Adverse events in patients with high platelet reactivity following successful chronic total occlusion PCI: The Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study

Matthew T. Finn, MD, MS, [a,b] Björn Redfors, MD, PhD, [b,c] Dimitri Karmpaliotis, MD, PhD, [a,b] Ajay J. Kirtane, MD, SM, [a,b] Philip Green, MD, [a] Thomas McAndrew, PhD, [b] Mengdan Liu, MS, [b] Michael B. Cloney, MD, MPH, [a] Bernhard Witzenbichler, MD, [d] Giora Weisz, MD, [e] Thomas D. Stuckey, MD, [f] Bruce R. Brodie, MD, [f] Michael J. Rinaldi, MD, [g] Franz-Josef Neumann, MD, [h] D. Christopher Metzger, MD, [i] Timothy D. Henry, MD, [j,k] David A. Cox, MD, [l] Peter L. Duffy, MD, MMM, [m] Ernest L. Mazzaferri, Jr., MD, [n] Roxana Mehran, MD, [b,n] and Gregg W. Stone, MD [a,b] *New York, Bronx, NY; Dachau, Bad Krozingen, Germany; Greensboro, Charlotte, Pinehurst, NC; Kingsport, TN; Los Angeles, CA; Birmingham, AL; and Columbus, OH*

Background Chronic total occlusion (CTO) percutaneous coronary intervention (PCI) typically requires a greater number of stents and longer stent length than non-CTO PCI, placing these patients at greater risk for adverse ischemic events. We sought to determine whether the association between high platelet reactivity (HPR) and the risk of ischemic events is stronger after CTO than non-CTO PCI.

Methods Patients undergoing successful PCI in the multicenter ADAPT-DES study were stratified according to whether they underwent PCI of a CTO. HPR was defined as VerifyNow platelet reaction units >208. The study primary endpoint was the 2-year risk target vessel failure ([TVF] defined as cardiac death, myocardial infarction, or target lesion revascularization).

Results CTO PCI was performed in 400 of 8448 patients. HPR was present in 34.5% of CTO PCI patients and 43.1% of non-CTO PCI patients (P = .0007). Patients undergoing CTO PCI with versus without HPR had significantly higher 2-year rates of TVF (15.0% versus 8.3%, P = .04) without significant differences in bleeding. HPR was an independent predictor of 2-year TVF (adjusted HR 1.16, 95% CI 1.02-1.34, P = .03) whereas CTO PCI was not (adjusted HR 0.89, 95% CI 0.65-1.22, P = .48). There was a significant interaction between CTO versus non-CTO PCI and PRU as a continuous variable for 2-year TVF ($P_{interaction}$ = 0.02).

Conclusions In ADAPT-DES, HPR was associated with an increased 2-year risk of TVF after PCI, an association that was at least as strong after CTO PCI compared with non-CTO PCI. (Am Heart J 2019;211:68-76.)

From the [a]New York–Presbyterian Hospital/Columbia University Medical Center, New York, NY, [b]Cardiovascular Research Foundation, New York, NY, [c]Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden, [d]Helios Amper-Klinikum, Dachau, Germany, [e]Montefiore Medical Center, Bronx, NY, [f]LeBauer-Brodie Center for Cardiovascular Research and Education/Cone Health, Greensboro, NC, [g]Sanger Heart and Vascular Institute/Atrium Health, Charlotte, NC, [h]Heart Center Bad Krozingen, Bad Krozingen, Germany, [i]Ballad Health CVA Heart Institute, Kingsport, TN, [j]Minneapolis Heart Institute Foundation at Abbott Northwestern Hospital, MN, [k]Cedars-Sinai Heart Institute, Los Angeles, CA, [l]CVA Brookwood Baptist Hospital, Birmingham, AL, [m]Reid Heart Center, FirstHealth of the Carolinas, Pinehurst, NC, [n]The Ohio State University Wexner Medical Center, Columbus, OH, and [o]Icahn School of Medicine at Mount Sinai, New York, NY.

Disclosures: Dr Finn has no disclosures. Dr Karmpaliotis: speaker honoraria from Abbot Vascular, Boston Scientific, and Medtronic; consultant: Vascular Solutions. Dr Kirtane: Institutional research grants to Columbia University from Boston Scientific, Medtronic, Abbott Vascular, Abiomed, St Jude Medical, Vascular Dynamics, and Eli Lilly. Dr Green: NIH grant support K23HL121142-03. Dr Witzenbichler: Consultant – Volcano. Dr Weisz: Advisory board member of: Corindus, Filterlex, TriSol; institutional grant support: Abbott, CSI, Svelte. Dr Stuckey: Advisory board – Boston Scientific; speaker honoraria – Boston Scientific, Eli Lilly/Daiichi-Sankyo. Dr Rinaldi: Advisory board – Abbott Vascular, Boston Scientific, Edwards Lifesciences. Dr Cox: Consultant – Abbott Vascular, Boston Scientific Corporation, Medtronic. Dr Duffy: Consultant/speaker – Philips Medical/Volcano Corporation. Dr Mehran: Institutional research grant support – Eli Lilly/Daiichi-Sankyo, Inc., Bristol-Myers Squibb, AstraZeneca, The Medicines Company, OrbusNeich, Bayer, CSL Behring, Abbott Laboratories, Watermark Research Partners, Novartis Pharmaceuticals, Medtronic, AUM Cardiovascular, Inc., Beth Israel Deaconess Medical Center; executive committee – Janssen Pharmaceuticals, Osprey Medical Inc.; data safety monitoring board – Watermark Research Partners; consulting – Medscape, The Medicines Company, Boston Scientific, Merck & Company, Cardiovascular Systems, Inc. (CSI); Sanofi USA, LLC, Shanghai BraccoSine Pharmaceutical Corp.; AstraZeneca; equity – Claret Medical Inc., Elixir Medical Corporation. Dr Stone is a consultant for Matrizyme. The remaining authors have nothing to disclose.

Submitted July 11, 2018; accepted February 12, 2019.

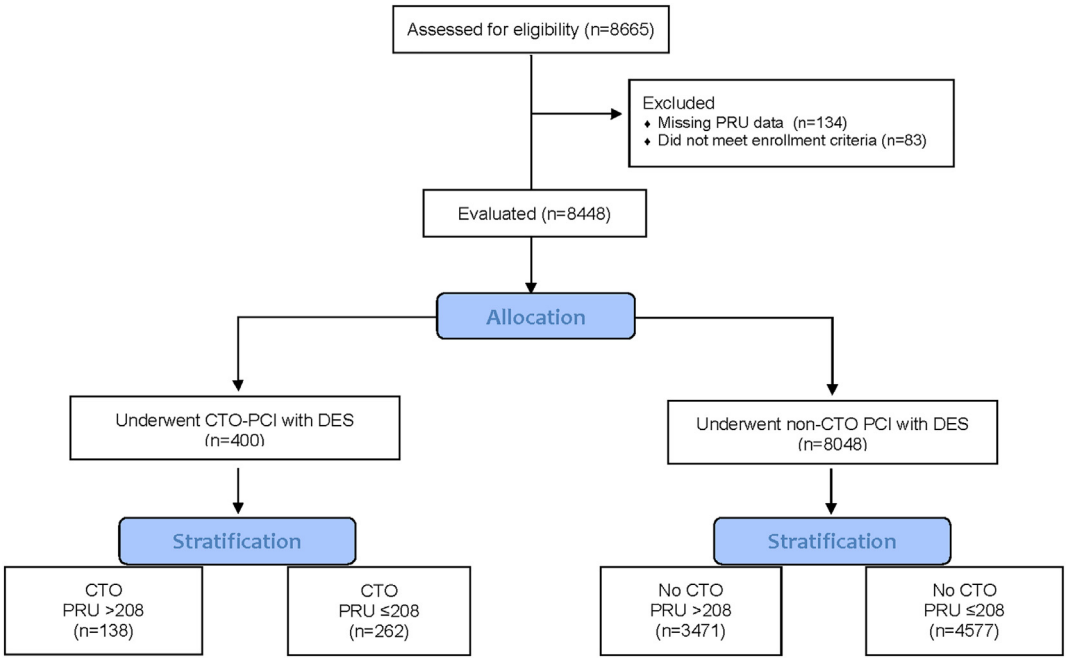
Reprint requests: Dimitri Karmpaliotis, MD, PhD, 161 Fort Washington Avenue, 6th Floor, New York, NY 10032.

E-mail: dk2787@cumc.columbia.edu

0002-8703

https://doi.org/10.1016/j.ahj.2019.02.002

Figure 1



CONSORT flow diagram: ADAPT-DES enrollment and chronic total Occlusion substudy stratified by platelet reactivity level. CTO, chronic total occlusion; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction units.

Chronic total occlusions (CTOs) are present in 18% to 30% of patients with coronary artery disease (CAD) undergoing cardiac catheterization.[1-3] Interest in CTO percutaneous coronary intervention (PCI) has grown in recent years due to improved success rates and data showing benefits such as improvement in anginal symptoms, quality of life, and left ventricular function in selected patients[4-8]; however, patients undergoing CTO PCI may be at greater risk for adverse ischemic events due to a higher prevalence of baseline comorbid disease, i.e., advanced age, diabetes, multivessel CAD, and previous myocardial infarction (MI) when compared to non-CTO patients with CAD.[9] Furthermore, CTO PCI frequently requires more stents and is procedurally more complex compared with non-CTO PCI.[8,10]

The ADAPT-DES study demonstrated that high on-treatment platelet reactivity (HPR) is associated with an increased risk of ischemic events including stent thrombosis (ST) and MI following successful implantation of drug-eluting stents (DES).[11] We hypothesized that the association between HPR and ischemic outcomes would be especially notable in complex lesion subsets, including CTOs. We therefore sought to assess the interaction of HPR among patients receiving CTO PCI in the ADAPT-DES study.

Methods

Study design

The ADAPT-DES study was a prospective, multicenter registry of consecutive patients treated at participating centers who were adequately loaded with dual antiplatelet therapy (DAPT; aspirin and clopidogrel) and treated with one or more DES. There were few exclusion criteria other than the occurrence of a major complication during the procedure or prior to platelet function testing and planned coronary artery bypass grafting.[11] The institutional review board at the 11 participating centers in the United States and Germany approved the study. The ADAPT-DES study was sponsored by the Cardiovascular Research Foundation with research support from Boston Scientific, Abbott Vascular, Medtronic, Cordis, Biosensors, The Medicines Company, Daiichi-Sankyo, Eli Lilly, Volcano, and Accumetrics. No additional funding was provided for the formulation of this secondary analysis. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Procedures and definitions

The ADAPT-DES study design has been previously published.[11] Briefly, P2Y12 reaction units (PRU) were assessed using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA) following clopidogrel loading after successful PCI with DES. HPR on clopidogrel was pre-specified as PRU >208.[12-15] Aspirin was given as either a non-enteric coated dose of at least 300 mg at least 6 hours before PCI, or a chewable dose of at least 324 mg or an intravenous dose of at least 250 mg at least 30 minutes before PCI. Clopidogrel was given as either a dose of 600 mg at least 6 hours before VerifyNow testing, a dose of

Table I. Baseline characteristics by CTO PCI status and HPR

	CTO PCI			No CTO PCI			All CTO PCI vs no CTO PCI
	HPR (n = 138)	No HPR (n = 262)	*P*	HPR (n = 3471)	No HPR (n = 4577)	*P*	*P*
Age (y)	65.1 ± 11.1	61.4 ± 10.2	.0009	64.7 ± 10.8	62.9 ± 10.8	<.0001	.08
Male	76.1% (105)	85.5% (224)	.02	68.7% (2386)	78.0% (3570)	<.0001	.0002
Body mass index	29.9 ± 5.6	28.5 ± 4.7	.02	30.5 ± 6.2	28.7 ± 5.2	<.0001	.08
Diabetes	44.2% (61)	23.3% (61)	<.0001	41.2% (1430)	25.6% (1174)	<.0001	.44
Insulin-treated	19.6% (27)	6.1% (16)	<.0001	15.4% (535)	8.8% (401)	<.0001	.59
History of PAD	10.9% (15)	11.1% (29)	.95	10.8% (376)	9.6% (441)	.08	.58
History of heart failure	15.2% (21)	10.7% (28)	.19	9.2% (321)	6.9% (317)	.0001	.002
Previous MI*	34.1% (47)	29.8% (78)	.38	25.0% (868)	24.8% (1135)	.83	.004
Previous CABG	11.6% (16)	16.8% (44)	.17	18.1% (627)	16.4% (751)	.051	.27
Previous PCI	47.8% (66)	43.9% (115)	.45	41.8% (1452)	43.4% (1986)	.16	.32
History of chronic kidney disease	10.9% (15)	6.1% (16)	.09	9.4% (326)	6.3% (290)	<.0001	.94
History of Dialysis	2.2% (3)	1.5% (4)	.70	2.0% (68)	1.3% (58)	.01	.77
Hypertension	83.3% (115)	80.9% (212)	.55	81.5% (2830)	78.0% (3569)	<.0001	.28
Hyperlipidemia	84.8% (117)	85.1% (223)	.93	74.7% (2594)	73.3% (3355)	.15	<.0001
Cigarette smoking, any	57.2% (79)	62.2% (163)	.33	55.1% (1914)	56.8% (2601)	.13	.08
Current (within 1 month)	21.7% (30)	24.0% (63)	.60	19.6% (679)	25.2% (1152)	<.0001	.82
Former (>1 month)	35.5% (49)	38.2% (100)	.60	35.6% (1235)	31.7% (1449)	.0002	.11
Ejection fraction %	53.7 ± 12.6	50.9 ± 14.2	.15	54.3 ± 12.6	55.5 ± 12.1	<.0001	.002
Acute coronary syndrome	34.8% (48)	34.0% (89)	.87	55.6% (1929)	49.8% (2279)	<.0001	<.0001
Unstable angina	19.6% (27)	24.4% (64)	.27	28.1% (975)	27.2% (1246)	.39	.03
Non-ST-segment elevation MI	8.0% (11)	5.3% (14)	.30	16.1% (559)	14.0% (640)	.008	<.0001
ST-segment elevation MI	7.2% (10)	4.2% (11)	.19	11.4% (395)	8.6% (393)	<.0001	.003
NYHA Class III	19.6% (27)	24.4% (64)	.27	25.6% (888)	22.7% (1040)	.003	.58
NYHA Class IV	11.6% (16)	6.5% (17)	.078	19.5% (677)	15.9% (728)	<.0001	<.0001
Hemoglobin (g/dL)	13.6 ± 1.4	14.5 ± 1.4	<.0001	13.5 ± 1.4	14.3 ± 1.5	<.0001	.01
Creatinine clearance (mL/min)†	94.3 ± 40.1	98.4 ± 33.8	.30	93.5 ± 39.8	94.4 ± 35.4	.31	.12
Platelet count ($\times 10^3/mm^3$)	217.9 ± 57.2	221.1 ± 55.5	.60	225.6 ± 62.3	228.0 ± 63.8	.10	.02

Categorical values are presented as frequency (n), continuous values are presented as mean ± standard deviation. *MI occurring >7 days before index PCI. †Cockroft-Gault. CABG, coronary artery bypass grafting; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

300 mg at least 12 hours before VerifyNow testing, or a dose of 75 mg or more daily for at least 5 days before VerifyNow testing. If glycoprotein IIb/IIIa inhibitors were used during PCI, an extended washout period was required before PRU testing. Trained research coordinators performed the VerifyNow testing, and the results were entered into a computerized database without informing the treating physicians to maintain blinding. Clinical follow-up was performed at 30 days, 1 year, and 2 years.

CTO lesions were defined as those with Thrombolysis in Myocardial Infarction (TIMI) 0 flow with an estimated occlusion duration of ≥3 months.[8] The composite primary endpoint of the study was target vessel failure (TVF), defined as the composite of cardiac death, MI or target lesion revascularization (TLR) at 2 years. Secondary outcomes included major adverse cardiac events ([MACE] defined as the composite of cardiac death, MI, or ST) and individual rates of all cause death, cardiac death, MI, and ST. ST events were evaluated according to the Academic Research Consortium definite or probable definition.[16] MI was assessed according to the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) criteria.[17] Clinically relevant major bleeding was defined as the presence of any of the following: ACUITY major bleeding, TIMI major or minor bleeding, Global Use of Strategies to Open Occluded Arteries (GUSTO) bleeding, or bleeding after discharge requiring medical evaluation.[11,18] An independent clinical events committee, which was blinded to the VerifyNow results, adjudicated events using original source documents.

Statistical analysis

Patients were stratified according to whether they underwent CTO PCI (alone or with PCI of other non-CTO lesions) or exclusively non-CTO PCI, as well as according to HPR status. Categorical characteristics were compared using the χ^2 test or Fisher's exact test as appropriate. Continuous variables were evaluated with the Student *t* test, and non-normal variables were evaluated with the Mann-Whitney *U* test or Kruskal-Wallis test. Time-to-event data are shown as Kaplan-Meier estimates and were compared with log-rank testing. To identify predictors of outcomes, we entered HPR and other baseline variables deemed clinically relevant from previous studies into multivariable Cox proportional hazards regression models. Candidate variables were selected based on clinically important baseline differences as well as prior literature.[11] The following candidate variables were used for multivariable analysis:

Table II. Procedural characteristics by CTO status and HPR

	CTO PCI			No CTO PCI			All CTO PCI vs No CTO PCI
	HPR (n = 138)	No HPR (n = 262)	*P*	HPR (n = 3471)	No HPR (n = 4577)	*P*	*P*
Number of diseased vessels							
1	29.0% (40)	29.0% (76)	1.00	38.3% (1330)	39.0% (1785)	.53	<.0001
2	29.0% (40)	34.7% (91)	.24	32.9% (1142)	33.0% (1510)	.93	.93
3	42.0% (58)	36.3% (95)	.26	28.8% (999)	28.0% (1282)	.45	<.0001
PCI lesion location							
Left anterior descending	38.4% (53)	40.8% (107)	.64	46.4% (1611)	46.4% (2123)	.98	.01
Right	55.8% (77)	54.2% (142)	.76	35.8% (1243)	36.6% (1674)	.48	<.0001
Left main	2.9% (4)	2.3% (6)	.74	3.8% (132)	3.7% (171)	.88	.19
Circumflex	27.5% (38)	30.9% (81)	.48	26.5% (1076)	26.3% (1419)	.87	.14
Bypass graft	0.7% (1)	1.5% (4)	.66	5.8% (201)	4.7% (216)	.03	.0004
Drug-eluting stents per patient	2.76 ± 1.60	2.73 ± 1.33	.86	1.64 ± 0.95	1.65 ± 0.95	.49	<.0001
Second-generation DES*	60.1% (83)	58.8% (154)	.79	63.3% (2197)	63.9% (2923)	.60	.08
First-generation DES**	33.3% (46)	29.0% (76)	.37	27.1% (939)	26.1% (1196)	.35	.08
Total stent length, mm	54.5 [32.0, 84.0]	56.0 [36.0, 81.0]	.98	24.0 [16.0, 40.0]	24.0 [16.0, 40.0]	.29	<.0001
In-hospital medication (any)							
Clopidogrel	100.0% (138)	99.2% (260)	.55	99.8% (3465)	99.9% (4572)	.55	.12
Ticlopidine	0.0% (0)	0.4% (1)	1.00	0.1% (3)	0.1% (3)	1.00	.29
Prasugrel	2.2% (3)	0.0% (0)	.04	0.1% (5)	0.4% (18)	.04	.12
Aspirin	100.0% (138)	99.6% (261)	1.00	99.9% (3469)	99.9% (4574)	1.00	.27
Beta blocker	83.3% (115)	86.3% (226)	.43	82.9% (2879)	81.2% (3715)	.04	.09
Statin	88.4% (122)	80.5% (211)	.05	83.3% (2893)	84.6% (3872)	.13	.67
IVUS use	24.6% (34/138)	23.3% (61/262)	.76	30.3% (1052)	28.6% (1310)	.10	.57
Bifurcation lesion	11.6% (16)	22.5% (59)	.01	11.6% (16)	22.5% (59)	.01	.06
Ostial lesion	24.6% (34)	23.3% (61)	.12	14.5% (503)	15.9% (728)	.08	.93
Femoral access	97.8% (135)	98.1% (257)	1.0	95.1% (3301)	95.3% (4362)	.68	.001
Sheath size							
5 Fr	2.2% (3)	5.7% (15)	.10	4.4% (154)	4.5% (207)	.85	.99
6 Fr	75.4% (104)	75.6% (198)	.96	80.0% (2776)	82.4% (3770)	.006	.004
7 Fr	15.9% (22)	13.0% (34)	.42	11.4% (397)	10.4% (476)	.14	.05
8 Fr	6.5% (9)	5.7% (15)	.75	4.1% (142)	2.7% (124)	.0006	.004

Categorical values are presented as frequency (n), continuous values as mean ± standard deviation or median [interquartile range]. CTO, chronic total occlusion; DES, drug-eluting stent; HPR, high platelet reactivity; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.
*Xience, Promus, or Endeavor;
**Taxus or Cypher;

CTO PCI (vs non-CTO PCI), HPR, age, sex, diabetes, hyperlipidemia, history of MI, history of heart failure, presentation with acute coronary syndrome (ACS versus stable CAD), and DAPT use (as a time-adjusted covariate). CTO and HPR were added as interaction terms to univariate and multivariable Cox models. Separately, CTO and ACS were examined as interaction terms to check for the potential of hidden confounding. As an additional exploratory analysis, platelet reactivity was assessed as a continuous variable (PRU) in these models. All P values were 2-tailed, and $P < .05$ was significant for all analyses. Statistical analyses and plots were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

Between January 2008 and September 2010, 8665 patients with CAD successfully treated with DES were prospectively enrolled; 8448 patients were included in the present study after excluding 217 patients due to missing PRU data or because platelet function testing was performed before completion of the pre-specified glycoprotein IIb/IIIa inhibitor washout period. Four hundred patients underwent CTO PCI (Figure 1), among whom 138 (34.5%) had a PRU >208. In contrast, HPR was present in 3471 (43.1%) of the 8048 patients not undergoing CTO PCI ($P = .0007$).

Comparison of baseline characteristics in the CTO vs non-CTO groups demonstrated a higher percentage of male sex, prior heart failure, prior MI, history of hyperlipidemia, and a lower baseline ejection fraction in CTO patients versus non-CTO patients (Table I and Supplemental Table I). ACS was less frequently the indication for PCI in CTO patients compared with non-CTO patients. When comparing CTO PCI and non-CTO PCI patients stratified by HPR (>208 versus ≤208), baseline characteristics varied significantly within the four patient groups. Those subjects with both CTO and PRU >208 had the highest overall comorbidity burden

Table III. Independent predictors of 2-year target vessel failure and major adverse cardiac events

Endpoint	Covariate	Adjusted hazard ratio (95% confidence interval)	*P*
Target Vessel Failure	CTO PCI	0.89 (0.65-1.22)	.48
	High platelet reactivity*	1.16 (1.02-1.34)	.03
	Age (per 10 years increment)	0.99 (0.93-1.06)	.87
	Male	0.98 (0.84-1.14)	.78
	Diabetes	1.59 (1.39-1.83)	<.0001
	History of heart failure	1.30 (1.06-1.58)	.01
	Prior myocardial infarction	1.35 (1.16-1.56)	<.0001
	Hyperlipidemia	1.23 (1.04-1.46)	.02
	Acute coronary syndrome	1.40 (1.22-1.60)	<.0001
	Dual antiplatelet therapy duration (per 10 days increment)	0.94 (0.94-0.95)	<.0001
MACE	CTO PCI	0.65 (0.40-1.06)	.09
	High platelet reactivity*	1.29 (1.08-1.54)	.005
	Age (per 10 years increment)	1.07 (0.99-1.17)	.08
	Male	0.99 (0.81-1.20)	.92
	Diabetes	1.48 (1.24-1.77)	<.0001
	History of heart failure	1.73 (1.37-2.19)	<.0001
	Prior myocardial infarction	1.37 (1.14-1.65)	.001
	Hyperlipidemia	1.18 (0.95-1.48)	.13
	Acute coronary syndrome	1.58 (1.32-1.89)	<.0001
	Dual antiplatelet therapy duration (per 10 days increment)	0.94 (0.93-0.94)	<.0001

* Platelet reactivity units >208. CTO, chronic total occlusion; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.

Table IV. Event rates and adjusted hazard ratios for high versus low platelet reactivity according to PCI of CTO lesions

	CTO PCI				No CTO PCI				
Endpoint	HPR (n = 138)	No HPR (n = 262)	*P**	Adjusted HR (95% CI)†	HPR (n = 3471)	No HPR (n = 4577)	*P**	Adjusted HR (95% CI)†	$P_{interaction}$‡
Target vessel failure	15.0% (20)	8.3% (21)	.04	1.61 (0.87-2.97)	12.2% (400)	9.7% (427)	.0008	1.15 (1.00-1.32)	.29
Major adverse cardiac events	7.4% (10)	2.7% (7)	.03	2.34 (0.89-6.15)	7.8% (259)	5.5% (241)	<.0001	1.26 (1.05-1.51)	.22
Death	3.1% (4)	2.0% (5)	.49	1.24 (0.33-4.61)	4.9% (161)	3.1% (136)	<.0001	1.36 (1.07-1.71)	.89
Cardiac death	1.5% (2)	0.0% (0)	.047	1.34 (0.98-1.84)	2.8% (89)	1.7% (74)	.002	1.45 (1.23-1.70)	.97
Myocardial infarction	6.7% (9)	2.7% (7)	.06	2.13 (0.79-5.74)	5.6% (187)	4.1% (180)	.001	1.22 (0.99-1.50)	.28
Periprocedural myocardial infarction	3.6% (5)	2.3% (6)	.44	1.60 (0.48-5.25)	1.4% (50)	1.2% (62)	.45	1.19 (0.81-1.75)	.64
Target lesion revascularization	10.9% (14)	6.7% (17)	.16	1.44 (0.71-2.93)	6.9% (223)	5.6% (244)	.03	1.14 (0.95-1.37)	.53
Stent thrombosis§	1.5% (2)	0.8% (2)	.5	1.70 (0.24-12.11)	1.6% (53)	0.8% (35)	.001	1.74 (1.12-2.70)	.98
Bleeding	13.6% (18)	14.5% (37)	.84	0.79 (0.45-1.40)	8.4% (275)	8.9% (391)	.35	0.90 (0.77-1.05)	.68

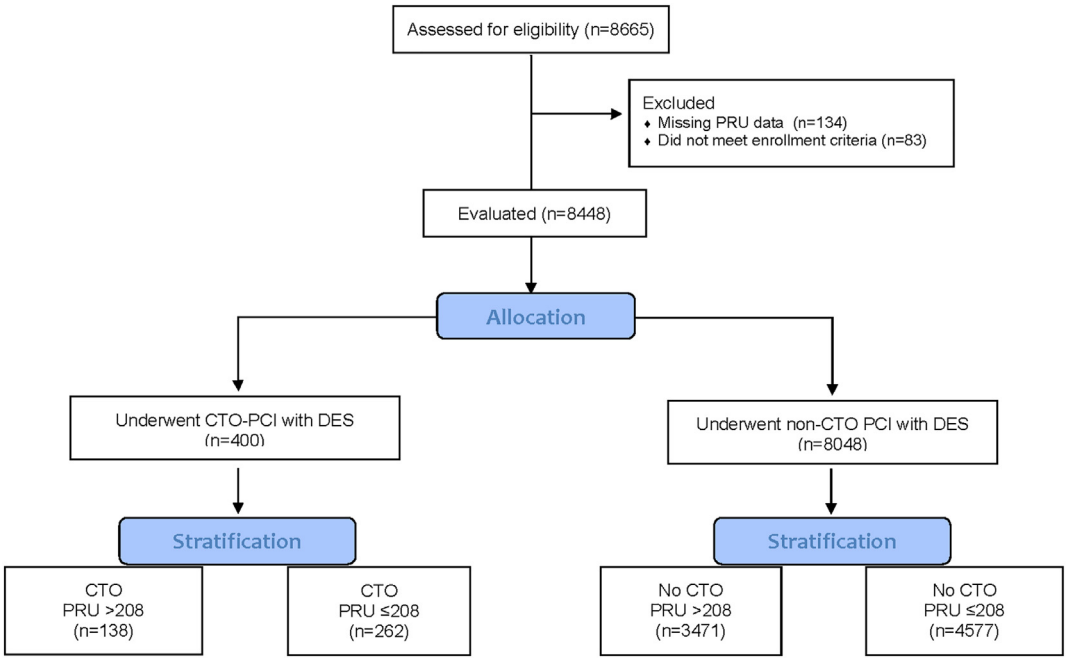
CI, confidence interval; CTO, chronic total occlusion; HPR, high platelet reactivity; HR, hazard ratio; PCI, percutaneous coronary intervention.
* Log-rank test for unadjusted comparison;
† Adjusted for male sex, history of heart failure, prior myocardial infarction, hyperlipidemia, and acute coronary syndrome;
‡ Adjusted interaction *P* value; §definite or probable.

including older mean age, a higher frequency of insulin-treated diabetes, prior heart failure, prior MI, prior PCI, chronic kidney disease, dialysis, and hypertension (Table I).

Procedural characteristics

CTO patients represented a more complex anatomic cohort than non-CTO patients with a higher percentage of angiographic 3-vessel disease (38.3% versus 28.3%, $P <$ .0001), greater mean number of stents placed (2.74 versus 1.67, $P <$ .0001), and a longer median stent length (56 mm versus 24 mm, $P <$ .0001). CTO PCI entailed a higher frequency of right coronary artery intervention (54.8% versus 36.2%, $P <$ .0001) whereas non-CTO patients had a higher frequency of left anterior descending (40.0% versus 46.4%, $P =$ .01) and bypass graft PCI (1.3% versus 5.2%, $P =$ .0004) intervention. Furthermore, CTO PCI required greater utilization of femoral access with larger sheath sizes than non-CTO PCI. When stratified by PRU, CTO and non-CTO groups were reasonably balanced within groups with no significant differences in the degree of multivessel disease, stent

Figure 2



Time-to-first event curves through 2-year follow-up for the main study endpoints. (A) Target vessel failure; (B) major adverse cardiovascular events (MACE); (C) all-cause death; (D) myocardial infarction; (E) target lesion revascularization; (F) stent thrombosis (definite or probable); (G) major bleeding. P values from log-rank test. CTO, chronic total occlusion; HPR, high platelet reactivity; NCTO, non-CTO; NHPR, no high platelet reactivity.

length, or the frequency of early vs late DES generation utilization (Table II).

Periprocedural dual antiplatelet administration and adherence

Aspirin and clopidogrel were prescribed at discharge in 99.2% and 99.7% of patients respectively. Adherence rates to DAPT in the study were high. Through 2 years the CTO group had fewer total days on DAPT than non-CTO patients (mean 466.3 versus 520.8 days, $P = .0001$). There were no differences in mean total days of DAPT use through 2 years in patients with vs without HPR both in CTO PCI patients (mean 456.5 versus 471.4 days, respectively, $P = .52$) and in non-CTO PCI patients (mean 524.4 versus 518.1 days, respectively, $P = .20$).

Platelet reactivity and clinical outcomes

Unadjusted analysis demonstrated no difference in the rate of TVF (10.6% versus 10.8%, HR 1.01, 95% CI 0.74-1.39, $P = .94$), all-cause death, TLR, or MI between the CTO and non-CTO groups (Supplemental Table II); however, the rate of periprocedural MI was greater after CTO PCI compared with non-CTO PCI (2.8% versus 1.3%, $P = .02$). The rate of major bleeding was also higher in the CTO group (14.2% versus 8.7%, $P < .0001$). The presence of HPR but not CTO was independently associated with increased 2-year rates of TVF and MACE (Table III).

Among the 400 CTO patients, those with compared to those without HPR experienced greater rates of TVF at 2 years, largely driven by increased MI (Table IV and Figure 2). Bleeding rates did not differ significantly between CTO patients with versus without HPR during the index hospitalization nor at 2 years (in-hospital: 6.5% versus 6.9%, RR 0.95, 95% CI 0.44-2.06; 2-years: 13.6% versus 14.5%, HR 0.94, 95% CI 0.54-1.66, $P = .84$). After adjusting for differences in baseline characteristics, there were no significant interactions present between HPR status and CTO versus non-CTO PCI for the 2-year rates of TVF or MACE; however, when platelet reactivity was modeled as a continuous variable the adjusted effect of increased platelet reactivity was stronger in patients with versus without CTO in regard to the 2-year rates of both TVF (HR 1.05, 95% CI 1.01-1.08 versus HR 1.01, 95% CI 1.00-1.01 per 10-U increase in PRU [$P_{interaction} = .02$]) and MACE (HR 1.07, 95% CI 1.02-1.13 versus HR 1.01, 95% CI 1.00-1.02 per 10-U increase in PRU [$P_{interaction} = 0.04$], Table V).

Lastly, an additional sensitivity analysis was performed examining the adjusted interaction among patient with CTO and ACS for MACE and TLR at 2 years. There was no

Table V. Multivariable regression models with PRU as a continuous variable

2-year endpoint	Adjusted HR (95% CI) for PRU* (per 10 PRU units)		$P_{interaction}$*
	CTO PCI	No CTO PCI	
Target vessel failure	1.05 (1.01-1.08)	1.01 (1.00-1.01)	.02
Major adverse cardiac events	1.07 (1.02-1.13)	1.01 (1.00-1.02)	.04
All-cause death	1.02 (0.96-1.10)	1.02 (1.00-1.03)	.81
Cardiac death	1.20 (0.99-1.45)	1.02 (1.00-1.03)	.09
Target lesion revascularization	1.04 (1.00-1.07)	1.00 (0.99-1.01)	.11
Myocardial infarction	1.06 (1.01-1.11)	1.01 (1.00-1.02)	.09
Periprocedural myocardial infarction	1.05 (0.99-1.12)	1.01 (0.99-1.03)	.24
Stent thrombosis	1.04 (0.94-1.16)	1.04 (1.02-1.06)	.83
Major bleeding	0.99 (0.97-1.02)	0.99 (0.98-1.00)	.92

CI, confidence interval; CTO, chronic total occlusion; HR, hazard ratio; PCI, percutaneous coronary intervention; PRU, platelet reactivity units.
* Adjusted for age, sex, diabetes, history of heart failure, prior myocardial infarction, hyperlipidemia, presentation with acute coronary syndrome and dual antiplatelet therapy use (as a time-adjusted covariate).

differential effect of ACS on CTO compared to non-CTO patients within the cohort (MACE $P_{interaction}$ = 0.41 and TVR $P_{interaction}$ = .29).

Discussion

The present post hoc analysis from the multicenter all-comers ADAPT-DES study represents the largest analysis to date of the impact of platelet reactivity in a CTO population undergoing PCI with DES. Our main findings are that (i) compared to patients undergoing non-CTO PCI, CTO PCI patients had more comorbidities and substantially more complex CAD; CTO PCI was associated with a higher risk of periprocedural MI and bleeding compared with non-CTO PCI, but comparable long-term rates of adverse clinical events; and (ii) HPR was associated with increased risk of adverse cardiac events after successful DES PCI in both CTO PCI and non-CTO PCI.

Our finding that CTO patients present with a greater comorbidity burden with more complex anatomic CAD was expected is consistent with prior studies of CTO PCI.[8-10] The observed higher rate of periprocedural MI was also unsurprising given the loss of collaterals and side braches with subintimal CTO crossing. This finding has been shown previously, particularly in retrograde CTO PCI.[19-21] Additionally, the observed higher bleeding rates with CTO PCI compared to non-CTO PCI may be explained by baseline difference inherent to CTO PCI, which frequently involves femoral access, dual access, and larger sheath sizes compared with conventional PCI.[8-10,19-21]

To our knowledge, only one prior study has assessed the impact of platelet reactivity after CTO PCI, in which a significant association between PRU and long-term mortality was noted in patients with diabetes.[22] Our larger study sought to further investigate whether HPR among patients undergoing CTO PCI would be associated with a greater incremental risk of adverse events than in those undergoing non-CTO PCI. Although the unadjusted rates of TVF and MACE were higher for CTO patients with vs without HPR, no significant interaction was observed between HPR and CTO vs non-CTO PCI for the 2-year rates of TVF and MACE. However, when platelet reactivity was treated as a continuous variable, a stronger association was observed between high PRU and CTO PCI versus non-CTO PCI for the 2-year rates of TVF and MACE ($P_{interaction}$ = .02 and $P_{interaction}$ = .04, respectively). Our study thus demonstrates that the deleterious impact of HPR on adverse ischemic outcomes is at least as great after successful CTO PCI as non-CTO PCI.

Of note, the rate of HPR in CTO patients was slightly lower than in non-CTO patients (34.5% versus 43.1% P = .0007). This may seem surprising, given the greater incidence of comorbidities in patients undergoing CTO intervention. However, presentation with ACS was much less frequent in the CTO group, a risk factor which has been strongly associated with greater baseline PRU levels compared to stable angina.[23]

Limitations

First, significant differences in the adjusted rates of the individual endpoints of cardiac death, TLR, and ST in CTO patients with PRU >208 vs ≤208 were not observed, in contrast to that seen in the non-CTO cohort and the entire ADAPT-DES study population.[11] This finding is likely due to the relative modest sample size of CTO patients. No significant interactions were present between HPR status and CTO-PCI vs non-CTO PCI for the risk of major 2-year adverse events, indicating that the primary results of the ADAPT-DES study as relates to the influence of HPR on ischemic and bleeding events applies to CTO-PCI patients as well. Second, the complexity of the CTO interventions including many of the technical aspects of the procedures was not assessed in our study. Procedural CTO approach (i.e., retrograde versus antegrade) and the lesion crossing strategy (i.e., wire escalation versus antegrade dissection re-entry) were also not specifically evaluated, knowledge of

which may have provided more insights into the effect of HPR and CTO-PCI.[21,24-27] Future studies evaluating the long-term effects of PRU in patients undergoing CTO PCI may more completely evaluate procedural complexity using tools such as the J-CTO score and the SYNTAX score.[28,29] Similarly, the ADAPT-DES cohort was recruited prior to the publication of the hybrid algorithm for CTO PCI now utilized by most major CTO centers in the United States; the impact of this practice on the present results is uncertain.[30] Finally, interaction testing is inherently under-powered, especially for low frequency endpoints such as stent thrombosis. However, a large number of composite ischemic endpoint events were reached in this large study, and significant interactions were present demonstrating a stronger association between high PRU and CTO PCI versus non-CTO PCI for the 2-year rates of TVF and MACE.

Conclusion

In the large-scale ADAPT-DES study, the 2-year risk of adverse events was similar after successful PCI of CTO and non-CTO lesions. Residual platelet reactivity conferred an increased risk of TVF and MACE after PCI for both lesion subsets, with a signal for a stronger adverse effect after CTO compared with non-CTO PCI. Additional studies are needed to determine whether platelet function testing to guide the choice of P2Y12 inhibitor used may safely improve outcomes in patients undergoing CTO (and non-CTO) PCI.

Funding sources

ADAPT-DES was sponsored by CRF with researchsupport from Boston Scientific, Abbott Vascular, Medtronic, Cordis, Biosensors, The Medicines Company, Daiichi Sankyo, Eli Lilly, Volcano, and Accumetrics.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.02.002.

References

1. Stone GW, Kandzari DE, Mehran R, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. Circulation 2005;112:2364-72.
2. Fefer P, Knudtson ML, Cheema AN, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol 2012;59:991-7.
3. Jeroudi OM, Alomar ME, Michael TT, et al. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. Catheter Cardiovasc Interv 2014;84:637-43.
4. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. Am Heart J 2010;160:179-87.
5. Mehran R, Claessen BE, Godino C, et al. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. JACC Cardiovasc Interv 2011;4:952-61.
6. Kirschbaum SW, Baks T, van den Ent M, et al. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. Am J Cardiol 2008;101:179-85.
7. Michael TT, Karmpaliotis D, Brilakis ES, et al. Procedural outcomes of revascularization of chronic total occlusion of native coronary arteries (from a multicenter United States registry). Am J Cardiol 2013;112:488-92.
8. Michael TT, Karmpaliotis D, Brilakis ES, et al. Temporal trends of fluoroscopy time and contrast utilization in coronary chronic total occlusion revascularization: insights from a multicenter United States registry. Catheter Cardiovasc Interv 2015;85:393-9.
9. Brilakis ES, Banerjee S, Karmpaliotis D, et al. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). JACC Cardiovasc Interv 2015;8:245-53.
10. Kelbaek H, Holmvang L, Richardt G, et al. Clinical results with the Resolute zotarolimus-eluting stent in total coronary occlusions. EuroIntervention 2015;11:650-7.
11. Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. Lancet 2013;382:614-23.
12. Parodi G, Marcucci R, Valenti R, et al. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA 2011;306:1215-23.
13. Geisler T, Zurn C, Simonenko R, et al. Early but not late stent thrombosis is influenced by residual platelet aggregation in patients undergoing coronary interventions. Eur Heart J 2010;31:59-66.
14. Price MJ, Angiolillo DJ, Teirstein PS, et al. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial. Circulation 2011;124:1132-7.
15. Breet NJ, van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA 2010;303:754-62.
16. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
17. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203-16.
18. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
19. Lo N, Michael TT, Moin D, et al. Periprocedural myocardial injury in chronic total occlusion percutaneous interventions: a systematic cardiac biomarker evaluation study. JACC Cardiovasc Interv 2014;7:47-54.
20. Finn MT, Doshi D, Cleman J, et al. Intravascular ultrasound analysis of intraplaque versus subintimal tracking in percutaneous intervention for coronary chronic total occlusions: One year outcomes. Catheter Cardiovasc Interv 2018, https://doi.org/10.1002/ccd.27958.
21. Song L, Maehara A, Finn MT, et al. Intravascular ultrasound analysis of intraplaque versus subintimal tracking in percutaneous intervention

for coronary chronic total occlusions and association with procedural outcomes. JACC Cardiovasc Interv 2017;10:1011-21.
22. Valenti R, Cantini G, Marcucci R, et al. Prognostic impact of high residual platelet reactivity after chronic total occlusion percutaneous coronary intervention in patients with diabetes mellitus. Int J Cardiol 2015;201:561-7.
23. Ahn SG, Lee SH, Yoon JH, et al. Different prognostic significance of high on-treatment platelet reactivity as assessed by the VerifyNow P2Y12 assay after coronary stenting in patients with and without acute myocardial infarction. JACC Cardiovasc Interv 2012;5:259-67.
24. Christopoulos G, Menon RV, Karmpaliotis D, et al. The efficacy and safety of the "hybrid" approach to coronary chronic total occlusions: insights from a contemporary multicenter US registry and comparison with prior studies. J Invasive Cardiol 2014;26:427-32.
25. Christopoulos G, Karmpaliotis D, Alaswad K, et al. The efficacy of "hybrid" percutaneous coronary intervention in chronic total occlusions caused by in-stent restenosis: insights from a US multicenter registry. Catheter Cardiovasc Interv 2014;84:646-51.
26. Karmpaliotis D, Michael TT, Brilakis ES, et al. Retrograde coronary chronic total occlusion revascularization: procedural and in-hospital outcomes from a multicenter registry in the United States. JACC Cardiovasc Interv 2012;5:1273-9.
27. Werner GS, Gitt AK, Zeymer U, et al. Chronic total coronary occlusions in patients with stable angina pectoris: impact on therapy and outcome in present day clinical practice. Clin Res Cardiol 2009;98:435-41.
28. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
29. Nombela-Franco L, Urena M, Jerez-Valero M, et al. Validation of the J-chronic total occlusion score for chronic total occlusion percutaneous coronary intervention in an independent contemporary cohort. Circ Cardiovasc Interv 2013;6:635-43.
30. Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC Cardiovasc Interv 2012;5:367-79.