Innovation in medical technology and medical procedures in between global network innovation drivers and complex local settings

An explorative study of the implementation of Trans-catheter-Aortic-Valve Implantation (TAVI) technology and medical treatment in Norwegian hospitals

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Abstract

The objective of this work in progress paper is to present and discuss an explorative case study focusing the problem of moving a radical innovation into a production that can be characterized as highly stabilized, complex and also densely organized at the local level. The case regards the introduction of minimal invasive technology and treatment procedures (Transcatheter-Aortic-Valve-Implantation (TAVI)) into the domain of heart surgery. It is based in a first round of explorative investigations into the history of this new technology and procedure in Norwegian hospitals as well as investigations into the trajectories of these new technologies and medical procedures internationally from their origins to their interactions with Scandinavian and Norwegian University hospitals and heart clinics. The ambition of the paper is to contribute to the IMP theory by investigating into the contradictory relationship and dynamics between highly stabilized social-material networks and radical, innovative change. The study do this by focusing on the processes and the forces that are mobilized to move a new technology, that necessitates very different network structures, into the local level of activity in hospitals. Secondly, the objective is to use this explorative study to develop research questions for further investigations into the networked innovation processes associated with TAVI in Scandinavia.

Introduction

The IMP approach can generally be interpreted as based on a process oriented view of the economy and economic life (Olsen, 2013). However, numerous IMP studies also demonstrate that for the most part, business networks tend to be very stable over time, not at least due to "investments in place" that ensures lasting structures of interactions to take advantage of their characteristics (Håkansson et al., 2009). These studies are still rooted in a general process view, however acknowledging that change processes often tends to be very slow indeed. How radical innovations nevertheless occur then, from time to time in such stable networked settings, is an intriguing issue that calls for focused investigations and more theorizing. One possibly typical way that this happens, is through the introduction of what Clayton Christensen has denoted "disruptive technologies" that cause major innovative shifts in industrial dominance, production methods and market share distributions (Christensen & Raynor, 2003). They analyzes these processes from the point of view of proprietary control over certain technologies and market positions of individual firms. The objective of this paper, however, is rather to investigate the emergence and moving of such a disruptive technology by focusing the processes of network dynamics, assuming that the moving of a new technology into wide spread use is not accomplished by a single company, but through interacting with those that are already occupying the field of activity where the new technology will have to be adopted and used.

Advanced medical procedures, such as surgery or cancer treatment, can be characterized as highly stabilized organizational phenomena at the very local level of activity that encompass "heavy" and complex interactional practices across a range of specialized professions, technologies, regulations and surrounding medical, organizational and managerial systems and structures (Håkansson & Olsen, 2012). They are typically the outcomes of lasting efforts to improve core procedures through incremental changes extending through out the resource-, activity- and actor networks that somehow relate to the given health problem and the established major treatment procedures. Adding to this, organizational, professional and public health care systems, politics and administration at multiple levels of governance contribute to the complex image of these activities. These local contexts are particularly demanding in relation to innovation, and in light of the stated ambitions of governments in Norway as well as across Scandinavia (and elsewhere) to stimulate innovation in the health care systems, this paper aims at illuminating and discussing what innovation is about when we think of medical technologies and treatment procedures.

This work in progress paper is part of a larger study of the processes of adoption of innovative medical technologies that imply significant and disruptive changes in heart surgery procedures at a number of university hospitals and heart clinics in the Nordic countries. These changes are challenging in the sense that a new and rather different procedure based on entirely different technology emerges in rivalry with the established "gold-standard" open surgery procedure within this domain. The ambition of this paper is

primarily to understand more about what it takes to actually implement such a disruptive technology and procedure in hospital practices through the various interactional projects and processes involved. The paper embarks on this by presenting three different histories about this innovation. One is about its early history of adaptation in Norway starting in 2007. The two others present short histories about how the technology was invented back in the late 1980s and gradually emerged into two major international businesses with extended business network activities across the world.

Adding to this, the objective is also to clarify a set of more precise research questions on the basis of early explorative investigations, starting from a set of rather broad questions such as: What are the drivers of these innovation processes? What characterizes the interactions between the technology suppliers and the specialized hospital units that are conducting these procedures? How does a new procedure actually enter into a domain fully occupied by a very different and highly complex organized practice? How do these solutions move from hospital to hospital? What are the roles of the medical practitioners in these innovation processes? What are the roles of the hospital organizations? And what are the roles of the technology providers? How do these actors and their resources and activities interact to expand or to restrict the expansion of the new technology and procedure into the various heart clinics? How can we explain the different outcomes across Scandinavian hospitals in terms of how this new procedure is being brought from experimental use to ordinary routine based practices that expands into the domain of open heart surgery?

What is TAVI?

The new Trans-catheter Aortic Valve Implantation/Replacement (TAVI/TAVR) procedure offers a new treatment for people who suffer from severe aortic stenosis - which is a narrowing of the heart valve between the left ventricle and the aorta substantially reducing the capacity of the heart to pump blood through the body and also causing blood to back up in the heart. The condition is life threatening and mostly concern the elderly. TAVI is a minimal invasive procedure where an artificial valve can be implanted using a wire passing for instance through the femoral artery instead of having an open heart surgery. TAVI as a technology and medical procedure has evolved in Europe since 2002, receiving a first so called CE approval of the technology in Europe in 2007 and a first FDA approval in the US in 2011 for the first generation of TAVI valves (Dvir et al, 2012). In 2007 the aggregated number of procedures conducted across the world summarized to approximately 1000. Two years later the number had grown to 10.000, and by early 2014 the total number of TAVI procedures had risen to 100.000, in particular due to a rapid growth in Germany since 2007 and in the US since 2011. However the procedure is still at an early stage in terms of challenging the established open heart surgery procedure in relation to the major share of the patient population. So, we are studying a new, potentially disruptive non-invasive procedure on the move.

The overall study of which this paper is part, is a comparative study of the implementation processes at different hospitals in Norway, Sweden and Denmark. The initial study conducted by the research projects, is a detailed anthropological study of practices, projects and processes associated with TAVI at the Intervention Center at Oslo University Hospital (Masovic , Mørk & Nicolini, 2013). Based on that study, the research project conducts less detailed, structured comparative studies at other hospitals in Norway, Sweden and Denmark. Finally, it will also include a study of the relevant activities of the two dominant international TAVI technology suppliers; Edwards Lifesciences Inc (Irwine, CA, USA) and Medtronic CoreValve LLD (Irwine, CA, USA) which is a subsidiary of Medtronic Inc. (Minneapolis, MI, USA.). This paper pulls from the first round of interviews at Rikshospitalet in Oslo and at the Feiring Heart Clinic north of Oslo, from the litterature as well as from the first interviews with representatives from the two technology suppliers, and finally from investigations into the history of TAVI in other secondary data sources.

The TAVI case

The presentation of the case is done by focusing three different historical processes that are essential to the early formatting of TAVI at the international level as well as at the level of Norwegian health care organizing of TAVI activities. We will start out by presenting the Norwegian case, and then move back to focus each of the two technology providers.

TAVI in Norway

The history of TAVI in Norway appears to have started in 2007 when discussions started between representatives of the technology suppliers and the physicists at the major Norwegian heart clinics. Both the two technology suppliers; Edwards and CoreValve, received a CE approval of their first generation TAVI valves for use on humans in this same year, and both immediately started a focused, competitive marketing operation cross Europe.

In Norway, MD cardiologist Yngvar Myreng at the Feiring Clinique located some 100 km north of Oslo, responded positively to the offer from CoreValve, and initiated the procedures through the autumn of 2007 required to start TAVI operations in early 2008. The Feiring clinic is a heart clinic owned and operated by “Landsforeningen for hjerte og lungesyke” which is a private self-governing foundation that is part of the “free choice of hospital care” system in Norway paid for by the Norwegian state. Being a clinic specialized in non-emergency heart surgery where procedures can be well prepared in advance, TAVI fitted very well into Feiring’s role and profile in the Norwegian hospital system. Also the leader of the heart surgical team; MD Sven Martin Amdal actively supported the initiative to establish a cross-professional team of heart thorax-surgeons and cardiologist to become educated by

CoreValve in the Netherlands in order to build the capacity to conduct TAVI at Feiring. The head of administration at Feiring at the time also supported the initiative, and all of this resulted in a rather fast and smooth establishing of TAVI activities performing the first 10 procedures at Feiring in January and February 2008.

To become a TAVI unit, one must be eligible by and comply with the standard requirements and guidelines represented by one of the two technology providers. At the cost of approximately 20.000 Euros per valve, CoreValve offered a package of services that included putting together the team, control and approve of facilities and equipment at the given hospital, instructions and training of the team in the Netherlands as well as at the client hospital, advanced laboratory services to evaluate patients, and provision of other advices and support to the team. The training was headed by a so called "proctor", who is a certified TAVI physicist having conducted at least 50 procedures. The proctor would also be leading the first procedures at a new TAVI Clinique until the local team can be certified. To obtain a certificate to lead a TAVI procedure requires at least having been on the team of 30 procedures. In addition to this, the supplier offered additional support to functions surrounding the core activity through the procedure, and maintains a continuous system of practical collaboration over time. This also includes presence by a local representative of the supplier on each an every TAVI procedure conducted at the hospital. Hence, there is no way that this new technology and medical procedure can move anywhere without a lot of work and support conducted by the technology suppliers.

In the case of Feiring, the team received its training during the autumn of 2007, and as the proctor was appointed MD. Jean-Claude Labord from the Interventional Cardiology Department at Clinique Pasteur in Toulouse, France. Dr. Labord was actually one of the inventors and founders of CoreValve and was actively involved in the technical as well as the clinical development of the system. He personally performed the majority of animal and cadaver procedures during the 2000-2004 research and development phase, and he was also directly involved with more than 50% of all human clinical trial cases until 2007, when CoreValve obtained its European CE approval. Since then he has held the position as Chief Physician Trainer for the CoreValve procedure serving as a proctor worldwide to teach physicians to perform the valve replacement procedure (http://www.zoominfo.com/p/Jean-Claude-Laborde/554024853).

To Feiring, this meant that they received the most competent expertise world wide to be responsible for the first procedures as well as for the training of the team. Because of the limited experience with TAVI and research evaluations of results, TAVI as offered to patients that for various reasons were declared inoperable in the sense that they were unsuitable for the "gold-standard" open heart procedure. It appears that world wide around 30% of the patients suffering from severe aortic stenosis are inoperable and hence potential candidates for TAVI treatment. Usually, this implies that they are very old (typically above 85) and suffers from multiple health issues leaving them too week to have their chests opened by

sawing over their chest-bone to get physical access to the heart. Hence, they are categorized as either extremely high risk or very high risk patients within the national regulatory systems. Their life expectancy in general is short, and with the severe aortic stenosis few will survive the first couple of years without TAVI treatment. Before TAVI, these patients were not offered any treatment opportunities at all.

The remaining two thirds of the severe aortic stenosis patients considered operable, are still not being offered TAVI as an alternative, because the traditional open surgery procedure is a well established procedure that is proven to be very safe through long term studies of treatment results, side-effects etc. For TAVI to compete with the open surgery procedure also for these patients, requires documentation of medical results at least at the same level of quality, including results also for the younger patients that will have to live a lot more years with the heart implant. A first study that provides data showing the TAVI performs better than the traditional open heart "gold-standard" was presented at The American College of Cardiology in Washington D.C. in March 2014 (http://www.startribune.com/business/253029961.html).

However, in February 2008 as Feiring was about to complete its 10 first TAVI procedures, it stopped its TAVI activities. Around the same time, there was a new administrative leader appointed at Feiring, who formally stopped the TAVI procedure arguing the institution did not obtain cost reimbursement for the procedure from the public health care system. He then initiated an internal committee to look into the matter. Prior to this however, physicians at Oslo University Hospital had initiated the stop order by alerting Feiring's TAVI activities to the top management of the regional public hospital system enterprise of South-East Norway, claiming that Feiring should not be involved with this kind of experimental treatment. Reimbursements of Feiring's TAVI expenditures were then declined, and the Clinic was effectively forced to stop its activities.

Then, the issue was brought to the "National council for quality and priorities in health care" which is a public body of expertise with the objective to provide solid advice on such matters. The council did a thorough process that also involved the team at Feiring, and finally concluded on September 9th 2008 that TAVI should be considered an experimental procedure in Norway that should not be offered to Norwegian patients. Hence, none of the Norwegian hospitals should be doing TAVI procedures other than as part of research and development activities, neither at Feiring nor at any of the public university hospitals. This evaluation concluded against the assessments made by the cardiology- as well as thorax-surgery professional associations who both considered it an emerging, not an experimental procedure. However, neither of them offered any substantial political support to Feiring, but appeared to support the view that the procedure should be done at the university hospitals.

Adding to this, someone sent a notice of warning to the Norwegian Health Directorate regarding the TAVI activity at Feiring, which resulted in a public investigation by the Health Directorate to evaluate the case. The investigation in the end concluded that apart from

minor details Feiring had done nothing worthy of critique. However, at that pint of time Feiring had already stopped its activities and was rejected reimbursements for TAVI procedures.

All the university hospitals in Norway initially accepted the conclusion by the council, except for the university hospital in Northern Norway (Tromsø). At the time it had entered a co-operation with the second technology supplier; Edwards, to establish a team to conduct TAVI procedures using the Edwards Sapien valve. In Tromsø, the physicists decided to move on with the activity, assessing that at the time the method was well established at so many foreign heart centers across Europe that it could not be considered experimental. As it was not experimental, they also decided it was not to be seen as a research project. It was therefor not necessary to obtain any in advance approval from the national committee for ethics in research. The hospital accordingly went on to do its first TAVI procedure on September 24th 2008, continuing with another24 procedures until September 2009 (Steigen et al, 2012). It accordingly did its first TAVI procedure only two weeks after the decision by the council to not offer it to Norwegian patients.

Similarly to Feiring, the team had been put together and approved of by a technology supplier who offered a similar package of services as the one offered by CoreValve , to have the procedure established, certified according to regulations and requirements, and supported as an ongoing business relationship over time. There are no particular reasons to believe that the procedures done in Tromsø were better or safer than those done at Feiring. On the contrary, it appears that Feiring had an extraordinary experienced proctor in charge of the procedures and the teaching.

The CoreValve and the Edward Sapien valves are somewhat different, which has the implication that the procedures are also somewhat different. For instance the CoreValve version can be crimped to a smaller size than the first generation Sapien valve, which implies that it could be conducted without any cutting of the patient that will require a surgeon to do it. Hence, from the point of view of the cardiologists, the CoreValve has certain benefits and gives the cardiologist the lead role in conducting the procedure. With the Edwards Sapien valve, the entrance point into the patient's body and the heart may be different and the surgeons will have a more important role to play, sometimes also leading the procedure. So, differently from Feiring, where the cardiologists were in the lead using the CoreValve, the thorax-surgeons in Tromsø were more in control of the new procedure.

Nobody intervened to stop Tromsø. Then, in the autumn of 2009, Rikshospitalet at Oslo University Hospital (OUH) also started doing TAVI procedures and managed to perform 5 procedures in 2009 and another 20 in 2010, using the Edwards Sapien valve. In 2010 the St. Olav University Hospital in Trondheim also did 10 TAVI (Edwards) procedures while Haugeland University Hospital in Bergen did 25 (CoreValve). In 2011 all together 115 TAVI procedures were done at these 4 hospitals in Norway, followed by 102 TAVI procedures in 2012. In 2013 Feiring restarted its TAVI activities as well, by re-entering a co-operation with

Medtronic CoreValve. Both Haukeland and Feiring still work exclusively with Medtronic CoreValve, where as the three others who started out with Edwards, have moved to work with both suppliers (Nasjonalt kunnskapssenter, 2012). In addition to this, Rikshospitalet has also started collaborations with a third supplier, the Swiss company Synetis SA.

The early history of the Edwards Sapien valve and its entrance into Scandinavia

The history of TAVI started with the Danish cardiologist Henning Rud Andersen at Århus University hospital, who as part of his training as an interventional cardiologist in Phoenix, Arizona in 1988 was inspired by a presentation of coronary artery stents to start thinking about how to enlarge the stent to place an artificial valve within it. Apparently, no one was listening, and back in Denmark he went on to build a prototype himself by constructing a large metal stent and sewing together and placing within the stent a valve made from pig hearts obtained from the local butcher shop. He then used a transcatheter delivery device that had been developed by MD Alain Cribier in France in the 1980s for the ballon aortic valvuloplastry (BAV) procedure (European-Hospital, 11.02.2012). Henning Rud Andersen managed to proof his concept by implanting the homemade prototypes in pigs over a three month period, where after he went on to present his idea at international conferences. He did not receive much attention though, and the rejection was devastating when also his paper presenting the experiences and the results was rejected from the leading heart medical journals. However, he filed a patent pending in 1991, and eventually in 1992, his article was accepted for publication by the at the time small, newly started European Heart Journal (Andersen, Knudsen & Hasenkam, 1992)

Andersen then started to find customers that would like to license and further develop his technology, and approached major international companies in the heart valve industry to offer them a deal. However, all of them rejected the offer, including a company in Minneapolis called Medtronic International and another in California called Baxter International; the two major payers in the heart valve industry.

However, in 1992 he had also been approached by a representative of a small company called Stanford Surgical Technologies, which had been established to commercialize heart surgery technologies out of Stanford University School of Medicine. With the help of patent experts at Danish Technology Institute, Andersen finally managed to sign a license agreement that provided the Stanford company with the exclusive right to use the technology world wide, for a modest yearly up-front fee and a license fee per item sold. Stanford Surgical Technologies later changed its name to Heartport. However it did nothing to develop Andersen's new technology, but appeared to keep it away from the market while focusing alternative, more traditional Stanford invented heart surgery technologies. Andersen then went on to try convince some of the bigger companies to acquire Heartport, but was unsuccessful until he met on of the leaders in Johnson & Johnson, a man called

Stanton Rowe who suggested to the board of J&J that they should buy the company. Andersen received a negative answer at the time, however somewhat later, in January 2001 J&J acquired Heartport for USD 81 million in stocks. However, one week before this another company called Percutaneous Valve Technologies (PVT) bought the world wide right to use the Andersen patent, so that this was not part of what J&J bought. The PVT was a new company owned by Stanton Rowe from J&J, who left the company together with his second hand in J&J; Stan Rabinowitz, and MD Martin Leon who is professor in Cardiology and interventional Cardiology at Columbia University. The three of them also invited MD Alain Cribier, the inventor of the ballon technology, to become part of the company. Andersen already knew Leon very well at the time, and now the four of them controlled the exclusive license agreement with Andersen and the balloon technology brought in by Cribier.

Martin Leon is a world famous cardiologist originally from Israel, and through his networks in Israel, they managed to bring in Isreali venture capital to the Mew Jersey based US company, to fund the development of the TAVI technology to be launched in the markets. This resulted in the first successful TAVI man-implantation in April 2002 conducted by Cribier in Rouen, France, an event which followed the first human percutaneous implantation by MD Philipp Bonhofer in 2000.

In the year 2000 Edwards Lifesciences in Irwine, California was spun out of Baxter International Inc. - a major US health care company. Edwards is a very specialized company focusing only on human heart valves, and the spin-out immediately established an internal R&D project called “patriot” to investigate the potential of Andersen’s technology. In 2004 Edwards acquired Corbier’s Percutaneous Valve Technologies Company with the exclusive license for the Andersen 1991 patent, for USD 125 million, and went on to further develop the technology and to organize the processes to obtain CE approval in the EU and FDA approval in the US for its balloon expandable Edwards Sapien Valve. The Sapien valve won the CE mark in 2007 and a first approval from the FDA in 2011 (Edward’s homepages). Both Rowe and Rabinowitz obtained core positions in Edwards.

Edward’s European headquarter is located in Nyon close to Geneva in Switzerland, and from there it initiated a broad marketing campaign as soon as it received the CE mark, to try to get ahead of its rival CoreValve. Among the hospitals involved in the all together 150 TAVI procedures required for the CE approval procedure, was Skejby University Hospital in Århus. The hospital where Henning Rud Andersen is still practicing as a cardiologist, got involved through establishing of the cooperation with Edwards. Hence, the circle of the invention got re-united in Århus, which thereby became an interesting narrative following Edward’s Sapien valve across the world. Skejby performed its first 100 TAVI procedures between February 2006 and June 2010 (Nielsen et al, 2011). The evaluation of the first 100 procedures indicated a substantial learning curve as the 30-days mortality rate declined from 12% for the first 50 patients, to only 4% for the following 50. By starting out early and due to Andersen’s close association with Erwards, Århus was in a position to scale up its TAVI

activities immediately after Edwards received its CE mark, thereby rapidly building experience that permitted core physicists to obtain roles as proctors hired by Edwards to establish and educate TAVI teams at other hospitals in Scandinavia, elsewhere in Europe and later on in the US in the wake of the 2011 FDA approval. Hence, Skejby Hospital became an important hub for Edwards in Scandinavia.

In 2007 Edwards offered “start-packages” also to the Norwegian heart surgery clincs, of which the largest and most important was at Rikshospitalet in Oslo. However, there was considerable resistance in Oslo towards the package, which required the hospital to commit to at least buying 50 valves in order to conduct the first 50 procedures. This corresponded to a start up cost of approximately 1 million Euros in direct purchasing costs in addition to necessary local costs. Apparently, this package was a copy of the initial 50 + 50 valve procedures that had been part of the Skejby Edwards deal that in effect permitted for the education of proctors, an element which for obvious reasons was important to Edwards. To Rikshospitalet, however, these requirements seemingly appeared somewhat arrogant and demanding, which turned the negotiations sour to the degree that it was put on halt.

In the meantime, Edwards received positive response from Tromsø, and as it did not manage to enter the deal it wanted with its preferred customer in Norway, the Company eventually settled a deal with the university hospital in Tromsø in 2009. This included a “start package” with only 25 valves. Hence at this point in time it appears that Edwards had reduced its requirements for establishing new TAVI teams at additional hospitals. One interpretation of this would be that the company had gotten “less arrogant”. Another would be that the company at this point in time had managed to establish a sufficient number for core partner institutions to educate the proctors required for the next round of expansion. The second round of customers would then include deals that did not necessarily include the expectation of rapid education of additional proctors.

Due to the dynamics of the expansion process as orchestrated by the supplier, Rikshospitalet in Oslo did not enter a deal that permitted it to establish a more central position in the Edwards network, a role which in Sweden appears to have been taken by Lund University Hospital outside Malmø. As a result, all the Norwegian hospitals that became involved with the Edwards Sapien valve, came into the Edwards network in relatively peripheral positions, through which they did not obtain the important early roles as proctors which would have permitted their core TAVI physicists to build more substantial personal international networks across Europe, in the US and Canada and possibly also in Asia. Over time, they may of course, but only after the first formatting patterns of the international TAVI networks have been established and the core roles have been taken by others.

In 2011 Edwards received its FDA approval of the Sapien valve after having conducted 1500 TAVI procedures at various hospitals in the US. This gave Edwards a monopoly situationfor TAVI in the US which lasted until January 2014 when Medtronics got approval for its CoreValve technology. T

To Edwards, the FDA process took 4 years from the European CE mark, from 2007 to 2011. Right after the FDA approval, Edwards started rolling out a rapid marketing and TAVI team establishing process departing on the basis of the teams that had been trained as part of the FDA process. To do this expansion, the company was dependent on European physicists with sufficient experience to serve as proctors in the US. Hence, from 2011 through 2013 a number of those who gathered substantial experience as proctors in Europe in between 2007 and 2011 were offered positions by Edwards to help start TAVI at many US hospitals. Later, when the 2. and 3. generation Edwards valves will eventually be approved by the FDA, they may be invited back to lead the upgrading because they have already been working a few years with these new versions of the valves in Europe. To be a proctor in the US is thus not only a personal honor and an opportunity to build a personal network. It is also likely to be a learning experience about how to improve the organizing of TAVI back home.

Despite the rapid roll-out in the US through which Edwards grew substantially larger than Medtronic CoreValve at the global market level, the expansion in the US was slower than Edwards had hoped and planned for. The reason for this was the strict reimbursement guidelines implemented by the US Federal Medicare system, which due to the old age of almost all TAVI patients, holds a monopsony purchasing position in the US. (When people retire at the age of 67, their private health insurances are converted into the Medicare system under the US government responsibility.) As a result, US hospitals run a deficit on TAVI procedures, which puts a severe pressure on Edwards to lower its prices and to support the efficient organizing of TAVI at US hospitals.

The early history of the CoreValve valve and its entrance into Scandinavia

CoreValve S.A.S. was funded in France in 2001 by Professor MD Jaques R. Segun and MD Jean-Claude Labarde with the aim to commercialize a TAVI technology based on their joint patent pendings filed form 2000 and forwards. Contrary to Edwards balloon expandable valve, they created a self expandable valve that contracts when put into ice water while returning to its original size at the temperature of the human body.

Jaques Segun retired from cardiac surgery in 2001 to devote himself to developing medical technology and to run and obtain funding for several medial start-up companies. He served as both the CEO and the President of CoreValve from its start until April 2008, when the process started that led to the acquisition by the large US med tech company Medtronics Inc. in 2009. In 2005 he also co-funded the company Stentys S.A.S: jointly with Jean-Claude Labard, which was also based on their joint patents. During this period, he grew CoreValve from an early patent based start-up company through its R&D development period until 2004, and from there through the process through which it obtained the CE mark in 2007 and then through its first year of commercial expansion in Europe. So, he was the inventor and business manager in the team (http://www.twst.com/interview/24705).

Another other major role was held by the younger colleage of Segun, MD Jean-Claude Laborde. He is serving as Co-Director of the interventional cardiology unit at Clinique Pasteur, Toulouse, France. Laborde is the practicing cardiologist that also serves as a Member of Scientific Advisory Board at Medtronic CoreValve LLD as well as Stentys S.A.S. He was trained in France and the USA as an interventional cardiologist and holds additional specialty certifications in Echocardiography Doppler, Cardiovascular Pathology, and Endovascular Techniques. He is currently Co-Director of the Interventional Cardiology Department at Clinique Pasteur in Toulouse. Additionally, he holds cardiology consultant positions at St George Hospital in London (UK); Glenfield Hospital in Leicester (UK), and the German Heart Center in Munich (Germany). (http://www.zoominfo.com/p/Jean-Claude-Laborde/554024853)

Laborde was intimately involved in the technical and clinical development of the Medtronic-CoreValve Transcatheter Aortic Valve Implantation (TAVI) system. He personally performed the majority of animal and cadaver experimentation during the 2000-2004 early research and development period and he was directly involved in a majority of human clinical trial cases during the 2004-2007 period. Since CE mark clearance of the device in mid-2007, Laborde has held the position of Chief Physician Trainer for this procedure and travels worldwide to teach other physicians how to perform the implantation. He has personally performed more Medtronic-CoreValve TAVI procedures than any other physician worldwide.

Hence, Segun and Lebard by performing different roles, managed to bring CorValve into a commercial breakthrough in Europe. However, the company both lacked resources, presence and networks to establish itself in the US, and also had problems raising the necessary resources and organizational capacities necessary to grow fast in Europe. So, through 2008 the company was searching for an industrial partner, ending in the acquisition by Medtronics Inc. in April 2009 at a price of USD 325 million. At this point in time CoreValve limited operations in the US and had only recently started the process required to obtain FDA approval for its valves. The FDA process was then handed over to Medtronic, and the approval process was successfully completed in January 2014 - three years after Edwards.

Medtronic Inc is located in Minnesota, where as its subsidiary Medtronic CoreValve LLD is located in Irwine, California close to the Edwards HQ. Medtronic Inc. is a world leading med tech company founded in 1949 by the Norwegian-Deutch immigrant Earl Bakken and his brother-in-law Palmer Hermundslie. Their company started out as a repair shop for hospital laboratoty equipement at the hospital in Minneapolis, while Earl as a student of electrical engineering at the University of Minnesota. There, he got to know Dr. C. Walton Lillehei who was an early pioneer in open heart surgery at the university, and jointly they developed and patented the first pacemaker, that around 1960 had reached a state where it could be implanted in a human body. From these early developments Medtronic grew to become a diversified med tech company that also expanded out of the US already in the 1960s and

1970s to Europe and later to Canada, Latin-America and Japan. It is valued at approximately 35 billion USD (NOK 200 billion) at the stock exchange (http://www.medtronic.com/).

Without FDA approval, CoreValve had to expand to build a competitive position in Europe and in Asia. So, after having received its CE mark in 2007, it set out to expand in Europe. One of the hospitals that early on got involved with CoreValve, was Rigshospitalet in Copenhagen which started regular TAVI procedures in 2007. Until recently the hospital has only been working with CoreValve. It has published the results from its first 280 procedures, which implies that Copenhagen is a major partner worldwide with Medtronic. On July 18th 2012 Medtronic announced that its had initiated its new SURTAVI trial at Copenhagen University hospital Rigshospitalet where MD interventional cardiologist Lars Søndergaard and MD cardiothoracic surgeon Daniel Steinbrüchel performed the first procedure in a global trial including approximately 2500 patients as part of the FDA process to obtain approval for medium-risk patients to be treated by TAVI. The event signifies the important role of Copenhagen in the international Medtronic CoreValve network.

Just like Edwards, CoreValve did not manage to establish a customer relationship at Rikshospitalet in Oslo when it approached the hospital in 2007. In Oslo, it appears that the surgeons have a rather dominant role vis a vis the cardiac cardiologists (interview Edwards, march 28, 2014), in which case it has been a hard sale for CorValve to convince Oslo to choose Medtronics over Edwards.

As a result, Medtronics approached the other heart surgery units in Norway, and quickly received a positive response from the private Feiringklinikken. Following the close down of TAVI activities after only 10 procedures in early 2008, CoreValve did not get any further in Norway before after the Medtronic acquisition. Then, in late 2009, the company appears to have entered discussions with Haukeland University Hospital in Bergen which resulted in 25 TAVI procedures in 2010, which appears to have been the standard start-up package at the time, before Feiring restarted its TAVI program in the autumn of 2013. At that point of time, the three hospitals in Norway using the Edwards sapien valve all seem to have started working with Medtronics as well, to be able to offer TAVI also to non-operable patients that can not have the Sapiens valve for some reason or other.

This convergence towards both suppliers at hospitals that started out using Edwards Sapien while the Medtronic CoreValve users appear to continue using only one kind, is a striking pattern. This reflects a development over time also for the Edwards Sapien valve where a larger share of the procedures is transfemoral rather than transaortic. This moves TAVI definitely towards the cardiologist side. As a consequence, the occasional power-games between the two groups of professions appear to be declining as the cardiologists are clearly taking the lead, and the thoracic surgeons are induced to collaborate in order to learn the new procedures to maintain relevant roles in the future of heart surgery – if and when TAVI moves further to include also the medium- and low-risk patients.

Analysis and discussion

The three stories about TAVI presented above provide an interesting image of many aspects of innovation in advanced medical technologies and procedures, about the drivers for such changes, the capacities required to actually move things like this into practice, and about the scale and scope of the operations. It certainly also provides interesting images of the importance of early network formation in between the technology developers and suppliers and the users of the technology at the hospital.

Firstly, the case exemplifies a situation where even though the early idea and invention by Henning Rud Andersen appeared to be a quite simple combination and extension of existing stent-, artificial heart valve- and balloon-expansion technologies, the challenges confronting the developers were tremendous. Hence, it took more than 10 years from the invention till the first human implantation occurred, and another 5 years before the developers could start selling anything at all. All of this required financing. Then, highly specialized manufacturing operations had to be established along with structured and quite sophisticated marketing operations with streamlined "start-packages" that included the technology, senior expertise, training of the hospital staff, laboratory support, operational support during the procedures, etc. targeted to core heart clinics across Europe. Through these first customer relations, the suppliers also had to systematically build the capacity to expand to additional hospitals by using the first customer clinics as educational laboratories to educate physicists that could take on the roles as proctors the following years.

To move such a new procedure into a local domain that can be characterized as densely organized, highly specialized professional work, requires that the new – from the very beginning – is organized and conducted at a similar level of quality and structure. This has to be developed, organized and tightly controlled while also being standardized and subjected to structured improvement processes based on a centralized infrastructure and organization to support and conduct all of these - including initiation of and support to clinical studies of results. While starting out as local inventions in Denmark, France and Israel, none of these countries managed to mobilize the necessary resources to develop these inventions into the commercial level.

Both ended up being purchased by US med-tech companies, of which one (Edwards) was a highly specialized spin-off from a major US med-tech company, and the other was one of the other major med-tech conglomerates (Medtronic). The route of the innovation did not go from the Danish inventor to some Danish hispital, or from the French inventors to some French hospital, and from there to other hospitals while building a local industry. It moved from the inventor in one country to a start-up company in the US, and then through international venture capital companies to industrial mergers with major global med-tech companies with particular strategic interest in this domain of medical technology. These

were the ones that were able to organize whatever required to move the new technology into the complex and demanding world of local heart clinics. Apparently, this could not be done by anyone in Denmark, France or Israel. Hence, in the perspective of a small state innovation policy, the value of an invention like this is dominantly related to the using of it, not the building of a supply industry that will generate a lot of jobs and represent an attractive source of future taxation.

Secondly, the structured CE and FDA trial procedures required to initiate the commercial expansion processes appear to play very important roles in the early formatting of the business networks of these new medical technologies and procedures. Those that engage in these early processes will be necessary partners in the following expansion processes as expertise in conducting the new procedure locally is a key bottleneck to the expansion process. By building experience and expertise in the early phase, these practitioners get the opportunity to educate other practitioners while building strong networks and network positions internationally that can be used to further strengthen and improve practices and exploit the resources and learning experiences of others. In both the Edwards and the CoreValve cases, Danish hospitals got involved in the early phase, and expanded to become the major TAVI hubs towards the Scandinavian hospitals, as well as major participants in the global TAVI networks through letting a few of their senior physicists work as proctors across the world, before bringing their direct experiences with organizing of TAVI in these many places back to their home institutions. Hence, a major research question raising from this concerns precisely what benefits these hospitals actually may collect from engaging in these roles, and also what the additional costs and challenges may be, in terms of quality, effectiveness and efficiency of TAVI related activities. Do they have lower costs, higher productivity and higher quality in treatment results than hospitals that are late adopters?

The Norwegian case is rather illustrative of a late adopter situation. None of the heart clinics had been involved in the early clinical trials associated with the CE approval process, and none of them managed to become part of the first round of expansion in 2007-2008. On the contrary, political processes led to the abortion of the initiative at Feiring to establish an early collaboration with CoreValve, while Rikshospitalet/Oslo University Hospital had obvious internal controversies with respect to the offer from Edwards to establish some collaboration in 2007. These controversies ended up in a centralized decision in Norway not to offer TAVI to Norwegian patients, but rather to wait for more clinical results from other countries. Hence, Norway appears to have taken a very reluctant approach which also implies taking a free rider position to let others absorb the early learning costs. So, obviously, there are some economic benefits associated with a late adopter strategy, however in this case at the possible expense of Norwegian patients that were not given any other effective treatment of their life-threatening condition. These different approaches in Denmark and Norway invite a comparative study of the pros and cons of early and late adopter strategies.

For the further investigations, we would like to learn more about how and why none of the Norwegian heart clinics managed to establish themselves in more central positions in any of the two supplier networks. Why did Oslo apparently represent this rather defensive position? Is it due to the individuals who are there, or is this just a mirror image of the broader policy of the Norwegian health care system to keep down the purchasing of new and costly treatments? Is this part of a broader reluctance in Norway to stay away from the forehead of international innovation processes, by reverting to more of a free rider role to wait and see to it that other nations use their resources to perform the sometimes rather expensive innovation processes that bring down costs and increase the quality through the many complex learning curves involved? If so, what is lost by such an approach? What does Denmark, Danish hospitals, Danish patients and the Danish health care system gain from taking the lead position in Scandinavia? What do they gain and what do they loose from working much closer with the suppliers? What do they obtain from their much more extended international TAVI networks and their better ability to learn from others across the world about things that are not published in medical journals?

Final comments

This paper reports from an early explorative investigation into the origins and emergence of TAVI internationally and into the history of TAVI in Norway. Through the presentation of three different stories, the aim has been to present the TAVI case in a rather simplistic and broad empirical format, in order to discuss what comes to mind as interesting observations at this level of analysis.

In the IMP perspective, the case presented in particular draws attention to the multiple effects of early network formation in innovation processes. These will be targeted in the continued research on TAVI practices at a number of Scandinavian hospitals. It also represents a very interesting case about what it really takes to create a new, fairly radical and to some extent disruptive technological change in the health care setting. Given the substantial demands on the developers and suppliers of such innovations to actually move the technology into widespread use, there is an interesting discussion in relation to innovation policies of small countries that are part of global technology markets. What are the core benefits of such innovations to these nations? What roles are realistic to take? And what roles and what strategies put such nations in positions from where more benefits can be obtained to deliver more and better health care services at sustainable or even lower costs? Regarding these roles, it should also be clarified whether or not different attitudes towards private-public collaboration in the different hospitals may contribute to explaining the different hospital strategies and roles observed.

This research project requires a research strategy where one has to zoom in on a variety of local practices in order to obtain a true empirically based understanding of the challenges of

innovative change in practice. On the other hand, it seems obvious that we also have to zoom out to obtain the broader view of the networked interactions at the international level of analysis. At this level, the case presents the emergence of two rival international TAVI networks associated with each of the two technology suppliers. However, more suppliers are moving into the market with their own versions of the technology and their own emerging networks. The trend seems to be that each hospital wants several suppliers, in part because not all patients can have the same type of valve, but probably also in order to negotiate better deals for the hospital. As a result, the supplier-networks are interacted at the hospitals, and the organizing of the procedures must include the flexibility required to manage different valves requiring different equipment.

At the same time, the technology seems to be converging towards solutions where the cardiologists may conduct the procedure themselves without the thorax surgeons. Hence, over time, if TAVI continues to improve and expand into additional parts of the patient group such as has already happened in Germany, we may be studying a next to complete disruptive innovation process during which the present "gold-standard" open surgery procedure and the profession conducting it, will be replaced by a very different procedure and a different medical profession - in the prestigious domain of heart valve replacement treatment.

It seems clear, that it is impossible to really understand what goes on with respect to TAVI within a local heart clinic without also understanding their interactions with the suppliers and the work conducted within the supplier networks themselves. TAVI does not move from hospital to hospital in any way; it moves from one of the suppliers in collaboration with a few core partnership heart clinics, directly to each additional hospital starting TAVI procedures.

Literature

Andersen, H.R., Knudsen, L.L. and Hasenkam, J.M. (1992). Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs, *European Heart Journal,* 13 (5): 704-708

Christensen, C. M., M.E. Raynor (2003): *The Innovator's Solution,* Harvard Business School Publishing Corporation

Dvir, D., Barbash, I.M, ben-Dor, I., Okubagzi, P., Satler, L.F., Waksman, R. and Pichard, A.D (2012): The development of transcatheer aortic valve replacement in the USA, *Archves of Cardiovascular Desease*, 105, pp160-164

Håkansson, H., D. Ford, L-E. Gadde & A. Waluszewski (2009): *Business in Notwrods,* John Wiley & Sons

Håkansson, H. and Olsen, P.I. (2012): "Innovations in the health care and construction industries - in light of new global interaction patterns and local dependencies", paper presented at IMP Conference, Rome, September 13 – 15, 2012

Masovic, J., Mørk, B.E. & Nicoloni, D., (2013). Innovative practices and professional jurisdiction in healthcare: The case of transcatheter aortic valve implantation (TAVI), Conference paper at EGOS conference, Montreal, June 5th.

Olsen, P. I. (2013): "IMP Theory in Light of Process-, and Systems Theories", *The IMP Journal*, 7(3), pp 159 - 170

Steigen, T.K., Schive, B., Næsheim, T. and Busund, B. (2011); Transkateter aortaimplantasjon ved aortastenose, *Tidsskrift for Den norske Legeforening*, 131 (4): 343-348