

# The “Off-label” TAVI

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**T**rans-catheter aortic valve implantation has become the standard of care for patients with symptomatic severe tri-leaflet native valve aortic stenosis who are considered to be at extreme risk for surgery. It is an acceptable alternative to surgery for those at high risk [1-5]. However, growing numbers of patients with diseases of the aortic valve other than TNV-AS have been considered candidates for TAVI, including patients with pure or predominant aortic regurgitation with or without aortic stenosis, patients with bi-leaflet (i.e., bicuspid) native valve aortic stenosis, and patients with failed bioprosthetic surgical valves in the aortic or mitral position. These heterogeneous indications are currently considered “off label,” or even relative contraindications, for TAVI. The pathologies are very different from one another, and certainly different from TNV-AS. In practical terms, a different set of TAVI procedures aimed at treating additional diseases needs to be explored. Thus, the approach to each of the diseases should be individualized and highly specialized.

Severe aortic regurgitation is not considered a conventional indication for TAVI. However, in some extreme cases with no surgical option, the feasibility of performing TAVI might be considered an “off-label” indication. Aortic regurgitation

often involves a combined pathology of the aortic leaflets, annular ring, and aortic root. All three can be excessively enlarged, and in most cases without associated valve calcification to anchor the implanted prosthesis. Valves that are currently used were designed for TAVI and are aimed to treat severely calcified aortic stenosis; this is true for self-expandable and, even more so, for balloon-expandable devices. The procedure mostly relies on a careful match between the prosthesis and the native stenotic valve in terms of size, position, annular symmetry, and degree of calcification. These parameters can be altered dramatically among patients with pure aortic regurgitation or BNV-AS. Thus, the ability of the transcatheter valve to seal the aortic annulus completely might be jeopardized under these circumstances.

Similar hurdles are anticipated in pure severe aortic regurgitation without valve calcification and bicuspid aortic stenosis with a very large and elliptic aortic annulus, even with heavy calcification. The challenges may result in less favorable outcomes following TAVI due to device malpositioning and/or excessive residual perivalvular leak causing aortic insufficiency. The preliminary results obtained from a self-reported retrospective multinational registry using the self-expandable CoreValve were less than optimal [6]. Feasibility was shown, but at the price of unpredictable results, lower than expected procedural success, and up to 20% of treated patients presenting with more than trivial residual leaks following implantation and during follow-up.

The transcatheter treatment of failed bioprosthetic surgical valves is com-

pletely different [7], though it is also considered an off-label indication for TAVI. Nonetheless, favorable experiences are being reported worldwide for this indication in the aortic and mitral position, and the results seem promising [8,9]. This procedure was designed to avoid a risky second valve replacement surgery. The challenge of the valve-in-valve implantation procedure depends on several parameters that should be recognized by the operator, including verification of the following details prior to valve implantation: valve type and size (internal and external diameters), ringed versus stentless valve shape, annular versus supra-annular implant location, mode of failure (stenosis, regurgitation, or both), lack of endocarditis or thrombosis, degree of calcification, and the valve distance from the coronary ostia. Careful procedural planning is mandatory in order to achieve valve-in-valve procedural success. The mitral bioprosthesis can be reached mostly via the trans-apical route, and the heart team (surgeons and cardiologists) should be intimately involved in the decision-making and planning processes for these procedures [10].

Finally, TAVI is a gratifying procedure when performed in the right patients. However, the procedure is associated with significant life-threatening risks, especially when patient selection is sub-optimal and/or the procedure is not well planned. In this issue of *IMAJ*, Segev et al. from Sheba Medical Center [11] report their experience with the procedure. These authors should be congratulated for bringing to light and discussing the matter of unique off-label TAVI procedures in their institution. The work should provoke a discussion about procedural suitability, case

TNV-AS = tri-leaflet native valve aortic stenosis  
TAVI = transcatheter aortic valve implantation

BNV-AS = bi-leaflet (i.e., bicuspid) native valve aortic stenosis

selection, procedural planning, and complex techniques. In the experienced hands of the authors, the exceptionally complex procedures went well. Nonetheless, more data beyond anecdotes are needed to verify whether TAVI can be a useful therapeutic tool for additional valve pathologies and indications.

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### Capsule

#### Inflammatory monocytes regulate pathologic responses to commensals during acute gastrointestinal infection

The commensal flora can promote both immunity to pathogens and mucosal inflammation. How commensal-driven inflammation is regulated in the context of infection remains poorly understood. Grainger et al. show that during acute mucosal infection of mice with *Toxoplasma gondii*, inflammatory monocytes acquire a tissue-specific regulatory phenotype associated with production of the lipid mediator prostaglandin E2 (PGE2). Notably, in response to commensals, inflammatory monocytes can directly inhibit neutrophil activation in a PGE2-dependent manner. Further, in the absence of inflammatory monocytes, mice develop severe neutrophil-mediated pathology in response to

pathogen challenge that can be controlled by PGE2 analog treatment. Complementing these findings, inhibition of PGE2 led to enhanced neutrophil activation and host mortality after infection. These data demonstrate a previously unappreciated dual action of inflammatory monocytes in controlling pathogen expansion while limiting commensal-mediated damage to the gut. These results place inflammatory monocyte-derived PGE2 at the center of a commensal-driven regulatory loop required to control host-commensal dialog during pathogen-induced inflammation.

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### Capsule

#### *Bacillus thuringiensis* (Bt) toxin to combat worms

Some humans share several characteristics with pigs, including very similar parasitic worms. *Ascaris* spp. roundworms are large and pungent, and can occur in sufficient numbers to block the gut, pierce the peritoneum, and invade the bile duct. In children, the morbidity caused by a heavy worm infection can have lifelong consequences. Surprisingly perhaps, roundworms can be killed by a *Bacillus thuringiensis* (Bt) toxin, a bacterium more usually encountered in crop pest control. Urban et al. have been exploring the potential of one Bt toxin, Cry5B, as an anthelmintic (a deworming drug), using young pigs as a human substitute. Experiments on the mode of action in the classic worm model *Caenorhabditis elegans* showed that Cry5B binds to galactose-containing glycolipid

receptors found only in invertebrates, and this was confirmed to be the case in *Ascaris* too. Cry5B was given by gavage to groups of five piglets as spore crystal lysate in two doses (20 mg/kg) 10 and 12 days after infection, when the penultimate larval worm stage emerges into the gut (unfortunately, there are severe practical constraints on testing the limited-availability Bt toxin on the slow-growing adult worms), and 6 days later 97% of these larvae were dead and the remainder disabled. The natural product Cry5B could thus be a valuable addition to the anthelmintic roster, especially as resistance is emerging to the standard drugs.

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