Through the Eye of the Needle: New Approaches to Treating Valvular Disease

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Until very recently, treatment of severe valvular disease was exclusively surgical. With the exception of balloon mitral valvuloplasty used to treat mitral stenosis, all other severe valvular pathologies were either surgically treated or doomed to follow the disease's natural course. However, over the past decade, transcatheter solutions have become available and are used increasingly in clinical practice. Aortic stenosis, together with mitral regurgitation, are the most common valvular disorders, afflicting millions of people in the developed world. Transcutaneous aortic valve implantation and MitraClip™ edge-to-edge percutaneous mitral valve repair have expanded the spectrum of patients who can be treated for severe AS and MR, respectively, and have ushered in a new era with regard to valvular heart disease.

Israel has been actively engaged in the development of some of these novel technologies and, as evidenced by the two reports in this edition of *IMAJ,* has been quick to adopt these new technologies with encouraging results. Finkelstein et al. [1] describe the 30 day clinical outcomes of the first 300 TAVI patients treated at their institution, while Perl et al. [2] present their initial 10 MitraClip patients. Both reports exemplify the rapid adoption of new technologies by the Israeli medical community in an attempt to offer Israeli patients the best that modern medicine has to offer.

Surgical treatment of severe AS has been shown to alleviate symptoms and prolong life expectancy. In low risk patients the perioperative risk of dying is about 1%, while in elderly patients with other comorbidities it is significantly higher [3]. In addition to old age, the following factors also inversely influence postoperative outcomes: female gender, pulmonary hypertension, multivessel coronary artery disease, small stature, previous heart surgery, and left ventricular dysfunction, which can increase perioperative mortality to more than 20%. Therefore, a significant proportion of patients with symptomatic AS are denied surgery due to perceived prohibitive risk. Indeed, in the European Valvular Disease Survey, comprising over 5000 patients with valvular heart disease, 32% of patients with symptomatic valvular disease were not operated on. Early studies explored balloon aortic valvuloplasty for inoperable patients with AS, but this technology fell out of favor due to limited durability of symptom relief and lack of effect on mortality.

Although the concept of transcutaneous valve implantation was conceived in the 1960s, the first-in-man implantation was performed by Alain Cribier only in 2002. Since then this technology has surged ahead and to date over 50,000 patients have been implanted with stent-based biological valves. Two commercially available valves are in use worldwide and in Israel: the Edwards-Sapien (balloon-expandable bovine valve) and the Medtronic CoreValve (self-expandable porcine valve), and a multitude of new valve designs are already in the pipeline. The recently published PARTNER trial, reporting on 5 year outcomes of patients implanted with the Edwards-Sapien valve and additional case series [4,5] support the safety and efficacy of this technology. Indeed, the 30 day outcomes published by Finkelstein and co-authors are consistent with previously published results from around the world, with some of the lowest 30 day mortality and complication rates. It is important to remember that these 300 high risk elderly patients who underwent successful TAVI implantation with low periprocedural risk would otherwise have been deprived of any solution to their illness.

Mitral regurgitation usually stems from malcoaptation of the anterior and posterior mitral leaflets and can be categorized broadly as organic or functional. In organic MR the primary disorder lies in a pathology of the valve leaflets (such as leaflet prolapse and/or flail), whereas in functional MR the primary disorder is myocardial remodeling (such as occurs in ischemic or non-ischemic cardiomyopathy). Ventricular remodeling results in tethering of the chordae and leaflet malcoaptation; however, the leaflets themselves are usually anatomically normal. Since a significant proportion of patients with MR have a primary myocardial disease (ischemic or non-ischemic cardiomyopathy), these patients have an inherently higher surgical risk and, in contrast to patients with organic MR, surgical treatment in these patients has not improved longevity. Therefore, a low risk non-surgical approach to MR is warranted.

The first (and currently only) approved percutaneous treatment of MR is the

AS = aortic stenosis
MR = mitral regurgitation
TAVI = transcutaneous aortic valve implantation

MitraClip device. The procedure is based on the Alfieri edge-to-edge surgical repair technique and is performed through the femoral vein with a large-bore sheath that is placed trans-septally into the left atrium. Under continuous transesophageal echo guidance, a clip is positioned at the point of maximal regurgitant jet and closed in order to capture the anterior and posterior leaflets, thus creating a double-orifice mitral inlet. The EVEREST II randomized controlled trial [6] demonstrated the favorable safety profile of this procedure, but the technique was inferior to surgery with regard to MR reduction. By design though, the EVEREST II trial was performed in low risk surgical candidates and is largely irrelevant to patients who are either high surgical risk or inoperable.

A growing number of clinical registries have reported the outcomes of MitraClip implantation in high risk patients [7,8]. While these series usually demonstrate high 1 year mortality rates, among survivors there are impressive improvements in symptoms, New York Heart Association class, and a reduction in recurrent hospitalizations. The small series by Perl and colleagues is the first series to emanate from Israel and shows that, even allowing for a procedural learning curve and the extremely high risk nature of the patients selected, favorable early outcomes can be achieved. To date, over 9500 MitraClip procedures have been performed worldwide, of which around 50 were performed in Israel. Based on the promising results reported by Perl et al. and the authors' experience, we are convinced that this technology assures a significant clinical improvement in this otherwise "no-option" patient subset.

While we are now able to offer treatment to high risk patients previously turned down for surgery, considerable challenges still remain. Technically, current TAVI technology carries the risk of leaving the patient without AS but with varying severity of aortic regurgitation. Additionally, a high proportion of patients will require permanent pacing after TAVI, especially after CoreValve implantation. MitraClip therapy is suitable for only a minority of patients with MR (about one in seven patients screened is found to be suitable). Thus technical improvements of existing technologies and introduction of new technologies are needed. We predict that new and improved technologies will become available within the near future to address current weaknesses of the current technologies. Most importantly, however, is the critical issue of patient selection. While we can now offer treatment to these patients, not all will benefit. Given that these patients often have multiple comorbidities that may continue to limit their quality of life even after successful treatment of the valvular disorder, it is often difficult to predict which patients will improve. The procedure-associated risk of death and disability, and the high cost to society, make this issue of paramount importance. The major challenge now, beyond the ongoing technical refinement of these procedures, is to understand better which patients will truly benefit from them.

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Capsule

The scavenger receptor SCARF1 mediates the clearance of apoptotic cells and prevents autoimmunity

The clearance of apoptotic cells is critical for the control of tissue homeostasis; however, the full range of receptors on phagocytes responsible for the recognition of apoptotic cells has yet to be identified. Ramirez-Ortiz et al. found that dendritic cells, macrophages and endothelial cells used the scavenger receptor SCARF1 to recognize and engulf apoptotic cells via the complement component C1q. Loss of SCARF1 impaired the uptake of apoptotic cells. Consequently, in SCARF1-deficient mice, dying cells accumulated in tissues, which led to a lupus-like disease, with the spontaneous generation of autoantibodies to DNA-containing antigens, activation of cells of the immune system, dermatitis and nephritis. The discovery of such interactions of SCARF1 with C1q and apoptotic cells provides insight into the molecular mechanisms involved in the maintenance of tolerance and prevention of autoimmune disease.

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