

ORIGINAL INVESTIGATIONS

P2Y₁₂ Inhibitor or Aspirin Monotherapy for Secondary Prevention of Coronary Events



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ABSTRACT

BACKGROUND Aspirin is the only antiplatelet agent with a Class I recommendation for long-term prevention of cardiovascular events in patients with coronary artery disease (CAD). There is inconsistent evidence on how it compares with alternative antiplatelet agents.

OBJECTIVES This study compared P2Y₁₂ inhibitor monotherapy vs aspirin in patients with CAD.

METHODS We conducted a patient-level meta-analysis of randomized trials comparing P2Y₁₂ inhibitor monotherapy vs aspirin monotherapy for the prevention of cardiovascular events in patients with established CAD. The primary outcome was the composite of cardiovascular death, myocardial infarction, and stroke. Prespecified key secondary outcomes were major bleeding and net adverse clinical events (the composite of the primary outcome and major bleeding). Data were pooled in a 1-step meta-analysis.

RESULTS Patient-level data were obtained from 7 trials. Overall, 24,325 participants were available for analysis, including 12,178 patients assigned to receive P2Y₁₂ inhibitor monotherapy (clopidogrel in 7,545 [62.0%], ticagrelor in 4,633 [38.0%]) and 12,147 assigned to receive aspirin. Risk of the primary outcome was lower with P2Y₁₂ inhibitor monotherapy compared with aspirin over 2 years (HR: 0.88; 95% CI: 0.79-0.97; *P* = 0.012), mainly owing to less myocardial infarction (HR: 0.77; 95% CI: 0.66-0.90; *P* < 0.001). Major bleeding was similar (HR: 0.87; 95% CI: 0.70-1.09; *P* = 0.23) and net adverse clinical events were lower (HR: 0.89; 95% CI: 0.81-0.98; *P* = 0.020) with P2Y₁₂ inhibitors. The treatment effect was consistent across prespecified subgroups and types of P2Y₁₂ inhibitors.

CONCLUSIONS Given its superior efficacy and similar overall safety, P2Y₁₂ inhibitor monotherapy might be preferred over aspirin monotherapy for long-term secondary prevention in patients with established CAD. (P2Y₁₂ Inhibitor or Aspirin Monotherapy as Secondary Prevention in Patients With Coronary Artery Disease: An Individual Patient Data Meta-Analysis of Randomized Trials [PANTHER collaborative initiative]; [CRD42021290774](https://doi.org/10.1016/j.jacc.2023.04.051)) (J Am Coll Cardiol 2023;82:89-105)
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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

DAPT = dual antiplatelet therapy

NACE = net adverse clinical events

PAD = peripheral artery disease

PCI = percutaneous coronary intervention

Long-term antiplatelet therapy is a cornerstone of secondary prevention in patients with established atherosclerosis.¹ The evidence for aspirin stems from historical trials, which were collectively summarized by the Antithrombotic Trialists' Collaboration,^{2,3} building the foundation for the use of low-dose aspirin therapy in patients with coronary artery disease (CAD).^{4–6}

The addition of an oral P2Y₁₂ receptor inhibitor to aspirin, referred to as dual antiplatelet therapy (DAPT), subsequently became the new standard of care for patients with acute coronary syndrome or those undergoing percutaneous coronary intervention (PCI) due to superior ischemic protection compared with aspirin alone, albeit with a higher risk of major bleeding events.⁷ While the recognition of the trade-offs between the benefits and risks of DAPT fuels the discussion on optimal DAPT duration, lifelong aspirin remains the standard of care after an initial course of DAPT in patients with CAD.^{4–9}

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CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) was the first large randomized controlled trial showing a significant, yet modest, reduction of cardiovascular events with clopidogrel monotherapy compared with aspirin in a heterogeneous patient cohort with coronary, cerebrovascular, and/or peripheral atherosclerosis.¹⁰ At subgroup analyses, the estimated relative risk reductions were 7.3% for patients with ischemic stroke,

–3.7% for patients with myocardial infarction, and a nominally significant 23.8% for patients with peripheral artery disease (PAD), with positive interaction testing.¹⁰ These findings supported, in the 2017 European Society of Cardiology guidelines¹¹ and the 2022 Canadian Cardiovascular Society guidelines for the management of PAD,¹² the preferential use of clopidogrel over aspirin in patients with PAD. Subsequent studies comparing P2Y₁₂ inhibitor monotherapy with clopidogrel or ticagrelor vs aspirin monotherapy yielded inconsistent results,^{13–19} possibly reflecting the heterogeneous patient populations, and no prior meta-analysis focused on patients with CAD.

To address this uncertainty, we conducted an individual patient-level meta-analysis of randomized controlled trials evaluating the effect of P2Y₁₂ inhibitor monotherapy vs aspirin monotherapy on adjudicated ischemic and bleeding outcomes in patients with established CAD.

METHODS

STUDY DESIGN. We performed a systematic review and individual participant data meta-analysis of randomized controlled trials that compared monotherapy with currently recommended oral P2Y₁₂ inhibitors (clopidogrel, prasugrel, or ticagrelor) vs aspirin monotherapy for the secondary prevention of adjudicated adverse events exclusively in patients with established CAD. Because ticlopidine is no longer recommended given its worse safety profile compared with clopidogrel, studies involving the use

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TABLE 1 Main Characteristics of Trials and Patient Populations Included in the PANTHER Meta-Analysis

	Year of Publication	Definition of CAD	Overall Population	P2Y ₁₂ Inhibitor Group	Aspirin Group	P2Y ₁₂ Inhibitor	P2Y ₁₂ Inhibitor Dose	Aspirin Dose	Initial DAPT Phase	Follow-Up (mo)
ASCET	2012	Stable CAD documented by coronary angiography (with or without PCI)	1,001	499	502	Clopidogrel	75 mg once daily	160 mg once daily	When clinically indicated (ie, PCI)	24
CADET	2004	Recent myocardial infarction (within 3-7 d)	184	94	90	Clopidogrel	75 mg once daily	75 mg once daily	No	6
CAPRIE ^a	1996	Previous myocardial infarction (at any time)	8,446	4,242	4,204	Clopidogrel	75 mg once daily	325 mg once daily	No	36
DACAB	2018	Post-CABG patients (within 24 h after surgery)	322	166	166	Ticagrelor	90 mg twice daily	100 mg once daily	No	12
GLASSY ^b	2019	Post-PCI patients (12 mo after index PCI)	7,065	3,536	3,529	Ticagrelor	90 mg twice daily	75-100 mg once daily	Yes	12
HOST-EXAM	2021	Post-PCI patients (6-18 mo after PCI)	5,438	2,710	2,728	Clopidogrel	75 mg once daily	100 mg once daily	Yes	24
TICAB	2019	Post-CABG patients (within 24 h after surgery)	1,859	931	928	Ticagrelor	90 mg twice daily	100 mg once daily	No	12

^aFor CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events), all patients with a history of myocardial infarction contributed to the meta-analysis. ^bFor GLASSY (GLOBAL LEADERS Adjudication Sub-Study), alive patients at 1 year after randomization who did not experience myocardial infarction, stroke, or Bleeding Academic Research Consortium type 3 or type 5 bleeding and who were not lost to follow-up during the first year after enrollment were included.

ASCET = Aspirin Non-responsiveness and Clopidogrel Clinical Endpoint Trial; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CADET = Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; DACAB = Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; DAPT = dual antiplatelet therapy; HOST-EXAM = Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Extended Antiplatelet Monotherapy; PANTHER = P2Y₁₂ Inhibitor or Aspirin Monotherapy; PCI = percutaneous coronary intervention; TICAB = Ticagrelor in Coronary Artery Bypass.

of the former drug were excluded. Studies with >2 groups, for which a subset of comparisons fulfilled the inclusion criteria, were deemed eligible for the analysis after excluding the study arms that did not meet the inclusion criteria. Trials with an initial DAPT phase after randomization were considered eligible, but their contribution was limited to the protocol-specified comparison of P2Y₁₂ inhibitor monotherapy vs aspirin monotherapy after excluding patients who prematurely terminated the trials or experienced death, myocardial infarction, stroke, or major bleeding during the initial DAPT phase. We excluded studies that included patients with an indication for chronic oral anticoagulation or that assessed antithrombotic agents different from contemporary P2Y₁₂ inhibitors or aspirin. No further restriction was applied for study selection.

Data analysis and reporting followed the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (Supplemental Table 1).²⁰ The protocol was prospectively registered on PROSPERO (CRD42021290774).

SEARCH STRATEGY. Two investigators (D.C. and M.C.) independently assessed trial eligibility criteria, and a third investigator (M.V.) was consulted in case of disagreement. Randomized trials, reported up to June 26, 2021, were identified by systematic searches of Ovid Medline, Embase, and 3 websites (tctMD,

European Society of Cardiology, American College of Cardiology CardioSource Plus) without language restrictions. Reference lists of collected articles were hand-searched for additional studies. The search strategy is described in the Supplemental Methods.

DATA EXTRACTION AND QUALITY ASSESSMENT. We contacted the principal investigators of eligible trials, requesting patient-level data in anonymized electronic data sets (Table 1). Data were checked for completeness and consistency and compared with the original publications. The principal investigators of included trials were contacted in case of missing information or if queries arose at integrity checks. Once queries had been resolved, the clean data were analyzed. Two investigators (F.G. and M.C.) independently assessed the risk of bias by using the revised version of the Cochrane risk-of-bias tool (ie, Rob 2).²¹ Disagreements were solved by discussion and, if unresolved, by consulting the senior author (M.V.).

Each trial had been approved by local medical ethics committees. All patients had provided written informed consent for inclusion in each trial.

STUDY ENDPOINTS. The prespecified primary efficacy outcome was the composite of cardiovascular death, myocardial infarction, and stroke throughout the duration of the randomized comparison between protocol-mandated P2Y₁₂ inhibitor monotherapy vs

TABLE 2 Baseline Characteristics

	N	Primary Study Population (N = 24,325)	P2Y ₁₂ Inhibitor (n = 12,178)	Aspirin (n = 12,147)
Study identifier	24,325			
ASCET		1,001 (4.1)	499 (4.1)	502 (4.1)
CADET		184 (0.8)	94 (0.8)	90 (0.7)
CAPRIE		8,446 (34.7)	4,242 (34.8)	4,204 (34.6)
DACAB		332 (1.4)	166 (1.4)	166 (1.4)
GLASSY		7,065 (29.0)	3,536 (29.0)	3,529 (29.1)
HOST-EXAM		5,438 (22.4)	2,710 (22.3)	2,728 (22.5)
TICAB		1,859 (7.6)	931 (7.6)	928 (7.6)
Age, y	15,879	64.3 ± 10.2	64.3 ± 10.2	64.3 ± 10.3
Sex	24,325			
Female		5,288 (21.7)	2,640 (21.7)	2,648 (21.8)
Male		19,037 (78.3)	9,538 (78.3)	9,499 (78.2)
Age and sex categories ^a	24,325			
Female patients aged ≤67 y		2,562 (10.5)	1,292 (10.6)	1,270 (10.5)
Female patients aged >67 y		2,726 (11.2)	1,348 (11.1)	1,378 (11.3)
Male patients aged ≤62 y		9,752 (40.1)	4,866 (40.0)	4,886 (40.2)
Male patients aged >62 y		9,285 (38.2)	4,672 (38.4)	4,613 (38.0)
Body mass index, kg/m ²	15,330	26.9 ± 4.4	26.9 ± 4.4	26.9 ± 4.3
Body mass index categories	23,768			
<25 kg/m ²		8,268 (34.8)	4,127 (34.7)	4,141 (34.9)
≥25 kg/m ² to <30 kg/m ²		10,731 (45.1)	5,383 (45.2)	5,348 (45.1)
≥30 kg/m ²		4,769 (20.1)	2,391 (20.1)	2,378 (20.0)
Geographical region	24,325			
Asia		5,770 (23.7)	2,876 (23.6)	2,894 (23.8)
Europe		13,974 (57.4)	6,997 (57.5)	6,977 (57.4)
North America		4,581 (18.8)	2,305 (18.9)	2,276 (18.7)
Diabetes mellitus	24,132	6,040 (25.0)	3,036 (25.1)	3,004 (24.9)
Insulin-treated diabetes	15,325	832 (5.4)	404 (5.3)	428 (5.6)
Current cigarette smoker	24,314	6,411 (26.4)	3,161 (26.0)	3,250 (26.8)
Hypercholesterolemia	22,868	13,749 (60.1)	6,862 (59.9)	6,887 (60.3)
Hypertension	24,299	14,674 (60.4)	7,388 (60.7)	7,286 (60.0)
Liver disease	15,363	102 (0.7)	53 (0.7)	49 (0.6)
Peripheral artery disease	24,098	2,203 (9.1)	1,085 (9.0)	1,118 (9.3)
Previous myocardial infarction	24,285	13,637 (56.2)	6,839 (56.2)	6,798 (56.1)
Previous revascularization	24,135			
PCI		13,241 (54.9)	6,634 (54.9)	6,607 (54.8)
CABG		2,547 (10.6)	1,260 (10.4)	1,287 (10.7)
PCI and CABG		1,053 (4.4)	501 (4.1)	552 (4.6)
No revascularization		7,294 (30.2)	3,687 (30.5)	3,607 (29.9)
Previous stroke	24,133	1,598 (6.6)	807 (6.7)	791 (6.6)
Previous bleeding	15,684	64 (0.4)	32 (0.4)	32 (0.4)
History of chronic kidney disease	15,678	1,719 (11.0)	870 (11.1)	849 (10.8)
Chronic lung disease	15,661	660 (4.2)	335 (4.3)	325 (4.1)
Clinical presentation	24,325			
Acute coronary syndrome		14,746 (60.6)	7,394 (60.7)	7,352 (60.5)
Chronic coronary syndrome		9,579 (39.4)	4,784 (39.3)	4,795 (39.5)
Type of P2Y ₁₂ inhibitor	24,325			
Clopidogrel		7,545 (31.0)	7,545 (62.0)	-
Ticagrelor		4,633 (19.0)	4,633 (38.0)	-

Continued on the next page

aspirin monotherapy. Prespecified key secondary outcomes were major bleeding and net adverse clinical events (NACE), defined as the composite of the primary outcome and major bleeding. Major bleeding

was defined as Bleeding Academic Research Consortium type 3 or 5 where available,¹⁶⁻¹⁸ or Thrombolysis In Myocardial Infarction major or minor bleeding,¹⁵ or (if not available) using trial-specific

TABLE 2 Continued

	N	Primary Study Population (N = 24,325)	P2Y ₁₂ Inhibitor (n = 12,178)	Aspirin (n = 12,147)
Aspirin dose ^b	24,325			
High dose		4,706 (19.3)	-	4,706 (38.7)
Low dose		7,441 (30.5)	-	7,441 (61.3)
Use of proton pump inhibitors	24,141	5,761 (23.9)	2,866 (23.7)	2,895 (24.0)
Statins	15,850	14,118 (89.1)	7,057 (89.1)	7,061 (89.0)
Ejection fraction, %	5,266	54.9 ± 10.8	54.6 ± 10.9	55.1 ± 10.8
PRECISE-DAPT score ^c	14,081	15.6 ± 9.8	15.6 ± 9.9	15.5 ± 9.7
PRECISE-DAPT score ≥25	14,081	2,500 (17.8)	1,240 (17.6)	1,260 (17.9)

Values are n (%) or mean ± SD. Proportions test for binary variables or individual categories within categorical variables; chi-square test for categorical variables; 2-sample Student's t-test for continuous variables. ^aAge and body mass index (BMI) were only available in categorical forms in CAPRIE. ^bHigh-dose aspirin defined as >100 mg/d. ^cIncludes 5 items: age, creatinine clearance, white blood cell count, hemoglobin, and history of bleeding.
PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; other abbreviations as in Table 1.

definitions.^{10,13,14} Other secondary outcomes were the individual components of the primary outcome, all-cause death, definite and/or probable stent thrombosis, ischemic or hemorrhagic stroke, any bleeding, and gastrointestinal bleeding. The outcome definitions were consistent across the included studies (Supplemental Table 2).

STATISTICAL ANALYSIS. We prespecified a 1-step approach to model the data from all trials simultaneously using a Cox proportional hazards regression model with baseline hazard stratified according to trial. Treatment effects were derived as HRs and 95% CIs. Prespecified sensitivity analyses were based on a 2-step approach using a fixed-effects model to combine trial-level estimates, and a 2-step approach using a DerSimonian-Laird random-effects model to combine trial-level estimates. Heterogeneity of the treatment effect between trials was quantified by using the variance of the random effect τ^2 . Data were analyzed up to the longest available time point with protocol-specified P2Y₁₂ inhibitor monotherapy in the experimental group and aspirin monotherapy in the control group. In trials with an initial DAPT phase after randomization,¹⁶ patients were left truncated before the time point when the study protocol specified the change from DAPT to aspirin monotherapy in the control group, and patients who had already experienced myocardial infarction, stroke, or major bleeding in this DAPT phase were excluded. A prespecified sensitivity analysis included patients who experienced myocardial infarction, stroke, or major bleeding during the initial DAPT phase after randomization, if present. Another sensitivity analysis censored all patients at 1 year.

We prespecified a set of subgroup analyses for the primary and key secondary outcomes according to clinical and treatment characteristics accompanied by tests of interaction.

RESULTS

A total of 2,748 unique citations were identified, of which 61 were judged potentially eligible by screening of titles and abstracts. After full-text review, 7 randomized trials were identified as eligible for inclusion (Supplemental Figure 1). Individual participant data were sought and obtained for all eligible trials. Trial characteristics, populations, and funding sources are described in Table 1 and Supplemental Tables 2 to 4. The risk of bias assessment identified 2 trials at low risk of bias, whereas 5 studies presented some concerns (Supplemental Table 5).

Data were obtained for 35,752 individual participants from 492 sites across Asia, Europe, and North America. A total of 10,739 patients were excluded owing to lack of established CAD in 1 trial¹⁰; 520 patients were excluded in 1 trial¹⁶ due to premature study termination or the occurrence of death, myocardial infarction, stroke, or major bleeding before the time point at which the study protocol specified the comparison of a P2Y₁₂ inhibitor with aspirin; and 168 patients were excluded due to the allocation to DAPT for the entire follow-up duration in 1 arm of another study¹⁵ (Supplemental Figure 2). Thus, 24,325 patients were available for analysis, including 12,178 assigned to receive P2Y₁₂ inhibitor monotherapy (clopidogrel in 7,545 [62.0%], ticagrelor in 4,633 [38.0%]) and 12,147 assigned to receive

TABLE 3 Clinical Outcomes of 1-Stage Individual Participant Data Meta-Analysis

	N	P2Y ₁₂ Inhibitor (n = 12,178)	Aspirin (n = 12,147)	HR (95% CI)	P Value
Cardiovascular death, myocardial infarction, or stroke	24,325	675 (3.58)	765 (4.07)	0.88 (0.79-0.97)	0.012
All-cause death	24,325	404 (2.10)	386 (2.00)	1.04 (0.91-1.20)	0.56
Cardiovascular death ^a	24,325	280 (1.45)	273 (1.42)	1.02 (0.86-1.20)	0.82
Myocardial infarction	24,325	283 (1.49)	366 (1.93)	0.77 (0.66-0.90)	<0.001
Stroke					
Any	24,325	202 (1.06)	239 (1.25)	0.84 (0.70-1.02)	0.076
Ischemic	23,324	178 (0.98)	192 (1.06)	0.93 (0.75-1.13)	0.45
Hemorrhagic	23,324	13 (0.07)	30 (0.17)	0.43 (0.23-0.83)	0.012
Stent thrombosis					
Definite	12,503	8 (0.09)	19 (0.21)	0.42 (0.19-0.97)	0.041
Probable	12,503	4 (0.04)	7 (0.08)	0.58 (0.17-1.97)	0.38
Definite or probable	12,503	12 (0.13)	26 (0.28)	0.46 (0.23-0.92)	0.028
Major bleeding ^b	24,325	146 (0.76)	167 (0.87)	0.87 (0.70-1.09)	0.23
Major GI bleeding	23,324	31 (0.17)	46 (0.25)	0.67 (0.43-1.06)	0.089
Any GI bleeding	23,324	99 (0.52)	132 (0.69)	0.75 (0.57-0.97)	0.027
Any bleeding	24,325	646 (3.54)	587 (3.22)	1.10 (0.98-1.23)	0.10
Net adverse clinical events ^c	24,325	785 (4.19)	874 (4.68)	0.89 (0.81-0.98)	0.020

Values in the 2 treatment groups are numbers (rates per 100 person-years). HRs and 95% CIs refer to the results of Cox proportional hazards models stratified according to component trial. Due to lack of information on event timings for all outcomes in ASCET and bleeding outcomes in DACAB, events were assumed to occur at the end of the follow-up period. ^aIn the ASCET trial, all fatal events were considered as of cardiovascular origin. ^bMajor bleeding was defined as Bleeding Academic Research Consortium type 3 or type 5 in GLASSY, HOST-EXAM, and TICAB, as Thrombolysis In Myocardial Infarction major or minor in DACAB, and according to study-specific definitions in ASCET, CADET, and CAPRIE. ^cNet adverse clinical events was defined as the composite of the primary efficacy outcome and major bleeding.

GI = gastrointestinal.

aspirin. The median treatment duration was 557 days [IQR: 369-734 days].

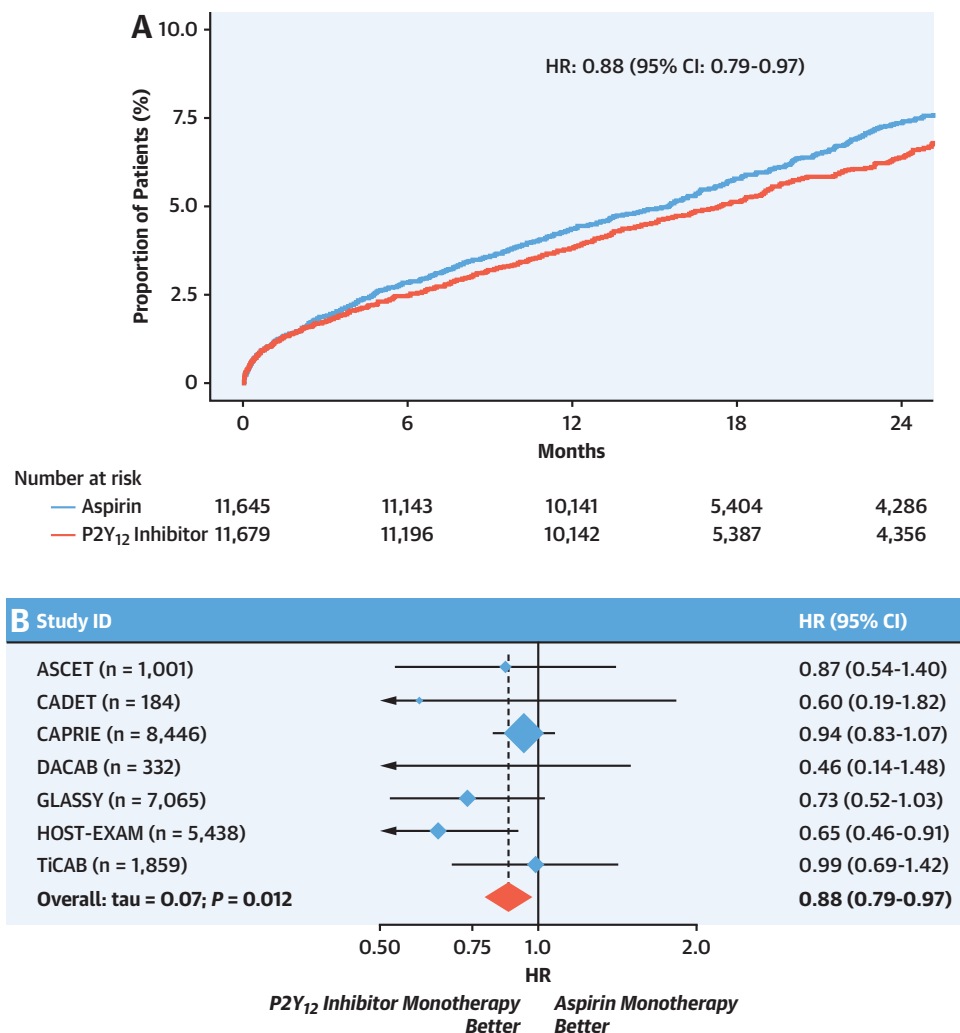
PATIENT CHARACTERISTICS. Baseline clinical characteristics were well balanced between the study groups (Table 2). The mean age was 64.3 years, and 21.7% participants were female. A diagnosis of diabetes was reported in 25.0% of patients, and 11.0% had chronic kidney disease. All patients had established CAD, of whom 56.2% had a history of myocardial infarction, 6.6% reported prior stroke, and 9.1% had PAD. Previous percutaneous or surgical revascularization, or both, were noted in 54.9%, 10.6%, and 4.4% of patients, respectively. In 60.6% of participants, an acute coronary syndrome was the qualifying coronary event for study inclusion, whereas 39.4% of patients experienced chronic coronary syndrome. Baseline characteristics according to individual trial are presented in Supplemental Table 6.

PRIMARY EFFICACY AND KEY SECONDARY OUTCOMES. Combining evidence across included trials, the overall incidence of the primary and key secondary outcomes according to treatment group is shown in Table 3. The primary efficacy outcome of cardiovascular death, myocardial infarction, and stroke was

assessed at a median follow-up time of 493 days [IQR: 369-732 days] (P2Y₁₂ inhibitors: 490 days [IQR: 369-732 days]; aspirin: 496 days [IQR: 369-731 days]; $P = 0.782$). The risk of the primary efficacy outcome was lower with P2Y₁₂ inhibitor monotherapy compared with aspirin monotherapy (HR: 0.88; 95% CI: 0.79-0.97; $P = 0.012$) (Figure 1). This corresponded to a number-needed-to-treat to benefit of 121 over 2 years (Supplemental Table 7). Risk of major bleeding was similar between a P2Y₁₂ inhibitor and aspirin (HR: 0.87; 95% CI: 0.70-1.09; $P = 0.23$) (Figure 2). The risk of NACE was reduced with P2Y₁₂ inhibitor monotherapy compared with aspirin monotherapy (HR: 0.89; 95% CI: 0.81-0.98; $P = 0.020$) for a number-needed-to-treat to benefit of 121 (Figure 3).

PRESPECIFIED SECONDARY OUTCOMES. P2Y₁₂ inhibitor monotherapy was associated with a lower risk of myocardial infarction compared with aspirin monotherapy (HR: 0.77; 95% CI: 0.66-0.90; $P < 0.001$) (Figure 4). The number-needed-to-treat to prevent 1 myocardial infarction with P2Y₁₂ inhibitors was 136. Although stroke was not significantly reduced with P2Y₁₂ inhibitor monotherapy, the HR was consistent with the primary composite endpoint (HR: 0.84; 95% CI: 0.70-1.02; $P = 0.076$). No difference was

FIGURE 1 Primary Endpoint With P2Y₁₂ Inhibitor Monotherapy or Aspirin



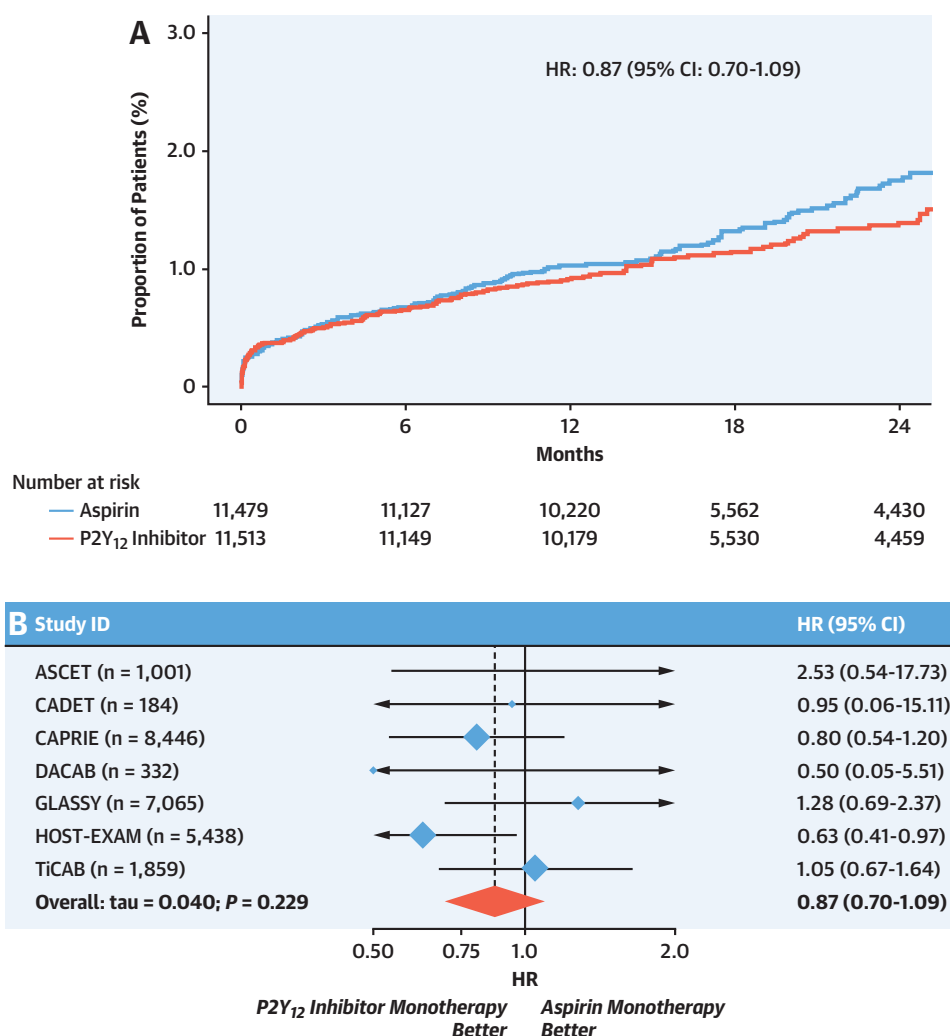
The primary endpoint was a composite of cardiovascular death, myocardial infarction, and stroke. Kaplan-Meier curves and HRs for the primary endpoint are from 1-step meta-analysis (A) and 2-step meta-analysis (B). ASCET = Aspirin Non-responsiveness and Clopidogrel Clinical Endpoint Trial; CADET = Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; DACAB = Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; GLASSY = GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM = Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Extended Antiplatelet Monotherapy; TiCAB = Ticagrelor in Coronary Artery Bypass.

observed for the risk of cardiovascular death (HR: 1.02; 95% CI: 0.86-1.20; $P = 0.82$) or all-cause death (HR: 1.04; 95% CI: 0.91-1.20; $P = 0.56$) (Table 3). The risk of gastrointestinal bleeding (HR: 0.75; 95% CI: 0.57-0.97; $P = 0.027$), definite stent thrombosis (HR: 0.42; 95% CI: 0.19-0.97; $P = 0.041$), definite or probable stent thrombosis (HR: 0.46; 95% CI: 0.23-0.92; $P = 0.028$), and hemorrhagic stroke (HR: 0.43; 95% CI: 0.23-0.83; $P = 0.012$) was significantly lower with P2Y₁₂ inhibitor monotherapy than with aspirin.

PRESPECIFIED SUBGROUP AND SENSITIVITY ANALYSES.

The treatment effect for the primary efficacy and key secondary outcomes was consistent across all predefined subgroups, including the type of P2Y₁₂ inhibitor (ticagrelor or clopidogrel) (Figure 5, Supplemental Figures 3 and 4). There was limited evidence suggesting that P2Y₁₂ inhibitors might be associated with greater benefit with respect to the primary efficacy outcome in patients with prior PCI compared with those with no prior revascularization or other revascularization strategies

FIGURE 2 Major Bleeding With P2Y₁₂ Inhibitor Monotherapy or Aspirin

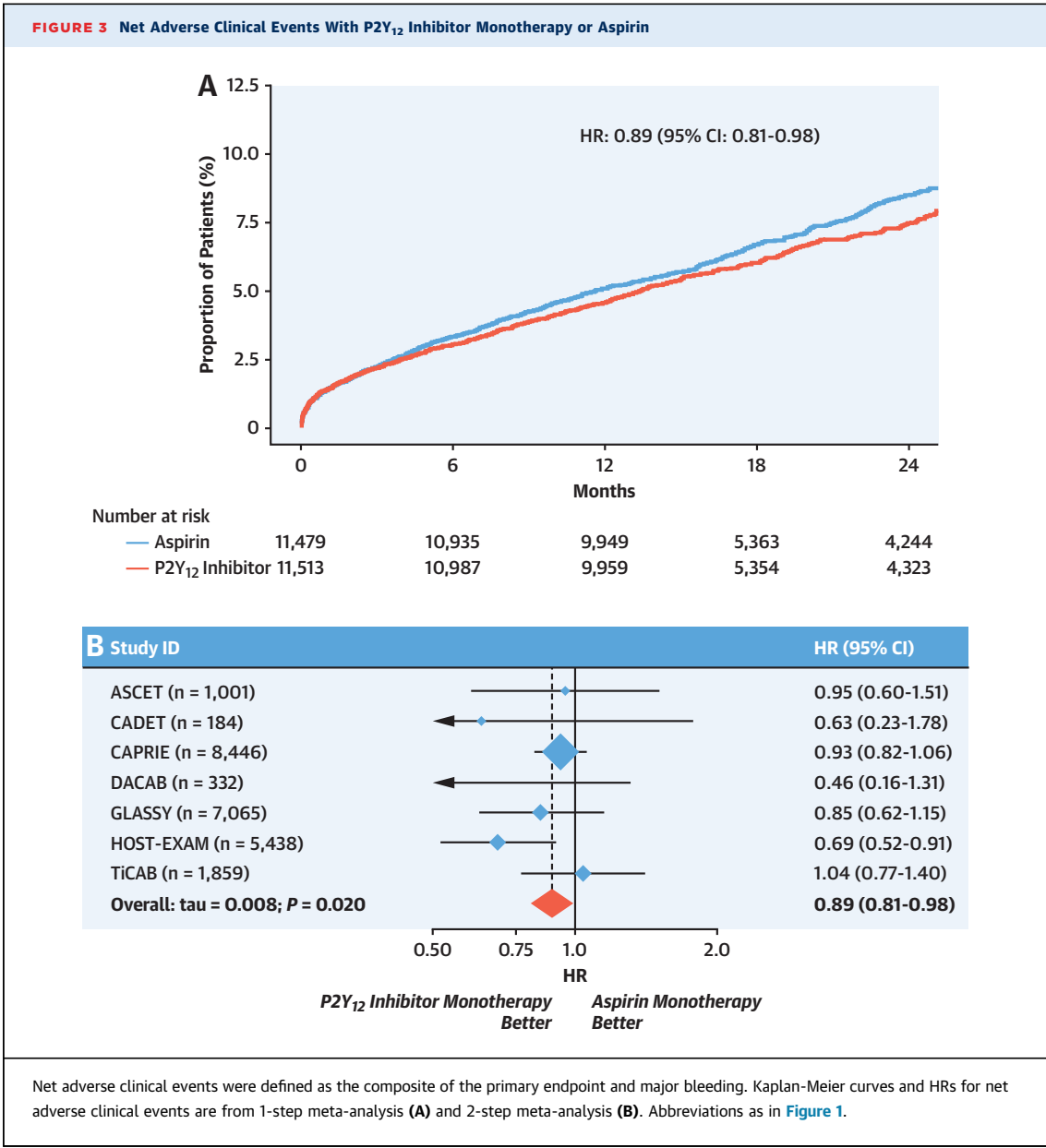


Major bleeding was defined as Bleeding Academic Research Consortium type 3 or 5 where available, or Thrombolysis In Myocardial Infarction major or minor bleeding, or (if not available) using trial-specific definitions. Kaplan-Meier curves and HRs for major bleeding are from 1-step meta-analysis (A) and 2-step meta-analysis (B). Abbreviations as in Figure 1.

($P_{\text{interaction}} = 0.080$). For the prevention of myocardial infarction, there was evidence supporting a pronounced treatment effect with P2Y₁₂ inhibitor monotherapy vs low-dose aspirin than high-dose aspirin ($P_{\text{interaction}} = 0.040$) (Supplemental Figure 5). In a post hoc analysis, we observed a treatment-by-subgroup interaction with geographical regions for the primary endpoint ($P_{\text{interaction}} = 0.034$), stroke ($P_{\text{interaction}} = 0.005$), and NACE ($P_{\text{interaction}} = 0.023$), suggesting that patients enrolled in Asia may derive enhanced benefit from P2Y₁₂ inhibitors compared

with patients from Europe and North America (Supplemental Figure 6).

A sensitivity analysis including the initial 1-year period in one study¹⁶ yielded consistent results for the primary and key secondary outcomes (Supplemental Table 8). The composite outcome of cardiovascular death, myocardial infarction, and stroke censoring events that occurred after 12 months of treatment comparison (yielding a uniform duration of follow-up across trials) occurred in 438 (3.6%) patients with P2Y₁₂ inhibitor

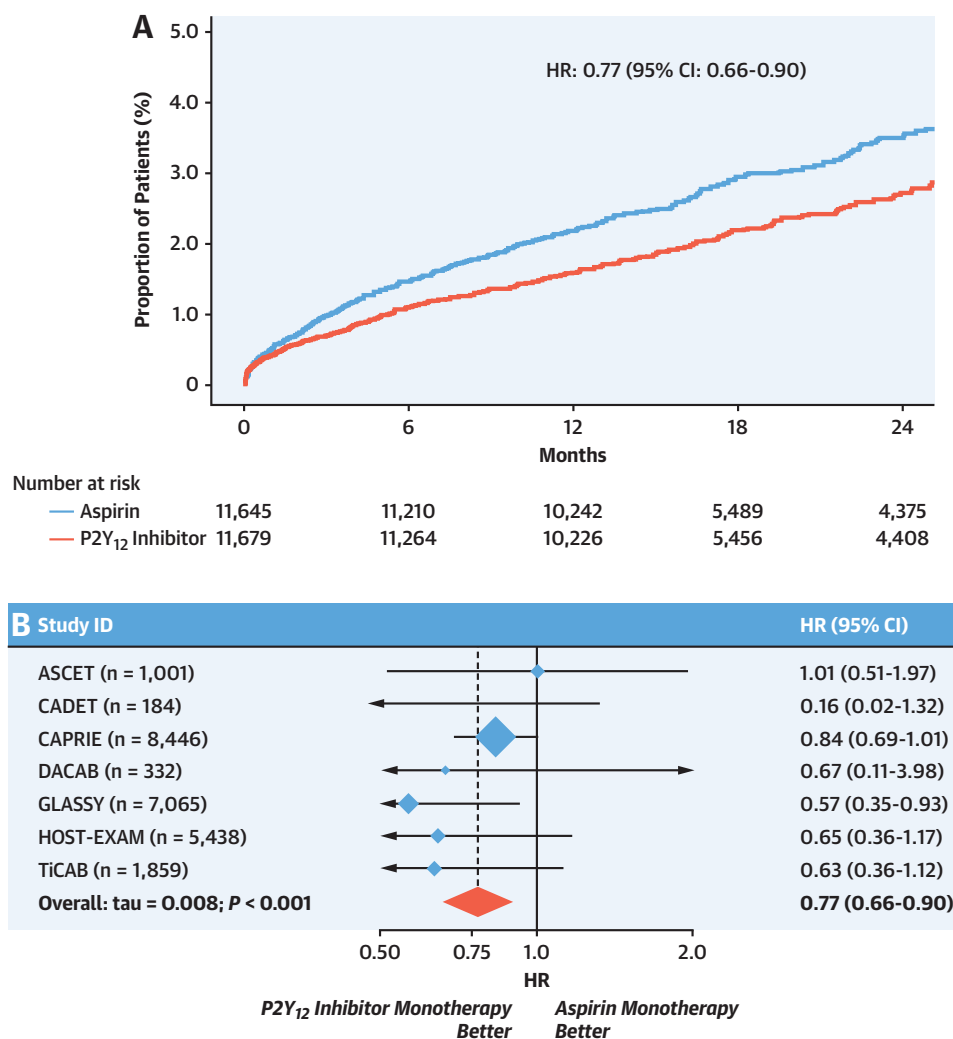


monotherapy and 501 (4.1%) with aspirin monotherapy (HR: 0.87; 95% CI: 0.76-0.99; $P = 0.031$) (Supplemental Table 9). Prespecified sensitivity analyses based on a 2-step approach with a fixed-effect model or a random-effect model provided largely consistent findings (Supplemental Table 10).

DISCUSSION

This comprehensive individual patient data meta-analysis of randomized controlled trials included

24,325 participants with established CAD, of whom a large proportion received modern pharmaco-invasive treatments. It provides evidence of a significant reduction of ischemic events with P2Y₁₂ inhibitor monotherapy compared with aspirin monotherapy for secondary cardiovascular prevention, with no increased risk of bleeding (Central Illustration). The relative risk of the primary composite endpoint of cardiovascular death, myocardial infarction, and stroke was reduced by 12% in patients receiving a P2Y₁₂ inhibitor. This benefit was primarily driven by a 23% relative reduction of myocardial infarction and,

FIGURE 4 Myocardial Infarction With P2Y₁₂ Inhibitor Monotherapy or Aspirin

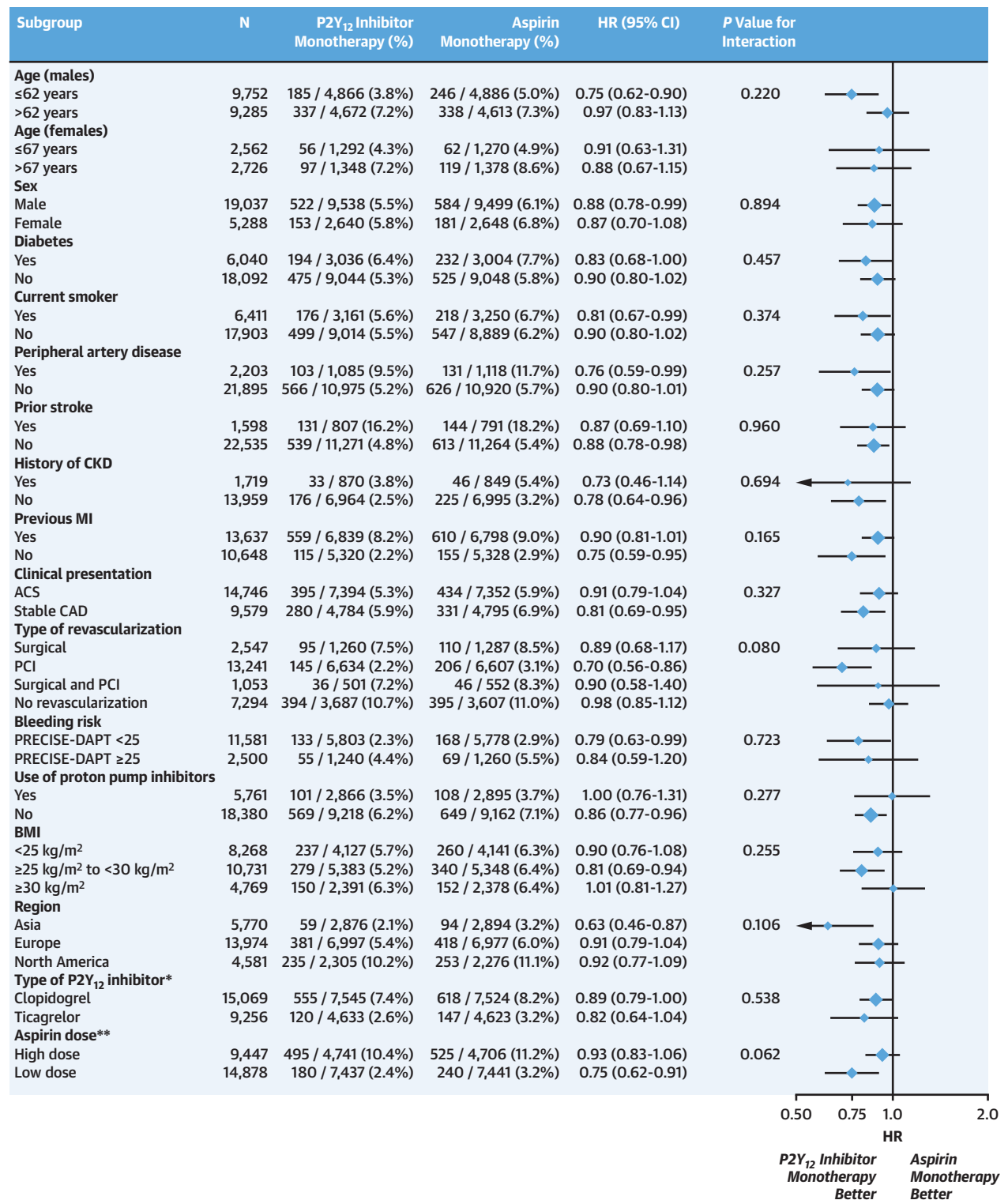
Myocardial infarction was defined according to the original definition used for event adjudication in each trial. Kaplan-Meier curves and HRs for myocardial infarction are from 1-step meta-analysis (A) and 2-step meta-analysis (B). Abbreviations as in Figure 1.

secondarily, by numerically but not significantly lower rates of stroke. No difference was observed between the 2 treatments for all-cause and cardiovascular mortality. The overall risk of major bleeding did not differ, whereas gastrointestinal bleeding and hemorrhagic stroke occurred significantly less frequently in patients receiving a P2Y₁₂ inhibitor than those receiving aspirin monotherapy.

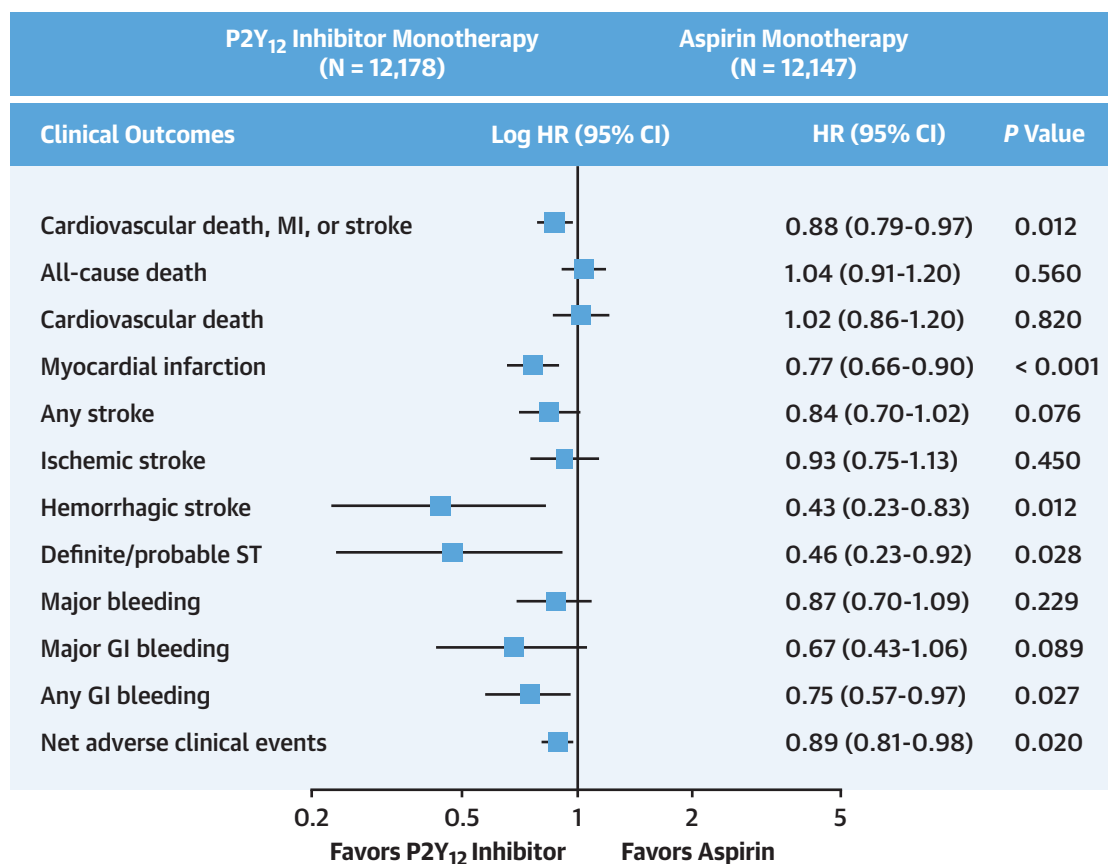
LONG-TERM ASPIRIN FOR SECONDARY CARDIOVASCULAR PREVENTION. The evidence supporting aspirin use for secondary prevention derives mainly from studies

conducted in the late 1970s and the early 1980s.¹⁻³ The latest report, in 2009, from the Antithrombotic Trialists' Collaboration, pooled data from 16 secondary prevention trials of aspirin vs controls in 17,000 patients with a history of stroke, transient cerebral ischemia, or myocardial infarction.³ Aspirin was found to be associated with a 20% proportional reduction and 1% yearly absolute difference in major coronary events (myocardial infarction, coronary death, or sudden death) with no evidence of heterogeneity among patients stratified according to qualitative index event.³

FIGURE 5 Subgroup Analysis for the Primary Endpoint



A set of prespecified subgroup analyses for the primary endpoint was performed to evaluate the treatment effect of P2Y₁₂ inhibitor monotherapy vs aspirin monotherapy across subgroups of interest. *Based on the protocol-mandated type of P2Y₁₂ inhibitor in the P2Y₁₂ inhibitor group in each trial. **Based on the protocol-mandated doses of aspirin in the aspirin group in each trial. High-dose aspirin defined as >100 mg/d. ACS = acute coronary syndrome; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

CENTRAL ILLUSTRATION P2Y₁₂ Inhibitor Monotherapy Versus Aspirin Monotherapy in Patients With Coronary Artery Disease

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P2Y₁₂ inhibitor monotherapy was associated with a lower risk of ischemic events than aspirin among 24,325 patients with coronary artery disease over 2 years. This benefit was primarily driven by a 23% relative reduction in myocardial infarction (MI). Overall risks of major bleeding were similar, but gastrointestinal (GI) bleeding and hemorrhagic stroke occurred less with inhibitors of P2Y₁₂ than with aspirin. ST = stent thrombosis.

Notwithstanding the proven benefits of aspirin, its status as the cornerstone of antiplatelet therapy in secondary prevention has been challenged.¹ Intracranial and extracranial (particularly gastrointestinal) bleeding complications occur in a sizeable proportion of patients taking long-term aspirin therapy.^{1,22} Moreover, the pivotal studies of aspirin were performed several decades ago,³ and it remains uncertain whether these results would be replicated in contemporary investigations implementing current secondary prevention strategies. In this context, the availability of other antithrombotic compounds with

different antiplatelet effects outlines alternative approaches for the long-term management of patients with CAD.^{1,22,23}

P2Y₁₂ INHIBITOR MONOTHERAPY FOR SECONDARY PREVENTION IN PATIENTS WITH CAD. CAPRIE was the first randomized trial to show that clopidogrel monotherapy reduces cardiac and cerebrovascular events compared with aspirin in patients with established atherosclerosis.¹⁰ These findings corroborated the preferential use of clopidogrel over aspirin in patients with PAD but not in those with CAD. The

results of subsequent study-level meta-analyses lend support to the concept that P2Y₁₂ inhibitor monotherapy may be superior to aspirin monotherapy for secondary prevention but failed to include all available studies²⁴ or to ascertain the treatment effects exclusively in patients with CAD.²⁴⁻²⁶ The lack of patient-level data prevented the investigators from offering any insight into the specific subgroup of patients with CAD.²⁴⁻²⁶ In addition, the inclusion of trials testing the P2Y₁₂ inhibitor ticlopidine, which is no longer recommended for secondary prevention, may limit the contemporary application of prior aggregate analyses.²⁴ Finally, previous meta-analyses did not assess comprehensively whether the treatment effects were modified by patient or treatment characteristics due to the lack of individual participant data.²⁴⁻²⁶

MAIN STUDY FINDINGS AND IMPLICATIONS FOR PRACTICE. The current meta-analysis is the largest and most comprehensive synthesis of individual patient data from randomized trials investigating the comparative effects of P2Y₁₂ inhibitor monotherapy vs aspirin monotherapy exclusively in patients with established CAD. The study population spanned the spectrum of coronary atherosclerosis, as the individual trials differed in their inclusion of medically managed, post-PCI, and post-coronary artery bypass grafting patients. We observed that the risk of the primary outcome of combined fatal and nonfatal ischemic events was lower with P2Y₁₂ inhibitor monotherapy than with aspirin, and most of the ischemic benefit was driven by a reduction in myocardial infarction, which emerged rapidly after treatment initiation (as shown by the early separation of the Kaplan-Meier curves) and was consistent across trials and endpoint definitions. The numbers-needed-to-treat to prevent 1 primary endpoint event or 1 myocardial infarction over 2 years were 121 and 136, respectively. This observation suggests that the additional ischemic protection provided by P2Y₁₂ inhibitors over aspirin is potentially relevant for practice and more pronounced than that reported in previous aggregate meta-analyses, which did not focus on patients with CAD.^{24,25} Of note, our results probably underestimate the cumulative benefit that could be achieved with longer-term treatment over decades, which is the intended duration in most patients.

More than one-third of patients in the P2Y₁₂ group were assigned to receive ticagrelor monotherapy, a strategy that has been shown to provide similar

ischemic protection and reduced bleeding compared with standard DAPT in the year after PCI.²⁷ Noteworthy, we observed a >50% reduction in definite or probable stent thrombosis occurrences with P2Y₁₂ inhibitor monotherapy vs aspirin, which may partly explain why the subgroup of post-PCI patients tended to derive greater benefit from such a strategy. The benefit of P2Y₁₂ inhibitors over aspirin did not seem to be more pronounced in high-risk cohorts (ie, previous coronary artery bypass grafting, polyvascular disease, diabetes), as previously observed in secondary analyses of the CAPRIE trial,²⁸ and was not affected by initial clinical presentation (ie, acute vs chronic coronary syndrome). In a post hoc subgroup analysis, patients from Asian institutions seemed to benefit more from P2Y₁₂ inhibitors than those from Europe and North America, particularly for stroke. Given the post hoc nature of this analysis and the lack of correction for multiplicity, this finding remains hypothesis-generating. Furthermore, because data on ethnicity, genetics, and drug response were not available in our database, the determinants of this possible regional heterogeneity are unclear. The significant interaction with daily aspirin dose for myocardial infarction, suggesting that the benefit of P2Y₁₂ inhibitors may be more pronounced compared with low-dose aspirin than with high-dose aspirin, is also of uncertain interpretation given the trial-related distribution of aspirin doses and robust contemporary evidence from a randomized trial showing similar efficacy of the 2 aspirin doses in patients with CAD.²⁹

We reported a reduction in ischemic events with P2Y₁₂ inhibitor monotherapy and no significant differences between the 2 treatment strategies in terms of any bleeding as well as major bleeding. Of note, hemorrhagic stroke was less common in the P2Y₁₂ inhibitor group, a finding that is aligned with earlier evidence indicating an increased risk of this serious and potentially life-threatening complication with aspirin therapy.^{30,31} This endpoint did not differ in a prior meta-analysis due to a small number of included studies that provided published information on this endpoint.²⁴ In a more recent aggregate meta-analysis, which included patients after a stroke, a significant reduction of intracranial bleeding was noted with the P2Y₁₂ inhibitor compared with aspirin.²⁵ It therefore remained unclear if P2Y₁₂ inhibitors reduce hemorrhagic stroke compared with aspirin in selected patients with CAD.

Chronic use of aspirin is an established risk factor for gastrointestinal erosions and ulcers resulting from disruption of the protective gastric phospholipid

barrier.³² We observed that P2Y₁₂ inhibitor monotherapy significantly reduced gastrointestinal bleeding, with a consistent numerical reduction of the events graded as major. These observations are of clinical relevance, particularly for patients at increased risk for gastrointestinal bleeding in whom treatment providing adequate long-term antithrombotic protection while minimizing bleeding complications is most desirable.

We did not observe any difference in all-cause or cardiovascular mortality between the 2 regimens. These findings may not be unexpected in view of the limited study follow-up and chronic clinical setting with relatively low death rates. Longer-term assessment may be needed for a survival benefit to emerge as a consequence of a reduction in nonfatal ischemic events. It is noteworthy that aspirin had previously been shown to reduce vascular mortality in secondary prevention studies.³ Hence, the null effect with precise risk estimates between the 2 antiplatelet strategies on all-cause and cardiovascular mortality suggests that the survival benefit of aspirin may be preserved with P2Y₁₂ inhibitors. Assessment of the potential benefits related to the chemopreventive effects of aspirin, which may begin 10 years after the initiation of chronic treatment, requires long follow-up studies.²²

STUDY LIMITATIONS. First, this patient-level meta-analysis shares the limitations of the individual trials, such as the open-label design in 4 of 7 studies. Nonetheless, the inclusion of studies reporting adjudicated outcomes reduces this potential bias. Second, although clinical outcomes were consistently defined across trials, we cannot exclude the possible influence of some study-specific definitions. Third, no correction for multiple testing was prespecified. Hence, the lower risks of myocardial infarction and NACE with P2Y₁₂ inhibitors must be interpreted with caution. Similarly, subgroup analyses might not have sufficient power to reliably detect true interactions. Fourth, the current results are not generalizable to patients treated with prasugrel monotherapy. This strategy has been recently tested in a single-arm trial including 201 patients undergoing PCI that was not included in our meta-analysis given the lack of a comparator group receiving aspirin monotherapy.³³ Fifth, in 1 trial, we censored post-PCI patients with ischemic events or bleeding during the initial DAPT phase,¹⁶ and the results remained consistent in a sensitivity analysis including these patients. However, because another trial excluded post-PCI patients

with ischemic events or bleeding during DAPT,¹⁸ our findings apply mainly to patients with an uncomplicated DAPT course. Finally, the duration of the treatment comparisons ranged from 6 to 36 months across the included studies. Notably, our findings were largely consistent after censoring events that occurred beyond 12 months. Of note, given that antiplatelet monotherapy is often used indefinitely for long-term cardiovascular prevention, the benefits of P2Y₁₂ inhibitors over aspirin may be understated in the current analysis. Given the acknowledged limitations, further randomized trials enrolling contemporary populations of patients with CAD are needed to corroborate our findings.

CONCLUSIONS

P2Y₁₂ inhibitor monotherapy was associated with lower risks of cardiovascular death, myocardial infarction, and stroke compared with aspirin monotherapy in patients with CAD, mainly owing to a lower risk of myocardial infarction and resulting in a reduced risk of NACE. The incidence of major bleeding was similar, but gastrointestinal bleeding and hemorrhagic stroke were lower with P2Y₁₂ inhibitor monotherapy. Based on available randomized evidence, long-term P2Y₁₂ inhibitor monotherapy may be warranted instead of long-term aspirin monotherapy for secondary prevention in patients with CAD.

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Terumo, V-Wave, and Xeltis but has not received personal payments by pharmaceutical companies or device manufacturers; is a member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration; is an unpaid member of the Pfizer Research Award selection committee in Switzerland and of the Women as One Awards Committee; is a member of the Clinical Study Group of the Deutsches Zentrum für Herz Kreislauf-Forschung and of the Advisory Board of the Australian Victorian Heart Institute; and is chairperson of the ESC Congress Program Committee and Deputy Editor of *JACC: Cardiovascular Interventions*. Dr Mehran has served on the scientific advisory boards of the American Medical Association, the American College of Cardiology (Board of Trustees Member), the Society for Cardiovascular Angiography & Interventions (Women in Innovations Committee Member), *JAMA Cardiology* (Associate Editor), and the Cardiovascular Research Foundation (Faculty) (no fee). Dr Woodward is a consultant for Freeline; and has recently been a consultant to Amgen. Dr Schunkert has received personal fees from Amgen, AstraZeneca, Bayer Vital GmbH, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Merck Sharp & Dohme, Novartis, Sanofi, Servier, and SYNLAB. Dr Franzone has received payment or honoraria for lectures, presentations, Speaker Bureaus, manuscript writing, or educational events from Edwards Lifesciences and Boehringer Ingelheim. Dr Bhatt discloses the following relationships—advisory board: AngloWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; board of directors: AngloWave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, and TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; consultant: Broadview Ventures; data monitoring committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the National Institutes of Health-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Canadian Medical and Surgical

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Patient-level meta-analysis of data from randomized trials suggests that monotherapy with a contemporary P2Y₁₂ inhibitor is superior to aspirin for prevention of fatal and ischemic events in patients with CAD, due mainly to a lower risk of myocardial infarction and consequently fewer adverse events.

TRANSLATIONAL OUTLOOK:

Further research is needed to compare monotherapy with a P2Y₁₂ inhibitor to dual pathway inhibition with aspirin and an anticoagulant in selected patients with CAD and other manifestations of atherosclerosis.

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APPENDIX For supplemental figures, Methods, and tables, please see the online version of this paper.