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REVIEW TOPIC OF THE WEEK

Left Main Coronary Artery Disease

Secular Trends in Patient Characteristics, Treatments, and Outcomes

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ABSTRACT

Left main coronary artery (LMCA) disease is the highest-risk lesion subset of ischemic heart disease, and has traditionally been an indication for coronary artery bypass grafting (CABG). Recent evidence suggests comparable clinical outcomes between percutaneous coronary intervention (PCI) and CABG for LMCA disease, with similar rates of mortality and serious composite outcomes, a higher rate of stroke with CABG, and a higher rate of repeat revascularization with PCI. These results have been translated to the current guideline recommendation that PCI is a reasonable alternative to CABG in patients with low to intermediate anatomic complexity. However, how the characteristics, treatment, and clinical outcomes of patients with unprotected LMCA disease have evolved over time has not yet been fully evaluated. We therefore described secular trends in the characteristics and long-term outcomes of unprotected LMCA disease using "real-world" clinical experience from the IRIS-MAIN (Interventional Research Incorporation Society-Left MAIN Revascularization) registry together with a broad review of this topic. (J Am Coll Cardiol 2016;68:1233–46)

Among the various anatomic types of obstructive coronary artery disease (CAD), significant left main coronary artery (LMCA) disease is the highest-risk lesion subset and is associated with poorer clinical outcomes compared with non-LMCA CAD. On the basis of early clinical trials demonstrating a definite survival benefit of coronary artery bypass grafting (CABG) over medical therapy (1,2), CABG has been the standard of care for the revascularization of significant LMCA disease for a long time. During this era, percutaneous coronary intervention (PCI) was performed on a limited basis, mostly in surgically ineligible patients. However, with the remarkable improvements in medical device technology, procedural techniques, antithrombotic agents, and background medical therapy during the last 2 decades, PCI with stenting for LMCA disease has become technically feasible and shows favorable clinical outcomes (3,4). Notably, with the widespread use of drug-eluting stents (DES) with a lower risk of angiographic and clinical restenosis, this less-invasive approach has achieved recognition as a reasonable therapeutic alternative for unprotected LMCA disease instead of CABG.

As such, practice patterns for LMCA disease have changed substantially in recent decades. However, long-term trends in patient characteristics, treatments, and associated outcomes have still not been systematically evaluated, and understanding such changes may be important for helping clinical decision-making and planning future medical progress toward improved management of LMCA disease.

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

CABG = coronary artery bypass grafting

CAD = coronary artery disease

DES = drug-eluting stent(s)

LMCA = left main coronary artery

MACCE = major adverse cardiac and cerebrovascular event

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized clinical trial

We therefore summarize the cumulative clinical data for LMCA treatment and guideline changes in the present work, and describe temporal trends in the characteristics and outcomes of LMCA disease over time in real-world practice using data from the large "all-comers" IRIS-MAIN (Interventional Research Incorporation Society-Left MAIN Revascularization) registry, involving consecutive patients with unprotected LMCA disease who underwent medical therapy, PCI, or CABG.

PCI FOR LMCA DISEASE OVER TIME

Because the LMCA is an initial part of the coronary tree and is relatively large in caliber and short in length, LMCA stenosis seemed to be an anatomically attractive target, even during the early period of PCI. However, because the LMCA has the most elastic tissue of the coronary vessels, plain balloon angioplasty was associated with immediate procedural unpredictability and also with unacceptable high rates of restenosis and early mortality (5). The adoption of bare-metal stents (BMS) rejuvenated interest in PCI for LMCA disease, with reduction of acute procedural complications (e.g., recoil, abrupt closure, or dissection). Coupled with the non-negligible risks of operative mortality and morbidity associated with CABG, as well as the high rate of saphenous vein graft attrition, many interventional cardiologists sought to explore less-invasive procedures throughout the 1990s to early 2000s (**Table 1**). However, because PCI was restrictively performed in poor surgical candidates during that era, most studies included many emergency cases or patients who were deemed inoperable, and thus showed considerably high rates of acute complications and early mortality (6–9). In contrast, among elective, low-risk patients, procedural and short-term results were acceptable (6,8,10); nonetheless, the rate of in-stent restenosis remained excessive (~20% to 40%), especially when distal bifurcation was involved.

After the introduction of DES, with a remarkable reduction of restenosis and repeat revascularization, PCI with DES has been widely performed for more complex clinical and anatomic subsets of LMCA disease. Several studies involving early-generation DES showed more favorable angiographic and clinical outcomes compared with BMS (**Table 1**). Even after safety concerns regarding very-late stent thrombosis associated with early-generation DES, the physicians' threshold for performing PCI at the LMCA became less restrictive, and the worldwide frequency of LMCA stenting started to sharply increase (11). Thereafter, several refined versions of DES, sharing common features of thinner struts and biocompatible polymers, have been rapidly adopted in clinical practice, and newer-generation DES further decreased the risk of stent thrombosis and restenosis compared to the previous ones (12,13). Although no randomized trial has specifically compared the outcomes of the first and second generations of DES for LMCA disease, newer-generation DES have already become the default device; several observational studies have suggested better outcomes with newer versions of DES for LMCA PCI.

PCI VERSUS CABG FOR LMCA DISEASE OVER TIME

Favorable early reports of elective LMCA stenting with DES inspired great interest in the role of PCI as a good alternative to CABG, and prompted several clinical studies comparing PCI and CABG for treating LMCA disease (**Table 2**).

The large MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry suggested that the risks of mortality and the composite of death, Q-wave myocardial infarction (MI), or stroke were similar between the PCI and CABG groups; however, the rate of repeat revascularization was significantly higher in the PCI group (14,15). Four consecutive randomized clinical trials (RCTs) comparing early-generation DES and CABG reported similar results (16–22). Overall, the rates of death or MI were similar between the 2 groups; however, stroke was more common with CABG, and repeat revascularization was more common with PCI. Subsequently, several meta-analyses have confirmed these findings (23–25). However, the benefit of CABG over PCI becomes more evident according to increasing anatomic complexities (i.e., SYNTAX [Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery] score); the rate of adverse events significantly increased in patients with PCI with high complexity of LMCA and concomitant CAD, whereas the rate was nearly similar in patients with lower anatomic complexity (18,19,26). In particular, the relative clinical benefits of CABG over PCI may become prominent over time; in this regard, the 5- or 10-year follow-up results of several important studies have become available, and the overall findings were consistent (15,17,19,22,27).

The practice patterns for both PCI and CABG are continuously changing. PCI for LMCA is widely

TABLE 1 Studies of PCI for LMCA Disease Over Time

First Author, Year (Ref. #)	Design	n	Bifurcation Disease (%)	Triple-Vessel Disease (%)	EF (%, Mean)	Endpoint	Follow-Up (yrs)	Key Findings
BMS								
Silvestri et al., 2000 (6)	Single-center registry	140	52	47	61	Death	1 month	Mortality 9% for high-risk patients, 0% for low-risk patients
Tan et al., 2001 (7)	Single-center registry	279	58	33	51	Death	1	85% treated with BMS, all-cause mortality 24.2%
Park et al., 2001 (10)	Single-center registry	127	39	6	Not reported	Death/cardiac death, nonfatal MI, or TLR	2	Mortality 3.1%, rates of cardiac death, nonfatal MI, or TLR 13.1%
Black et al., 2001 (8)	Single-center registry	92	16	66	56	Death	6 months	Mortality 20.5% for patients contraindicated for surgery, 3.8% for those feasible for surgery
Takagi et al., 2002 (9)	Single-center registry	67	60	30	57	Cardiac death	2.6	96% treated with BMS, cardiac mortality 11.9%
BMS vs. early-generation DES								
Park et al., 2005 (49)	Single-center registry	223	55	Not reported	61	Cardiac death, nonfatal MI, or TLR	1	Lower rates of cardiac death, nonfatal MI, or TLR with DES
Valgimigli et al., 2005 (50)	Single-center registry	181	72	48	41	Death, nonfatal MI, or TVR	1.4	Lower rates of death, nonfatal MI, or TVR with DES
Chieffo et al., 2005 (51)	Single-center registry	149	72	Not reported	54	Cardiac death, MI, or TVR	6 months	Lower rates of cardiac death, MI, or TVR with DES
Erglis et al., 2007 (52)	Single-center, randomized study	103	75	Not reported	55	Death, MI, or TLR	6 months	Lower rates of death, MI, or TLR with DES
Kim et al., 2009 (53)	Multicenter registry	1217	50	26	60	Death or MI	3	Comparable rates of death or MI
Buszman et al., 2009 (54)	Multicenter registry	252	59	33	49	Death/death, MI, stroke, TLR, or acute ST	4	Comparable rates of death, lower rates of death, MI, stroke, TLR, or acute ST with DES
Paclitaxel- vs. sirolimus-eluting stent								
Valgimigli et al., 2006 (55)	Single-center registry	110	70	55	44	Death, nonfatal MI, or TVR	1.8	Comparable rates of death, nonfatal MI, or TVR
Mehilli et al., 2009 (56)	Multicenter randomized study	607	63	72	54	Death, MI, or TLR	2	Comparable rates of death, MI, or TLR
Lee et al., 2009 (57)	Multicenter registry	858	57	31	61	Death, MI, or TVR	3	Comparable rates of death, MI, or TVR
Early- vs. second-generation DES								
Valenti et al., 2012 (58)	Single-center registry	390	86	30	44	Cardiac death, nonfatal MI, TVR, or stroke	1	Lower rates of cardiac death, nonfatal MI, TVR, or stroke with newer DES
Kim et al., 2012 (59)	Multicenter registry	661	69	Not reported	61	Death, MI, stroke, or ischemia-driven TVR	1.5	Comparable rates of death, MI, stroke, or ischemia-driven TVR
Moynagh et al., 2013 (60)	Multicenter registry	464	80	Not reported	Not reported	Cardiac death, target vessel MI, or clinically driven TLR	2	Lower rates of cardiac death, target vessel MI, or clinically driven TLR with newer DES
Buchanan et al., 2013 (61)	Multicenter registry	186	78	40	54	Death, MI, or TVR	2	Trend toward lower rates of death, MI, or TVR with newer DES
de la Torre Hernandez et al., 2013 (62)	Multicenter registry	770	53	37	54	Death, MI, or TLR	3	Comparable rates of death, MI, or TLR
Cassese et al., 2015 (63)	Multicenter registry	1,257	72	71	57	Death, MI, TLR, or stroke	3	Comparable rates of death, MI, TLR, or stroke
Second-generation DES								
Mehilli et al., 2013 (64)	Multicenter randomized study	650	80	71	53	Death, MI, or TLR	1	Comparable rates of death, MI, or TLR with everolimus- and zotarolimus-eluting stents

BMS = bare-metal stent(s); DES = drug-eluting stent(s); EF = ejection fraction; LMCA = left main coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization; TVR = target vessel revascularization.

TABLE 2 Comparisons of PCI Against CABG for LMCA Disease Over Time

Study/First Author, Year (Ref. #)	Design	n (PCI/CABG)	Bifurcation Disease (%)	Triple-Vessel Disease (%)	EF, (%, Mean)	Endpoint	Follow-Up (yrs)	Key Findings
BMS or early-generation DES vs. CABG								
MAIN COMPARE, 2008, 2010 (14,15)	Multicenter registry	1,102/1,138	52	41	61	Death; death, Q-wave MI, or stroke; TVR	5	Similar rates of mortality and death, Q-wave MI, or stroke; higher rates of TVR with PCI
LE MANS, 2008, 2016 (16,17)	Multicenter randomized study	52/53	58	68	54	Change in ejection fraction at 1 yr	10	Improvement in ejection fraction only with PCI, comparable rates of death, MI, stroke, or TVR at 10 yrs
SYNTAX, 2010, 2014 (18,19)	Multicenter randomized study	357/348	61	37	Not reported	Death, MI, stroke, or repeat revascularization	5	Comparable rates of death, MI, stroke, or repeat revascularization at 1 and 5 yrs
Boudriot et al., 2011 (20)	Multicenter randomized study	100/101	72	14	65	Death, MI, or repeat revascularization	1	PCI with sirolimus-eluting stent inferior to CABG at 1 yr
PRECOMBAT, 2011, 2015 (21,22)	Multicenter randomized study	300/300	64	41	61	Death, MI, stroke, or ischemia-driven TVR	5	PCI noninferior to CABG at 1 yr, comparable rates of death, MI, stroke, or ischemia-driven TVR at 5 yrs
DELTA, 2012 (65)	Multicenter registry	1,874/901	60	Not reported	54	Death, MI, or stroke	3.5	Comparable rates of death, MI, or stroke. Higher TVR in PCI
Second-generation DES vs. CABG								
PRECOMBAT-2, 2012 (59)	Multicenter registry	334/272	67	Not reported	61	Death, MI, stroke, or ischemia-driven TVR	1.5	Comparable rates of death, MI, stroke, or ischemia-driven TVR
NOBLE (NCT01496651)	Multicenter randomized study	600/600	NA	NA	NA	Death, stroke, nonindex treatment-related MI, or new revascularization	2	Results are expected by fall 2016
EXCEL (NCT01205776)	Multicenter randomized study	948/957	NA	NA	60	Death, MI, or stroke	3	Results are expected by fall 2016

CABG = coronary artery bypass graft; DELTA = Drug-Eluting Stent for Left Main Coronary Artery Disease; EXCEL = Evaluation of Xience Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; LE MANS = Left Main Coronary Artery Stenting; MAIN COMPARE = Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization; NA = not available; NOBLE = Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis; PRECOMBAT = Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; other abbreviations as in Table 1.

performed in conjunction with the latest versions of DES, functional concepts for decision making, adjunctive imaging support, and newer antithrombotic agents. For CABG, off-pump surgery has been increasingly used, the choice of conduits has become more sensible, and the perioperative care has become more organized. However, none of the available RCTs of DES versus CABG were adequately powered and included contemporary devices with newer-generation DES. Two large RCTs comparing contemporary DES and CABG (the EXCEL [Evaluation of Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NCT01205776] and NOBLE [Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis; NCT01496651] trials) will provide new evidence regarding the role of second-generation DES compared with CABG for treating patients with significant LMCA disease.

REVASCULARIZATION GUIDELINES CHANGE OVER TIME

In the 2005 U.S. and European guidelines, PCI for LMCA was not recommended as long as CABG was a viable option for the patient (**Table 3**) (28,29). Since then, favorable results from comparative-effectiveness studies have continued to be updated; therefore, the recommendations of PCI for LMCA from the 2009 American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines were revised to a Class IIb indication for anatomically-eligible LMCA disease that is expected to have a low risk of procedural complications (30). In 2010, the European guideline reflected the results of the SYNTAX trial and other nonrandomized studies and, thus, upgraded PCI as a reasonable treatment mainly according to the anatomic complexity (31). The 2011 American College of Cardiology Foundation/AHA/SCAI guideline recommendations incorporated

TABLE 3 Changes in PCI Guideline Recommendations for LMCA Disease Over Time

Guideline	Class of Recommendation	LOE
2005 ACC/AHA/SCAI (28)	III—PCI is not recommended in patients with unprotected LMCA disease and eligibility for CABG	C
2005 ESC/EACTS (29)	IIb—Stenting for unprotected LMCA disease should only be considered in the absence of other revascularization options	C
2009 ACC/AHA/SCAI (30)	IIb—PCI of the LMCA with stents as an alternative to CABG may be considered in patients with anatomic conditions that are associated with a low risk of PCI procedural complications and clinical conditions that predict an increased risk of adverse surgical outcomes	B
2010 ESC/EACTS (31)	IIa—LMCA isolated or + 1VD, ostium/shaft IIb—LMCA isolated or + 1VD, distal bifurcation IIb—LMCA + 2VD or 3VD, SYNTAX score ≤32 III—LMCA + 2VD or 3VD, SYNTAX score ≥33	B
2011 ACCF/AHA/SCAI (32)	IIa—For SIHD patients when both of the following are present: • Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcomes (e.g., a low SYNTAX score [≤22], ostial or trunk left main stenosis) • Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%)	B
	IIb—For SIHD patients when both of the following are present: • Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcomes (e.g., low-intermediate SYNTAX score of < 33, bifurcation left main stenosis) • Clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate-severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery; STS-predicted risk of operative mortality >2%)	B
	III: HARM—For SIHD patients (vs. performing CABG) with unfavorable anatomy for PCI who are good candidates for CABG	B
2014 ESC/EACTS (33)	I—LMCA with a SYNTAX score ≤22 IIa—LMCA with a SYNTAX score 23-32 III—LMCA with a SYNTAX score ≥33	B
2014 ACC/AHA/AATS/PCNA/SCAI/STS (34)	IIa—For SIHD patients when both of the following are present: • Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcomes (e.g., a low SYNTAX score [≤22], ostial or trunk left main stenosis) • Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%)	B
	IIb—For SIHD patients when both of the following are present: • Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low-intermediate SYNTAX score of <33, bifurcation left main stenosis) • Clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate-severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery; STS-predicted risk of operative mortality >2%)	B
	III: HARM—For SIHD patients (vs. performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B

AATS = American Association for Thoracic Surgery; ACC = American College of Cardiology; AHA = American Heart Association; EACTS = European Association for Cardio-Thoracic Surgery; EAPCI = European Association of Percutaneous Cardiovascular Interventions; ESC = European Society of Cardiology; LMCA = left main coronary artery; LOE = Level of Evidence; PCNA = Preventive Cardiovascular Nurses Association; SCAI = Society for Cardiovascular Angiography and Interventions; SIHD = stable ischemic heart disease; STS = Society of Thoracic Surgeons; VD = vessel disease; other abbreviations as in Tables 1 and 2.

not only the results of the SYNTAX trial, but also the risks of procedural complications of PCI and the operative mortality of CABG (32). Although considerations of clinical and anatomic factors are slightly different, the most recent recommendations from the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery and 2014 ACC/AHA/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association (PCNA)/SCAI/Society of Thoracic Surgeons guidelines similarly provide a Class II indication for PCI in patients with low to intermediate anatomic complexity (Class IIa for relatively simple anatomy and Class IIb for intermediate complexity) and provide a Class III indication for PCI in those with highly complex disease (33,34). It is likely that any future changes in recommendations will strongly depend on the results of the EXCEL and NOBLE trials.

SECULAR TRENDS IN LMCA DISEASE: RESULTS FROM THE IRIS-MAIN REGISTRY

To evaluate patient characteristics and long-term outcomes for the treatment of LMCA disease over time in "real-world" clinical practice, we analyzed data from a large "all-comers" registry that includes patients who received medical therapy, PCI, or CABG for unprotected LMCA disease.

STUDY POPULATION. The study population was a part of the IRIS-MAIN registry that comprised consecutive patients with unprotected LMCA disease (defined as stenosis of >50%) between January 1995

and December 2013 (NCT01341327). The IRIS-MAIN registry is a nonrandomized, multinational, multicenter observational study, and the study patients were recruited from 50 academic and community hospitals in Asia (China, India, Indonesia, Japan, Malaysia, South Korea, Taiwan, and Thailand). The study had an "all-comers" design, involving the consecutive enrollment of patients with unprotected LMCA disease who were treated with medical therapy, PCI, or CABG. Patients who had prior CABG and those who underwent concomitant valvular or aortic surgery were excluded.

Patient demographics, cardiovascular risk factors, clinical manifestations, hemodynamic status, left ventricular function, the extent of CAD, details of the procedures, and outcomes during follow-up were collected from each center. The choice of revascularization was at the discretion of the treating physician or the patient. Details regarding factors that were likely to have influenced the selection of a procedure for individual patients, medical therapy, PCI, and CABG procedures are described in the Online Appendix. The local ethics committee at each hospital approved the use of clinical data for this study, and all patients provided written informed consent.

OUTCOMES AND ANALYSIS. The clinical outcomes of interest were all-cause death, serious composite outcome (death, MI, or stroke), repeat revascularization, and major adverse cardiac and cerebrovascular events (MACCE), which were defined as the composite of death, MI, stroke, and repeat revascularization. Definitions of each clinical outcome are described in the Online Appendix. Clinical follow-up was performed at 1 month, 6 months, and 1 year, and then annually thereafter via an office visit or telephone contact. Data on baseline and outcome variables were recorded in the dedicated databases by independent research personnel.

For the analyses, 3 historical time periods were chosen on the basis of the generation of stent used in PCI: wave 1 (BMS) for 1995 to 2002; wave 2 (first-generation DES) for 2003 to 2006; and wave 3 (second-generation DES) for 2007 to 2013. Baseline characteristics, risk-factor profiles, medications, and procedure characteristics were summarized for the individual patients in each wave over time and for each treatment group. Cumulative event curves for outcomes were constructed with Kaplan-Meier estimates, and Cox proportional hazards models were used to compare the clinical endpoints of each treatment strategy according to each wave and vice versa. Details regarding the statistical analysis are described in in the Online Appendix.

RESULTS. Trends of patient characteristics and treatments. A total of 5,833 patients with significant LMCA disease were identified between January 1995 and December 2013 at 50 participating sites. Of these, 616 received medical therapy alone, 2,866 were treated with PCI, and 2,351 were treated with CABG. The patient characteristics according to treatment modality are summarized in Online Table 1. Over time, the proportion of patients treated with PCI rather than CABG increased substantially, whereas the proportion of patients who received medical therapy remained steady (Online Figure 1).

Temporal changes of the patients' characteristics over time in each treatment stratum are shown in **Table 4**. During the study period, there was an increase of age for all 3 treatments, and more patients tended to present with stable angina. Among the patients who underwent coronary revascularization, there was an increased risk of patient comorbidities and anatomic complexity over time. These changes were not evident in the medical therapy group. Changes in medications and procedural and surgical features over time in each treatment stratum are shown in **Table 5**. Improved chronic pharmacotherapy was found for all treatment groups, particularly in terms of greater use of antiplatelet agents and statins. In the PCI group, the type of stents used dramatically changed, and the number and length of stents significantly increased with increasing disease complexities. Despite an increased proportion of patients with distal bifurcation involvement, more patients were treated with the simple 1-stent crossover technique. In the CABG group, over time, off-pump surgery was more frequently performed, and the total number of grafts has decreased. Grafting using the internal mammary artery was more frequently performed, but adoption rates varied for the radial artery.

Outcome trends. The median follow-up time was 9.7 years (interquartile range [IQR]: 7.0 to 12.4 years), 5.6 years (IQR: 4.1 to 8.0 years), and 3.0 years (IQR: 1.9 to 4.1 years) for patients treated in waves 1, 2, and 3, respectively. Cumulative event curves for clinical outcomes in each treatment stratum are illustrated in Online Figure 2. In the medical therapy group, the cumulative incidence of death and the composite of death, MI, or stroke tended to decrease over time. In the PCI group, the rate of MACCE substantially decreased over time due to a significant reduction of repeat revascularization, without a significant change in death and the composite of death, MI, or stroke. In the CABG group, none of the cumulative rates of any of the outcomes changed remarkably over time. After multivariable adjustment for confounding clinical

TABLE 4 Trends in Patient Characteristics Over Time in Each Treatment Stratum*

	Medical Therapy				PCI				CABG			
	Wave 1 (n = 129)	Wave 2 (n = 131)	Wave 3 (n = 356)	p Value	Wave 1 (n = 271)	Wave 2 (n = 937)	Wave 3 (n = 1,658)	p Value	Wave 1 (n = 683)	Wave 2 (n = 964)	Wave 3 (n = 704)	p Value
Age, yrs	66 ± 11	65 ± 10	68 ± 10	0.01	57 ± 12	62 ± 11	64 ± 11	<0.001	61 ± 10	64 ± 9	65 ± 9	<0.001
Male	93 (72.1)	87 (66.4)	245 (68.8)	0.61	171 (63.1)	677 (72.3)	1,293 (78.0)	<0.001	514 (75.3)	717 (74.4)	557 (79.1)	0.07
BMI, kg/m^2	24 ± 3	24 ± 3	25 ± 3	0.14	25 ± 3	24 ± 3	24 ± 3	0.69	25 ± 3	25 ± 3	24 ± 3	0.53
Atrial fibrillation	5 (3.9)	4 (3.1)	15 (4.2)	0.84	4 (1.5)	24 (2.6)	45 (2.7)	0.49	18 (2.6)	26 (2.7)	15 (2.1)	0.74
Hypertension	71 (55.0)	84 (64.1)	238 (66.9)	0.06	110 (40.6)	499 (53.3)	1,027 (61.9)	<0.001	354 (51.8)	528 (54.8)	464 (65.9)	<0.001
Diabetes mellitus												
Any	45 (34.9)	40 (30.5)	143 (40.2)	0.13	58 (21.4)	297 (31.7)	570 (34.4)	<0.001	215 (31.5)	370 (38.4)	299 (42.5)	<0.001
Requiring insulin	11 (8.5)	6 (4.6)	35 (9.8)	0.18	7 (2.6)	72 (7.7)	95 (5.7)	0.006	47 (6.9)	90 (9.3)	69 (9.8)	0.11
Current smoker	47 (36.4)	42 (32.1)	82 (23.0)	0.007	82 (30.3)	233 (24.9)	410 (24.7)	0.14	226 (33.1)	262 (27.2)	182 (25.9)	0.006
Hyperlipidemia	32 (24.8)	35 (26.7)	191 (53.7)	<0.001	90 (33.2)	286 (30.5)	823 (49.6)	<0.001	228 (33.4)	334 (34.6)	354 (50.3)	<0.001
Previous MI	16 (12.4)	10 (7.6)	38 (10.7)	0.44	38 (14.0)	73 (7.8)	122 (7.4)	0.001	106 (15.5)	128 (13.3)	86 (12.2)	0.19
Previous PCI	16 (12.4)	14 (10.7)	70 (19.7)	0.02	39 (14.4)	178 (19.0)	275 (16.6)	0.13	74 (10.8)	119 (12.3)	94 (13.4)	0.35
Previous stroke	11 (8.5)	17 (13.0)	36 (10.1)	0.48	11 (4.1)	69 (7.4)	134 (8.1)	0.07	49 (7.2)	67 (7.0)	67 (9.5)	0.12
Previous heart failure	10 (7.8)	6 (4.6)	18 (5.1)	0.45	9 (3.3)	25 (2.7)	38 (2.3)	0.56	42 (6.1)	37 (3.8)	23 (3.3)	0.02
Family history of CAD	5 (3.9)	3 (2.3)	29 (8.1)	0.03	27 (10.0)	63 (6.7)	156 (9.4)	0.04	74 (10.8)	106 (11.0)	85 (12.1)	0.72
Chronic lung disease	5 (3.9)	7 (5.3)	12 (3.4)	0.61	4 (1.5)	25 (2.7)	38 (2.3)	0.51	12 (1.8)	35 (3.6)	24 (3.4)	0.07
Chronic renal failure	7 (5.4)	6 (4.6)	19 (5.3)	0.94	4 (1.5)	27 (2.9)	67 (4.0)	0.05	12 (1.8)	34 (3.5)	33 (4.7)	0.01
Peripheral vascular disease	6 (4.7)	15 (11.5)	27 (7.6)	0.12	6 (2.2)	23 (2.5)	63 (3.8)	0.11	101 (14.8)	68 (7.1)	48 (6.8)	<0.001
Clinical presentation				0.001				<0.001				<0.001
Stable angina	37 (28.7)	52 (39.7)	168 (47.2)		80 (29.5)	355 (37.9)	737 (44.5)		101 (14.8)	250 (25.9)	305 (43.3)	
Unstable angina	73 (56.6)	56 (42.7)	121 (34.0)		170 (62.7)	466 (49.7)	654 (39.4)		528 (77.3)	620 (64.3)	318 (45.2)	
NSTEMI	14 (10.9)	14 (10.7)	40 (11.2)		14 (5.2)	91 (9.7)	181 (10.9)		44 (6.4)	79 (8.2)	57 (8.1)	
STEMI	5 (3.9)	9 (6.9)	27 (7.6)		7 (2.6)	25 (2.7)	86 (5.2)		10 (1.5)	15 (1.6)	24 (3.4)	
Shock at presentation	4 (3.1)	2 (1.5)	2 (0.6)	0.09	1 (0.4)	3 (0.3)	12 (0.7)	0.38	4 (0.6)	5 (0.5)	5 (0.7)	0.88
Disease extent				0.40				<0.001				<0.001
LM only	9 (7.0)	16 (12.2)	36 (10.1)		116 (42.8)	162 (17.3)	186 (11.2)		52 (7.6)	33 (3.4)	20 (2.8)	
LM with 1VD	16 (12.4)	14 (10.7)	59 (16.6)		72 (26.6)	212 (22.6)	416 (25.1)		86 (12.6)	81 (8.4)	43 (6.1)	
LM with 2VD	31 (24.0)	29 (22.1)	87 (24.4)		53 (19.6)	264 (28.2)	609 (36.7)		175 (25.6)	211 (21.9)	140 (19.9)	
LM with 3VD	73 (56.6)	72 (55.0)	174 (48.9)		30 (11.1)	299 (31.9)	447 (27.0)		370 (54.2)	639 (66.3)	501 (71.2)	
Right CAD	90 (69.8)	91 (69.5)	231 (64.9)	0.47	52 (19.2)	404 (43.1)	674 (40.7)	<0.001	448 (65.6)	735 (76.2)	566 (80.4)	<0.001
LM lesion location				0.001				<0.001				0.001
Ostium or midshaft	43 (33.3)	51 (38.9)	182 (51.1)		163 (60.1)	433 (46.2)	587 (35.4)		214 (31.3)	352 (36.5)	196 (27.8)	
Distal bifurcation	86 (66.7)	80 (61.1)	174 (48.9)		108 (39.9)	504 (53.8)	1071 (64.6)		469 (68.7)	612 (63.5)	508 (72.2)	
Ejection fraction, %	54 ± 13	56 ± 11	55 ± 12	0.56	61 ± 8	60 ± 10	59 ± 10	<0.001	58 ± 11	56 ± 11	55 ± 11	<0.001

Values are mean ± SD or n (%). *Wave 1 represents the time period 1995 to 2002, wave 2 represents 2003 to 2006, and wave 3 represents 2007 to 2013.

CAD = coronary artery disease; LM = left main; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; VD = vessel disease; other abbreviations as in Table 1.

covariates, risk-adjusted trends of hazard ratios for outcomes over time in each treatment stratum are shown in **Figure 1**. The adjusted risks for mortality; composite of death, MI, or stroke; and MACCE gradually decreased over time for the medical therapy group. For the PCI group, trends toward decreasing risks for mortality, composite outcomes, and repeat revascularization were also statistically significant. However, the risks for any clinical outcomes remained relatively stable for the CABG group, with the exception of a decreasing risk of repeat revascularization.

During all time periods, medically treated patients had an extremely higher rate of mortality and composite of death, MI, or stroke than those who received PCI or CABG (Online Figure 3). The adjusted risks for comparative effectiveness between the treatment strategies are shown in **Figure 2**. The risks of death and the composite of death, MI or stroke for medical therapy were always inferior to those for both PCI and CABG. The risks of mortality and the composite of death, MI, or stroke were comparable between PCI and CABG, but the risks of repeat revascularization and MACCE were higher in the PCI group than in the CABG group. Nevertheless, the adjusted hazard ratios for the risks of all clinical outcomes after PCI relative to CABG gradually decreased over time, suggesting that the gap in the

TABLE 5 Trends in Medications and Procedural and Surgical Characteristics Over Time in Each Treatment Stratum*

	Medical Therapy				PCI				CABG			
	Wave 1 (n = 129)	Wave 2 (n = 131)	Wave 3 (n = 356)	p Value	Wave 1 (n = 271)	Wave 2 (n = 937)	Wave 3 (n = 1,658)	p Value	Wave 1 (n = 683)	Wave 2 (n = 964)	Wave 3 (n = 704)	p Value
Drugs prescribed within 1 month after hospital discharge												
Aspirin	105 (81.4)	108 (82.4)	312 (87.6)	0.14	247 (91.1)	908 (96.9)	1,633 (98.5)	<0.001	641 (93.9)	920 (95.4)	674 (95.7)	0.21
ADP receptor antagonists	15 (11.6)	66 (50.4)	238 (66.9)	<0.001	194 (71.6)	897 (95.7)	1,578 (95.2)	<0.001	353 (51.7)	780 (80.9)	637 (90.5)	<0.001
Beta-blocker	54 (41.9)	37 (28.2)	201 (56.5)	<0.001	109 (40.3)	472 (50.4)	875 (52.8)	0.001	224 (32.8)	401 (41.6)	323 (45.9)	<0.001
Calcium-channel blocker	52 (40.3)	39 (29.8)	162 (45.5)	0.007	120 (44.3)	378 (40.3)	743 (44.8)	0.08	338 (49.5)	462 (47.9)	304 (43.2)	0.046
RAS blocker	19 (14.7)	17 (13.0)	150 (42.1)	<0.001	32 (11.8)	462 (45.5)	650 (39.3)	<0.001	157 (20.3)	303 (31.4)	182 (25.9)	<0.001
Statin	17 (13.3)	50 (38.2)	232 (65.1)	<0.001	56 (20.7)	483 (51.5)	1,626 (96.7)	<0.001	123 (18.0)	561 (58.2)	541 (76.9)	<0.001
Procedural characteristics for PCI												
Stent technique								<0.001				
Left main stenting only					192 (70.8)	308 (32.9)	310 (18.7)					
Simple crossover					50 (18.5)	427 (45.6)	970 (58.5)					
2-stent technique					29 (10.7)	202 (21.6)	378 (22.8)					
Final kissing balloon					41 (15.1)	316 (33.7)	530 (32.0)	<0.001				
Total stent number†					1.5 ± 0.7	2.1 ± 1.2	2.3 ± 1.3	<0.001				
Total stent length†					17.8 ± 14.3	38.4 ± 29.9	54.3 ± 35.1	<0.001				
Stent number in LMCA					1.2 ± 0.5	1.4 ± 0.7	1.8 ± 0.9	<0.001				
Stent type								<0.001				
BMS					271 (100)	111 (11.8)	26 (1.6)					
First-generation DES					0	822 (87.7)	232 (14.0)					
Second-generation DES					0	4 (0.4)	1,400 (84.4)					
Use of IVUS					197 (72.7)	693 (74.0)	1,288 (77.7)	0.04				
Use of IABP or ECMO					27 (10.0)	33 (3.5)	87 (5.2)	<0.001				
Surgical characteristics for CABG												
Off-pump surgery									149 (21.9)	445 (46.5)	486 (69.0)	<0.001
Total conduit									3.5 ± 1.3	2.9 ± 1.0	2.9 ± 0.9	<0.001
Artery graft									1.9 ± 1.2	2.2 ± 0.9	1.6 ± 0.9	<0.001
Vein graft									1.6 ± 1.6	0.7 ± 0.8	1.3 ± 1.1	<0.001
Use of IMA									633 (92.7)	919 (95.3)	665 (94.5)	0.07
Use of radial artery									278 (40.7)	592 (61.4)	264 (37.5)	<0.001

Values are n (%) or mean ± SD. *Wave 1 represents the time period 1995 to 2002, wave 2 represents 2003 to 2006, and wave 3 represents 2007 to 2013. †Number per patient.

ACEi = angiotensin-converting enzyme inhibitor; ADP = adenosine diphosphate; ARB = angiotensin II receptor blocker; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; IMA = internal mammary artery; RAS = renin-angiotensin system; other abbreviations as in Tables 1 and 4.

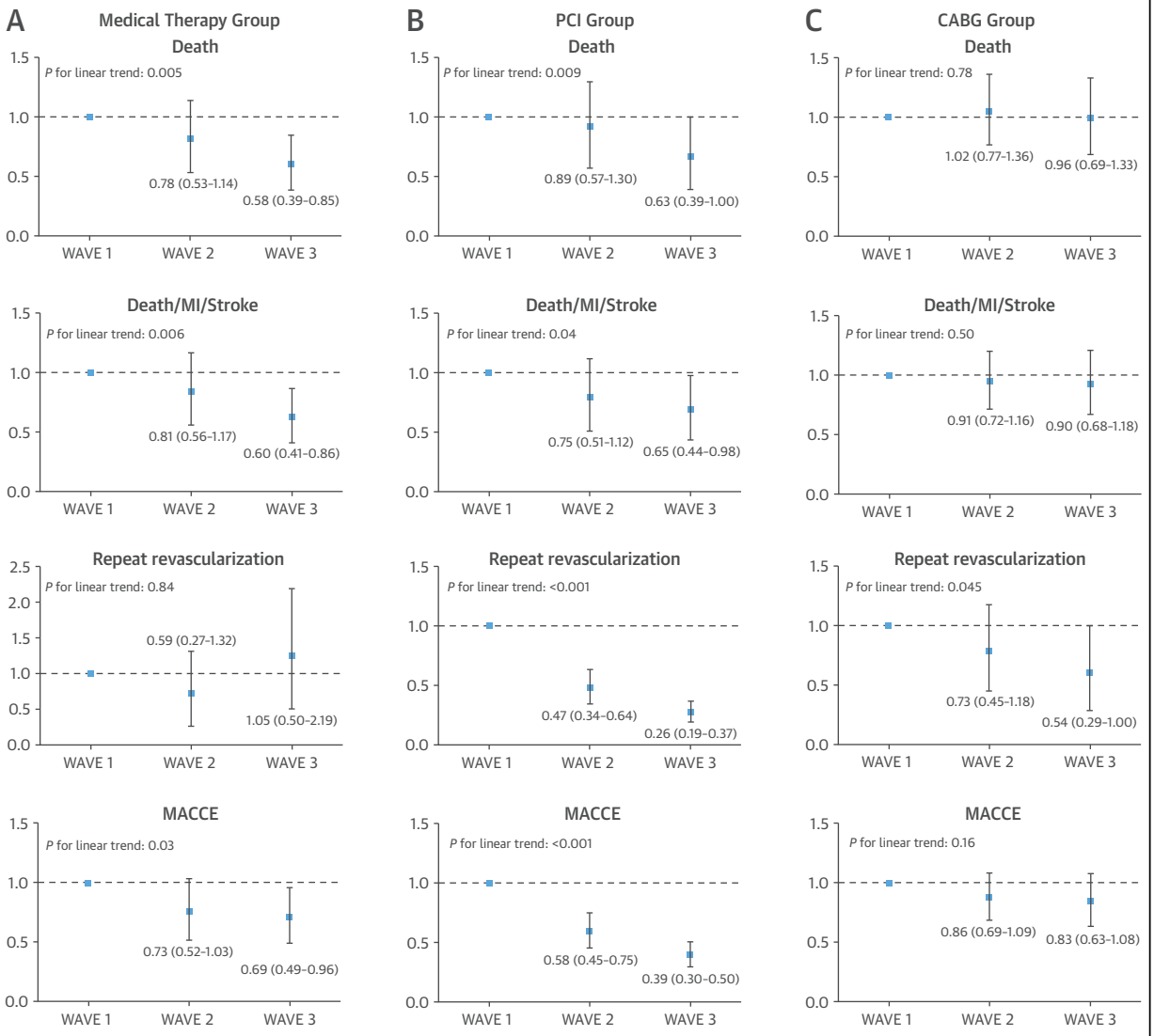
treatment effect between PCI and CABG has been narrowed.

EXPLANATION OF SECULAR CHANGES FOR LMCA DISEASE AND FUTURE PERSPECTIVES

In this large, multinational, "all-comers" IRIS-MAIN registry, there have been remarkable changes in the risk-factor profiles, lesion complexities, and concomitant medical therapy among patients with unprotected LMCA disease over the last 2 decades. Over time, the proportion of PCI treatment has progressively increased, whereas the opposite trend has been noted for CABG treatment. Notably, risk-adjusted survival, composite outcomes, and repeat revascularization have significantly improved for PCI over time, but have relatively remained stable for CABG. As a result, the gap in the treatment effect between PCI and CABG has gradually diminished from the BMS period to the early DES period and then to the late DES period. Although the outcomes of medical therapy alone were also observed to improve, medical therapy has always been inferior to revascularization strategies.

With regard to the demographic and risk profiles of patients with significant CAD who underwent coronary revascularization, several studies using large registries or nationwide databases have reported advancing age and a higher risk of patient comorbidities over time (35-38). Similar findings were also observed in the IRIS-MAIN registry. Although it is not feasible to exactly determine the effects of the clinical drivers or risk factors on secular trends in characteristics of patients with LMCA disease, this trend could be partially explained by the aging of the population because of increased life expectancy, epidemiological changes in the disease, or a delayed symptomatic onset or threshold requiring coronary

FIGURE 1 Risk-Adjusted Trends of Hazard Ratios for Clinical Outcomes Over Time in Each Treatment Stratum

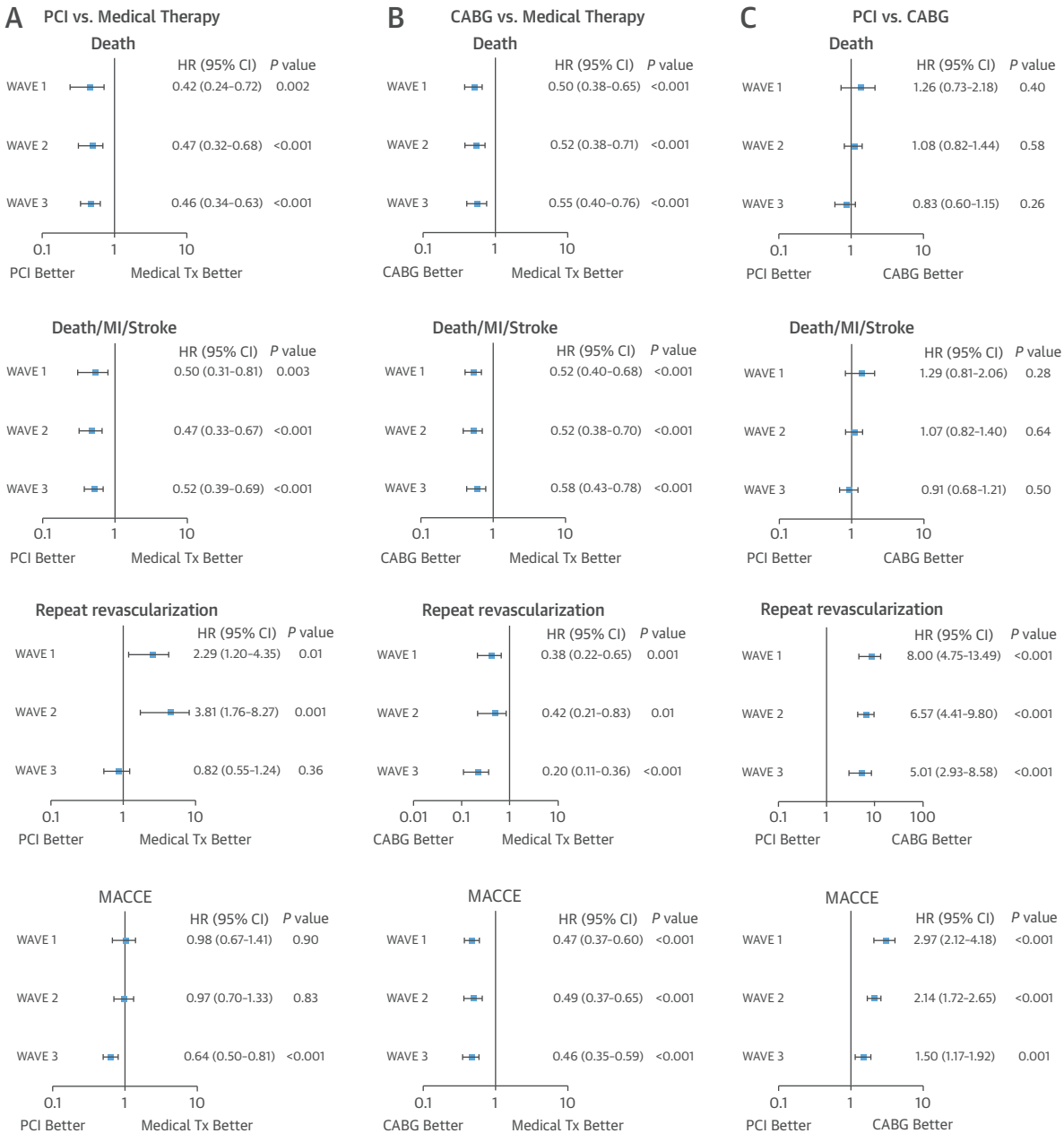


Changes in hazard ratios for outcomes over time (with wave 1 as the reference) in **(A)** the medical therapy group, **(B)** the PCI group, and **(C)** the CABG group. Wave 1 represents the time period from 1995 to 2002, wave 2 represents 2003 to 2006, and wave 3 represents 2007 to 2013. Adjusted variables are described in the Online Appendix. Numbers are hazard ratio (95% confidence interval). MACCE was defined as the composite of death, MI, stroke, and repeat revascularization. CABG = coronary artery bypass grafting; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

revascularization due to early and more aggressive cardiovascular preventive medications. Over time, all of these factors may result in more complex and higher-risk LMCA disease being treated with either PCI or CABG.

During the last 2 decades, the proportion of patients receiving PCI rather than CABG has significantly increased, but the proportion of patients receiving medical therapy alone has remained relatively steady. There has been a substantial change in the detailed practice and a steady improvement in clinical outcome. Although the medical therapy groups have always had a higher risk of mortality and hard endpoints than the revascularization strategy groups, which might be due to frailty, patient refusal, short life expectancy, and clinical/anatomic ineligibility, there has also been a significant improvement in outcomes in the medication group. The better

FIGURE 2 **Risk-Adjusted HRs of Relative Clinical Outcomes Between Treatment Strategies Over Time**

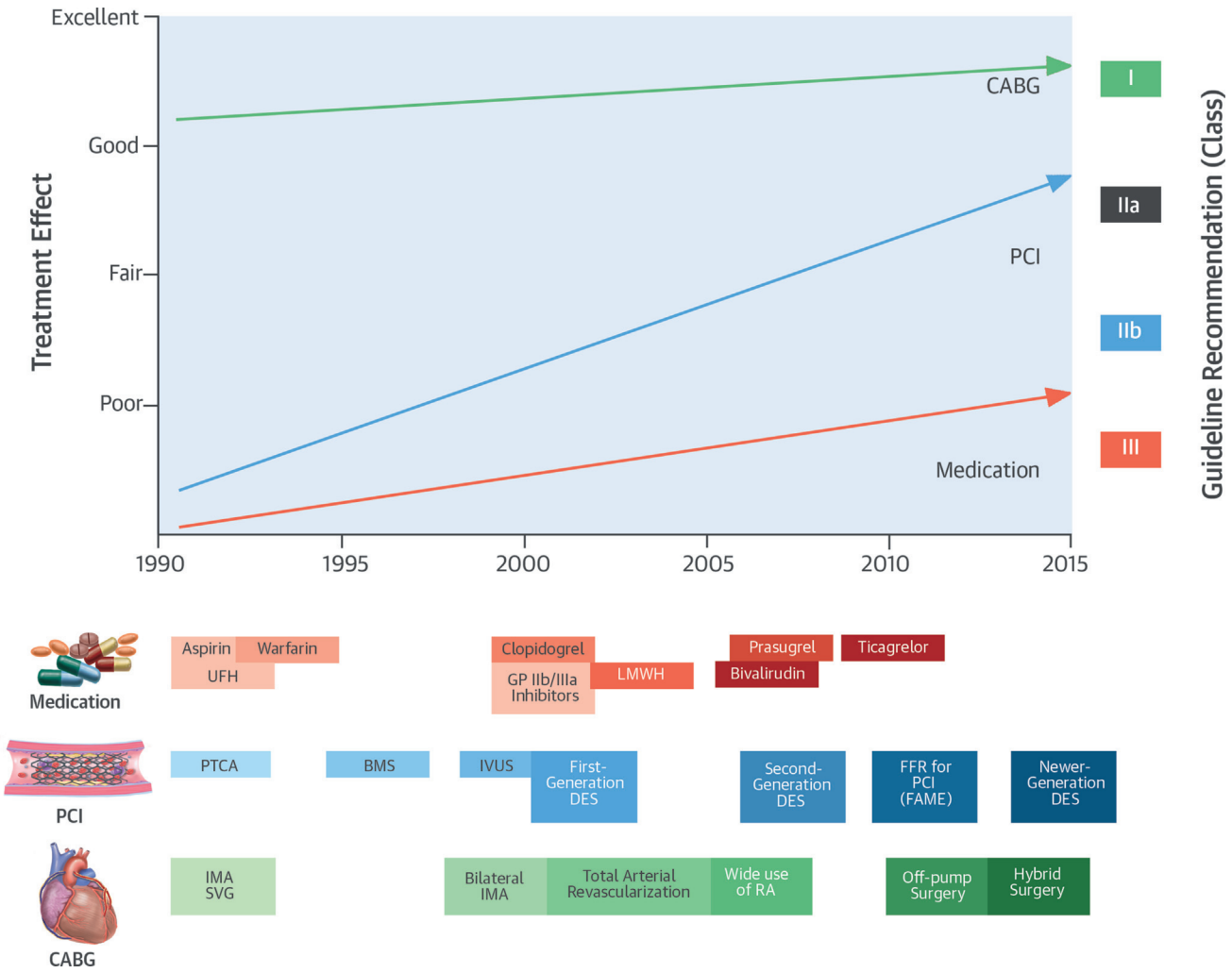


Changes in hazard ratios (HRs) for relative outcomes over time between **(A)** PCI and medical therapy (with the medical therapy group as the reference); **(B)** CABG and medical therapy (with the medical therapy group as the reference); and **(C)** PCI and CABG (with the CABG group as the reference). Wave 1 represents the time period from 1995 to 2002, wave 2 represents 2003 to 2006, and wave 3 represents 2007 to 2013. Adjusted variables are described in the Online Appendix. Numbers are hazard ratio (HR) (95% confidence interval [CI]). MACCE was defined as the composite of death, MI, stroke, and repeat revascularization. Abbreviations as in **Figure 1**.

control of risk factors and more frequent use of proven pharmacological therapies may have contributed to the decline of cardiovascular disease mortality and morbidity (39,40).

Improved PCI outcomes over time may be attributable to several therapeutic advancements, as well as changes in cardiovascular risk factors (**Central Illustration**). In the PCI strategy, along with

CENTRAL ILLUSTRATION **Secular Changes of Treatment Effect and Guideline Recommendations in Relation to Medical Advances of Each Treatment Stratum for Left Main Coronary Artery Disease**



Lee, P.H. et al. J Am Coll Cardiol. 2016;68(11):1233–46.

The timeline shows the steady increase in treatment effects and the change in guideline recommendations for each treatment strategy from the early 1990s to 2015, along with major advances in cardiovascular science and medicine. BMS = bare-metal stents; CABG = coronary artery bypass graft; DES = drug-eluting stents; FAME = Fractional Flow Reserve versus Angiography for Multivessel Evaluation; FFR = fractional flow reserve; GP = glycoprotein; IMA = internal mammary artery; IVUS = intravascular ultrasound; LMWH = low molecular weight heparin; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RA = radial artery; SVG = saphenous vein graft; UFH = unfractionated heparin.

the marked improvements in the stent technology itself, great efforts have been continuously made to optimize the PCI procedure, including an increasing number of stents (with more lesions) for full lesion coverage and complete revascularization, increased utilization of invasive functional or imaging tools (e.g., fractional flow reserve or intravascular ultrasound), simplified stenting techniques for distal LMCA bifurcations, and concomitant development of adjunctive pharmacotherapy, especially periprocedural antithrombotic agents (e.g., unfractionated heparin, low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitor, fondaparinux, or bivalirudin), antiplatelet therapy (e.g., ticlopidine, clopidogrel, prasugrel, or ticagrelor), and statins (first-, second-, and third-generation statins) (41-43). In addition, increased experience in complex LMCA stenting has further improved interventional device-oriented outcomes. The practice of CABG has also evolved over time, with the increasing use of off-

pump surgery, more frequent grafting with the internal mammary artery, and improved secondary prevention medications. Despite these changes in CABG practice, our registry has failed to demonstrate a substantial improvement in clinical outcomes for CABG over time. Although off-pump surgery was expected to provide several benefits for operative complications or morbidities, the greater use of off-pump CABG was accompanied by a decrease in the construction of the graft conduits. It might be possible that less visualization of the operative field and technical limitations could have resulted in poor graft quality and incomplete revascularization (44,45). Several trials comparing off- versus on-pump surgery have failed to demonstrate a difference in long-term outcomes (46–48). Further research is needed to adequately resolve this issue. In summary, although there was a continuous improvement in devices, techniques, drugs, and outcomes for percutaneous and surgical revascularization over time, such changes were more remarkable for PCI; therefore, the treatment gap between PCI and CABG has progressively diminished.

Remaining issues include how much the PCI-related outcomes in LMCA can be improved; how much the treatment gap between PCI and CABG can be narrowed; and whether, like CABG, PCI with contemporary or evolving devices and adjunctive drugs can be the standard of care (Class I) for patients with low- or intermediate-risk LMCA disease, rather than just an alternative option (Class II). Compelling evidence from 2 adequately powered, contemporary RCTs of PCI versus CABG (i.e., the EXCEL and NOBLE trials) will likely provide reliable answers regarding whether or not PCI can be upgraded to a Class I indication for revascularization of LMCA disease. However, although the guidelines provide evidence-based recommendations for optimal management, these recommendations are not a substitute for clinical judgment. The decision of PCI or CABG should be guided by the local heart team, including noninvasive and invasive cardiologists, and cardiac surgeons, who carefully consider the possible benefits and risks inherent to PCI and CABG, as well as the clinical characteristics and circumstances of each individual patient.

Using data from the IRIS-MAIN registry, we comprehensively evaluated changes in practice pattern, patient characteristics, and overall outcomes in LMCA disease. Such findings would be helpful for understanding the paradigm shifts in “real-world” practice and might provide complementary clinical value to RCTs as comparative-effectiveness research. However, the overall findings are observational, and therefore, there are several limitations that deserve comments (for details, see the Online Appendix).

CONCLUSIONS

Over the last 2 decades, among patients with unprotected LMCA disease from the mid-1990s to the mid-2010s, patient risk profiles and treatment of medical and revascularization therapy have evolved remarkably over time. The gap in treatment effect between PCI and CABG has progressively diminished, mainly due to more improved outcomes with PCI. The results of the EXCEL and NOBLE trials may reposition the therapeutic role and change the recommendation for PCI relative to CABG for patients with LMCA disease.

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KEY WORDS clinical decision making, coronary artery bypass, coronary disease, percutaneous coronary intervention, revascularization, stents

APPENDIX For an expanded Methods section as well as supplemental figures and a table, please see the online version of this article.