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JACC HISTORICAL BREAKTHROUGHS IN PERSPECTIVE

Percutaneous Coronary Revascularization

JACC Historical Breakthroughs in Perspective

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ABSTRACT

Over the last 4 decades, percutaneous coronary intervention has evolved dramatically and is now an acceptable treatment option for patients with advanced coronary artery disease. However, trialists have struggled to establish the respective roles for percutaneous coronary intervention and coronary artery bypass graft surgery, especially in patients with multivessel disease and unprotected left-main stem coronary artery disease. Several pivotal trials and meta-analyses comparing these 2 revascularization strategies have enabled the relative merits of each technique to be established with regard to the type of ischemic syndrome, the coronary anatomy, and the patient's overall comorbidity. Precision medicine with individualized prognosis is emerging as an important method of selecting treatment. However, the never-ending advancement of technology, in conjunction with the emergence of novel pharmacological agents, will in the future continue to force us to reconsider the evolving question: "Which treatment strategy is better and for which patient?" (J Am Coll Cardiol 2021;78:384–407) © 2021 by the American College of Cardiology Foundation.

When the first percutaneous transluminal coronary angioplasty (PTCA) was performed by Andreas Grüntzig on September 16th, 1977 (Supplemental Figures 1 and 2), coronary artery bypass surgery (CABG) was already a maturing sibling that had progressively evolved since the first human attempt by Robert H. Goetz in 1960 (Supplemental Table 1) (1,2).

Between 1986 and 1994, balloon-expandable and self-expanding stents struggled to address multiple technical and clinical problems, including poor crimping of the stent on the balloon, incomplete and inaccurate deployment of the self-expanding "endoprosthesis," bulkiness, stiffness, and the thrombogenic nature of this alien body in the coronary bloodstream (Supplemental Tables 2 and 3). The STRESS (Stent Restenosis Study) (3) and BENESTENT trials (4) finally succeeded in validating this new technique, but dual antiplatelet therapy became a must (5,6).

The early results of the RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) trial (7) comparing first-generation drug-eluting stents (DES) with bare-metal stents (BMS) showed what could

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HIGHLIGHTS

- PCI techniques have evolved over 4 decades, as indications have expanded and outcomes improved.
- Numerous studies have addressed the role of PCI as an alternative to CABG in specific patient populations.
- Further studies are needed to clarify the optimum approach to selection of one revascularization strategy over another for individual patients with coronary artery disease.

potentially be achieved by using DES, with ideal results and no untoward events in this first trial. However, new problems were subsequently identified, including a new Damocles' sword: late (1 to 12 months) and very late (≥1 year) stent thrombosis and long-term dependence on dual antiplatelet therapy (8). Long-lasting and careful watching became the new rule, as very late stent thrombosis was perceived as an unpredictable time bomb.

Today's stents have ultrathin struts that are made from alloys different to the initial bulky stainless steel, with sophisticated platform designs and biocompatible, bioresorbable, or biostable coatings that have dramatically helped mitigate the problems of restenosis and thrombosis. Consequently, historical strategies of dual antiplatelet therapy (9) are now being challenged by monotherapy using just potent and selective $P2Y_{12}$ inhibitors (10-14).

The dream of "leaving nothing behind" with the hype of bioresorbable scaffolds (BRS) was very seductive, but the target rate of major adverse cardiac events (MACE) achieved with current DES was missed by a single digit (15-17). That dream may one day be resurrected with more efficient and reliable iterations.

Indeed, the old dream to eliminate flow-limiting lesions by balloon dilatation and at the same time inhibit constrictive remodeling and neointima without "leaving anything behind" has been resurrected with drug-coated balloons. Passive vessel wall transmission of biophilic cytotoxic drugs such as paclitaxel has been replaced by active penetration with electrostatic attachment and long-term residency of microspheres or even nanospheres containing hydrophilic cytostatic sirolimus, so that the vessel wall itself serves as a natural drug reservoir for a duration almost comparable with that of the DES. Beyond the treatment of restenosis, native large and small vessels are the current and future target of this technology (18). There are several ongoing studies aiming to compare drug-coated balloon with DES including patients with large de novo coronary arteries, and it would be an ironic paradox to see the stent being again relegated to its historical function of "bail-out" device.

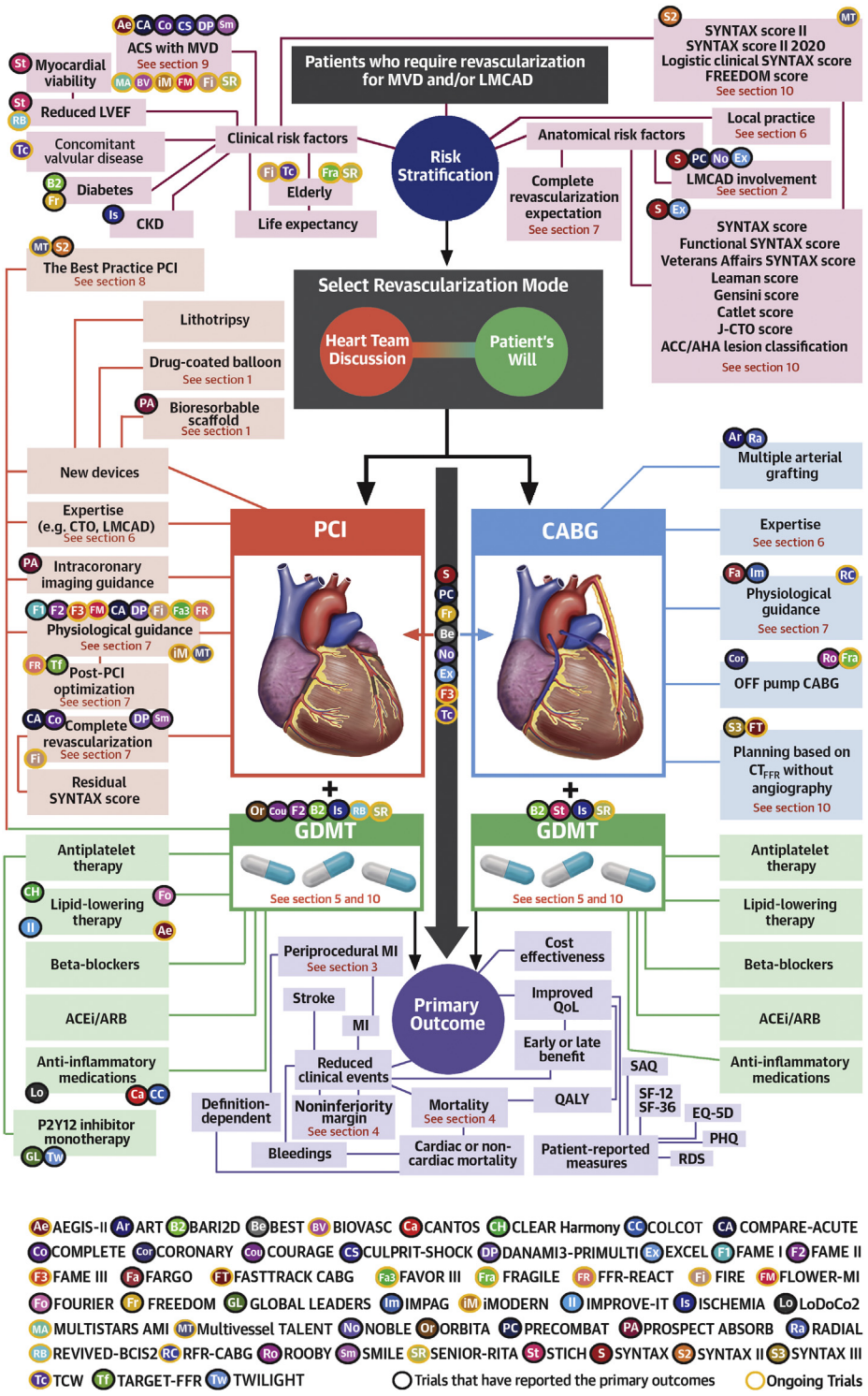
1. VULNERABLE PLAQUE, THE UBIQUITOUS AND RESILIENT ENEMY: TO BE SEALED, BYPASSED, OR DRUG PASSIVATED

An important clinical challenge is managing acute coronary syndromes with nonflow-limiting, rupture-prone plaques located proximal to stented segments (19) or in previously untreated vessels (**Central Illustration**). The surgical strategy of bypassing the proximal origins of the 3 major epicardial vessels, in which life-threatening rupture-prone plaques are more prominent, seems to have a long-term cardioprotective effect (19). Preventing spontaneous myocardial infarction (MI) may be more efficiently achieved by bypassing the vulnerable segments, rather than focal stenting, which may leave the minefield located upstream to the stenosis unprotected. Only pharmacological agents inducing regression and passivation of those vulnerable plaques upstream to the stented lesion could eventually bridge the existing therapeutic gap between percutaneous coronary intervention (PCI) of a focal lesion versus surgery bypassing the treacherous pathway leading to the narrowed site and sustaining optimal flow beyond the stenotic lesion. It was hypothesized that BRS—by sealing vulnerable plaque and restoring a safe endoluminal lining—would play a role in stabilizing these plaques. Notably, although BRS failed in the treatment of flow-limiting lesions, they did not fail as a preventive treatment for rupture-prone plaques. Serial imaging data have shown that after implantation, neointimal tissue was generated on top of the BRS, covering the underlying plaque with a relatively thick cap (20). The PROSPECT ABSORB (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II Combined with a Randomized, Controlled, Intervention) trial (21) has shown the feasibility and potential efficacy of implanting a BRS in nonflow-limiting (diameter stenosis ≤40% or negative fractional flow reserve [FFR] or instantaneous wave-free ratio [iFR]) lesions with large plaque burden, and is an encouraging (small) step forward. At 25-month follow-up,

ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease
BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CAD = coronary artery disease
DES = drug-eluting stent(s)
MI = myocardial infarction
MVD = multivessel disease
PCI = percutaneous coronary intervention
ULM = unprotected left main

CENTRAL ILLUSTRATION **State-of-the-Art Treatment Flow for Patients Who Require PCI or CABG**



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Contemporary treatment flow with recent evidences or ongoing trials. ACC = American College of Cardiology; ACEi = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CKD = chronic kidney disease; GDMT = guideline directed medical therapy; LMCAD = left main coronary artery disease; MI = myocardial infarction; MVD = multivessel disease; PCI = percutaneous coronary intervention; QoL = quality of life.

patients receiving BRS compared with guideline-directed medical therapy (GDMT) alone had a significantly larger minimum lumen area (6.9 ± 2.6 mm^2 vs 3.0 ± 1.0 mm^2; $P < 0.0001$) on intravascular ultrasound, and had significantly lower maximum lipid core burden index on near-infrared spectroscopy. However, it remains to be seen whether this approach would ever realistically compete with either an effective strategy of bypass surgery or aggressive pharmacological treatment.

2. THE FIRST-GENERATION DES VERSUS CABG: WERE INTERVENTIONAL CARDIOLOGISTS OVERCONFIDENT?

In 2002, at least in Europe, the era of DES was triumphantly inaugurated by the presentation at the European Society of Cardiology (ESC) of the landmark RAVEL trial. With "early" restenosis, the worst enemy of interventional cardiologists now defeated the temptation to challenge the hegemony of the surgeon was renascent once again.

Cordis, a Johnson & Johnson company at the time, and most importantly, the manufacturer of the new savior of PCI—the Cypher DES—hesitated to engage in a new randomized trial, and only endorsed a single-arm study: ARTS II (Arterial Revascularization Therapies Study II) (22). ARTS-II subsequently reported a 5-year safety record (absence of death, MI, or cerebrovascular events) with the sirolimus-eluting Cypher stent that was significantly better than the same bare-metal VELOCITY stent platform (87.1% vs 81.9; $P = 0.008$), and comparable to the historical surgical cohort treated in the original ARTS trial (87.1% vs 86.0%; $P = 0.42$). Moreover, the 20.1% absolute difference in MACE between surgery and PCI with BMS seen in ARTS I dropped substantially to a mere single-digit 6.4% absolute difference in ARTS II. However, a critical observation made at the time was that the Kaplan-Meier curves for MACE following surgery and PCI crossed over between the first and second year of follow-up and kept diverging thereafter; this observation would be continually repeated over the next decade.

In 2008 the LE MANS (Left Main Coronary Artery Stenting) study (23) was the first to randomize patients with an unprotected left main (ULM)—a PCI taboo at the time—between surgery and PCI with stents (35% first-generation DES). From the outset, the trial of only 105 patients (53 CABG, 52 PCI) triggered vehement waves of protests from surgeons, who raised concerns about the quality of surgery performed, as only 72% of surgical patients received a left internal mammary artery graft, despite its well-established survival benefit (24). The primary endpoint was mechanistic and unusual: a change in ejection fraction (EF). In the CABG cohort, the EF was unchanged between baseline and 12-month follow-up (53.7 ± 6.7% vs 54.1 ± 8.9%; $P = 0.85$), whereas it increased significantly with PCI from 53.5 ± 10.7% to 58.0 ± 6.8% ($P = 0.04$); the between-group difference at 12 months was also significant ($P = 0.01$) (25). At 10 years, there was a trend toward a higher EF with PCI (54.9 ± 8.3% vs 49.8 ± 10.3%; $P = 0.07$), albeit without any statistical significance because of incomplete follow-up (n = 46; 43.9%) (23). A more relevant, and at the time, intriguing observation in this very small cohort was the absence of any significant between-group difference in the rate of major adverse cardiac and cerebrovascular events (MACCE) at 36 months and 10 years (Supplemental Figure 3).

The SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial (26) was, and still is, a remarkable trial with very long follow-up (≥10 years in the SYNTAXES [SYNTAX Extended Survival] study) (27). The surgical principal investigator, Frederick Mohr, a key opinion leader in surgery, put his stamp on the trial design by virtually eliminating any exclusion criteria. He did not want patients to be cherry-picked for enrollment and thereby open the trial to the same criticism that had been directed to previously conducted trials of PCI versus CABG, which excluded 88% to 98% of the screened population (28,29). Running parallel to the randomized group were 2 nested registries: a surgical one that included patients where the extent and complexity of coronary artery disease (CAD) was judged by the PCI operator to preclude a percutaneous approach; and a percutaneous one that included those patients where comorbidities prohibited surgery (29).

In addition, a semiquantitative tool for assessment of the extent and complexity of CAD was created from an amalgam of existing scores, and among them, the Leaman score that weighted the individual physiological impact of an occluded or narrowed vessel. The SYNTAX score was born as just an angiographic tool to force the surgeons and interventional cardiologists to meticulously examine the extent and complexity of the patient's coronary disease before their inclusion into the trial (30,31).

When the outcome of the trial was analyzed, the SYNTAX score transformed from a diagnostic tool to a prognostic one. Indeed, outcomes with PCI using the first-generation TAXUS DES (Boston Scientific) were safe and comparable to CABG for patients with 3-vessel disease (3VD) and a score ≤22 (the first tercile of the score) and in those patients with ULMCAD who had a score <33. Around the same time, the Korean

TABLE 1 Randomized Trials Comparing PCI With DES vs CABG

Trial (Ref. #)	Published Year	Disease Type	Patients, n		EuroSCORE		SYNTAX Score		Outcomes	Follow-up
			PCI	CABG	PCI	CABG	PCI	CABG		
LE MANS (23,25)	2009 2016	LMCAD	52	53	3.3 ± 23	3.5 ± 2.3	25.2 ± 8.7	24.7 ± 6.8	LVEF All-cause death 	1 y 10 y 1 y 10 y
SYNTAX (26,27,125)	2009 2013 2019	3VD or LMCAD	903	897	3.8 ± 2.6	3.8 ± 2.7	28.4 ± 11.5	29.1 ± 11.4	MACCE* All-cause death 	1 y 5 y 1 y 5 y 10 y
CARDia (126)	2010	DM with MVD or complex 1VD (3VD: 61.8%)	256	254	NA	NA	NA	NA	All-cause death, MI, or stroke All-cause death	1 y 1 y
Boudriot et al. (42)	2011	LMCAD	100	101	2.4 (1.5-3.7)	2.6 (1.7-4.9)	24.0 (19.0-29.0)	23.0 (14.8-28.0)	MACE† All-cause death	1 y 1 y
PRECOMBAT (32,127,128)	2011 2015 2020	LMCAD	300	300	2.6 ± 1.8	2.8 ± 1.9	24.3 ± 9.6	25.3 ± 10.9	MACCE‡ All-cause death 	1 y 2 y 5 y 10 y 1 y 2 y 5 y 10 y
FREEDOM (34,129)	2012 2019	DM with MVD (3VD: 83.4%)	953	947	2.7 ± 2.4	2.8 ± 2.5	26.2 ± 8.4	26.1 ± 8.8	All-cause death, MI, or stroke All-cause death 	5 y 5 y 7.5 y
VA CARDS (130)	2013	DM with MVD or isolated proximal LAD disease	104	103	NA	NA	22.7 ± 10.6	21.5 ± 8.9	Death or nonfatal MI All-cause death	2 y 2 y
BEST (37)	2015	MVD (3VD: 77.2%)	438	442	2.9 ± 2.0	3.0 ± 2.1	24.2 ± 7.5	24.6 ± 8.1	Death, MI, or TVR All-cause death	2 y Median 4.6 y Median 4.6 y
NOBLE (36,131)	2015 2020	LMCAD	598	603	2 (2-4)	2 (2-4)	22.5 ± 7.5	22.4 ± 8.0	MACCE§ All-cause death	5 y 5 y
EXCEL (35,132)	2016 2019	LMCAD and SS ≤32	948	957	NA	NA	26.9 ± 8.8	26.0 ± 9.8	Death, MI, or stroke All-cause death 	3 y 5 y 3 y 5 y

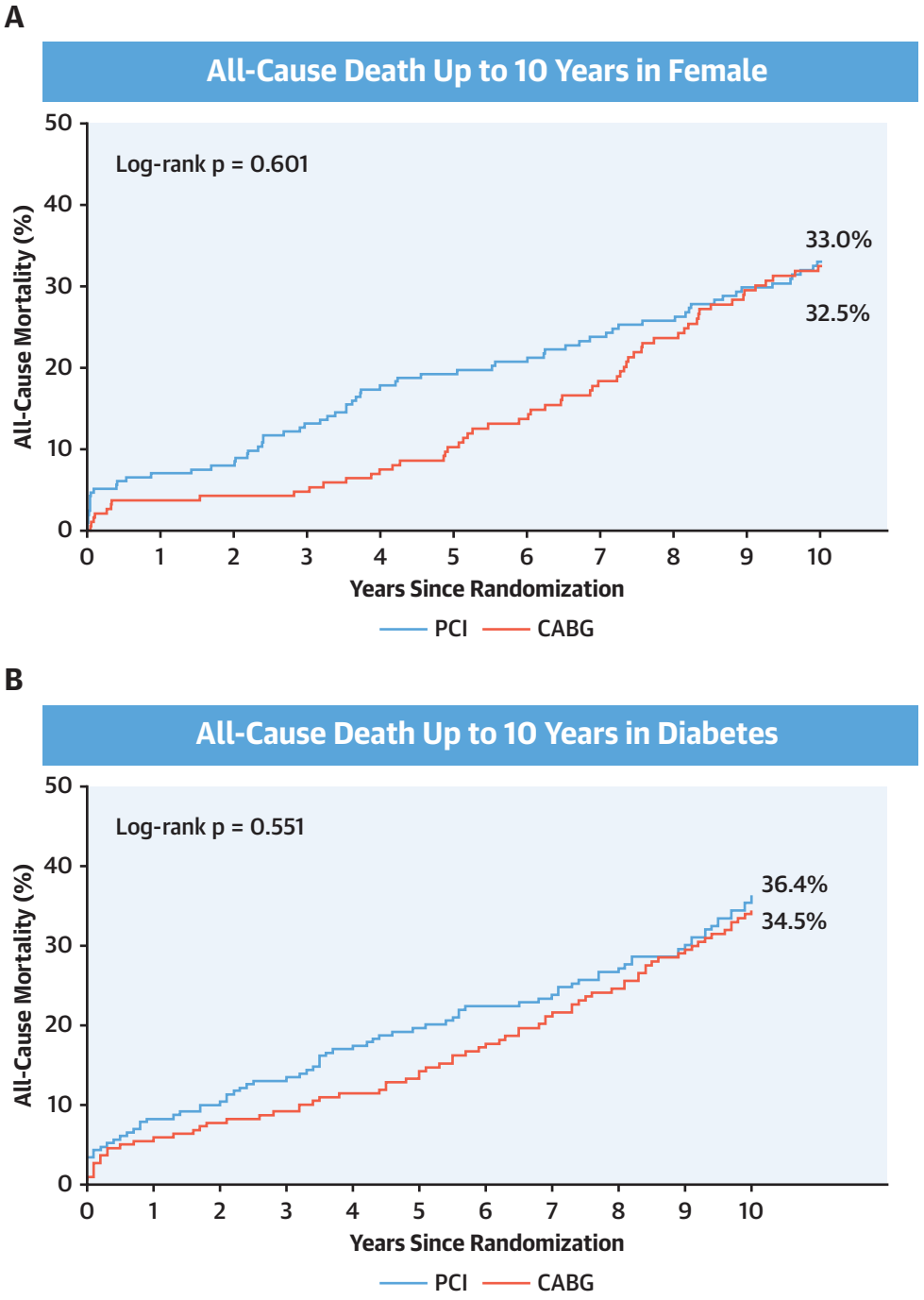
*Defined as a composite of death, MI, stroke, and repeat revascularization. †Defined as a composite of cardiac death, MI, and TVR. ‡Defined as a composite of death, MI, stroke, and ischemia-driven TVR. §Defined as a composite of death, nonprocedural MI, repeat revascularization, and stroke.

1VD = 1-vessel disease; 2VD = 2-vessel disease; 3VD = 3-vessel disease; BMS = bare-metal stent; CABG = coronary artery bypass graft; CAD = coronary artery disease; DES = drug-eluting stent; DM = diabetes mellitus; EES = everolimus-eluting stent; LAD = left anterior descending artery; LIMA = left internal mammary artery; LVEF = left ventricular ejection fraction; LMCAD = left main coronary artery disease; MACE = major adverse cardiac events; MI = myocardial infarction; MVD = multivessel disease; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; PMI = procedural myocardial infarction; TVR = target-vessel revascularization.

TABLE 1 Continued

Event Rates PCI vs CABG (%)	Strengths	Limitations
58.0% vs 54.1% $P = 0.01$ 54.9% vs 49.8% $P = 0.07$ 1.9% vs 7.5% $P = 0.37$ 21.6% vs 30.2% $P = 0.41$	The first prospective randomized study dedicated to LMCAD. The unique primary endpoint of improvement in LVEF. Available 10-y follow-up data.	Small number of patients. BMS use (30%). First-generation DES use (70%). Limited use of LIMA (73%).
17.8% vs 12.4% $P = 0.002$ 37.3% vs 26.9% $P < 0.0001$ 4.4% vs 3.5% $P = 0.37$ 13.9% vs 11.4% $P = 0.10$ 28.4% vs 24.5% $P = 0.066$	The first large randomized trial comparing PCI with DES with CABG. All-comers trial with minimum exclusion criteria and nested registries. Excluding less-severe CAD (ie 1VD or 2VD without LMCAD). High-risk population/lesions suggested by the mean EuroSCORE and mean SYNTAX score. Uniform use of DES (Taxus PES). Prospective validation of the SYNTAX score. Available 10-y follow-up data High follow-up rate up to 10 y.	First-generation DES use. Relatively small sample size when focusing on disease-specific subgroups (eg, 3VD or LMCAD). 10-y follow-up data was only for vital status.
13.0% vs 10.5% $P = 0.393$ 3.2% vs 3.2% $P = 0.97$	The first randomized trial dedicated to patients with diabetes and MVD.	Small number of patients. BMS use (31%). First-generation DES use (69%). Limited-term follow-up data (up to 1 y). Including complex 1VD.
19.0% vs 13.9% 2.0% vs 5.0%	Uniform use of DES. Dedicated to LMCAD.	Small number of patients. First-generation DES use. Limited-term follow-up data (up to 1 y). Relatively low-risk population suggested by the median EuroSCORE. Relatively less-severe CAD suggested by the median SYNTAX score.
8.7% vs 6.7% 12.2% vs 8.1% $P = 0.12$ 17.5% vs 14.3% $P = 0.26$ 29.8% vs 24.7% 2.0% vs 2.7% 2.4% vs 3.4% $P = 0.45$ 5.7% vs 7.9% $P = 0.32$ 14.5% vs 13.8%	Randomized trial dedicated to LMCAD with relatively larger number of patients. Uniform use of DES. Available 10-y follow-up data.	Relatively small number of patients First-generation DES use. Relatively wide noninferiority margin (absolute difference of 7 percentage points in MACCE). Relatively low-risk population suggested by the mean EuroSCORE. Relatively less-severe CAD suggested by the mean SYNTAX score. Possibility of under-reported events caused by lack of yearly follow-up between 5 and 10 y. Dedicated to East Asian population.
26.6% vs 18.7% $P = 0.005$ 16.3% vs 10.9% $P = 0.049$ 24.3% vs 18.3% $P = 0.01$	The largest randomized trial dedicated to diabetic patients with MVD. Uniform use of DES. Available 7.5-y follow-up data.	The target sample size was amended from 2,400 to 1,900 patients. First-generation DES use. Relatively low-risk population suggested by the mean EuroSCORE. Limited number of patients for extended follow-up study (49.6% of the original study population).
25.3% vs 18.4% 21.0% vs 5.0%	Dedicated to diabetic patients with severe CAD (MVD including LAD or proximal LAD disease). Uniform use of DES.	Early termination caused by slow enrollment (25% of the intended sample size). Small number of patients. Limited-term follow-up data (up to 2 y). First-generation DES use. Including complex 1VD (proximal LAD disease). Relatively less-severe CAD suggested by the mean SYNTAX score.
11.0% vs 7.9% 17.0% vs 11.7% $P = 0.04$ 6.6% vs 5.0% $P = 0.30$	Randomized trial dedicated to MVD with relatively large number of patients. 77.2% of patients had 3VD Uniform use of newer-generation DES (EES).	Early termination caused by slow enrollment (50% of intended sample size). Relatively small number of patients Relatively low-risk population suggested by the mean EuroSCORE. Relatively less-severe CAD suggested by the mean SYNTAX score. Dedicated to East Asian population.
28.4% vs 19.0% $P = 0.0002$ 9.4% vs 8.7% $P = 0.68$	Randomized trial dedicated to LMCAD with relatively large number of patients. Use of newer-generation DES (Biomatrix BES) after treatment of 73 patients with first-generation DES. Available 5-y follow-up data.	Primary endpoints excluding PMI. Use of first-generation DES (approximately 10%). Relatively low-risk population suggested by the median EuroSCORE. Relatively less-severe CAD suggested by the mean SYNTAX score.
15.4% vs 14.7% $P = 0.98$ 22.0% vs 19.2% $P = 0.13$ 8.2% vs 5.9% $P = 0.11$ 13.0% vs 9.9%	The largest randomized trial dedicated to LMCAD. Uniform use of newer-generation DES (Xience EES). Available 5-y follow-up data.	Specific definition of PMI. 25% of included patients met exclusion criteria of high SYNTAX score (≥33) according to core laboratory assessments.

FIGURE 1 **Kaplan-Meier Curves in Subgroups of the SYNTAX Study**



Cumulative incidence of all-cause mortality up to 10 years comparing PCI versus CABG in **(A)** women or **(B)** diabetic patients in the SYNTAXES study. **(C)** MACCE rates in the SYNTAX trial (n = 1,652). **(C-1)** Prevalence of PMI according to various definitions, **(C-2)** SYNTAX definition, **(C-3)** Fourth UDMI definition, **(C-4)** ISCHEMIA definition, **(C-5)** SCAI or EXCEL definition, and **(C-6)** MACCE rates excluding PMI as in the NOBLE trial. Reprinted with permission from Hara et al. (33,38). MACCE = major adverse cardiac or cerebrovascular events; PMI = periprocedural myocardial infarction; SCAI = Society for Cardiovascular Angiography and Interventions; UDMI = Universal Definition of Myocardial Infarction.

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FIGURE 1 Continued

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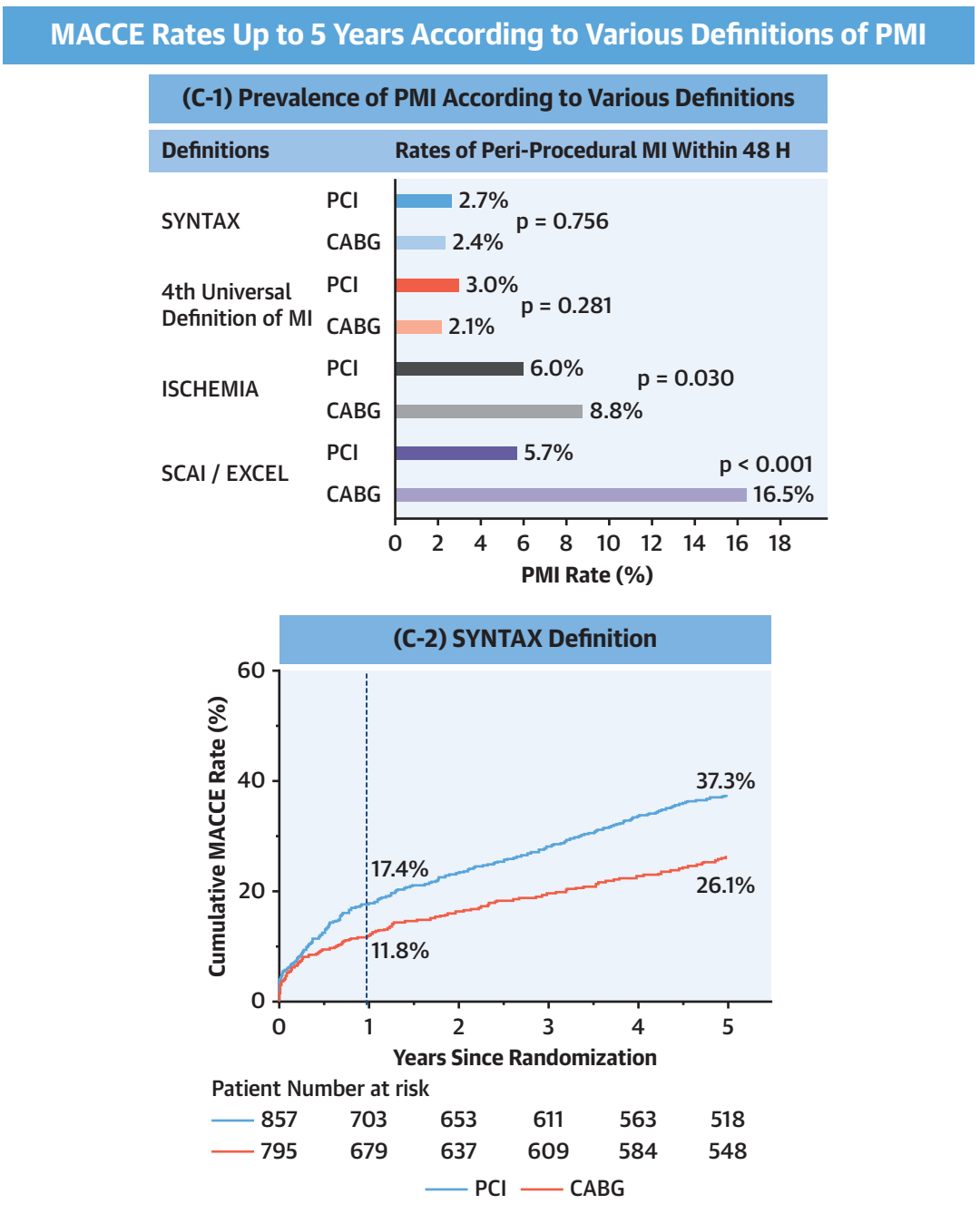

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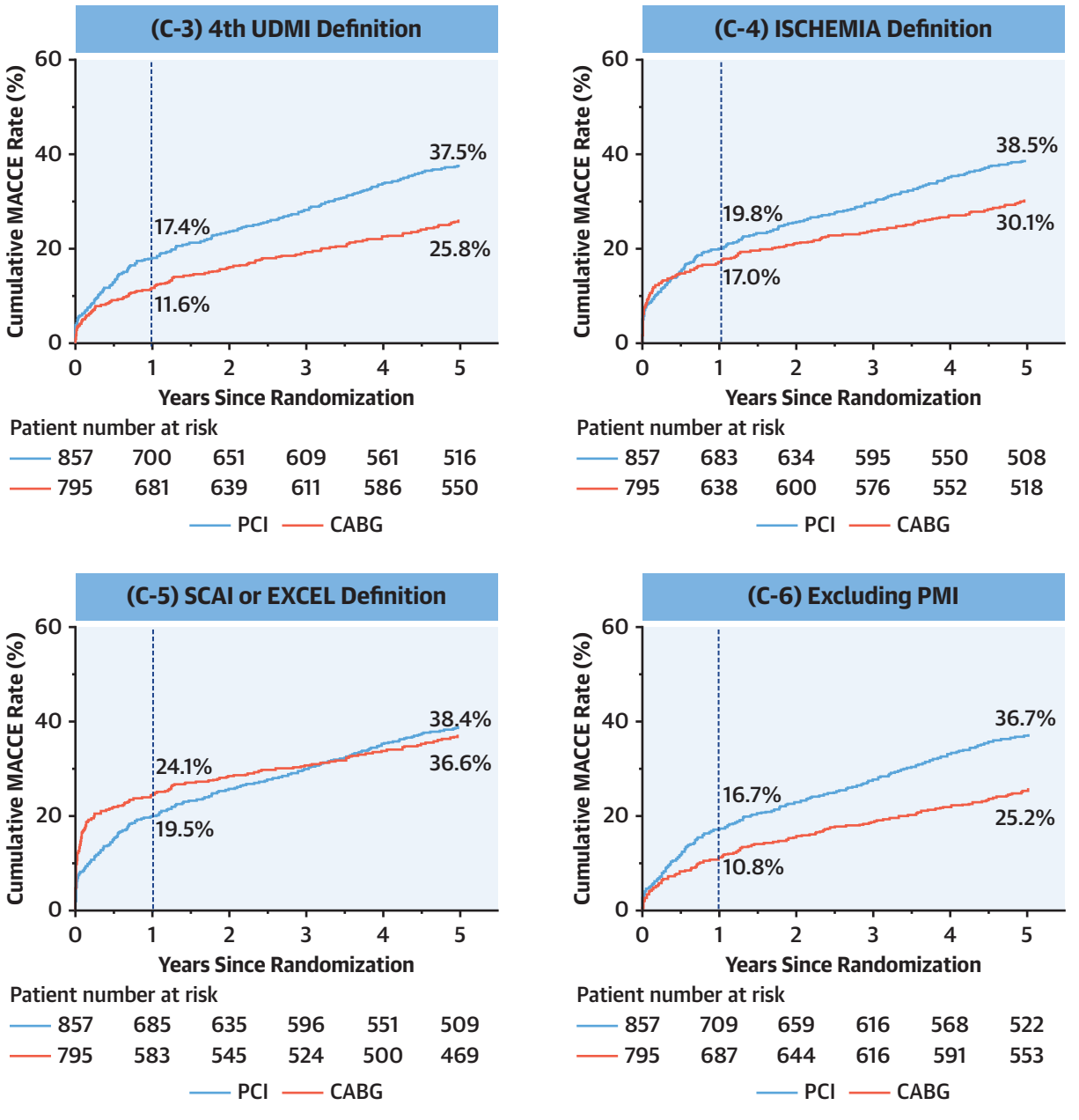
team led by S.J. Park published the 2- and 5-year results of PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease), a trial with 600 patients testing the first-generation Cypher DES in ULMCAD with a primary endpoint of MACCE, a composite of death, stroke, MI, and ischemia-driven target-vessel revascularization (TVR) (32). At 1 year, PCI was noninferior to CABG (PCI 8.7% vs CABG 6.7%; $P_{\text{noninferiority}} = 0.01$), whereas at 5 years, MACCE rates were comparable (PCI 17.5% vs CABG 14.3%; $P_{\text{superiority}} = 0.26$). The rates of death, MI, or stroke

FIGURE 1 Continued



were 4.0% for CABG and 3.3% for PCI at 1 year, and 9.6% and 8.4%, respectively, at 5 years. Recently the 10-year results were reported, with again no significant between-group differences in MACCE (29.8% vs 24.7%; HR: 1.25; 95% CI: 0.93-1.69) (32).

The SYNTAX and PRECOMBAT trials opened a new avenue of revascularization options for ULMCAD with favorable long-term results (**Table 1**). It has to be underscored that trialists, mainly surgeons, always assume that outcome curves that diverge in the first 5 years will continue to do so over time, way beyond the first 5 years; contemporary data, however, have questioned this. In the SYNTAX trial, the survival benefit of women was significantly lower with CABG at 5 years, but this advantage completely subsided by 10 years, with a similar mortality rate with PCI and CABG of around 33% (33). In a similar fashion, the diverging curves for all-cause mortality at 5 years in

diabetic patients converge at 10 years, with the caveat that insulin-dependent patients kept benefitting from CABG (**Figure 1A**).

The FREEDOM trial was the last important trial with first-generation DES (Cypher 51%, Taxus 43%), and specifically targeted 1,900 diabetic patients with multivessel disease (MVD) (34). The Kaplan-Meier curves here started to diverge at 2 years, and by 5 years the rate of the primary endpoint (a composite of death, MI, and stroke) was 26.6% with PCI and 18.7% with CABG (*P* = 0.005). Notably, although mortality was significantly lower with CABG (PCI 16.3% vs CABG 10.9%; *P* = 0.049), the rate of stroke was not (PCI 2.4% vs CABG 5.2%; *P* = 0.03).

3. TACKLING THE LEFT MAIN STEM AND 3-VESSEL DISEASE WITH THE SECOND-GENERATION DES

The potential role of PCI in ULMCAD, as suggested by SYNTAX and PRECOMBAT, drove the hunger for the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British left main revascularisation study) trials, which were specifically designed to explore the outcomes of these patients randomized to CABG or PCI using second-generation DES (35,36). Meanwhile, in patients with MVD, the BEST trial, which was terminated prematurely because of slow enrollment after recruiting only 880 of the planned 1,776 patients (37), failed to show noninferiority for the composite primary endpoint of death, MI, and TVR at 2 years with PCI using the Xience everolimus-eluting stents (Abbott Vascular) compared with CABG (37). Once again, the superiority of CABG over PCI was seen at 5 years, with significantly lower rates of the composite of death, stroke, MI, and repeat revascularization (PCI 19.9% vs CABG 13.3%; HR: 1.54; 95% CI: 1.11-2.14). Notably, at a median 4.6 years of follow-up, the absolute difference in repeat revascularization was in the single digits: 5.6% (PCI 11.0% vs CABG 5.4%).

In the design of NOBLE (36)—a trial randomizing 1,201 patients with ULMCAD to CABG or PCI (11% first-generation DES, 89% biolimus-eluting stents)—procedural myocardial infarction (PMI) was not included in the composite endpoint consisting of death, non-PMI, stroke, and repeat revascularization at 5 years. In this trial, the absence of any difference in all-cause mortality at 5 years (PCI 9.4% vs CABG 8.7%; HR: 1.08; 95% CI: 0.74-1.59) was reassuring; however, the higher incidence and HR of spontaneous MI was not (PCI 7.6% vs CABG 2.7%; HR: 2.99; 95% CI:1.66-5.39).

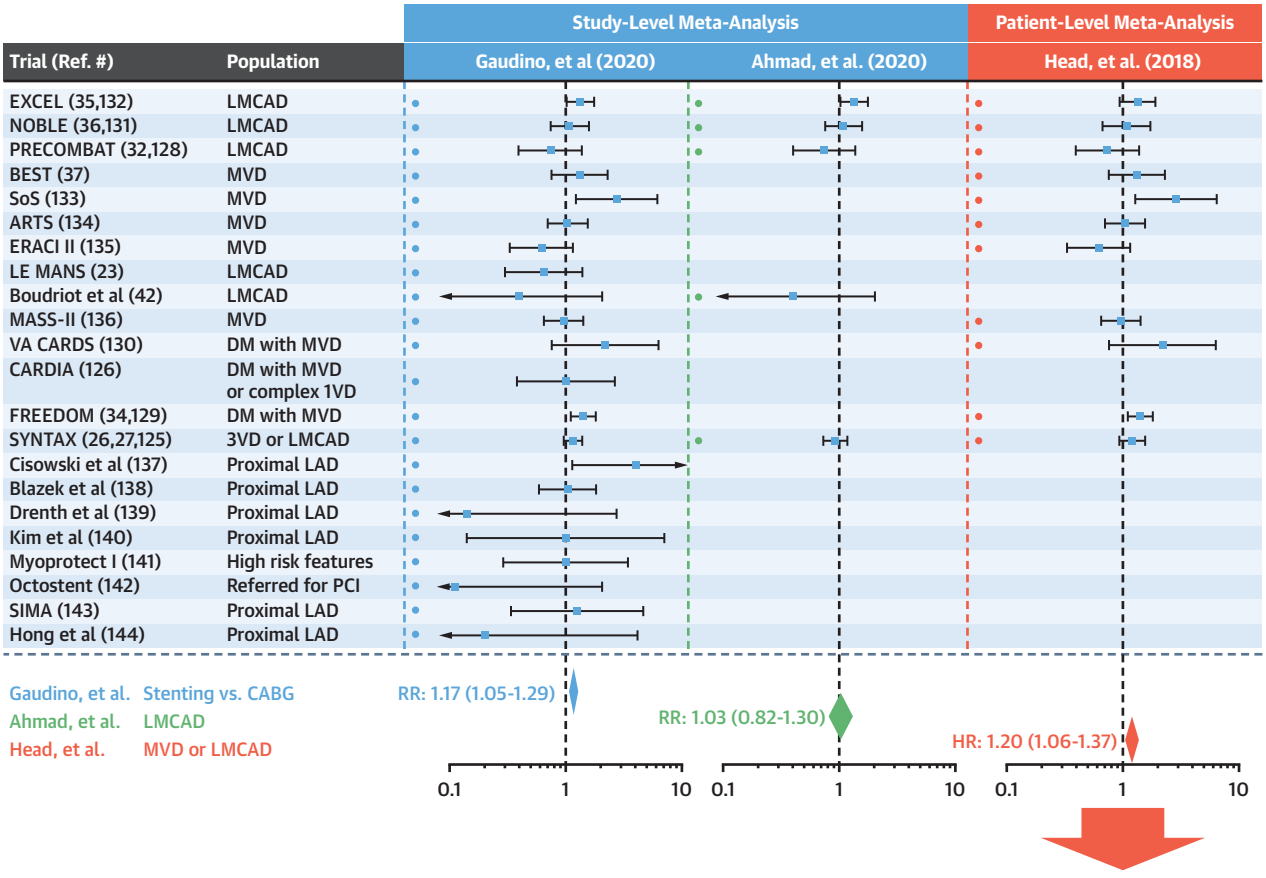
The EXCEL trial, which randomized 1,900 patients with ULMCAD and a SYNTAX score ≤32 (35), aimed to demonstrate noninferiority of PCI at 3 years compared with CABG ($P_{\text{noninferiority}}$ = 0.02 and $P_{\text{superiority}}$ = 0.98; HR: 1.00; 95% CI: 0.79-1.26) for the composite primary endpoint of death, MI, and stroke. In the last 2 years of follow-up, the Kaplan-Meier curves for the composite endpoint crossed-over and steadily diverged with a final HR at 5 years of 1.19 (95% CI: 0.95-1.50; $P_{\text{superiority}}$ = 0.13). The rate of all-cause mortality favored surgery (13.0% vs 9.9%; HR: 1.38; 95% CI: 1.03-1.85), whereas the rate of cardiovascular death did not differ.

The difference in outcomes between the NOBLE and EXCEL trials is heavily dependent on the inclusion of PMI as an endpoint. Although criticized at the time, the decision of the NOBLE trialists to omit PMI from their composite primary endpoint is now fully appreciated following the published debate and critical appraisal of PMIs and their definitions (38,39). Their clinical relevance and impact on time-event curves and composite endpoints is indeed now more transparent (38,39). Contrast this with the EXCEL trial, where the higher initial in-hospital primary endpoint with CABG was driven by the EXCEL definition of PMI, which required an isolated enzyme release of CK-MB >10× the upper limit of normal without the necessity of other supporting evidence, whereas an elevation of CK-MB >5× the upper limit of normal had to be accompanied by a new Q-wave.

In the SYNTAXES, we retrospectively applied the 5 definitions of PMI, together with reassessing the study's 10-year composite endpoint following their removal (38). These various analyses emphasize the impact of the definition of PMI on time-to-event curves and the primary composite endpoint, reiterating the need for harmony among trialists (**Figure 1B**). Whether PMI should be considered a timed endpoint in future trials is currently being seriously debated.

Moving forward, there will be 3 possible ways to proceed with the assessment of PMIs: 1) to eliminate them from the composite endpoint when comparing surgery and PCI; 2) to apply, at least for the time being, the 4 competing definitions; or 3) to compel trialists to use without question the Fourth Universal Definition, which only defines a PMI as occurring when an elevation of a sensitive cardiac biomarker is accompanied by other evidence of new MI evidenced by ECG or imaging, or complications leading to reduced coronary blood flow (38,39).

FIGURE 2 All-Cause Mortality Between PCI Versus CABG in Recent Meta-Analyses



(Top) Three recent meta-analyses includes different population with study- or patient-level data (40,43,44). The ORs were derived from the fixed-effects models. **(Top)** The patient-level meta-analysis by Head et al (40) enables the subgroup analyses. Reprinted with permission from Head et al (40), Ahmad et al (43), and Gaudino et al (44). CABG = coronary artery bypass graft; LAD = left anterior descending artery; LMCAD = left-main coronary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MVD = multivessel disease; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease.

Continued on the next page

4. META-ANALYSES: BIGGER IS NOT ALWAYS BETTER

A patient-level meta-analysis by Head et al (40), including 11,518 patients randomized to PCI (n = 5,753) and CABG (n = 5,765) from 11 randomized controlled trials, conducted between 2011 and 2017, seems to almost be the current "final word" on the topic (**Figure 2**). At 5 years, PCI for MVD (3VD ± LMCAD) had a higher mortality (HR: 1.44; 95% CI: 1.20-1.74), particularly in those with diabetes and higher coronary complexity; in nondiabetic patients, mortality was almost identical (PCI 8.7% vs CABG 8.4%). In patients with ULMCAD, there was no mortality benefit for CABG over PCI. These differences in prognosis were perfectly reflected in the 2018 ESC/EACTS Guidelines on Myocardial Revascularization (41). A more recent meta-analysis by Ahmad (43) focusing more specifically on the last 5 trials enrolling large cohorts with ULMCAD (a trial by Boudriot et al (42), SYNTAX, PRECOMBAT, EXCEL, and NOBLE) concluded that there was no difference in all-cause mortality between surgery and PCI with an HR of 1.03 (95% CI: 0.81-1.32; $P = 0.779$) (**Figure 2A**) (43). A meta-analysis on the itemized endpoints of these 4 studies is currently being conducted by the TIMI (Thrombolysis In Myocardial Infarction) group, under the leadership of Eugene Braunwald and Marc Sabatine, without involvement of the respective trial investigators. The latest published meta-analysis by Gaudino et al (44) was performed by a consortium of surgeons and cardiologists, and we cannot resist quoting their conclusions (**Figure 2A**): "This meta-analysis found that PCI is associated with higher all-

FIGURE 2 Continued

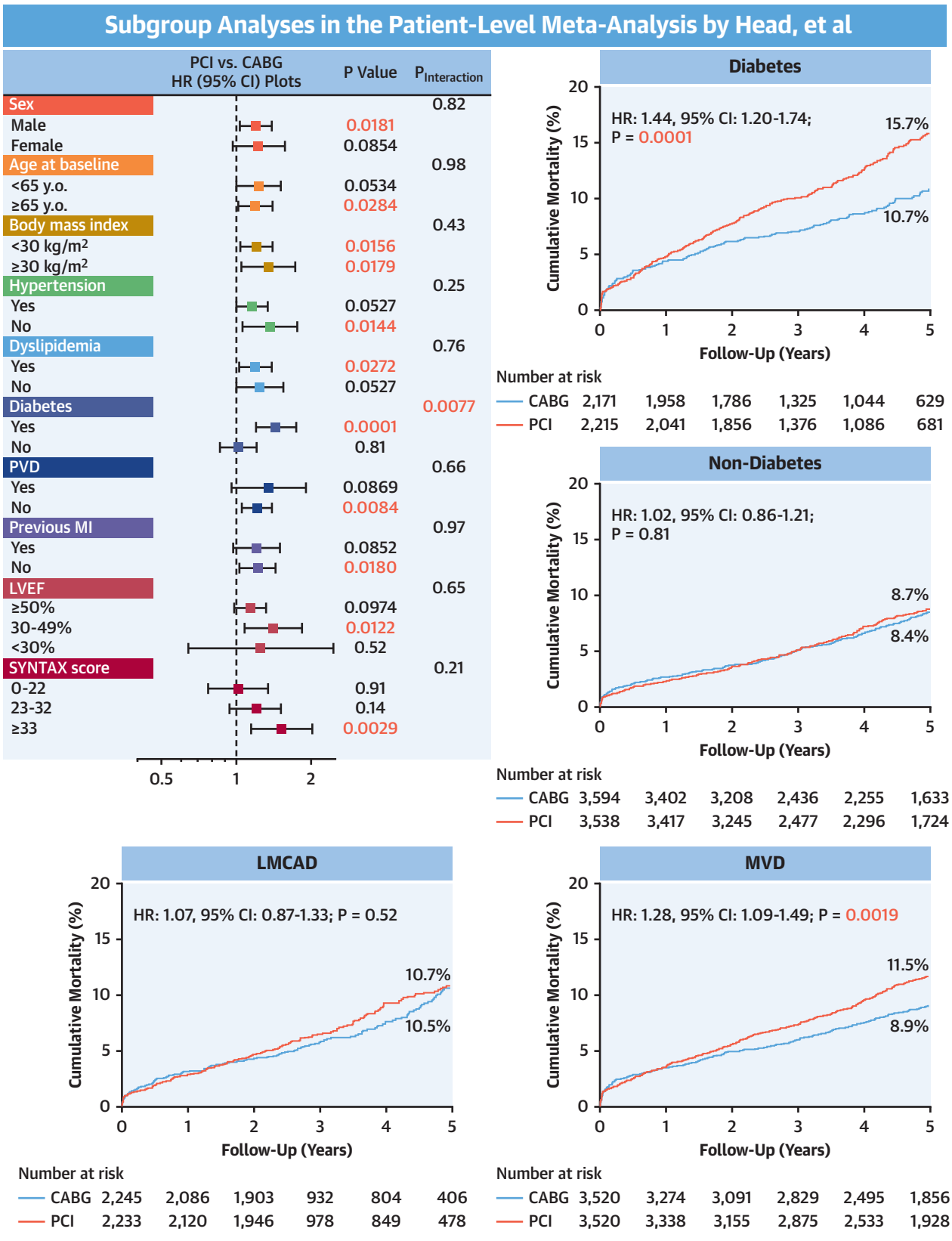


FIGURE 3 Cardiac-Related Medications After Revascularization in the Contemporary Large RCTs

Trials (Ref. #)	Treatment Arm	Medication at Discharge (%)											
		Aspirin (%)	P Value	P2Y12 Inhibitor (%)	P Value	Statins (%)	P Value	Beta Blockers (%)	P Value	ACE Inhibitor (%)	P Value	ARB (%)	P Value
SYNTAX (125)	PCI	96.3	< 0.001	96.8	< 0.001	86.7	< 0.001	81.3	0.17	55.1	< 0.001	13.3	< 0.001
	CABG	88.5		19.5		74.5		78.6		44.6		7.0	
PRECOMBAT (145)	PCI	99.0	0.69	98.3	0.001	72.1	0.72	61.1	< 0.001	15.1	0.028	24.5	0.055
	CABG	98.6		92.5		73.5		41.2		9.2		18.0	
FREEDOM*1 (129)	PCI	99.1	< 0.05	98.4	< 0.05	88.4	> 0.05	83.7	> 0.05	74.3	< 0.05	22.1	< 0.05
	CABG	88.4		24.6		88.6		83.2		67.9		15.9	
BEST (37)	PCI	97.0	0.72	96.6	< 0.001	83.1	0.88	68.5	< 0.001	44.5			< 0.001
	CABG	96.6		89.4		83.5		42.8		25.3			
NOBLE*2 (131)	PCI	92.9	NA	97.4	NA	NA							
	CABG	NA		NA									
EXCEL (132)	PCI	98.5	0.43	97.6	< 0.001	96.7	< 0.001	83.4	< 0.001	56.8			< 0.001
	CABG	98.0		32.3		92.4		92.5		42.2			

*1 At the time of discharge or 30 days post-procedure. *2 The timing is unknown. Abbreviations as in Figure 2.

cause, cardiac, and noncardiac mortality compared with CABG. The significantly higher noncardiac mortality associated with PCI suggests that even noncardiac deaths after PCI may in fact be related to the procedure and/or subsequent management, and our data strongly support the use of all-cause mortality as the most comprehensive and unbiased endpoint for myocardial revascularization trials" (44). Provocatively, the discussions of their publication (44) might trigger a second "ESC firestorm"; lest we forget the first in 2006, when statisticians and epidemiologists from Basel claimed in the main arena, and subsequently published in the *European Heart Journal* (45), that DES with cytostatic agents could trigger cancer "due to a rapid impairment of the immune system." It should be noted that, per definition, any death that cannot be clearly attributed to a noncardiac cause (of course, including any remote possible procedural mortality) is adjudicated as cardiac (46). However, contemporary improvements in periprocedural management, such as increased adoption of the radial approach and more tailored antiplatelet strategies, may mitigate the so-called noncardiac mortality (eg, critical bleedings) observed in previous randomized studies (10,11,47).

These contemporary meta-analyses convey an important clinical message for interventionalists and surgeons: there may be a substantial proportion of patients with severe CAD who derive a survival benefit from surgery compared with PCI. However, needless to say, the final decision should be made on an individual basis in the context of precision medicine, taking into account all of the patient's risk factors. As an editorial note, we have to emphasize the very similar HRs between the patient level meta-analysis by Head et al (40) (HR: 1.20; 95% CI: 1.06-1.37) and the study level meta-analysis of Gaudino et al (44) (HR: 1.17; 95% CI: 1.05-1.29), and highlight that both upper 95% CIs were within 1.4, which is commonly used as the margin of noninferiority (as a side note, the margin is 1.65 in the FAME 3 [Fractional Flow Reserve versus Angiography for Multivessel Evaluation 3] trial), with the connotation that below this threshold, differences are "not clinically meaningful." Although a study-level meta-analysis can be pooled more easily than a patient-level meta-analysis, complex statistical approaches with or without statistical adjustment to find the most beneficial/harmful treatment in a subgroup analysis are not permitted in a study-level analysis. Consequently, it would be hard to apply the results of a study-level meta-analysis to an individual, and hence, they should be used more cautiously than patient-level studies during practical decision making. Therefore, the patient-level meta-analysis of Head et al (40) provides more granular, specific, and balanced information with respect to precision medicine (LM vs MVD, diabetic vs nondiabetic patients, complex MVD vs simple MVD) (**Figure 2B**).

5. GUIDELINE-DIRECTED MEDICAL THERAPY AFTER PCI OR CABG

Optimizing medications is of paramount importance in complex CAD, and following the established benefits seen in numerous studies, current guidelines clearly state that any revascularization must be accompanied by optimal GDMT (41,48-52). Despite this, the prescription of cardiac-related medications post-procedure varies considerably, even in large randomized trials (**Figure 3**). Notably, in patients with 3VD and/or LMCAD in the SYNTAX study, the effect of adherence to GDMT (36% relative reduction in mortality over 5 years) was greater than the treatment effect of revascularization strategy (26% relative reduction in mortality with CABG vs PCI over 5 years) (53). The latest medical strategies, including aspirin-free $P2Y_{12}$ inhibitor monotherapy post-PCI, anti-inflammatory therapy with canakinumab or colchicine, and intensive lipid-lowering therapy with proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, ezetimibe, bempedoic acid, or icosapent ethyl, on top of statins, all have the potential to further improve outcomes in high-risk patients (10,11,54-59).

6. EXPERIENCE WITH REVASCULARIZATION PROCEDURE

The local standard-of-care and experience/expertise of PCI or CABG operators plays an essential part in deciding the optimal modality of revascularization mode. A meta-analysis by Post et al (60) suggested that in-hospital mortality was significantly lower for PCI (OR: 0.87; 95% CI: 0.83-0.91) and CABG (OR: 0.85; 95% CI: 0.79-0.92) when performed in hospitals with high-volume compared with low-volume activity, although the cutoff points to define high-volume varied from 33 to 600 cases annually (60). The 2018 ESC/EACTS Guidelines on Myocardial Revascularization recommended that procedures were performed in institutions with sufficient annual volumes (CABG ≥200, PCI: acute coronary syndrome [ACS] ≥400, or chronic coronary syndrome [CCS] ≥200) and sufficient operator experience (41). For CABG, the experience/expertise of the operator directly affects the planned strategy, such as use of off-pump coronary artery bypass and/or bilateral internal mammary artery grafting, more than for PCI, potentially resulting in better/worse clinical outcomes (61-64). For PCI, especially in case of high-risk CAD, such as ULMCAD or chronic total occlusions, experience/expertise (eg, ≥25 annual ULMCAD cases) has to be better emphasized (65,66).

TABLE 2 Geographic Regions and Outcomes in the FREEDOM and the EXCEL Trials

Trial, (Ref. #)	Region	n	Outcomes	Follow-up	Event Rates PCI vs CABG (%)	*P* Value for Interaction
FREEDOM, (34,129)						
	North America	770	All-cause death, MI, or stroke	5 y	28 vs 16	0.05
	Other	1,130			25 vs 21	
	North America	770	All-cause death	8 y	26.0 vs 13.8	0.02
	Other	1,130			23.0 vs 21.5	
EXCEL, (35,132)						
	North America	752	Death, MI, or stroke	3 y	15.5 vs 12.4	0.14
	Europe	1,075			15.5 vs 15.6	
	Other	78			9.5 vs 22.2	
	North America	752		5 y	24.2 vs 17.3	NA
	Europe	1,075			21.1 vs 19.6	
	Other	78			9.6 vs 29.6	

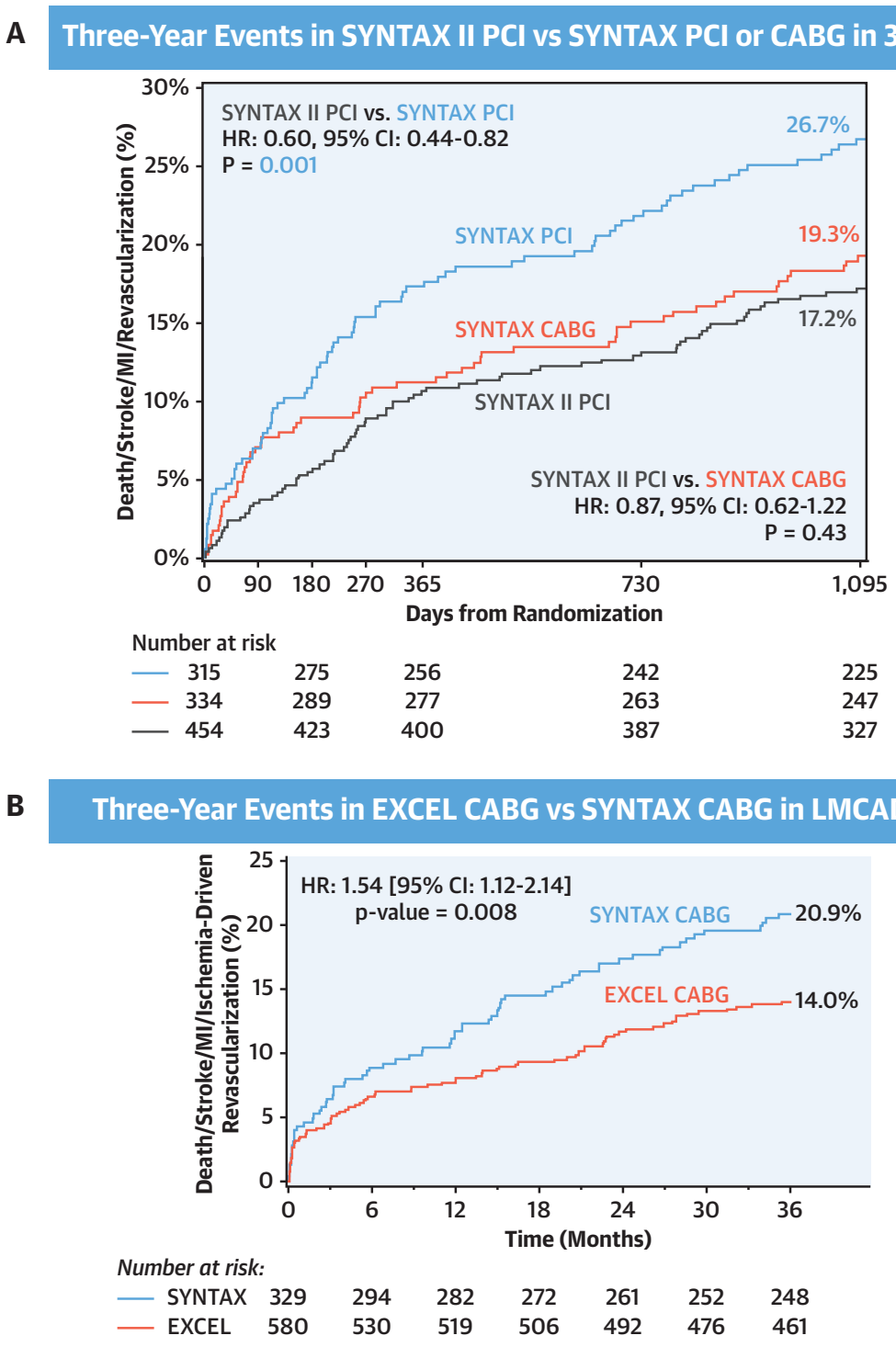
Abbreviations as in **Table 1**.

Geography may also be a factor influencing revascularization strategy and subsequent clinical outcomes. Subgroup analyses of the FREEDOM and EXCEL trials suggested that the favorable effects of CABG over PCI for complex CAD seen more frequently in North America than Europe or other regions (**Table 2**). However, these findings are obviously insufficient to determine the full impact of regional differences. Given the diversity in race and ethnicity, as well as medical services and reimbursement practices worldwide, those studies dedicated to particular regions, such as PRECOMBAT and BEST, may be better suited to investigate this (67).

7. WILL PHYSIOLOGY-GUIDED PCI OR CABG IMPROVE OUTCOMES FOR 3VD?

The FAME trial (N = 1,005) showed that FFR-guided PCI is associated with lower rates of MACE (a composite of death, nonfatal MI, and repeat revascularization) and resource utilization compared with angiography-guided PCI in patients with a stenosis >50% in at least 2 major epicardial vessels (68,69). The mean number of stents was significantly lower in the FFR vs angiography-only arm (1.9 vs 2.7; $P < 0.001$), whereas rates of angina were comparable. Results at 5 years showed comparable rates of MACE (FFR 28% vs angiography-only 31%; relative risk 0.91; 95% CI: 0.75-1.10; $P = 0.31$), and its components, suggesting that an FFR-guided strategy is safe, efficacious, and cost-effective (69). Of note, the ESC guidelines for management of CCS recommend the use of FFR or iFR in patients with MVD, even in the

FIGURE 4 Historical Improvement in Percutaneous or Surgical Outcomes



The SYNTAX II **(A)** and EXCEL **(B)** trials highlight the historical improvements both in PCI and CABG compared with the SYNTAX trial (90,92). Reprinted with permission from Modolo et al. (92). 3VD = 3-vessel disease; CABG = coronary artery bypass graft; LMCAD = left-main coronary artery disease; PCI = percutaneous coronary intervention.

presence of documented ischemia, to localize target lesions. Recently, Di Gioia et al (70) suggested that it would be interesting to assess whether FFR-guided PCI would affect hard endpoints (eg, mortality and MI) in diabetic patients following PCI as observed in the FREEDOM trial.

In contrast to PCI, the efficacy of physiological guidance for CABG is still debated, as although observational data (71) are supportive, results from randomized studies are inconsistent.

The randomized FARGO (Fractional Flow Reserve Versus Angiography Randomization for Graft Optimization) (n = 100) and GRAFFITI (Graft Patency After FFR-guided Versus Angio-guided CABG) (n = 172) trials both showed that compared with angiography-guided CABG, FFR-guided CABG (lesions with FFR >0.80 were not grafted) had no impact on graft failure at 6 months (16% vs 12%; P = 0.97) and 12 months (19% vs 20%; P = NS) (72,73). Of note, in FARGO, FFR values were significantly lower in deferred lesions after 6 months, suggesting disease progression after CABG. Compare these data to the IMPAG (Impact of Preoperative FFR on Arterial Bypass Graft Functionality) trial, where a pre-procedural vessel FFR ≤0.78 was associated with functional anastomoses and high patency rates at 6 months after CABG (74). Although the IMPAG trial demonstrated the utility of preprocedural FFR as a risk prediction tool for graft failure, further trials (eg, the RFR-CABG [Resting Full-cycle Flow Ratio (RFR) Versus Angiography to Guide Revascularization Strategy in Patients Undergoing Coronary Artery By-pass Grafting (CABG)] trial; NCT04375306) are needed to define the role of physiological assessment as a decision-making tool for planning CABG.

The next prospective step will be to assess the functional optimization of PCI by physiological assessment and try to optimize the hemodynamics and ideally normalize the value of FFR/iFR/quantitative flow ratio (QFR) beyond the recommended thresholds (75-77). In patients with MVD, frequent post-stenting physiological assessments will be needed, so angiography-derived FFR, which enables functional assessment by 2 angiographic projections without wire insertion or hyperemia, may become an ideal tool (78,79). Retrospective analyses have already documented the benefit of this strategy, in which the residual functional stenosis based on QFR post-PCI was associated with an increased risk of adverse events (76,77). Although the TARGET-FFR trial highlighted the difficulties in achieving physiological optimization after PCI, even with the intensive treatment following stenting (80), ongoing trials such as FFR-REACT may clarify the feasibility of this approach (81).

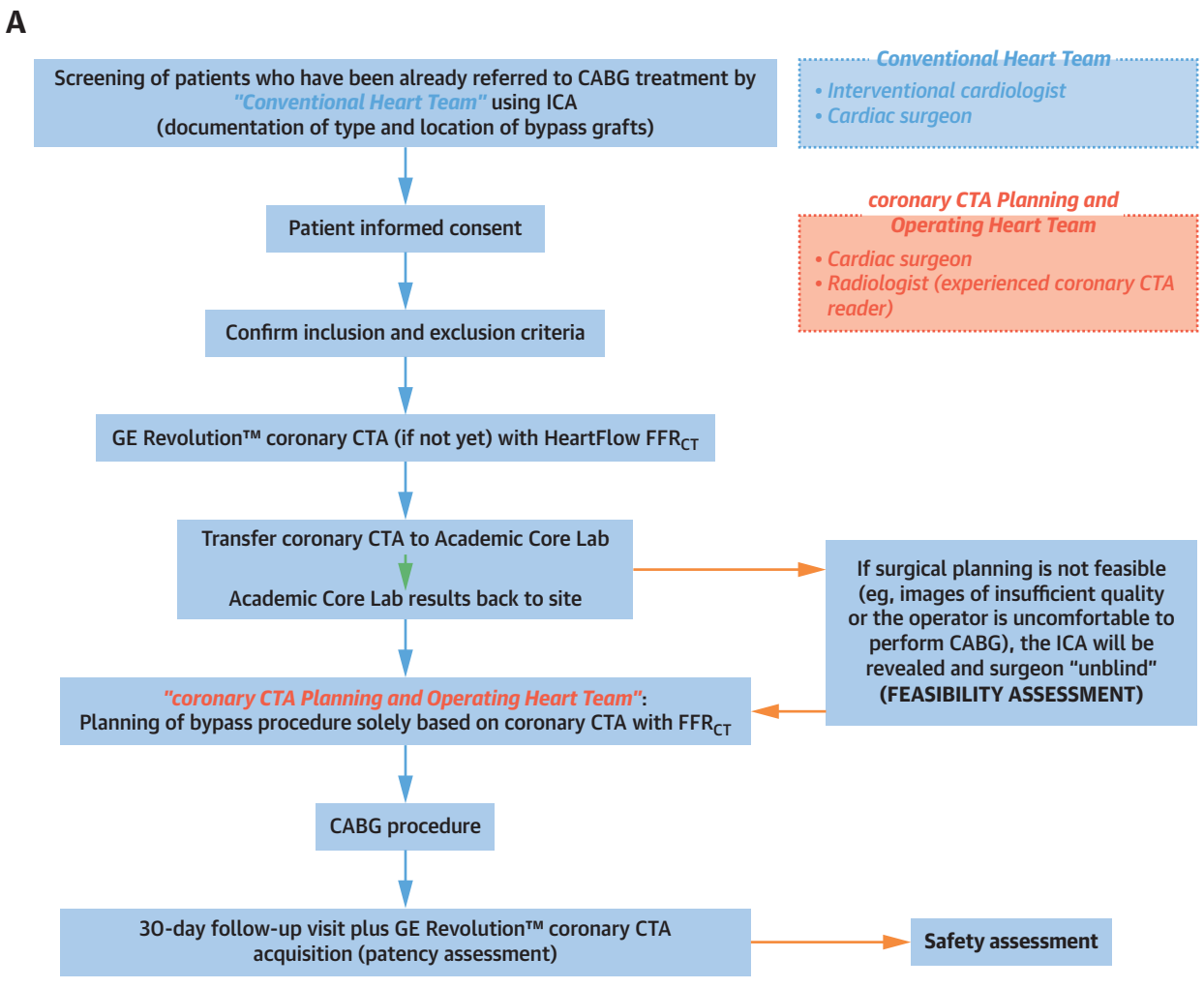
In addition to physiological optimization, contemporary data have now established the prognostic benefit of complete revascularization in patients with ACS or CCS and MVD, especially with PCI (82-85). The 2018 ESC/EACTS Guidelines on Myocardial Revascularization gave prioritizing completeness of revascularization when selecting revascularization mode a Class IIa recommendation (41). In this respect, the residual SYNTAX score has a role in predicting recurrent events, with a value >8 associated with a significantly higher risk of mortality (82). The combination with functional assessment, particularly angiography-derived FFR, may help establish "functional completeness" after PCI to further improve prognosis (78,79,86-89).

8.THE SYNTAX II TRIAL, SO FAR "THE BEST PRACTICE": TO BE CONFIRMED BY FAME III?

The single-arm SYNTAX II trial aimed to introduce and then assess the benefits of contemporary improvements in PCI (90). To justify a single arm, the SYNTAX score II was used as a selection criteria and a form of propensity score to compare outcomes between patients receiving contemporary PCI with those receiving PCI and CABG performed in the SYNTAX trial. Patients could only be included if the predicted mortality at 4 years for the PCI patient was comparable to the predicted mortality of the same propensity-matched patient undergoing CABG (equipoise). Best contemporary PCI practice compromised of: 1) only PCI of those lesions that were physiologically assessed and identified as flow-limiting; 2) intracoronary imaging, such as intravascular ultrasound, for stent optimization; 3) inclusion in the PCI team of an accredited expert in chronic total occlusion treatment; 4) usage of thin-strut, biodegradable-polymer, newer-generation DES; and 5) mandatory use of GDMT, to include a combination of antiplatelet drug, statin, β-blocker, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker during follow-up. In their editorial "The 2010-2014-2018 Trilogy of ESC-EACTS Guidelines on Myocardial Revascularization" (91), David Glineur and William Wijns stated: "We cannot jump 3 steps this way and then return to where we began." The 3-year results of this trial were quite amazing and reflect what the community describes as "best practice."

The lack of a control arm in the SYNTAX II study is a major methodological limitation, and although the results are provocative, they need to be challenged by a randomized trial (90). Notably, no crossover was

FIGURE 5 The FASTTRACK CABG Trial (120)



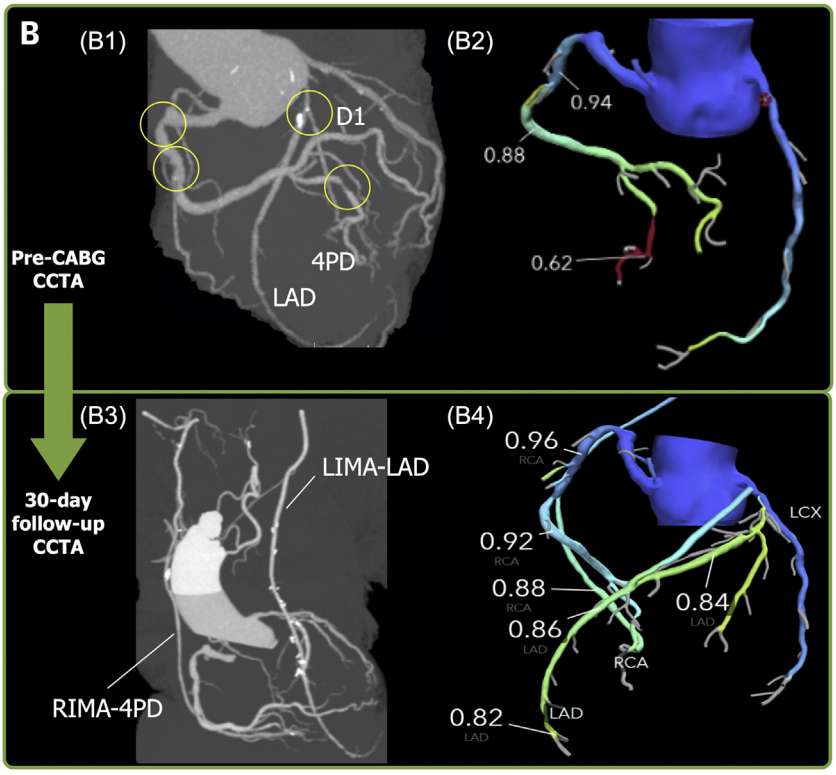
The FASTTRACK CABG trial is investigating the feasibility and safety of surgical decision making, planning, and the execution of bypass surgery, solely based on MSCT. **(A)** Flowchart. **(B1)** Pre-procedural MPR image. **(B2)** Pre-procedural FFRct. **(B3)** Post-CABG MPR image. **(B4)** Post-CABG FFRct. CABG = coronary artery bypass graft; CTA = computed tomography angiography; D1 = first diagonal branch; FFR = fractional flow reserve; LIMA = left internal mammary artery; MPR = multiplanar reformation or reconstruction; MSCT = multislice CT scans; RIMA = right internal mammary artery.

Continued on the next page

evident when the Kaplan-Meier curves for outcomes from PCI in SYNTAX II were compared with the matched surgical cohort of SYNTAX I (90) (**Figure 4A**); however, over almost 2 decades, there has understandably been tremendous evolution in CABG, as exemplified by the comparison of the surgical outcomes of SYNTAX I and EXCEL (92) (**Figure 4B**).

Whether FFR-guided PCI with second-generation DES is noninferior to CABG in patients with MVD, and if so, for how long—3, 5, or 10 years—is of genuine interest (70). Hence, the paramount importance of the FAME III study, which will randomize 1,500 patients with 3VD to FFR-guided PCI (n = 750) with new-generation DES if the FFR ≤0.80 or angiography-based CABG (n = 750), cannot be over emphasized (93). The trial aims to demonstrate noninferiority of FFR-guided PCI to CABG with a noninferiority margin of 1.65 in the HR (changed from 1.45 [94]) in terms of the primary endpoint for MACCE (a composite of all-cause death, MI including PMI according to the third universal definition, stroke, and any repeat revascularization) at 1 year (93), with clinical follow-up continuing for 5 years.

FIGURE 5 Continued



Along similar lines, whether FFR/iFR can be substituted by QFR derived from 3-dimensional coronary angiography or even from a single angiographic view (95) is of utmost importance, especially in patients with MVD who require multiple cumbersome functional assessments necessitating guidewire insertion in every vessel. The FAVOR III trial (NCT03656848), comparing QFR with visual guidance, and the Multivessel TALENT trial (NCT04390672), incorporating prospective QFR assessment as a part of "best practice PCI" in patients with 3VD, are currently exploring the possibility of replacing iFR/FFR with QFR (96).

9. ACS WITH MULTIVESSEL DISEASE

Recent studies have emphasized the importance of complete revascularization in cases of ST-segment elevation myocardial infarction (STEMI) and MVD. The large randomized COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI) trial (N = 4,041) demonstrated that complete revascularization resulted in a significant reduction in the hard endpoint of cardiovascular death or new MI compared with culprit-lesion-only revascularization in STEMI patients with MVD (HR: 0.74; 95% CI: 0.60-0.91) (97). Importantly, in the COMPLETE trial, nonculprit lesion PCI was performed with angiography guidance, and the efficacy of physiological guidance in this context remains to be established. In contrast to the angiography-guided complete revascularization studies (COMPLETE, PRAMI [Preventive Angioplasty in Acute Myocardial Infarction], and CvLPRIT [Complete versus Lesion-only Primary PCI Trial] trials), the Compare-Acute trial and the DANAMI-3-PRIMULTI (Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) trial showed that the favorable effects of FFR-guided complete revascularization over culprit-lesion-only treatment were mainly driven by the significant reduction in repeat revascularization, without any reduction in hard endpoints (98-101). This may be attributable to the underestimation of FFR in this specific condition (102-104) and/or a preventive overtreatment of nonflow-limiting vulnerable lesions by angiography-guided PCI (21,105,106). The ongoing FLOWER-MI (FLOW Evaluation to Guide Revascularization in Multivessel ST-elevation Myocardial Infarction) trial

(NCT02943954) is expected to clarify the true benefit of FFR-guided versus angiography-guided PCI in STEMI patients with MVD (107). Of note, the COMPLETE trial also demonstrated that nonculprit lesion PCI performed during index hospitalization or after discharge confers similar benefit on major cardiovascular events (cardiovascular death or MI) (during initial hospitalization: HR: 0.77; 95% CI: 0.59-1.00; after initial hospitalization: HR: 0.69; 95% CI: 0.49-0.97; $P_{\text{interaction}} = 0.62$) (108), potentially suggesting that CABG is feasible after stabilizing patients with very complex CAD (eg, SYNTAX score ≥33). The ongoing MULTISTARS AMI (MULTivessel Immediate Versus STAged RevaScularization in Acute Myocardial Infarction-The MULTISTARS AMI Trial) (NCT03135275) or BIOVASC (Direct Complete Versus Staged Complete Revascularization in Patients Presenting With Acute Coronary Syndromes and Multivessel Disease) trial (NCT03621501) aim to further clarify the best timing for nonculprit vessel revascularization in STEMI with MVD (109,110).

The SMILE (Impact of One Stage Compared With Multistaged PCI Complete Revascularization on Clinical Outcome in Multivessel NSTEMI Patients) trial is the only randomized trial to date assessing the efficacy of single vs staged complete revascularization in patients with non-ST-segment elevation ACS (111). The trial demonstrated the efficacy of single-stage complete revascularization with a significant reduction in MACCE (cardiac death, death, reinfarction, rehospitalization for unstable angina, repeat revascularization, or stroke) at 1 year compared with a multistaged strategy (HR: 0.549; 95% CI: 0.363-0.828), mainly driven by the significant reduction in repeat revascularization (HR: 0.522; 95% CI: 0.310-0.878) (111). However, because of limited robust clinical data, current guidelines recommend selecting the modality of revascularization (PCI or CABG) or the strategy for treating MVD as though patients had CCS or STEMI (41,52). In fact, several studies have suggested the feasibility and efficacy of CABG over PCI in this setting (112,113).

10. IN THE NEAR FUTURE

WHAT CAN WE EXPECT IN THE NEAR FUTURE? First, precision medicine for decision making between surgery and PCI will become fully individualized and accurate, and will have to be shared with the patient's families and relatives (**Central Illustration**) (114). In this regard, the redevelopment and validation of the SYNTAX score II 2020 for prediction of 10-year mortality after PCI or CABG is a major step forward (115). External validation in the pooled population of the FREEDOM, BEST, PRECOMBAT, and EXCEL trials has confirmed its impressive predictive performance to stratify patients who will benefit from either CABG or PCI (Supplemental Figure 4) (115). The score is derived using data from the SYNTAX trial, which used the first-generation paclitaxel-eluting stent, and although this is a major limitation, these are the only 10-year outcome data available to date. Recently the score was validated in the CREDO-Kyoto PCI/CABG registry cohort 3 (116,117), in which 90.3% of PCIs were performed using newer-generation DES, supporting the utility of decision making using the SYNTAX score II 2020 in contemporary practice. Its availability on smartphones and other devices renders its use more accessible and applicable than ever.

Second, the fact that similar decision making can now be derived from multislice CT scans (MSCT), instead of conventional cine angiography, may become a game-changer and have an impact on the traditional gatekeeper relationship between the invasive cardiologist and surgeon, and promote a new interaction between radiologist and surgeon (118,119). Indeed, the invasive cardiologist may be replaced as the provider of surgical cases by the radiologist or by the cardiologist/radiologist in a direct dialog between the surgeon and/or the noninvasive "cardio-radiologist"—the hybrid expert of the future. A pilot study, the FASTTRACK CABG trial (Safety and Feasibility Evaluation of Planning and Execution of Surgical Revascularization Solely Based on Coronary CTA and FFRCT in Patients With Complex Coronary Artery Disease) (NCT04142021), is currently testing the feasibility and safety of surgical decision making, planning, and execution of bypass surgery, solely based on MSCT (**Figure 5**) (120).

Third, the decade of 2020-2030 will probably witness the emergence and combination of metabolic and anti-inflammatory (54,58,59) (CANTOS [Canakinumab Antiinflammatory Thrombosis Outcome Study], COLCOT [Colchicine Cardiovascular Outcomes Trial], LoDoCo2 [Low-dose Colchicine 2], and so on) interventions that will curb the need for percutaneous and surgical revascularization. Because the potential for plaque regression now exists with novel pharmacological interventions such as PCSK9 inhibition by micro-RNA and neutralization by monoclonal antibodies administered quarterly or biannually (121), patients with diffuse nonobstructive CAD (122) without flow limiting stenosis—thereby not candidates for any type of mechanical revascularization—will become the target of choice for these pharmacological interventions (Supplemental Figure 5) (31).

11. FURTHER PERSPECTIVES

At a certain point of time, the illusion that the "device" could replace "the surgeon," existed; however, the real debate was, and still is, of a totally different nature. In the future, maybe both treatments, percutaneous and surgical, might be replaced by intelligent primordial primary prevention dictated and guided by the precognitive detection of ominous "omics" with combined noninvasive imaging and detection of the diseased phenotype: the era of the "imagomics." Time will tell.

In the upcoming decade, noninvasive imaging will be the game changer: conventional invasive cine fluoroscopy will be replaced progressively, but inescapably, by MSCT (50). The sensitivity and specificity of the technique to rule out CAD is high and is recognized by experts in the field (123). Patients with nonobstructive CAD defined by the presence of (multiple) lumen encroachments without flow limitation (Leaman score >5, with FFRct >0.8 [122,124]) are not candidates for either percutaneous or surgical revascularization, and their long-term outcomes can only be improved by lifestyle modification supported by intensive and aggressive pharmacological interventions (122). When single or double "functional vessel disease" (with FFRct <0.80) is diagnosed by noninvasive MSCT, the 3-dimensional angiographic view will be sufficient as a reliable diagnostic tool, which can then be converted into a 2-dimensional angiographic view, so that on the day of the intervention planning of the optimal gantry geometry in the fluoroscopic interventional suite can be anticipated and the treatment strategy planned and elaborated in advance.

When 3VD with or without LMCAD is observed on MSCT, the decision between CABG and PCI can be made immediately, following on from the SYNTAX III trial, which demonstrated the concordance of decision making (Cohen's kappa value of 0.82, almost perfect in the statistical jargon of the kappa statistics) in favor of either PCI or CABG, based either on conventional invasive fluoroscopic angiography or solely on MSCT and FFRct (118). As mentioned in section entitled "In the Near Future," if the FASTTRACK trial confirms the feasibility and safety of this noninvasive imaging strategy for CABG (without knowledge of the conventional cine fluoroscopy), then in the future the surgeon may, can, and will operate safely on the most complex patients of the CAD pyramid using the sole guidance of MSCT and FFRct. Logically, the interventional cardiologist should no longer have any reluctance in treating patients based on noninvasive imaging provided advanced knowledge of the coronary anatomy and that both the functionality and tissue composition of stenotic lesions are known, even before entering the "catheterization laboratory" now upgraded to "an interventional suite." Over the next decade, the progressive but inevitable replacement of invasive angiography by noninvasive MSCT for excluding CAD, diagnosing ischemic and nonobstructive CAD patients, noninvasive follow-up after prescribing aggressive pharmacological interventions, planning percutaneous treatment of 1 and 2 functional vessel disease, deciding between surgery and PCI, and planning CABG without conventional cine fluoroscopy will have major implications on the relationships among the noninvasive cardiologist, the invasive cardiologist, the interventional cardiologist, the surgeon, and the cardiac imager. It is hoped that these technological advances will enable the patient and physician to make better informed decisions.

CONCLUSIONS

Recent studies have enabled the relative merits of PCI and CABG to be established with regard to the type of ischemic syndrome, coronary anatomy, and the patient's overall comorbidity, with updated precision medicine. However, the never-ending advancement of technology, in conjunction with the emergence of novel pharmacological agents, will force us to continually re-evaluate the best revascularization strategy.

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