Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study

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Summary

Background The relation between platelet reactivity and stent thrombosis, major bleeding, and other adverse events after coronary artery implantation of drug-eluting stents has been incompletely characterised. We aimed to determine the relation between platelet reactivity during dual therapy with aspirin and clopidogrel and clinical outcomes after successful coronary drug-eluting stent implantation.

Methods ADAPT-DES was a prospective, multicentre registry of patients successfully treated with one or more drug-eluting stents and given aspirin and clopidogrel at 10–15 US and European hospitals. We assessed platelet reactivity in those patients after successful percutaneous coronary intervention using VerifyNow point-of-care assays, and assigned different cutoffs to define high platelet reactivity. The primary endpoint was definite or probable stent thrombosis; other endpoints were all-cause mortality, myocardial infarction, and clinically relevant bleeding. We did a propensity-adjusted multivariable analysis to determine the relation between platelet reactivity and subsequent adverse events. This study is registered with ClinicalTrials.gov, number NCT00638794.

Findings Between Jan 7, 2008, and Sept 16, 2010, 8665 patients were prospectively enrolled at 11 sites, of which 8583 were eligible. At 1-year follow-up, stent thrombosis had occurred in 70 (0·8%) patients, myocardial infarction in 269 (3·1%), clinically relevant bleeding in 531 (6·2%), and death in 161 (1·9%) patients. High platelet reactivity on clopidogrel was strongly related to stent thrombosis (adjusted HR 2·49 [95% CI 1·43–4·31], p=0·001) and myocardial infarction (adjusted HR 1·42 [1·09–1·86], p=0·01), was inversely related to bleeding (adjusted HR 0·73 [0·61–0·89], p=0·002), but was not related to mortality (adjusted HR 1·20 [0·85–1·70], p=0·30). High platelet reactivity on aspirin was not significantly associated with stent thrombosis (adjusted HR 1·46 [0·58–3·64], p=0·42), myocardial infarction, or death, but was inversely related to bleeding (adjusted HR 0·65 [0·43–0·99], p=0·04).

Interpretation The findings from this study emphasise the counter-balancing effects of haemorrhagic and ischaemic complications after stent implantation, and suggest that safer drugs or tailored strategies for the use of more potent agents must be developed if the benefits of greater platelet inhibition in patients with cardiovascular disease are to be realised.

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Introduction

The occurrence of stent thrombosis after coronary artery implantation of drug-eluting stents is associated with high rates of myocardial infarction and death.[1] Dual antiplatelet therapy with aspirin and an adenosine diphosphate (ADP)-receptor inhibitor is presently recommended for at least 1 year after drug-eluting stent implantation since most episodes of stent thrombosis occur within this period.[2] Aspirin inhibits cyclooxygenase-1, a key enzyme involved in the conversion of arachidonic acid to thromboxane A2, an important agonist that amplifies platelet aggregation. Clopidogrel, the most widely used ADP-receptor inhibitor, undergoes a two-step metabolic transformation before binding to the platelet P2Y12 ADP receptor.[3] The conversion of clopidogrel to its active metabolite is regulated by the CYP450 system, and the presence of genetic polymorphisms partly determines the extent to which clopidogrel inhibits ADP-induced platelet activation.[4,5] Results from pharmacodynamic studies in patients treated with clopidogrel have shown wide variability in platelet responsiveness, and high platelet reactivity on clopidogrel has been linked to stent thrombosis and adverse cardiovascular events after stenting.[5–12] Variability in platelet responsiveness to aspirin has also been described, although its association with cardiac events and stent thrombosis is less clear.[13–16]

Previous studies examining the relation between platelet reactivity and stent thrombosis have been limited in size, and have often enrolled a stable, elective population in whom event rates were low.[17] Additionally, the effect of platelet reactivity on major bleeding, the

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*The names of the investigators, institutions, and research organisations participating in the Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study appear in the appendix

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See Online for appendix

occurrence of which has been associated with mortality, has been incompletely characterised, with previous studies reporting conflicting results.[6,17–19] We therefore undertook a large-scale, prospective, multicentre registry study designed to determine the relation between platelet reactivity during dual therapy with aspirin and clopidogrel and subsequent adverse events after successful coronary drug-eluting stent implantation.

Methods

Study design and patients

ADAPT-DES was a prospective, multicentre registry specifically designed to determine the relation between platelet reactivity and subsequent clinical events in patients with coronary artery disease treated with aspirin and clopidogrel after successful drug-eluting stent implantation. We planned to enrol 11 000 patients at 10–15 US and European hospitals. Consecutive patients at every centre successfully treated with one or more drug-eluting stents approved by the US Food and Drug Administration (FDA) or CE mark and who were adequately loaded with aspirin and clopidogrel were eligible for enrolment, regardless of patient or lesion complexity. The only major exclusion criteria were the occurrence of a major complication during the procedure or before platelet function testing, or if bypass surgery was planned after percutaneous coronary intervention (PCI).

The study was approved by the institutional review board at every participating centre, and all eligible patients signed written informed consent.

Procedures

We assessed platelet reactivity after successful PCI, and after an adequate period to ensure full anti-platelet effect, using the VerifyNow Aspirin, P2Y12 and IIb/IIIa assays (Accumetrics, San Diego, CA, USA). Aspirin was given as either (1) a non-enteric coated oral dose of 300 mg or more at least 6 h before PCI, or (2) a chewed dose of 324 mg or intravenous dose of 250 mg or more at least 30 min before PCI. Clopidogrel was given as either (1) a dose of 600 mg at least 6 h before VerifyNow testing, (2) a dose of 300 mg at least 12 h before VerifyNow testing, or (3) a dose of 75 mg or more for at least 5 days before VerifyNow testing. If eptifibatide or tirofiban were used during PCI, a 24 h washout period was required before VerifyNow testing. A 10-day washout period was required if abciximab was used, and thus no patients receiving abciximab were enrolled.

After PCI, patients were treated with aspirin indefinitely, and clopidogrel was recommended for at least 1 year. All other treatments were per standard of care. Research coordinators did the VerifyNow testing, and the results were entered into a computerised database without informing the treating physicians or affecting management decisions. Clinical follow-up was scheduled at 30 days, 1 year, and 2 years. At the time of the present report all patients have reached 1-year follow-up, the time period during which dual anti-platelet therapy was recommended in all patients.

We assessed the following tests of platelet function as continuous measures: VerifyNow Aspirin reaction units (ARU); VerifyNow P2Y12 baseline reactivity (BASE), P2Y12 reaction units (PRU), and P2Y12 percent inhibition; and VerifyNow IIb/IIIa overall on-treatment platelet aggregation units (PAU). Additionally, based on previous studies in which thresholds for platelet reactivity were identified, we defined high platelet reactivity on clopidogrel using two discrete cutoff levels of high platelet reactivity to ADP (VerifyNow P2Y12 >208 PRU, and ≥230 PRU).[6,8,9,11] For brevity, results are shown using the cutoff value higher than 208 PRU, although analogous results were noted for that equal to or higher than 230 PRU. Similarly, we defined high platelet reactivity on aspirin as VerifyNow Aspirin higher than 550 ARU.[13]

The primary endpoint for which the study size was calculated was definite or probable stent thrombosis, according to the Academic Research Consortium definition.[20] Additional endpoints included all-cause mortality, myocardial infarction, and clinically relevant bleeding. We defined myocardial infarction according to the ACUITY criteria.[21] We defined clinically relevant bleeding as the occurrence of any of the following: a TIMI major or minor bleed, a GUSTO bleed, an ACUITY major bleed, or any post-discharge bleeding event requiring medical attention. An independent clinical events committee masked to VerifyNow results adjudicated all death, myocardial infarction, and stent thrombosis events using original source documents.

Statistical analysis

We estimated the sample size of 11 000 patients to provide high power to identify variables associated with stent thrombosis on the basis of assumptions of stent thrombosis rates during different periods and the hazard ratio (HR) for each risk factor, including VerifyNow platelet function testing. We expected a 1·0% rate of stent thrombosis at 1-year follow-up.[1] Thus, if the HR for high platelet reactivity on clopidogrel was 3·0–4·0,[5–12] the study would have more than 99% power to demonstrate this relation. Specifically, for purposes of sample size estimation, we defined high platelet reactivity on clopidogrel as those patients with VerifyNow P2Y12 PRU in the highest quintile (highest 20% of values). Assuming that 75% of all stent thrombosis episodes would occur in patients with high platelet reactivity on clopidogrel, and conservatively assuming 75 total stent thrombosis events, 56 events would occur in patients with high platelet reactivity and 19 events would occur in patients with normal high platelet reactivity. Thus, with 10 000 patients with follow-up, 2000 patients with high platelet reactivity will have 56 stent thrombosis events (2·8% stent thrombosis rate), and 8000 patients with normal platelet reactivity will have 19 stent thrombosis events (0·2%). With a two-sided α of 0·05, the study would have 99%

power to demonstrate this difference. If only 50% of all stent thrombosis episodes occur in patients with high platelet reactivity, then 38 stent thrombosis events would occur in 2000 patients with high platelet reactivity (1·9% stent thrombosis rate) and 38 events would occur in 8000 patients with normal platelet reactivity (0·5% stent thrombosis rate). The study would have 99% power to demonstrate this difference.

We compared categorical outcomes by χ^2 test unless the expected number of observations in any cell of a contingency table was lower than five, in which case we used Fisher's exact test. We compared continuous variables by Student's *t* test and present them as mean (SD). We assessed the relation between high platelet reactivity and subsequent clinical outcomes using standard receiver operating characteristic (ROC) analyses, and the risk reclassification by high platelet reactivity using net reclassification index (NRI) classified by tertiles of risk in the overall cohort, as well as the integrated discriminatory index (IDI). We compared time-to-event data with log-rank tests and present them as Kaplan-Meier estimates. To identify the independent predictors of outcomes, we entered the platelet reactivity plus other baseline variables deemed clinically relevant from previous studies into multivariable Cox proportional hazards regression models for every event type, which we further adjusted for the propensity for platelet reactivity. We carefully chose the number of variables included on the basis of the total number of events to ensure parsimony of every model.[22] We also created a multivariable model for mortality in which ischaemic and bleeding events were entered as time-adjusted covariates. We treated missing values as missing completely at random (MCAR) and imputed them by the SAS MI procedure using the expectation-maximisation algorithm. A Kolmogorov-type supremum test verified that the proportional hazard assumption was not violated (p>0·10 for all multivariable analyses). All p values are two-tailed, and we deemed a p value lower than 0·05 to be significant for all analyses. We did the statistical analyses using SAS version 9·1.3, Cary, NC. This study is registered with ClinicalTrials.gov, number NCT00638794.

Role of the funding source

The study was designed by the principal investigator and executive committee, and was sponsored by the

	Number of patients (%)
Age (years)	63·6 (10·9)
Male sex	6358 (74·1%)
Hypertension	6834 (79·6%)
Hyperlipidaemia	6380 (74·3%)
Diabetes mellitus	2783 (32·4%)
Insulin-treated	998 (11·6%)
Cigarette smoking, current	1939 (22·6%)
Previous myocardial infarction	2164 (25·2%)
Previous percutaneous coronary intervention	3676 (42·8%)
Previous coronary artery bypass graft surgery	1467 (17·1%)
History of congestive heart failure	699 (8·1%)
History of peripheral arterial disease	876 (10·2%)
History of renal insufficiency	660 (7·7%)
Current dialysis	138 (1·6%)
Body-mass index (kg/m²)	29·5 (5·7)
Presenting clinical syndrome	
Stable ischaemic heart disease	4147 (48·3%)
Acute coronary syndrome	4436 (51·7%)
Unstable angina	2373 (27·6%)
Non-ST-segment elevation myocardial infarction	1250 (14·6%)
ST-segment elevation myocardial infarction	813 (9·5%)
Angiographic features	
Number of diseased vessels	
One	3284 (38·3%)
Two	2835 (33·0%)
Three	2464 (28·7%)
Left main disease	257 (3·0%)
Left ventricular ejection fraction (%)	54·9 (12·4)
(Continues in next column)	

	Number of patients (%)
(Continued from previous column)	
Procedural data	
Access site	
Femoral access	8190 (95·4%)
Radial	375 (4·4%)
Brachial	18 (0·2%)
Anticoagulation	
Bivalirudin (±heparin)	4945 (57·6%)
Heparin only	3638 (42·4%)
Glycoprotein IIb/IIIa inhibitor	140 (1·6%)
Lesions treated per patient	1·5 (0·8)
Stents implanted per patient	1·7 (1·0)
Total stent length per patient (mm)	32·5 (22·4)
Maximum vessel diameter (mm)	3·1 (0·7)
Maximum device diameter (mm)	3·3 (0·5)
Maximum diameter stenosis pre (%)	88·1 (10·0)
Maximum diameter stenosis post (%)	1·7 (6·9)
Drug-eluting stent type*	
Everolimus-eluting	5538 (64·5%)
Paclitaxel-eluting	1415 (16·5%)
Sirolimus-eluting	1155 (13·5%)
Zotarolimus-eluting fast release	535 (6·2%)
Zotarolimus-eluting slow release	187 (2·2%)
Other	21 (0·2%)

Data are number of patients (%) or mean (SD). *Some patients had more than one stent type implanted. Data are complete (denominator=8583) for all patients except for left ventricular ejection fraction (n=6683) and total stent length per patient (n=8582).

Table 1: **Baseline characteristics and procedural details in 8583 patients**

Cardiovascular Research Foundation, New York, NY, under an FDA investigational device exemption. The study was funded by various sources (see acknowledgments section), which had no role in study design, site selection, data collection, data analysis, or data interpretation, but had the right to a non-binding review of the manuscript before submission. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Stent thrombosis	No stent thrombosis	p value
Aspirin ARU	426 (58)	419 (55)	0·30
>550	5/69 (7·2%)	473/8458 (5·6%)	0·54
P2Y12 base	305 (60)	310 (58)	0·56
P2Y12 PRU	234 (97)	188 (97)	<0·0001
>208	45/69 (65·2%)	3565/8380 (42·5%)	0·0002
≥230	37/69 (53·6%)	2924/8380 (34·9%)	0·001
P2Y12 percent inhibition	24·8 (27·0)	40·1 (28·2)	<0·0001
IIb/IIIa PAU	194 (56)	193 (54)	0·92

Data are mean (SD) or n/N (%). ARU=aspirin reaction units. PRU=P2Y12 reaction units. PAU=platelet aggregation units.

Table 2: **Relationship between platelet reactivity and subsequent definite or probable stent thrombosis through 1 year follow-up**

Results

Between Jan 7, 2008, and Sept 16, 2010, 8665 patients in whom drug-eluting stents were successfully implanted were prospectively enrolled at 11 hospitals in the USA and Germany (enrolment was terminated before the planned 11000 patient target for financial constraints; appendix). 82 (0·9%) patients were excluded because platelet function testing was done before the protocol-required glycoprotein IIb/IIIa inhibitor washout period. Thus, the final study population consisted of 8583 patients (appendix). A high-risk cohort was enrolled, with a large proportion of patients having diabetes, previous myocardial infarction, acute coronary syndromes, and multivessel disease (table 1). Stents were implanted in 12942 lesions in 10113 vessels (1·7 lesions [SD1·0] treated per patient, with total stent length of 32·5 mm [22·4]; table 1). About two-thirds of patients received everolimus-eluting stents.

We obtained valid measurements in 8449 (98·4%) patients for VerifyNow P2Y12 and in 8527 (99·3%)

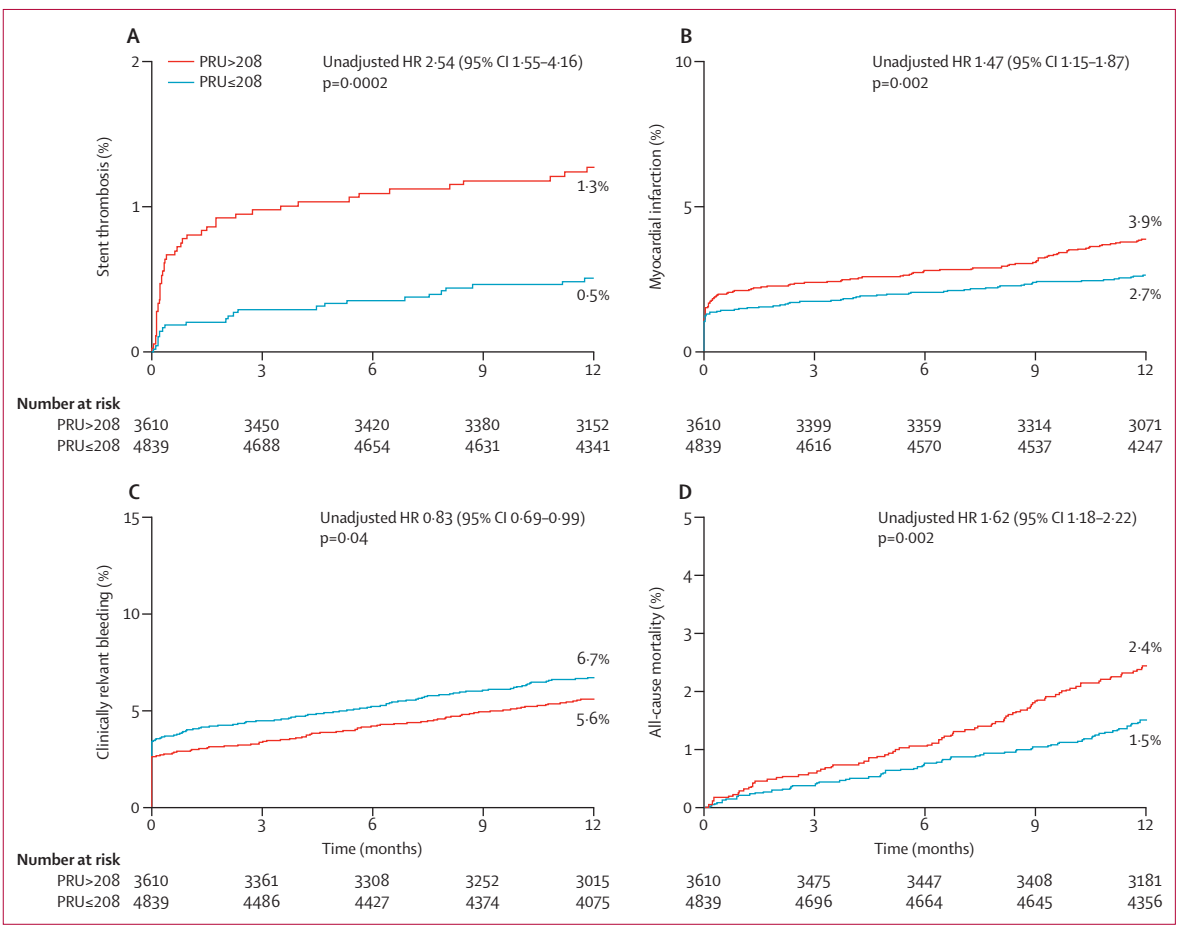

Figure 1: **Time-to-event curves through 1-year for selected adverse events according to platelet reactivity to clopidogrel**
PRU=P2Y12 reaction units. (A) Definite or probable stent thrombosis. (B) Myocardial infarction. (C) Clinically relevant bleeding. (D) All-cause mortality.

patients for VerifyNow Aspirin, at a mean time of 20·3 h (SD 8·3) after PCI. Mean PRU was 188 (97) and mean ARU was 419 (55). 3610 (42·7%) patients had high platelet reactivity on clopidogrel when we applied the prespecified cutoff PRU value higher than 208, and 2961 (35·0%) patients had high platelet reactivity on clopidogrel when we used the PRU cutoff value of 230 or higher. 478 (5·6%) patients had high platelet reactivity on aspirin when we applied the prespecified ARU cutoff value higher than 550. Mean value for P2Y12 BASE was 310 (SD 58), for percentage inhibition 40·0% (28·3), and IIb/IIIa PAU 193 (53).

A thienopyridine (99·7% clopidogrel) was prescribed at discharge in all patients, and was taken through the first year of follow-up for a mean duration of 334 days (SD 120). Aspirin was prescribed at discharge in 8510 (99·1%) patients, and was taken for 345 days (120). A thienopyridine was taken without any daily interruption during the first year (or until the time of a major adverse event) in 7045 (82·1%) patients, and so was aspirin in 7583 (88·3%) patients.

8246 (96·1%) patients completed 1-year follow-up. The mean duration of follow-up was 350 days (64), with median follow-up of 365 days (IQR 365–365). Stent thrombosis within 1-year occurred in 70 (0·84%) patients; 53 (0·63%) of these events were angiographically-confirmed definite stent thrombosis, whereas 17 (0·20%) were probable stent thrombosis. The appendix shows the timing of the stent thrombosis events. 40 (57·1%) of the stent thromboses occurred within 30 days.

P2Y12 PRU and percent inhibition after PCI were strongly related to subsequent stent thrombosis (table 2 and figure 1). The unadjusted rate of definite or probable stent thrombosis was increased in patients with high platelet reactivity compared with patients without high platelet reactivity with the cutoff of a PRU higher than 208 (1·3% with high platelet reactivity *vs* 0·5% without, HR 2·54 [95% CI 1·55–4·16], p=0·0002) and with the cutoff of 230 PRU or higher (1·3% with high platelet reactivity *vs* 0·6% without, HR 2·16 [1·35–3·47], p=0·001). In 6723 patients who took a thienopyridine without interruption for the full year, definite or probable stent thrombosis was also increased in patients with PRU higher than 208, compared with that in those with 208 PRU or less (1·4% *vs* 0·6%, p=0·002). We noted no significant associations between P2Y12 Base, IIb/IIIa PAU, or ARU, and stent thrombosis (table 2). Table 3 shows clinical, angiographic, and laboratory test correlates of 1-year stent thrombosis. By propensity-adjusted multivariable analysis, a PRU higher than 208 was an independent predictor of stent thrombosis (table 4). At this cutpoint, PRU was able to reclassify the risk of definite stent thrombosis for 35% of patients (with NRI) when stratified by overall tertiles of risk within the cohort (risk categories 0–0·39%, >0·39–0·77%, and >0·77%), although the absolute magnitude of the change in risk was low, as portrayed in the low IDI (table 5). The sensitivity, specificity, and diagnostic accuracy of high platelet reactivity on clopidogrel for subsequent stent thrombosis were poor to fair (table 5 and appendix). Also of note, by ROC analysis the optimum PRU cutoff for both definite-probable and definite stent thrombosis was 206. The relation between high platelet reactivity on clopidogrel and stent thrombosis was greater within the first 30 days than between 30 days and 1 year (appendix).

Different loading doses of clopidogrel (≤75 mg, >75–<600 mg, and ≥600 mg) were given to patients before VerifyNow testing and were associated with progressively lower PRU values (212 [SD 94] for 1146 patients receiving ≤75 mg, *vs* 190 [93] for 2295 patients receiving >75–<600 mg, *vs* 183 [98] for 5142 patients receiving ≥600 mg; $p_{trend}<0·0001$). However, the 1-year rate of definite-probable stent thrombosis did not significantly differ according to clopidogrel loading dose (1·1% for ≤75 mg *vs* 0·9% for >75–<600 mg *vs* 0·8% for ≥600 mg, $p_{trend}=0·62$).

	Stent thrombosis (n=70)	No stent thrombosis (n=8513)	p value
Age (years)	62·1 (12·3)	63·6 (10·8)	0·23
Female sex	22 (31·4%)	2203 (25·9%)	0·29
Body-mass index (kg/m^2)	30·8 (7·1)	29·5 (5·7)	0·049
Hypertension	60 (85·7%)	6774 (79·6%)	0·21
Hyperlipidaemia	55 (78·6%)	6325 (74·3%)	0·43
Cigarette smoking (within 1 month)	18 (25·7%)	1921 (22·6%)	0·51
Diabetes	33 (47·1%)	2750 (32·3%)	0·009
Insulin-treated	17 (24·3%)	981 (11·5%)	0·001
History of peripheral arterial disease	13 (18·6%)	863 (10·1%)	0·02
History of congestive heart failure	7 (10·0%)	692 (8·1%)	0·55
Previous myocardial infarction (>7 days before percutaneous coronary intervention)	28 (40·0%)	2136 (25·1%)	0·005
Previous coronary artery bypass graft surgery	18 (25·7%)	1449 (17·0%)	0·06
Previous percutaneous coronary intervention	35 (50·0%)	3641 (42·8%)	0·22
History of renal insufficiency	13 (18·6%)	647 (7·6%)	0·0009
US site	54 (77·1%)	6059 (71·2%)	0·24
Acute coronary syndrome	50 (71·4%)	4386 (51·5%)	0·001
Unstable angina	20 (28·6%)	2353 (27·6%)	0·86
Non ST-segment elevation	15 (21·4%)	1235 (14·5%)	0·10
ST-segment elevation	15 (21·4%)	798 (9·4%)	0·0009
Lesion in left anterior descending artery treated	37 (52·9%)	3915 (46·0%)	0·24
Number of lesions treated per patient	1·54 (0·81)	1·51 (0·78)	0·71
Number of stents implanted per patient	1·94 (1·20)	1·72 (1·02)	0·07
Total stent length (mm)	37·7 (26·3)	32·4 (22·3)	0·051
Maximum stent diameter (mm)	3·15 (0·54)	3·26 (0·54)	0·10
Maximum balloon pressure (atm)	16·3 (3·6)	16·8 (3·6)	0·25
Baseline creatinine clearance (mL/min)	86·8 (47·4)	94·2 (37·3)	0·10
Baseline haemoglobin (g/dL)	13·5 (1·6)	14·0 (1·5)	0·01
Baseline white blood cell count (×10^3 cells per mm^3)	9·1 (3·5)	7·9 (3·2)	0·003
Baseline platelet count (×10^3 cells per mm^3)	242·2 (72·0)	226·6 (62·9)	0·04

Data are number of patients (%) or mean (SD).

Table 3: **Clinical, angiographic and laboratory test correlates of stent thrombosis occurring within 1 year (unadjusted analyses)**

	PRU				ARU			
	Event rate at 1 year (unadjusted)		Adjusted HR (95% CI)	p value	Event rate at 1 year (unadjusted)		Adjusted HR (95% CI)	p value
	PRU >208 (n=3610)	PRU ≤208 (n=4839)			ARU >550 (n=478)	ARU ≤550 (n=8049)		
Stent thrombosis								
Definite or probable	1·3% (45)	0·5% (24)	2·49 (1·43–4·31)	0·001	1·1% (5)	0·8% (64)	1·46 (0·58–3·64)	0·42
Definite	1·0% (35)	0·4% (18)	3·05 (1·62–5·75)	0·0006	0·9% (4)	0·6% (48)	1·60 (0·57–4·48)	0·37
Myocardial infarction	3·9% (137)	2·7% (126)	1·42 (1·09–1·86)	0·01	2·8% (13)	3·2% (253)	0·81 (0·46–1·42)	0·46
Clinically relevant bleeding	5·6% (198)	6·7% (320)	0·73 (0·61–0·89)	0·002	5·4% (26)	6·2% (501)	0·65 (0·43–0·99)	0·04
Death, all-cause*	2·4% (85)	1·5% (71)	1·20 (0·85–1·70)	0·30	3·7% (17)	1·8% (143)	1·42 (0·83–2·43)	0·20

Rates are Kaplan-Meier estimates at 1 year (number of events). p values correspond to the adjusted HR (95% CI). In addition to the propensity score for PRU or ARU, the stent thrombosis models were adjusted for diabetes, presentation with acute coronary syndrome, previous myocardial infarction (definite or probable stent thrombosis only), baseline CrCl, baseline haemoglobin, baseline white blood cell count, and baseline platelet count (definite or probable stent thrombosis only). All the other models were adjusted by age, sex, diabetes, hypertension, hyperlipidaemia, current smoker, previous myocardial infarction, presentation with acute coronary syndrome, baseline haemoglobin, baseline white blood cell count, baseline platelet count, baseline CrCl, and multivessel disease. PRU=P2Y12 reaction units. ARU=aspirin reaction units. HR=hazard ratio. CrCl= creatinine clearance. *Among 161 patients who died, PRU was unavailable in five patients and ARU was unavailable in one patient.

Table 4: **Propensity-adjusted multivariable risk of high platelet reactivity for subsequent 1-year adverse events**

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC*	NRI		IDI	
							Index	p value	Index	p value
Stent thrombosis, definite or probable	65·2%	57·5%	1·2%	99·5%	57·5%	0·624	0·1292	0·04	0·0009	0·04
Stent thrombosis, definite	66·0%	57·4%	1·0%	99·6%	57·5%	0·631	0·2436	0·003	0·0008	0·08
Myocardial infarction	52·1%	57·6%	3·8%	97·4%	57·4%	0·568	0·0448	0·04	0·0009	0·05
Clinically relevant bleeding	38·2%	57·0%	5·5%	93·4%	55·8%	0·537	0·0440	0·01	0·0012	0·001
Death, all-cause	54·5%	57·5%	2·4%	98·5%	57·4%	0·568	0·0196	0·31	0·0002	0·44
Cardiovascular	53·6%	57·4%	1·4%	99·1%	57·4%	0·562	0·0120	0·60	<0·0001	0·80
Non-cardiovascular	55·9%	57·4%	0·9%	99·5%	57·4%	0·575	−0·0049	0·90	0·0002	0·65

PRU=P2Y12 reaction units. PPV=positive predictive value. NPV=negative predictive value. ARU=area under the curve. NRI=net reclassification index (tertiles analysis, stratified by propensity quintiles). IDI=integrated discriminatory index. *AUC from receiver operating characteristic (ROC) analyses.

Table 5: **Predictive accuracy of P2Y12 PRU higher than 208 for 1 year events in 8449 patients**

	Event	No event	Unadjusted HR (95% CI)	p value
Definite ST				
Number of events	53	8530		
Deaths	5 (9·6%)	156 (1·9%)	5·47 (2·25–13·31)	<0·0001
MI without ST				
Number of events	224	8359		
Deaths	21 (9·7%)	140 (1·7%)	5·78 (3·65–9·14)	<0·0001
Bleeding				
Number of events	531	8052		
Deaths	45 (8·6%)	116 (1·5%)	5·97 (4·23–8·42)	<0·0001

HR=hazard ratio. MI=myocardial infarction. ST=stent thrombosis.

Table 6: **Relationship between adverse events and death though 1 year follow-up**

Through 1-year follow-up, 269 (3·1%) patients had a myocardial infarction, 531 (6·2%) patients had clinically relevant bleeding, and 161 (1·9%) patients died. In patients with PRU higher than 208, the 1-year rates of myocardial infarction were significantly increased, whereas the 1-year rates of clinically relevant bleeding were significantly decreased in both unadjusted and multivariable analyses (table 4, figure 1 and appendix). By univariable analysis, 1-year all-cause mortality was greater in patients with a PRU after PCI higher than 208 (figure 1). However, platelet reactivity was also associated with several other known predictors of mortality, including age, diabetes, previous myocardial infarction, acute coronary syndrome presentation, and anaemia (appendix). After propensity-adjusted multivariable analysis, a PRU higher than 208 was no longer significantly associated with mortality (table 4). Consistent with these data, PRU higher than 208 contributed to accurately classifying the likelihood of myocardial infarction and clinically relevant bleeding in tertiles of risk, but not death (table 5).

The baseline PRU was significantly higher in patients with acute coronary syndromes than in those presenting with stable coronary artery disease (194 [SD 96] *vs* 182 [97], p<0·0001). The relation between platelet reactivity on clopidogrel and both ischaemic and bleeding events were directionally similar in patients with and without acute coronary syndromes (appendix).

ARU higher than 550 was not significantly related to myocardial infarction or death, but was inversely associated with clinically relevant bleeding (table 4).

Table 6 shows the effects of ischaemic and haemorrhagic events on all-cause mortality. By multivariable analysis, stent thrombosis, myocardial infarction, and clinically relevant bleeding were all strongly associated with all-cause mortality through 1-year follow-up (table 7). Figure 2 shows the potential effects of modulating platelet reactivity on the rates of stent thrombosis and clinically relevant bleeding.

Discussion

The principal findings from the present prospective, multicentre study, the largest investigation so far examining the relation between platelet reactivity and ischaemic and haemorrhagic complications after coronary drug-eluting stent implantation, are: (1) high platelet reactivity on clopidogrel was an independent predictor of 1-year stent thrombosis and myocardial infarction after drug-eluting stent placement, but was also protective against clinically relevant bleeding; (2) ischaemic and haemorrhagic complications were strongly related to all-cause mortality; (3) high platelet reactivity on clopidogrel was not an independent predictor of mortality; and 4) high platelet reactivity on aspirin was not significantly associated with stent thrombosis, myocardial infarction or death, but was protective from clinically relevant bleeding.

The present large-scale study of 8583 patients confirms smaller reports linking high platelet reactivity on clopidogrel with stent thrombosis and myocardial infarction,[6–11,17] illustrating the central role of the ADP-P2Y12 pathway in ischaemic complications after coronary drug-eluting stent (panel). Moreover, VerifyNow P2Y12 PRU strongly correlates with active metabolite levels of clopidogrel,[23] and the present report validates the capability of this point-of-care assay to identify clopidogrel-treated patients at increased risk for stent thrombosis and myocardial infarction after drug-eluting stent implantation. Analysis of the NRI and IDI showed that PRU was able to reclassify the risk of developing stent thrombosis and myocardial infarction (as well as clinically relevant bleeding, as described below) beyond baseline clinical characteristics, although the absolute magnitude of the change in risk was small. Similarly, the sensitivity, specificity and overall diagnostic accuracy of high platelet reactivity for ischaemic events were at best fair, partly due to their low frequency. Breet and colleagues[6] also found a positive correlation between VerifyNow P2Y12-assessed platelet reactivity and ischaemic events after stent implantation, but with only fair discrimination. Thus, most patients with high platelet reactivity on clopidogrel will not develop stent thrombosis or myocardial infarction, and many patients in whom future events will develop exhibit low platelet reactivity on clopidogrel.

	Adjusted HR (95% CI)	p value
Age (years)	1·03 (1·01–1·06)	0·002
Male gender	1·96 (1·33–2·89)	0·0007
Diabetes mellitus	1·85 (1·30–2·63)	0·0006
Current smoking	1·48 (0·96–2·29)	0·08
Hyperlipidaemia	0·60 (0·41–0·86)	0·006
Creatinine clearance (per mL/min)	0·99 (0·98–1·00)	0·003
Haemoglobin (per g/dL)	0·73 (0·65–0·83)	<0·0001
WBC (per 10^3/mL)	1·03 (1·01–1·05)	0·006
Acute coronary syndrome (*vs* stable CAD)	1·39 (0·96–2·01)	0·08
Premature antiplatelet agent discontinuation within 6 months	4·35 (3·00–6·32)	<0·0001
Adverse events		
Definite stent thrombosis	4·68 (1·68–13·01)	0·003
Myocardial infarction (without definite stent thrombosis)	4·41 (2·67–7·28)	<0·0001
Clinically relevant bleeding	4·02 (2·74–5·90)	<0·0001

All variables remaining in the final model with p<0·10 are displayed. Other variables entered in the model include previous myocardial infarction, hypertension, platelet count, and multivessel disease. Note: In a second model in which PRU and ARU were added, high platelet reactivity was not independently related to mortality.

Table 7: **Independent predictors of all-cause mortality, including adverse events occurring during follow-up as time-adjusted covariates**

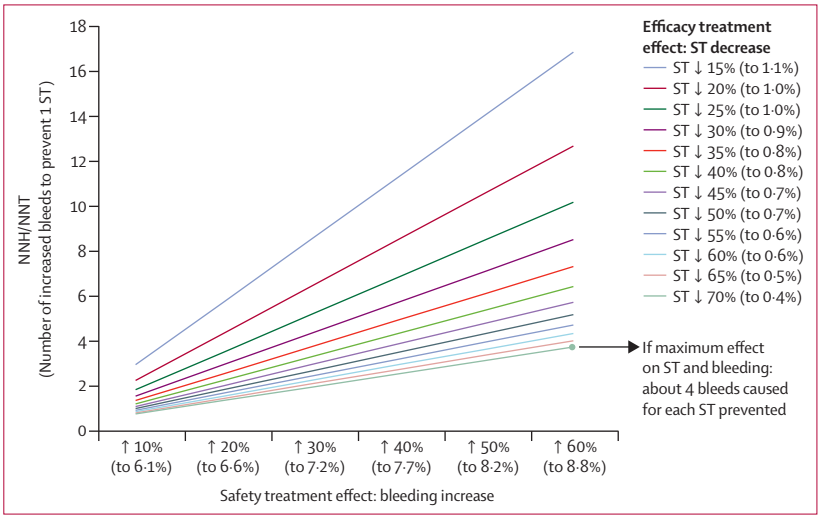

Figure 2: **Hypothetical incremental decrease in definite or probable stent thrombosis (from 1·3%) versus incremental increase in clinically relevant bleeding (from 5·6%) by overcoming high platelet reactivity in patients with PRU higher than 208**

From the fully adjusted multivariable model, the HR for PRU >208 *vs* ≤208 was 2·49 for ST and for clinically relevant bleeding 0·73. The family of curves thus represents the range of trade-off of decreasing ST *vs* increasing clinically relevant bleeding that might occur if high platelet reactivity on clopidogrel was eliminated to varying degrees (taking into account the incidence of every event). The most rightward point of the lower curve (green dot) represents the maximum effect: about four bleeds would be caused for every stent thrombosis prevented. If this maximum protective effect against stent thrombosis could be preserved with a lesser effect on bleeding, the bleeding rate (and therefore the ratio of number needed to harm versus number needed to treat (NNH:NNT) would be reflected by a more leftward point on the same curve. If a lesser protective effect against stent thrombosis were noted, the tradeoff of bleeds caused *vs* stent thromboses prevented would be reflected on one of the higher curves. PRU=P2Y12 reaction units. ST=stent thrombosis. HR=hazard ratio. NNT=number needed to treat. NNH=number needed to harm.

Nonetheless, as stent thrombosis and myocardial infarction were both strongly associated with mortality, a reasonable hypothesis might be that more potent inhibition of ADP-induced platelet activation would

Panel: Research in Context

Systematic review.

We searched PubMed for all studies with more than 1000 patients undergoing stent implantation reporting the relation between high platelet reactivity (HPR) on clopidogrel and subsequent individual rates of stent thrombosis, myocardial infarction, bleeding, or death. In one study[9] of light transmission aggregometry (LTA) in 1019 patients, HPR was associated with increased 3 month rates of stent thrombosis (OR 2·32, 95% CI 1·05–5·14), non-fatal myocardial infarction (2·15, 1·01–4·57), and cardiovascular death (3·02, 1·33–6·87). Also using LTA in 1051 patients, Breet and colleagues[6] found that HPR was associated with greater 1-year rates of stent thrombosis (OR 3·85, 1·18–12·57) and myocardial infarction (OR 2·76, 1·63–4·68), but not all-cause mortality. In the same study,[6] using the VerifyNow P2Y12 assay in 1052 patients (PRU cutoff of 236), HPR was associated with increased rates of myocardial infarction (2·96, 1·74–5·03), but not stent thrombosis or death. Neither test predicted bleeding in that study.[6] Park and colleagues[12] reported that in 2849 patients who received drug-eluting stents, HPR (defined as VerifyNow P2Y12 PRU >235) was not significantly associated with the subsequent occurrence of stent thrombosis, myocardial infarction, or death at a median 2·2 years follow-up.[12] Using the Multiplate analyser in 1608 patients, Sibbing and colleagues[10] reported that HPR was significantly associated with greater rates of stent thrombosis (OR 7·43, 2·44–22·06) and non-fatal myocardial infarction (OR 4·03, 1·16–14·00) at 30 days following drug-eluting stent implantation, but not cardiovascular death.[10] In a follow-up study of 2533 patients, Sibbing and colleagues[19] reported that "enhanced responders" to clopidogrel (40% of patients) had increased rates of clinical bleeding. In 1789 patients with acute coronary syndromes undergoing stenting, Parodi and colleagues[11] reported that HPR by LTA was an independent predictor of cardiac death at 2 years (HR 1·81, 95% CI 1·18–2·76).

Interpretation

Most (but not all) previous studies have suggested that HPR on clopidogrel as assessed by a variety of platelet function assays is associated with stent thrombosis and non-fatal myocardial infarction, whereas the relation between HPR and bleeding and mortality has been inconsistent. These studies have been limited by a modest number of endpoint events and variably by the different assays used (with different agonist concentrations), inconsistent cutpoints to define HPR (often determined post hoc), variable stent types, non-blinding of the investigators to the platelet function results, variable time to follow-up, lack of monitoring and independent event adjudication, or lack of multivariable adjustment. The present large-scale study thus overcomes these limitations, and while confirming a strong independent relation between HPR on clopidogrel and ischaemic events at 30 days and 1 year, also establishes an inverse correlation between HPR and clinically relevant bleeding, consequently with a neutral effect on mortality. These data should be useful in informing future clinical trials investigating potent antiplatelet and antithrombotic drugs, as well as the role of platelet function testing, in patients with cardiovascular disease.

prevent ischaemic complications of drug-eluting stent implantation and therefore improve survival, absent adverse effects from more potent platelet inhibition. In this regard, an important finding of the present large-scale study was identification of a strong inverse relationship between platelet reactivity on clopidogrel and clinically relevant bleeding, a relationship present in some, but not all prior studies.[6,17–19] Moreover, high platelet reactivity on clopidogrel was not an independent predictor of mortality in the present study, and PRU did not provide utility beyond the baseline risk profile in reclassifying patient propensity for death. The explanation for the absence of relation between P2Y12-mediated platelet reactivity and mortality might lie in the offsetting effects of ischaemic and haemorrhagic complications on survival. Consistent with previous findings,[24,25] clinically relevant bleeding was strongly associated with mortality with an adjusted HR similar to that of stent thrombosis and myocardial infarction. Indeed, in view of the greater frequency of bleeding than stent thrombosis or myocardial infarction, more deaths were associated with bleeding than with ischaemia (table 6). Modelling the inverse relation between ischaemia and bleeding and their effects on mortality suggests that overcoming high platelet reactivity on clopidogrel with more potent antiplatelet agents might not improve survival unless the beneficial effects of reducing stent thrombosis and myocardial infarction can be uncoupled from the potential increase in prognostically important bleeding with greater platelet inhibition (figure 2).

Three randomised trials have examined the utility of more potent P2Y12 inhibition in patients with high platelet reactivity on clopidogrel, but were unable to show a reduction in stent thrombosis or myocardial infarction with this approach.[26–28] However, limitations of these trials included enrolment of low-risk patients resulting in lower event rates and study power than expected;[26–28] non- or infrequent use of a potent ADP-receptor antagonist;[26,28] and inclusion of liberally-defined periprocedural myocardial infarction events that drove the primary endpoint,[28] which might or might not be preventable by greater inhibition of platelet function (by contrast with later myocardial infarction events). The results of the present study suggest that PRU-guided selection of more potent ADP receptor antagonists in high-risk patients with high platelet reactivity on clopidogrel should be effective in reducing stent thrombosis and myocardial infarction, although at the cost of increased bleeding, with a neutral effect on mortality.

High platelet reactivity on aspirin was not significantly associated with stent thrombosis, myocardial infarction, or mortality after drug-eluting stent implantation, but was an independent predictor of freedom from clinically relevant bleeding. Consistent with these findings, results from a small randomised trial[29] (n=583) showed that treatment with clopidogrel alone compared with aspirin plus clopidogrel reduced bleeding without an increase in ischaemic complications in patients undergoing coronary stenting also treated with chronic oral anticoagulation.[29] However, the proportion of patients with high platelet reactivity on aspirin in the present study was low, and our findings in this regard should be considered hypothesis-generating. An adequately powered randomised trial is required before withholding aspirin in drug-eluting stent-treated patients (with or without chronic oral anticoagulation) can be recommended.

Our study has limitations. First, although only 8583 of a planned 11000 patients were enrolled, the present sample size still provided 99% power to demonstrate the relation between high platelet reactivity and the primary

stent thrombosis endpoint. Moreover, stent thrombosis occurred in 70 (0·84%) patients within the first year in the present study (despite the use of second generation drug-eluting stents in most patients), reflecting the all-comers nature of the enrolled cohort. Myocardial infarction, bleeding, and death rates were also substantial. Nonetheless, a small effect of suboptimum platelet inhibition on mortality cannot be excluded. Further analyses are also needed to identify the effect of high platelet reactivity in high-risk subgroups, such as those with acute coronary syndromes and diabetes. Second, more than 40 baseline and procedural variables associated with high platelet reactivity were identified. The importance of adequately adjusting for these confounders is portrayed in the fact that high platelet reactivity on clopidogrel was associated with mortality before, but not after, accounting for the relation between these variables and PRU. Nonetheless, unmeasured confounders might still be present, adding some degree of imprecision to the final models. The extent to which unmeasured confounders contribute to the relation between adverse events (eg, myocardial infarction and bleeding) and subsequent mortality is also undetermined. Residual confounding might also partly explain why premature antiplatelet agent discontinuation within 6 months was a powerful predictor of mortality, whereas ARU higher than 550 and PRU higher than 208 per se were not. Third, we assessed platelet reactivity at only a single timepoint, typically the day after adequate anti-platelet agent loading. As some[8,30] but not all[31] studies have suggested that platelet responsiveness varies over time, platelet function testing at different time periods (or serial testing) might have provided incremental prognostic information. Testing after PCI also precludes examining the effect of high platelet reactivity on peri-procedural events. However, a single test as performed in the present study during the index procedure hospital admission is most relevant to clinical practice, and high platelet reactivity on clopidogrel at this timepoint was a powerful independent predictor of subsequent adverse ischaemic events and (freedom from) haemorrhagic complications. Finally, although the results of the present study do not support the routine performance of platelet function testing to guide selection or dosing of anti-platelet agents, it is unknown whether the inverse relation between ischaemia and bleeding as a function of ADP-induced platelet inhibition is linear. Further study is required to determine whether an optimal therapeutic window exists which might be targeted.[17–19] Similarly, high platelet reactivity on clopidogrel had the greatest effect on both ischaemic and bleeding complications within the first 30 days, the time period during which both of these events occur most frequently. Whether the selective administration of more potent platelet inhibitors during a circumscribed time period might favourably affect the balance between these events is unknown.

In conclusion, in the present large-scale prospective study of patients treated with coronary drug-eluting stents, high platelet reactivity on clopidogrel was an independent predictor of the 1-year occurrence of stent thrombosis and myocardial infarction, but was also protective against clinically relevant bleeding, each of which were independently related to all-cause mortality. High platelet reactivity on clopidogrel was not independently predictive of mortality, however, possibly a consequence of the offsetting effects of P2Y12-mediated platelet reactivity on haemorrhagic and ischaemic complications. High platelet reactivity on aspirin was not related to ischaemic events or mortality, but was protective from clinically relevant bleeding. These findings emphasise the importance of haemorrhagic as well as ischaemic complications, and suggest that safer drugs or tailored strategies for the use of more potent agents must be developed if the benefits of greater platelet inhibition in patients with cardiovascular disease are to be realised.

Contributors

GWS, TDS, BRB, PAG, and HP designed the study. HP, KX, AJK, and GWS did the statistical analysis and interpretation of statistical data. GWS wrote the report. All the authors reviewed the report and provided critical input for its revision.

Conflicts of interest

GWS has served as a consultant for Osprey, Reva, Merck, Boston Scientific, Abbott Vascular, AstraZeneca, Eli Lilly-Daiichi Sankyo partnership, Bristol-Myers Squibb-Sanofi partnership, Otsuka, The Medicines Company, Ortho-McNeil, Gilead, InspireMD, TherOx, Atrium, Volcano, InfraReDx, Medtronic, Genentech, GlaxoSmithKline, Miracor, MPP Group, Lutonix, Velomedix, CSI, AGA, and Thoratec; has received honoraria from Edwards and Vascular Solutions; and has hold stock or options from CoreValve, Biostar I and II funds, MedFocus I, II, and Accelerator funds, Caliber, Flowcardia, Guided Delivery Systems, Arstasis, Micardia, Access Closure, Embrella and VNT. BW has received lecture honoraria from Volcano Corp, Boston Scientific, and Abbott Vascular. GW has been a board member on Bloxr; has served as a consultant for Tryton, Bloxr, Infraredx, Phillips, Svelte, Sync-Rx, Simbionix; and his wife holds a patent and stock options in MGVS. F-JN has served as a consultant for Eli Lilly, Daiichi Sankyo, and AstraZeneca; has received grants from Eli Lilly, Daiichi Sankyo, AstraZeneca, The Medicines Company, Boston Scientific, Medtronic, Cordis, and Roche Pharma; and has received speaker fees from Eli Lilly, Daiichi Sankyo, AstraZeneca, The Medicines Company, Biotronik, Boston Scientific, and Medtronic. CM has served as a consultant for Abbott Vascular and The Medicines Company; and has received honoraria from Abbott Vascular and speaker fees from The Medicines Company. DAC has served as a consultant for Abbott Vascular, Boston Scientific, and The Medicines Company. PAG has served as a consultant to Daiichi Sankyo, Lilly, Boehringer Ingleheim, Merck, Medtronic, Iverson Genetics, Pozen, Novartis, Bayer, Astrazeneca, Accumetrics, Nanosphere, Sanofi-Aventis, CSL, and Hemonetics; has received grants from NIH, Daiichi Sankyo/Lilly, Pozen, CSL, Astra Zeneca, Sanofi-Aventis, Haemoscope, HCRI, and DCRI; has received lecture honoraria from Lilly/ Daiichi Sankyo; has received payment for preparation of educational presentations from Schering Plough, Discovery Channel, Primed; and has stock or stock options from Merck, Pfizer, and Medtronic. RM has served as a consultant for AstraZeneca, Janssen (Johnson & Johnson), Regado, Abbott, Merck, Maya Medical; and has received grants from Sanofi/BMS, The Medicines Co, and Lilly/ Daiichi Sankyo. TDS has received honoraria and lecture fees from Boston Scientific. The other authors declare they have no conflicts of interest.

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