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Therapy focus – Transcatheter mitral valves prove trickier than aortic

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The competition to bring the first non-surgical mitral valve to the world's markets has begun in earnest, and Medtronic is in the most advantageous position, believing that it can achieve European approval of its Intrepid device next year. But what about the others?

The valve specialist Edwards Lifesciences is surprisingly far behind considering its pioneering stance when it came to transcatheter aortic devices. Owing to a clinical hold on its CardiAQ product it now appears to be lagging Abbott Laboratories, which despite being the larger company is less well versed in this particular technology.

Edwards bought Cardiaq, the developer of CardiAQ, in summer 2015. This period saw several acquisitions of mitral valve developers – Medtronic and Abbott both obtained their candidate devices via acquisitions around the same time.

The CardiAQ project ran into difficulty this February, with Edwards placing studies including the CE mark trial, Relief, on hold (*Edwards puts a second mitral valve trial on hold, February 3, 2017*). On the company's second-quarter conference call in July, chief executive Michael Mussallem said Edwards had resumed implants of the valve, but only in the US feasibility study. This is enrolling 28 patients with degenerative or functional mitral valve regurgitation and is due to conclude in December. Mr Mussallem added that CE mark for CardiAQ was expected in 2019.

Three months later the picture had changed: Mr Mussallem said that the mitral valve the group would bring to market would be an updated version of CardiAQ, smaller and more easily delivered via the femoral vein. The company was "refining our CE mark timing", he said.

The listing on Clinicaltrials.gov for the Relief study gives a conclusion date of October 2017. It has not been updated since last December. Edwards declined to clarify the status of the trial or the expected CE mark timing for CardiAQ, telling *EP Vantage* that this might be addressed in its investor call next week.

Global

This could mean that Edwards gets pipped to the European market not only by Medtronic but by Abbott too. Abbott's transcatheter mitral valve, Tendyne, is on course for CE mark in the second half of 2019, a spokesperson told *EP Vantage*.

Like Medtronic, the company reported data on its mitral device at the Transcatheter Cardiovascular Therapeutics meeting in Denver last month. One-year results from a global feasibility trial in 30 patients reported a mortality rate of 16.7%. The one-year mortality rate with Medtronic's Intrepid was 24%, though at this early stage these data do not mean a lot – comparisons will only really be worth making on data from larger trials pitting the devices against surgery (*Medtronic aims for world's first transcatheter mitral valve approval, November 9, 2017*).

The next trial of Tendyne is also global. Abbott is enrolling 110 patients in Europe, the US and Australia, with data to be used for a CE mark application. Enrolment completion in this study is expected next year, and with 30-day primary endpoints – freedom from device or procedure-related adverse events and freedom from device malfunction – results ought to emerge swiftly.

US pivotal trials of Tendyne will be launched in 2018, and Abbott is in discussions with the FDA and CMS to finalise the design of the trial. Chances are that the study will be similar to Medtronic's pivotal US trial, with at least part of it randomised against surgical valve implantation.

If Abbott is indeed second to market it might still be able to do well, since Tendyne and Intrepid could end up treating slightly different populations. Medtronic is "focusing very much on functional mitral regurgitation", Pieter Kappetein, chief medical officer of the company's coronary and structural heart division, told *EP Vantage* earlier this month.

Functional regurgitation occurs after another event, often a heart attack, whereas the other form of the disease, degenerative regurgitation, is inherent to the mitral valve itself. Abbott appears to be agnostic to the form it treats, and its CE mark trial is enrolling patients with severe mitral regurgitation of primary or secondary aetiology.

Others

At least one other company is out of the running. Neovasc was considered a shoo-in for a takeout in 2015, but no one bought, perhaps because it had been sued a year earlier by Cardiaq for misappropriation of trade secrets.

Edwards continued the suit after acquiring Cardiaq, and finally won a decisive victory this month. The full judgment of $112m, which Neovasc said exceeded its cash resources, became due on November 13; Neovasc is no longer any kind of threat to the other mitral valve developers.

Another smaller group, Mvalve Technologies – which Boston Scientific has an option to acquire – appears to have stalled. A 30-patient first-in-human study in Europe and Brazil was expected to conclude last June, but no announcement was made; Mvalve does not even have a website. The study's record on Clinicaltrials.gov has not been verified since early 2016.

The most interesting aspect of the mitral valve derby is that, unless there is a surprise announcement from Edwards next week, it is beginning to look like it will be the third company to gain approval. This could hardly have been predicted considering its phenomenal success in spearheading transcatheter aortic valves. Owing to cardiac anatomy delivering mitral prostheses via catheter was always going to be a greater challenge than aortic valves, but Edwards seems to have found it more problematic than its peers.

Transcatheter mitral valves: who, where and when

Company	Valve	Study	N	Completion	Trial ID	CE mark possible
Medtronic	Intrepid	Open-label European approval trial	82	2018	-	2018
Medtronic	Intrepid	US approval trial, part-randomised vs surgery (Apollo)	1,380	Oct 2021	NCT03242642	2018
Abbott Laboratories	Tendyne	Open-label US, European and Australian trial	110	May 2018	NCT02321514	H2 2019
Edwards Lifesciences	CardiAQ	Open-label phase I/II European approval trial (Relief) - believed to be still on hold	200	Oct 2017	NCT02722551	2019 or 2020?
Edwards Lifesciences	CardiAQ	Open-label phase I US feasibility trial	28	Dec 2017	NCT02718001	2019 or 2020?

Sources: interviews and clinicaltrials.gov.

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