Effect of Cerebrovascular and/or Peripheral Artery Disease With or Without Attainment of Lipid Goals on Long-Term Outcomes in Patients With Coronary Artery Disease

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Involvement of atherosclerosis in extracardiac vascular territories may identify coronary artery disease (CAD) patients at higher risk for adverse events. We investigated the long-term prognostic implications of polyvascular disease in patients with CAD, and further analyzed lipid goal attainment and its relation to patient outcomes. The study was a retrospective analysis of 10,297 patients who underwent coronary revascularization, categorized as having CAD alone (83.1%) or with multisite artery disease (MSAD) (16.9%) including cerebrovascular disease (CBVD) and/or peripheral artery disease (PAD). Incidence rates and hazard ratios (HR) for major adverse cardiovascular events (MACE) (myocardial infarction, ischemic stroke, or all-cause death) according to vascular territories involved, and in relation to most-recent lipid levels attained, were analyzed. Patients with MSAD were older with higher burden of co-morbidities. The rate of MACE (myocardial infarction, ischemic stroke, or all-cause death) and its individual components increased with the number of affected vascular beds. Adjusted HR (95% confidence interval) for MACE was 1.41 (1.24 to 1.59) in patients with CAD and CBVD, 1.46 (1.33 to 1.62) in CAD and PAD, and 1.69 (1.49 to 1.92) in those with CAD and CBVD and PAD, compared with CAD alone. Most-recent low-density lipoprotein cholesterol (LDL-C) levels <55 mg/dl and <70 mg/dl were attained by 21.8% and 44.6% of patients with CAD alone, in comparison to 22.7% and 43.3% in MSAD. Compared with patients with most-recent LDL-C > 100 mg/dl, attaining LDL-C < 70 mg/dl had an adjusted HR for MACE of 0.52 (0.47 to 0.57) in CAD only patients and 0.66 (0.57 to 0.78) in MSAD patients. In conclusion, the presence of CBVD and/or PAD in patients with CAD is associated with higher burden of co-morbidities and progressive increase in long-term MACE. More than half of CAD patients with or without MSAD do not achieve lipid goals, which are associated with a significantly lower risk for adverse events. **(Am J Cardiol 2020;128:28−34)**

Patients with coronary artery disease (CAD) may have multisite artery disease (MSAD) involving additional vascular beds, including cerebrovascular disease (CBVD) and/or peripheral artery disease (PAD).[1,2] A direct correlation exists between the number of arterial territories affected by atherosclerosis and the risk for future cardiovascular events.[3,4] However, most data originate from studies evaluating short-term outcomes after myocardial infarction,[5−7] or analyzing CAD patients with PAD but without the involvement of CBVD.[8−13] Patients with noncoronary atherosclerotic disease are often reported to be undertreated.[14−16] Similar to CAD, they benefit from treatments aimed at lowering low-density lipoprotein cholesterol (LDL-C) levels.[17−21] We aimed to investigate the characteristics and long-term prognostic implications of the presence of PAD and/or CBVD in patients with CAD who underwent revascularization, and further analyze lipid goal attainment and its relation to patient outcomes.

Methods

Retrospective analysis of patients who underwent coronary revascularization between the years 2000 and mid-2015 at a single center (Carmel Medical Centre, Haifa, Israel). The analysis was restricted to 10,297 consecutive patients who are members of the Clalit Health Services, for whom we had full access to outcomes data during follow-up. Patients were categorized as having CAD alone or MSAD defined as any additional vascular involvement including CBVD and/or PAD. CBVD was defined as prior stroke and/or carotid artery disease; PAD included atherosclerotic arterial disease of extremities and/or abdominal aortic aneurysm. Demographic data, risk factors, and co-morbidities were most often prospectively collected from patients' medical files at the time of coronary angiography. Data that were not originally collected were retrieved from computerized database of Clalit Health

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Services. Patients were classified as presenting with or without acute coronary syndrome. The primary study end point was major adverse cardiovascular events (MACE), defined as a composite of myocardial infarction, ischemic stroke, or death. The cause of death was not consistently available and therefore we included all-cause and not cardiovascular death. Data on myocardial infarction and ischemic stroke during follow-up were retrieved from the hospitalizations database and were defined as primary discharge diagnosis with ICD-9 code (410.xx) for myocardial infarction and ICD-9 codes (433.x1, 434.x1, 436) for ischemic stroke. Data on vital status were retrieved from the Ministry of Interior. Cohort participants were followed up until reaching the first occurrence of study outcomes (MACE), maximum 10 years of follow-up, or end of follow-up at November 2018, whichever came first.

Most-recent plasma lipid levels of LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and total cholesterol (TC) were documented in each patient. Most-recent levels were defined as those closest to the end of follow-up. Patients in whom data on lipid levels were absent in the period of 2 years before the end of follow-up (n = 381), were excluded from lipid analysis. The study database was approved by Carmel Medical Center Ethics Committee with waiving of the need for individual patient consent due to the retrospective nature of the study.

Descriptive data are presented according to classification of patients with CAD alone or MSAD, categorized as CAD + CBVD, CAD + PAD or CAD + CBVD + PAD. Continuous data are reported as means and standard deviation or median (interquartile range) and categorical variables as numbers and percentages. One-way ANOVA test was used to compare continuous variables and chi-square to compare categorical variables. For each vascular territory involved the number of events and incidence rates per 100 person-years were calculated for the primary composite end point and its individual components. Cox proportional hazard regression models were used to assess the association between vascular territories involved and time to each end point, and to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CI), with the group of patients with "CAD alone" serving as the reference category. Kaplan-Meier curves were used to estimate the 10 years cumulative incidence of MACE according to the vascular territories, with comparison between curves performed using the log-rank test.

Attainment rates of customary LDL-C lipid goals were analyzed. Cox proportional hazard regression models were used to estimate the adjusted HRs for MACE associated with each 10 mg/dl increase in LDL-C, non-HDL-C, and TC/HDL-C ratio, as well as a decrease of 3 mg/dl in HDL-C levels. In addition, most-recent LDL-C levels were stratified into 3 sequential subgroups of clinically relevant target values: LDL-C < 70 mg/dl, between 70 and 100 mg/dl, and >100 mg/dl and its association with MACE were assessed, using LDL-C > 100 mg as reference category. Multivariable adjustment included adjustment to presentation with or without acute coronary syndrome. The associations of the different attained lipid levels with MACE were assessed in patients with CAD alone and in patients with MSAD. An interaction between LDL-C categories and the extent of vascular involvement (CAD only vs MSAD) was tested by introducing a cross product of the 2 variables in the multivariable model. Study results were considered statistically significant when the 2-sided p value was <0.05. SPSS

Table 1
Baseline patients' characteristics, according to vascular territories involved

Group:	Overall	CAD alone	Multisite artery disease	CAD + CBVD	CAD + PAD	CAD + CBVD + PAD
No. of pts.	10297	8557 (83.1%)	1740	511	812	417
Variable	(100%)		(16.9%)	(5.0%)	(7.9%)	(4.0%)
Age (years)	65±12	64±12	70±10	71±10	70±12	72±9
Men	7703 (75%)	6416 (75%)	1287 (74%)	355 (70%)	631 (78%)	301 (72%)
Body mass index (kg/m^2)	28.0±4.5	28.1±4.4	27.3±4.4	27.2±4.2	27.4±4.5	27.2±4.3
Hypertension	7402 (72%)	5942 (69%)	1460 (84%)	434 (85%)	653 (80%)	337 (89%)
Hyperlipidemia*	7346 (71%)	5979 (70%)	1367 (79%)	390 (76%)	634 (78%)	343 (82%)
Active smoker	2213 (21%)	1891 (22%)	322 (19%)	78 (15%)	171 (21%)	73 (18%)
Past smoker	2055 (20%)	1646 (19%)	409 (24%)	104 (20%)	204 (25%)	101 (24%)
Any smoker	4268 (41%)	3537 (41%)	731 (42%)	182 (36%)	375 (46%)	174 (42%)
Diabetes mellitus	3934 (38%)	3001 (35%)	933 (54%)	260 (51%)	442 (54%)	231 (55%)
eGFR < 60 (mL/min/1.73m^2)	2338 (23%)	1685 (20%)	653 (37%)	183 (36%)	288 (36%)	182 (44%)
Prior MI	6381 (62%)	5128 (60%)	1253 (72%)	348 (68%)	588 (72%)	317 (76%)
Prior CABG	1430 (14%)	1049 (12%)	381 (22%)	91 (18%)	164 (20%)	126 (30%)
Coronary presentation						
Non-ACS	3492 (34%)	2967 (35%)	525 (30%)	178 (35%)	229 (28%)	118 (28%)
UAP/NSTEMI	5335 (52%)	4298 (50%)	1037 (60%)	286 (56%)	494 (61%)	257 (62%)
STEMI	1470 (14%)	1292 (15%)	178 (10%)	47 (9%)	89 (11%)	42 (10%)

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CBVD = cerebrovascular disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; NSTEMI = non ST-segment elevation myocardial infarction; PAD = peripheral artery disease; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

Variables are presented as number (percent) or mean ± SD.

p <0.05 for all variable comparisons between vascular groups (except gender).

Multisite artery disease includes CAD with all combinations of CBVD and/or PAD.

* Diagnosis was given by primary care physicians according to clinical judgment and customary definitions.

statistical software version 20.0 and MEDCALC version 16.8.4 were used to perform all statistical analyses.

Results

A total of 10,297 patients underwent coronary revascularization during the study period. CAD alone was diagnosed in 83.1% and MSAD in 16.9%. Median follow-up was 101 months (interquartile range 62 to 145 months). Baseline patients' characteristics are presented in Table 1, classified according to the vascular territories involved. Compared with CAD only patients, those with MSAD were older, with higher rates of risk factors and co-morbidities including hypertension, hyperlipidemia, diabetes mellitus, renal dysfunction, and previous cardiac surgery, but similar rates of smoking. Subgroup analysis shows that among MSAD patients, smoking was more prevalent in those with PAD.

Incidence density rate of MACE and its individual components increased according to the number of vascular territories involved, from patients with CAD only to patients with 1 additional vascular territory (CBVD or PAD) to those with 2 additional vascular territories (CBVD and PAD; Table 2). A graded increment in the HRs for both MACE and the individual end points was observed with the rise in the number of vascular territories involved. Compared with patients with CAD alone (reference group), the multivariable adjusted HRs (95% CI) for MACE were 1.41 (1.24 to 0.159) in patients with CAD + CBVD, 1.46 (1.33 to 1.62) in CAD + PAD, and 1.69 (1.49 to 1.92) in those with CAD + CBVD + PAD (Table 2). Kaplan-Meier plot displaying the distribution of time to MACE stratified by the vascular territories involved is presented in Figure 1. During long-term follow-up, additional 778 patients with CAD were diagnosed with PAD, 492 CBVD, and 264 with both PAD + CBVD. Accordingly, at the end of follow-up, an additional 14.9% of the overall study population joined the MSAD group.

Most-recent LDL-C in study population (n = 9,916) was 81 ± 35 mg/dl. Overall, 2,177 patients (22%) achieved LDL-C level < 55 mg/dl, 4,400 (44.4%) achieved LDL-C level < 70 mg/dl, and 7,608 (76.7%) LDL-C < 100 mg/dl. Attainment rates of LDL-C goals were similar across the vascular territories involved (Figure 2). Compared with patients attaining LDL-C levels > 100 mg/dl, the multivariable adjusted HR (95% CI) for long-term MACE was 0.771 (0.717 to 0.828), p <0.001 in patients with LDL-C 70 to 100 mg/dl and 0.548 (0.509 to 0.590), p <0.001 in those with LDL-C < 70 mg/dl. This trend was observed in both patient

Table 2
Descriptive statistics, incidence rates, and hazard ratios for the association between vascular territories involved and major adverse cardiovascular events

Group outcome	CAD alone	CAD + CBVD	CAD + PAD	CAD + CBVD + PAD
Myocardial infarction				
No. of events/patients	1206/8557	104/511	168/812	93/417
Incidence rate per 100 person-years	2.00	3.63	3.61	4.48
Hazard ratio (95% CI)				
Model 1	1 (Ref.)	1.73 (1.42-2.12)		2.07 (1.68-2.56)
			1.72 (1.47-2.03)	
Model 2		1.39 (1.18-1.64)	1.50 (1.23-1.84)	1.59 (1.28-1.97)
	1 (Ref.)			
Ischemic stroke				
No. of events/patients	294/8557	29/511	53/812	25/417
Incidence rate per 100 person-years	0.46	0.92	1.07	1.10
Hazard ratio (95% CI)				
Model 1	1 (Ref.)	1.77 (1.21-2.61)	2.17 (1.61-2.92)	2.12 (1.41-3.21)
Model 2		1.57 (1.07-2.31)	1.82 (1.35-2.45)	1.80 (1.19-2.72)
	1 (Ref.)			
All-cause death				
No. of events/patients	1908/8557	221/511	388/812	234/417
Incidence rate per 100 person-years	2.93	6.79	7.59	9.94
Hazard ratio (95% CI)				
Model 1	1 (Ref.)	1.57 (1.37-1.81)	1.90 (1.71-2.13)	2.21 (1.93-2.54)
Model 2		1.44 (1.25-1.66)	1.71 (1.53-1.90)	1.95 (1.69-2.24)
	1 (Ref.)			
MACE				
No. of events/patients	2940/8557	279/511	473/812	271/417
Incidence rate per 100 person-years	4.94	10.00	10.45	13.37
Hazard ratio (95% CI)				
Model 1	1 (Ref.)	1.54 (1.36-1.74)	1.69 (1.53-1.86)	1.97 (1.74-2.23)
Model 2		1.41 (1.24-1.59)	1.46 (1.33-1.62)	1.69 (1.49-1.92)
	1 (Ref.)			

CAD = coronary artery disease; CBVD = cerebrovascular disease; CI = confidence interval; MACE = major adverse cardiovascular events; PAD = peripheral artery disease.

Model 1: adjusted for age and gender; **Model 2:** adjusted for age, gender, hypertension, hyperlipidemia, diabetes, chronic kidney disease, obesity, smoking, and presentation with acute coronary syndrome.

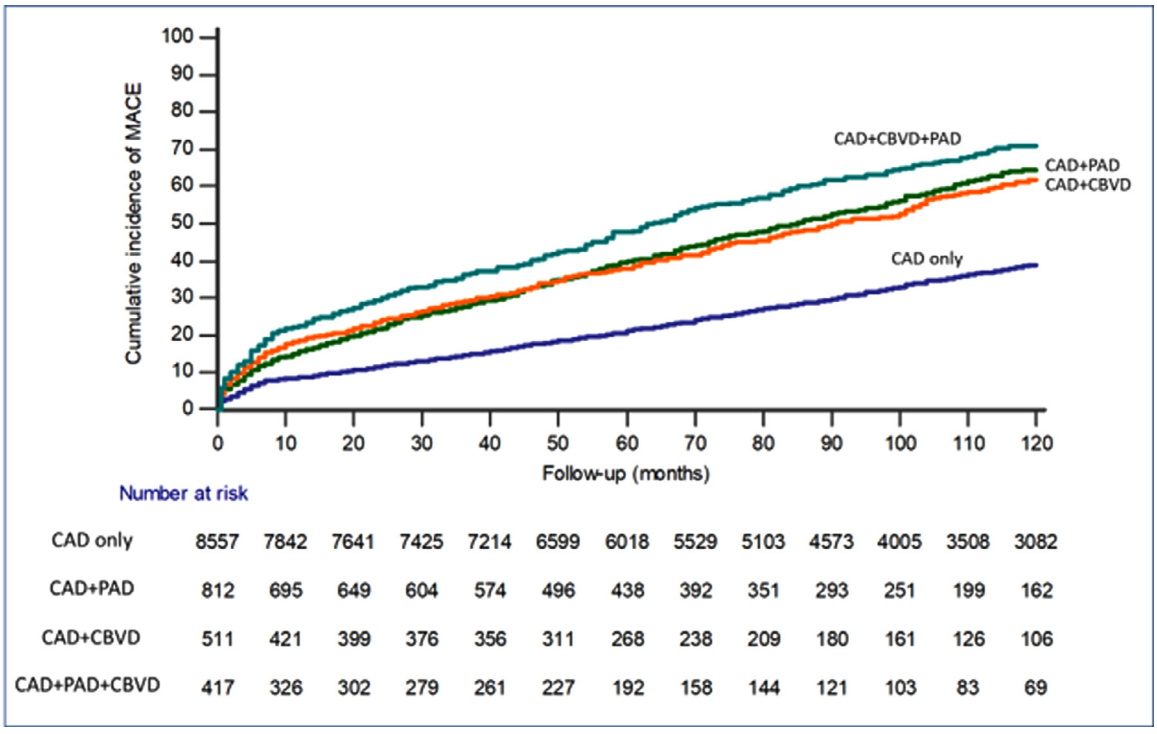
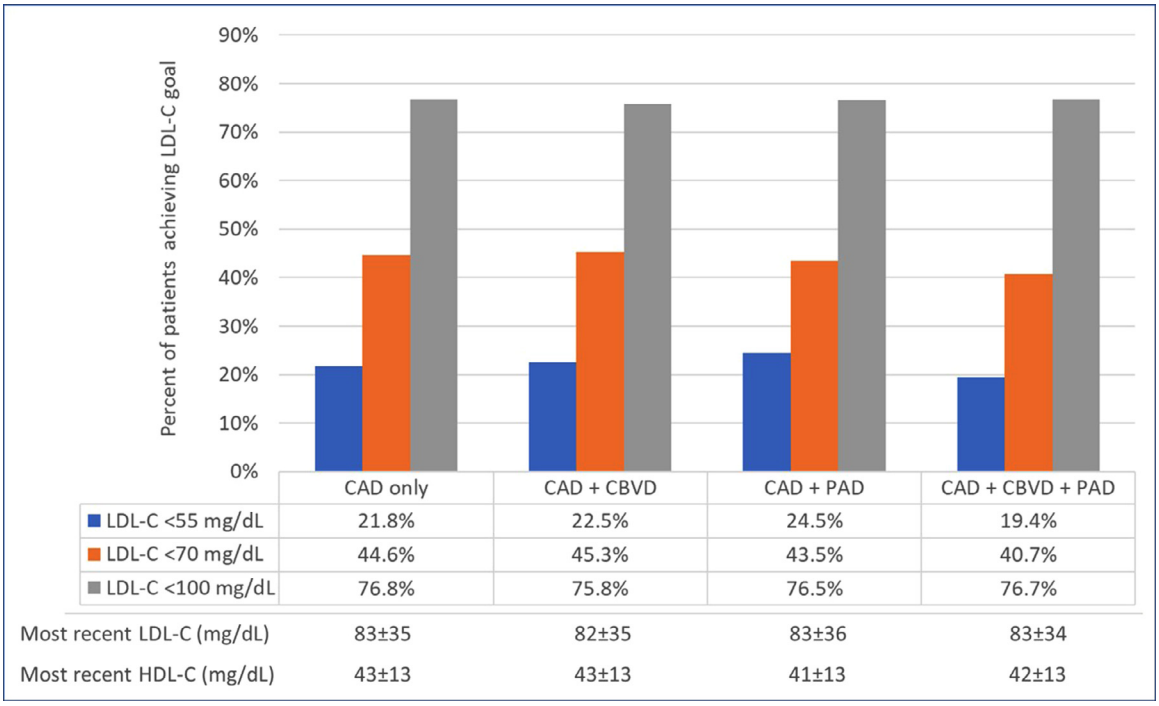


Figure 1. Cumulative 10-year incidence of MACE, according to the vascular territories involved.
CAD = coronary artery disease; CBVD = cerebrovascular disease; CI = confidence interval; MACE = major adverse cardiovascular events; PAD = peripheral artery disease.



	CAD only	CAD + CBVD	CAD + PAD	CAD + CBVD + PAD
LDL-C <55 mg/dL	21.8%	22.5%	24.5%	19.4%
LDL-C <70 mg/dL	44.6%	45.3%	43.5%	40.7%
LDL-C <100 mg/dL	76.8%	75.8%	76.5%	76.7%
Most recent LDL-C (mg/dL)	83±35	82±35	83±36	83±34
Most recent HDL-C (mg/dL)	43±13	43±13	41±13	42±13

Figure 2. Rate of patients achieving LDL-C goals, according to vascular territories involved.
CAD = coronary artery disease; CBVD = cerebrovascular disease; LDL-C = low-density lipoprotein cholesterol; PAD = peripheral artery disease.
Most recent lipid levels are presented as mean ± standard deviation.

subgroups with CAD only and MSAD patients (p-for-trend <0.0001; Table 3). A significant interaction was found between LDL-C categories and the extent of vascular involvement (CAD only vs MASD). Compared with LDL-C > 100 mg/dl, attaining LDL-C < 70 mg/dl was associated with a greater decrease in the risk for MACE among patients with CAD only than in patients with MSAD (p for interaction 0.021), suggesting that

Table 3
Crude and adjusted hazards ratios for MACE associated with most-recent LDL-C attained, according to vascular site involved

Lipid groups (mg/dL)		Unadjusted		Age and gender adjustment		Multivariable adjustment*	
		HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Overall population							
LDL-C	<70	0.521 (0.485-0.561)	<0.001	0.563 (0.523-0.606)	<0.001	0.548 (0.509-0.590)	<0.001
	70-100	0.727 (0.677-0.781)	<0.001	0.765 (0.712-0.822)	<0.001	0.771 (0.717-0.828)	<0.001
	>100	Reference		Reference		Reference	
CAD only							
LDL-C	<70	0.492 (0.453-0.535)	<0.001	0.526 (0.484-0.573)	<0.001	0.519 (0.477-0.566)	<0.001
	70-100	0.709 (0.653-0.770)	<0.001	0.747 (0.688-0.811)	<0.001	0.754 (0.694-0.818)	<0.001
	>100	Reference		Reference		Reference	
Multisite artery disease							
LDL-C	<70	0.605 (0.522-0.702)	<0.001	0.661 (0.570-0.767)	<0.001	0.631 (0.543-0.734)	<0.001
	70-100	0.771 (0.665-0.894)	0.001	0.796 (0.687-0.923)	0.003	0.815 (0.702-0.946)	0.007
	>100	Reference		Reference		Reference	

CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol.
P for trend in multivariate analyses: LDL-C, p <0.0001.
* Covariates included in the multivariable adjustment: age, gender, hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking, chronic kidney disease, presentation with acute coronary syndrome.

lowering LDL-C to level <70 mg/dl has a greater effect in decreasing the risk of MACE in CAD only patients than in other atherosclerotic disease. In addition, a continuous increase in LDL-C, non-HDL-C, TC/HDL-C as well as decrease in HDL-C were associated with a statistically significant increment in the adjusted HR for MACE (Table 4).

Table 4
Continuous association between most-recent lipid levels and hazard ratios for MACE

Lipid groups	Hazard ratio* (95% CI) for MACE	p Value
Coronary artery disease only		
For each 10 mg/dL increase in LDL-C levels	1.070 (1.061-1.080)	<0.0001
For each 3 mg/dL decrease in HDL-C levels	1.057 (1.049-1.066)	<0.0001
For each 10 mg/dL increase in Non-HDL-C levels	1.064 (1.057-1.072)	<0.0001
For each 0.4 mg/dL increase in TC/HDL-C levels	1.038 (1.034-1.042)	<0.0001
Multisite artery disease		
For each 10 mg/dL increase in LDL-C levels	1.039 (1.023-1.055)	<0.0001
For each 3 mg/dL decrease in HDL-C levels	1.039 (1.025-1.053)	<0.0001
For each 10 mg/dL increase in non-HDL-C levels	1.041 (1.028-1.053)	<0.0001
For each 0.4 mg/dL increase in TC/HDL-C levels	1.010 (1.005-1.014)	<0.0001

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular events; TC = total cholesterol.
* Age and gender adjusted.

Discussion

In the current study, the presence of CBVD or PAD in patients with CAD was found to be associated with an increase in long-term MACE that was more prominent when both conditions existed. Attainment of LDL-C treatment goals was related to lower risk for adverse events, which appeared to result in a greater benefit for patients with CAD only compared with MSAD. Nevertheless, more than half of CAD patients with or without MSAD did not achieve lipid goals.

MSAD patients were older, with more significant burden of co-morbidities. Similar to previous observations, smoking was more common in CAD patients with concomitant PAD, whereas hypertension was more prevalent in those with CBVD.[2,22] It seems that MSAD patients suffer from more advanced coronary disease, as reflected by higher rates of cardiac surgery performed compared with CAD only patients. CAD patients with MSAD had significantly higher risk for long-term MACE and each of its individual components compared with patients with CAD alone. These differences in prognosis appeared regardless of the additional vascular site involved, were prominent as early as the first year into follow-up, and proceeded for the long term. Importantly, within the MSAD group, we found that a 3-site disease bares poorer outcome than that of a 2-site disease. The seminal global REACH registry has highlighted the role of noncoronary atherosclerosis, demonstrating that cardiovascular event rates increase substantially with the number of atherosclerotic disease locations.[4,5,23] Multiple observations have since emphasized the growing and often unrecognized burden of vascular disease associated with multifocal atherosclerosis.[22] Nevertheless, limited data exist regarding the longer term outcomes of CAD patients with both CBVD and

PAD involvement.[12,13] Our results strengthen previous observations, with a significantly longer term median follow-up period of 8.5 years, concluding that in patients with CAD prognosis worsens progressively and continuously with the number of affected arterial vascular beds.

Although all patients in this study were diagnosed with CAD, it appears that any concomitant noncardiac vascular involvement significantly increased the risk for subsequent myocardial infarction. Interestingly, the relative increase in risk for all the individual components of MACE was somewhat higher when CAD was accompanied with PAD, rather than with CBVD, in the fully adjusted model. This may stem from the more specific and well-studied treatments for CBVD, as well as the awareness for the risk of stroke in patients in whom CBVD has already been established. It was also suggested that PAD patients are both underdiagnosed and undertreated, and are less provided with optimal prophylactic pharmacological treatments.[16,24]

Less than half of the patients had attained LDL-C < 70 mg/dl, and less than a quarter <55 mg/dl, regardless of the vascular site involved. These findings remain a source of concern, in light of recent guidelines[25] advising further reduction of LDL-C target levels to less than 55 mg/dl in patients with atherosclerotic cardiovascular disease, and even under 40 mg/dl in those with recurrent events, which is more expected to occur in CAD patients with MSAD.

It was previously shown that patients with than without prior PAD receive less aggressive treatment with proven cardiac medications, including statins.[11] Even nowadays there is a lack of improvement in care for PAD patients that is explained by underuse of secondary prevention medications.[15] Nevertheless, the similar attainment rates of LDL-C goals between vascular groups currently observed, might be related to the fact that all patients with MSAD had concomitant CAD and therefore were anticipated to have better risk factor control.[26]

In both groups, CAD alone or CAD with MSAD, achieving lower LDL-C levels correlated with a reduction in risk for long-term MACE. However, attaining LDL-C levels under 70 mg/dl appeared to result in a greater benefit for patients with CAD only, compared with MSAD. This may suggest that patients with MSAD require a more aggressive approach and even lower lipid target levels than those with CAD, in order to reach a similar protective effect. In this context, the Odyssey Outcomes and Fourier Trials demonstrated both a higher risk and a more pronounced reduction in MACE in patients with MSAD and/or PAD, when attaining significantly lower LDL-C levels (30 to 50 mg/dl) than were customary before, by adding PCSK9 monoclonal antibodies to high-intensity statin therapy.[19–21] Previous studies have suggested that focusing on LDL-C only in terms of atherosclerotic risk prediction may underestimate the risk of PAD, and that additional dyslipidemia parameters such as non-HDL-C and TC/HDL-C may be stronger risk predictors in this population.[27]

The present study has several limitations. Data were acquired from patients presenting to coronary revascularization, and the conclusions are therefore limited only to the population in question, though we did adjust the data to the presence of acute coronary syndromes, thus controlling for the acuity of coronary presentation. Importantly, diagnosis of PAD and CBVD was based on electronic database coding, and therefore there may have been subjects with subclinical or undiagnosed MSAD that were misclassified as CAD only; however, such misclassification is likely to be nondifferential and expected to bias the results toward the null. We also did not have data on the severity of the noncoronary atherosclerotic disease. In addition, misclassification bias may have occurred when assigning patients to categories of lipid cutoffs based on single sampling of laboratory values at different timepoints.

In conclusion, the presence of CBVD and/or PAD in patients with CAD is associated with higher burden of comorbidities and a progressive increase in long-term adverse cardiovascular outcomes and mortality that is correlated with the number of vascular sites involved. More than half of CAD patients with or without MSAD do not achieve LDL-C treatment goal, even though it appears to be associated with a significantly lower risk for MACE. These results underscore the importance of recognizing the accumulating risk associated with noncoronary atherosclerotic disease in patients with CAD who underwent revascularization, due to its implications for risk prediction and allocation of intensive and preventive medical treatments.

Disclosures

The authors have no conflicts of interest to disclose.

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