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Editorial

Antiplatelet Strategies in Patients Undergoing Transcatheter Aortic Valve Implantation–Data Sharing Is Caring

Tratamiento antiagregante para pacientes sometidos a implante percutáneo de válvula aórtica: hora de compartir datos

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Fortunately, in modern western cardiovascular medicine, serious complications after clinical interventions are relatively rare. From an epidemiological point of view, these low event rates are perhaps less convenient. For researchers, large investments are needed to conduct adequately powered clinical trials. Consequently, in the ongoing quest for evidence-based strategies, alternative methodological strategies have been developed with the aim of tackling these low event rates and increasing power. The first approach is to alter a primary clinical endpoint to a surrogate endpoint. Surrogate endpoints are frequently used in hypothesis-generating exploratory studies. It is hypothesized that if a specific treatment strategy positively influences a cardiovascular risk factor (eg, blood pressure, or a certain biomarker), this may reduce clinical events (death, stroke, myocardial infarction).

A second common strategy is the use of a combined endpoint as the primary outcome. The main advantage of these endpoints is statistical efficacy (smaller sample sizes, earlier availability of the study results); additionally, a summary measure for efficacy can be defined. One of the limitations of composite endpoints is that a negative separate outcome can be camouflaged. These first 2 options make statistical comparisons possible by increasing the absolute incidence of events.

A third convenient option is to expand the total population size by combining the available evidence. Achieving a higher purpose by combining data fits the current trend of sharing and collectivism among research communities. Cooperation between study centers may strongly be encouraged since it increases the sample size and also the validity of individual study results. In this editorial we will evaluate the current combined evidence on antiplatelet strategies after transcatheter aortic valve implantation (TAVI), from registries to data from randomized controlled trials (RCTs).

Following the trend of modern medicine, TAVI is nowadays a relatively safe intervention, with low rates of serious complications. However, these rare serious outcomes are associated with increased morbidity and mortality and therefore deserve appropriate treatment strategies. Two of the most feared complications associated with TAVI are thromboembolic and bleeding events. Myocardial infarction occurs in 1% of all patients in the first 30 days after TAVI. Stroke after TAVI, including transient ischemic attack (TIA), is more frequently reported (5%-6%).[1] These clinical strokes seem to be the tip of the iceberg of the real cerebral embolization burden associated with the TAVI procedure. Cerebral diffusion-weighted magnetic resonance imaging scans performed within a week after TAVI show new ischemic lesions in three-quarters of patients undergoing TAVI, with an average of 4 lesions per patient, dispersed through all brain regions.[2] Nevertheless, their clinical relevance remains unclear.[3] Stroke in this frail elderly TAVI population is associated with a 3.5-fold increase in mortality in the first 30 days after the procedure.[4] To reduce these thromboembolic events, current expert-based guidelines recommend 3 to 6 months of dual antiplatelet therapy (DAPT) after TAVI. The underlying motivation for periprocedural DAPT was mainly derived from the common practice of percutaneous coronary interventions, to support the incorporation process of the device. Additionally, in the early days of TAVI, it was feared that hemodynamic support using extracorporeal circulation induced platelet activation and consumption.[5]

However, nowadays extracorporeal hemodynamic support is barely used during TAVI. Moreover, the use of large catheters and delivery systems in combination with antithrombotic drugs during TAVI is associated with a considerable risk of bleeding complications. Bleedings were reported in 41% of the patients after TAVI, most of them being defined as major (22%) or life threatening (16%).[6] The majority of these bleedings are related to the procedure; nevertheless, bleeding complications after the periprocedural phase occur in 6% of all patients and are strongly correlated with mortality in the first year after TAVI (adjusted hazard ratio, 3.91; 95% confidence interval [95%CI], 2.67-5.71; $P < .001$).[7] In conclusion, both thromboembolic and bleeding complications after TAVI are associated with poor outcomes, compromising quality of life and increasing health care costs. Therefore, data on antithrombotic strategies aimed at lowering these events in TAVI patients are more than welcome.

As described in their article recently published in *Revista Española de Cardiología*, Verdoia et al.[8] performed a meta-analysis

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combining the current available evidence on antithrombotic therapy in patients undergoing TAVI. We congratulate the authors for conducting a well-executed meta-analysis on such an important matter. Tackling the problem of relatively low event rates, the meta-analysis included 5 studies comparing DAPT with single antiplatelet therapy (SAPT) and 4 studies comparing DAPT with SAPT plus oral anticoagulation (OAC). In total, approximately 8000 patients were included. The authors conclude that overall mortality was significantly reduced in patients treated with DAPT vs SAPT (with or without OAC) (odds ratio [OR], 0.81; 95%CI, 0.70-0.93; $P = .003$). This effect was similar when selecting the studies comparing DAPT vs SAPT without OAC (OR, 0.80; 95%CI, 0.69-0.93; $P = .004$), and was not significant in the studies comparing DAPT vs SAPT with OAC (OR, 0.86; 95%CI, 0.55-1.35; $P = 0.51$). Moreover, there was a nonsignificant trend toward lower stroke rates in patients treated with DAPT vs SAPT with or without OAC (OR, 0.83; 95%CI, 0.63-1.10, $P = 0.20$). Additionally, the authors conclude that bleeding rates were similar in patients treated with DAPT compared with patients treated with SAPT with or without OAC (OR, 1.69; 95%CI, 0.86-3.31; $P = 0.13$). The authors conclude that treatment with DAPT was associated with a significant reduction in mortality, without a significant increase of major bleedings, and therefore support the current strategy recommended by the guidelines.

The results from the meta-analysis are interesting and stand in contrast to the outcomes of the current available (combined) RCTs.[9] The largest RCT to date (n = 222) on the same topic[10] was published simultaneously with the meta-analysis by Verdoia et al. Consequently, there are currently a total of 3 RCTs assessing DAPT vs SAPT in patients undergoing TAVI, with 421 patients in total. At 30-days' follow-up, mortality was comparable in patients treated with DAPT vs SAPT (13 vs 10 patients). Similarly, the occurrence of stroke/TIA was equal in both treatment groups (n = 5).[10–12] Absolute numbers of bleedings were reported in only 2 of the trials (n = 301): life-threatening and major bleedings were more than 2-fold higher in patients treated with DAPT (n = 16) vs patients treated with SAPT (n = 7) and this difference was statistically significant in the ARTE trial ($P = .038$).[10,12] Currently, there are no randomized data comparing DAPT with OAC. The POPular TAVI trial (NCT02247128) is enrolling and randomizing patients on OAC to receive additional clopidogrel or no additional antiplatelet therapy. In summary, the currently available RCTs seem to suggest that SAPT is noninferior to DAPT regarding mortality or stroke and is additionally associated with less serious bleedings.

How can this discrepancy between the recent meta-analysis and the current available randomized data be explained? Well-conducted, large-scale RCTs are considered the gold standard. However, it is not uncommon for meta-analyses and subsequent large RCTs to reach different conclusions. Approximately one-third of the outcomes of large RCTs was not predicted accurately by previously published meta-analyses on the same topic.[13] A partial explanation may be the heterogeneity of studies included in meta-analyses. The meta-analysis by Verdoia et al. included 5 studies evaluating SAPT vs DAPT. Among these studies (2 small RCTs, 2 small observational studies, and 1 large registry), considerable divergence was evident regarding the odds ratios of both mortality and stroke. The 4 small studies adopted positions on both sides of the no-difference line, without reaching individual statistical significance due to the low number of total event rates (mortality rates = 3-12; stroke rates = 1-3).[11,12,14,15] In contrast, the fifth study, a large US registry, presented at the Transcatheter Cardiovascular Therapeutics conference in 2015, contained 4132 patients and also a high number of events (mortality, n = 550; stroke, n = 140).[16] Consequently, the conclusion of the meta-analysis (comparing DAPT vs SAPT, without OAC) was for more than 90% driven by the results from a single large registry. Potentially, in this case, the summarizing of results from different types of studies into 1 odds ratio may oversimplify a complex matter.

How, then, should we interpret this meta-analysis? The challenge is that currently the only other available evidence-based alternative is composed of a series of small RCTs. Clinicians should realize that the meta-analysis by Verdoia et al. and the series of small RCTs perhaps both answer different questions and are complementary. We speculate from our own experience that participants consenting to randomized controlled TAVI studies are often younger and have fewer comorbidities compared with those refusing to participate. This may limit the generalizability of RCTs to the total TAVI population and may also result in relatively low event rates, as reported in the previously discussed trials. Alternatively, despite being severely confounded, a large-scale registry such as that included in the meta-analysis provides real-life data on antiplatelet strategies tailored per patient. It is likely that low-risk patients for thromboembolism in the registry received SAPT rather than DAPT. Consequently, it could be postulated that this tailor-made strategy prevented increased rates of bleeding complications. Therefore, both study methods have their advantages and pitfalls. Clinicians may consider combining both when searching for answers. We believe that pooling individual subject data, despite being time-consuming and requiring extensive cooperation, may enhance statistical power and at the same time allow comparison of outcomes across different study and site settings. Additionally, the variation in study patients in pooled datasets may be used for subgroup analysis and interaction testing.

The current meta-analysis underlines the need for more data on this important topic. We encourage the initiation of both large-scale randomized trials, as well as registries containing real-life data. Sharing these data between researchers and clinicians in open-access databases seems to be the way forward. Clinicians and patients will benefit from the diversity of trial types in the decision-making process regarding the optimal antithrombotic strategy after TAVI.

CONFLICTS OF INTEREST

None declared.

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