Prolonged Clopidogrel Use After Bare Metal and Drug-Eluting Stent Placement

The Veterans Administration Drug-Eluting Stent Study

David P. Faxon, MD; Elizabeth Lawler, PhD; Melissa Young, MPH; Michael Gaziano, MD, PhD; Scott Kinlay, MBBS, PhD

Background—Current guidelines recommend combining clopidogrel with aspirin for up to 1 year after coronary stenting, but the value of clopidogrel beyond this time is uncertain.

Methods and Results—We evaluated all patients in the Veterans Administration healthcare system receiving either drug-eluting or bare metal stents from 2002 to 2006. The Veterans Administration National Patient Care and Pharmacy databases were used to extract patient characteristics, duration of clopidogrel use, and outcomes for up to 4 years after the index procedure. We used Cox proportional hazards to estimate hazard ratios for death, myocardial infarction, revascularization, and bleeding from a 12-month landmark after stenting that excluded patients with events within the first 12 months. Of 42,254 patients, 29,175 met the study inclusion criteria. Compared with ≤12 months of clopidogrel, prolonged clopidogrel (>12 months) was associated with a lower adjusted risk of death for both drug-eluting stents (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.61, 0.82; P<0.01) and bare metal stents (HR, 0.85; 95% CI, 0.76, 0.96; P=0.01) as well as for death and myocardial infarction but was unrelated to stroke or major bleeding. The effect of prolonged clopidogrel on death or myocardial infarction was significantly greater among patients receiving drug-eluting (HR, 0.70; 95% CI, 0.64, 0.84) compared with bare metal stents (HR, 0.88; 95% CI, 0.79, 0.98; interaction P=0.024).

Conclusions—Patients receiving clopidogrel beyond 12 months had a lower risk of death or myocardial infarction compared with patients receiving clopidogrel ≤12 months. The risk reduction was greater for drug-eluting stents. These data support longer durations of dual antiplatelet therapy for patients receiving a stent, particularly for those receiving a drug-eluting stent. (Circ Cardiovasc Interv. 2012;5:372-380.)

Key Words: clopidogrel ■ dual antiplatelet therapy ■ long-term outcome ■ PCI ■ stents

Drug-eluting stents revolutionized the treatment of symptomatic coronary artery disease due to less restenosis compared with bare metal stents.1 However, stents require dual antiplatelet therapy with aspirin and thienopyridines (eg, clopidogrel) after stent deployment to prevent stent thrombosis, which often presents as sudden death or a myocardial infarction. Both drug-eluting and bare metal stents share an increased risk of early stent thrombosis often related to premature discontinuation of antiplatelet therapy within 6 months and particularly within the first month after the procedure.2,3

Recent concerns about the long-term safety of drug-eluting stents relate to a small but higher risk of late (>6 months after stenting) and very late stent thrombosis (>1 year stenting), with rates of 0.2% to 0.6% per year.4,5 As a result, the Food and Drug Administration recommended at the end of 2006 that the duration of clopidogrel treatment after coronary stents be extended from 3 to 6 months to 12 months.6 Current American College of Cardiology/American Heart (ACC/AHA) Association guidelines recommend dual antiplatelet therapy for a minimum of 12 months with drug-eluting stents and bare metal stents.7 They also suggest that clopidogrel may be continued beyond 1 year but classified this as a class IIb indication, as studies have shown conflicting results.8–15

Prolonged use of clopidogrel is not only costly but restricts elective surgical procedures and increases the risk of major bleeding and subsequent mortality. The relatively low incidences of very late stent thrombosis and major bleeding make it difficult to determine the impact of prolonged dual antiplatelet therapy on these events in randomized trials and...
registry studies due to patient selection and restricted numbers of subjects.

Registry studies have shown conflicting results. A study from Duke University showed a significant reduction in death and death and myocardial infarction in patients receiving drug-eluting stents but not bare metal stents when clopidogrel was continued for >12 months. However, in a large registry from Korea, no difference in stent thrombosis or death and myocardial infarction was seen between those on clopidogrel for more than 1 year. This is supported by the only randomized trial to date, but this study was underpowered for clinical events.

We used data from the unrestricted very large national Veteran Affairs population to examine whether prolonged clopidogrel use >12 months after coronary stenting was associated with better clinical outcomes in patients with bare metal or drug-eluting stents. We hypothesized that prolonged clopidogrel therapy was associated with a lower risk of death and myocardial infarction after coronary drug-eluting stenting but not after bare metal stenting.

WHAT IS KNOWN

• Dual antiplatelet therapy with aspirin and clopidogrel is recommended for 12 months for patients with drug-eluting stents and for at least 1 month for bare metal stents and preferably for 1 year.
• It is not known whether prolonged dual antiplatelet therapy is of value beyond 1 year, as current trials have shown mixed results.

WHAT THE STUDY ADDS

• In the national VA database, patients with both drug-eluting stents and bare metal stents demonstrated a reduced mortality and myocardial infarction rate without an increase in major bleeding with prolonged clopidogrel use beyond 12 months.
• The benefit was significantly stronger for drug-eluting stents.

Methods

We identified patients receiving coronary stents and their demographic data, laboratory data, and pharmacy data from the VA National Patient Care Database. This database records up to 10 disease diagnoses coded according to the International Classification of Disease, 9th Revision (ICD-9) from inpatient, outpatient, and compensated non-VA care. This database tracks long-term drug use and healthcare outcomes among veterans for several years.

Patient Population

We identified all veterans receiving coronary stents between April 2002 and September 2006 at any VA facility nationwide. This was the period when drug-eluting stents were introduced and before the changes in guidelines advocating longer clopidogrel use from 3 to 6 months to 12 months in patients with drug-eluting stents. Patients were identified by the ICD-9 procedure code for placement of a bare metal coronary artery stent (36.06) or a drug-eluting coronary artery stent (36.07). We considered the first stent placement to be the index procedure. We excluded patients who had both drug-eluting and bare metal stent procedures during the index procedure. We also excluded patients with metastatic cancer during the year before baseline (defined by ICD-9: 140–208 with a chemotherapy medication). Since the focus of this investigation was the impact of long-term clopidogrel prescribed after coronary stents, we excluded patients who did not receive clopidogrel after coronary stenting or those who may have received clopidogrel for another reason (defined as clopidogrel used >30 days before the index procedure). Subjects were followed using the two databases for procedures and end points from 12 months after the index stent up until the end of September 2007, or for a maximum of 36 months (range, 1–3 years).

Demographic Data

We extracted patient demographics including age, sex, clinical presentation including myocardial infarction (ICD9: 410), prior angioplasty (ICD9: 36.01–2, 36.05–7, 00.66) or coronary bypass surgery (ICD9: 36.1) and comorbidities including diabetes mellitus (ICD9: 250), smoking (ICD9: 305.1), hypertension (ICD9: 401), chronic kidney disease (ICD9: 585), congestive heart failure (ICD9: 428), prior stroke (ICD9: 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, V1254), peripheral vascular disease (ICD9: 443), chronic obstructive lung disease (ICD9: 496), and anemia (ICD9: 281–285).

Medication and Clopidogrel Use

Since VA prescriptions are usually written for 90-day time periods, we defined baseline medication as a prescription filled within 90 days before and up to 7 days after the index procedure. These included lipid-lowering drugs, antihypertensives, oral and insulin treatment for diabetes, anticoagulants including heparin and warfarin, and antiplatelet agents including aspirin and clopidogrel. Because aspirin is often obtained over the counter (cheaper than the VA copay), we do not have pharmacy verification of aspirin use in most patients. VA quality assurance studies have shown that in the VA population, outpatient use of aspirin remains extremely high. For the purpose of this study, we assumed that patients were taking aspirin if it was noted on the medical discharge summary or in the outpatient record.

Over the follow-up time of the study, we were able to track the date of prescription, the amount, and the delivery of all prescribed drugs. If a clopidogrel prescription lapsed >30 days from the last day of supply, the patient was considered not taking clopidogrel.

We divided clopidogrel use into 2 groups, which were prolonged clopidogrel use for more than 12 months, versus clopidogrel ≤12 months. Prolonged clopidogrel use was defined as filling a prescription for 12 months with or without an interruption, beginning with the date of the initial percutaneous coronary intervention (PCI).

Outcomes

We evaluated the outcomes after the index stent placement using ICD-9 codes up until October 2007. These included death, the combined end point of death or acute myocardial infarction, and admissions with a new discharge diagnosis of revascularization by PCI or coronary artery bypass grafting (CABG), ischemic stroke, and hospitalization with a new diagnosis of major bleeding. The ICD 9 codes used to define these outcomes were myocardial infarction (ICD9: 410), revascularization by PCI (ICD9: 36.01, 36.02, 36.05, 00.66) or by CABG (ICD9: 36.1), ischemic stroke (ICD9: 436, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and major bleed (ICD9: 569.3, 530.82, 578, 535.01–535.61, 430–432, 379.23, 459).

Statistics

The primary objective of this study was to determine if prolonged clopidogrel use was associated with a reduction in death and death and myocardial infarction. The secondary objective was to determine if prolonged use was associated with a reduction in repeat revascularization, stroke, or an increase in the risk of bleeding that required hospitalization.

Since baseline characteristics of the patients who received a bare metal or drug-eluting stent were significantly different and we...
hypothesized a different impact of prolonged clopidogrel for each stent type, the analysis was stratified by drug-eluting and bare metal stenting. We used event curves and a landmark analysis assessing outcomes from 12 months after the index procedure among patients who were initially event-free from the event of interest as well as stroke and major bleeding at the beginning of the analysis period 12 months after their index stenting. We also performed a sensitivity analysis including only patients who were initially event-free of all events (myocardial infarction, PCI, or CABG, stroke, or major bleeding) at 12 months. Patients were followed for the clinical outcomes until they died or had an event. Follow-up was censored after September 2007, 12 months after their last recorded VA visit, or 48-months after the index procedure. The hazard ratio for prolonged clopidogrel use versus clopidogrel used for ≤12 months was assessed for each outcome within each stent type, using Cox proportional hazards models. Multivariable models were developed from >50 variables and included if they were related to outcomes. The hazards from final multivariable models were adjusted for baseline characteristics related to outcomes including age, diabetes mellitus, acute coronary syndrome presentation at the index procedure, hypertension, peripheral vascular disease, heart failure, warfarin use within 7 days of the index procedure, and year of stent placement. To test whether prolonged clopidogrel had a greater effect in patients receiving drug-eluting compared with bare metal stents, we combined data from both stent types and assessed the interaction between prolonged clopidogrel use and type of stent for each outcome.

As a second method of adjustment, we used propensity models to adjust for confounding related to the propensity for prolonged clopidogrel treatment based on variables at the index procedure. For each stent type, we developed a propensity score for clopidogrel use beyond 12 months using multivariable logistic regression. The propensity score was derived from 47 variables that were thought to have a potential impact on prolonged use including a history of bleeding or warfarin use. We used inverse probability weighting of the propensity score in the Cox proportional hazards models to assess the hazard associated with prolonged clopidogrel use.

In exploratory analyses, we assessed different durations of clopidogrel use using Cox proportional hazards for landmark analyses with clopidogrel treatment defined by durations of use equal to or exceeding 3, 6, 9, 12, 18, and 24 months and death up to 36 months after each landmark as the outcome.

All programming used SAS statistical software with probability values of <0.05 as statistically significant.

Results

Bare metal or drug-eluting stents were placed in 42,254 patients in VA facilities between April 2002 and September 2006. After exclusion from the study, 29,175 subjects were included for analysis (Figure 1). Among this study population, 14,925 (51%) received a drug-eluting stent and 14,250 (49%) patients received a bare metal stent during the index procedure. The stent choice was the decision of the interventional cardiologist and varied over time with bare metal stents exclusively placed in 2002, and a rapid increase in drug-eluting stents as they were introduced into the market, so that by 2006, 86% of stents were drug-eluting (Figure 2).

The patients in this study had many high-risk baseline characteristics (Table 1), including acute coronary syndrome at presentation in two-thirds, heart failure in >20%, diabetes mellitus in >40%, and chronic lung disease in >20%. Patient-defined race was recorded in 93% of subjects, including 23,464 (80%) white, 3,386 (12%) black, and 202 (0.7%) other. Use of cardiovascular medications at the index procedure was high. More than 84% received aspirin, 91% of subjects were taking lipid-lowering drugs, >89% were on a β-blocker, and >70% on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (Table 1). More than 8% were taking warfarin in addition to aspirin and clopidogrel.

Between the index procedure and 1 year, in the bare metal stent group 4.3% had a myocardial infarction, 0.4% had a stroke, 1.1% had a major bleeding episode, and 13% had a repeat revascularization. The event rates in the drug-eluting stent group during this same time was 4.5% for myocardial infarction, 0.3% for stroke, 1.1% for major bleeding episodes, and 11% for repeat revascularizations.

Clopidogrel Use Over Follow-Up

The use of clopidogrel decreased over time for both stent types, but the duration was shorter among patients receiving bare metal stents (Figure 3). At 12 months, clopidogrel was still being taken by 43% of patients who received drug-eluting stents and 25% of patients who received bare metal stents (Figure 3). The mean duration of clopidogrel use in those on prolonged clopidogrel was 21.8 months in the bare
metal stent group and 18.3 months in the drug-eluting stent group, and the mean duration in those on for <12 months was 4.3 months in the bare metal stent group and 6.1 month in the drug-eluting stent group.

Univariate Risk Associated With Prolonged Clopidogrel Use
During the 1 to 3 years after the 12-month landmark (average follow-up, 2.5 years), there were 1600 deaths, 1927 deaths or myocardial infarcts, 107 ischemic strokes, and 219 major bleeds in patients receiving bare metal stents. Over the same time period, there were 756 deaths, 978 deaths or myocardial infarcts, 41 ischemic strokes, and 109 major bleeds in patients receiving drug-eluting stents.

Figure 4 shows the event curves for death and the combined end point death and myocardial infarction for each stent type. For both stent types, patients receiving clopidogrel for >12 months had fewer deaths and myocardial infarctions than those taking clopidogrel for <12 months.

Table 2 shows the hazard ratios for prolonged versus <12 months of clopidogrel. Among patients receiving drug-eluting stents, prolonged clopidogrel was associated with a 30% lower risk of death and 27% lower risk of death or myocardial infarction. Smaller but statistically significant differences were observed in those receiving bare metal stents, where prolonged clopidogrel was also associated with

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**Table 1. Baseline Characteristics by Stent Type and Length of Clopidogrel Treatment**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Drug-Eluting Stent Clopidogrel Use</th>
<th>Bare Metal Stent Clopidogrel Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤12 Months (n=8436)</td>
<td>&gt;12 Months (n=6489)</td>
</tr>
<tr>
<td></td>
<td>≥12 Months (n=10 644)</td>
<td>&gt;12 Months (n=3606)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>63.8 (10.1)</td>
<td>63.7 (9.5)</td>
</tr>
<tr>
<td></td>
<td>64.0 (10.3)</td>
<td>64.2 (10.0)</td>
</tr>
<tr>
<td>Comorbidities 5 y before to 1 y after index procedure, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>3704 (43.9)</td>
<td>2691 (41.5)</td>
</tr>
<tr>
<td></td>
<td>4397 (41.3)</td>
<td>1455 (40.4)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>2424 (28.7)</td>
<td>2094 (32.3)</td>
</tr>
<tr>
<td></td>
<td>3485 (32.7)</td>
<td>1270 (35.2)</td>
</tr>
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<td>Angina</td>
<td>3339 (39.6)</td>
<td>2479 (38.2)</td>
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<tr>
<td></td>
<td>5005 (47.0)</td>
<td>1631 (45.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7728 (91.6)</td>
<td>6031 (92.9)</td>
</tr>
<tr>
<td></td>
<td>9788 (92.0)</td>
<td>3379 (93.7)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3609 (42.8)</td>
<td>2873 (44.3)</td>
</tr>
<tr>
<td></td>
<td>4514 (42.4)</td>
<td>1642 (45.5)</td>
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<tr>
<td>COPD</td>
<td>2414 (28.6)</td>
<td>1858 (28.6)</td>
</tr>
<tr>
<td></td>
<td>3111 (29.2)</td>
<td>1050 (29.1)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>752 (8.9)</td>
<td>593 (9.1)</td>
</tr>
<tr>
<td></td>
<td>874 (8.2)</td>
<td>306 (8.5)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1503 (17.8)</td>
<td>1122 (17.3)</td>
</tr>
<tr>
<td></td>
<td>2097 (19.7)</td>
<td>713 (19.8)</td>
</tr>
<tr>
<td>Anemia, Hbg &lt; 12 mg/dL</td>
<td>1438 (17.1)</td>
<td>866 (13.4)</td>
</tr>
<tr>
<td></td>
<td>1976 (16.8)</td>
<td>613 (17.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>444 (5.3)</td>
<td>331 (5.1)</td>
</tr>
<tr>
<td></td>
<td>719 (6.8)</td>
<td>230 (6.4)</td>
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<tr>
<td>Heart failure</td>
<td>2208 (26.2)</td>
<td>1617 (24.9)</td>
</tr>
<tr>
<td></td>
<td>3001 (28.2)</td>
<td>1031 (28.6)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>145 (1.7)</td>
<td>71 (1.1)</td>
</tr>
<tr>
<td></td>
<td>211 (2.0)</td>
<td>71 (2.0)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>126 (1.5)</td>
<td>72 (1.1)</td>
</tr>
<tr>
<td></td>
<td>486 (4.6)</td>
<td>120 (3.3)</td>
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<tr>
<td>ACS (during index admission)</td>
<td>5314 (63.0)</td>
<td>4237 (65.3)</td>
</tr>
<tr>
<td></td>
<td>6734 (63.3)</td>
<td>2429 (67.4)</td>
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<tr>
<td>Baseline medication, n (%)</td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>6929 (82.1)</td>
<td>5177 (79.8)</td>
</tr>
<tr>
<td></td>
<td>9517 (89.4)</td>
<td>3080 (85.4)</td>
</tr>
<tr>
<td>Statin or lipid-lowering</td>
<td>7620 (90.3)</td>
<td>5917 (91.2)</td>
</tr>
<tr>
<td></td>
<td>9674 (90.9)</td>
<td>3298 (91.5)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>7315 (86.7)</td>
<td>5665 (87.3)</td>
</tr>
<tr>
<td></td>
<td>9654 (90.7)</td>
<td>3246 (90.0)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>2083 (24.7)</td>
<td>1723 (26.6)</td>
</tr>
<tr>
<td></td>
<td>3075 (28.9)</td>
<td>1077 (29.9)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>5958 (70.6)</td>
<td>4626 (71.3)</td>
</tr>
<tr>
<td></td>
<td>8053 (75.7)</td>
<td>2691 (74.6)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>3977 (47.1)</td>
<td>3271 (50.4)</td>
</tr>
<tr>
<td></td>
<td>4867 (45.7)</td>
<td>1805 (50.1)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>742 (8.8)</td>
<td>491 (7.6)</td>
</tr>
<tr>
<td></td>
<td>981 (9.2)</td>
<td>276 (7.7)</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

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**Figure 3.** Duration of clopidogrel use from index procedure by stent type.

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**Figure 4.** Duration of clopidogrel use from index procedure by stent type.
15% less death and 12% less death or myocardial infarction. Over the same time period, prolonged clopidogrel (>12 months after the index procedure) was not associated with the risk of subsequent coronary revascularization, ischemic stroke, or major bleeding (Table 2).

**Adjusted Analyses**

Table 2 shows the hazard ratios for prolonged clopidogrel use from multivariable models and from the propensity adjusted models. The multivariable predictors used for the propensity analysis are shown in Online Data Supplement Appendix 1. The C-statistic for prediction of prolonged clopidogrel use 12 months was 0.587 for the drug-eluting stent and 0.662 for the bare metal stent. The hazards for the endpoints were very similar after both forms of multivariable adjustment, suggesting that these estimates were robust to the known confounders included in these models. In a sensitivity analysis that only included patients who were event-free of all major outcomes up to the 1-year landmark, similar findings were seen with the propensity adjusted risk of mortality for drug-eluting stents (hazard ratio [HR], 0.75 [0.63–0.90]; P<0.01) but was not significant for bare metal stents (HR, 0.90 [0.79, 1.02]).

**Effect of Prolonged Clopidogrel and Stent Type**

In a combined model testing the interaction between clopidogrel use and stent type, prolonged clopidogrel was associated with a lower risk of death or myocardial infarction very similar after both forms of multivariable adjustment, suggesting that these estimates were robust to the known confounders included in these models. In a sensitivity analysis that only included patients who were event-free of all major outcomes up to the 1-year landmark, similar findings were seen with the propensity adjusted risk of mortality for drug-eluting stents (hazard ratio [HR], 0.75 [0.63–0.90]; P<0.01) but was not significant for bare metal stents (HR, 0.90 [0.79, 1.02]).

**Table 2. Landmark Analysis of the Risk of Clinical End Points With Clopidogrel Use Beyond Versus ≤12 Months for Outcomes Up to 4 Years After Index Stenting**

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Stent Type</th>
<th>Univariate Hazard Ratio</th>
<th>95% CI</th>
<th>Multivariable-Adjusted† Hazard Ratio</th>
<th>95% CI</th>
<th>Propensity-Adjusted‡ Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>DES</td>
<td>0.70*</td>
<td>(0.61, 0.82)</td>
<td>0.72*</td>
<td>(0.62, 0.84)</td>
<td>0.78*</td>
<td>(0.67, 0.91)</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>0.85*</td>
<td>(0.76, 0.96)</td>
<td>0.83*</td>
<td>(0.73, 0.94)</td>
<td>0.90</td>
<td>(0.79, 1.02)</td>
</tr>
<tr>
<td>Death or MI</td>
<td>DES</td>
<td>0.73*</td>
<td>(0.64, 0.84)</td>
<td>0.74*</td>
<td>(0.65, 0.84)</td>
<td>0.78*</td>
<td>(0.69, 0.89)</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>0.88**</td>
<td>(0.79, 0.98)</td>
<td>0.85*</td>
<td>(0.76, 0.95)</td>
<td>0.91</td>
<td>(0.81, 1.02)</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>DES</td>
<td>0.93</td>
<td>(0.79, 1.10)</td>
<td>0.94</td>
<td>(0.79, 1.10)</td>
<td>0.93</td>
<td>(0.78, 1.09)</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>0.97</td>
<td>(0.84, 1.12)</td>
<td>0.99</td>
<td>(0.86, 1.14)</td>
<td>0.97</td>
<td>(0.83, 1.12)</td>
</tr>
<tr>
<td>Stroke</td>
<td>DES</td>
<td>0.81</td>
<td>(0.43, 1.53)</td>
<td>0.85</td>
<td>(0.45, 1.60)</td>
<td>0.94</td>
<td>(0.50, 1.79)</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>0.79</td>
<td>(0.49, 1.28)</td>
<td>0.78</td>
<td>(0.48, 1.26)</td>
<td>0.81</td>
<td>(0.49, 1.33)</td>
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<tr>
<td>Major bleeding</td>
<td>DES</td>
<td>0.99</td>
<td>(0.67, 1.44)</td>
<td>0.99</td>
<td>(0.68, 1.46)</td>
<td>1.02</td>
<td>(0.69, 1.50)</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>0.93</td>
<td>(0.67, 1.27)</td>
<td>0.94</td>
<td>(0.68, 1.30)</td>
<td>0.98</td>
<td>(0.71, 1.37)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DES, drug-eluting stent; BMS, bare metal stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft.

*P<0.01; **P=0.02.
†Adjusted for age, diabetes, acute coronary syndrome during index admission, hypertension, peripheral vascular disease, heart failure, or warfarin within 7 days of index discharge, and year of stent.
‡Adjusted for the propensity to use clopidogrel for ≥12 months.
among patients receiving drug-eluting versus bare metal stents (interaction \( P=0.024 \)), and with a similar trend for death alone (interaction \( P=0.073 \)). There was no significant interaction between prolonged clopidogrel and stent type for risk of revascularization by PCI or CABG (interaction \( P=0.77 \)), stroke (interaction \( P=0.29 \)), or major bleeding (interaction \( P=0.57 \)).

**Exploratory Analysis of Different Durations of Clopidogrel Use**

The hazard of death for different durations of clopidogrel use, using landmark analyses at 3-month intervals from 3 to 24 months, was also explored. The results were similar for each time period favoring prolonged clopidogrel for both drug-eluting stents and bare metal stents (data not shown).

**Subgroup Analysis**

To explore the impact of prolonged clopidogrel in high-risk subgroups, patients with acute coronary syndromes on presentation or during the first year (n=21 815) were separately analyzed. Patients with acute coronary syndrome who received a drug-eluting stent and stayed on clopidogrel for >12 months had a significantly lower rate of death over 3 years than those not on clopidogrel (HR, 0.75 [0.62–0.90]; \( P<0.01 \)) for the propensity-adjusted analysis). However, similar patients with a bare metal stent had a similar rate of death on clopidogrel than those with <12 months (HR, 0.89 [0.77–1.03] for the propensity adjusted analysis). In the subgroup with treated diabetes (n=9605), patients with drug-eluting stents on clopidogrel for >12 months had a significantly lower rate of death than those not on clopidogrel (HR, 0.62 [0.49–0.79]; \( P<0.01 \)), whereas those with a bare metal stent did not demonstrate a benefit (HR, 0.88 [0.72–1.07]; \( P=0.20 \)). Among patients without diabetes, prolonged clopidogrel was not associated with death in patients receiving drug-eluting stents (HR, 0.87 [0.69, 1.09]; \( P=0.23 \)) or bare metal stent (HR, 0.88 [0.72, 1.08]; \( P=0.21 \)). Thus, both these high-risk subgroups showed an improved outcome with prolonged clopidogrel in those with drug-eluting stents but not in patients with bare metal stents. The unadjusted and multivariable adjusted analyses were similar. These findings are similar to that seen in the overall population.

**Discussion**

Our study addressed the pragmatic clinical question of whether continuing clopidogrel >12 months after an index coronary stent might be a beneficial treatment strategy. The main findings of this study were that in patients who were event-free 12 months after receiving drug-eluting stents, prolonged clopidogrel for >12 months was associated with less death and the combined end point of death and myocardial infarction over 4 years after stenting compared with those not on clopidogrel. Prolonged clopidogrel in patients with bare metal stents had a similar but significantly smaller relationship to these two adverse outcomes in the unadjusted and multivariable analysis but not in the propensity-adjusted model, where no benefit was seen. Prolonged clopidogrel was not associated with the risk of stroke or repeat coronary revascularization, and, importantly, was not associated with an increase in major bleeding requiring hospitalization. This cohort is 3 to 10 times larger than prior studies and the estimates of risk were robust to two methods of multivariable adjustment.

The use of clopidogrel for >12 months after drug-eluting stents is controversial. The risk of acute (<24 hours) and subacute (1–30 days) stent thrombosis is similar for drug-eluting and bare metal stents and causes death in 10% to 30% of cases and myocardial infarction in 3% to 50% cases.\(^{18,19}\)

After the first 6 months, the risk of stent thrombosis is much lower, with an incidence of 1% to 3% in large observational studies.\(^{5,20}\) Over this time period, the risk of stent thrombosis is higher in patients receiving stents for off-label indications and those with other high-risk features such as chronic kidney disease.\(^{19,20}\) In some large registries and meta-analyses, the risk of very late stent thrombosis, >12 months after stenting, is higher with drug-eluting stents (0.4% to 0.6%) compared with bare metal stents (0.0% to 0.1%).\(^{21–23}\) These results are supported by trends toward a higher incidence with drug-eluting stents in some randomized trials, but these studies are limited by a small number of events and selection of low-risk patients.\(^{24–27}\) Because very late stent thrombosis typically presents as sudden death or myocardial infarction, these data prompted the Food and Drug Administration to recommend clopidogrel for up to 12 months in patients with drug-eluting stents,\(^{28}\) and, more recently, the ACC/AHA extended this by recommending that this duration should ideally be used with bare metal stents.\(^{7}\)

The evidence for prolonged use of clopidogrel beyond 1 year is controversial. In several observational studies, patients receiving prolonged clopidogrel use for >6 to 12 months had fewer deaths and myocardial infarctions and less stent thrombosis.\(^{8–10,29}\) In 4666 patients who were event-free 12 months after coronary stenting, Eisenstein et al\(^{8}\) reported fewer deaths and myocardial infarctions up to 24 months after stenting among patients continuing clopidogrel beyond 12 months with drug-eluting stents but not with bare metal stents. Among 749 patients with diabetes mellitus receiving drug-eluting or bare metal stents, Brar et al\(^{9}\) also showed fewer deaths and myocardial infarctions with clopidogrel treatment beyond 9 months. In another small registry study, patients receiving 24 months of clopidogrel had less very late stent thrombosis than those stopping clopidogrel at 12 months.\(^{10}\)

In contrast, other studies show no difference in clinical outcomes or stent thrombosis with prolonged clopidogrel versus more conventional treatment durations.\(^{3,11–15}\) In 3021 patients discontinuation of clopidogrel in the first 6 months, but not after this duration.\(^{3}\) In meta-analyses of the randomized trials of the TAXUS paclitaxel stent, clopidogrel use beyond 1 year compared with >1 year of use, was not associated with a decrease in stent thrombosis, death, and myocardial infarction.\(^{11}\) Among 2851 patients who received sirolimus stents and were event-free, Park et al\(^{12}\) found prolonged clopidogrel was not associated with death or myocardial infarction. In a recent small randomized trial among patients who were event-free after drug-eluting stents at 12 months, there was no difference with prolonged versus no clopidogrel therapy on death, myocardial infarction, and bleeding over the subsequent 2 years.\(^{16}\) However,
the clinical events in this study were extremely low, with the primary end point of death and myocardial infarction occurring in 1.8% of the dual antiplatelet therapy group and 1.2% in the aspirin monotherapy group. The trial anticipated a 5% event rate and a 50% reduction in the primary end point and therefore was underpowered to detect a difference. Two additional small trials have been reported. The PRODIGY trial randomly assigned 2013 patients to 4 different types of stents (3 drug-eluting stents and 1 bare metal stent) and to 6 months or 24 months of dual antiplatelet therapy (Valgimigli, European Society of Cardiology; August 30, 2011). There was no difference in the primary end point of death, myocardial infarction, and stroke between the two dual antiplatelet therapy groups (10.0% for 6 months of dual antiplatelet therapy versus 10.1% for 24 months). Bleeding, however, was significantly lower in those on dual antiplatelet therapy for only 6 months. The EXCELLENT trial also failed to show long-term benefit. In this study, 1443 patients were randomly assigned to 6 months or 12 months of dual antiplatelet therapy. The primary end point of target vessel failure (cardiac death, myocardial infarction, or ischemia-driven target vessel revascularization) was not different (4.8% for the 6-month group and 4.3% for the 12-month group), although stent thrombosis occurred more frequently in the 6-month group. This trial was also underpowered as it anticipated an event rate of 10% with a 40% reduction with prolonged clopidogrel. All of studies to date are limited by anticipated an event rate of 10% with a 40% reduction with 6-month group. This trial was also underpowered as it anticipated an event rate of 10% with a 40% reduction with prolonged clopidogrel. All of studies to date are limited by long-term benefit. In this study, 1443 patients were randomly assigned to 6 months or 12 months of dual antiplatelet therapy. The primary end point of target vessel failure (cardiac death, myocardial infarction, or ischemia-driven target vessel revascularization) was not different (4.8% for the 6-month group and 4.3% for the 12-month group), although stent thrombosis occurred more frequently in the 6-month group. This trial was also underpowered as it anticipated an event rate of 10% with a 40% reduction with prolonged clopidogrel. All of studies to date are limited by the small numbers of patients examined after 1 year and the low numbers of adverse events during follow-up. The largest registry experience is from the j-CYPHER registry, which reported the outcomes of 10 778 patients. Although stopping both aspirin and thienopyridine therapy after 6 months increased the risk of death or myocardial infarction, discontinuing thienopyridine alone was not associated with an increase risk of stent thrombosis.

Relationship of Events to Very Late Stent Thrombosis and Target Vessel Revascularization

Death and myocardial infarction after stenting are due to stent factors (thrombosis and/or restenosis) and progression of disease beyond the stented segment often due to plaque disruption. We would expect prolonged clopidogrel to have a similar effect on preventing occlusive thrombosis associated with plaque disruption in nonstented regions. Therefore, prolonged clopidogrel therapy should prevent death and myocardial infarction from this cause in patients regardless of stent type. In contrast, if late stent thrombosis is more likely after drug-eluting stents, clopidogrel should prevent death and myocardial infarction from this cause to a greater extent in patients receiving drug-eluting stents. For this reason, we hypothesized that prolonged clopidogrel use would more strongly relate to risk reduction among those with drug-eluting compared with bare metal stents. Our study supports this concept because the effect of prolonged clopidogrel on death or myocardial infarction was greater for drug-eluting than bare metal stents.

Late target revascularization has also been found to be increased in patients with drug-eluting stents. Recent studies have suggested that it may occur at a rate of approximately 2.6% per year without change over a 5-year period. A number of studies suggest that this is not only due to intimal hyperplasia but also to neoatherosclerosis that can progress to cause restenosis or can rupture and cause acute coronary syndromes, including myocardial infarction. Prolonged dual antiplatelet therapy may be useful in preventing these thrombotic events that in turn lead to a lower rate of myocardial infarction and death, as shown in our study. It is not known if the incidence is higher with drug-eluting stents than bare metal stents, but antitodal observations suggest that it is higher.

Our study differs from other studies by having a much larger number of adverse clinical events. This is likely a result of the much larger patient sample size and the greater frequency of comorbidities including prior coronary events, stroke, and atherosclerosis risk factors compared with other studies. Our results in a cohort receiving coronary stents are similar to the conclusions of the CHARISMA trial in a nonstented population with stable vascular disease, in which prolonged dual antiplatelet therapy lowered clinical events by 17% over 30 months without increasing major bleeding in subgroup of high-risk patients with prior myocardial infarction or stroke or symptomatic peripheral artery disease. This difference might even be greater in patients with acute coronary syndrome, because the CURE trials showed a 20% reduction in events over 1 year.

Safety of Prolonged Clopidogrel Therapy

We did not find an increase in major bleeding requiring hospitalization with prolonged clopidogrel therapy. This contrasts with prior studies and several meta-analyses in which prolonged clopidogrel was associated with an increase in major and minor bleeding of 1.4- to 1.8-fold greater than aspirin alone and the CHARISMA study, in which prolonged clopidogrel caused more minor bleeding. In many studies, the risk of bleeding is largely confined to the index procedure and hospitalization. This is supported by the randomized CHARISMA and CREDO trials, where overall, bleeding was significantly greater in the first 6 months but not after 1 to 2 years, although gastrointestinal bleeding was more common in the clopidogrel-treated patients in CREDO. It is possible that patients susceptible to bleeding may have stopped clopidogrel before 12 months due to an earlier bleeding episode. However, our study suggests that in those who are event-free at 12 months, major bleeding was not increased by prolonged clopidogrel.

Limitations

This is a registry study and therefore the results could be affected by unmeasured confounders. The use of clopidogrel was not randomly assigned and therefore we may not have captured factors that influence continued clopidogrel use for >12 months in our database. However, we did use 2 multivariable adjustments, including a propensity-adjusted method, and our results were robust in that adjusted models did not substantially change the hazard ratios. It is possible that physicians prescribed prolonged clopidogrel due unmeasured risk factors not captured in our database, but we would have expected these patients to have more events that would have biased the study toward no difference in outcome.
Likewise, in our landmark analysis, eliminating those patients not on clopidogrel at 12 months who had a major event in the first year should have biased the study toward a better outcome in these patients also reducing the differences between the two clopidogrel groups. Our study is also limited to data available in the VA database, and nonfatal events that occurred outside of VA facilities may not have been captured. Patients with acute myocardial infarction are often hospitalized at a non-VA facility. However, most of these patients are subsequently transferred to a VA facility after stabilization or are followed up in the VA system, allowing documentation of these adverse events. Since the results seen with myocardial infarction closely parallel the findings seen with mortality, and there is no reason to expect a bias based on clopidogrel use, our findings probably reflect the true relationship of prolonged clopidogrel treatment to combined end point of death and myocardial infarction. Because we used a landmark analysis that excluded patients with events in the first year, prolonged use would not have been due to an adverse event before 1 year. We also were unable to determine the occurrence of stent thrombosis because this was not recorded in the longitudinal medical record. Because the major complications of stent thrombosis are death and myocardial infarction, we expect that some of the improvement in long-term outcome was the result of a reduction in late stent thrombosis. We have limited information concerning the coronary anatomy and procedural factors because the computerized catheterization laboratory system (CART-CL) was only introduced in 2006 and was not uniformly adopted until 2009. We have detailed information on the use of all VA-prescribed medication including the number of pills dispensed but do not have data on prolonged aspirin use because the majority of patients in the VA system obtain this medication over the counter. Aspirin use is a VA quality measure, with quality assurance surveys showing very high rates of recorded aspirin use. In a national VA survey, compliance with aspirin use in the outpatient setting after myocardial infarction was 97%,17 and in another study, in hospital compliance with aspirin is high and patients were twice as likely to receive aspirin than similar Medicare patients admitted to non-VA hospitals.37

The drug-eluting stents used during this study were first-generation, and newer second- and third-generation drug-eluting stents have been shown to have better efficacy and lower rates of late stent thrombosis.38 It is possible that the results of this study would be different if these stents had been used.

Ultimately, the definitive answer on the value of prolonged clopidogrel treatment after coronary stenting will need to await the results of randomized clinical trials that are underway including the ISAR-SAFE,39 PRODIGY, CYPRESS, and the DAPT trial (www.clinicaltrials.gov). This later study (NCT00977938) will randomly assign 20,000 patients to 12 months or 30 months of dual antiplatelet therapy and will evaluate major cardiac events, stent thrombosis, and bleeding. Of interest is that when we performed an analysis of patients similar to those who qualify for random assignment in the DAPT trial (eg, exclusion of patients with any major event during the first 12 months), we found the same results as our primary analysis.

Conclusions
In conclusion, we found that in patients who are event-free 12 months after coronary stenting, prolonged clopidogrel use >12 months after stenting was associated with fewer deaths and myocardial infarctions, without differences in the risk of repeat revascularization, stroke, or major bleeding. The finding of long-term benefit in bare metal stents has not been shown previously. This relationship was significantly stronger in patients receiving drug-eluting compared with bare metal stents. Our findings support the use of prolonged clopidogrel therapy, particularly in patients receiving drug-eluting stents who are tolerating dual antiplatelet therapy and who have similar high rates of comorbidities and atherosclerotic risk factors until randomized, controlled trials can definitively test the value of prolonged clopidogrel therapy after coronary stenting.

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David P. Faxon, Elizabeth Lawler, Melissa Young, Michael Gaziano and Scott Kinlay

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Supplemental Table

Supplemental Table 1. Variables used in the propensity adjusted model

Age, mean (SD), years
Sex
Initial Presentation
    Acute MI
    ACS
    Stable angina or ischemic heart disease
Co-morbidities (5-years before and up to 1-year after index procedure)
    Smoking
    Prior myocardial infarction
    Angina
    Hypertension
    Diabetes mellitus
    COPD
    Acute kidney disease
    Chronic kidney disease
    Stroke
    Heart Failure
    Prior CABG
    Prior PCI
    History of alcoholism
    Peripheral artery disease
    GI bleeding
    Gastritis
    Anemia (Hbg<12 mg/dL)
Medication at one year
    Aspirin (pre procedure)
    Warfarin
Beta-blocking agent
Calcium channel blocking agent
Antiarrhythmic
ACE or ARB
Insulin
Oral anti-hypoglycemic agents
Alpha agonists
Year of stent placement