reveal a misunderstanding of the paper because all the points they raised were already discussed and clarified in the paper. First, the aim of the study was to test the hypothesis that nonresponsiveness to clopidogrel is a modifiable risk factor and not the comparison of prasugrel with clopidogrel, and ethical issues make unlikely the possibility to perform a randomized study using clopidogrel in the control arm in clopidogrel nonresponders. Second, in the RECLOSE-2 study, as well as in the GRAVITAS (Gauging Responsiveness with a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety) trial, tailored therapy with an increased dose of clopidogrel in clopidogrel nonresponders had some effect on in vitro tests, but no clinical benefit (2,3). Thus, the historical cohort of the RECLOSE-2 trial may be used as the control arm. Third, the differences in baseline characteristics between the 2 patients groups were rigorously considered in the multivariable analyses. Fourth, the duration of prasugrel treatment, as well as the major and minor bleeding events, was clearly reported, with an increase in minor bleeding rate in prasugrel-treated patients, whereas no difference between groups was revealed in major bleeding, and the last finding supports the safety profile of prasugrel in clopidogrel nonresponders. Finally, the demonstration that high residual platelet reactivity on clopidogrel is a modifiable risk factor puts an end to what Dr. Bonello and colleagues define inappropriately as an odyssey.

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http://dx.doi.org/10.1016/j.jcin.2015.10.015

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Cerebral Embolization After Implantation of a Balloon-Expandable Aortic Valve Without Prior Balloon Valvuloplasty

When Is Doing Less More?

Transcatheter aortic valve replacement (TAVR) is an established therapeutic option for patients with severe symptomatic aortic stenosis. However, the periprocedural stroke rate continues to be relatively high, ranging between 3% and 5% in randomized clinical trials and large registries (1,2). Despite the evolution of the transcatheter valve, delivery system design, and procedural techniques, stroke rates have not diminished. Additionally, studies that have utilized diffusion-weighted magnetic resonance imaging have demonstrated a high rate of silent cerebral emboli upwards of 70% during TAVR (3). Although these findings may reflect, to some extent, the nature of TAVR in a high-risk patient with multiple comorbidities, this may also reflect a fundamental limitation of the procedure. In fact, transcranial Doppler studies during TAVR have highlighted the occurrence of cerebral embolization at virtually all of the time points during the procedure but seem most frequent during valve positioning and implantation, suggesting a mechanical interaction between the transcatheter valve and the native aortic valve. In particular, procedural variables suggest that mechanical factors such as balloon post-dilation, valve dislocation or embolization, or the need for a second valve are associated with a higher cerebrovascular event rate (4). Additionally, these studies have identified the lowest number of transcranial Doppler events occurring during balloon aortic valvuloplasty (BAV).

Given these considerations, we read with much interest the recent paper by Bijuklic et al. (5) in *JACC: Cardiovascular Interventions* evaluating the effect of TAVR without versus with prior BAV on the risk of cerebral embolization in 87 patients who received a balloon-expandable valve. Their procedural success rate was 93.5% with and 98.2% without BAV, and procedure duration and contrast volume were significantly lower without BAV. The incidence of new cerebral ischemic lesions in the total cohort was 66.7%. Compared with patients with BAV, those without BAV had a significantly higher total volume

of cerebral ischemic lesions (235.4 ± 331.4 mm^3 vs. 89.5 ± 128.2 mm^3; p = 0.01) (5).

Despite the important findings of this study, there are some concerns that would limit the broader application of this study to a larger patient population. Despite the overwhelming association between various procedural variables during the TAVR procedure, the authors do not detail procedural variables with sufficient granularity to postulate a mechanism for their findings. Specifically, they do not mention the number of times the aortic valve is crossed, duration of the pacing run, implantation duration, degree of oversizing, number of inflations, need for post-dilation, extent of the aortic and aortic valve calcification, and activated clotting time in the 2 groups. A difference in the procedural variables may explain the lack of significant difference between the overall number of new cerebral ischemic lesions and the significant difference in the volume of cerebral ischemic lesions between the 2 groups.

Cerebral embolization and stroke will always be a concern during invasive aortic procedures. Now that the safety and efficacy of transcatheter valves are established, optimizing TAVR-related cerebrovascular outcomes is the next fundamental challenge that will determine the future role of this technology as we move to treat a younger and lower-risk patient subset. For now, is doing less more?

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http://dx.doi.org/10.1016/j.jcin.2015.10.020

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REPLY: Cerebral Embolization After Implantation of a Balloon-Expandable Aortic Valve Without Prior Balloon Valvuloplasty

When Is Doing Less More?

We thank Dr. Philip and colleagues for their interest in our study (1) and appreciate their comments.

In our study comparing transcatheter aortic valve implantation replacement (TAVR) with versus without balloon aortic valvuloplasty (BAV) in patients receiving a balloon-expandable aortic valve, we found a significantly shorter procedural duration and contrast volume, but a significantly higher total volume of cerebral ischemic lesions in patient without prior BAV (1).

Dr. Philip and colleagues hypothesized that a difference in procedural variables, not mentioned in our paper, may explain the difference in the observed findings.

The procedure variables were as follows:

In all patients, the aortic valve was crossed only 1 time, and the prosthesis was implanted using a routine 2-step slow-inflation technique. In the TAVR group with prior BAV, only 1 balloon inflation was performed.

In all patients, heparin was administered after insertion of the sheath, and an activated clotting time >250 s was maintained throughout the procedure.

In our study, post-dilation, which has been shown to be a significant predictor for stroke in TAVR (1), was only considered when a paravalvular leak more than mild was observed. Of 87 patients, 5 required post-dilation (5.7%): 1 patient in the BAV group (3.1%) and 4 patients in the group without BAV (7.3%). When patients with post-dilation were excluded from the analysis, the difference in the mean volume of ischemic lesions between the 2 groups remained statistically significant (243.4 ± 334.9 mm^3 for 55 patients without BAV and 79.7 ± 117.4 mm^3 for patients with BAV; p = 0.006).

Sizing was performed by transesophageal echocardiography or computed tomography. We therefore cannot provide data on the degree of oversizing. However, the use of the 3 available sizes (23, 26, and 29 mm) did not differ between the 2 groups (p = 0.79). In addition (as shown under *Results*) the echocardiographic baseline characteristics including mean