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Influence of practice patterns on outcome among countries enrolled in the SYNTAX trial: 5-year results between percutaneous coronary intervention and coronary artery bypass grafting†

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Abstract

OBJECTIVES: To examine differences among participating countries in baseline characteristics, clinical practice, medication strategies and outcomes of patients randomized to coronary artery bypass grafting and percutaneous coronary intervention in the SYNTAX trial.

METHODS: In SYNTAX, centres in 18 different countries enrolled 1800 patients, of which 8 countries enrolled ≥80 patients, what was projected to be a large enough sample size to be included in the analysis. Baseline characteristics, practice patterns and clinical outcomes were compared between the USA ($n = 245$), the UK ($n = 267$), Italy ($n = 197$), France ($n = 208$), Germany ($n = 179$), Netherlands ($n = 148$), Belgium ($n = 91$) and Hungary ($n = 83$). The remaining patients from other participating countries were pooled together ($n = 382$).

RESULTS: Five-year results demonstrated significantly different outcomes between countries. After adjustment, percutaneous coronary intervention patients in France had lower rates of major adverse cardiac and cerebrovascular events [hazard ratio (HR) = 0.60, 95% confidence interval (CI) 0.37–0.98], while the incidence of repeat revascularization was higher in Hungary (HR = 1.89, 95% CI 1.14–3.42). Coronary artery bypass grafting showed the lowest rate of repeat revascularization in the UK (HR = 0.32, 95% CI 0.12–0.85). There were numerous differences in the risk profile of patients between participating countries, as well as marked differences in surgical practice across countries in the use of blood cardioplegia (range 3.1–89.0%; $P < 0.001$), bilateral internal mammary artery usage (range 7.8–68.2%; $P < 0.001$) and off-pump procedures (range 3.9–44.4%; $P < 0.001$). Variation was also found for percutaneous coronary intervention in the number of implanted stents (range 4.0 ± 2.3 to 6.1 ± 2.6; $P < 0.001$) as well as for the entire stents length (range 69.0 ± 45.1 to 124.1 ± 60.9; $P < 0.001$). Remarkable differences were observed in the prescription of post-coronary artery bypass grafting medication in terms of acetylsalicylic acid (range 79.6–95.0%; $P = 0.004$), thienopyridine (6.8–31.1%; $P < 0.001$) and statins (41.3–89.1%; $P < 0.001$).

CONCLUSIONS: Patient characteristics and clinical patterns are significantly different between countries, resulting in significantly different 5-year outcomes. This article presents specific data that can further improve outcomes in each country.

Clinical Trials Registry: NCT00114972.

Keywords: Coronary artery bypass grafting • Percutaneous coronary intervention • Geographic • Country • SYNTAX

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INTRODUCTION

In order to expedite recruitment, there is a growing trend to involve centres from many different countries in large randomized clinical trials. As a consequence, participants can be enrolled more rapidly, the time span of trials is reduced, costs are less and the external validity of trial results is larger [1, 2]. However, internal consistency may also be affected by differences in baseline characteristics, medical practice patterns and outcomes within participating countries or sites. Several recent reports have addressed the fundamental difficult issues of generalizability and cross-geographical clinical variations [1–3]. Results from the PLATO trial suggested a significant treatment interaction of ticagrelor among patients with acute coronary syndromes enrolled in the USA or outside the USA, which was the result of differences in aspirin maintenance dose [4]. Other studies have reported significant differences in baseline characteristics, practice patterns and clinical outcomes in subgroup analyses stratified according to site enrolment volume [5] and geographic region [6] among different clinical scenarios.

Findings from subgroup analyses may allow for a better understanding of risk–benefit ratios, can alter treatment recommendations and improve prognosis [7]. In addition, these findings may identify areas in which practice varies between countries and may therefore generate awareness among outliers to improve patient care.

Coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) are both options for myocardial revascularization. Although many studies have been performed to aid decision-making of PCI versus CABG [8–10], no such data on geographic enrolment within a randomized controlled trial exists to date. We, therefore, evaluated differences in baseline characteristics, practice patterns and outcomes among countries that enrolled patients in the SYNTAX trial.

METHODS

Study design

The SYNTAX trial design has been described elsewhere [11]. Briefly, it was an all-comers population of patients with *de novo* left main (LM) or 3-vessel disease, who were randomized to PCI with paclitaxel-eluting stents ($n = 903$) or CABG ($n = 897$) or went into nested PCI ($n = 198$) or CABG ($n = 1077$) registries [12]. This analysis encompasses the randomized cohorts only.

Only those countries that had enrolled 80 or more patients in the randomized trial were analysed; this was the case in (i) the USA ($n = 245$; 13.6%), (ii) the UK ($n = 267$; 14.8%), (iii) Italy ($n = 197$; 10.9%), (iv) Germany ($n = 179$; 9.9%), (v) France ($n = 208$; 11.6%), (vi) the Netherlands ($n = 148$; 8.2%), (vii) Belgium ($n = 91$; 5.1%) and (viii) Hungary ($n = 83$; 4.6%). Patients from the remaining countries were pooled together in 1 group [Poland ($n = 66$; 3.7%), Sweden ($n = 54$; 3.0%), Spain ($n = 53$; 2.9%), Austria ($n = 52$; 2.9%), Czech Republic ($n = 40$; 2.2%), Latvia ($n = 40$; 2.2%), Denmark ($n = 32$; 1.8%), Finland ($n = 24$; 1.3%), Portugal ($n = 13$; 0.7%) and Norway ($n = 8$; 0.4%)], as recommended by Pocock *et al* [1]. This study therefore consists of 9 groups of patients. Analyses of differences between countries were not pre-specified in this study. Therefore, the results of these subgroup analyses should be interpreted as 'hypothesis generating' only.

The institutional review board of all participating sites approved the protocol, which is consistent with the International Conference on Harmonisation Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki and all local regulations. Written consent was obtained from all participating patients before enrolment. The trial is registered on the National Institute of Health website with identifier NCT00114972.

End-points and definitions

The primary end-point of this study was the composite rate of major adverse cardiac or cerebrovascular events (MACCE) at 5 years, which included all-cause death, stroke, myocardial infarction (MI) and repeat revascularization. Secondary end-points consisted of the composite safety end-point of all-cause death, stroke and MI as well as the individual component of repeat revascularization. Specific definitions of these end-points have been reported previously [11]. All end-points were adjudicated by an independent Clinical Events Committee that included a cardiac surgeon, a cardiologist and a neurologist.

Statistical analyses

Analyses were based on the intention-to-treat principle. Data are presented using descriptive statistics, as percentage, count of sample size or mean ± standard deviation. The Kruskal–Wallis test was used to compare continuous variables. Differences in discrete variables were compared by means of χ^2 or Fisher's exact test, where appropriate. Time-to-event unadjusted and adjusted Kaplan–Meier estimates with log-rank testing were used to compare clinical outcomes after PCI and CABG among different countries. Hazard ratios (HRs) and corresponding 95% confidence intervals (CI) for the primary end-point and the secondary end-points were calculated relative to using Cox proportional hazards model. Treatment-by-country interactions were explored using χ^2 test. Outcomes were adjusted for a combination of pre- and intraoperative variables that were deemed clinically important and significantly different between countries or believed to be clinically relevant (Supplementary Material, Appendix). Schoenfeld residuals were used and showed no significant departure from the proportional hazards assumption. A 2-sided P-value of <0.05 was considered to be statistically significant. Analyses were performed using SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline characteristics

Of the 1800 patients enrolled in the SYNTAX trial, complete follow-up data were obtained for 1676 patients (93.1%). Completeness of follow-up was comparable between groups of countries ($P = 0.084$) (Table 1). The risk profile of patients varied significantly among countries (Table 2, complete results are in Supplementary Material, Table S1). Patients in Hungary were the youngest, had the highest number of patients with medically treated hypertension and medically treated diabetes, while perioperative risk expressed by the logistic EuroSCORE was the lowest. In contrast, patients from the USA and Italy were at greater operative risk according to the logistic EuroSCORE. Patients in

Table 1: Participating countries in the SYNTAX randomized cohort

Country	Hospitals	PCI patients	CABG patients	Total no. of patients (%)	Completeness of follow-up (%)
Austria	2	28	24	52 (2.9)	44/52 (84)
Belgium	4	44	47	91 (5.1)	83/91 (91)
Czech Republic	1	20	20	40 (2.3)	40/40 (100)
Denmark	1	17	15	32 (1.8)	30/32 (93)
Finland	1	12	12	24 (1.3)	24/24 (100)
France	6	103	105	208 (11.6)	201/208 (96)
Germany	8	86	93	179 (9.9)	161/179 (89)
Hungary	3	44	39	83 (4.6)	75/83 (90)
Italy	7	101	96	197 (10.9)	187/197 (94)
Latvia	1	20	20	40 (2.3)	37/40 (92)
Netherlands	6	74	74	148 (8.2)	137/148 (92)
Norway	1	4	4	8 (0.4)	8/8 (100)
Poland	3	33	33	66 (3.7)	62/66 (93)
Portugal	1	6	7	13 (0.7)	12/13 (92)
Spain	4	27	26	53 (2.9)	48/53 (90)
Sweden	3	26	28	54 (3.0)	52/54 (96)
United Kingdom	8	135	132	267 (14.8)	255/267 (95)
United States	22	123	122	245 (13.6)	220/245 (89)
TOTAL	82	903	897	1800 (100.0)	1676/1800 (93)

Values are present as *N* (%) or *n/N* (%).
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table 2: Baseline characteristics of patients within countries

	USA (*n* = 245)	UK (*n* = 267)	IT (*n* = 197)	GE (*n* = 179)	FR (*n* = 208)	NL (*n* = 148)	BE (*n* = 91)	HU (*n* = 83)	Other (*n* = 382)
Age	65.1 ± 10.3	65.4 ± 9.3	66.5 ± 9.1	66.6 ± 9.7	65.9 ± 10.7	64.6 ± 9.1	63.4 ± 10.9	59.0 ± 8.6	64.9 ± 9.1
Male	160 (65.3)	214 (80.1)	158 (80.2)	135 (75.4)	173 (83.2)	117 (79.1)	72 (79.1)	57 (68.7)	312 (81.7)
BMI	30.3 ± 6.2	27.7 ± 4.5	26.7 ± 3.6	27.9 ± 4.1	27.1 ± 4.7	28.1 ± 4.2	27.1 ± 4.0	29.5 ± 4.2	27.7 ± 4.3
Medically treated diabetes	78 (31.8)	48 (18.0)	60 (30.5)	54 (30.2)	51 (24.5)	32 (21.6)	16 (17.6)	28 (33.7)	85 (22.3)
Hypertension	208 (85.9)	187 (70.8)	157 (80.1)	161 (89.9)	140 (68.0)	95 (65.5)	53 (59.6)	79 (95.2)	269 (70.6)
Hyperlipidaemia	194 (79.5)	249 (93.6)	137 (69.5)	132 (73.7)	155 (75.2)	113 (76.9)	65 (72.2)	60 (76.9)	286 (75.7)
Carotid artery disease	28 (11.4)	8 (3.0)	31 (15.7)	22 (12.3)	14 (6.7)	5 (3.4)	5 (5.5)	8 (9.6)	27 (7.1)
Unstable angina	79 (32.2)	65 (24.3)	83 (42.1)	47 (26.3)	78 (37.5)	25 (16.9)	23 (25.3)	14 (16.9)	99 (25.9)
Previous MI	57 (23.3)	117 (44.3)	66 (33.5)	48 (28.4)	47 (22.6)	53 (36.1)	23 (25.8)	29 (34.9)	145 (38.4)
Congestive heart failure	19 (7.8)	8 (3.0)	6 (3.0)	7 (4.2)	4 (1.9)	3 (2.1)	1 (1.1)	5 (6.1)	30 (7.9)
Logistic EuroSCORE	4.5 ± 4.6	3.5 ± 2.3	4.8 ± 5.1	4.4 ± 5.8	3.9 ± 3.7	3.2 ± 3.4	3.7 ± 8.5	2.5 ± 3.0	3.3 ± 3.4
Number of lesions	3.6 ± 1.8	3.7 ± 1.6	4.4 ± 1.7	4.3 ± 1.7	3.9 ± 1.6	3.7 ± 1.3	3.9 ± 1.5	4.7 ± 1.8	4.0 ± 1.7
Left main, any	138 (56.3)	109 (40.8)	66 (33.5)	70 (39.3)	88 (42.3)	45 (30.4)	29 (31.9)	29 (34.9)	131 (34.3)
Left main + 2 vessel disease	49 (20.0)	40 (15.0)	18 (9.1)	19 (10.6)	32 (15.4)	7 (4.7)	9 (9.9)	6 (7.2)	38 (9.9)
Three-vessel disease only	107 (43.7)	158 (59.2)	131 (66.5)	108 (60.7)	120 (57.7)	103 (69.6)	62 (68.1)	54 (65.1)	251 (65.7)
SYNTAX score	25.7 ± 11.7	28.8 ± 10.3	31.4 ± 11.3	29.7 ± 10.8	30.5 ± 12.6	26.9 ± 10.7	26.9 ± 11.3	24.5 ± 11.4	29.9 ± 11.2

$P < 0.001$ for all comparison between groups. Values are shown as mean ± SD or *n/N* (%).
USA: United States of America; UK: United Kingdom; IT: Italy; GE: Germany; FR: France; NL: Netherlands; BE: Belgium; HU: Hungary; Other: Poland, Sweden, Spain, Czech Republic, Latvia, Denmark, Finland, Portugal and Norway; BMI: body mass index; MI: myocardial infarction.

the UK had the highest rates of prior MI and therefore more frequent pretreatment left ventricular dysfunction. The SYNTAX score was substantially lower in Hungary, while more patients in the USA had LM disease (Table 2).

Procedural characteristics

Several differences were noted in PCI characteristics (Table 3, complete results are in Supplementary Material, Table S2). Particularly in Hungary a larger number of stents were implanted, a higher stent length, and more patients had >100 mm stents. There were no significant differences in the rates of complete revascularization. Patients in the USA received the lowest total length of implanted stents. Remarkably, patients in Germany more often underwent staged procedures compared with patients in Italy and France.

Differences in CABG procedural characteristics are listed in Table 4 and Fig. 1 (complete results are in Supplementary Material, Table S3). First of all, the necessity for emergent treatment was significantly higher in Hungary compared with the other groups. Secondly, the procedure, bypass and cross-clamp

Table 3: Procedural characteristics in PCI randomized cohort

	USA (*n* = 123)	UK (*n* = 135)	IT (*n* = 101)	GE (*n* = 86)	FR (*n* = 103)	NL (*n* = 74)	BE (*n* = 44)	HU (*n* = 44)	Other (*n* = 193)
Procedure duration	90.1 ± 42.7	98.1 ± 33.3	123.7 ± 47.1	89.1 ± 40.9	87.6 ± 40.7	106.4 ± 58.2	88.5 ± 31.1	95.9 ± 36.6	121.2 ± 50.8
Total overlapping stent	0.5 ± 0.6	0.9 ± 0.6	0.7 ± 0.6	0.6 ± 0.6	0.4 ± 0.6	0.7 ± 0.7	0.4 ± 0.5	0.9 ± 0.8	0.5 ± 0.6
Bi-/trifurcation lesions treated	63 (51.2)	87 (64.4)	63 (62.4)	57 (66.3)	78 (75.7)	45 (60.8)	36 (81.8)	34 (77.3)	140 (72.5)
Left anterior descending artery stent treated	62 (50.4)	100 (74.1)	50 (49.5)	58 (67.4)	62 (60.2)	37 (50.0)	20 (45.5)	32 (72.7)	103 (53.4)
Stents implanted	4.0 ± 2.3	4.4 ± 1.9	5.1 ± 2.2	5.1 ± 2.3	4.2 ± 2.1	4.9 ± 2.4	4.2 ± 1.9	6.1 ± 2.6	4.7 ± 2.3
Total length implanted	69.0 ± 45.1	83.8 ± 41.5	101.6 ± 49.3	89.0 ± 44.9	75.3 ± 41.4	96.7 ± 55.7	83.0 ± 42.9	124.1 ± 60.9	84.4 ± 45.9
Long stenting (>100 mm)	25 (21.2)	43 (23.0)	46 (45.5)	30 (35.3)	23 (22.8)	29 (42.6)	12 (28.6)	24 (58.5)	62 (33.0)
SYNTAX score	24.9 ± 11.4	28.7 ± 10.2	29.7 ± 11.8	29.7 ± 11.6	30.4 ± 13.2	27.4 ± 10.4	26.3 ± 10.7	22.3 ± 10.6	30.3 ± 10.9
Logistic EuroSCORE	4.5 ± 4.6	3.8 ± 3.5	4.2 ± 4.7	4.1 ± 4.0	4.0 ± 3.8	3.3 ± 3.7	4.4 ± 12.0	3.1 ± 3.9	3.0 ± 2.5

$P < 0.001$ for all comparison between groups. Abbreviations as in Table 2. Values are shown as mean ± SD or *n*/*N* (%).

Table 4: Procedural characteristics in CABG randomized cohort

	USA (*n* = 122)	UK (*n* = 132)	IT (*n* = 96)	GE (*n* = 93)	FR (*n* = 105)	NL (*n* = 74)	BE (*n* = 47)	HU (*n* = 39)	Other (*n* = 189)
Elective procedure	104 (89.7)	124 (96.9)	87 (94.6)	88 (87.8)	89 (89.0)	68 (97.1)	42 (93.3)	20 (62.5)	166 (91.7)
Procedure time	235.9 ± 72.2	181.5 ± 58.3	230.0 ± 51.7	236.4 ± 71.6	207.4 ± 48.1	190.5 ± 59.8	198.1 ± 49.8	183.3 ± 51.6	203.1 ± 57.8
Bypass time	103.6 ± 41.5	72.2 ± 31.6	86.2 ± 26.4	93.9 ± 39.9	88.2 ± 37.1	84.3 ± 35.9	79.6 ± 25.6	78.0 ± 22.1	87.4 ± 33.8
Cross-clamp time	75.2 ± 34.7	49.3 ± 66.3	57.7 ± 16.6	59.9 ± 25.7	61.5 ± 23.7	51.9 ± 21.2	42.5 ± 19.1	45.2 ± 14.4	50.1 ± 21.8
Blood cardioplegia	75 (64.7)	78 (60.9)	55 (60.4)	38 (42.2)	89 (89.0)	18 (25.7)	2 (4.4)	1 (3.1)	71 (39.2)
Complete revascularization	87 (75.0)	87 (68.0)	49 (53.3)	68 (75.6)	46 (46.0)	54 (77.1)	34 (75.6)	10 (31.3)	110 (60.8)
Off-pump surgery	37 (31.9)	5 (3.9)	10 (10.9)	17 (18.9)	4 (4.0)	2 (2.9)	20 (44.4)	3 (9.4)	30 (16.6)
Grafts per patient	3.0 ± 0.7	2.9 ± 0.8	2.8 ± 0.7	2.7 ± 0.6	2.7 ± 0.6	2.2 ± 0.5	2.9 ± 0.7	3.1 ± 0.8	2.7 ± 0.7
Arterial	1.2 ± 0.5	1.2 ± 0.5	1.4 ± 0.5	1.7 ± 0.7	1.9 ± 0.8	1.2 ± 0.6	1.7 ± 0.6	0.9 ± 0.6	1.3 ± 0.6
Distal anastomoses	3.3 ± 0.9	3.0 ± 0.7	3.1 ± 0.9	3.2 ± 0.9	2.9 ± 0.8	3.7 ± 1.0	3.4 ± 1.0	3.2 ± 0.8	3.2 ± 0.9
LIMA use	114 (98.3)	123 (96.1)	91 (98.9)	89 (98.8)	97 (97.0)	64 (91.4)	44 (97.8)	26 (83.9)	179 (98.9)
Double LIMA/RIMA	15 (13.0)	10 (7.8)	29 (32.2)	39 (43.3)	60 (60.6)	18 (25.7)	30 (68.2)	4 (12.5)	31 (17.5)
Radial artery use	9 (7.8)	15 (11.7)	5 (5.4)	21 (23.3)	29 (29.0)	3 (4.3)	3 (6.7)	0	35 (19.3)
Complete arterial revascularization	8 (6.9)	10 (7.8)	9 (9.8)	33 (36.7)	48 (48.0)	8 (11.4)	6 (13.3)	2 (6.3)	37 (20.4)
SYNTAX score	26.5 ± 12.0	29.0 ± 10.3	33.3 ± 10.4	29.8 ± 10.2	30.5 ± 12.1	26.3 ± 11.0	27.4 ± 11.9	27.0 ± 11.9	29.5 ± 11.6
Logistic EuroSCORE	4.4 ± 4.6	3.3 ± 3.1	5.5 ± 5.4	4.8 ± 7.1	3.7 ± 3.7	3.2 ± 3.0	3.0 ± 2.7	1.9 ± 1.5	3.6 ± 4.0

$P < 0.001$ for all comparison between groups. Abbreviations as in Table 2. Values are shown as mean ± SD or *n*/*N* (%).
LIMA: left internal mammary artery; RIMA: right internal mammary artery.

times showed significant variations. Thirdly, in the Netherlands, less grafts were used than in other countries, but the number of distal anastomoses was the highest, indicating that more jump grafts were used compared with other countries. When comparing type of conduits, the use of an arterial graft to the left anterior descending artery, as well as the rate of complete arterial grafting, were lowest in Hungary. In France, the use of arterial grafts was highest, resulting in the highest rate of complete arterial grafting. In Belgium, the rate of bilateral internal mammary artery (IMA) use was highest, but the rate of complete arterial grafting was lower because of the use of additional venous grafts.

Medication at discharge

There were only marginal differences across groups in prescribing antiplatelet treatment after PCI; the prescription of thienopyridine and dual antiplatelet therapy was lowest in the Netherlands. There were, however, significant differences in the prescription of statins, beta-blockers and antihypertensive medication (Supplementary Material, Table S4).

After CABG, there were differences in the prescription of all secondary prevention medications (Supplementary Material, Table S4). In the Netherlands and Germany, the prescription of antiplatelet therapy was lowest, but the prescription of Coumadin derivates was higher. Thienopyridines were prescribed at the highest rate in the USA, as was the prescription of dual antiplatelet therapy.

Five-year outcomes

For the entire cohort, the 5-year unadjusted Kaplan–Meier estimates of MACCE were lowest in the group of other countries (28.0%) and highest in Germany (39.4%, log-rank for all groups $P = 0.076$) (Fig. 2A). Also, the unadjusted rate of the composite safety end-point of death/stroke/MI was highest in Germany (26.4%) but lowest in Hungary (12.9%) (log-rank for all groups $P = 0.096$) (Fig. 2B). Repeat revascularization was lowest in the UK

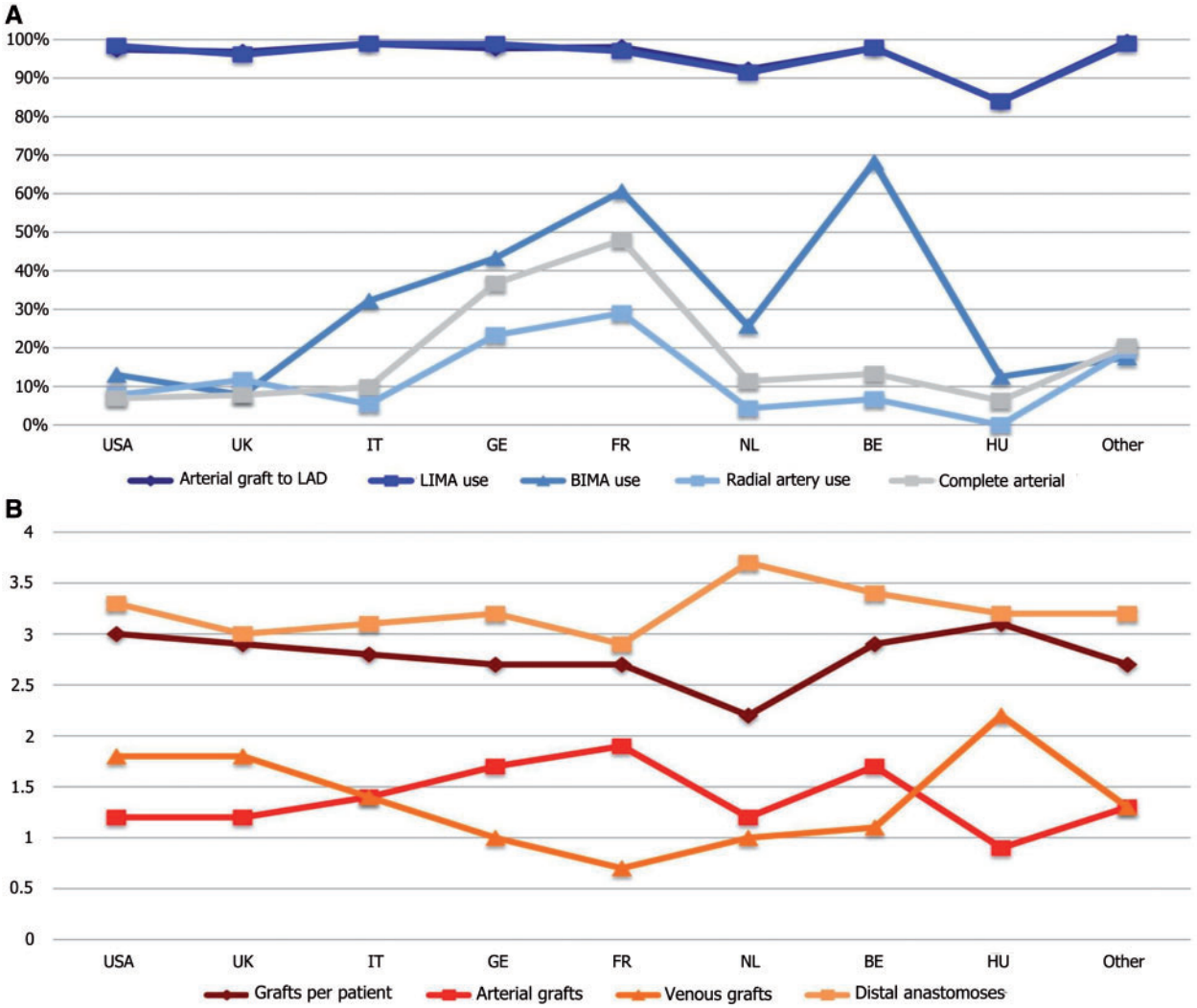

Figure 1: A graphical display showing differences among investigating countries in use percentage of arterial conduits (**A**) and a number of implanted grafts (**B**). USA: United States of America; UK: United Kingdom; IT: Italy; GE: Germany; FR: France; NL: Netherlands; BE: Belgium; HU: Hungary; Other: Poland, Sweden, Spain, Czech Republic, Latvia, Denmark, Finland, Portugal and Norway; LIMA: left internal mammary artery; BIMA: bilateral internal mammary artery; LAD: left anterior descending artery.

(14.1%) and highest in Hungary (31.6%), with significant differences across groups ($P = 0.008$) (Fig. 2C).

After PCI, patients in France had the lowest unadjusted event rates of MACCE (28.9%), the composite safety end-point of death/stroke/MI (13.7%) and rate of repeat revascularization (20.3%), while these rates were highest in Hungary (50.4, 18.2 and 44.9%, respectively) and Germany (46.8, 29.2 and 29%, respectively; Fig. 3A and C). After adjustment for baseline and procedural characteristics and with the USA as reference, patients in France had a lower risk of MACCE (HR = 0.60, 95% CI 0.37–0.98) and for the composite safety end-point of death/stroke/MI (HR = 0.45, 95% CI 0.22–0.89), while patients enrolled in Hungary had a higher risk of repeat revascularization (HR = 1.89, 95% CI 1.14–3.42) (Supplementary Material, Table S5).

After CABG, rates of unadjusted MACCE were lowest in Hungary and highest in France (15.3% vs 34.6%), with significant differences among the 9 groups studied (log-rank for all; $P = 0.026$; Fig. 3B). Differences in the unadjusted rates of repeat revascularization just failed to reach statistical significance ($P = 0.07$; Fig. 3D and F). After adjustment for baseline and procedural characteristics and with the USA as reference, patients enrolled in Germany had a higher adjusted risk for the composite of death/stroke/MI (HR = 2.38, 95% CI 1.03–5.67), and in the UK, patients had a lower adjusted risk of repeated revascularization (HR = 0.32, 95% CI 0.12–0.85; Supplementary Material, Table S5).

The PCI versus CABG treatment effect did not show a significant interaction among countries for the end-point of MACCE (Fig. 4A) or the composite safety end-point of death/stroke/MI (Fig. 4B). For repeat revascularization, there was a significant treatment-by-countries interaction (P for interaction = 0.045) (Fig. 4C).

DISCUSSION

This study demonstrates important differences in the baseline characteristics, clinical practice, medication regimens and outcomes among patients undergoing revascularization in the different countries involved in the SYNTAX trial. Comorbidities and hence the logistic EuroSCORE differed between countries, there was a major variation in the complexity of coronary disease according to SYNTAX score, and there was a significant difference in 5-year outcomes between countries.

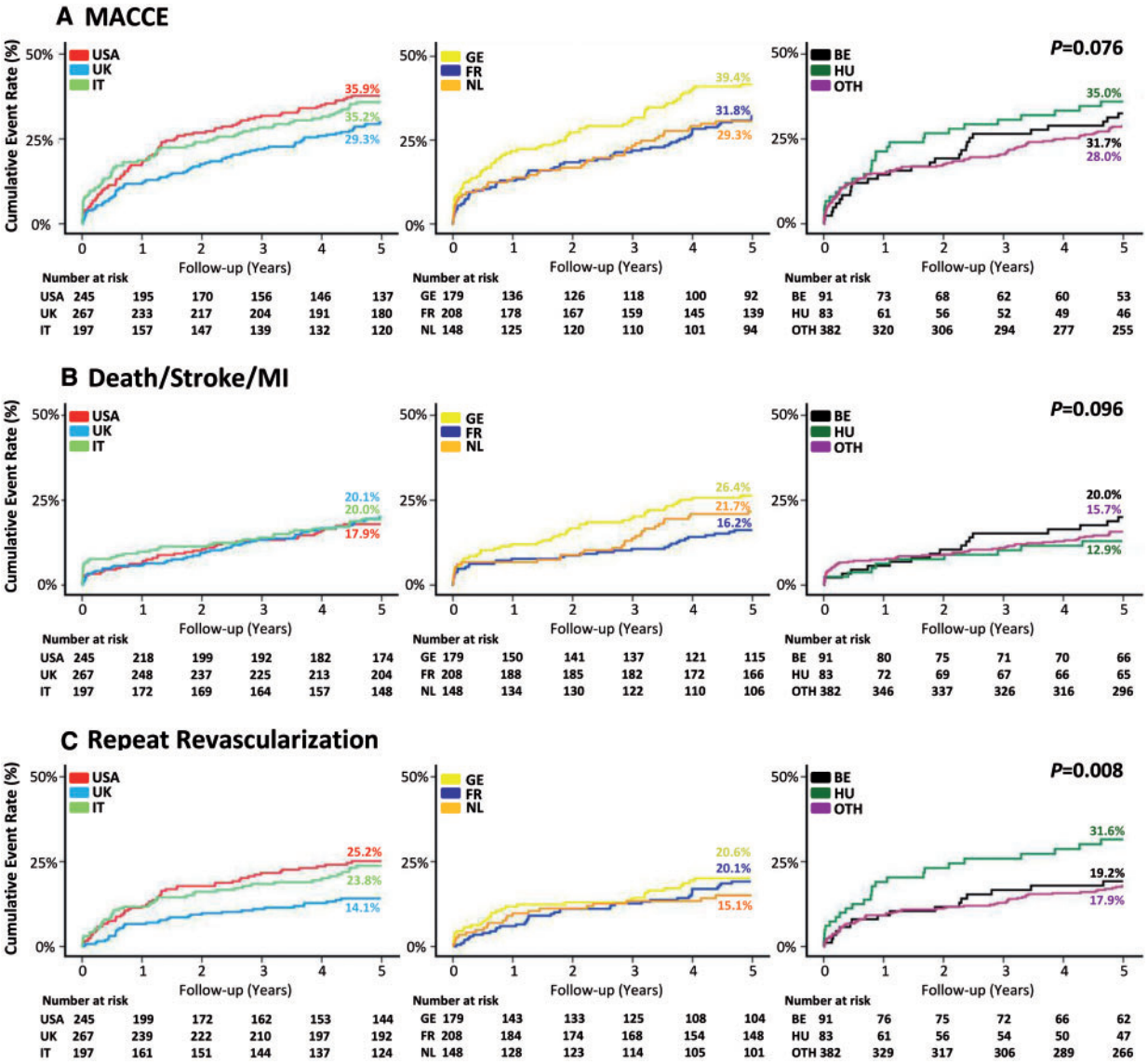

Figure 2: The Kaplan–Meier cumulative event curves by investigating countries in the SYNTAX trial for MACCE (**A**), the composite safety end-point of death/stroke/MI (**B**) and repeat revascularization (**C**). Abbreviations as in Fig. 1. PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; MACCE: major adverse cardiac and cerebrovascular events; MI: myocardial infarction.

Geographical variations in patient characteristics and the impact on outcome have recently been reported in cardiovascular trials like the EVEREST and ASTRONAUT trial [4, 13–15]. The current analysis is unique, as for the first time, it estimates the impact of the difference in patient characteristics and clinical practice on outcomes after PCI and CABG in specific countries. The number of patients with clinically relevant comorbidities was highest in the USA and Italy, while patients from countries with lower enrolment (Hungary and the pooled group of other (small) countries) had less comorbidities. In concordance with other studies, countries with low recruiting centres tended to enrol lower risk patients [5].

PCI-treated patients in Hungary were the youngest and had the lowest SYNTAX score, while the number of implanted stents was higher, less optimal use of secondary prevention medication and they experienced significantly more repeated revascularizations. These findings may therefore confirm the importance of functional assessment of coronary lesions as opposed to anatomical assessment and the use of secondary prevention. Despite recommendations provided in the SYNTAX trial protocols, differences in prescription of secondary prevention medications are notable and could have had a negative impact on the outcome. Lack of optimal therapy and correlation with long-term mortality has been reported in previous studies [16, 17]. Antiplatelet agents and statins were more often used after PCI than after CABG. Preventive medications to maintain stent patency after PCI were rigorously prescribed by cardiologists, whereas usefulness of secondary prevention was probably underestimated after CABG [18]. These findings provide an opportunity for quality improvement in discharge medication after CABG in several countries but also remind and encourage cardiologists, intensivists and cardiac surgeons to start with secondary prevention as soon as possible and to discharge patients with optimal therapies, since there is a possibility that primary care doctors who will follow-up these patients will not initiate treatment.

Substantial differences were noted in surgical techniques across countries. Despite clear recommendations of more arterial grafting in guidelines [19, 20], the published rates of arterial

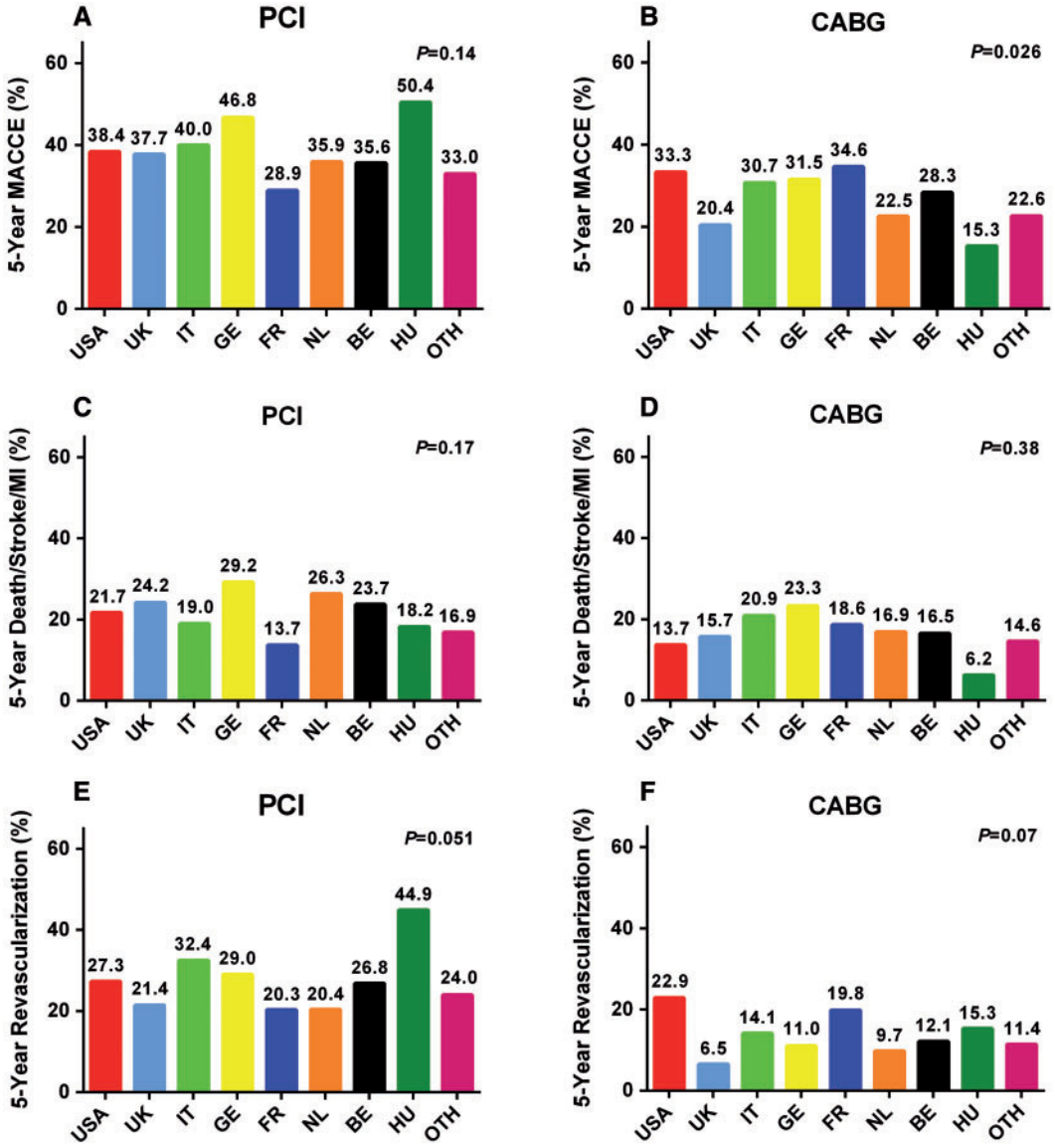

Figure 3: A graphical display of 5-year outcomes of CABG and PCI cohorts by investigating countries in the SYNTAX trial for MACCE (**A** and **B**), the composite safety end-point of death/stroke/MI (**C** and **D**) and repeat revascularization (**E** and **F**). Abbreviations as in Fig. 1. Values are Kaplan–Meier rates with *P*-values from log-rank test.

grafting are still relatively low [21]. Differences in the use of the left and/or right IMAs, total arterial revascularization, the number of grafts, myocardial protection and the use of off-pump procedures are likely to be influenced by surgical training rather than the risk profile of the patient. It is remarkable that a procedure that is performed with such a high rate since its introduction more than 50 years ago remains far away from being standardized globally. Despite evidence of a survival benefit in favour of the use of 2 IMAs over the use of a single IMA graft [22], their use in the USA, the UK and Hungary was disappointingly low. On the other hand, in the majority of the patients who underwent CABG in Belgium and France, 2 IMAs graft were used. In this regard, it is important to consider the absence of a midterm benefit on clinical outcomes from 2 IMAs over single IMA graft in the recent 5-year findings from the Arterial Revascularization Trial [23], although the benefits of 2 IMA grafts increase with the duration of follow-up, which formed the basis for the current Arterial Revascularization Trial with 10-year follow-up.

After adjustment for baseline clinical patterns, PCI-treated patients in France had a significantly lower MACCE rate and CABG patients in Germany had a higher incidence of the composite of death, stroke and MI. It remains unclear whether any unmeasured confounding may play a role or whether these findings indeed represent higher risks of adverse events in specific countries. Furthermore, a large difference in repeat revascularization among countries persisted, even after adjustment. It is notable that the Netherlands and the UK cohorts had the lowest rates of repeated revascularization, whereas other countries (USA, Hungary and Italy) had a higher incidence of repeat revascularization [24].

In order to reduce the difference in outcome between different institutions and countries, future trials should include standardized protocols for techniques and treatment strategies. Rigorous training and monitoring to improve adherence to these protocols will be key to improving the quality of a trial. Moreover, the design of the SYNTAX trial did not ensure balanced allocation within participating countries, which may have

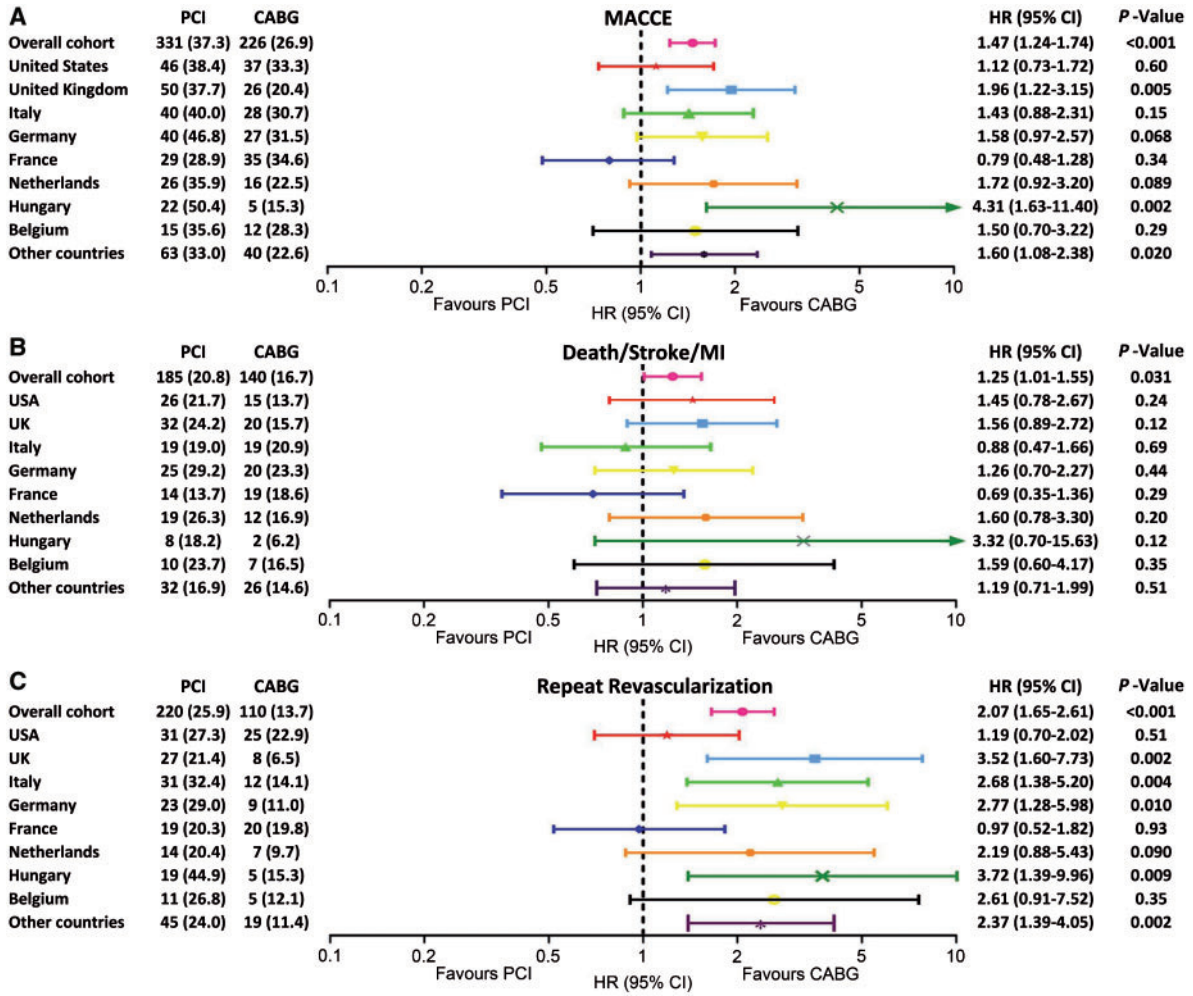

Figure 4: A graphical display of 5-year outcomes between investigating countries for MACCE (**A**), the composite safety end-point of death/stroke/MI (**B**) and repeat revascularization (**C**). Treatment-by-country interaction failed to reach statistical significance for MACCE ($P = 0.12$) and the composite safety end-point ($P = 0.38$), but there is significant interaction for repeat revascularization ($P = 0.045$). Abbreviations as in Fig. 1. Values are Kaplan–Meier rates with *P*-values from log-rank test. HR: hazard ratio.

had an impact on trial outcomes. Stratifying enrolment per country will strengthen the external validation of trial results.

Study limitations

Since the SYNTAX trial was designed to test the difference between PCI and CABG and not differences among countries, this *post hoc* analysis should be interpreted as hypothesis generating. However, exploration of clinical patterns by countries provides a better insight of the trial in order to investigate a possible geographical heterogeneity [1]. These analyses were restricted to specific countries based on the number of included patients and adverse events during 5-year of follow-up. Pooling data from countries with few participants into 1 group might be somewhat arbitrary and heterogeneity within this subgroup is likely [1]. Unmeasured factors such as the medical care delivery system, disease awareness on a population-based scale and patient culture might also play an important role beyond clinical and procedural characteristics [25]. In addition, another bias might be a lower threshold for repeat revascularization that may influence the results [15, 26].

CONCLUSIONS

Baseline characteristics, clinical practice, secondary prevention medication regimens and outcomes were different across countries in the SYNTAX trial. These data can be used to improve treatment strategies to reduce adverse events after myocardial revascularization in specific countries. It points to the fact that, in strategy trials like SYNTAX, the results are relevant to a definable group of patients in a particular clinical setting. Standardization of treatment strategies may help to improve the external validity of trial results and improve recommendation in guidelines.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: Keith D. Dawkins owns stock in and is a full-time employee of Boston Scientific. All other authors declare that they have no conflicts of interest.

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