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Valvular heart disease: the unanswered questions

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Valvular heart disease (VHD) is common yet poorly researched and an important cause of heart failure, arrhythmia, recurrent hospital admission, reduced quality of life and early mortality. Due to the ageing of the population in developed nations, a new epidemic of degenerative VHD is upon us, heralding a major increase in the healthcare resources required for its optimal management[1].

The evidence base to guide the optimal management of VHD was remarkably weak in comparison with other areas of cardiovascular disease until the recent advent of transcatheter valve therapies. There have been virtually no randomised controlled trials (RCTs) and international guidelines were largely based upon expert consensus[2,3]. Accordingly, there remains a pressing need to coordinate and conduct high-quality research in an attempt to answer a series of key questions.

Who gets VHD and why? And how much is out there?

The genetics and developmental biology of VHD and their interaction with environmental factors are poorly understood. Collation of genetic analyses from existing and emerging biobanks, twin studies and rigorously conducted longitudinal studies using contemporary subjects and high-quality imaging will improve understanding of the current clinical and epidemiological characteristics of VHD (particularly in the elderly population) and identify new determinants of disease progression. In turn, these data will guide policy makers and economists in the planning of the services required to provide surgical and percutaneous interventions and long-term medical care.

What are the factors which govern disease progression?

Although the natural history of VHD is relatively well understood, the rate of evolution varies widely in individual patients. While some are inevitably destined for early deterioration and need for intervention, others remain quiescent for many years or decades. Accordingly, there is considerable scope for the investigation of genetic, biochemical and imaging biomarkers which may be used to finesse current pathways of assessment, allowing targeted early intervention in high-risk subjects and more sedate follow-up (or none at all) in others. Beyond the clinical benefits, future application of such intelligently focused management is likely to be highly cost-effective.

Is there a role for medical therapy?

Although the pathophysiology and natural history of VHD are well described[4,5], there are no medical therapies that influence disease progression (other than, perhaps, vasodilators for chronic aortic regurgitation)[6,7]. Whilst animal studies suggested benefits of lipid lowering in aortic stenosis (AS), clinical trials examining the role of statins in this setting proved negative[8], largely as a result of

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the enrolment of patients with established AS, long after the interval when altered cell signalling and reversal of atherosclerosis-like processes would be of benefit. Recent studies targeting inflammatory cell infiltrates, lipoproteins, extracellular bone matrix proteins and bone mineral have demonstrated favourable effects *in vitro* and clinical investigations exploring these pathways in patients with AS are underway.

Beta-blockers decrease regurgitant volume in mitral regurgitation, and an RCT is needed to establish whether this can delay intervention. Beta-blockers and angiotensin receptor blockers reduce aortic events in Marfan syndrome, though there are no equivalent data for bicuspid aortic valve disease. ACE inhibitors are safer in AS than previously understood and may exert favourable effects on the myocardial response to pressure overload[9]. Whether this translates into clinical benefits remains unclear. Finally, atrial fibrillation frequently accompanies VHD (before and after surgical and percutaneous intervention), and there is no clear evidence to guide the appropriate choice of antithrombotic therapy (or mitigate the associated risk of bleeding, particularly in elderly, frail subjects). RCTs to resolve these uncertainties would be easy to perform and are long overdue.

Or should we intervene earlier?

Severe symptomatic VHD is fatal if untreated, but timely intervention prolongs survival and, in many cases, can restore normal life expectancy. Although non-randomised studies suggest that early surgery is superior to watchful waiting in very severe AS[10,11], uncertainty remains about the optimal timing of aortic valve replacement (AVR) in asymptomatic patients. Novel magnetic resonance imaging markers may be helpful in identifying patients with asymptomatic severe AS at highest risk of haemodynamic compensation[12] and are set for incorporation into forthcoming RCTs examining the role of earlier AVR in this setting.

There is a similar requirement for an RCT to address the old debate of whether immediate surgery is superior to "watchful waiting" for primary MR[5,13]. Collaborative initiatives in the Netherlands and UK may fulfil this need. Guidelines for secondary MR suggest that surgery should only be considered after failure of optimal medical therapy (OMT), including resynchronisation therapy[14]. However, the evidence in this field is limited with wide variations in surgical practice and there is a need for an RCT of surgery versus OMT in patients with and without left ventricular remodelling.

And when will percutaneous interventions supersede conventional surgery?

There have been few advances in prosthetic valve technology since the introduction of the bileaflet mechanical valve in 1977. The failure of novel oral anticoagulants in patients with mechanical valves[15] coupled with increased durability of modern bioprosthetic valves and the likelihood of future percutaneous "valve-in-valve" options for valve degeneration mean that mechanical valves are now used less and less. In contrast, transcatheter aortic valve implantation (TAVI) has become the new standard of care for high surgical risk or inoperable patients with severe AS, affording excellent periprocedural, early and midterm outcomes[16,17]. Now that this disruptive technology has become accepted therapy, important questions concerning its applicability in younger and lower-risk patients and in those with less frequent indications for aortic valve intervention (e.g., bicuspid valve, low-flow low-gradient AS, aortic regurgitation) remain, together with the need to establish the durability of current devices, optimal medical therapy before, during and after the procedure, and further design advances to reduce procedural complications.

These advances in the treatment of AS have paved the way for increasingly novel percutaneous approaches to the mitral and tricuspid valve. The anatomy and pathophysiology of the atrioventricular valves are more complex, and these procedures are often more technically challenging. The rate of scientific, technical and clinical progress is likely to be slower in this domain, and continued close collaboration with surgeons and imaging specialists will be key. Structured research and follow-up audit will be required to validate this "Heart Team" approach and demonstrate its clinical and cost effectiveness[18]. Indeed, as TAVI becomes a routine, simple "PCI-like" procedure, the continued engagement of the entire Heart Team will require enthusiasm and commitment from all parties.

The dialogue continues

Although answers to many of the dilemmas in VHD are now within our grasp, many questions remain. At least some of these are comprehensively addressed in the compelling series of articles within this Supplement. We commend it to you.

Conflict of interest statement

B. Prendergast has received speaker fees from Edwards. J. Fajadet has received educational grants from Abbott, Medtronic and Boston Scientific. C. Tamburino has received honorary fees with Medtronic and Abbott. M. Haude is a consultant for Biotronik, Orbusneich and has received institutional grants and research support from Abbott Vascular, Biotronik, Medtronic, Orbusneich, Volcano and Cardiac Dimensions. S. Windecker has received research funding (to his institution) from Abbott, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, The Medicines Company, and St. Jude Medical; and has received speaker's fees from Astra Zeneca, Eli Lilly and Company, Abbott, Biotronik, Boston Scientific, Medtronic, and Bayer.

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