Comparative Effectiveness of Clopidogrel in Medically Managed Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

Matthew D. Solomon, MD, PhD,*† Alan S. Go, MD,§†‡ David Shilane, PhD,† Derek B. Boothroyd, PhD,† Thomas K. Leong, MPH,* Dhruv S. Kazi, MD, MSc, MS,†‡ Tara I. Chang, MD, MS,† Mark A. Hlatky, MD†
Oakland, Stanford, and San Francisco, California

Objectives This study sought to examine the effectiveness of clopidogrel in real-world, medically managed patients with unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI).

Methods A retrospective cohort study was conducted of Kaiser Permanente Northern California members without known coronary artery disease or prior clopidogrel use who presented with UA or NSTEMI between 2003 and 2008 and were medically managed (i.e., no percutaneous coronary intervention or coronary artery bypass grafting during the index hospitalization or within 7 days post-discharge). Over 2 years of follow-up, we measured the association between clopidogrel use and all-cause mortality, hospital stay for MI, and a composite endpoint of death or MI using propensity-matched multivariable Cox analyses.

Results We identified 16,365 patients with incident UA (35%) or NSTEMI (65%); 36% of these patients were prescribed clopidogrel within 7 days of discharge. In 8,562 propensity score–matched patients, clopidogrel users had lower rates of all-cause mortality (8.3% vs. 13.0%; p < 0.01; adjusted hazard ratio [HR]: 0.63; 95% confidence interval [CI]: 0.54 to 0.72) and the composite of death or MI (13.5% vs. 17.4%; p < 0.01; HR: 0.74; CI: 0.66 to 0.84), but not MI alone (6.7% vs. 7.2%; p = 0.30; HR: 0.93; CI: 0.78 to 1.11), compared with nonusers of clopidogrel. The association between clopidogrel use and the composite of death or MI was significant only among patients presenting with NSTEMI (HR: 0.67; CI: 0.59 to 0.76; p_intercept < 0.01), not among those presenting with UA (HR: 1.25; CI: 0.94 to 1.67).

Conclusions In a large, community-based cohort of patients who were medically managed after UA/NSTEMI, clopidogrel use was associated with a lower risk of death and MI, particularly among patients with NSTEMI. (J Am Coll Cardiol 2014;63:2249–57) © 2014 by the American College of Cardiology Foundation

In 2001, the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial showed that dual-antiplatelet therapy with aspirin and clopidogrel improved outcomes among patients with unstable angina (UA) or non–ST-segment myocardial infarction (NSTEMI) (1). Patients randomly assigned to long-term treatment with aspirin in combination with clopidogrel had a lower rate of the combined endpoint of CV death, nonfatal MI, or stroke within 1 year compared with patients assigned to aspirin alone. On the basis of the results of CURE, clopidogrel was given a Class I recommendation in the American College of Cardiology/American Heart Association (ACC/AHA) guideline statements for patients treated medically after UA or NSTEMI for 1 month and ideally up to 9 months (2).
Most patients in CURE were medically managed (only one-fifth initially underwent revascularization procedures), and the rate of subsequent revascularization during the first 12 months was low (15% in the clopidogrel arm of the study and 14% in the aspirin arm). Although clopidogrel therapy led to similar risk reductions in patients who were medically managed or who underwent revascularization, the role of clopidogrel in percutaneous coronary intervention (PCI) has received more attention, both periprocedurally (3–11) and post-PCI (12). Perhaps as a result, rates of clopidogrel use after PCI are extremely high (13). In contrast, 50% to 60% of patients with UA or NSTEMI in clinical practice are medically managed (i.e., do not undergo revascularization during the index hospital stay) (14–16). In addition, clopidogrel use in medically managed patients with UA or NSTEMI remains low; less than one-half of medically managed patients with UA or NSTEMI will receive clopidogrel on discharge (13,17–19). Further, the impact of clopidogrel among medically managed patients with UA or NSTEMI who are treated outside a clinical trial remains unclear. We therefore examined the effectiveness of clopidogrel in a real-world, community-based cohort of patients who were medically managed after hospital discharge for UA or NSTEMI.

Methods

This study was approved by the Institutional Review Boards of the Kaiser Foundation Research Institute (Oakland, California) and of Stanford University (Stanford, California). Waiver of informed consent was obtained because of the nature of the study.

Source population. The source population was from Kaiser Permanente Northern California, a large, integrated healthcare delivery system that provides care to >3.2 million individuals in San Francisco and the greater Bay Area. The health plan membership is broadly representative of the local and statewide population, apart from slightly lower representation at the extremes of age and income.

Study population. We assembled an incident disease cohort by first identifying all adult (age >30 years) members hospitalized for an initial episode of UA or NSTEMI between January 1, 2003 and December 31, 2007. UA was defined by a primary hospital discharge diagnosis (International Classification of Diseases-Ninth Edition) of 411.x or a combination of a primary discharge diagnosis code of 414.0 and a secondary discharge diagnosis of 411.x for the same hospital stay. NSTEMI was defined by a primary diagnosis code of 410.7, 410.8, or 410.9. To ensure an incident disease cohort, we excluded any patients with earlier diagnoses of UA, NSTEMI, ST-segment elevation myocardial infarction (STEMI), coronary artery bypass grafting (CABG), or PCI for at least the previous 12 months, although most patients had a much longer (>12 months) lookback period for these diagnoses and procedures.

We defined the index date for this analysis as 7 days after hospital discharge, to allow subjects the opportunity to fill a clopidogrel prescription after hospital stay. To identify medically managed patients, we excluded patients who received any coronary revascularization procedures (CABG or PCI) during their initial hospital stay or within 7 days of hospital discharge. Patients with any clinical event, including UA, MI, or death, within the first 7 days post-discharge were also excluded. We adopted a new-user design (20) by excluding patients who had used clopidogrel in the 120 days before developing UA or NSTEMI. To match the eligibility criteria of the CURE study, we also excluded patients with an earlier history of stroke or transient ischemic attack (TIA), as well as patients taking warfarin or those with uncontrolled hypertension (systolic blood pressure >180 mm Hg) at baseline. We also excluded patients with a history of maintenance dialysis or organ transplantation.

Covariates and exposure of interest. We defined clopidogrel users as patients who filled a prescription within 7 days post-discharge. To mimic an intention-to-treat design, we defined nonusers as patients who never started clopidogrel or who did so after the first 7 days of follow-up, and we did not allow patients to cross over into the clopidogrel arm of the study. To capture complete data on demographic characteristics, comorbidities, and medication use, we restricted the analysis to patients with complete demographic data and at least 12 months of continuous membership and continuous pharmacy benefit before the index date.

We obtained data on age, sex, and self-reported race or ethnicity from health plan databases. We identified co-morbid conditions up to 4 years before the index date by using previously validated approaches using diagnosis and procedure codes and current procedural terminology codes recorded in health plan hospital stay, ambulatory, laboratory, and pharmacy databases for the following comorbidities: a history of heart failure, peripheral arterial disease, valvular heart disease, diabetes mellitus, hypertension, dyslipidemia, or bleeding during hospital stay (21–27). We used pharmacy data to identify post-discharge use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and statins. We also included indicator variables for the year of the index date to control for secular trends, an indicator for the type of presenting event (UA or NSTEMI), and an indicator for patients in the group that had not received clopidogrel who underwent PCI between days 7 and 14 who subsequently started taking clopidogrel.
Outcomes. We examined a composite outcome of all-cause mortality and acute myocardial infarction (MI) requiring hospital stay during the 2 years after discharge, as well as the individual endpoints of death and MI. All-cause mortality was identified from health plan databases, supplemented by linkage with Social Security Administration vital status files and California state death certificate records. MI was defined as a hospital admission with a primary diagnosis code of 410.x1.

Propensity score matching. We used propensity score matching to control selection bias and to create demographically and clinically comparable cohorts (28). The propensity score for use of clopidogrel within 7 days was developed on the basis of the following variables: age; race or ethnicity; sex; year of index date; type of presenting event (UA or NSTEMI); smoking status; estimated glomerular filtration rate; systolic blood pressure; a history of bleeding, heart failure, hypertension, hyperlipidemia, or diabetes; and the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, or statins. Patients in the clopidogrel-treated cohort were matched with the group that had not received clopidogrel in a 1:1 ratio by using a modified greedy matching algorithm without replacement, on the basis of propensity scores within 1%.

Statistical analysis. We conducted the analysis in an intention-to-treat framework (i.e., not an on-treatment analysis because we did not allow crossover between study arms after 7 days post-discharge). We compared means of baseline characteristics by using 2-sided Student t tests. We used Kaplan-Meier estimators to describe survival functions for the selected outcomes and multivariable Cox regression analysis to test the association of clopidogrel use with outcomes, after adjustment for the covariates described earlier. We conducted analyses on unadjusted and propensity-matched models and performed sensitivity analyses, and we examined interaction effects (p_inter) between outcomes and the type of initial presentation (UA or NSTEMI) and several patient subgroups (history of diabetes, history of smoking, and older age). Sensitivity analyses were performed as follows: by varying the time window after discharge that defined clopidogrel use; by including patients who were excluded by our eligibility criteria (patients using warfarin at baseline, dialysis recipients, patients with very high blood pressure, and patients with an earlier stroke or TIA); and, to examine whether proton pump inhibitor (PPI) use modifies the effect of clopidogrel in this population, by restricting analyses to those patients who filled baseline prescriptions for PPIs in both the clopidogrel user group and the nonuser group. All analyses were performed with the R statistical package, version 2.15.3 (R Development Team, Vienna, Austria).

Results

We identified 39,455 patients 30 years of age or older with incident disease between 2003 and 2008. After applying the exclusion criteria, the analysis sample included 16,365 eligible patients, 5,961 (36%) of whom filled a prescription for clopidogrel with the first 7 days after discharge (Fig. 1).

In the overall study population, patients who used clopidogrel were younger and more likely to be male and to smoke, but they were otherwise healthier with fewer comorbidities (Table 1). Use of CV medications before the incident event was lower among clopidogrel users (see Table 1), but after hospital discharge, CV drug use was
higher among clopidogrel users (Table 1). Mean length of follow-up was 976 days for clopidogrel users and 876 days for clopidogrel nonusers. Median and mean duration of continuous clopidogrel use among users was 188 days (interquartile range: 82 to 603 days) and 206 days, respectively. Most (97%) clopidogrel users filled their prescriptions on the day of discharge.

Patients who did not fill a prescription for clopidogrel within 7 days of discharge from the index hospital stay had a low rate of subsequent initiation of clopidogrel: of the 10,404 initial nonusers, 3.4% initiated clopidogrel between 7 and 30 days after discharge, and another 7.4% initiated clopidogrel after 30 days post-discharge. More than one-third (38%) of the patients who initiated clopidogrel more than 7 days after discharge (332 of 859) did so after subsequent PCIs, most of which occurred well after discharge (24% between days 7 and 30, 58% between 30 and 365 days, and 18% between 1 and 2 years post-discharge).

The c-statistic for the propensity score model for predicting clopidogrel use within 7 days after discharge was 0.72. We matched 72% of clopidogrel users (4,281 of 5,961) with nonusers (1:1 match) within 1% (2 decimal places); 97% of pairs were matched within 0.1% (3 decimal places). Baseline covariates were well balanced in the matched cohort (see Table 1), and there were no statistically significant differences among measured covariates for clopidogrel users and nonusers.

In unadjusted analyses, the composite endpoint of all-cause mortality and MI requiring hospital stay over 2-years of follow-up was lower in patients receiving clopidogrel in both the overall population and in the propensity score

### Table 1 Characteristics of Study Population

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<td>PPI, %</td>
<td>20.3</td>
<td>23.1</td>
<td>&lt;.01</td>
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*Prior Rx or started within 7 days of discharge.
ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HTN = hypertension; NSTEMI = non-ST-segment elevation myocardial infarction; PPI = proton pump inhibitor; Rx = treatment; SBP = systolic blood pressure; UA = unstable angina.
matched cohort (Fig. 2). In the propensity-matched cohort, the composite of death or MI was lower among clopidogrel users (13.5% vs. 17.4%; p < 0.01; adjusted hazard ratio [HR]: 0.74, 95% confidence interval [CI]: 0.66 to 0.84) (Fig. 3). All-cause mortality over 2 years was also lower for clopidogrel users (8.3% vs. 13.0%; p<0.01; HR: 0.63, CI: 0.54 to 0.72), but the rate of acute MI was not significantly different (6.7% vs. 7.2%; p = 0.30; HR: 0.93; CI: 0.78 to 1.11).

There was evidence of treatment effect modification by clinical presentation (NSTEMI vs. UA) and by a history of smoking, but not by a history of diabetes. The impact of older age yielded mixed results, with a significant interaction for the composite of death and MI, but not for the individual endpoint of all-cause mortality (Figs. 3 and 4). Compared with patients who presented with UA, patients who presented with NSTEMI had a stronger association of clopidogrel use with the composite of death or MI (HR: 0.67 vs. 1.25; p_int < 0.01), as well as with the individual endpoints of mortality (HR: 0.56 vs. 1.20; p_int < 0.01), and acute MI (0.84 vs. 1.38; p_int = 0.03).

The association of clopidogrel with the composite of death or MI was similar, however, among patients with and without diabetes (HR: 0.83 vs. 0.69; p_int =0.14), but it was stronger among patients more than 70 years of age (HR: 0.70 vs. 0.88; p_int =0.04), as well as among nonsmokers (HR: 0.69 vs. 0.86; p_int = 0.02). Results were similar for the individual endpoint of all-cause mortality, although the interaction between older age and clopidogrel use was not significant (Fig. 4).

Results were not materially changed in sensitivity analyses that defined clopidogrel use as any prescription filled within 30 days, that included subjects excluded by our eligibility criteria (i.e., patients taking warfarin, or undergoing dialysis, or with very high blood pressure, or with an earlier stroke or TIA), and that restricted the analysis to patients taking PPIs at baseline (data not shown).

### Discussion

In our analysis of a large, community-based cohort of medically managed patients with UA or NSTEMI, initiation of
Clopidogrel within the first week after hospital discharge was associated with a lower risk of the composite outcome of death or MI over 2 years of follow-up. The association between clopidogrel use and outcomes was significantly greater among patients who presented with NSTEMI, among nonsmokers, and among older patients.

The reduction in the composite endpoint of death and MI replicates, in a real-world cohort, the findings of the landmark CURE trial. Indeed, the HR for the composite primary outcome in CURE (HR: 0.80) was similar to the HR for the composite outcome of death or MI in our study (HR: 0.74). In CURE, as well as in CRUSADE, early administration of clopidogrel was associated with a significant improvement of in-hospital and 1-year outcomes (1,18). Our study demonstrates that long-term outcomes are also improved for survivors of coronary events requiring hospital stay and further supports the use of clopidogrel in medically managed patients with acute coronary syndrome (ACS). Although significant advances in antiplatelet therapy have occurred, the use of these agents would not have affected patient selection in our study because these agents were approved for use after our study period.

Interestingly, clopidogrel use did not reduce the risk of MI requiring hospital stay in this study cohort. These results differ from those of the CURE trial (1), in which clopidogrel use was associated with a reduction in the composite endpoint of CV death, nonfatal MI, and stroke, but among individual endpoints, clopidogrel use reduced the risk of MI (notably, only Q-wave MIs), but not CV mortality. These differences in individual endpoints may be chance findings, may represent secular trends in outcomes for patients with UA or NSTEMI unrelated to antiplatelet therapy, or may be the result of important differences in study design between the CURE trial and our study.

First, ours was a retrospective study of administrative and clinical data from a real-world cohort, not a prospective randomized controlled trial. Real-world observational data can be analyzed reliably by applying design and analytic techniques such as new-user design, restriction of the population to trial-eligible patients, propensity score matching, and multivariable adjustment; nevertheless, these techniques may not entirely eliminate selection bias. However, a key strength of observational research is its ability to examine more diverse populations and to generalize trial findings to real-world patients and practice settings.

Another important distinction between our study and CURE is the definition of study endpoints. We do not have data on the cause of death (e.g., CV mortality), and the MI endpoint in our study was a mixture of fatal and nonfatal events. Patients who died out of hospital of an MI were coded as a death, not an MI, in our data. Thus, a strict comparison of the MI endpoint between CURE and our study is not feasible. Patients taking clopidogrel in our study may have been less likely to suffer fatal, out-of-hospital MIs, thus leading to fewer deaths among users while increasing the number of patients who survived to be hospitalized for...
an MI. The CURE data support this potential explanation. In CURE, clopidogrel decreased the number of Q-wave MIs, which may be more likely to cause sudden cardiac death than non-Q-wave MIs. It is possible that clopidogrel reduces the “severity” of an MI, such that otherwise fatal, out-of-hospital MIs become less severe, nonfatal MIs that allow more clopidogrel users to make it to the hospital for treatment. Given the difficulty of identifying the cause of death in observational data, the composite outcome of death and MI requiring hospital stay is the most comparable endpoint from our study. Interestingly, in a substudy of the PLATO (Platelet Inhibition and Patient Outcomes) trial of more than 5,000 medically managed patients, ticagrelor reduced mortality compared with clopidogrel, but it did not reduce the rate of MI (29). Future research should examine the mechanism driving mortality reductions that are disproportionate to reductions in MI for patients receiving these agents.

Although we did not examine stroke outcomes, in the CURE trial and other trials of antiplatelet and anticoagulant use in ACS and high-risk groups (30–33), strokes were uncommon, and stroke rates were not different among treatment groups. The CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial found no difference in CV events among more than 12,000 patients with a previous history of stroke.

Another difference between this study and CURE was that we analyzed a longer follow-up period (2 years vs. 1 year). We excluded patients who received revascularization either in the hospital or within the first week post-discharge, whereas 15% of patients in the CURE trial received in-hospital revascularization. Finally, we excluded patients with a previous history of coronary artery disease (CAD), whereas one-third of patients in the CURE trial had a previous MI, and nearly 20% had previously undergone CABG or PCI. The combination of these differences may possibly account for the disparities seen in the individual endpoints.

An important finding from this study was that a patient’s clinical presentation affected the effectiveness of clopidogrel. Clopidogrel was associated with a significant improvement in outcomes only among patients with NSTEMI, but not among patients presenting with UA. Patients with NSTEMI had elevated cardiac enzymes, an objective marker of myocardial damage, whereas patients with UA were identified by using more subjective signs and symptoms. Therefore, some patients with a discharge diagnosis of UA in our study may not have had underlying CAD and would have been unlikely to benefit from clopidogrel. In addition, although both NSTEMI and UA are usually caused by atherosclerotic plaque rupture and superimposed thrombosis, long-term antiplatelet therapy may be more effective in patients with more severe ischemia that ultimately leads to infarction, as occurs in NSTEMI but not UA. Patients with NSTEMI and UA may also differ in other factors that influence the risk of MI or death, such as thrombogenicity, which could affect the response to clopidogrel.

Our results suggesting that patients with NSTEMI may receive a greater benefit from clopidogrel than patients with UA are consistent with a subanalysis of CURE that demonstrated a greater absolute risk reduction among high-risk subjects (Thrombolysis In Myocardial Infarction risk score of 5 to 7) (34). Similarly, in the secondary prevention subgroup analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial (35), patients with prior MI had a larger protective effect from clopidogrel than did patients with ischemic stroke or peripheral vascular disease, with effect sizes similar to those in our study (HR: 0.74 [95% CI: 0.66 to 0.84] for death and MI in our study; HR: 0.83 [95% CI: 0.72 to 0.96] for CV death, MI, or stroke in CHARISMA). Further, in CHARISMA, there was no benefit from clopidogrel among patients with CAD but without MI (HR: 1.10 [95% CI: 0.77 to 1.58]), similar to our finding for patients with UA (HR: 1.25 [95% CI: 0.94 to 1.67]). In addition, the ability to discern MI in clinical trials is likely better than in regular clinical practice because rigorous protocols and additional scrutiny are in place to monitor study patients, and the coronary events identified through our claims-based algorithms may represent clinically larger MIs.

Unlike results from a Danish registry (36), we found similar effectiveness for clopidogrel among patients with and without diabetes, but we did find a similar direction of the effect (i.e., trend toward less effectiveness among patients with diabetes) (Fig. 4). We also found a stronger association for clopidogrel with outcomes among nonsmokers than among smokers. These results differ from those of CAPRIE (37) and other trials, although this discrepancy may signify differences in characterization of smoking status in routine care from those in a clinical trial. Our data suggesting that clopidogrel may be more protective among older patients (age ≥70 years), at least for our composite outcome, is consistent with findings of the CURE trial and may reflect greater benefit of clopidogrel among higher-risk patients. This finding is important because concern over the risk of bleeding from dual-antiplatelet therapy can often tilt the perceived benefit/risk ratio against aggressive treatment in older populations. In TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes), a dedicated trial of prasugrel versus clopidogrel in medically managed patients, older patients did not receive a benefit from more potent platelet inhibition with prasugrel (33).

Less than one-half (36%) of medically managed patients with UA or NSTEMI were prescribed clopidogrel during the study period (2003 to 2008), even though it was given a Class I indication in the 2002 AHA/ACC guidelines (2). In similar patient populations, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) registry reported clopidogrel adherence rates of 28% in 2002 and 53% in 2005 (13), the
GRACE registry (Global Registry of Acute Coronary Events) reported almost 50% usage of clopidogrel in Canadian patients between 2003 and 2007 (17), and in the ACTION Registry-GWTG (Get With The Guidelines), 55% of medically managed patients with NSTEMI between 2009 and 2011 were discharged on clopidogrel (15). Both GRACE and CRUSADE demonstrated increasing use of clopidogrel for UA or NSTEMI over time (18,19). Although the reported use of clopidogrel was slightly lower in this study, given the wide availability of PCI for Kaiser Permanente Northern California members, the population of medically managed patients with ACS in our cohort may be sicker than the U.S. average, with more clinical contraindications to clopidogrel use. Nevertheless, this finding lends additional support to more rigorous use of clopidogrel use among medically managed patients with ACS. Indeed, the results of the medically managed arm of PLATO, in which ticagrelor was superior to clopidogrel on the composite outcome of death, MI, and stroke, suggest that potent platelet inhibition is indeed beneficial in this patient population (29). Despite recent advances in antplatelet therapy, clopidogrel remains a viable option; TRILOGY ACS found no benefit for prasugrel over clopidogrel in a similar patient population.

Study limitations. Our analysis had limitations. It was not possible to confirm the use of aspirin therapy because most aspirin use is over the counter and is not captured within our pharmacy dispensing database. We could not ascertain the cause of death, details of the coronary event, the extent and severity of CAD (i.e., single-vessel or multivessel disease), or heart failure severity. Even though we used advanced statistical methods, including propensity score matching and covariate adjustment, we cannot rule out residual or unmeasured confounding. In addition, although our study provides insights into clopidogrel use over the past decade, changes in guideline recommendations over this period may have altered selection of patients for invasive versus conservative strategies.

Conclusions

Examining the strength and durability of clinical trial findings is a core mission of comparative effectiveness research. Our results show that clopidogrel use initiated within 7 days post-discharge was associated with improved outcomes among medically managed patients after ACS. These findings suggest that the results of antplatelet trials for this patient population translate well to “real world” practice.

REFERENCES


Reprint requests and correspondence: Dr. Matthew D. Solomon, Kaiser Permanente Oakland Medical Center, 3600 Broadway, Oakland, California 94611. E-mail: Matthew.D.Solomon@kp.org.


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