EDITORIAL
American Heart Association | American Stroke Association

Association Between Peripheral Artery Disease and Incident Risk of Atrial Fibrillation: Strong Evidence Coming From Population-Based Cohort Studies

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Peripheral artery disease (PAD) is largely prevalent and evident among the general population.[1] PAD recognizes multiple risk factors, and it is associated with an increased risk of morbidity and mortality.[1] Similarly, atrial fibrillation (AF) is the most prevalent and incident arrhythmia, associated with an increased risk for stroke and major cardiovascular outcomes.[2] In recent years, accumulating evidence suggests that a strong relationship exists between PAD and AF.[3] Both the conditions share similar major risk factors and common epidemiologic characteristics. Also, it is largely known that the concomitant presence of these conditions significantly increases the risk of major adverse events.[3]

Ankle-Brachial Index and AF

Some data suggest that a direct link can exist between the presence of PAD and an increased risk of incident AF.[4,5] In particular, it has been reported that an inverse "dose-effect response" relationship exists between ankle-brachial index (ABI) and the risk of newly detected AF.[6,7] ABI is a simple, costless, and noninvasive test used as the first-line diagnostic approach to PAD.[1] Current guidelines recommend performing an ABI evaluation for all patients who report suggestive symptoms of PAD; an ABI value ≤0.90 is diagnostic for the presence of PAD.[1] An ABI value between 0.91 and 0.99 is currently considered as "borderline," requiring further assessments.[1] Furthermore, an ABI ≥1.40 still indicates a vascular disease, although it is usually related to tunica media wall, associated with diabetes mellitus.[1] ABI is also considered a strong marker of generalized atherosclerosis and cardiovascular risk.[1]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Bekwelem and colleagues present an analysis derived from the ARIC (Atherosclerosis Risk in Communities) Study, about the association between PAD and risk of new-onset AF.[8] ARIC is a large, prospective, epidemiologic study conducted in 4 US communities, aimed to investigate causes and mechanisms of atherosclerosis, the variation and interaction between relevant risk factors and demographic variables, and the influence on long-term outcomes.[9] With 15 792 patients followed up for 20 years, the ARIC Study published >2000 articles and represents a robust study still providing relevant and reliable insights into the pathophysiological mechanisms of atherosclerosis and its clinical sequelae. In this new analysis, the authors reported that diagnosis of PAD according to ABI classes is associated with an incident diagnosis of AF. Indeed, patients with an ABI ≤0.90 had, after adjustment for age, sex, and race, an increased risk of developing AF (hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.21–1.51). After full adjustment for all the concomitant risk factors and cardiovascular comorbidities, despite being attenuated, the association remained significant, with 13% increase in relative risk compared with subjects with normal ABI (1.00–1.40).[8]

Conversely, patients with ABI ≥1.40 did not have an increased risk of AF in both unadjusted and adjusted analyses. These results, although assessed on a larger cohort, substantially confirmed the previous data on the relationship between ABI and incident AF.[8] The article from Bekwelem and colleagues reported that borderline ABI (0.91–0.99) is significantly associated with incident AF after both age-sex-race adjustment (HR, 1.32; 95% CI, 1.16–1.50) and full adjustment (HR, 1.14; 95% CI, 1.00–1.30).[8] Conversely, although ABI

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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J Am Heart Assoc. 2018;7:e009126. DOI: 10.1161/JAHA.118.009126.

≤0.90 remained associated with incident AF after age-sex-race adjustment (HR, 1.43; 95% CI, 1.17–1.75), full adjustment strongly attenuated the relationship (HR, 1.10; 95% CI, 0.90–1.34). The age-sex-race adjusted cubic spline also proved the inverse dose-effect response between ABI and risk of AF.[8]

Finally, the authors have been able to report that both "pathological" ABI (≤0.90) and borderline ABI (0.91–0.99) were associated with an increased risk for all-cause death, compared with subjects with ABI of 1.00 to 1.40, in both patients who developed and did not develop AF. The magnitude of association was lower in patients who did not develop AF and has also been found progressively lower from pathological to borderline ABI.

This interesting article, beyond confirming the previous evidence about the causal relationship between PAD and AF, extends previous findings and adds significant knowledge about this relevant issue. Indeed, the evidence that even borderline ABI is associated both with incident AF and increased all-cause death reinforces the concept that there is a direct proportion between the entity of vascular disease and the burden of risk for incident AF (and associated adverse events). Also, it has been proved that borderline ABI is not harmless and should be considered and assessed cautiously.

Accumulating Evidence for a New Pathophysiological Paradigm

To date, 2 studies have analyzed the relationship between ABI levels and risk of incident AF. O'Neal and colleagues[6] performed an analysis from the MESA (Multi-Ethnic Study of Atherosclerosis), a population-based study aimed at exploring the characteristics of subclinical cardiovascular disease and the relationship with risk factors that could predict its progression to clinically overt disease. In that study, they showed that PAD (defined as both ABI <1.00 and ABI >1.40) was associated with incident AF. Also, although ABI <1.0 alone was still found associated with the risk of AF, ABI >1.40 showed a nonsignificant trend in association.[6] Similar results were also reported by Griffin and colleagues, who performed an analogous analysis in the CHS (Cardiovascular Health Study) cohort, an observational population-based study about risk factors for cardiovascular disease and their influence in disease progression in elderly (≥65 years) subjects.[7]

To obtain more robust evidence about the relationship between PAD and AF, we merged together data coming from these 3 large population-based studies: ARIC Study, MESA, and CHS. To reach our aim, we performed a meta-analysis and meta-regression of data coming from the 3 studies[6–8] (Table), including a total of 26 505 subjects. Bayesian meta-analyses under heterogeneity were conducted by means of hierarchical (log-) gaussian models with informative priors, according to previously published articles.[10] For meta-regression, a linear model was assumed for the pooled location estimates. For curve pooling, one meta-analysis was conducted for each point in a grid and the resulting pooled estimates were then smoothed by means of lowest regression.

Table. Meta-Analysis and Meta-Regression of Included Studies

Meta-Analysis	N	Incident AF	
		HR	95% CI
Overall PAD			
PAD vs non-PAD	4441 vs 22 064	1.31	1.20–1.44
ABI classes			
ABI <1.00 vs ABI 1.00–1.40	3925 vs 22 064	1.32	1.18–1.47
ABI >1.40 vs ABI 1.00–1.40	516 vs 22 064	1.08	0.86–1.35

Meta-Regression*	ΔHR	95% CI	*P* Value
Age, y	1.001	0.996–1.007	0.419
Follow-up, y	0.999	0.972–1.021	0.819
Male sex, %	1.002	0.994–1.010	0.313
White ethnicity, %	1.000	0.995–1.005	0.687
BMI, kg/m^2	1.004	0.990–1.019	0.225
Ever smoker, %	1.001	0.994–1.008	0.483
Diabetes mellitus, %	1.010	0.981–1.038	0.162
SBP, mm Hg	1.001	0.998–1.004	0.443
CHD, %	1.001	0.968–1.029	0.896
Heart failure, %	0.973	0.858–1.097	0.378
Antihypertensive drugs, %	1.002	0.993–1.011	0.287

ABI indicates ankle-brachial index; AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; PAD, peripheral artery disease; and SBP, systolic blood pressure.
*Meta-regression is referred to overall PAD.

The presence of PAD, defined as ABI <1.00 or ABI >1.40, was associated with a 31% increase in risk for incident AF (Table). Considering the 2 ABI classes distinctly, we found that ABI <1.00 was associated with an increased risk of developing AF (HR, 1.32; 95% CI, 1.18–1.47), whereas ABI >1.40 class was not associated with an increased risk of AF. A meta-regression analysis, according to the main demographic characteristics and cardiovascular risk factors, showed that no predictor was able to significantly affect the association between PAD and AF (Table). Similar data were retrieved when the meta-regression analysis was performed according to the ABI classes (data not shown). A cumulative cubic spline model was obtained, pooling together the spline curves from the 3 studies included in the analysis,[6–8] confirming the inverse dose-effect response between ABI and the risk of incident AF (Figure 1). The pooled cubic spline also confirmed

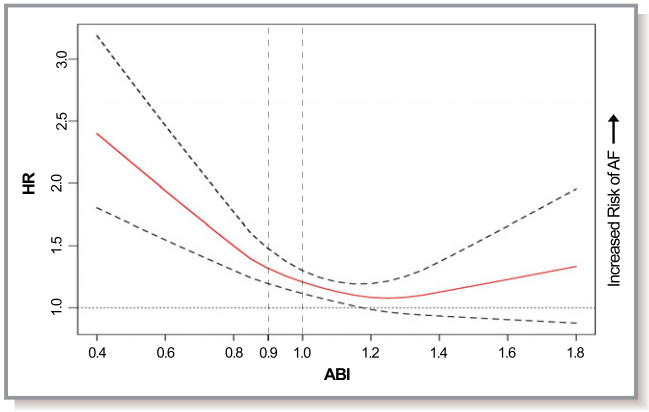

Figure 1. Pooled cubic spline model for risk of atrial fibrillation (AF) according to ankle-brachial index (ABI). Full red line stands for hazard ratio (HR); black dashed lines stand for 95% confidence interval.

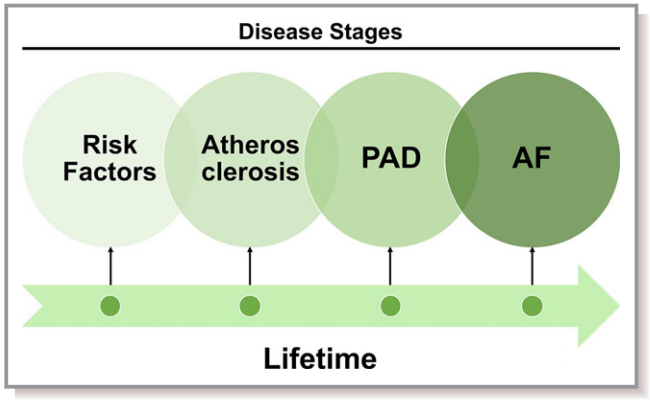

Figure 2. The multiple-stage disease process leading from risk factors to atherosclerosis, diagnosis of peripheral artery disease (PAD), and finally the onset of atrial fibrillation (AF).

that the risk is still present, despite being lower, in the borderline ABI class (Figure 1).

Data from our meta-analysis and meta-regression reinforce and strengthen the evidence about the association between PAD and AF. The large number of subjects gathered from the 3 studies provide robust confirmation of the strict causal relationship between the 2 conditions. In all the 3 original studies, the adjustment with baseline characteristics and concomitant risk factors mitigates the association; however, no covariate significantly affected the pooled HR between PAD and AF. Also, the evidence that although the association between ABI <1.00 and incident risk of AF is confirmed, our results gave us the proof that likely the lack of association between ABI >1.40 and AF is factual. Indeed, gathering >500 subjects, this evidence appears more robust than it was on the single studies. Last, the pooled cubic spline confirmed that as much as the vascular disease progresses, the risk is as high to develop an incident AF episode.

The data gathered from the meta-analysis, discussed in the context of current knowledge, give us the opportunity to provide several considerations.

The difference in the association between ABI <1.00 and ABI >1.40 could be based on the difference in the pathogenesis of the vascular disease. The finding of an ABI <1.00 is based on intimal and endothelial disease, sustained by systemic atherosclerosis. Conversely, ABI >1.40 represents arterial stiffening, based on medial wall calcification.[1] So, in subjects with ABI <1.00, the presence of multiple risk factors carries a relevant inflammatory burden, which triggers systemic atherosclerosis and, subsequently, generates PAD.[1,11] We can postulate that both the persistence of inflammatory burden, given by the perpetuating risk factors and the endothelial dysfunction directly related to systemic atherosclerosis and PAD presence, could interact together to influence the onset of AF. Indeed, data indicate the increased inflammatory burden in patients with AF, connecting the presence of atherosclerosis and incident AF.[12] These postulates are also corroborated by other studies underlining a strict relationship between another sign of systemic atherosclerosis, the intima-media thickness, and AF.[13,14] From this perspective, we should probably start considering the onset of AF as the last stage of a multiple-stage process, spanning throughout the entire lifetime, beginning with the presence of multiple risk factors and progressing throughout the development of systemic atherosclerosis and diagnosis of PAD (Figure 2). This new pathophysiological "paradigm" could contribute to partially understand the current burden of AF. Indeed, some data indicate that (subclinical) atherosclerosis is more likely associated with persistent/permanent AF,[14] whereas conversely, paroxysmal AF is more likely associated with an electrophysiological mechanism.[15]

Conclusions

The available evidence, as emphasized by our meta-analysis, strongly underlines the strict causal relationship between PAD and AF. In the context of the current literature, the data presented point out how the onset of the arrhythmia could be considered as the ultimate stage of a multiple-stage disease process, that starting from the presence of risk factors, leads to the development of atherosclerosis, diagnosis of PAD, and incident AF.

Disclosures

Proietti reports consulting activity for Boehringer Ingelheim. Farcomeni has no disclosures to report.

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Key Words: Editorials • atherosclerosis • atrial fibrillation • peripheral artery disease