(1.09 vs. 2.78 per 100 person-years; IRR: 0.39; 95% CI: 0.25 to 0.62; $p < 0.001$) and a similar risk of thromboembolism (1.0 vs. 1.39 per 100 person-years). None of the dabigatran users with GFR <30 ml/min/1.73 m^2 had a thromboembolic event compared with 2.95 events per 100 person-years in the warfarin group, but there was a higher rate of major bleeding on dabigatran compared with warfarin (19.23 vs. 5.37 per 100 person-years; $p < 0.01$).

In this large cohort of real-world patients with atrial fibrillation receiving oral anticoagulation, we demonstrate significant heterogeneity in treatment effects between dabigatran and warfarin across the range of baseline renal function. The risk-benefit ratio favored dabigatran for patients with mild or moderate renal impairment, but there was a higher risk of thromboembolism in subjects with normal renal function. The small number of subjects in the severe renal impairment group precludes a definitive conclusion. Further studies addressing the interaction of renal function and the safety and efficacy of dabigatran versus warfarin are needed to confirm our findings.

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Pulse Pressure and Cardiovascular Death

We read with great interest the study of Selvaraj et al. (1), which provides robust evidence on the predictive role of pulse pressure (PP) for cardiovascular (CV) outcomes. Surprisingly, however, when the predictive ability of a 10 mm Hg increase in PP was assessed, a "protective" effect of higher PP was found (Figure 3 in Selvaraj et al. [1]). This misleading finding, not fully explained in the paper, is in line with the reverse-J-shaped relationship between PP and CV death (Figure 2 in Selvaraj et al. [1]) that remains even after excluding patients with heart failure, who have low PP and high CV death risk. Selvaraj et al. (1) wonder whether patients with aortic stenosis (not identified in the REACH Registry) may account for the high CV mortality rates in the low-PP group. However, this is not likely because such patients are usually older, with stiff arteries, and they frequently have high (and sometimes difficult to control) systolic pressure and high PP.

Systolic pressure and PP typically increase as we move from the aorta to the periphery (amplification) (2). In a previous meta-analysis, we showed that noninvasive central (aortic) PP is a marginally better predictor than peripheral (brachial) PP (3). Central PP could reclassify patients and would potentially provide a more realistic PP-CV death relationship. For example, a subject with a peripheral PP in the middle or high quartiles could be a sick patient with a theoretically higher CV death risk; this patient would have blunted pressure amplification (a usual case in high-CV risk patients [4]) and therefore almost equal peripheral and central PP. This patient's position across the central PP-CV death plot would not change significantly. However, he or she could be a "less sick" subject with a theoretically lower risk and more physiological pressure amplification, whose central PP would be substantially lower than the peripheral PP. This subject would "move" toward the left side of the curve and would "linearize" the PP-CV death relationship. What may dissociate central from peripheral PP further in this study (1) is the high prevalence of hypertension (81%) and the use of antihypertensive medications, which are known to influence central pressures more than is apparent from the corresponding brachial pressures because of significant effects on wave reflections (5).

Although it is not always feasible to measure central pressures in large-scale studies, the discrepancies between peripheral and central PP may account for

the rather unexpected and difficult to interpret PP-CV death relationship in the heterogeneous population of this important study.

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REPLY: Pulse Pressure and Cardiovascular Death

We appreciate the thoughtful comments of Dr. Aznaouridis and colleagues on our paper studying the relationship between brachial pulse pressure (PP) and adverse cardiovascular outcomes in the REACH (REduction of Atherothrombosis for Continued Health) registry (1). As Dr. Aznaouridis and colleagues point out, the J-shaped relationship between PP and cardiovascular death may not be fully explained by confounding from unmeasured aortic stenosis. A few explanations may account for this finding. First, many REACH participants were prescribed blood pressure (BP) medications for secondary prevention, and the sickest patients may have been maintained on their BP medications to achieve ancillary benefits (anti-ischemic or anti-remodeling effects) while yielding a lower PP. Second, heart rate, a potentially confounding variable, was not collected in the REACH database (2). Third, the associations between low BP and PP with higher event rates are derived largely from observational studies; thus, low PP may reflect "reverse causality" and mark frail or sicker patients, as hypothesized in published reports on systolic and diastolic BP (3). The results of the randomized SPRINT (Systolic Blood Pressure Intervention Trial) study support this hypothesis, wherein frequent standing BP measurements were performed and treatment was decreased in cases of orthostatic hypotension, thus explaining the low rate of related adverse events (4). Therefore, the participants with lower systolic BP (and PP) on treatment were necessarily healthier, given their ability to tolerate higher-dose treatment.

We share concerns similar to those of Dr. Aznaouridis and colleagues regarding the feasibility of measuring central PP in large-scale analyses. In addition, the prognostic value of central hemodynamic measurements over peripheral measurements has not been established, given several conflicting studies, partly driven by underpowered analyses as well as high correlation between the two methods (2). Therefore, the additional benefit of central PP may exist for a select subgroup of patients, and identifying this subgroup is of clinical interest. Ambulatory BP monitoring also improves risk stratification, and whether it provides significant benefit in lieu of central BP measurements has been studied with promising results (5), but it needs larger confirmatory studies. Such important questions with broad implications, however, merit further adequately powered research investigations on the ideal risk stratification methods using central versus peripheral BP measurements.

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