Having Stable Coronary Artery Disease) trial, smokers showed a greater clopidogrel active metabolite exposure and lower residual platelet function assessed with VerifyNow and VASP assay (1).

The reason why we cast a doubt to the current concept of smokers' paradox is based on several observations. First, VerifyNow P2Y12 reaction unit (PRU) is significantly influenced by hemoglobin level, which is likely a laboratory association (2). In our study, the regression coefficient between PRU and hemoglobin was -21.4 (21.4 decrease in PRU for every 1 g/dl increase in hemoglobin) and the observed difference in PRU between non-smokers and current smokers was -17.9 (3). Because the mean hemoglobin of current smokers was 0.9 g/dl higher than that of nonsmokers, this amount of association is sufficient to account for the observed difference in PRU between nonsmokers and current smokers. The association between PRU and hemoglobin (or hematocrit) is reported consistently across various studies and should not be overlooked. Second, PRU of prasugrel-treated patients is also influenced by smoking, with current smokers having a lower PRU value (4). If we consider enhanced metabolism of clopidogrel is responsible for a lower PRU in smokers, we cannot explain the observed low PRU in current smokers taking prasugrel because metabolism of prasugrel is not affected by smoking (1). A recent study by Patti et al. (5) also indicates that smoking lowers PRU of clopidogrel-, prasugrel-, and ticagrelor-taking patients without any significant interactions (5). Third, platelet function tests other than VerifyNow, such as VASP or light transmittance aggregometry (which are assumed to be independent from the influence of hemoglobin), failed to demonstrate a consistent association with smoking status (6).

There is and will be a hot debate about whether cigarette smoking enhances clopidogrel response. Cigarette smoking is a strong risk factor for thrombosis and is associated with an increased hemoglobin level (3), which will increase the viscosity of blood, rendering it more vulnerable to thrombosis. We think more evidence is needed to confirm the enhanced clopidogrel response in smokers, and considering the prothrombotic effect of smoking and many other deleterious effects, cessation of smoking should be our recommendation to patients taking clopidogrel.

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Antithrombotic Regimen in Post-TAVR Atrial Fibrillation

Not an Easy Decision

We read with great interest the paper by Abdul-Jawad Altisent et al. (1). The investigators should be congratulated for their detailed work, as they deal with a rather unclear field regarding the appropriate antithrombotic strategy in the relatively common but demanding population of patients undergoing transcatheter aortic valve replacement (TAVR) with concomitant need for anticoagulant therapy because of atrial fibrillation (AF). Collecting retrospective clinical and prescription data from 12 centers, they have shown that adding of a single or two antiplatelet agents to a vitamin K antagonist (VKA) does not reduce adverse events, whereas it increases the risk for major or life-threatening bleeding.

Although we think that this work represents a significant contribution to the complex field of antithrombotic treatment after TAVR, we have some concerns regarding the findings and their interpretation that need to be discussed.

According to baseline population characteristics, the incidence of coronary artery disease (CAD), as expected, was less among the monotherapy group. Therefore, the conclusion that only VKAs could be sufficient for patients undergoing TAVR, without matching the severity of the underlying CAD, previous stenting, bifurcation lesions, and so on, is rather unjustifiable from the data provided in the paper. Similarly, it is of concern that the incidence of myocardial infarction in patients receiving multiple-antithrombotic therapy was about 3%, whereas there were no myocardial infarctions in the monotherapy group. Therefore, we cannot exclude selection bias, because it was not a randomized trial, and as expected, there was more severe disease background in the multiple-antithrombotic therapy group. Finally, bleeding risk, expressed with the HAS-BLED score, as well VKA compliance, expressed with the therapeutic international normalized ratio range, are 2 important factors not estimated but essential when comparison of different therapeutic strategies and outcomes is attempted for these 2 groups of patients.

On the basis of our published findings, studying a quite limited but age-matched population undergoing TAVR with concomitant AF, we have shown that during an almost 2-year follow-up period, treatment with a VKA plus clopidogrel for 3 months, followed by VKA plus acetylsalicylic acid, seems equally safe and effective enough compared with the standard antiplatelet regimen of TAVR patients without AF (2). Therefore, we believe that it is very premature to recommend only VKAs in this population, especially when CAD is present in more than 50% of the patients, as in the multiple-antithrombotic therapy group. Furthermore, the different pathophysiological basis of thrombotic and bleeding events during the follow-up period should be considered. Specifically, early thromboembolic events can be attributed to procedural aspects and surgical maneuvers, while late events are usually imputed to AF episodes (3). Besides, concomitant CAD undoubtedly demands enhanced antiplatelet coverage, especially during the early post-acute coronary syndrome or post-percutaneous coronary intervention period.

The findings of Abdul-Jawad Altisent et al. (1) add significant information to the field of antithrombotic therapy in TAVR patients with concomitant AF. The need for anticoagulation with or without antiplatelet therapy in this population must be individualized, taking into account the severity of the clinical situation, comorbidities, and the time period elapsed since implantation.

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REPLY: Antithrombotic Regimen in Post-TAVR Atrial Fibrillation

Not an Easy Decision

We appreciate the comments of Dr. Vavuranakis and colleagues regarding our recently published paper (1). In their letter, Dr. Vavuranakis and colleagues emphasize that the differing distribution of coronary artery disease (CAD) across the patient and treatment groups within our study, more frequent in the group receiving multiple antithrombotic agents than in the monotherapy group, was likely due to the presence of a selection bias. They therefore express doubts about the recommendation to only prescribe vitamin K antagonists in transcatheter aortic valve replacement recipients with concomitant atrial fibrillation and CAD, claiming an individualized antithrombotic therapy approach in these patients. Of note, and as clearly detailed in the "Methods" section of our paper, the results