

Transcatheter aortic valve implantation: know the differences between the currently available technologies

This follow-on article (see below) comparing the differences between the Edwards-Sapien valve (ESV) and the Medtronic CoreValve (MCV) discusses transcatheter valve technologies from the point of view of a world-renowned team of cardiac experts led by Dr Sanjeevan Pasupati from Waikato Hospital, New Zealand, which has deployed both the ESV and the MCV technology since 2008.



ESV left MCV right

Since its initial success in 2002, transcatheter valve implantation (TAVI) has emerged as a viable treatment option for patients with symptomatic severe aortic stenosis (AS) who are at very high or prohibitive risk for operative mortality. To date, ~10,000 patients have been treated with this technology worldwide.

Transcatheter valve implantation has been predominantly performed using either the balloon-expandable Edwards-Sapien valve (ESV) or the self-expanding Medtronic CoreValve (MCV) device, both of which have received CE Mark approval and are currently available for commercial use. Clinical results have so far provided excellent safety and efficacy with excellent intermediate term durability for both technologies. The first randomized multicentre trial using the ESV vs. surgical aortic valve replacement (AVR), PARTNER (Placement of AoRTic traNscathetER valves), has just

completed enrolment of over 1000 high-risk patients. The trial results are expected to answer many questions regarding the value, indications, and outcomes of the transcatheter aortic valve implants. Transcatheter valve implantation offers a number of potential advantages to patients and healthcare providers over surgical AVR, including the avoidance of sternotomy and cardiopulmonary bypass, a shorter hospital stay, and faster return to functional status.

Both valve procedures require implantation by highly skilled operators. As noted in a 2008 position statement released by the European Association of Cardio-Thoracic Surgery and European Society of Cardiology, procedural success is closely linked to experience and is around 90% in experienced centres; an evident learning curve leads to better patient selection and outcomes.¹ Centres undertaking these technologies must understand the core features and the differences between these devices, to offer the best care for their patients.

Valve design

The balloon-expandable ESV consists of three pericardial leaflets initially equine (Cribier-Edwards), currently bovine, fixed using the Carpentier-Edwards ThermaFix™ tissue process and presented in glutaraldehyde in a naturally open manner. The leaflets are positioned at the bottom of the stent and function intra-annularly following deployment. The leaflets are mounted within a stainless steel tubular-slotted stent which has an outer diameter of 23 mm (14.3 mm height) or 26 mm (16.1 mm height), depending on the size of the valve (23 or 26 mm inflow). The latest iteration (Sapien XT) has a cobalt-chromium lower profile frame with an enhanced semi-closed leaflet design. A fabric cuff with an unscalloped construction at the inflow provides an effective seal for 7–8 mm of the stent, which is the target for placement across the aortic annulus. The valve is specifically designed to fit into an aortic annulus of 18–25 mm and

usually positioned below the coronary ostium. The advantage of this design is that it facilitates coronary intervention in future. However, during deployment the stent usually flares at the outflow, increasing the chance of coronary obstruction (a 26 mm stent may flare at the aortic end to more than 26 mm). Magnetic resonance imaging data show that the device is safe in magnetic fields up to 3 Tesla.

The self-expandable MCV consists of three pericardial tissue leaflets, initially bovine and currently porcine, presented in glutaraldehyde in a naturally closed manner. The leaflets are positioned at the smallest dimension of the frame and function in the supra-annular position following deployment, i.e. implants placed intra-annularly but function supra-annularly. Leaflet inner diameter measurements are 22 or 24 mm, depending on the size of the valve (26 or 29 mm inflow), which is designed to fit into an aortic annulus of 20–27 mm. A pericardial skirt with a scalloped construction at the inflow provides an effective seal for 8 mm of the frame, which is the target for placement across the aortic annulus. The stent frame is 53–55 mm tall, allowing implants to be placed from the annulus to the ascending aorta across the coronary ostium. The self-expandable nitinol stent has three levels of radial force: the lower (inlet) portion has a high radial force to expand against the calcified native leaflets; the middle portion carrying the valve is constrained to avoid obstructing the coronary arteries; the upper portion (outlet) is flared to fixate and align the frame in the ascending aorta. An advantage of this design is that it is less likely to result in coronary obstruction: a 29 mm frame has high hoop strength at the coronary height and opens to a maximum outer diameter of 25 mm. However, there is a greater difficulty when wanting to perform future coronary intervention, especially if the implant is high. Magnetic resonance imaging data document safety of this valve in magnetic fields up to 4 Tesla.

Delivery system

The ESV is manually crimped on to a balloon using a disposable crimper. The crimping needs to be done meticulously as there is potential for leaflet damage. The incorporation of the nosecone has improved the crossing of the native valve; however, there are multiple transition points from the nosecone to the delivery catheter occasionally requiring manipulation during crossing. A 'steerable tip' retroflex delivery system with a short stent mounted at the tip helps to negotiate tortuous aortic anatomy. Current devices use 22 and 24 Fr sheaths for delivery. The Sapien XT with the NovaFlex delivery is designed to use an 18 and 19 Fr sheath for the 23 and 26 mm valves, respectively. There are more vascular complications with sheath sizes >20 Fr, which limit the arterial approaches. However, with the ESV, if arterial access is not appropriate, a transapical access can be utilized, by easily mounting the valve in the opposite direction on the stent balloon. Currently, there is a dedicated Ascendra delivery system designed for this approach, utilizing a 26 Fr sheath.

The MCV is manually loaded on to an 18 Fr capsule using a disposable loading system. A single smooth transition point from the nosecone to the delivery catheter facilitates smooth crossing of the native valve. Despite a flexible 12 Fr shaft with a tall frame inside, the 70 mm-long capsule requires a large-radius aortic arch with less

aortic tortuosity to achieve successful device tracking. Using the axillary approach helps to overcome some of these issues. Current devices use an 18 Fr sheath for delivery (reduced from 25 Fr) and are associated with reduced rates of vascular complications, as well as higher success rates of percutaneous closure. The transarterial approach (transaxillary and transfemoral) is most commonly used; some attempts to deliver transapically have not been widely adopted.

Procedure

The ESV is positioned using fluoroscopy and transoesophageal echo in most centres, under general anaesthesia. The valve is deployed under rapid pacing without cardiopulmonary support and cannot be repositioned. Anchoring the valve at the annular level has the following advantages:

- May be deployed in patients with a dilated ascending aorta/root;
- Easier to deploy in unfolded aorta;
- The annulus to the ascending aorta angle does not hinder deployment.

The disadvantages are that any errors in deployment are less forgiven and there is a greater chance of valve embolization. The ESV is less suited to the bicuspid aortic valve, as poor uneven expansion can cause significant valvular aortic regurgitation (AR) due to incomplete coaptation of the leaflets. This valve has been successfully implanted in many patients with severe mitral regurgitation (MR) and an ejection fraction (EF) of <20%.

The MCV is positioned using fluoroscopy only and can thus be performed under local or general anaesthesia. The valve is deployed in a controlled manner without pacing or cardiopulmonary support. There is allowance for limited repositioning. The valve is anchored at the annulus and ascending aorta. Advantages of this approach include: easier deployment with less chance of valve migration; less precise positioning is more easily forgiven with less valve embolization. Disadvantages are that the valve cannot be used in dilated ascending aorta. In addition, the MCV is more likely to tilt during deployment in a steeply angulated aortic root or unfolded aorta, making placement challenging, and potentially less favourable. This valve is better suited to the bicuspid aortic valve, as the leaflets function supra-annularly and poor, uneven expansion is more easily forgiven. As less experience exists in patients with severe MR and an EF <20%, the MCV is not recommended for use in this population. Currently, implantation in such patients is acceptable upon improvement in MR and/or EF following balloon aortic valvuloplasty.

Valve deployment inside a pre-existing valve

The ESV is easily deployed inside a pre-existing ESV and results in good valve function. Valve placement inside a pre-existing surgical valve is best achieved via a transapical approach, which allows better control of the ESV during deployment. The valve may be used for both aortic and mitral valve failures.

The MCV is easily deployed inside a pre-existing MCV, resulting in good valve function. However, if the frame is not in alignment,

coronary cannulation can be challenging. Valve placement inside a pre-existing surgical valve is undertaken in a controlled fashion, using transarterial access. The CoreValve is only used for valve failure in the aortic position.

Outcomes

The ESV carries less risk of significant paravalvular AR due to malposition, as most valves in this scenario will embolize. Low rates of left bundle branch block (LBBB) and a reduced need for a permanent pacemaker (~5%) have been observed. Late heart block is less of a concern. Specific anti-calcification treatment should promote longer leaflet durability, but this is yet to be proved in human studies. However, valve failure may occur in the long-term in incompletely expanded stents, as the leaflets function intra-annularly, which may affect the coaptation.

Significant paravalvular AR due to malposition of the MCV is more evident as the valve is more forgiving and will function normally without embolizing under less precise deployment. Under this scenario, a slightly higher AR is acceptable, if tolerated by the patient on the table. Aortic regurgitation due to deep positioning of the valve may be treated by repositioning the valve. High rates of LBBB and pacemaker dependency (25–35%) may have implications for long-term left ventricular (LV) function. The need for a pacemaker is increased by the scalloped inflow skirt design, forcing the valve to be deployed 4 mm towards the LV compared with an ESV, and a higher inflow diameter to annular thickness ratio than the ESV is likely to damage the electrical conduction. Notably, late heart block can occur due to continued expansion of the frame post-deployment; the majority occur in the first 48 h. Long-term monitoring (for a minimum of 4 days) is required, slightly prolonging hospital stay. Incomplete expansion of the MCV frame is less of an issue, as the leaflets function supra-annularly.

Training

Training in the use of the ESV necessitates being flown to a proctor centre for case observation. Simulator training is combined with didactic lectures. Hands-on proctorship at the local site is offered for a minimum of four cases.

Training for the MCV involves didactic lectures and hands-on proctorship experience at the local centre for a minimum of 15 cases.

Pasupati notes that one valve is occasionally preferred over the other in diverse scenarios, as described above. A full appreciation of their differences leads to more suitable patient selection to either programme, although many patients are potentially a good fit for either valve.

Pasupati began his implantation training in Vancouver during 2005 under the renowned transcatheter-valve pioneer Dr John Webb, an acknowledged specialist in the use of the ESV. After gaining experience with the implanting of over 100 valves with Webb, Pasupati returned to New Zealand in order to establish this procedure in Australasia. The MCV was the first procedure to become available in New Zealand and CoreValve welcomed Pasupati's experience, enabling him to be part of the first five hospitals in Australasia introducing TAVI procedures. When the ESV became available, it was duly incorporated into Pasupati's

TAVI repertoire, with his centre becoming the first to use both technologies in Australasia.

As on 8 April 2010, Waikato hospital has implanted 37 valves (20 femoral and 4 axillary MCV; 6 femoral and 7 apical ESV). The procedural success rate is 95%. Of two patients dying during the transapical series, one death is attributed to coronary obstruction and consequent complications and the other to valve embolization into the left ventricle due to a tear and prolapse of the native leaflet. The 30-day survival is 100% with the transarterial approach. Four strokes occurred in the first 10 patients, but none has occurred since the introduction of aggressive anticoagulation. Four CoreValve recipients have required a pacemaker implant. There have been no cases of surgical conversion to AVR or aortic dissection. One patient had post-dilatation for better expansion of the MCV, which was placed inside an old surgical Carpentier-Edwards valve. Two patients had moderate (ACC/AHA angiographic grade 2) AR; the remaining were classified as none to mild (grade ≤ 1). Median discharge time is 5 days. The overall 1-year survival is 90% (transarterial survival 94%).

Valves of the future

Pasupati expressed his thoughts about valves of the future that would enable physicians to treat virtually all high-risk AS cases with transcatheter valves:

- A low profile allowing for delivery via smaller sheaths.
- A device that tracks easily through tortuous anatomy.
- A nosecone with smooth transition with smoother crossing of the native valve.
- A valve that can be repositioned if initially deployed at the wrong location.
- The cuff material's composition will ensure a tight seal of the valve to the native anatomy and so reduce PVAR rates.
- The stent height will extend from the tip of the native leaflets (in the open position) to only a few millimetres below the annulus, to prevent over-hanging of the native leaflets and also reduce the risk of heart block. This will also ensure improved access in future to the coronaries.
- A larger range of valve diameters will better accommodate variable annular sizes. The height of the valve will need to vary with the diameter of the valve as the length of the displaced native leaflet will also vary.
- Durable leaflets composed of non-thrombogenic material.

First article: An introduction to current transcatheter aortic valve insertion. *Eur Heart J* 2010;**31**:1025.

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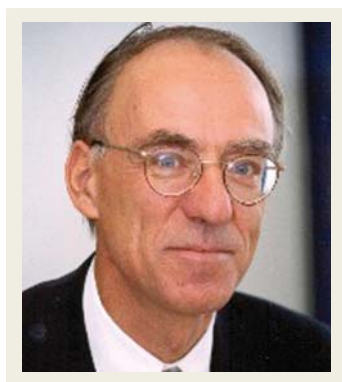
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Climbing the academic ladder in cardiology: The Netherlands

In the Netherlands, pursuing a career in academic cardiology is dependent on decisions made at three crucial stages

The first is early on as a medical student, when the best students are invited to do extra research training on top of their basic medical training. In addition to an MD these students receive an MSc in clinical research or epidemiology. The MSc is not essential but it does make the road to academia easier.



Prof. Maarten L. Simoons, PhD, FRCP, FESC, Professor of Cardiology and Chief of the Department of Cardiology at the Thoraxcenter, Erasmus Medical Centre, in Rotterdam, says: 'If you do the research programme you're on the right track, but if you don't, you can still pick it up by choosing the academic environment for your specialty training'.

Students should do a PhD at some point and the most efficient route is to devote 3 or 4 years before starting specialty training. In the Netherlands, successful completion of a PhD requires a minimum of four publications with a first authorship in an international journal. A PhD thesis in clinical cardiology may include 10 or more publications.

The second crucial stage is deciding where to go for the 6-year specialty training: to an academic centre or a large non-academic hospital. There are 16 places in the country which offer cardiology training, 8 in academic centres and 8 in large non-academic hospitals. The quality of medical care is very similar, but the academic centres put more emphasis on research and complex patients. Few people who start their training in a non-academic programme will move to an academic career.

'If your training is aimed at high volume patient care that is different from the academic position. In the academic centres, we treat fewer patients, with a larger staff-patient ratio, accordingly, we can spend more time per patient which is essential for the care of certain complex cases and for clinical research', explains Simoons.

The third decision, and the moment of truth, comes when the specialty training is completed and it is time to choose a place

to work, either a general hospital or an academic one. Most people intent on academia will choose the latter because it is difficult to leave academia and return at a later stage. This is largely due to the different demands of the two work environments. Cardiologists in general hospitals are expected to see many patients and to do many procedures, after which there is little time left. In academic centres cardiologists have more time for research and teaching. Nevertheless, the total workload in a top academic centre is higher than in most general hospitals.

Having chosen to stay in an academic centre, the usual practice is to focus on a specific area of cardiology and develop a name in the medical community by becoming an expert in that field. The Netherlands Society of Cardiology recognizes six subspecialties: general cardiology, imaging, interventional cardiology, electrophysiology, adult congenital heart disease, and intensive care. Developing a reputation requires focusing on a sub-section of one subspecialty, such as intracoronary imaging with ultrasound or optical coherence tomography, non-invasive imaging with CT-angiography, or pulmonary vein ablation.

Cardiologists at this stage of their academic career are not distinguished as post-docs (the title is reserved for basic scientists) but will be appointed as staff members in a cardiology department and mix clinical work with research and teaching. In this way people hope to develop their own name and become recognized in one of the fields of the profession.

The next step forwards is senior lecturer, a more or less automatic progression when someone is also in charge of a research group within a department. Since 1998 all medical specialists in university centres, including senior lecturers and professors, are on full salaries, without private practice.

The final step on the ladder is a professorship and its achievement is about prestige. There is a dual system for career progression in Holland. First, there are the official chairs of cardiology and for a few subspecialties. If a chair is occupied, it is occupied. On the other hand, cardiologists can be awarded a personal professorship in recognition of their achievements. At the Thoraxcenter there are four official chairs (cardiology, interventional cardiology, experimental cardiology, and biomedical technology), and currently four personal professorships.

The scientific achievements or 'quality' of an academic cardiologist may be expressed by the number of citations, measured by the Hirsch factor. The h-factor for professors in clinical cardiology is 20 or above, for most current department chiefs it is around 40, and for the top players it is between 60 and 100. The top three in the Netherlands are all at the Thoraxcenter: Profs Serruys, Simoons, and De Feyter. Achieving the required h-factor does not mean automatic progression to the next level, because creating

the personal chair requires permission from the Dean of the university, who will need to consider similar requests from other departments. Limits on the numbers of professorships means that many world class cardiologists will never become a professor.

Moving elsewhere in Europe in an effort to progress is rarely successful. 'Our European attitude is mostly restricted to looking within your own environment', says Simoons. 'I've sometimes said it might be easier for me to move to San Diego than to move to Brussels, because the American attitude is much more about finding the best persons, independent of where they come from'. Language is a barrier to moving around in Europe. An even larger hurdle is knowing how a country's financial system works. This requires knowledge of the clinical and academic reimbursement system, the key players, and where and how to apply for grants. It helps to be a member of the grants committee of, for example, the Dutch Heart Foundation or the Dutch Science Foundation, which is only achieved after years of being involved at different levels in the organization. Simoons says: 'If you know exactly how the system works you also know which buttons to push, and then how to instruct or help your own people to write the proper applications'.

Cardiologists at all levels are involved in the day-to-day teaching of Interns and Fellows training in cardiology. Lecturing is shared

and is not burdensome. In some universities one member of the cardiology staff has specific responsibilities for the teaching programme.

With progression up the ranks, what changes is the organizational responsibility. At one stage this means being responsible for leading and coordinating a research group of three or more investigators and/or Fellows. At this level the administrative burden should be minimal, but at the top of the ladder 20–40% of a cardiologist's time is spent with patients and 60–80% is time for management work, including management of research.

Every 5 years all medical specialists, including full professors, must renew their specialty registration. This requires a minimum of 40% (16 h per week) direct clinical work, and documentation of adequate participation in CME activities during the preceding 5 years. Simoons says: 'Cardiologists who work in private institutions can make more money, but the developments in cardiology are very rapid and they continue to be very rapid. That is the excitement and the fun of this type of career. It has been and continues to be, exciting to be part of and to lead some of these developments which result in ever better prevention and patient care'.

Jennifer Taylor, MPhil

School for clinical and epidemiological researchers, Ferrara, Italy

In 2006 a new 2 year educational course for researchers was established at one of Italy's oldest universities. Details are given by Roberto Ferrari, Department of Cardiology, University of Ferrara and Salvatore Maugeri Foundation, IRCCS, Ferrara, Italy

Clinical researchers are essential to verify and to assess the safety and efficacy of new treatments or therapeutic and rehabilitation approaches.

The conduction of clinical multi-centre research is becoming more and more complex as it needs to be in compliance with the stringent rules of evidence-based medicine and requiring knowledge of regulatory and legal aspects unheard of for the practising doctor. The result is that clinical research today is suffering, at least in Italy (one of the leading European countries for clinical research, known for having successfully conducted six GISSI studies involving more than 60 000 patients). On the one hand, doctors are more and more involved in daily clinical routines leaving limited time to conduct multi-centre research, while on the other hand, multi-centre research is very demanding, requiring much time and appropriate knowledge.

This is the background that prompted the University of Ferrara, one of the oldest universities in Italy, hosting students such as Nicholas Copernicus (born 1473), Paracelsus (born 1493), and

Giovanni Pico of Mirandola (born 1463), to establish The School for Clinical and Epidemiological Researchers.



The School's current Directors are Luigi Tavazzi and Roberto Ferrari. It is under the umbrella of the Istituto Universitario di Studi Superiori (IUSS—University Institute for Higher Studies),

established in 1391 by Alberto V d'Este, and is responsible for awarding the highest university degrees in Italy.



Alberto V d'Este

There are essentially two objectives: to create (i) a new professional figure ideally located within hospitals, to help interested groups deal with all the aspects of multi-centre research (legal, regulatory, conduction, etc), and (ii) a professional figure able to design protocols, and to interpret and publish the results of trials.

There is a 2-year course with theory and practical teaching. Theory is taught by one-on-one instruction 1 week every month at the IUSS in Ferrara; where lodging is also provided. The practical tutorials are 3 weeks every month and are held in academic

Contract Research Organizations (CROs) such as, Medical Trials Analysis (MTA) of the University of Ferrara or the Research Centre of the Associazione Nazionale Cardiologi Ospedalieri (ANMCO) or Mario Negri Sud Foundation, which were both responsible for the GISSI trials in Italy; and the Salvatore Maugeri Foundation. Alternatively, practical tutorials are also held at institutions heavily involved in clinical research such as the European Institute of Oncology in Milan. In the tutorials, tutors are involved in all aspects of clinical and epidemiological research from planning and writing protocols, monitoring and data collection logging, statistical analysis etc.

Although the methodology for multi-centre research is common to almost all of the sub-specialities, at the moment, tutorials are mainly in cardiology, pulmonology, oncology, and dermatology.

At the end of the course a Thesis is written consisting of a paper to be published in a scientific journal with an impact factor.

The school is not a one-unit (University) enterprise—there are other institutions involved in addition to the University of Ferrara: The Agenzia Italiano del Farmaco (AIFA), the ANMCO Research Centre, Salvatore Maugeri Foundation, and the European Institute for Oncology. The school admits 8–30 students per year from very different backgrounds, obstetrics, biology, nursing, technical diagnostics, and pharmacy. At present teaching and tutorials are in Italian, however, a course in English is being considered.

To date, 28 trainees have completed the course and received their degrees. They have all found employment within CROs, hospitals, or regulatory agencies. We hope that the School for Clinical and Epidemiological Researchers will be an asset in future research.

Additional information is available from Dr Terese Krook at roberto.ferrari@unife.it.

The Helmholtz Association: big questions, big science

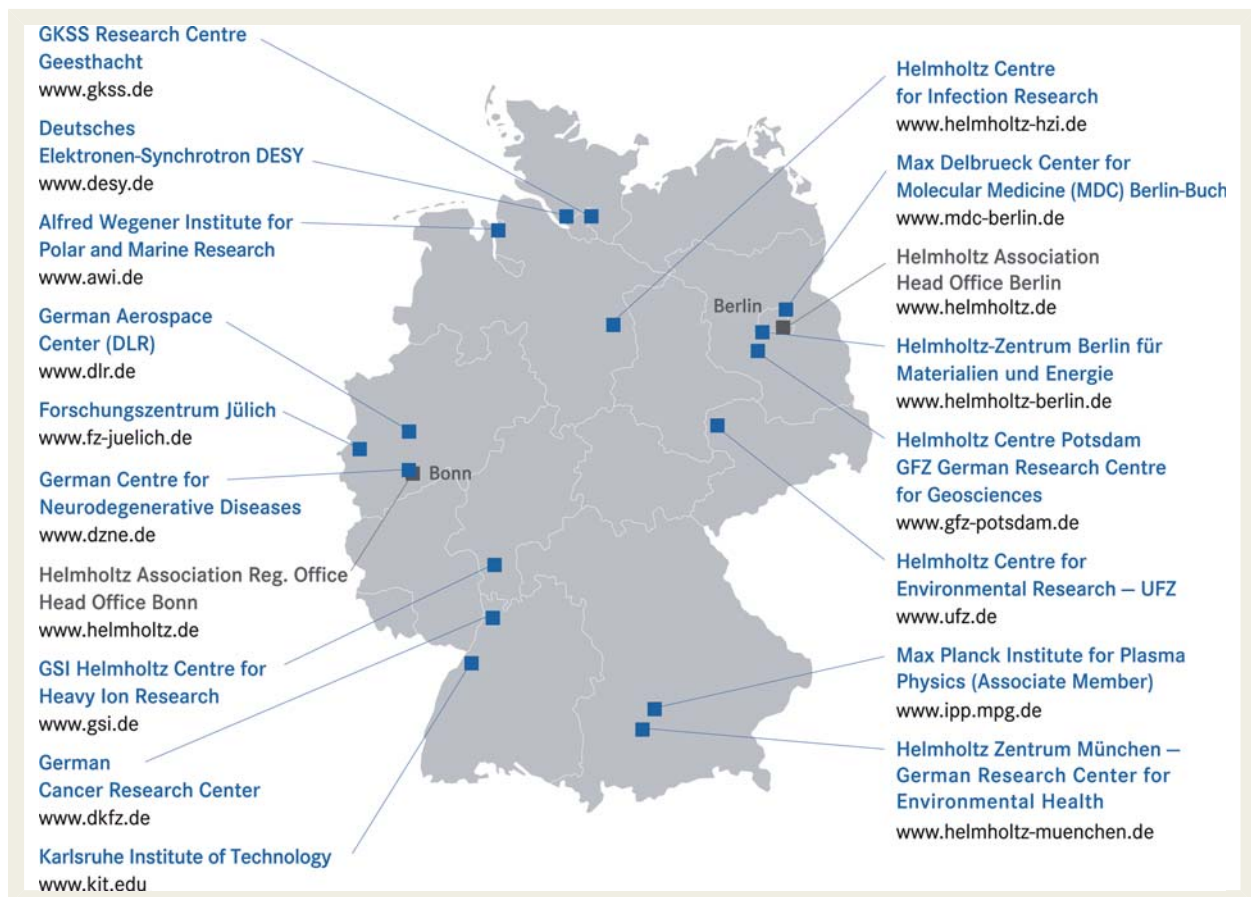


Helmholtz Logo

The Helmholtz Association is Germany's biggest research organization, with an overall budget of around €3 billion. Helen Jaques reports on the Association's novel approach to distributing this funding among member institutions and the research it sponsors in the field of cardiovascular medicine.

The Helmholtz Association is nothing if not ambitious: the aim of the scientific organization is 'to answer great and pressing questions of science, society, and economics'. And it certainly seems to have the resources to do it, with about 30 000 staff in 16

affiliated research centres all around Germany and 28 ongoing research programmes in the fields of energy; earth and environment; health; key technologies; structure of matter; and aeronautics, space, and transport.



Helmholtz Centres Germany

The Helmholtz Association, named after German physiologist and physicist Hermann von Helmholtz, started out in 1958 as a loose collaboration between a handful of research institutes that wanted to share knowledge on developing nuclear reactors. More and more institutions from different disciplines joined this information-sharing network, until in 1995 the Helmholtz Association of German Research Centres was formed. In 2001, this loose grouping of centres was transformed into a registered association with legally independent member centres. 'Many many years ago the federal government decided that it should support research in some of the major science fields on a long-term basis in order to tackle some of the major challenges for science and society', says Prof Otmar Wiestler, vice president of the Helmholtz Association and coordinator of the research field health. The Helmholtz Association helps facilitate this goal by distributing about €3 billion of state and national tax revenue, €230 million of which went into health research in the 2003–08/09 funding period. 'The way that the funding works is that about 10 years ago Helmholtz decided to put the research money that's given to them by the government into certain topics', explains Prof. T. Willnow PhD, Head of cardiovascular and metabolic disease research, Helmholtz Institute, Max Delbrück Center for Molecular Medicine, Berlin.

'There was an overall decision that certain topics and disease entities are important for socioeconomic and biomedical aspects of society and the association put the money in there'.



Thomas Willnow

Crucially, this funding is distributed to scientific programmes that are spread across several of the affiliated institutions, rather than to specific scientists or research centres. In order to obtain funding, scientists group together on the basis of their research interests and develop a research programme for a topic in one of the six big research fields. International experts then review these funding proposals and visit the institutions involved to determine how much funding will be provided.

However, institutional funding only makes up about 70% of the budget of these programmes. Research centres need to make up the remaining 30% from public and private sector sponsors, for example, via EU grants or grants from German funding agencies. In the 2003–08/09 funding period, the 15 institutions involved at

that time managed to secure such contract funding to the tune of between €600 and €900 m. 'It sounds an intense process', says Willnow, 'but I think it is important because money talks, it forces institutes within the Helmholtz Association to really work together and sit down at least every once in a while to decide about a common strategy. What are the important issues in biomedical research for the next five years, how they are going to approach these, and with which partners in the Helmholtz Association and also other bodies'.

And working together is the second key facet of the Helmholtz Association approach. The 16 centres that currently make up the association share funding and large-scale facilities such as particle accelerators. Most importantly, they also share expertise.

The three pillars of the health research field are basic research, systems biology, and translational research. The Helmholtz Association sponsors research in six key disciplines within health: cancer; cardiovascular and metabolic disease; function and dysfunction of the nervous system; infection and immunity; environmental health; and systemic analysis of multifactorial diseases.

The cardiovascular and metabolic diseases research programme is made up of three Helmholtz associated institutions. The first is the German Cancer Centre, which focuses on cell biology of vascular signalling pathways. Then there is the Max Delbrück Center, which largely researches the physiological and pathophysiological aspects of cardiovascular disease. The Last is the GKSS Research Centre Geesthacht, which is dedicated to the development of biomaterials for therapeutic approaches including cardiovascular diseases. One of the success stories of the cardiovascular and metabolic diseases programme is the research of Dominik N. Muller and his team at the Max Delbrück Center and the Experimental and Clinical Research Center in Berlin. 'My group is in general interested in understanding the role of the immune system in target organ damage with respect to cardiovascular disease', says Dr Muller. 'There is more and more evidence that the immune system is a kind of amplifier of cardiovascular disease'.

Muller and his team tried treating mouse models that had hypertension and cardiac damage with regulatory T cells, which are known to be beneficial in several autoimmune disease states. Although the regulatory T cells did not affect blood pressure, they improved cardiac function and reduced inflammation. He and his team also found that treatment with regulatory T cells improved electrical remodelling in the heart and substantially reduced the risk of arrhythmia after myocardial infarction, which occurs as a result of a surge in cytokine release. 'This kind of state would be appropriate for this kind of treatment: you would do a time specific treatment for a short period to interrupt the pathogenesis', says Muller.

For the second Helmholtz Association funding period, which started in 2009 and will run until 2013, €1.84 billion has been earmarked for the health research area, roughly €174 million of which is going to be spent on research into cardiovascular and metabolic diseases.



Max Delbrück centre for Molecular Medicine at Berlin-Buch campus. (copyright-BBB Management GmbH Campus Berlin-Buch)

However, future biomedical research, Helmholtz funded or otherwise, faces two major challenges, points out Wiestler. One is to develop novel treatments for major diseases. The second major challenge is preventing diseases before they happen by early detection. 'For virtually all major human diseases, there is the major problem that these diseases can only be diagnosed once they are already at an irreversible stage', he says. 'Myocardial infarction, for example, is often only diagnosed once the infarct has occurred'.

The Helmholtz Association aims to tackle the first of these issues by investing heavily in translational research, which will receive a total of €13 million in the next funding period. Five of the nine Helmholtz centres involved in the 2009–13 period are establishing translation centres in cooperation with university hospitals. The Max Delbrück Center, for example, has set up the Experimental and Clinical Research Center. One recent success of this new translational research centre is in the investigation of a gene thought to have a role in sudden cardiac death. This gene, which is important for cell-to-cell contact and formation of cell contacts in the heart, was identified in knockout mouse models at the Max Delbrück Center. The findings were then transferred to the Experimental and Clinical Research Center, where clinical researchers found that about 30% of patients with sudden cardiac death had a mutation in the very same gene that was identified in the mouse model. Now such patients can be genetically identified a priori and can receive a pacemaker as a precaution to prevent sudden cardiac death.

But what about preventing diseases before they happen? 'There's only one possibility to tackle this major problem for biomedical research', says Wiestler. 'That is to develop novel tools that allow us to identify persons at risk for developing these diseases and to develop novel tools for early detection and early diagnosis'.

And that leads us to the second key cross-programme priority for 2009–13: epidemiology or, more specifically, large cohort studies. The Helmholtz Association is spending ~€20 million establishing a cohort of 200 000 healthy individuals, the largest ever nationwide population study in Germany. These people will be followed up with medical examinations, questionnaires, and biochemical tests—including biomarkers of cardiovascular disease and metabolic diseases—for 10–20 years. 'During the course of this study, a certain number of people will develop disease', says Wiestler. 'We can then go back to blood samples taken 15 or 20 years ago and ask whether it would have been possible to identify the risk for disease'. The cohort study is being led by Wiestler and his colleagues at the German Cancer Research Centre and by scientists at the Helmholtz Zentrum München. However, all Helmholtz centres will expand competency in epidemiology.

By pooling scientific expertise and resources, the Helmholtz Association hopes to meet the major challenges facing future research. Given the success of funded research in the first 50 years of the Association, the plan seems to be going well so far.

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