acid compared to placebo in patients with hypercholesterolemia treated with maximally tolerated medical therapy with residual risk for future ASCVD. Meanwhile, pro-protein convertase subtilisin/Kexin type 9 inhibitors, a class 1 recommendation for the secondary prevention of ASCVD in patients at very high risk for future ASCVD, have been shown to significantly reduce LDL levels and MACE in a meta-analysis of 35 trials.[8,9] One explanation for the lack of efficacy of bempedoic acid in reducing MACE is the relatively short follow-up period in individual trials. Limitations of this meta-analysis include the lack of individual patient-level data and the absence of trials with follow-up data extending beyond one year.

In conclusion, this study demonstrates that the significant reductions in LDL levels in patients treated with bempedoic acid compared to placebo reported in individual trials were not consistent with significant reductions in MACE. Meanwhile, a significant 59% reduction in noncoronary revascularization procedures was observed. Therefore trials with adequate power to detect efficacy outcomes and extended follow-up intervals are needed to delineate the benefit of bempedoic acid on cardiovascular outcomes.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abdul Aziz A. Asbeutah, MD[a,*]
Saad A. Asbeutah[b]
Mona A. Abu-Assi, PhD[c]
[a] Department of Internal Medicine, University of Tennessee Health Sciences Center, Memphis, Tennessee
[b] Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait City, Kuwait
[c] Department of Science, College of Basic Education, Public Authority for Applied Education and Training, Kuwait City, Kuwait
13 June 2020

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https://doi.org/10.1016/j.amjcard.2020.06.058

Drug-Eluting Stents Versus Bypass Surgery for Left Main Disease: An Updated Meta-Analysis of Randomized Controlled Trials With Long-Term Follow-Up

Debate is ongoing regarding the optimal mode of revascularization for patients with left main coronary artery disease (LMCAD). Longer-term follow-up from randomized trials has recently become available. We recently published a study-level meta-analysis that demonstrated similar mortality after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) when compared with coronary artery bypass grafting (CABG).[1] There were also no differences in cardiac death, stroke or myocardial infarction (MI), although there was a greater risk of unplanned revascularization after PCI. A limitation of this study was that only 1 trial had data beyond 5 years, that for all-cause mortality only from the SYNTAX trial.[2] An open question thus remains as to whether CABG will outperform PCI during long-term follow-up.

The PRECOMBAT trial, in which 600 patients with LMCAD were randomized to PCI with sirolimus-eluting stents versus CABG, has now reported 10-year data.[3] Unlike SYNTAX, the PRECOMBAT trial reported detailed long-term outcomes on major adverse cardiovascular events, including MI, stroke, and revascularization. We therefore performed an updated meta-analysis to better inform clinicians, patients, and guideline committees with regards to the long-term clinical outcomes seen with the 2 therapies.

Methods

The present analysis was conducted in accordance with published PRISMA guidance and prospectively registered (CRD42020163240). We systematically identified all randomized clinical trials comparing PCI with DES and CABG in patients with LMCAD. The primary efficacy endpoint was all-cause mortality. Secondary endpoints were cardiac death, MI, stroke, and unplanned revascularization. All analyses were by intention-to-treat, and all outcomes assessed as relative risks (RRs). The last available follow-up was used for all trials. Random-effects meta-analyses were performed using the restricted maximum likelihood estimator. Methods otherwise were as recently described in detail.[1]

Results

There were 5 eligible trials[2–6] in which 4,612 patients were included. The weighted mean follow-up duration was 74.9 months. Baseline characteristics are shown in Table 1. There was no

Table 1
Characteristics of included studies

Study acronym	Author	Year	Region	N	Mean age*	Mean SYNTAX score	Follow-up years**	Entry criteria	Stent type	Primary outcome§	Secondary outcomes§
EXCEL	Stone et al	2019	Asia, Europe, North America, South America	1905	66.0 (± 9.6)	Site-reported 20.6 in PCI group, 20.5 in CABG group (26.9 and 26.0 core lab assessed)	5 (median)	≥70% LMCA visual stenosis, 50-70% stenosis if significant by invasive or non-invasive testing, SYNTAX ≤32. Silent ischemia, angina, or ACS.	Everolimus-eluting	Composite of all-cause mortality, MI, or stroke at median 3-year follow-up	Primary outcome composite and components, and addition of unplanned revascularization and graft occlusion/stenosis (+symptomatic), at 3y, 2y, 1y, 6m, 30d and 7d. Stent thrombosis (definite/probable: acute, subacute, early, late, very late). Baseline complete revascularization. Bleeding: 30d, 3y transfusion, TIMI (major/minor) and BARC.
SYNTAX	Thijs et al	2019	Europe, USA	705^	65.2 (± 9.7)	29.6 in PCI group and 30.2 in CABG group (core-lab assessed)	11.2 (IQR 7.7-12.1)	≥50% LMCA visual stenosis. Silent ischemia or stable/unstable angina.	Paclitaxel-eluting	Composite of all-cause mortality, stroke, MI or unplanned revascularization at 1-year follow-up	Primary outcome and individual components, QoL and cost-effectiveness at 5y, 3y, 6m and 1m.
PRECOMBAT	Ahn et al	2015	South Korea	600	61.8 (± 10.0)	24.4 in PCI group and 25.8 in CABG group (core-lab assessed)	10	≥50% LMCA visual stenosis. Silent ischemia, angina, NSTEACS.	Sirolimus-eluting	Composite of all-cause mortality, MI, stroke or ischemia-driven revascularization at 1-year follow-up	Primary outcome and components + non-ischemia driven revascularization and stent thrombosis/restenosis at 5y, 4y, 3y, 2y, 1y, 6m and 30d. Graft patency and stent/segment luminal loss at 9 month angiogram.
NOBLE	Holm et al	2020	Europe	1184	66.2 (± 9.9)	22.5 in PCI group and 22.4 in CABG group (core-lab assessed)	4.9 (median)	≥50% LMCA visual stenosis or FFR ≤0.8. Angina, ACS.	Biolimus-eluting	Composite of all-cause mortality, stroke, non-index treatment-related MI or unplanned revascularization at 5 years or until 275 events	Primary outcome excluding revascularization, components of primary outcome, definite stent thrombosis / graft occlusion, CCS and NYHA at 275 events, 5y, 4y, 3y, 2y, 1y and 30d
NA	Boudriot et al	2011	Germany	200	66 (IQR 62-73)	24.0 in PCI group and 23.0 in CABG group (site-reported)	1	≥50% LMCA visual stenosis. Angina, silent ischemia.	Sirolimus-eluting	Composite of cardiac death, MI or unplanned revascularization at 1-0 year follow-up.	Components of primary outcome, all-cause mortality and CCS.

* Mean age in years (±SD); value for stent group provided where values differ between stent and surgery groups and overall value not reported.

** Mean ± SD, where provided, exact follow-up or median ± interquartile range (IQR) if mean not reported; value for stent group provided where values differ between stent and surgery groups and overall value not provided. Where multiple publications exist for different follow-up durations, the longest follow-up is provided here.

§ ClinicalTrials.gov registration outcomes listed here. Further details of definitions are provided in Table 3 in the supplementary material.

^ LMCA stratified substudy.

ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; CCS = Canadian Cardiovascular Society score; CT.gov = ClinicalTrials.gov; ECG = electrocardiogram; LMCA = left main coronary artery; LTFU = loss to follow up; MACE = major adverse cardiac events; MI = myocardial infarction; NYHA = New York Hospital Association functional class; TIMI = thrombolysis in myocardial infarction; ULN = upper limit of normal.

significant difference in all-cause mortality between PCI with DES and CABG: RR 1.08, 95% confidence interval (CI) 0.89 to 1.31, p = 0.444 (see Figure 1). Similarly, there was no significant difference in the long-term risk of cardiac death: RR 1.08, 95% CI 0.84 to 1.38, p = 0.561. Nor were there significant differences in the long-term risk of stroke (RR 0.74, 95% CI 0.39 to 1.40, p = 0.355). However, marked heterogeneity (I^2 = 58.4%) was evident for this endpoint due to the increased rate of stroke after PCI beyond 1 year in the NOBLE trial which has not otherwise been reported.[5] In as sensitivity analysis, a lower risk of stroke with PCI was evident (RR 0.59 95% CI 0.40 to 0.87, p = 0.007) after removal of this outlier. There was no significant difference in the long-term risk of all MI between PCI and CABG (RR 1.21, 95% CI 0.95 to 1.55, p = 0.114). There was, however, a lower risk of procedural MI after PCI (RR 0.70, 95% CI 0.50 to 0.99, p = 0.042) and a lower risk of non-procedural MI after CABG (RR 2.23,

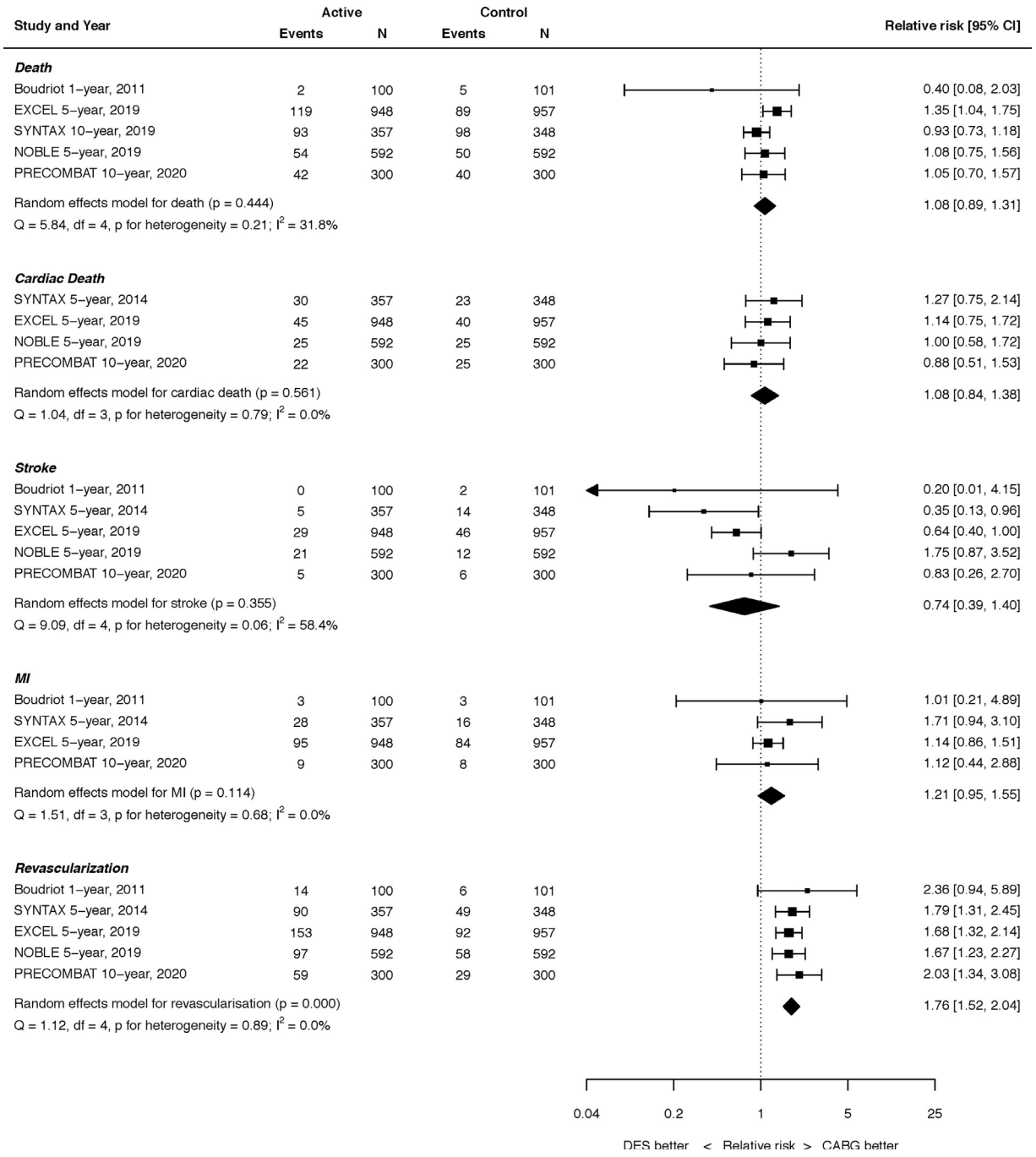

Figure 1. Long-term risk of death, cardiac death, stroke, myocardial infarction and unplanned revascularization from five randomized trials of PCI with DES versus CABG.

95% CI 1.53 to 3.27, p < 0.001). The risk of unplanned revascularization was greater following PCI: RR 1.76, 95% CI 1.52 to 2.04, p < 0.001.

Discussion

The present analysis represents the most up-to-date synthesis of all available randomized clinical trial data of patients undergoing revascularization of LMCAD. The most important finding is that PCI with DES and CABG resulted in similar survival at a weighted mean follow-up duration of 6.3 years. The long-term results also showed no significant difference in cardiac death, stroke or MI between the 2 therapies. The risk of unplanned revascularization was greater with PCI than CABG (weighted absolute difference ~7%). The similar cardiac and all-cause mortality of the 2 therapies at long-term follow-up should reassure clinicians and patients that PCI provides a safe alternative to CABG for selected patients with LMCAD.

The present study has several limitations. Only 2 of the 5 trials have 10-year follow-up currently available. To our knowledge, however, follow-up beyond 5 years is not planned for EXCEL or NOBLE. These data are thus not likely to change over time. The PRECOMBAT trial did not separately report the rates of procedural and nonprocedural MI, and thus the long-term data from this trial did not contribute to those relative rates which are unchanged from our prior publication.[1] Small differences in outcomes between the groups cannot be excluded, as reflected in the 95% CIs. Differences in patient characteristics, enrolment geographies and operator skill, background medications, and endpoint definitions may have added some imprecision to the present results. An individual-patient data pooled analysis from these studies is planned and should provide further insight as to whether certain LMCAD subgroups might preferentially benefit with PCI or CABG, such as patients with diabetes and high SYNTAX scores.

In conclusion, based on the totality of data there is no difference in survival between PCI with DES and CABG for patients with LMCAD, up to a weighted mean follow-up duration of 6.3 years, including 2 studies in which survival after both procedures were comparable for 10 years. Patients, clinicians, societies, and guideline committees may find these data useful.

Disclosures

ADA reports honoraria and sponsorship from Medtronic and Bayer. ZAA reports grant support from National Heart, Lung, and Blood Institute; grant support and advisory board fees from Abbott Vascular and Cardiovascular Systems Inc; and speaker fees from Amgen and Astra Zeneca; advisory board from Abiomed, advisory board and speaker fees from Boston Scientific, advisory board and speaker fees from Cardinal Health, advisory board and consultancy from Opsens Medical, advisory board from Acist Medical; and equity from Shockwave Medical. MBL reports consultancy to Abbott Vascular and Boston Scientific. AJK reports institutional funding to Columbia University and/or Cardiovascular Research Foundation from Medtronic, Boston Scientific, Abbott Vascular, Abiomed, CSI, Philips, and ReCor Medical. DK reports honoraria from Abbott Vascular, Boston Scientific, and Abiomed and holds equity in Soundbite, Saranas, and Traverse Vascular. And all other authors have no conflict of interest to declare. GWS reports having received speaker or other honoraria from Cook, Terumo, QOOL Therapeutics and Orchestra Biomed; serving as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme; receiving equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, Valfix.

Yousif Ahmad, MRCP, PhD[a,b,*]
James P. Howard, MRCP[b]
Ahran D. Arnold, MRCP[b]
Ziad A. Ali, MD, D.Phil[a,c]
Darrel Francis, MD, FRCP[b]
Jeffrey W. Moses, MD[a,c]
Martin B. Leon, MD[a,c]
Ajay J. Kirtane, MD[a,c]
Dimitri Karmpaliotis, MD, PhD[a]
Gregg W. Stone, MD[c,d]

[a] Columbia University Medical Center/New York-Presbyterian Hospital, New York, New York
[b] National Heart and Lung Institute, Imperial College London, London, United Kingdom
[c] The Cardiovascular Research Foundation, New York, New York
[d] Mount Sinai Hospital and Icahn School of Medicine at Mount Sinai, New York, New York

15 June 2020

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https://doi.org/10.1016/j.amjcard.2020.06.059

Excessive Rotational Speed May Be Associated With the Transection of Guidewires in Rotational Atherectomy

Among several specific devices for calcified lesions, rotational atherectomy (RA) has been a cornerstone for severely calcified coronary lesions. Unique complications such as burr entrapment were observed in percutaneous coronary intervention with RA, and one of unique complications was the transection of the RotaWire (Boston Scientific, Marlborough, MA), which might result in fatal complications such as vessel perforation.[1] There were few reports mentioning the incidence of transection. Our group previously reported the incidence of transection of the RotaWire as 0.8% from the analysis of 250 RA cases.[2] However, the reasons or the specific risk factors for the transection have not been systematically analyzed.

Although manufacturer recommended the rotation speed <19,000 rotation per minute (rpm), the maximum rotational speed greater than 190,000 rpm is sometimes used in clinical practice.[3] Our group revealed that the RotaWire may be spinning under the maximum rotational speed in a bench test,[4] whereas the RotaWire theoretically would not spin during high-speed mode because of the internal brake and WireClip Torquer (Boston Scientific, Marlborough, MA). If the RotaWire was spinning during RA, the RotaWire would be fatigued, which might be a risk of the transection of the guidewire. Our group conducted a randomized control study regarding the rotational speed (high speed vs low speed),[5] which started at November 2014. This randomized control study served as a trigger to reconsider the rotational speed in our catheter laboratory. Our group had adopted a liberal rule regarding the rotational speed ranging 140,000 to 220,000 rpm until November 2014 (beyond 200,000 rpm was occurred frequently), whereas our group has adopted a conservative rule regarding the rotational speed ranging 140,000 to 190,000 rpm (beyond 190,000 rpm was tried only occasionally) since November 2014. We retrospectively compared the incidence of the transection of the RotaWire between the period of liberal rotational speed (April 2007 to November 2014) and that of conservative rotational speed (November 2014 to May 2020). This study was approved by the institutional review board of Saitama Medical Center, Jichi Medical University (S20-029), and written informed consent was waved because of the retrospective study design. The incidence of the transection of the RotaWire was significantly higher in the period of liberal rotational speed than in the period of conservative rotational speed, while the incidence of burr entrapment or vessel perforation due to burrs were not different between the 2 periods (Table 1). Although we did not register each rotational speed before December 2009, the rotational speed was significantly faster in the period of liberal rotational speed than in the period of conservative rotational speed. Of 4 cases with the transection of the RotaWire, each rotational speed was not available in 2 cases before December 2009, but was available in 2 cases after December 2009 (211,800 rpm and 197,700 rpm, respectively). Since the incidence of transection was only 1% even in the period of liberal rotational speed, the excessive rotational speed would not be an only reason for the transection of the RotaWire. Moreover, only 4 events out of 901 RA cases would not allow us to perform a multivariate logistic regression analysis to adjust confounding factors, which usually require at least 20 events for 2 variables and at least 30 events for 3 variables. However, our analysis would provide a hypothesis that the excessive rotational speed might fatigue the RotaWire. Previous large-scale registries regarding RA did not provide each rotational speed. Our preliminary data suggest that future large-scale registries should include each rotational speed to analyze the association between the excessive rotational speed and adverse events.

Disclosures

Dr Sakakura has received speaking honoraria from Abbott Vascular, Boston Scientific, Medtronic Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, and NIPRO. He has served as a proctor for Rotablator for Boston Scientific and has served as a consultant for Abbott Vascular and Boston Scientific. Prof. Fujita served as a consultant for Mehergen Group Holdings, Inc.

Kenichi Sakakura, MD*
Yousuke Taniguchi, MD
Kei Yamamoto, MD
Takunori Tsukui, MD
Hiroyuki Jinnouchi, MD
Hideo Fujita, MD

Table 1
Comparison of frequency of complications in the period of liberal rotational speed versus in the period of conservative rotational speed

	Period of liberal rotational speed (April 2007 to November 2014, n = 418)	Period of conservative rotational speed (November 2014 to May 2020, n = 483)	p Value
RotaWire transection- n, (%)	4 (1.0)	0	0.046
Perforation due to burr- n, (%)	0	2 (0.4)	0.502
Burr entrapment- n, (%)	2 (0.5)	1 (0.2)	0.600
Mean rotational speed x 1,000 rpm (n = 685)	197.8 ± 12.9 (n = 202)	170.3 ± 14.8 (n = 483)	<0.001*

Fisher exact test for RotaWire transection, perforation due to burr, burr entrapment.
Student *t* test for mean rotational speed.
* No mean rotational speed data before December 2009.