Antiplatelet Therapy and Clinical Outcomes Following Myocardial Infarction Among Patients in a U.S. Employer-Based Insurance Database

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ABSTRACT

BACKGROUND: Estimates of residual cardiovascular risks among patients who have experienced a recent acute myocardial infarction (MI) are predominantly derived from secondary prevention trial populations, patient registries, and population-based cohorts.

OBJECTIVE: To generate real-world evidence of antiplatelet treatment and recurrent events following MI in patients on antiplatelet treatment among commercial, employer-based insured patients in a large administrative database.

METHODS: This was a retrospective cohort claims database study using the Truven Health MarketScan Commercial Claims and Encounters and Medicare Supplemental databases between 2007-2011. Patients with an acute MI hospitalization with a discharge date between 2008 and 2010 were included. Excluded were those patients with documentation of stroke, transient ischemic attack (TIA), or severe bleeding at or before index hospitalization and with concomitant use of anticoagulant therapy following index hospitalization. Patients treated with clopidogrel following the index MI hospitalization were followed up to 1 year for repeat MI, stroke, and coronary revascularization.

RESULTS: Among 33,943 post-MI continuous clopidogrel users without history of stroke, TIA, or bleeding, 22% had diabetes, whereas angina and renal impairment were less prevalent (5% and 7%, respectively). Over the 1-year follow-up, 2.4% experienced a repeat MI or stroke, and 8.2% underwent coronary revascularization. Angina, diabetes, and renal impairment were associated with elevated 1-year risk of repeat MI or stroke.

CONCLUSIONS: This study suggests that there is residual cardiovascular risk, although relatively low, in an insured, secondary prevention population on antiplatelet treatment following an MI. In patients with MI, identifying angina, diabetes, and renal impairment may aid risk stratification and guide the effective management of these higher-risk patients.

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What this study adds

- Myocardial infarction (MI) patients with angina, diabetes, or renal impairment are at higher risk of recurrent events and may benefit from more aggressive management.
- Among insured, post-MI clopidogrel users, 2.4% experienced a repeat MI or stroke, and 8.2% underwent coronary revascularization within 1 year.

Cardiovascular disease is the leading cause of death globally.¹ Myocardial infarction (MI) accounts for nearly half of all cardiovascular-related deaths.² Patients who survive MI place substantial clinical and economic burden on health care systems and societies.³⁻⁵ In such patients, platelet inhibitors, such as aspirin and thienopyridines initiated in the hospital setting, reduces the rate of recurrent infarctions and thrombotic events.⁶⁻⁸

To reduce recurrent ischemic events, guidelines recommend that acute coronary syndrome patients (ST-elevation myocardial infarction [STEMI] or non-ST-segment elevation myocardial infarction [NSTEMI]) receive dual antiplatelet therapy consisting of aspirin with a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) for 12 months following hospitalization or percutaneous coronary intervention (PCI), such as drug eluting or bare metal stent implantation.^{9,10} However, despite these robust treatment guidelines and the availability of pharmacological therapies, recurrence of cardiovascular events still occurs in a proportion of post-MI patients. A large-scale Swedish study showed that 18% of patients with MI experienced a recurrent MI, stroke, or cardiovascular death in the first year after the index event,¹¹ and 1-year case-fatality rates for STEMI and NSTEMI in the Worcester Heart Attack Study were reported to be around 12% and 25%, respectively.¹² Short- and long-term mortality rates remain elevated following an acute MI.^{11,13}

Antiplatelet therapy options in patients with stable atherosclerosis are well established. Aspirin is the primary component of antiplatelet therapy at present,^{14,15} since aspirin is effective in the prevention of cardiovascular events.¹⁶⁻¹⁸ Long-term aspirin therapy reduces the annual harm of serious vascular

What is already known about this subject

- Antiplatelet therapy options in patients with stable atherosclerosis are well established.
- More potent, long-term therapies have the potential to further reduce risks of recurrent thrombotic events in secondary prevention patients.

disease by approximately 25%.¹⁹ In addition to aspirin, clopidogrel is also recommended as part of the standard of care in secondary prevention in post-acute MI patients.^{14,15} However, more potent, long-term therapies have the potential to further reduce risks of recurrent thrombotic events in secondary prevention patients.

There are limited real-world data describing patient attributes, antithrombotic treatment, and residual cardiovascular risks among patients who have experienced a recent acute MI. To better understand why patients continue to have elevated cardiovascular risk, estimates of the burden of recurrent events and unmet need for novel therapies are necessary. To address these data gaps, this study generated real-world evidence of clinical and demographic characteristics associated with increased cardiovascular risk in acute MI patients treated with clopidogrel in a large, employer-based insurance claims database.

Methods

Design and Population

This retrospective claims database study was conducted using the Truven Health Analytics MarketScan Research Databases (2007-2011) with U.S. commercial and Medicare supplemental claims for over 180 million unique patients since 1995. Patients with a hospitalization for acute MI (inpatient medical claim with primary diagnosis using *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 410.xx) with a discharge date of the first observed claim (index date) between 2008 and 2010 were identified and included in the study if they were aged at least 18 years at index date and continuously enrolled for at least 12 months before (baseline period). Continuous enrollment was defined as no observed enrollment gap greater than 45 days. Age, gender, and insurance type were defined at index date.

We excluded those with documentation of stroke, transient ischemic attack (TIA), or severe bleeding (defined by a diagnosis code list compiled with expert clinical input) in the baseline period or on index date and those with concomitant use of anticoagulant therapy following the index date (i.e., a pharmacy claim within 7 days following discharge post-MI).²⁰ For this study, these patients were excluded because they have been shown to have a higher risk of bleeding events, which can complicate studies of cardiovascular outcomes, and warrant a separate analysis.²¹ Patients treated with clopidogrel were selected to represent those receiving recommended care for secondary prevention.^{15,22} Since MarketScan data only capture prescription medication use in outpatient pharmacy claims, clopidogrel users, for this study, were identified by a pharmacy claim (prescription fill) within 7 days following hospital discharge after the index MI. Based on expert clinical input, we expected that most patients were discharged with some

supply of clopidogrel, so it was assumed that patients underwent treatment between discharge and first fill date. Patients were followed from discharge up to 1 year for repeat MI, stroke, and coronary revascularization.

Definitions and Variables

Clopidogrel adherence was defined by proportion days covered (PDC), that is, number of days of supply divided by number of days of follow-up, beginning at discharge date for this study. In an analysis of the post-MI continuous clopidogrel users, follow-up time was censored at the date of clopidogrel discontinuation, defined as the date on which no new fill or a gap between fills resulted in $PDC < 80\%$. Continuous clopidogrel users through 12 months were chosen to represent patients undergoing optimal pharmacological therapy. In another analysis, follow-up was continued regardless of clopidogrel discontinuation, and PDC was calculated over the course of follow-up and used to define adherence ($PDC \geq 80\%$). In all analyses, follow-up time was censored at the end of the 12-month follow-up or end of continuous enrollment, whichever occurred first.

Baseline comorbid conditions (angina, ischemic heart disease [excluding anginal], diabetes, liver disease, hyperlipidemia, hypertension, and renal impairment); coronary revascularization; and medication history (lipid-lowering therapy, antiplatelet therapy, antihypertensive therapy, and anticoagulant therapy) were defined using ICD-9-CM and Current Procedural Terminology, 4th edition (CPT-4) codes from inpatient and outpatient medical claims and pharmacy claims occurring in the 12 months before the index MI hospitalization. MI and stroke outcomes were identified by inpatient primary diagnosis during follow-up. Coronary revascularization was identified by ICD-9-CM and CPT-4 procedure codes for PCI and coronary artery bypass graft (CABG). Repeat MI and stroke were the primary outcomes and were also studied as a primary composite endpoint during the follow-up. Coronary revascularization was a secondary endpoint, and repeat MI, stroke, and coronary revascularization were included as a secondary composite endpoint.

Statistical Analysis

Baseline characteristics were compared between patient groups using descriptive statistics: t-tests (for continuous variables) and chi-square tests (for categorical variables). Unadjusted incidence rates (and 95% confidence intervals) were estimated with Poisson regression allowing for an offset for differential follow-up time. Cox proportional hazards regression was used to model time to event adjusting for patient characteristics (age, gender, comorbidities, and baseline clopidogrel use) among continuous clopidogrel users following MI. We also fit models in patients followed regardless of clopidogrel discontinuation and adjusted for the same set of patient characteristics

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FIGURE 1 Accrual of Study Patients

MI = myocardial infarction; TIA = transient ischemic attack.

TABLE 1 Demographic and Clinical Characteristics of MI Patients Treated with Clopidogrel

Baseline Characteristics ^a	Clopidogrel Users (N=33,946, %)	
Age, mean [SD]	61.28	[12.45]
Age groups		
18 to 24	18	(0.05)
25 to 34	240	(0.71)
35 to 44	2,072	(6.10)
45 to 54	7,927	(23.35)
55 to 64	13,512	(39.80)
65 to 74	4,405	(12.98)
75+	5,772	(17.00)
Female	9,742	(28.70)
Insurance type		
HMO	4,997	(14.72)
PPO/EPO	18,771	(55.30)
POS/POS with capitation	2,519	(7.42)
Comprehensive	5,987	(17.64)
Other	985	(2.90)
Unknown	687	(2.02)
Comorbid conditions		
Angina	1,586	(4.67)
IHD (excluding angina)	11,161	(32.88)
Diabetes	7,494	(22.08)
Liver disease	638	(1.88)
Hyperlipidemia	12,185	(35.90)
Hypertension	15,821	(46.61)
Renal impairment	2,368	(6.98)
Coronary revascularization ^b	6,053	(17.83)
Medication history		
Lipid-lowering therapy	13,671	(40.27)
Antiplatelet therapy	1,951	(5.75)
Clopidogrel	1,666	(4.91)
Antihypertensive therapy	19,100	(56.27)
Anticoagulant therapy	1,055	(3.11)

Note: All values given as n (%) unless otherwise noted.

^aDefined at or 12 months before index date.

^bPCI or CABG procedures.

CABG = coronary artery bypass graft; EPO = exclusive provider organization; HMO = health maintenance organization; IHD = ischemic heart disease; PCI = percutaneous coronary intervention; POS = point of service; PPO = preferred provider organization; SD = standard deviation.

including adherence (PDC ≥ 80% vs. < 80%). Since not all patients would have filled a clopidogrel pharmacy claim within the first week, we evaluated the sensitivity of results to the clopidogrel treatment definition window by also examining pharmacy claims within 14 and 28 days following discharge.

Results

There were 123,377 patients with an acute MI-related hospitalization in the MarketScan databases during the index period. After excluding those patients with history of stroke, TIA, or severe bleeding during the baseline period and excluding patients for concomitant use of anticoagulant therapy, 82,287 patients remained. Of those, 33,946 (41%) patients were identified as post-MI clopidogrel users and included in the analysis of the recommended care population (Figure 1).

At index date, the mean age (standard deviation) of the group of post-MI continuous clopidogrel users was 61.3 (12.5) years, and the majority were male (71.3%; Table 1). More than half (56.3%) were taking antihypertensive therapy, and 40.3% were taking lipid-lowering therapy. Only 4.9% were previously taking clopidogrel, and use of anticoagulant therapy was also relatively low at 3.1%. Just under half (46.6%) of the patients were diagnosed as hypertensive at baseline, while about a third of the patients entered the study with hyperlipidemia (35.9%) or ischemic heart disease (32.9%). In addition, 17.8% of

post-MI continuous clopidogrel users had a history of coronary revascularizations at baseline.

Figure 2 summarizes the frequency of outcomes over the 1-year follow-up period in the group of post-MI continuous clopidogrel users. The unadjusted incidence of repeat MI was 36 per 1,000 person-years (1-year risk of 2.0%). About one third of these events occurred within 7 days after the index MI. The incidence of the primary composite outcome of MI or stroke was 42 per 1,000 person-years (1-year risk of 2.4%). Coronary revascularization (PCI or CABG procedures) was the

FIGURE 2 Frequency of Outcomes over 1-Year Follow-up Among Post-MI Continuous Clopidogrel Users (N=33,943)

Note: Bars represent 95% confidence intervals.

^aEarliest occurrence of MI or stroke.

^bEarliest occurrence of MI, stroke, or coronary revascularization.

MI=myocardial infarction.

most common outcome with an incidence rate of 152 per 1,000 person-years (1-year risk of 8.2%). Only 14% of these procedures occurred within 7 days after the index MI, while over 60% occurred more than 28 days after the index MI.

Table 2 summarizes the associations of outcomes and patient characteristics among post-MI continuous clopidogrel users. A history of angina, diabetes, and renal impairment were significantly associated with repeat MI and the primary composite endpoint of repeat MI or stroke. Also, baseline clopidogrel therapy (any prescription filled in the 12 months before the index date) was associated with repeat MI and the primary composite endpoint. Liver disease was associated with a greater risk of coronary revascularization (hazard ratio [HR]=1.36), and the younger age groups were associated with greater likelihood of coronary revascularization relative to the oldest age group, 75+ years (HRs ranged from 1.34 to 2.31).

The results of the sensitivity analysis showed that estimates were similar when compared with longer windows to identify post-MI clopidogrel treatment (i.e., patients with prescriptions filled within 14 days or 28 days of index date; data not shown).

When patients were followed regardless of clopidogrel discontinuation (extended follow-up analysis) with models adjusted for clopidogrel adherence over follow-up, similar associations with comorbid conditions were observed (Table 3). Clopidogrel use in the baseline period was associated with greater risk of adverse clinical outcomes, and while clopidogrel

adherence (PDC $\geq$ 80%) did not appear associated with repeat MI, it was significantly associated with coronary revascularization.

Discussion

The results of this study showed that among 33,943 post-MI continuous clopidogrel users with no history of stroke or TIA, a considerable number of patients remained at risk for recurrent cardiovascular events. Although the rate of the primary composite outcome (repeat MI or stroke) was relatively low, it is important considering that our population was continuously treated with recommended antiplatelet therapy and insured by employer-sponsored plans. Furthermore, these rates may be underestimated because of the healthy worker effect. Comorbid angina, diabetes, and renal impairment were associated with elevated 1-year risk of the primary composite endpoint of repeat MI or stroke. In this study population, a substantial proportion of patients had diabetes (22%), whereas angina and renal impairment were less prevalent (5% and 7%, respectively). Relative to other study outcomes, a large number of coronary revascularizations were observed during follow-up. This outcome included urgent and elective revascularizations, which are not discernible with medical claims, so it represents adverse events in addition to scheduled procedures. In addition to angina and diabetes, liver disease was associated with greater risk of coronary revascularization, although to our knowledge no previous studies have demonstrated this link.

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TABLE 2 Adjusted Associations of Outcomes and Patient Characteristics Among Post-MI Continuous Clopidogrel Users (N=33,943)^a

Independent Variables	Repeat MI HR (95% CI)	Stroke HR (95% CI)	Primary Composite ^b HR (95% CI)	Coronary Revascularization HR (95% CI)	Secondary Composite ^c HR (95% CI)
Age group, years					
<45	0.82 (0.56-1.19)	0.32 (0.11-0.91)	0.69 (0.48-0.99)	2.16 (1.79-2.61)	1.69 (1.42-2.01)
45-54	0.88 (0.69-1.13)	0.23 (0.12-0.46)	0.74 (0.59-0.92)	2.24 (1.94-2.59)	1.75 (1.53-1.99)
55-64	1.02 (0.83-1.26)	0.58 (0.37-0.90)	0.93 (0.76-1.12)	2.31 (2.02-2.65)	1.82 (1.61-2.05)
65-74	0.81 (0.63-1.06)	0.62 (0.36-1.05)	0.77 (0.61-0.97)	1.34 (1.14-1.58)	1.12 (0.96-1.30)
75+ (reference)	1	1	1	1	1
Female	1.04 (0.88-1.23)	1.45 (1.00-2.10)	1.09 (0.94-1.27)	0.96 (0.88-1.04)	0.99 (0.91-1.07)
Comorbid conditions^d					
Angina	1.45 (1.08-1.94)	0.78 (0.31-1.93)	1.36 (1.03-1.79)	1.28 (1.08-1.51)	1.30 (1.11-1.52)
IHD excluding angina	1.11 (0.94-1.31)	1.05 (0.72-1.55)	1.10 (0.94-1.28)	1.00 (0.92-1.09)	1.02 (0.94-1.10)
Diabetes	1.45 (1.22-1.72)	1.34 (0.89-2.00)	1.43 (1.22-1.67)	1.24 (1.13-1.35)	1.27 (1.16-1.38)
Liver disease	1.15 (0.70-1.90)	0.44 (0.06-3.19)	1.06 (0.66-1.72)	1.36 (1.08-1.73)	1.27 (1.01-1.61)
Hyperlipidemia	0.93 (0.79-1.10)	1.16 (0.80-1.69)	0.97 (0.84-1.13)	1.00 (0.93-1.09)	1.01 (0.93-1.09)
Hypertension	1.07 (0.91-1.26)	0.95 (0.66-1.38)	1.05 (0.91-1.22)	1.08 (1.00-1.17)	1.09 (1.01-1.17)
Renal impairment	1.47 (1.15-1.89)	1.24 (0.67-2.29)	1.39 (1.10-1.76)	1.02 (0.87-1.19)	1.08 (0.94-1.25)
Clopidogrel use^d	1.61 (1.21-2.15)	0.87 (0.35-2.17)	1.49 (1.13-1.96)	1.05 (0.87-1.26)	1.05 (0.88-1.25)

^aCensored at clopidogrel discontinuation, end of continuous enrollment, or end of 1-year follow-up.

^bEarliest occurrence of MI or stroke.

^cEarliest occurrence of MI, stroke, or coronary revascularization.

^dDefined in baseline period.

CI=confidence interval; HR=hazard ratio; IHD=ischemic heart disease; MI=myocardial infarction.

The current result showed that clopidogrel use in the baseline period was associated with greater risk of repeat MI and the primary composite endpoint of repeat MI and stroke. We posit that this estimate more likely represents the risk conferred by comorbid cardiovascular disease before the index MI rather than the effect of treatment. In this study, previous use of clopidogrel could be a proxy for indicated disease, disease severity, and perceived risk.

Since it was expected that most patients would be discharged with a supply of clopidogrel, a 7-day window was used to identify prescription fills and then was expanded to 14 and 28 days in a sensitivity analysis. Extending the window did not change the main results or findings, which increased our confidence in the robustness of our findings. That is, among post-MI patients without history of stroke or TIA who filled a prescription for clopidogrel within 14 or 28 days of index MI, clinical history of angina, diabetes, and renal impairment were still associated with an elevated 1-year risk of repeat MI or stroke.

Limitations

Several limitations of the data are worth noting. As with all administrative claims databases, clinical comorbidities and outcomes were defined with the presence of diagnosis and procedure codes on claims, so some degree of misclassification

is expected. Because of the small number of events, imprecise estimates for the stroke outcome should be interpreted with caution. Event rates of MI and stroke, however, were comparable to those seen in randomized clinical trials.^{23,24}

The MarketScan database includes information on commercially insured individuals collected from mostly larger employers, so our results may not be generalizable to other populations. Because the MarketScan database includes outpatient pharmacy claims for prescription drugs, over-the-counter medications, such as aspirin and medications provided in the inpatient setting, are not captured. Death data, including date and cause, are not provided in this claims database. Although not used in this study, there are published algorithms to estimate death in a claims-based population.²⁵ While longer follow-up (approximately 3 years) is typically observed in randomized controlled trials, a substantial proportion of patients were not captured in the MarketScan database for this length of time. Furthermore, loss to follow-up could be due to leaving the health plan or dying, which was not discernible in the database. Nonetheless, these results further support the premise that underlying cardiovascular disease plays a role in post-acute MI mortality risk, and more aggressive management may be needed to enhance long-term survival in these patients.

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TABLE 3 Adjusted Associations of Outcomes and Patient Characteristics Among Post-MI Clopidogrel Users Followed Regardless of Discontinuation (Extended Follow-up; N = 33,943)^a

Independent Variables	Repeat MI HR (95% CI)	Stroke HR (95% CI)	Primary Composite ^b HR (95% CI)	Coronary Revascularization HR (95% CI)	Secondary Composite ^c HR (95% CI)
Age group, years					
<45	0.73 (0.53-0.99)	0.34 (0.16-0.71)	0.62 (0.46-0.83)	1.98 (1.69-2.33)	1.45 (1.25-1.69)
45-54	0.73 (0.60-0.89)	0.28 (0.17-0.45)	0.62 (0.52-0.75)	2.02 (1.79-2.28)	1.48 (1.33-1.65)
55-64	0.76 (0.64-0.91)	0.53 (0.38-0.73)	0.70 (0.60-0.82)	1.98 (1.76-2.22)	1.47 (1.33-1.63)
65-74	0.67 (0.54-0.84)	0.67 (0.46-0.98)	0.67 (0.56-0.82)	1.25 (1.09-1.44)	1.00 (0.88-1.13)
75+ (reference)	1	1	1	1	1
Female	1.10 (0.95-1.26)	1.39 (1.06-1.83)	1.14 (1.01-1.30)	0.99 (0.92-1.07)	1.03 (0.96-1.11)
Comorbid conditions^d					
Angina	1.35 (1.05-1.72)	0.84 (0.45-1.56)	1.27 (1.01-1.60)	1.30 (1.13-1.50)	1.32 (1.16-1.51)
IHD excluding angina	1.32 (1.15-1.52)	1.00 (0.75-1.34)	1.24 (1.09-1.41)	1.08 (1.00-1.16)	1.08 (1.01-1.16)
Diabetes	1.52 (1.31-1.75)	1.42 (1.06-1.91)	1.50 (1.32-1.71)	1.29 (1.19-1.39)	1.32 (1.23-1.42)
Liver disease	0.89 (0.55-1.45)	0.93 (0.35-2.52)	0.92 (0.59-1.41)	1.36 (1.11-1.68)	1.27 (1.04-1.55)
Hyperlipidemia	0.92 (0.79-1.06)	1.00 (0.75-1.33)	0.93 (0.82-1.05)	0.95 (0.88-1.02)	0.95 (0.88-1.01)
Hypertension	1.14 (1.00-1.32)	1.18 (0.89-1.56)	1.15 (1.02-1.31)	1.12 (1.04-1.20)	1.13 (1.06-1.21)
Renal impairment	1.37 (1.11-1.69)	1.25 (0.81-1.92)	1.28 (1.06-1.56)	1.10 (0.97-1.25)	1.16 (1.03-1.30)
Clopidogrel use^d	1.91 (1.53-2.37)	1.48 (0.90-2.45)	1.83 (1.50-2.24)	1.39 (1.21-1.59)	1.39 (1.22-1.58)
Clopidogrel adherence (PDC ≥ 80%)	0.91 (0.79-1.04)	1.23 (0.91-1.65)	0.95 (0.84-1.08)	1.53 (1.42-1.66)	1.45 (1.35-1.57)

^aCensored at end of continuous enrollment or end of 1-year follow-up.

^bEarliest occurrence of MI or stroke.

^cEarliest occurrence of MI, stroke, or coronary revascularization.

^dDefined in baseline period.

CI = confidence interval; HR = hazard ratio; IHD = ischemic heart disease; MI = myocardial infarction; PDC = proportion of days covered.

While our study focused on clinical outcomes in continuous users of clopidogrel at low risk of severe bleeding, future studies with more recent data on newer antiplatelet agents and other recommended therapies such as statins and beta blockers and that weight benefits and risks would be a valuable contribution to literature on this topic.

Conclusions

This study suggests that there is residual cardiovascular risk, although relatively low, in an insured, secondary prevention population treated with antiplatelet therapy following an acute MI. Furthermore, post-MI patients with angina, diabetes, or renal impairment are at increased risk of repeat events and may benefit from more aggressive management strategies.

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DISCLOSURES

Funding for this research was provided by Merck & Co. Although Merck & Co. formally reviewed a penultimate draft, the opinions expressed are those of the authorship and may not necessarily reflect those of the company. Reed Chase, Wu, Mavros, Heithoff, and Hanson are employees of Merck Sharp & Dohme, a subsidiary of Merck & Co., and may own stock and/or hold stock options in the company. Patel was an employee of Merck & Co. during the conduct of this study and preparation of the manuscript. Simpson is a paid consultant for Merck, Pfizer, and Amgen and has received speaker's fees from Merck and Pfizer.

Study concept and design were contributed by all authors except Hanson. Heithoff and Patel collected the data, and data interpretation was performed by Simpson, Mavros, Patel, Wu, and Hanson. The manuscript was written by Hanson, Mavros, and Patel and revised by Heithoff, Wu, Simpson, and Reed Chase.

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