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Impact of Low Ankle-Brachial Index on the Risk of Recurrent Vascular Events

Insights From the OPTIC Registry

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Background and Purpose—Low ankle-brachial index (ABI) identifies a stroke subgroup with high risk of recurrent stroke, cardiovascular events, and death. However, limited data exist on the relationship between low ABI and stroke in low and middle-income countries. Therefore, we evaluated the prevalence of ABI ≤0.90 (which is diagnostic of peripheral artery disease) in nonembolic stroke patients or transient ischemic attack and assessed the correlation of low ABI with stroke risk, factors, and recurrent vascular events and death.

Methods—Patients ≥45 years with acute transient ischemic attack or minor ischemic strokes were recruited consecutively from over 17 low-income and middle-income countries (Latin America [1543 patients], Middle East [1041 patients], North Africa [834 patients], and South Africa [217 patients]). The ABI measurement was performed at a single visit. Stroke recurrence and risk of new vascular events were assessed after 24 months of follow-up.

Results—Among 3487 enrolled patients, abnormal ABI (<0.9) was present in 22.3 %. Patients with an ABI of ≤0.9 were more likely (P<0.05) to be male, older, and have a history of peripheral artery disease, hypertension, and diabetes mellitus. During 2-year follow-up, the rate of major cardiovascular event was higher in patients with ABI <0.9 than those with ABI ≥0.9 (Kaplan-Meier estimates, 22.5%; 95% CI, 19.6–25.8 versus 13.7%; 21.4–15.1; P<0.001), and when ABI was categorized into 4 groups (≤0.6; 95% CI, 0.6–0.9; 0.9–1; 1–1.4), the rate of major cardiovascular event was higher in those with ABI ≤0.6 than the other groups (Kaplan-Meier estimates, 32.6%; 95% CI, 21.0–48.3 for ABI≤0.6 versus 21.7%; 95% CI, 18.8–25.0 for ABI 0.6–0.9 versus 14.3%; 95% CI, 12.4–16.6 for ABI 0.9–1 versus 13.3%; 95% CI, 11.6–15.2 for ABI 1–1.4; P<0.001).

Conclusions—Among patients with nonembolic ischemic stroke or transient ischemic attack, those with low ABI had a higher rate of vascular events and death in this population. Screening for ABI in stroke patients may help identify patients at high risk of future events. **(*Stroke*. 2019;50:853-858. DOI: 10.1161/STROKEAHA.118.022180.)**

Key Words: ankle-brachial index ■ atherosclerosis ■ hypertension ■ prevalence ■ risk factors

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Ankle-brachial index (ABI), defined as the ratio between systolic blood pressures measured at the ankle and arm of a patient in the supine position, is a reliable, noninvasive, and inexpensive tool to evaluate patients with known or suspected lower extremity peripheral artery disease (PAD).[1] In addition, the ABI is useful for identifying high-risk patients who might have no symptoms related to PAD.[2] Low ABI is also a highly sensitive marker of systemic atherosclerosis[3] and is a strong, independent predictor of fatal and nonfatal cardiovascular events.[4,5] However, it remains unclear whether ABI is a useful tool for assessing recurrent stroke risk. Some studies have shown that decreased ABI is associated with increased recurrent stroke risk[6,7] and require aggressive optimized vascular risk-reduction strategies, whereas others have not.[8,9] Although the association between low socioeconomic status and ischemic stroke is well established,[10] there are few studies

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that have examined the relationship between socioeconomic status and PAD in nonembolic stroke patients especially in low- and middle-income countries.[11–13]

The OPTIC registry (Outcomes in Patients With TIA and Cerebrovascular Disease) provides the opportunity to study the association between PAD, socioeconomic status, and stroke recurrence in low- and middle-income countries. In this study, we examined the association between low ABI and the risk of stroke, myocardial infarction, or death in patients with ischemic stroke or transient ischemic attack (TIA). We also examined whether low ABI is associated with socioeconomic factors.

Methods

The OPTIC registry database is handled by an academic group at Bichat Stroke Center (Paris Diderot, Sorbonne University). The data that support the findings of this study are available from the author Dr Amarenco on reasonable request.

The OPTIC Registry is a large international observational registry of nonembolic stroke patients recruited to the registry from over 17 low and middle-income countries across the regions of Latin America (Brazil, Chile, Colombia, Dominican Republic, Ecuador, Mexico, Peru, Venezuela), Middle East (Egypt, Iran, Jordan, Lebanon, Saudi Arabia), North Africa (Algeria, Morocco, Tunisia), and South Africa.

The methods and design of OPTIC study have been described elsewhere in greater detail including baseline description of the population and collection of follow-up data.[14]

Briefly, from January 2007 for a period of 1 year, consecutive patients 45 years and older, with TIA within the last 2 weeks, or minor ischemic stroke (National Institutes of Health Stroke Scale ≤3) of less than 24 hours of duration, or first-ever ischemic stroke (modified Rankin Scale score ≤4) of <6 months confirmed by imaging were enrolled in this study.

Patients with any stroke defined by category 3 in the TOAST classification (Trial of ORG 10 172 in Acute Stroke Treatment; stroke associated with cardiac source of embolism),[15] or if they were already in a clinical trial, or those who might have difficulty returning for a follow-up visit were excluded from enrollment.

The study was conducted according to the principles of the Declaration of Helsinki (Edinburgh Amendment, 2000), and signed informed consent was obtained for all patients.

Data Collected

Data were collected centrally via the use of a standardized international case report form, which was completed at the study visit. Patients were followed every 6±1 month during the 2-year follow-up for major adverse vascular events, medication use, and for any change in employment status.

Risk factors, such as hypertension, diabetes mellitus (type 1 or 2), and dyslipidemia were defined by the use of medications for these conditions at hospital discharge or at the time of study enrollment. The data for baseline information on smoking status, current alcohol intake, and physical activity were collected.

Education level, housing, living conditions, employment status, and health insurance coverage were used as indicators of socioeconomic status.

The ABI was measured at baseline with the patients in the supine position according to standard clinical guidelines.[16] The ABI was calculated by dividing the highest systolic blood pressure at the ankles by the highest systolic pressure of the upper arms (highest of the right and left sides). The lower of the ABI values calculated for the left and right ankles were used for analyses. A detailed instruction on ABI measurement was included in the case report form, and all participating centers received an Omron automatic blood pressure monitor. In this study, only patients with available ABI measurement at baseline were analyzed. Patients were classified into 2 ABI categories: low when at least 1 leg had a value <0.9 versus normal when both legs had values 0.9–1.4.

Statistical Analysis

Quantitative variables are presented as mean±SD in case of normal distribution or median and interquartile range otherwise. Categorical variables are presented as frequency and (percentages). Normal distribution was assessed graphically and using Shapiro-Wilks test.

Patients were classified in 2 groups according to their ABI values (ABI <0.9 versus ABI ≥0.9). Baseline characteristics and socioeconomic profiles were compared between the 2 groups using Student test for quantitative variables and χ^2 test for categorical variables. Because of skewed distributions for triglycerides, creatinine, and glucose, Student test was made using log-transform values.

Cumulative events rate were estimated using Kaplan-Meier estimates. Two years events rate between the 2 groups was compared using Cox proportional hazard method adjusted on age and sex (model 1). Events that occurred after 2 years were not considered. Effect size measures were assessed with hazard ratios with their 95% CIs using ABI ≥0.9 as reference group. The proportional hazard assumptions were checked using the log-log survival plots and by introducing a time-dependent variable into models.

For a given end point, deaths that were not included in the end point were treated as censoring events.

All variables independently associated with ABI (P<0.1) at baseline were included in multivariate analysis. After backward selection, age, sex, PAD, diabetes mellitus, current smoking, coronary artery disease, body mass index, and systolic blood pressure were included in a model (model 2).

The level of significance was set at P<0.05.

Data handling and statistical analyses were performed with SAS statistical software 9.3 (SAS Institute, Cary, NC).

Results

Of the 3487 patients enrolled in the Optic registry, 93 had missing data for ABI. Among the remaining 3394 patients, 2,637 (77.7%) had ABI ≥0.9 and 757 (22.3%) <0.9.

Baseline Characteristics

Table 1 shows the main baseline demographic and clinical history characteristics of patients. The biggest difference was observed for PAD. Patients with ABI <0.9 had a higher prevalence of symptomatic PAD (15.9% versus 5.1%; P<0.0001). There were also significant differences in congestive heart failure, coronary artery disease, diabetes mellitus, hypertension, current smoking, and socioeconomic characteristics.

Patients with ABI <0.9 lived more in rural area (P=0.02), were more often unemployed (P<0.001), had less health insurance coverage (P=0.03), and had a lower educational level than those with ABI ≥0.9 (Table 2).

Age, sex, medical history of congestive heart failure, PAD, coronary artery disease, diabetes mellitus, hypertension, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL (low-density lipoprotein)-cholesterol, glucose, and socioeconomic factors like living in rural area, employment status, no health insurance coverage, and low educational level were included in multivariable analysis. Age (P=0.008), sex (P=0.006), PAD (P<0.001), diabetes mellitus (P=0.008), smoking status (P=0.012), coronary artery disease (P=0.031), body mass index (P=0.002), and systolic blood pressure (P<0.001) were independently associated with ABI <0.9. There were no significant differences among the treatments between low ABI and ABI >0.9. In fact, both groups were well treated during the follow-up period (Table I in the online-only Data Supplement).

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Table 1. Baseline Characteristics of Patients According to ABI Level

	Optic Registry		
	ABI≥0.9 (n=2637)	ABI<0.9 (n=757)	*P* Value
Age, y, mean±SD	64±11	67±11	<0.001
Men	1535 (58.2)	385(50.9)	<0.001
Medical history			
Congestive heart failure	79 (3.0)	37 (5.0)	0.01
Coronary artery disease	305 (11.7)	129 (17.2)	<0.001
Diabetes mellitus	901 (34.2)	331 (43.7)	<0.001
Dyslipidemia	1933 (73.3)	561 (74.1)	0.66
Hypertension	2144 (81.3)	661 (87.3)	<0.001
Peripheral artery disease	129 (5.1)	114 (15.9)	<0.001
TIA	597 (23.2)	171 (23.0)	0.92
Current smoking	523 (20.4)	183 (25.1)	0.006
Presentation characteristics			
BMI, kg/m^2, mean±SD	27.6±4.9	27.0±4.6	0.004
Systolic BP, mm Hg, mean±SD	142±24	152±26	<0.001
Diastolic BP, mm Hg, mean±SD	84±13	86±14	0.004
Laboratory findings			
Total cholesterol, mg/dL, mean±SD	195±51	205±57	<0.001
LDL-cholesterol, mg/dL, mean±SD	120±41	128±44	0.001
HDL-cholesterol, mg/dL, mean±SD	45±17	45±19	0.17
Triglycerides, mg/dL, median (IQR)*	138 (100–195)	143 (106–208)	0.12
Triglycerides >200 mg/dL	411 (23.3)	129 (25.9)	0.23
Creatinine, mg/dL, median (IQR)*	0.99 (0.8–1.20)	0.92 (0.8–1.20)	0.47
Glucose, mg/dL, median (IQR)*	109.0 (94.0–150.0)	110.0 (95.0–164.0)	0.09

Data are number (%) unless otherwise indicated. Percentage is based on available data. ABI indicates ankle-brachial index; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IQR, interquartile range; and TIA, transient ischemic attack.

*Logarithmic values.

Table 2. Socioeconomic Profile of Patients According to ABI Level

	Optic Registry		
	ABI≥0.9 (n=2637)	ABI<0.9 (n=757)	*P* Value
Living alone	210 (8.0)	71 (9.5)	0.19
Living in rural area	318 (12.2)	114 (15.4)	0.025
Living in fully serviced house/ apartment	2405 (92.8)	680 (91.4)	0.22
Unemployed*	803 (46.8)	258 (56.1)	<0.001
No health insurance coverage	580 (22.0)	194 (25.7)	0.035
Low educational level†	392 (26.3)	87 (21.3)	0.038

Data are number (%). ABI indicates ankle-brachial index.

*Excluding social pensioner on disability grand or old-age pensioner.

†The threshold was <2 y of schooling.

Two-Year Vascular Event Rates

During the 2-year follow-up, 504 patients had at least 1 major cardiovascular event (fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, or cardiovascular death). The rate of major cardiovascular event was higher in those with ABI <0.9 than those with ABI ≥0.9 (Kaplan-Meier estimates, 22.5%; 95% CI, 19.6–25.8 versus 13.7%; 95% CI, 21.4-15.1; *P*<0.001). When adjusted on age, sex, PAD, diabetes mellitus, current smoking, coronary artery disease, body mass index, and systolic blood pressure, the results remained significant (fully adjusted hazard ratio 1.62; 95% CI, 1.30–2.03; *P* value <0.001; Table 3).

Two-Year Vascular Event Rates According to ABI in 4 Groups

Two-year vascular event rates were categorized according to ABI in 4 groups (≤0.6; 95% CI, 0.6–0.9; 0.9–1; 1–1.4). Baseline characteristics according to ABI in 4 groups are described in Table 4. The rate of major cardiovascular event was higher in those with ABI ≤0.6 than the other groups (Kaplan-Meier estimates, 32.6%; 95% CI, 21.0–48.3 for ABI ≤0.6 versus 21.7%; 95% CI, 18.8–25.0 for ABI 0.6–0.9 versus 14.3%; 95% CI, 12.4–16.6 for ABI 0.9–1 versus 13.3%; 95% CI, 11.6–15.2 for ABI 1–1.4; *P*<0.001; Figure).

Discussion

In the present study, low ABI was detectable in 1 out of 5 patients with acute cerebral ischemia or TIA. Coronary artery disease, diabetes mellitus, increasing age, hypertension, and PAD were associated with the presence of ABI <0.9. Finally, low ABI was associated with a higher risk of major adverse vascular events (cardiovascular death, myocardial infarction, and stroke).

These findings underscore the high prevalence of low ABI in patients with cerebrovascular disease. This prevalence was in concordance with previous studies that reported low ABI prevalence (9%–57%) in patients with ischemic stroke.[17] Interestingly, the prevalence of ABI <0.9 (22%) in this study was lower compared with rates ranging from 30% to 51% as previously reported in Western countries. For example, the prevalence of ABI <0.9 was 34% among 755 patients with stroke or TIA in an Italian study,[18] and 51% among 852 patients with stroke or TIA admitted to 85 stroke units across Germany.[19] This higher prevalence reflected a higher mean age in these studies, geographic and genetic factors,[20] as well as different methodological aspects.[21,22]

The incidence of major adverse vascular event (cardiovascular death, myocardial infarction, and stroke) in this study was markedly higher when the ABI was low (ABI <0.9). An important finding is that, after additional adjustment for a variety of risk factors an ABI <0.9 has a strong association with stroke mortality and stroke recurrence during the follow-up period. Another important finding from

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Table 3. Two-Year Events According to ABI Level

	Events (%)*		*P* Value	Model 1, HR (95%CI)	*P* Value	Model 2, HR (95%CI)	*P* Value
	ABI≥0.9	ABI<0.9					
	N=2637	N=757					
CV death, stroke, MI	343 (13.5)	161 (22.5)	<0.001	1.76 (1.43–2.15)	<0.001	1.62 (1.30–2.03)	<0.001
Fatal or nonfatal MI	72 (3.0)	42 (6.1)	<0.001	2.25 (1.50–3.39)	<0.001	1.63 (1.03–2.60)	0.038
Fatal or nonfatal stroke	229 (9.2)	103 (14.8)	<0.001	1.75 (1.36–2.24)	<0.001	1.60 (1.21–2.10)	<0.001
CV death	125 (4.9)	59 (8.2)	0.001	1.61 (1.14–2.28)	0.008	1.72 (1.17–2.53)	0.006

Model 1: Cox proportional hazard model adjusted for age and sex. Model 2: adjustment for age, sex, peripheral artery disease, diabetes, current smoking, coronary artery disease, body mass index, and systolic blood pressure. ABI indicates ankle-brachial index; CV, cardiovascular; HR, hazard ratio; and MI, myocardial infarction.

*Kaplan-Meier estimates.

this study was that the incidence of major adverse vascular event was even higher with a low ABI (<0.6) when compared with other ranges of ABI (Figure). This highlights the role of ABI as a predictor of stroke recurrence and concurs with recent meta-analyses that have investigated the relationship between low ABI and recurrent stroke risk.[23] Likewise, the relationship of ABI <0.9 associated with higher rates of vascular events in this study is comparable to observations from some European[4,7,17] and American[6] studies, which also reported that low ABI is an independent predictor of stroke

Table 4. Baseline Characteristics of Patients According to ABI Level (4 Groups)

	Optic Registry					
	ABI ≤0.6 (n=49)	ABI 0.6–0.9 (n=718)	ABI 0.9–1 (n=1112)	ABI 1–1.4 (n=1474)	*P* Value	*P* for Trend
Age. y, mean±SD	70±11	67±11	65±11	63±10	<0.001	<0.001
Men	28 (57.1)	361 (50.3)	589 (53.0)	911 (61.8)	<0.001	<0.001
Medical history						
Congestive heart failure	1 (2.0)	37 (5.3)	42 (3.9)	36 (2.5)	0.009	0.003
Coronary artery disease	4 (8.2)	126 (17.7)	138 (12.6)	163 (11.1)	<0.001	<0.001
Diabetes mellitus	25 (51.0)	311 (43.3)	402 (36.2)	481 (32.6)	<0.001	<0.001
Dyslipidemia	36 (73.5)	535 (74.5)	809 (72.8)	1085 (73.6)	0.87	0.78
Hypertension	39 (79.6)	630 (87.7)	926 (83.3)	1185 (80.4)	<0.001	<0.001
Peripheral artery disease	4 (8.5)	111 (16.4)	73 (6.8)	52 (3.7)	<0.001	<0.001
TIA	7 (14.6)	166 (23.6)	286 (26.5)	301 (20.9)	0.005	0.16
Current smoking	7 (14.6)	176 (25.5)	244 (22.5)	274 (19.1)	0.004	0.004
Presentation characteristics						
BMI, kg/m^2, mean±SD	26.3±4.7	27.0±4.6	27.6±4.8	27.6±5.0	0.015	0.021
Systolic BP, mm Hg, mean±SD	158±30	151±28	146±24	140±23	<0.001	<0.001
Diastolic BP, mm Hg, mean±SD	86±14	85±13	83±13	83±13	<0.001	<0.001
Laboratory findings						
Total cholesterol, mg/dL, mean±SD	215±64	204±56	198±54	194±50	<0.001	<0.001
LDL-cholesterol, mg/dL, mean±SD	125±42	123±43	117±40	117±40	0.006	<0.001
HDL-cholesterol, mg/dL, mean±SD	42±15	46±19	46±18	44±16	0.016	0.12
Triglycerides. mg/dL, median (IQR)*	159 (122–249)	143 (105–200)	141 (103–195)	135 (100–196)	0.08	0.10
Triglycerides >200 mg/dL	12 (37.5)	117 (24.8)	174 (23.1)	233 (23.7)	0.29	0.37
Creatinine, mg/dL, median (IQR)*	1.1 (0.7–1.5)	0.9 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.0)	<0.001	0.002
Glucose, mg/dL, median (IQR)*	106 (95–199)	110 (95–162)	110 (95–157)	107 (94–148)	0.24	0.005

Data are number (%) unless otherwise indicated. Percentage is based on available data. ABI indicates ankle-brachial index; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IQR, interquartile range; and TIA, transient ischemic attack.

*Logarithmic values.

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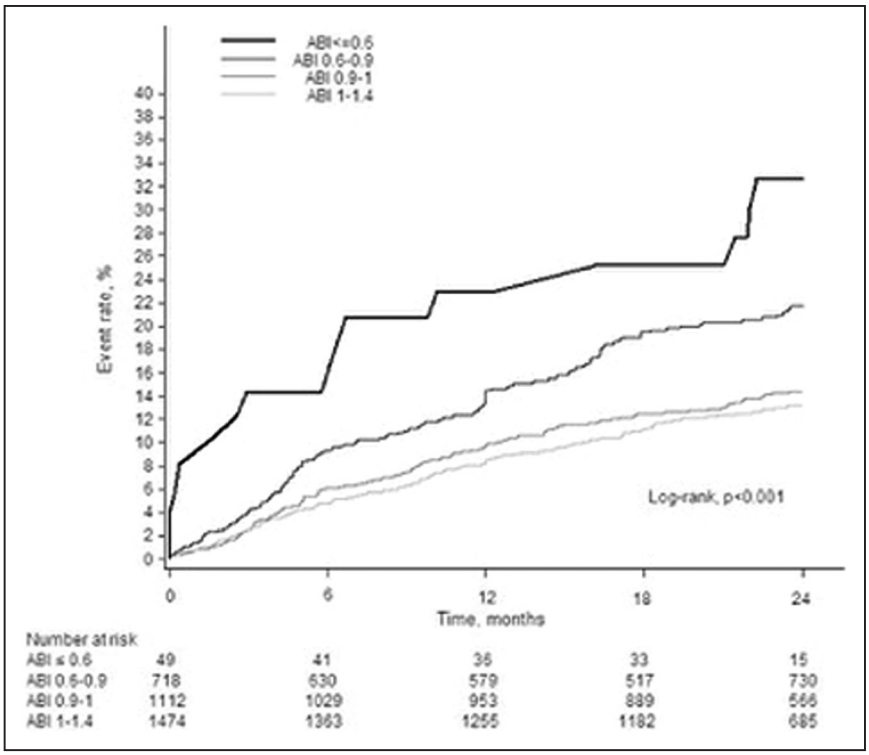

Figure. Cumulative incidence curves for nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death according to ankle-brachial index (ABI) level (4 groups).

recurrence in patients with cerebral ischemia. Our results add to the accumulating evidence that low ABI is associated with vascular events in patients with nonembolic stroke, including those from low- and middle-income countries. In addition, accumulating evidence that highlights the independent prognostic value of a low ABI raise the importance of routine screening for low ABI in patients with stroke, which may help to improve recommended medical therapies as appropriate antiplatelet and antihypertensive agents and thereby reduce cardiovascular morbidity and mortality in nonembolic stroke population.

In our study, patients with a low ABI were more likely to be older and have diabetes mellitus, hypertension, current smoking, and dyslipidemia. ABI <0.9 was also more likely to be found in patients with coronary artery disease, providing further evidence that an abnormal ABI is primarily a marker of advanced generalized atherosclerosis.[23]

Finally, as might be expected, we observed a relationship between indicators of lower socioeconomic status and low ABI. In fact, patients with ABI <0.9 had poorer socioeconomic status than those with ABI ≥0.9. A potential mechanism underlying the association between socioeconomic status and low ABI is the high prevalence of traditional cardiovascular risk factors in low socioeconomic status groups.[24]

One limitation of this article is that only stroke patients who can return for follow-up were eligible for inclusion. Socioeconomic status might be one-off reasons not allowing follow-up visits because low-income people were infrequently seen for routine checkups compared with middle-income people.[25] Therefore, the reported prevalence of low socioeconomic status has been actually underestimated. However, our study showed that even with this limitation, patients with ABI <0.9 had poorer socioeconomic status than those with ABI ≥0.9.

In conclusion, this study found that low ABI in patients with noncardio embolic stroke or TIA independently predicts future cardiovascular events and mortality. Screening for ABI in stroke patients may help identify high-risk patients who could potentially benefit from intensive strategies for secondary vascular events prevention.

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Disclosures

Dr Amarenco reports in the past 2 years receiving grants from Pfizer, AstraZeneca, Sanofi, BMS, Boston Scientific, and French Government; lecture fees from Bayer and Amgen, consulting or advisory board fees from BMS, Daiichi Sankyo, Amgen and Regeneron Sanofi; personal fees from Pfizer, AstraZeneca, KOWA Company, Fibrogen and Bayer. Dr Steg reports in the past 2 years receiving grants from Bayer, Sanofi, and Servier; personal fees from Bayer, Amarin, AstraZeneca, Boehringer Ingelheim, BMS, Amgen, Pfizer, Sanofi and Novo Nordisk; consulting or advisory board fees from Novartis and Sanofi. Dr Vicault reports in the past 2 years receiving consulting or advisory board fees from Abbott, Boehringer, Bristol Myers Squibb, Lilly, Novartis, Pierre Fabre, Roche, and Sanofi. The other authors report no conflicts.

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