [§] , n (%)						
2009	13,653 (20.9)	371 (3.4)	53.6%	366 (3.3)	371 (3.4)	0.3%
2010	23,460 (35.9)	3420 (31.2)	9.9%	3525 (32.2)	3420 (31.2)	2.1%
2011	19,993 (30.6)	4675 (42.6)	25.1%	4734 (43.2)	4675 (42.6)	1.1%
2012	8286 (12.7)	2497 (22.8)	26.5%	2338 (21.3)	2497 (22.8)	3.5%
Charlson Comorbidity Index [§] , mean (SD)	2.07 (1.69)	1.65 (1.29)	28.2%	1.64 (1.32)	1.65 (1.29)	0.6%
0	6361 (9.7%)	1118 (10.2%)	1.6%	1200 (10.9%)	1118 (10.2%)	2.4%
1	24,215 (37.0%)	5217 (47.6%)	21.4%	5200 (47.4%)	5217 (47.6%)	0.3%
2	15,859 (24.3%)	2662 (24.3%)	0.1%	2593 (23.7%)	2662 (24.3%)	1.5%

Variable	Pre-matched cohorts			Matched cohorts*		
	Clonidogrel	Prasugrel	Std Diff [†] , n (%)	Clonidogrel	Prasugrel	Std Diff [†] , n (%)
3	8685 (13.3%)	1154 (10.5%)	8.5%	1149 (10.5%)	1154 (10.5%)	0.1%
4	4601 (7.0%)	443 (4.0%)	13.1%	457 (4.2%)	443 (4.0%)	0.6%
5 or more	5671 (8.7%)	369 (3.4%)	22.3%	364 (3.3%)	369 (3.4%)	0.3%
Other comorbidities [‡] , n (%)						
Acute myocardial infarction	46,559 (71.2)	8441 (77.0)	13.2%	8363 (76.3)	8441 (77.0)	1.7%
Hypertension	39,929 (61.1)	6090 (55.6)	11.2%	6113 (55.8)	6090 (55.6)	0.4%
Dyslipidemia	27,664 (42.3)	5115 (46.7)	8.8%	5116 (46.7)	5115 (46.7)	0.0%
Diabetes	19,430 (29.7)	2917 (26.6)	6.9%	2866 (26.1)	2917 (26.6)	1.1%
Congestive heart failure	11,042 (16.9)	1157 (10.6)	18.4%	1154 (10.5)	1157 (10.6)	0.1%
Substance abuse (drug or alcohol)	9228 (14.1)	1934 (17.6)	9.7%	1978 (18.0)	1934 (17.6)	1.0%
Ischemic stroke or TIA	7594 (11.6)	465 (4.2)	27.3%	458 (4.2)	465 (4.2)	0.3%
Anemia	7455 (11.4)	584 (5.3)	21.9%	556 (5.1)	584 (5.3)	1.2%
Ventricular arrhythmias	2805 (4.3)	474 (4.3)	0.2%	465 (4.2)	474 (4.3)	0.4%
Cirrhosis/hepatic disease	1784 (2.7)	255 (2.3)	2.6%	271 (2.5)	255 (2.3)	1.0%
End stage renal disease	882 (1.3)	52 (0.5)	9.2%	54 (0.5)	52 (0.5)	0.3%
Hemophilia	473 (0.7)	59 (0.5)	2.3%	75 (0.7)	59 (0.5)	1.9%
Prior hemorrhagic stroke	169 (0.3)	5 (0.0)	5.5%	3 (0.0)	5 (0.0)	1.0%
History of HIV infection	147 (0.2)	43 (0.4)	3.0%	50 (0.5)	43 (0.4)	1.0%
Maternity patient	69 (0.1)	15 (0.1)	0.9%	18 (0.2)	15 (0.1)	0.7%
Procedure [‡] , n (%)						
PCI	47,036 (71.9)	10,475 (95.5)	64.0%	10,475 (95.5)	10,475 (95.5)	0.0%
Baseline medication [‡] , n (%)						
Anti-hypertensive	30,009 (45.9)	4599 (42.0)	7.9%	4526 (41.3)	4599 (42.0)	1.4%
Anti-hyperlipidemic	31,369 (48.0)	5070 (46.2)	3.5%	5026 (45.8)	5070 (46.2)	0.8%
Anti-coagulant	3243 (5.0)	225 (2.1)	15.8%	196 (1.8)	225 (2.1)	1.9%

HIV, human immunodeficiency virus; HMO, health maintenance organization; PCI, percutaneous coronary intervention; POS, point of service; PPO, preferred provider organization; Std Diff, standardized difference; SD, standard deviation; TIA, transient ischemic attack.

* Clonidogrel-treated patients were matched exactly 1:1 to prasugrel patients on the following variables: propensity score percentiles (5th, 10th, 15th, 90th, 95th, and 100th), and PCI.

[†] For continuous variables, the standardized difference is calculated by dividing the absolute difference in means of the clopidogrel and the prasugrel cohorts by the pooled standard deviation of both groups. The pooled standard deviation is the square root of the average of the squared standard deviations.

[‡] For binary outcomes, the standardized difference is calculated using the equation below, where P_i is the respective proportion of participants in each group: $(P_{\text{clopidogrel}} - P_{\text{prasugrel}}) / [\chi^2(1 - p)]$, where $p = (P_{\text{clopidogrel}} + P_{\text{prasugrel}}) / 2$.

[§] Evaluated during the 6-month baseline period.

[¶] Evaluated during the 6-month baseline period.

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Table 2.Strength of evidence using Bayes factors²¹.

Strength of evidence	Evidence against H_0	Evidence for H_0
Not worth more than a bare mention	1–3	0.33–1
Positive	3–20	0.05–0.33
Strong	20–150	0.0067–0.05
Very strong	<150	<0.0067

 H_0 , hypothesis in the denominator.This table has been reproduced with permission from Olson *et al.*²⁶. © 2014 John Wiley & Sons Ltd.

Mean ACS-related healthcare cost and all-cause healthcare costs per patient for up to 30 and 365 days of follow-up for clopidogrel/prasugrel matched-cohort.

Table 3.

Mean healthcare cost incurred over 30/365 days (2011 \$USD)	Time period, days	Clopidogrel vs prasugrel		
		Clopidogrel (n = 10,963)	Prasugrel (n = 10,963)	Cost difference* (95% CI)
ACS-related healthcare				
Hospitalizations	30	\$1500	\$1587	-\$87 (-\$399; \$196)
	365	\$6137	\$5930	\$207 (-\$615; \$946)
ER visits	30	\$83	\$85	-\$1 (-\$19; \$16)
	365	\$305	\$290	\$14 (-\$35; \$65)
Outpatient visits	30	\$1337	\$1538	-\$201 (-\$337; -\$67) [‡]
All-cause healthcare	365	\$5839	\$6158	-\$319 (-\$805; \$183)
Hospitalizations	30	\$1542	\$1620	-\$78 (-\$393; \$206)
	365	\$6635	\$6317	\$318 (-\$527; \$1063)
ER visits	30	\$137	\$137	\$1 (-\$21; \$21)
	365	\$571	\$587	-\$16 (-\$131; \$74)
Outpatient visits	30	\$1740	\$1893	-\$153 (-\$305; -\$8) [‡]
	365	\$9857	\$9748	\$109 (-\$554; \$754)

CI, confidential interval; ER, emergency room.

* Difference in cost for clopidogrel-treated patients and prasugrel-treated patients; negative numbers indicate lower costs with clopidogrel.

[‡] Statistically significant.

Mean healthcare costs were calculated with the Lin's cost history method, assuming that all patients were censored at the end of follow-up and had no event that terminated cost accumulation (e.g., death). The Kaplan-Meier estimates thus remained equal to 1 in Lin's cost history method calculations.

The 95% CI was based on non-parametric bootstrap samples using 1000 replications.

Table 4.

Bayesian analysis: posterior distribution of ACS-related mean healthcare cost and all-cause mean healthcare costs for matched-cohorts.

Type of cost	Time period, days ^{a,b}	Clopidogrel		Prasugrel		Ratio of mean cost	
		Mean (SD) (\$)	CI*	Mean (SD) (\$)	CI*	Mean (SD)	CI*
ACS related mean healthcare							
Hospitalizations	30	1489 (36)	1422–1562	1603 (40)	1527–1679	0.930 (0.032)	0.873–0.999
	365	4485 (216)	4089–4929	4754 (252)	4275–5269	0.946 (0.068)	0.821–1.086
ER visits	30	84 (5)	75–94	87 (5)	77–97	0.978 (0.083)	0.819–1.153
	365	294 (21)	254–336	294 (19)	258–334	1.001 (0.095)	0.828–1.205
Outpatient visits	30	1362 (23)	1317–1407	1557 (27)	1504–1614	0.875 (0.021)	0.833–0.917
	365	5622 (140)	5354–5895	6382 (177)	6047–6765	0.882 (0.033)	0.814–0.947
All-cause mean healthcare							
Hospitalizations	30	1531 (39)	1457–1609	1638 (41)	1562–1718	0.935 (0.033)	0.873–1.003
	365	4870 (228)	4442–5348	5023 (269)	4535–5583	0.972 (0.071)	0.829–1.115
ER visits	30	139 (6)	127–151	139 (6)	128–151	1.003 (0.06)	0.883–1.121
	365	552 (26)	503–605	534 (28)	483–587	1.038 (0.075)	0.899–1.199
Outpatient visits	30	1770 (25)	1721–1818	1934 (27)	1880–1989	0.915 (0.018)	0.879–0.951
	365	9492 (196)	9120–9880	9989 (218)	9574–10,425	0.951 (0.028)	0.895–1.006

ACS, acute coronary syndrome; CI, credible interval; ER, emergency room; SD, standard deviation.

* CI, 2.5% lower bound; 97.5% upper bound.

Healthcare costs were modeled using a zero-inflated Gamma distribution.

^a A total of 10,562 clopidogrel patients and 10,584 prasugrel patients were included in the 30-day analysis.

^b A total of 2743 clopidogrel patients and 2366 prasugrel patients were included in the 365-day analysis.

Table 5.

Posterior superiority probabilities and superiority Bayes factors for ratio of means of healthcare cost at 30 days (clopidogrel mean/prasugrel mean; clopidogrel, $n = 10,562$; prasugrel, $n = 10,584$).

Type of cost	Hypothesis	Posterior probabilities	Bayes factor (C superior/P superior)
All-cause hospitalization	Clopidogrel superior	0.969	31.258
	Prasugrel superior	0.031	
All-cause ER	Clopidogrel superior	0.484	0.938
	Prasugrel superior	0.516	
All-cause outpatient	Clopidogrel superior	1.000	∞
	Prasugrel superior	0	
ACS-related hospitalization	Clopidogrel superior	0.976	40.667
	Prasugrel superior	0.024	
ACS-related ER	Clopidogrel superior	0.613	1.584
	Prasugrel superior	0.387	
ACS-related outpatient	Clopidogrel superior	1.000	∞
	Prasugrel superior	0	

ACS, acute coronary syndrome; ER, emergency room.

Table 6.

Posterior superiority probabilities and superiority Bayes factors for ratio of means of healthcare cost at 365 days (clopidogrel mean/prasugrel mean; clopidogrel, $n = 2743$; prasugrel, $n = 2366$).

Type of cost	Hypothesis	Posterior probabilities	Bayes factor (C superior/P superior)
All-cause hospitalization	Clopidogrel superior	0.662	1.959
	Prasugrel superior	0.338	
All-cause ER	Clopidogrel superior	0.324	0.479
	Prasugrel superior	0.676	
All-cause outpatient	Clopidogrel superior	0.964	26.778
	Prasugrel superior	0.036	
ACS-related hospitalization	Clopidogrel superior	0.800	4.000
	Prasugrel superior	0.200	
ACS-related ER	Clopidogrel superior	0.536	1.158
	Prasugrel superior	0.463	
ACS-related outpatient	Clopidogrel superior	1.000	∞
	Prasugrel superior	0	

ACS, acute coronary syndrome; ER, emergency room.

Posterior equivalence and non-inferiority probabilities of healthcare cost at 30 days based on posterior distribution of ratio of means (clopidogrel mean/prasugrel mean; clopidogrel, $n = 10,562$; prasugrel, $n = 10,584$).

Table 7.

Type of cost	Clopidogrel vs prasugrel	Margins			
		0.05	0.10	0.15	0.20
All-cause hospitalization	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.320	0.860	0.997	1.000
	Clopidogrel non-inferior	1.000	1.000	1.000	1.000
All-cause ER	Prasugrel non-inferior	0.320	0.860	0.997	0.969
	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.599	0.900	0.985	0.999
All-cause outpatient	Clopidogrel non-inferior	0.789	0.944	0.991	0.999
	Prasugrel non-inferior	0.810	0.956	0.994	1.000
	Posterior probabilities				
ACS-related hospitalization	Clopidogrel is equivalent to prasugrel	0.030	0.802	1.000	1.000
	Clopidogrel non-inferior	1.000	1.000	1.000	1.000
	Prasugrel non-inferior	0.030	0.802	1.000	1.000
ACS-related ER	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.264	0.819	0.998	1.000
	Clopidogrel non-inferior	1.000	1.000	1.000	1.000
ACS-related outpatient	Prasugrel non-inferior	0.264	0.819	0.998	1.000
	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.442	0.762	0.913	0.977
ACS, acute coronary syndrome; ER, emergency room.	Clopidogrel non-inferior	0.816	0.935	0.973	0.993
	Prasugrel non-inferior	0.626	0.827	0.940	0.984
	Posterior probabilities				
ACS, acute coronary syndrome; ER, emergency room.	Clopidogrel is equivalent to prasugrel	0.000	0.117	0.877	1.000
	Clopidogrel non-inferior	1.000	1.000	1.000	1.000
	Prasugrel non-inferior	0.000	0.117	0.877	1.000

Table 8.

Posterior equivalence and non-inferiority probabilities for ratio of means of healthcare cost at 365 days (clopidogrel mean/prasugrel mean; clopidogrel, n = 2743; prasugrel, n = 2366).

Type of cost	Clopidogrel vs prasugrel	Margins			
		0.05	0.10	0.15	0.20
All-cause hospitalization	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.500	0.807	0.950	0.992
	Clopidogrel non-inferior	0.871	0.959	0.991	0.999
All-cause ER	Prasugrel non-inferior	0.629	0.848	0.960	0.993
	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.477	0.777	0.917	0.976
All-cause outpatient	Clopidogrel non-inferior	0.591	0.803	0.919	0.976
	Prasugrel non-inferior	0.886	0.974	0.997	1.000
	Posterior probabilities				
ACS-related hospitalization	Clopidogrel is equivalent to prasugrel	0.525	0.956	1.000	1.000
	Clopidogrel non-inferior	1.000	1.000	1.000	1.000
	Prasugrel non-inferior	0.525	0.956	1.000	1.000
ACS-related ER	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.401	0.736	0.926	0.988
	Clopidogrel non-inferior	0.937	0.983	0.996	0.999
ACS-related outpatient	Prasugrel non-inferior	0.464	0.754	0.931	0.988
	Posterior probabilities				
	Clopidogrel is equivalent to prasugrel	0.400	0.707	0.891	0.959
ACS, acute coronary syndrome; ER, emergency room.	Clopidogrel non-inferior	0.713	0.844	0.927	0.969
	Prasugrel non-inferior	0.686	0.863	0.964	0.990
	Posterior probabilities				
ACS, acute coronary syndrome; ER, emergency room.	Clopidogrel is equivalent to prasugrel	0.021	0.294	0.823	0.990
	Clopidogrel non-inferior	1.000	1.000	1.000	1.000
	Prasugrel non-inferior	0.021	0.294	0.823	0.990

ACS, acute coronary syndrome; ER, emergency room.