Balancing Long-Term Risks of Ischemic and Bleeding Complications After Percutaneous Coronary Intervention With Drug-Eluting Stents

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Although trials comparing antiplatelet strategies after percutaneous coronary intervention report average risks of bleeding and ischemia in a population, there is limited information to guide choices based on individual patient risks, particularly beyond 1 year after treatment. Patient-level data from Patient Related Outcomes With Endeavor vs Cypher Stenting Trial (PROTECT), a broadly inclusive trial enrolling 8,709 subjects treated with drug-eluting stents (sirolimus vs zotarolimus-eluting stent), and PROTECT US, a single-arm study including 1,018 subjects treated with a zotarolimus-eluting stent, were combined. The risk of ischemic events, cardiovascular death/non-periprocedural myocardial infarction (MI)/definite or probable stent thrombosis, and bleeding events, Global Use of Strategies to Open Occluded Arteries moderate or severe bleed, were predicted using logistic regression. At median follow-up of 4.1 years, major bleeding occurred in 260 subjects (2.8%) and ischemic events in 595 (6.3%). Multivariate predictors of bleeding were older age, smoking, diabetes mellitus, congestive heart failure, and chronic kidney disease (all $p < 0.05$). Ischemic events shared all the same predictors with bleeding events and gender, body mass index, previous MI, previous coronary artery bypass graft surgery, ST-segment elevation MI on presentation, stent length, and sirolimus-eluting stent use (all $p < 0.05$). Within individual subjects, bleeding and ischemic risks were strongly correlated; 97% of subjects had a greater risk of ischemic events than bleeding. In conclusion, individual patient risks of ischemia and bleeding are related to many common risk factors, yet the predicted risks of ischemic events are greater than those of major bleeding in the large majority of patients in long-term follow-up. **(Am J Cardiol 2015;116:686–693)**

Although clinical studies regarding duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) generally summarize average treatment effects, in clinical practice, treatment choices are made for individual patients according to their perceived risks for benefit and harm based on their unique clinical presentation and characteristics. Since the first reports of an increase in very late stent thrombosis with drug-eluting stents (DES), the appropriate antiplatelet regimen has been a matter of debate.[1] Although several trials evaluating duration of DAPT were underpowered to detect differences in infrequent events such as stent thrombosis, a meta-analysis showed that the extended duration of DAPT was associated with a reduction in stent thrombosis at the expense of an increase in clinically significant bleeding.[2–9] A decision analytic model evaluating this balance at the population level found that a small reduction in ischemic events is needed to offset the higher bleeding risk associated with longer duration of DAPT.[10] Determining this balance for individual patients requires understanding the correlation between both risks. We sought to estimate individual patient risks of long-term ischemic and bleeding complications after PCI with DES and to compare the magnitude of these risks in individual patients and subgroups.

Methods

The study population consisted of 9,727 subjects enrolled in the Patient Related Outcomes With Endeavor vs Cypher Stenting Trial (PROTECT) or in the PROTECT US study.[11,12] The PROTECT trial was a large, broadly inclusive, multicenter randomized controlled trial comparing the long-term safety of 2 different DES, the Endeavor zotarolimus-eluting stent (Medtronic Inc, Santa Rosa, CA),

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See page 692 for disclosure information.

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Table 1
Baseline characteristics according to clinical outcomes

Variable	Ischemic Event		Bleeding Event	
	No (n=8815)	Yes (n=595)	No (n=9150)	Yes (n=260)
Age, mean ± SD (years)	62.1 ± 10.5	66.2 ± 11.2*	62.2 ± 10.6	67.3 ± 10.1†
Age ≥ 75 years old	1079 (12.2%)	152 (25.6%)	1165 (12.7%)	66 (25.4%)
Male	6705 (76.1%)	458 (77.0%)	6691 (76.4%)	172 (66.2%)†
Body mass index, mean ± SD (kg/m^2)	28.0 ± 4.6	28.4 ±5.7	28.1 ± 4.7	27.9 ± 5.6
Active smoking	2170 (24.6%)	151 (25.4%)	2261 (24.7%)	60 (23.1%)
Hypertension	5719 (64.9%)	441 (74.1%)*	5967 (65.2%)	193 (74.2%)†
Diabetes	2378 (27.0%)	262 (44.0%)*	2548 (27.9%)	92 (35.4%)†
Prior myocardial infarction	1695 (19.2%)	175 (29.4%)*	1820 (19.9%)	50 (19.2%)
Prior percutaneous coronary intervention	1096 (12.4%)	96 (16.1%)*	1161 (12.7%)	31 (11.9%)
Known peripheral vascular disease	414 (4.7%)	53 (8.9%)*	442 (4.8%)	25 (9.6%)†
Prior stroke	261 (3.0%)	34 (5.7%)*	283 (3.1%)	12 (4.6%)
Prior coronary artery bypass graft surgery	446 (5.1%)	55 (9.2%)*	484 (5.3%)	17 (6.5%)
Prior congestive heart failure	260 (3.0%)	49 (8.2%)*	289 (3.2%)	20 (7.7%)†
Creatinine clearance, mL/min				
≥60	7099 (80.5%)	379 (63.7%)*	7308 (79.9%)	170 (65.4%)†
30-59	1120 (12.7%)	151 (25.4%)*	1196 (13.1%)	75 (28.9%)†
<30	44 (0.5%)	20 (3.4%)*	56 (0.6%)	8 (3.1%)†
Missing	552 (6.3%)	45 (7.6%)*	590 (6.4%)	7 (2.7%)†
Presentation				
Stable angina	5073 (57.6%)	317 (53.3%)*	5252 (57.4%)	138 (53.1%)
Non-ST elevation acute coronary syndrome	3077 (34.9%)	218 (36.6%)*	3194 (34.9%)	101 (38.9%)
ST elevation myocardial infarction	665 (7.5%)	60 (10.1%)*	704 (7.7%)	21 (8.1%)
Stent				
C-SES	3934 (44.6%)	301 (50.6%)*	4126 (45.1%)	109 (41.9%)
E-ZES	4881 (55.4%)	294 (49.4%)*	5024 (54.9%)	151 (58.1%)
Left main percutaneous coronary intervention	103 (1.2%)	13 (2.2%)*	110 (1.2%)	6 (2.3%)
Lesion length > 18 mm	3823 (43.4%)	299 (50.3%)*	4007 (43.8%)	115 (44.4%)
Stent length (mm)	31.1 ± 20.6	35.4 ± 24.2*	31.3 ± 20.8	32.1 ± 23.3
Vessel diameter ≤2.75 mm	3500 (39.7%)	278 (46.7%)*	3677 (40.2%)	101 (39.0%)
Bifurcation	1854 (21.0%)	140 (23.5%)	1939 (21.2%)	55 (21.2%)
Multivessel intervention	1648 (18.7%)	145 (24.4%)*	1751 (19.1%)	42 (16.2%)
Saphenous vein graft intervention	27 (0.3%)	7 (1.2%)*	33 (0.4%)	1 (0.4%)
In-stent restenosis	124 (1.4%)	6 (1.0%)	124 (1.4%)	6 (2.3%)
Stent number				
0	84 (0.9%)	9 (1.5%)*	86 (0.9%)	7 (2.7%)†
1	5191 (58.9%)	286 (48.1%)*	5333 (58.3%)	144 (55.4%)†
2	2270 (25.8%)	185 (31.1%)*	2386 (26.1%)	69 (26.5%)†
≥3	1270 (14.4%)	115 (19.3%)*	1345 (14.7%)	40 (15.4%)†

C-SES = cypher sirolimus eluting stent; E-ZES = endeavor zotarolimus eluting stent.
* $p < 0.05$ for the comparison of no ischemic event versus ischemic event.
† $p < 0.05$ for the comparison of no bleeding event versus bleeding event.

and the Cypher sirolimus-eluting stent (Cordis J&J, Fremont, CA); 8,709 subjects were randomized from May 2007 to December 2008 and have reached at least 4 -year follow-up. The PROTECT US study was a single-arm study following the PROTECT inclusion/exclusion criteria of 1,018 patients who received an Endeavor zotarolimus-eluting stent and were followed for at least 3 years. Both excluded patients with previous bare-metal stent in the last 12 months, previous DES, previous brachytherapy, or need for oral anticoagulation. Long-term use of DAPT was recommended for a minimum of 3 months up to 12 months or longer according to guidelines and treating physicians.

The primary ischemic end point for the current analysis was a composite of cardiovascular death, myocardial infarction (MI), and Academic Research Consortium definite/probable stent thrombosis. MI was defined according to the universal definition.[13] Periprocedural MI events (occurring within 48 hours from PCI) were excluded (not the patients) to evaluate more precisely the long-term ischemic risk. The primary bleeding end point was the occurrence of a Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate/severe bleeding event. GUSTO severe bleed is defined by the occurrence of an intracranial hemorrhage or a bleed resulting in hemodynamic compromise requiring treatment, and GUSTO moderate bleed requires blood transfusion without hemodynamic compromise. All end points were adjudicated by an independent clinical event committee. Detailed baseline characteristics were available for analysis, such as demographic factors, risk factors for coronary artery disease, cardiovascular history, and presentation for index procedure and angiographic/procedural data.