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EDITORIAL COMMENT

Dapagliflozin post-transcatheter aortic valve implantation: the need for further evidence

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This article refers to 'Rationale and design of the Dapagliflozin after Transcatheter Aortic Valve Implantation (DapaTAVI) randomized trial' by I.J. Amat-Santos *et al.*, published in this issue on pages 581–588.

The prevalence of degenerative valvular heart disease has been increasing significantly in the last decades. In particular, the global burden of calcific aortic valve disease has seen a dramatic increase, mostly due to the ageing population. At the same time, it has been clearly shown older patients are exceptionally vulnerable.[1] For those who actively practice cardiovascular medicine, aortic valve stenosis is likely the first true epidemic of the 21st century.

Once aortic valve stenosis becomes symptomatic, poor prognosis is usually the rule unless intervention in undertaken. Ageing of the population with a significant rate of associated comorbidities accompanies this trend in the escalation of degenerative aortic valve stenosis prevalence making aortic valve management complex. Therapeutic options have expanded significantly, almost two decades after the first transcatheter aortic valve implantation (TAVI).[2] The advent of TAVI has allowed for the expansion of aortic valve intervention even in patients previously considered inoperable and at high surgical risk. Its use in younger and less 'risky' patients has been assessed in the last decade in several non-inferiority randomized clinical trials with encouraging early results. Therefore, the complex decision to undertake surgical aortic valve replacement (SAVR) or TAVI is based on a Heart Team feedback, after carefully revisiting clinical, anatomical and procedural aspects, as recommended by the most recent European guidelines.[3]

Still, it is clear that not all is resolved once the intervention is undertaken. In patients undergoing SAVR, survival is nearly equivalent to the standard population, but late complications arise in older patients, with a high rate of comorbidities and in patients with late-stage heart disease before intervention. Arrhythmias, conduction abnormalities, cerebrovascular events, prosthesis-related complications or congestive heart failure are examples of outcomes arising in this population. On the other hand, most patients that underwent TAVI in the last 20 years had a higher risk profile, mainly the result of a negative selection bias by cardiac surgery. This results in a cohort of older patients, with more advanced structural heart disease and with a higher rate of comorbidities. If current evidence shows favourable short-term results on survival, limited data on long-term outcomes do not allow for additional definitive conclusions.[4]

Heart failure is the commonest cause of rehospitalization in patients undergoing TAVI as shown in the recent long-term (5-year) analysis by the PARTNER 2 investigators.[5] Heart failure hospitalization is associated with higher mortality in these patients.[6–8] It is therefore clinically critical to further understand its pathophysiology and to find the evidence to improve its prevention. Structural conditions such as patient–prosthesis mismatch, prothesis deterioration or endocarditis, other valve disease progression or left ventricular dysfunction should promptly be excluded by the Heart Valve Team.[3] Further management of heart failure should take into account the European Society of Cardiology heart failure guidelines,[9] even though treatment options are not specified.

In this issue of the Journal, Amat-Santos et al.[10] describe the protocol of a randomized, controlled, prospective, open-label trial on the use of dapagliflozin after TAVI. Patients with severe aortic stenosis with a previous hospitalization for heart failure and reduced left ventricular ejection fraction (<40%) or diabetes mellitus or glomerular filtration rate 25–75 ml/min/1.73 m^2 are eligible for recruitment during the TAVI hospitalization or within 2 weeks after hospital discharge. Thirty-seven Spanish centres will recruit 1020 patients that will be randomized to dapagliflozin 10 mg/day versus no dapagliflozin. The primary outcome will assess reduction of the incidence of all-cause death or worsening heart failure episodes, as time to first event.

When first assessing this trial design one might wonder – do we still need further evidence on the use dapagliflozin in this population? Is this even ethical?

In fact, in patients with heart failure and reduced ejection fraction, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)[11] trial showed that the use of the

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sodium–glucose co-transporter 2 inhibitor dapagliflozin added to therapy with angiotensin-converting enzyme inhibitors or an angiotensin receptor–neprilysin inhibitor, beta-blockers, and mineralocorticoid receptor antagonists, reduced the risk of cardiovascular death and worsening heart failure.

Single dose, haemodynamically well tolerated and with a favourable safety profile make the use of dapagliflozin in the context of heart failure an appealing drug to be used by cardiologists and cardiac surgeons. Still, the DAPA-HF trial excluded patients that underwent valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo any of these operations after randomization. Which makes the evidence less obvious. On the other hand, we could argue why test dapagliflozin at this stage, when little is known about protective effects of sacubitril/valsartan against cardiac remodelling after successful TAVI.

Recurrent heart failure hospitalization can occur within 1 year in up to half of patients undergoing TAVI.[6,7] So, we need prevention, which means we need to gather all the best treatment options to prevent this older population with comorbidities and more advanced myocardial damage (hypertrophy and fibrosis after long-standing aortic stenosis) from being hospitalized with heart failure. And foremost we need to ensure that patients are safe and no harm is being induced additionally.

This is a pragmatic randomized clinical trial designed to be a part of daily clinical routine. In this way, regulatory procedures are simplified, much less costly as compared to conventional clinical trials and allow for the evidence to be derived from real-world experience.[12] Which is probably the best option in this situation.

Inclusion criteria used for this trial are quite inclusive as patients only need to present a previous heart failure hospitalization to be eligible, resulting in a very heterogeneous final sample. Which is after all the real-world population we normally see in our daily clinical practice. On the other hand, outcome data displayed by the investigators will be part of their clinical routine (hospitalization data, outpatient clinics evaluation, biomarkers, echocardiography re-evaluation), so we should expect more input on the impact of clinical events rather than on echocardiographic parameters or other surrogates.

Finally, we leave an open question for future discussion: why not aim at all patients post-aortic valve intervention for aortic stenosis? Why exclude patients undergoing conventional cardiac surgery?

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