

Transcatheter aortic valve implantation (TAVI): risky and costly

Many of the 40 000 transcatheter procedures carried out so far cannot be justified on medical or cost effectiveness grounds. **Hans Van Brabandt, Mattias Neyt, and Frank Hulstaert** examine why practice has gone beyond the evidence

Around the world, tens of thousands of people have been treated for a life threatening heart condition using a minimally invasive technique that many see as the wave of the future. Transcatheter aortic valve implantation (TAVI) offers hope to patients too old or too ill for conventional aortic valve replacement operations, and since its introduction 10 years ago it has spread swiftly—by the end of 2011, an estimated 40 000 transcatheter implantations had been done.¹ But serious unanswered questions remain over the clinical outcomes and the cost effectiveness of TAVI, as well as the regulatory process that enabled it to gain such a large market so rapidly, particularly in Europe.

Aortic stenosis, the progressive failure of the aortic valve to open fully, is the commonest type of valve disease in elderly people. It is usually treated by valve replacement surgery, but around a third of those who might benefit are turned down because the risks of surgery are too high or because problems such as a calcified aorta or scarring from previous surgery make them unsuitable for surgery.² Untreated, most will die within five years.³ TAVI offers an alternative, in which a replacement valve is introduced through an artery via a small incision (usually the femoral artery) or, less often, surgically with an incision into the chest and then into the left ventricular apex—the transapical approach.

The numbers who could potentially benefit from TAVI are very large.⁴ Almost 3% of people over 75 have aortic valve disease,⁵ which means that in England alone there are more than 100 000 patients in whom aortic valve surgery might at a given moment be contemplated. But only around 1200 aortic valve replacements are carried out in this age group

in England each year. This helps explain the enthusiasm with which TAVI has been taken up, and the large potential market. In April 2011, a New York securities analyst for the financial services company Wells Fargo estimated that TAVI could generate more than \$2.4bn (£1.5bn; €2bn) in sales in the US and account for more than a third of aortic valve replacements by 2015.⁶ Cardiologists in the US also expect growing demand from patients who are suitable for conventional surgery but who prefer the quicker and less painful transcatheter option.

Data reported at the European Society of Cardiology (EuroPCR) meeting in Paris in May⁷ suggested that transcatheter procedures have more than tripled in Europe since 2009, rising to 18 372 in 2011. Germany is far ahead of other European nations, being responsible for 43% of all TAVIs, followed by France (13%), Italy (10%), and the UK and Ireland (7%).¹

Approval processes

Given the enthusiasm with which the procedure has been adopted, we might expect the evidence for its efficacy to be solid. But a health

technology assessment we carried out, commissioned by the Belgian government, concluded that the Belgian health authorities should pay for TAVI in only a minority of patients (10%) of those currently considered for treatment—those who are deemed inoperable for technical reasons such as a series of previous operations or irradiation of the chest wall.⁸ The United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidance issued in March this year said that for patients considered unsuitable for surgery, the evidence for TAVI was adequate from a clinical point of view but it did not take costs into account.⁹ But NICE said that for patients for whom surgery is suitable, albeit risky, the evidence for using TAVI was inadequate, and it should be used in these circumstances only when special arrangements for clinical governance, consent, and data collection or research were in place.⁹

In the European Union, medical devices fall outside the scope of the European Medicines Agency and need only a simple quality certificate (CE mark) to gain access to the market, putting them on the same footing as domestic appliances such as toasters. Two different

One year mortality and stroke rate in the PARTNER trial¹³⁻¹⁵

	High risk patients*			Inoperable patients				
	TAVI		P value	Pivotal trial†		P value	Continued access study‡	
	TAVI	AVR		TAVI	Control		TAVI	Control
No of patients	348	351		179	179		41	49
1 year all cause mortality (% (No of events))§	24.2 (84)	26.8 (89)	0.44	30.7 (55)	50.7 (89)	<0.001	34.3 (13)	21.6 (10)
1 year stroke rate (% (No of events))¶	8.3 (27)	4.3 (13)	0.04	10.6 (19)	4.5 (8)	0.04	2.4 (1)	0 (0)

TAVI= transcatheter aortic valve implantation, AVR=surgical aortic valve replacement.

*Hazard ratio with TAVI in high risk patients: 0.93 (95% CI 0.71 to 1.22; P=0.62)

†Hazard ratio with TAVI in inoperable patients (pivotal trial): 0.55 (95% CI 0.40 to 0.74; P<0.001);

‡No P value or hazard ratio was published for the continued access study.

§Kaplan-Meier estimates.

¶Includes any stroke and transient ischaemic attack; stroke rate in continued access study includes "major stroke" only.

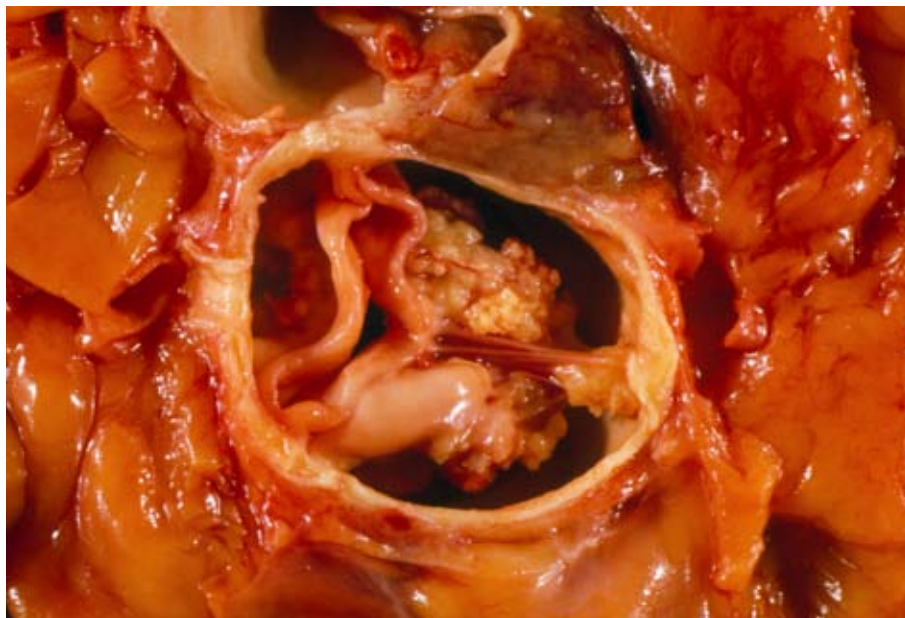
Europe's lax licensing laws set up in an era where medical devices typically comprised hearing aids, walking frames, and spectacles are not appropriate for implantable devices

valves for transcatheter implantation gained their CE marks in 2007, long before any substantial clinical trial evidence was available: the Edwards Sapien valve and the Medtronic CoreValve. In the US the law demands evidence of efficacy in a randomised trial before the Food and Drug Administration can license any innovative device. Thus TAVI was in use in Europe four years before the FDA licensed the Sapien valve in November 2011, and—in contrast to Europe—only for the transfemoral approach and for patients considered unsuitable for standard valve surgery.¹⁰ The transapical route was not approved. In June 2012, a panel of expert advisers recommended that the FDA approved the Sapien valve for high risk operable patients, including a transapical delivery option.¹¹ The advisory panel does not take economic considerations into account.

The European system for approving medical devices has already come in for criticism over breast and hip implants, with the new executive director of the EMA, Guido Rasi, acknowledging in January that there is an urgent need to regulate devices with the same care as medicines. “I think, at the end of the day, we will see everyone moving to increasing use of comparative trials,” Rasi said in an interview with Reuters.¹² He expected that concerns about the now defunct French breast implant company Poly Implant Prothese might help to speed the process.

But while the evidence demanded by the FDA exceeded that required in Europe, we remain far from convinced that it is adequate. The Sapien valve was approved on the basis of a trial called PARTNER (Placement of Aortic Transcatheter Valve). We reviewed the conduct and results of the trial through papers published in peer reviewed journals, proceedings from congresses, press releases, and direct contacts with the manufacturer, the FDA, the *New England Journal of Medicine (NEJM)* (where it was published), and the principal investigators.

Our rigorous analysis of all the available data, in combination with a study of real world TAVI practice in Europe, led us to conclude that the arguments supporting the widespread use of TAVI do not stand up to scrutiny. In addition, the PARTNER trial seems to have important problems, the most relevant being publication bias and lack of data transparency, unbalanced patient characteristics, and incompletely declared conflicts of interest.



One in forty over-75s has some degree of aortic stenosis

What the evidence shows

PARTNER was a randomised controlled trial in 26 sites, most of them in the US. It allocated patients with severe aortic valve stenosis to two groups: those at very high risk from surgery (cohort A)¹³ and those deemed inoperable (cohort B).¹⁴ The 699 patients in cohort A were randomised either to TAVI or to surgical valve replacement, and the 358 in cohort B were randomised to TAVI or standard therapy, which was balloon aortic valvuloplasty in most cases, combined with medical supportive treatment.

The results showed that in the high risk operable patients, mortality at one year was similar for TAVI and surgical insertion (24.2% v 26.8%, $P=0.44$) (table). PARTNER was designed as a non-inferiority trial, with a difference of 7.5 percentage points in survival set as the margin, so TAVI met this target. But strokes and transient ischaemic attacks were significantly commoner in the TAVI group at one year (8.3% v 4.3%, $P=0.04$) and major vascular complications significantly commoner at 30 days (11.0% v 3.2%, $P=0.001$). Major bleeding and new onset atrial fibrillation were significantly higher in the surgical group. At one year, symptoms were about the same in both groups.¹³

In the patients deemed inoperable, results were relatively better. Mortality at one year was significantly lower for TAVI (30.7% v 50.7%, $P<0.001$). Again, however, there was a higher

incidence of stroke and major vascular events in the TAVI group (10.6% v 4.5%, $P=0.04$).¹⁴

Taken together, these results suggest that TAVI can be justified for inoperable patients on clinical grounds, though cost effectiveness calculations are more equivocal. But even this conclusion is thrown into doubt by a follow-up study authorised by the FDA, in which 41 inoperable patients were randomised to TAVI and 49 to standard therapy. This study remains unpublished, and our attempts to gain access to further details have been rebuffed by the FDA and the study sponsor. But the data presented at an FDA meeting on 20 July 2011 showed that the TAVI patients fared worse than those given standard therapy (one year mortality 34.3% v 21.6%).¹⁵

We have repeatedly sought access to further details of this follow-on trial, carried out under FDA auspices as a formally approved “continued access study,” the purpose of which is to enable sponsors of clinical investigations to continue to enrol patients while a market application is being sought. The FDA responded that any further data analysis of a premarket application is proprietary information and that it was up to the sponsor to release it, if so inclined. But our requests to the sponsor (Edwards) and the principal investigator went unanswered. In our view, this behaviour is both ethically and scientifically unacceptable and should be legally regulated in future.

NICE said that for patients for whom surgery is suitable, albeit risky, the evidence for using TAVI was inadequate, and it should be used in these circumstances only when special arrangements for clinical governance, consent, and data collection or research were in place

Study sponsors should be obliged to make the results of a negative trial public so that policy makers can reach rational and balanced decisions.

Given our failure to make progress with the FDA or the sponsor, we approached the *NEJM* which had published the PARTNER trial. We put our objections to the *NEJM*, which passed them on to the investigators. Their response convinced the *NEJM* editors that “while each of the points we raised deserved a thoughtful review, they did not, either individually or together, fundamentally place the findings of the PARTNER trial in serious doubt.” Asked what the responses of the investigators had been, *NEJM* responded that it had not requested permission from them to pass them on, since they were intended for its own confidential evaluation. We were recommended to request this information directly from the study sponsor, which we did, to no avail.

NEJM has, however, published two year follow-up results that essentially confirmed the one year data.^{16 17} However, it did so without demanding that the study sponsor publish or discuss the negative results of the follow-on trial. It is difficult to understand this decision.

Our concerns about the PARTNER trial go further than this, however. Published data on the inoperable patients, who had the most convincing results, show that the treatment and control groups are unbalanced in a way that would favour TAVI. The control group contained more patients with comorbidities, more who had had a previous heart attack, and more who were classified as frail than the TAVI group. There were fewer patients with an extensively calcified aorta. All these differences could have arisen from a flawed randomisation or by chance; but since they favour TAVI, an analysis that adjusted for prognosis at baseline would have produced a more realistic estimate of the effect size.

Disclosure of interests

Martin Leon, the principal investigator of the PARTNER trial, has substantial financial interests that we do not believe were fully disclosed. As the original developer of the Sapien valve, he is reported to have received \$6.9m from Edwards Lifesciences when it bought the company he founded, Percutaneous Valve Technologies, for \$125m in 2004.¹⁸ The *NEJM* paper article acknowledges under Leon’s conflicts of interest “2004—payment for equity

holdings as company was sold to Edwards Lifesciences.” But it does not mention that he was to receive three further payments on the achievement of three milestones: successful treatment of 50 patients, regulatory approval in Europe, and limited approval in the US.¹⁸ In an interview with *Businessweek*, Leon said that he had donated his milestone payments to a Manhattan school.¹⁸

Practice beyond the evidence

What concerns us most is that in Europe the use of TAVI in the transapical route far exceeds what is justified by the clinical evidence. The PARTNER trial does not provide clear evidence on this route. A subgroup analysis suggests that the transapical approach is not inferior to surgery but has double the risk of stroke. Although the FDA proposed it,¹⁹ the trial sponsor declined to include a transapical arm in inoperable patients. But despite this dearth of evidence, TAVI is widely used transapically in Europe.

The UK TAVI registry, for example, shows that 409 of 1620 TAVI patients (25%) were treated transapically, with a one year mortality of 25.5%.²⁰ The FRANCE-2 registry shows that of 2430 patients treated in 2010 and 2011, 20% had transapical TAVI, with a six month mortality of 20.2%.²¹ We cannot know, of course, what the survival rate of these patients would have been if they had been treated medically or by standard surgery. A position statement by the British Cardiovascular Intervention Society and the Society of Cardiothoracic Surgeons does not distinguish between the transfemoral and transapical approaches despite the different evidence bases.²² It states that TAVI should currently be reserved for patients in whom “the risk/benefit ratio of open heart surgery versus TAVI favours TAVI.” It calls for randomised trials, but only when centres in the UK have got “beyond their learning curve.” Patients may be surprised to hear that trials are being delayed to allow cardiologists and surgeons time to learn the technique.

Concerns about transapical TAVI were heightened by the early termination of a Danish trial called STACCATO,²³ which compared transapical TAVI against conventional surgery. Five of 34 TAVI patients and only one of 36 surgically treated patients had either died or had a major stroke or renal failure within 30 days, prompting the data safety monitoring board to call a halt. This discourag-

ing result was reported at the 2011 transcatheter cardiovascular therapeutics conference in San Francisco and drew criticism from Michael Mack, of the University of Texas at Dallas, who said the study was poorly designed and poorly executed.²⁴ Mack, an investigator in the PARTNER trial, said: “I think there is some misinformation here, based on an invalid trial design, that is likely to hurt the field.”

Leif Thuesen, of Aarhus University Hospital in Denmark, who presented the STACCATO results, was more concerned with patients than with the field. “There is no doubt that there are patients who can’t be operated on, and they should be treated with TAVI” he told *Heartwire*. “But the patient who can be operated on—here, we should be very, very cautious. It’s the operable patients, the low-risk patients, they should not have the TAVI procedures, but that’s what is happening. We had one patient, for instance, who did not want the conventional operation, so he had the TAVI procedure in Canada. That’s how it is. Indications are slipping.”²⁴ In contrast to the current situation in Europe, we recommend that marketing approval for a high risk device should be granted for specific indications only. Each of these indications should be supported by clinical evidence from high quality randomised trials. Patients may be at risk if the high risk device is routinely used outside those indications. Payers may have an interest in limiting reimbursement of such high risk devices only to those indications for which there is a high level of evidence of efficacy and cost effectiveness.²⁵

Based on current evidence, and considering efficient use of limited resources, it is difficult to see how healthcare payers can justify reimbursing TAVI for patients suitable for surgery, given that the risk of stroke is twice as high after TAVI. In addition, TAVI is much more expensive, on average about €20 000 more per patient in our analysis of Belgian data. Based on observational data, the costs during the initial hospital admission, inclusive of an Edwards Sapien valve of €18 000, are on average €43 600 for TAVI versus €23 700 for surgical valve replacement. The average cost of transapical TAVI is higher than for the transfemoral approach (€49 800 v €40 900).²⁶ The NICE guidance did not include a cost-benefit analysis, but these costs should be taken into account by local NHS commissioners in decisions about whether to fund the procedure. If

policy makers are willing to pay for TAVI, they should give priority to anatomically inoperable patients.^{8 26}

Europe's lax licensing laws set up in an era where medical devices typically comprised hearing aids, walking frames, and spectacles are not appropriate for implantable devices. It should require high quality randomised trials to show clinical efficacy and safety before granting marketing approval to innovative, high risk medical devices. And a major improvement in transparency of information is also needed to allow clinicians to practise evidence based medicine, patients to make informed decisions, and health technology assessment agencies to make the right judgments.

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BMJ BLOG Liz Wager

Deworming the literature



A recent Cochrane systematic review caught my eye, not so much for its conclusions but for what it shows about the state of the medical literature.

According to Paul Garner, one of the review's authors, they found a study on nearly 28 000 children, which was published in the *BMJ* in 2006, which concluded that deworming preschool children in Uganda helped them gain weight but, in fact, when correctly analysed, showed no significant difference. They also found that the largest study, of a million Indian children, carried out in 2004, had never been published.

These two findings, which you might find depressing, actually cheer me up in a funny sort of way. That's because I've spent a lot of time in the last few years talking about (and trying to train people in) research reporting and publication ethics. Telling people that you are passionate about publication ethics is similar to admitting that you are a train spotter. Most people think it is a dry, academic discipline, almost totally disconnected from real life and anything interesting. But this systematic review shows how badly reported research and non-publication of research can harm people. Supposing policy makers had based their findings on the wrongly analysed *BMJ* article they would, at the very least, have wasted money, and perhaps, at worst, harmed some children.

Similarly, without the diligence of reviewers to uncover unpublished research, most clinicians and policy makers would have had access only to a biased selection of the data. This could also force them into reaching the wrong conclusions.

I'm not clever enough to enter the arguments on either the benefits of deworming, or the correctness of the statistical methods (although I plan to follow these discussions as far as I can understand them). But I'm oddly delighted at this clear demonstration that my obsession with good research reporting and publication ethics might seem just a bit more understandable to some people now. Thanks, Paul! (and, by the way, does anybody know if deworming cats is evidence based?)

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