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Prevention of aortic valve stenosis: A realistic therapeutic target?☆

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ABSTRACT

Aortic valve stenosis (AS) is the most common form of valvular heart disease in the Western world, affecting ~40% of the population over the age of 80; to date the only established treatment is valve replacement. However, AS progression occurs over many years, and is associated from its earliest stages with increased risk of coronary events.

Recent insight into the pathophysiology of AS has included central roles for angiotensin II, for diminished nitric oxide effect at the level of valve endothelium and matrix, and for inflammatory activation/redox stress culminating in activation of pro-calcific stimuli. Despite the presence of atheroma within the stenotic valve, hyperlipidemia per se does not play a critic role in the development of obstructive disease.

We review emerging options for pharmacotherapy of AS, including in particular retardation of disease progression. The various clinical evaluations of lipid-reducing therapy have been uniformly unsuccessful in slowing AS progression. However, recent studies in animal models and retrospective evaluations in humans suggest that ACE inhibitors and/or angiotensin receptor blockers may be effective in this regard. Furthermore, agents normally utilized to treat osteoporosis also offer promise in retarding AS. Given the considerable morbidity, mortality and health care costs associated with AS, such therapeutic developments should be expedited.

Contents

Abbreviations: 5-HT, serotonin; ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; Ang II, angiotensin II; apo, apolipoproteins; AS, aortic valve stenosis; ASc, aortic valve sclerosis; ATP, adenosine triphosphate; AVA, aortic valve area; AVR, aortic valve replacement; BK, bradykinin; BK-2R, bradykinin-type 2 receptor; CAD, coronary artery disease; CRP, C-reactive protein; CT, computed tomography; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; FMD, flow mediated dilatation; GTN, glyceryl trinitrate; MC, mast cell; MGP, matrix Gla-protein; MMP, matrix metalloproteinase; LDL, low density lipoproteins; LV, left ventricular; NEP, neutral endopeptidase; NO, nitric oxide; PGI_2, prostaglandin I_2; RANKL, receptor activator of nuclear factor kappa B ligand; RAS, renin–angiotensin system; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; SNP, sodium nitroprusside; TAVI, transcatheter aortic valve implantation; TGF-β1, transforming growth factor β1; TIMP, tissue inhibitors of matrix metalloproteinase; TNF-α, tumor necrosis factor- α; Trx, thioredoxin; TXNIP, thioredoxin-interacting protein; VICs, valvular interstitial cells.

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1. Introduction: Aortic valve stenosis: causes, epidemiology, health care implications

Aortic valve stenosis (AS), or progressive narrowing of the aortic valve, is the most common valve disease and the primary indication for aortic valve replacement (AVR) in the Western world (Carabello & Paulus, 2009). AS occurs as a result of progressive calcium deposition within the aortic valve, leading to increased stiffness and progressive narrowing of the valve. The earlier stages of AS are designated as aortic valve sclerosis (ASc), which implies the presence of abnormal aortic valve morphology in the absence of marked obstruction.

AS can present at any age, and causes of AS in adolescents and adults under the age of 60 years include congenital stenosis, development superimposed on congenitally bicuspid aortic valves, and post-rheumatic stenosis. Other rare causes are: familial hypercholesterolemia, hyperuricemia, hyperparathyroidism, Paget's disease, ochronosis, Fabry disease, and systemic lupus erythematosus (Braunwald & Goldman, 2003). Bicuspid aortic valve is a relatively common anomaly, affecting ~1% of the general population, with most patients subsequently develop aortic valve calcification by the age of 30 (Yener et al., 2002); however this review will not specifically address this form of AS, as the pathophysiology is potentially different. With the decline of incidence of rheumatic fever, and increasing duration of survival in Western populations, the occurrence of progressive AS on previously normal aortic valves is of major importance.

The prevalence of AS increases exponentially with age and varies between studies: generally AS is present in 2–7% of all patients over 65 years of age, while ASc occurs in about 25% of these patients, and in as many as 50% of those over the age of 84 years (Lindroos et al., 1993; Stewart et al., 1997; Otto et al., 1999). Novaro et al. (2007), in a follow-up of the Cardiovascular Health Study, documented that about 9% of individuals with ASc progress to AS over a 5 year period.

With recent medical advances resulting in increased longevity, the prevalence of AS is expected to rise significantly in the near future (Cowell et al., 2004). In fact, one study found that 50% of patients admitted to hospital with chest pain had ASc (Chandra et al., 2004). Therefore, the health and socioeconomic burden associated with AS is likely to increase substantially.

The presence of ASc, previously thought of as a "benign" finding, is actually independently associated with a significant increase in cardiovascular mortality and morbidity (Otto et al., 1999). In the Cardiovascular Health Study (Novaro et al., 2007), it was also found that patients with ASc had approximately twice the chance of developing new coronary events than those without ASc (Aronow et al., 1999).

Progression to significant valve narrowing can result in development of left ventricular hypertrophy, angina, heart failure, and sudden death (Braunwald & Goldman, 2003). A more recently recognized aspect of the clinical consequences of advanced AS is modification of von Willebrand's factor via shear stress on stenosed valves, leading to increased bleeding risk (Vincentelli et al., 2003).

However, currently, the only effective treatment, usually reserved for critical or symptomatic cases of AS is still prompt AVR whether via open-chested operation or transcutaneous implantation, with poor prognosis (via the development of increasing heart failure and arrhythmias) if surgery is contraindicated, and medical symptomatic management is prescribed (Ross & Braunwald, 1968; Braunwald & Goldman, 2003; Pai et al., 2006; Varadarajan et al., 2006; Bakaeen et al., 2010). Among elderly patients with severe AS and concomitant major non-cardiac morbidity, only a minority ever receive AVR. However, these patients are at serious risk of ongoing disability and multiple hospital admissions prior to death. There is evidence of under-referral of elderly patients who would potentially benefit from AVR (Iung et al., 2005).

Thus therapeutic options with regard to modifying the "natural history" of AS can be categorized according to primary objectives such as:

a) limitation of associated risk for coronary events
b) retardation of valve narrowing, or
c) facilitation of surgical access/symptomatic palliation for advanced cases as summarized in Fig. 1.

Over the past 15 years, there has been significant increase in understanding of the pathophysiology of AS, and it is now understood that AS involves an active disease process, not the previously suggested "wear and tear" theory (Freeman & Otto, 2005). Clinical and experimental studies have been performed to assess pathological changes of aortic valve fibrosis/calcification; to examine factors associated with development and progression of AS; and numerous animal models of the disease have been developed: all aimed at finding medical therapy that could prevent the development as well as retard progression of AS.

To date, no medical therapies have been demonstrably successful in reducing progression of AS in humans. However, clinical trials of this type are limited to the 3 interventions with the use of various statins (Cowell et al., 2005; Rossebo et al., 2008; Chan et al., 2010). In all cases, these interventions were undertaken when patients already had moderate AS. Notably, there have been no interventions in ASc, with other agents in mild/moderate AS, or in high risk patients with early AS and chronic renal failure. All of these are substantial gaps in current therapeutics and will be discussed further in this review.

2. Current treatment strategies

2.1. Surgical/percutaneous transcatheter aortic valve implantation (TAVI)

Aortic valve replacement surgery, and for inoperable cases the more recently developed percutaneous transcatheter aortic valve implantation (TAVI) represent definitive therapy for severe/symptomatic AS. Recent advances in surgical techniques and perioperative care have led to substantial improvements in aortic valve replacement outcomes: mortality has decreased by ~24%, stroke risk by 27% despite population risk profile being worse, particularly increasing age of patients, undergoing surgery (Brown et al., 2009). After successful valve replacement, long-term survival rates are close to those in age-adjusted control subjects, symptoms are less marked and quality of life is greatly improved (Kvidal et al., 2000). However, it is clear that symptomatic status frequently remains impaired, due primarily to the presence of substantial pre-existing intramyocardial fibrosis in many patients (Dweck et al., 2011).

For those elderly patients and those with multiple co-morbidities, who are frequently declined surgery and previously been managed palliatively, recent development of TAVI offers new hope. TAVI has been shown to be associated with sustained clinical and functional cardiovascular benefits in high-risk patients with symptomatic aortic valve stenosis up to a 3-year follow-up (Ussia et al., 2012). Finally, percutaneous aortic valvuloplasty, first described by Cribier et al.