THE SAHLGRENSKA ACADEMY

Improving the Safety of Transcatheter Aortic Valve Replacement

– Comparison of Swedish and American Approach

Degree Project in Medicine

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Programme in Medicine

New York, Gothenburg, Linköping 2018

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Abstract

Introduction: Aortic stenosis is the most common structural heart disease. After symptom onset, the prognosis is very poor – over 50% of patients die within 2 years – unless they undergo aortic valve replacement. Transcatheter aortic valve replacement (TAVR) is the minimally invasive method for valve replacement. Being a relatively new procedure, it is executed in different fashions in different institutions. Accordingly, complications and results vary a lot. Further research is needed to identify ways to reduce complications.

Aim: The aim of this project was to identify the milestones in the development of TAVR protocols in different institutions and to investigate how the different protocols affect the complication rates.

Methods: A total of 1153 patients were included in the study. The data was collected from national TAVR registries in Sweden and the United States – Swedeheart and TVT registry respectively. The hospitals were compared regarding the entire TAVR process – from preparation for the procedure, through procedural differences in the cath lab to complication rates afterwards.

Results: There were numerous significant periprocedural differences: anaesthesia type, procedure time, contrast use, rates of pre- and postdilation. There were no significant differences in stroke rates between the institutions. The rate of pacemaker implantation post-TAVR was significantly lower in Linköping than in New York (P=0.003) 1-Year mortality was significantly lower in New York than in Gothenburg. (P=0.02)

Conclusion: Overall all three centers have low mortality and morbidity rates - lower than those reported in the literature. In addition, the TAVR results are non-inferior or superior to published surgical AVR series. Excellent TAVR results can be achieved using substantially different procedural protocols and perioperative logistics. It is feasible to avoid stroke, complete heart block and risk for kidney failure. Further research is needed to combine the best procedural practises to develop the ultimate TAVR.

Key Words: TAVR, procedure, stroke, mortality, pacemaker

Introduction - Aortic Stenosis

Aortic stenosis is one of the most common structural heart diseases. The prevalence increases with age and is in the elderly (>75 years old) population in epidemiological studies reported to be 7-12%.(1, 2)

After the onset of symptoms (shortness of breath, angina pectoris, syncope), it is rapidly fatal. More than half the patients die within 12-18 months, unless they undergo aortic valve replacement (AVR). (3) It is therefore important for all physicians to have enough knowledge about this condition to correctly refer their patients for heart valve replacement.

Transcatheter aortic valve replacement (TAVR) which is a minimally invasive procedure has been a major improvement in the treatment of aortic stenosis. At its introduction for more than a decade ago TAVR was considered a therapeutic option only for patients with a prohibitive risk for surgical AVR. Over the years, mostly due to an improvement in its safety TAVR has become a first-choice treatment for elderly people with moderate and recently even low perioperative risks.(4) Being a relatively young procedure TAVR is executed in different fashions in different institutions. Accordingly, complications and results vary a lot. Further research is needed to identify ways to reduce complications.

Specific Aims of this Study

The aim of this degree project is to identify the milestones in the development of TAVR protocols in different institutions and to investigate how the different protocols affect the complication rates, because better understanding could allow for more ubiquitous use of this breakthrough technology. The specific objectives analysed are pre- peri- and postoperative differences between the three hospitals. Are there any significant differences in the perioperative setup and techniques? Are there any significant differences in complication rates after TAVR – new permanent pacemaker implantation, stroke and mortality?

Introduction - Management of Aortic Stenosis

Medical therapy: There is no effective medical treatment of aortic stenosis. For temporary symptom relief, diuretics and ACE inhibitors may be used but in the long term, the only definitive treatment is aortic valve replacement.

Aortic valve replacement: Before the introduction of TAVR, the only way to replace the valve was with open heart surgery - surgical aortic valve replacement. There was no satisfactory alternative therapy for patients with a prohibitive risk for surgery. BAV may provide some symptom relief but it is only a palliative treatment in high-risk patients where no other invasive treatment is obtainable. (5)

The first implantation of a transcatheter aortic valve in 2002 revolutionized the treatment of patients unsuited for surgery and it is considered a major milestone in interventional cardiology.

Since then, the field of TAVR has been rapidly expanding - more than 350 000 procedures have been executed in over 70 countries. (6)

TAVR has become much safer and more streamlined. The complication rates are getting smaller. While early studies comparing SAVR to TAVR at first found higher stroke rates in the later(7), more recent studies show no difference or even less stroke after TAVR. This is mainly due to the refinements in procedural techniques and devices.

TAVR – About the procedure

This minimally invasive procedure can be executed in different fashions but the general idea is to replace the damaged aortic valve with a new one without the need for a sternotomy. Instead it delivers the new valve through a catheter, somewhat similar to how a stent can be placed in an artery. Once the valve is in place, it pushes the native leaflets away and takes

over.

Devices: There are multiple approved devices for TAVR. The two most commonly used in the centers compared in this study are the Edwards Sapien Heart Valve System (Edwards Lifesciences) and the Medtronic CoreValve Evolut. The main difference between the two is their construction, see images below. The Sapien is a bovine valve in a balloon expandable stainless-steel frame while the CoreValve is porcine and mounted on a self-expandable nitinol frame.(8)
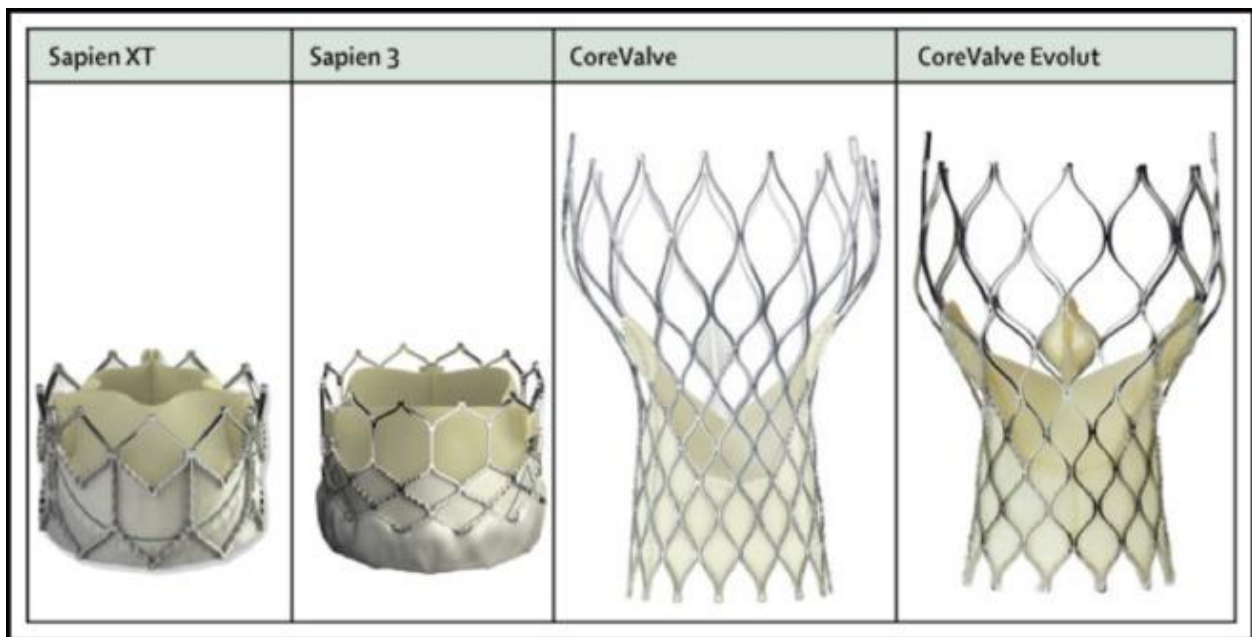

Figure 1 – Left to right: Sapien XT valve, Sapien 3 valve is a newer-generation valve that conforms more naturally to anatomy, thus having a better fit than the prior Sapien XT valve. The new conformation decreases paravalvular leak. Corevalve Evolut is a re-capturable valve that allows for recapturing and repositioning of the valve. (9)

A randomized clinical trial (10) and published registry data (11, 12) comparing the self-expandable and balloon expandable valve showed no significant differences in stroke, major vascular injury or mortality rates between the devices.

The Medtronic CoreValve was however associated with a higher incidence of pacemaker implantation and aortic regurgitation post TAVR. (11-13)

Nevertheless, the choice of device depends on patient anatomy, the operator's preference, the center's own experience and other factors.(8)

Access site: There is a number of access sites that can be used for a transcatheter valve implantation. The trans-femoral access using the common femoral artery is the most widespread. However, in cases with peripheral arterial disease or a presence of possible thromboembolic material in the aorta there are alternatives: the trans-apical, trans-aortic, trans-carotid, trans-subclavian and trans-caval approach.

Indications for TAVR

History: When the procedure was introduced in 2002 by prof. Alain Cribier, using the valve construction of Dr Henning Andersen, it was only performed on patients who were prohibitive risk for surgery for whom there was no alternative treatment aside from medical therapy. Excellent outcomes were reported in several studies showing that TAVR is superior to medical therapy (14) (15). El Bardissi et al showed that there was no difference in long-term survival after this minimally invasive surgery as compared to an age- and gender matched population.(16)

The PARTNER trial (14) compared standard therapy with trans-catheter implantation of a balloon-expandable valve (Sapien) in patients with severe aortic stenosis whom surgeons deemed unsuited for surgery. The results were as follows:

- At 1 year, death from any cause was 30.7% with TAVR and 50.7% with standard therapy

- The rate of death from any cause or repeat hospitalization was 42.5% with TAVR and 71.6% with standard therapy

- The rate of cardiac symptoms at 1 year was 25.2% in the TAVR group vs 58.0% in the standard therapy group

A similar trial only with a self-expanding bioprosthesis (CoreValve) implanted in patients with prohibitive risk for surgery published a couple years later also showed significantly

better results with TAVR as compared to medical therapy. At 1 year, all-cause mortality or major stroke was 26% in the TAVR group vs 43% with standard therapy. (15)

After it was shown to be a feasible procedure in patients with prohibitive risk for surgery, new trials started to investigate whether TAVR could be a better option than SAVR for patients with a high risk for surgery (7). TAVR and SAVR in this patient group were associated with comparable rates of survival at 1 year.

As the results from this large-scale trial suggested that TAVR is non-inferior to SAVR in high risk patients, the next step was to examine if this would be true in intermediate risk patients as well.

This was investigated in many trials, including PARTNER 2 (balloon expanding prosthesis) (17) and SURTAVI (self-expanding prosthesis) (18)

In the PARTNER trial, transfemoral TAVR resulted in a lower rate of death and stroke than SAVR (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P=0.05). Transthoracic TAVR resulted in similar outcomes. The pattern of complications differed between the procedures. In both trials, surgery resulted in higher rates of acute kidney injury, severe bleeding and new onset atrial fibrillation while TAVR was associated with more vascular complications and paravalvular aortic regurgitation. Lower mean gradients and larger aortic valve areas as well as faster recovery and shorter ICU & hospital stay were observed post TAVR.

These satisfying results led to the approval of TAVR as an alternative to surgery in intermediate-surgical risk patients by the American Heart Association and American College of Cardiology in 2017. The focus has now shifted to low risk patients with a goal to expand TAVR to all-risk patients. (19)

A Scandinavian randomized trial published in 2015 found no significant difference between TAVR and SAVR in regards to stroke, myocardial infarction or death from any cause at 1 year in low risk patients. (4) There are large ongoing trials for low risk patients in the United States at the moment.

It seems to be just a matter of time before TAVR manifests as an option for aortic valve replacement regardless of surgical risk score. However, some essential questions considering paravalvular leak, leaflet thrombosis, valve longevity and the need for new permanent pacemaker post TAVR need to be addressed. (19)

The indications above include symptomatic patients. In asymptomatic patients with severe stenosis, the question of valve replacement is less clear. Rosenhek A et al. suggest that generally it is relatively safe to postpone surgery until symptoms develop. It seems improbable that the potential benefit of valve replacement could outweigh the risks associated with the surgery. However, patients identified with a very poor prognosis, for example with severe valvular calcification and rapid increase in aortic-jet velocity should be considered for earlier intervention.(20)

Patients with severe, non-symptomatic aortic stenosis are frequently referred for TAVR prior to other major surgeries in order to lower their anaesthesiologic risks.

Even patients with a bicuspid aortic valve or a degenerated surgical bio prosthesis can undergo TAVR. The latter is a so called "valve in valve" (VIV) TAVR and it has been shown to generate excellent outcomes. (21)

Recently the technique has also been utilized in the mitral position to repair mitral regurgitation or stenosis (22, 23)

In summary, available data from large randomized trials and registries suggests that in terms of mortality, TAVR is superior to medical therapy in symptomatic patients at extreme surgical risk (14), non - inferior or superior to surgical AVR in high risk patients (24, 25) and non - inferior or superior (transfemoral access) in intermediate risk patients.(24) The evidence for superiority of TAVR over SAVR in low risk patients is not very strong yet but there are large ongoing randomized trials.

Asymptomatic patients should not undergo aortic valve replacement with the exception of specific situations described above.

Guidelines:

The current guidelines on choosing between surgical and transcatheter aortic valve replacement by the American Heart Association for high risk patients recommend that a heart valve team involving a multidisciplinary group of professionals collaborates to provide optimal patient care. They state that "the patient's values and preferences, comorbidities, vascular access, anticipated functional outcome, and length of survival after AVR should be considered in the selection".

Regarding symptomatic patients with an intermediate surgical risk, TAVR is stated to be a reasonable alternative to surgical AVR, depending on patient-specific procedural risks, vascular access, comorbid conditions, expected functional status after AVR and patient preferences. (26)

The European guidelines provided by the European Society of Cardiology (ESC) also emphasise that the decision between surgical AVR and TAVR should be made by a heart team in a heart valve centre with surgeons and cardiologists. Risks and benefits of both procedures should be weighed and factors like age, comorbidities, anatomy, local experience and outcomes should be discussed.

Similarly, to the American guidelines, the indications for TAVR broadened in 2017 to include patients at intermediate surgical risk. This promises to increase the population suitable for TAVR globally.

The guidelines point out that currently available data favours TAVR in patients at increased operative risk. Nevertheless, exact criteria for the decision between TAVR and SAVR is not well defined. Instead they refer to careful evaluation of every case by the heart team.(27)

Aspects to be considered by the Heart Team for the decision between SAVR and TAVR in patients at increased surgical risk are summarized in a table attached in the appendix below.

Complications

Stroke

Stroke is a rare but most feared complication, associated with severe disability and high mortality.(28) It is mainly confined in the peri-procedural and 30-day post-TAVR period. A possible cause of stroke in TAVR is dislodgement of atheromatous, calcific plaques.(29) Catheter manipulation in the aorta or during crossing of the calcified valve may also cause scraping of debris. Smaller and more flexible catheters are developed to prevent this. Balloon pre-dilatation of the native valve which crushes the calcified native valve may also increase the risk of cerebral embolism. A few years ago (2011 in Linköping, Sweden), operators began to omit pre-dilatation in balloon-expandable prosthesis to streamline the procedure,

reduce the number of pacing periods and shorten OR-time. Their experience show that it is safe and feasible.(30, 31) Another possible cause of stroke is build-up of thrombi on catheters or on the prosthesis during implantation. Heparin is therefore administrated during the procedure.

Operator experience is another factor affecting the outcomes.(32)

For stroke prophylaxis, improved design of the procedure, cautious patient selection and antithrombotic strategies during and after the procedure are crucial. The valve and delivery systems are continuously refined and new embolic protection devices are produced.

The 1-year incidence of stroke post TAVR is in large recent European meta-analyses (9786 and 29034 patients respectively, both CoreValve and Sapien, TF and TA approach) reported to be approximately 3% (28, 33). An older article based on 12182 patients from 299 US hospitals who underwent TAVR between 2011 and 2013 reported a stroke rate of 4.1%(34). The incidence of stroke is consistently decreasing and is as mentioned previously comparable with SAVR.(24, 32-38)

Regarding antithrombotic therapy post TAVR, there is no consensus yet, due to lack of proper studies so far.(39) Current AHA/ACC guideline recommendation is ASA and Clopidogrel for 6 months post TAVR.(40) Patients being on anticoagulants for other reasons before TAVR either continue on anticoagulants only, or combine them with one anti-platelet.

Cerebral protection devices have not yet shown any positive clinical effects (41, 42) but there are reports suggesting a significant decrease of new ischemic cerebral lesions.(42, 43)

It is interesting to further investigate the stroke rates correlation with different operative techniques and medications.

Pacemaker

Conduction abnormalities are a common and serious complication of TAVR. Recent reports suggest permanent pacemaker (PPM) implantation post-TAVR increases exacerbation of heart failure, length of ICU stay and even overall mortality.(44, 45) It also exposes patients to potential complications of the implantation procedure itself. The need for new PPM implantation is one of the complications that still in most centres is higher in TAVR than in surgical AVR, which makes it an interesting subject to study. In the PARTNER2 trial with balloon-expandable valve: 8.5% in TAVR and 6.9% in surgical AVR.(17) However, some centres have already reduced new PPM implantation rate under the surgical prevalence for a few years now. Also, some valve models, e.g. Symetis Accurate, have a very good PPM record. Furthermore, some patients are diagnosed with conditions being indications for a pacemaker during the evaluation for TAVR. Thus they may have a pacemaker implanted within 30 days after TAVR procedure not as addressing the TAVR complication but due to the conduction abnormalities discovered before TAVR.

Current guidelines are unclear regarding the exact indications and timing of PPM implantation with the result that it is a controversial subject at this time. To eliminate this problem, more research regarding the role of PPM implantation in TAVR is needed.

An analysis of the literature leaves one with more questions than answers. A recent review of 40 studies found that the incidence of new PPM post-TAVR ranges between 2.3% and 36.1% which is incredibly variable.(46) The rate is higher with self-expandable devices compared to balloon-expandable. For new generation Sapien 3 device, the rate was between 4%(47) and 24% (48), while the new Evolut R ranged between 14.7%, as reported by Kalra et al.(49) and 26.7% in the SURTAVI trial (18). As the authors of the review point out, specific recommendations for implantation of each prosthesis are needed to reduce the rate of new PPM.

There are predisposing factors predicting conduction abnormalities affiliated with TAVR. Clinical studies show that anatomical factors like thick baseline interventricular septum (>17mm), non-coronary cusp thickness >8mm and small LVOT diameter are associated with higher risk of PPM. (50, 51). Furthermore, the volume of LVOT calcification below the level of right and left coronary cusps (52), pre-existing right bundle branch block, large ratio of the prosthesis to LVOT diameter(measured in mid-systole), small left ventricle end diastolic diameter (45) and low valve position (depth of implantation >25.5% with Sapien 3 (53)) are other independent predictors. Moreover, AV-block I, bifascicular block and atrial fibrillation with slow ventricular rate increase the risk.

New onset of LBBB post-TAVR increases PPM implantation (54), heart failure hospitalization and mortality.(55)

A German study by Hoffmann et al. concluded that LVEF improves after TAVR in absence of new conduction defects, while patients with new conduction defects do not experience improvement in LVEF at follow up. (56)

Mechanisms of conduction system injury have been shown to include compression, trauma, infarction or haemorrhage.(57)

The most common conduction disturbances after TAVR are AV-block (AVB) and left bundle branch block (LBBB).

Current guidelines from the ESC recommend considering PPM in patients with complete heart block (CHB) and high grade AVB if they persist 7 days after TAVR. However, most studies recommend PPM implantation 24-48 hours after the procedure if CHB was noted in the periprocedural period to not delay ambulation and discharge and to prevent morbidity from immobility with the temporary pacemaker. The ACC does not provide any official guidelines on this matter and PPM implantation is left to the discretion of the physician.

It is interesting to investigate if there are any procedural factors that have the potential to minimize conduction abnormality after TAVR. Therefore, one of the aims of this study is to investigate which changes in TAVR protocol lead to a decrease in PPM implantation rate post TAVR.

Material and method

Total of 1153 patients were included in the study. The data was collected from national TAVR registries in Sweden (Gothenburg and Linköping) and in the United States (New York), Swedeheart and TVT registry respectively. Three university hospitals were included in the study: New York Presbyterian Hospital, Sahlgrenska University Hospital in Gothenburg and Linköping University Hospital.

Referral population to the hospitals:

Sahlgrenska University Hospital gets referrals from an area covering approximately 1.8 million people.

Linköping University Hospital covers an area of around 1 million people.

The size of the referral population to Weill Cornell Presbyterian Hospital was difficult to determine. Patients from Manhattan, Brooklyn, Bronx, New Jersey and Upstate NY are referred to all the different hospitals in the area – Weill Cornell Presbyterian, Columbia Presbyterian, Mount Sinai, Lenox Hill, NYU, Montefiore, NYP Methodist, Northwill.

The inclusion criteria were: patients who have undergone TAVR with either Edwards or Medtronic valves between 2014 and 2018. The reason for the dates chosen was that data from the period before 2014 was not complete in regard to the endpoints of pacemaker and stroke in the American TVT registry. The choice of valves studied was made to be able to compare

the results based on valve type. Even though there are many commercially available valve types in Europe, only Edwards and Medtronic valves are approved in the United States.

The registries are filled out by either the cardiologist performing the procedure – in Sweden, or a nurse practitioner involved with the cases – in New York. They are considered very good quality and all patients, besides research cases in the PARTNER trial in New York undergoing the procedures are followed up. The way the registries are filled out differs between the hospitals. In the Swedish institutions, the data is systematically inserted directly after the procedure by the cardiologist performing the procedure. The in-hospital complications are added at discharge – in Linköping by the anaesthesiologist and in Gothenburg by the cardiologist. In New York Presbyterian, a nurse practitioner fills out the registry using the data in the patient chart usually within a month of the procedure.

Of the 1153 patients, 547 were taken from the TVT registry in New York (398 Sapien & 149 Medtronic), 350 from Linköping (Sapien) and 256 from Gothenburg (Medtronic). See figure 1 below.
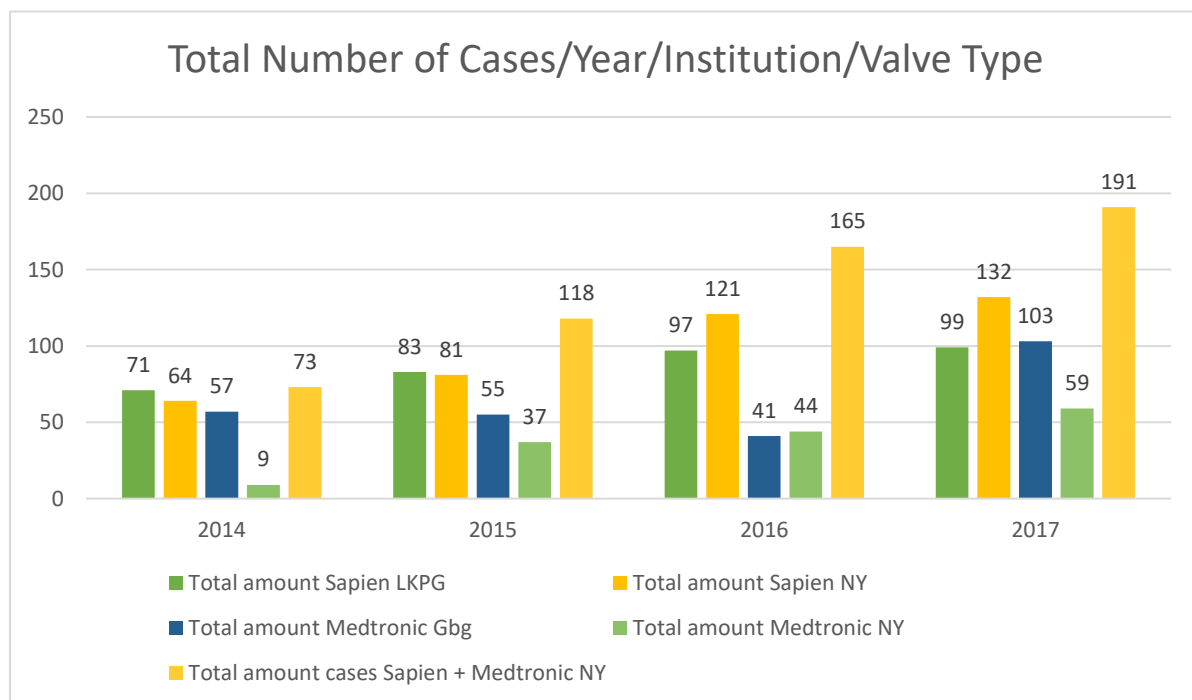

Figure 2 – Number of TAVR cases per institution over time according to valve type

The data was de-identified from names and personal identification numbers.

It was organized to be outlined in similar ways from the different registries to make the statistical analysis possible. Patients who received valves different from Edwards or Medtronic and valves in all extra-aortic positions (mitral, tricuspid, pulmonary, caval) were excluded.

Parameters analysed to describe the epidemiology of patients in the different institutions were: age, sex, percentage of hypertension, diabetes, chronic lung disease, myocardial infarction prior to the procedure, prior heart surgery and stroke in the previous medical history. Chi square test was used for statistical analysis and p-value < 0.05 was considered statistically significant. As the table below shows, the populations were very similar in regard to all factors except for history of hypertension which showed to be higher in NYP than in the Swedish hospitals.
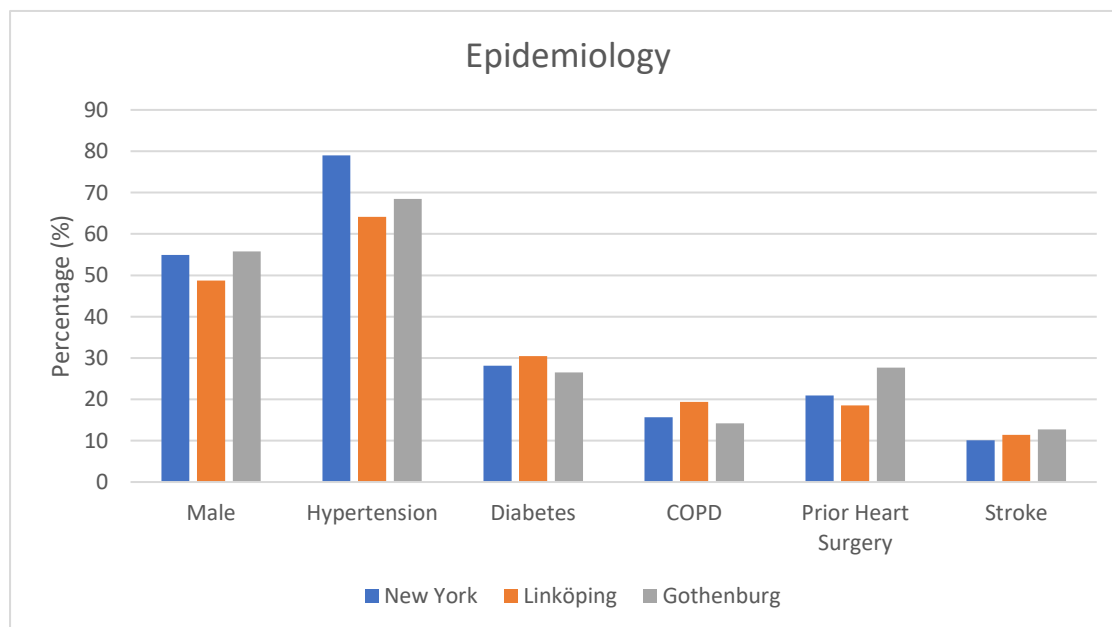

Figure 3 - Epidemiology of patients included in the study

The proportion of men undergoing the procedure was statistically significantly lower in Linköping than in Gothenburg and New York (p=0.015) but it was around 50%.

Patients with hypertension were overrepresented in New York ($p<0.0001$) while patients in Gothenburg had significantly higher proportion of heart surgery prior to TAVR ($p=0.02$) There was no significant difference in diabetes, chronic obstructive pulmonary disease and history of stroke among the patients in the three institutions (p-value 0.55, 0.18 and 0.52 respectively). The original plan was to look at proportion of pacemaker before the procedure as well but this was not documented in the registries.

Table 1 - Demographics and Baseline Characteristics of TAVR patients

Characteristic	New York	Linköping	Gothenburg
	(N=634)	(N=351)	(N=260)
Male Sex – no. (%)	286 (55%)	171 (49%)	145 (56%)
Hypertension – no. (%)	501 (79%)	225 (64%)	178 (68%)
Diabetes – no. (%)	178 (28%)*	107 (30%)	69 (27%)
Prior Heart OP – no. (%)	132 (21%)**	65 (19%)	72 (28%)
Chronic Obstructive Pulmonary Disease – no. (%)	99 (16%)***	68 (19%)	37 (14%)
Stroke – no. (%)	64 (10%)[×]	40 (11%)	33 (13%)

*Data missing for 2 patients; **Data missing for 4 patients; ***Data missing for 3 patients; [×]Data missing for 2 patients

There were no statistically significant differences in average age of patients at the time of the procedure in the three institutions: 82 years at NYP, 80 years in LKPG and 81 in GBG.

Method

The three hospitals were compared regarding the entire TAVR process – from preparation for the procedure, through procedural differences in the cath lab to complication rates afterwards.

The procedural differences analysed were:

- the set up in the cath lab – personnel involved in TAVR in regard to which specialty – cardiologist vs cardiothoracic surgeon is performing the procedure

- anaesthesia type used

- total time of the procedure

- contrast volume used during the procedure

- fluoroscopy time

- echo-guidance

- number of arterial accesses

- balloon aortic valvuloplasty

- post-dilatation

- access to cardiopulmonary bypass machine

The differences in preparation for TAVR – variables studied were:

- decision making for TAVR vs sAVR – who is in charge?

- clinical visits before TAVR – physical exams, tests – TTE, TEE, ECG, CT, cardiac cath, x-ray, labs

- heart team rounds – when in relation to the procedure? Which categories of physicians are involved?

The complication rates analysed were:

- new PPM implantation post TAVR

- stroke

- in hospital mortality

- 1-year mortality

- contrast induced nephropathy

Special emphasis was laid on stroke, pacemaker and mortality rates for which the rates were analysed per year to recognize trend changes over time.

All the above endpoints were included in the registries. The definitions used for complications in the registries are as follows:

New permanent pacemaker:

New York: Conduction/Native Pacer Disturbance Req Pacer (In hospital & follow up): "Indicate whether patient developed a new dysrhythmia requiring insertion of a permanent pacemaker."

Gothenburg & Linköping: Indications for NPPM after TAVR in LKPG are consistent with 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. The most common causes being acquired AV block grade III or II irrespective of symptoms, sinus node disease, incl. tachy/brady syndrome with symptoms or Afib with AV-block with symptoms.

Stroke:

New York: (In hospital & follow up): Definition taken from the FDA draft "Standardized Definitions for Cardiovascular Endpoints in Clinical Trials": "An ischemic stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of infarction of central nervous system tissue. Haemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with haemorrhagic transformation and not a haemorrhagic stroke."

Gothenburg & Linköping: Stroke is defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death with other aetiologies excluded.

<u>In-hospital mortality:</u>

<u>Linköping & Gothenburg</u>: Defined as either occurring during the intervention or before

discharge from the hospital.

<u>New York:</u> Defined as status at discharge – alive vs deceased.

<u>1-year mortality:</u>

<u>Linköping & Gothenburg</u>: Defined in the registry as deceased within 365 days from the

procedure date. The registry is linked to the national mortality-registry.

<u>New York:</u> "1-year mortality" was deducted from information about follow-up status – alive

vs deceased. That data was organized to pinpoint the date of death and then calculated for the

proportion of patients deceased within 365 days from the procedure date.

Statistical Analysis:

The data was divided according to the valve type used – Edwards vs Medtronic for the

analysis of incidence of new PPM and stroke following TAVR for each of the valve types in

the three centres.

Chi square test (for categorical variables), t-test (to compare means) and ANOVA (for

variation between more than two groups) were used for statistical analysis of all variables and

p-value <0.05 was considered significant. Continuous variables are demonstrated as mean ±

SD. Categorical variables are presented as frequencies.

All statistical analysis was performed using IBM SPSS Statistics 25 and Excel 2016.

Following data analysis, cath-lab visits were carried out and interviews were conducted with

the operators to determine how they perform the procedures and to identify what changes

they have made to their TAVR protocols. Subsequently, the different protocols were analysed

and compared to identify procedural differences and to explain the differences observed in results.

Ethical Considerations

There was no need for institutional ethical board consent for the planned study design. Neither for an informed patient consent. No individual patient data were to be disclosed to third parties. The study had an observational and retrospective design. Basic principles for medical research enunciated in the Declaration of Helsinki were respected during the project.

Results

Table 2 – Procedural Data

	NYP	GBG	LKPG
General Anaesthesia	85% (536/628)	4% (11/260)	90% (317/351)
Transfemoral access	89% (487/547)	98.8% (257/260)	85.5% (300/351)
Procedure time (min)	113 ± 58 (n=628)	71 ± 27 (n=250)	48 ± 40 (n=351)
Fluoroscopy time (min)	11.9 ± 9.0 (n=395)	20.1 ± 9.3 (n=260)	17.4 ± 14.1 (n=351)
Contrast (ml) mean	48 ± 33 (n=378)	99 ± 60 (n=260)	7 ± 18 (n=351)
BAV	All TF but ViV	82.1% (211/257)	2.8% (10/351)
Post-Dilatation	estimated 5% *	16.9% (44/260)	4.6% (16/351)
Echo guidance Y/N	Y&N	N	Y
No of arterial access sites	2 femoral ± 1 radial(if Sentinel)	2 femoral/1 femoral + 1 radial starting 2018	1 femoral
No of operators and specialities	1 CT surgeon 1-2 cardiologists	2 cardiologists	1 CT surgeon 1-2 cardiologists

*no data available in the registry

There was a significant difference in approach used for TAVR with higher rate of

transfemoral access in GBG as compared to LKPG and NYP ($p<0.0001$). No significant

difference between LKPG and NYP ($p=0.1394$)

There was a significant difference in procedure time between LKPG and GBG ($p<0.0001$),

GBG and NYP ($p<0.0001$) and LKPG and NYP ($p<0.0001$)

The contrast use in LKPG was significantly lower than in GBG and NYP ($p<0.0001$ for both)

At NYP the contrast use was significantly lower than in GBG ($p<0.0001$)

The rates of predilation were significantly lower in Linköping than in Gothenburg

($p<0.0001$). There was 0% predilation in LKPG in 2015,2016 and 2017.

There was significantly less postdilation in LKPG than in GBG ($p<0.0001$)

As the graph below shows, there was a major difference in anaesthesia type used in the three

institutions. Gothenburg stands out with almost no cases performed in general anaesthesia.

Interestingly, the trends over time were opposite in New York and Linköping. While in New

York the trend is to move towards more cases in monitored anaesthesia care (MAC), in

Linköping after experimenting with both types, they chose to use general anaesthesia in most
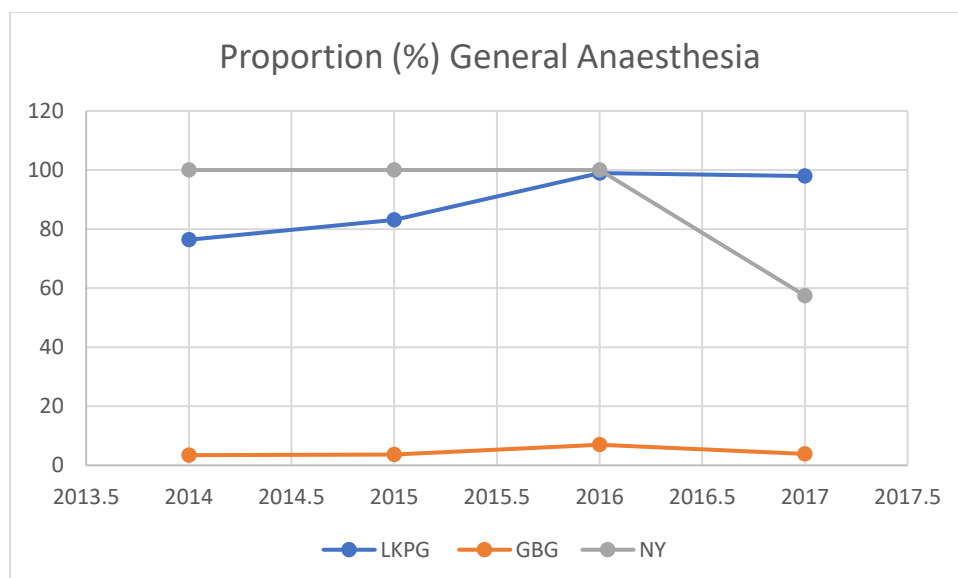
cases 2017.

Figure 4 – Proportion of patients undergoing TAVR in general anaesthesia

Creatinine before and after the procedure was also analysed. Both change in creatinine in all patients and the percentage of patients with an increase of >25% from baseline, which is the definition of contrast induced nephropathy were analysed.

The results were as follows:

Table 3 - Creatinine changes and proportion of contrast induced nephropathy after TAVR

	NYP	GBG	LKPG
Mean change in Creatinine before vs. after TAVR	-2.5 (N=549)	-10.4 (N=255)	-7.9 (N=344)
Percentage (%) >25% increase in Creatinine after TAVR	9.1% (N=549)	4.7% (N=255)	4.0% (N=344)

The changes in creatinine before vs after the procedure were not significant in any of the three hospitals.

There was however a significant difference in proportion of patients with >25% increase in creatinine between NYP and LKPG (*p*=0.007)

In LKPG, a systematic approach aimed at the reduction of contrast usage had been employed resulting in the reduction of contrast volume per procedure as well as the fraction of completely contrast free procedures: history of 300 cases between 2008 and 2015:
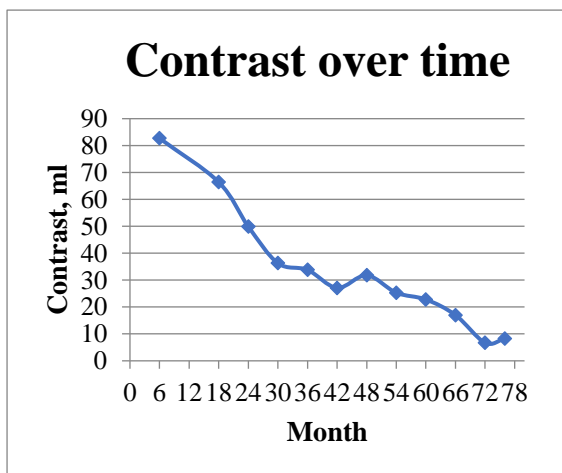

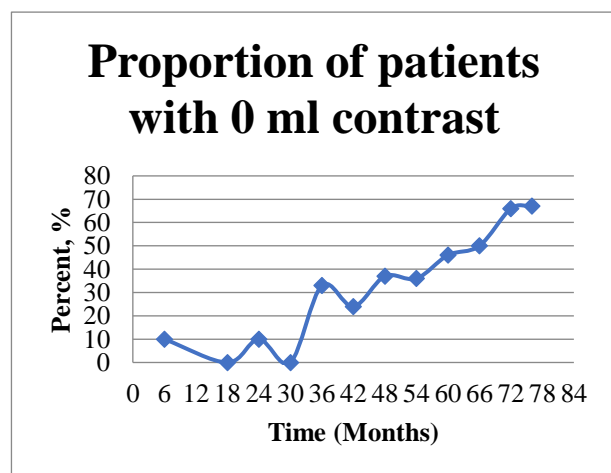**Figure 5** – Mean contrast use during TAVR in LKPG 2011-2018

Figure 6 – Proportion of patients operated without contrast during TAVR 2011-2018

Since 2008, no clinically overt AKI following TAVR has been reported in LKPG as a result of this approach. The mean contrast usage stands at 8mL per procedure. Nowadays, 75% of TAVRs in LKPG are performed without contrast.

TAVR Protocols

Table 4 – Workup for TAVR in the three hospitals

NYP	GBG	LKPG
Appointment with two cardiothoracic surgeons	Appointment with cardiologist	Appointment with cardiologist
TTE	TTE	TTE & TEE
CT angiography	CT with contrast	CT with contrast
Cardiac catheterisation	Coronary angiogram	Coronary angiogram
ECG	ECG	ECG
Labs – complete blood count, urine culture, NT BNP, troponin I, complete metabolic profile w glucose plasma, GFR, bilirubin, CK, INR, urinalysis dipstick with microscopic exam	Labs – complete blood count, electrolytes, NTproBNP, creatinine, GFR, INR	Labs – complete blood count, electrolytes, NTproBNP, creatinine, GFR, INR
Chest xRay		
Ultrasound of carotids (for Sentinel device screening)		

At New York Presbyterian Hospital, the preparation for TAVR includes a physical examination and evaluation of symptoms by two cardiothoracic surgeons to determine whether the patient is a good candidate for TAVR.

In Sahlgrenska University Hospital, the TTE is used for heart function assessment, grading of aortic stenosis and assessment of other valve problems. The CT with contrast is used to inspect a.femoralis, a.iliaca, aorta and to measure annular size for selection of the appropriate

valve size. As for the coronary angiogram, patients >85 yr do not routinely undergo coronary angiogram unless they have symptoms of ischemic heart disease.

At the heart team rounds in GBG, a general cardiologist, an interventional cardiologist, a cardiothoracic surgeon and a thoracic anaesthesiologist attend the meeting.

Factors that are taken into account when discussing TAVR vs sAVR are; age – the default for patients >85 is TAVR. Younger patients are referred for TAVR if they have pronounced comorbidities (e.g. renal insufficiency, anaemia, cancer, lung disease, calcium in aorta etc.) or if they have previously undergone thoracic surgery.

In Linköping University Hospital, aside from symptomatic patients, some asymptomatic patients are evaluated - those with severe aortic stenosis scheduled for a major surgery, where TAVR before the major surgery improves the safety of the subsequent surgery.

The TTE & TEE is in LKPG used for; grading of AS, valve morphology, sizing, ascending aorta diameter, identifying other cardiac problems requiring repair, identifying thromboembolic material, ventricular function, pericardial effusion, bulging septum.

The CT with contrast is used for; valve sizing, valve morphology, valve calcification pattern, annular rupture risk, aortic dimensions, coronary artery occlusion risk evaluation, access evaluation, thromboembolic material in aorta, iliac-femoral vessel diameter and tortuosity and pleural effusion.

The ECG is made to evaluate if the patient has pacemaker indications before TAVR and recognize the risk factors for post TAVR new PPM mentioned in the introduction.

The afternoon on the day before the procedure in LKPG, the heart team consisting of cardiologists, cardiothoracic surgeons, radiologists and anaesthesiologists attends a meeting

where the case is discussed, CT and echo images are presented (by radiologist and cardiologist respectively) and the team agrees on approach, anaesthesia type, valve type and size. Furthermore, the degree of addressing a possible complication is discussed – use of cardiopulmonary bypass, conversion to open heart surgery and HLR.

TAVR Procedure GBG

The procedure is performed by two cardiologists. The rest of the crew in the operating room consists of three nurses: 1 OR nurse assisting in the procedure, 1 nurse handling the medications and 1 nurse preparing the valve.

Uniquely for Gothenburg, there is no anaesthesiologist in the operating room – most cases are performed without sedation.

A temporary pacemaker is placed through v.jugularis interna by one of the cardiologists.

The default valve is Medtronic Evolut R. A.femoralis is punctured with ultrasound guidance.

6F introducer is inserted in the right a.radialis (since beginning of 2018 – a.femoralis previously). 14F in a.femoralis. Straight end regular guidewire is used to cross the valve with help of AL1 catheter. Change to pre-curved stiff guidewire through pigtail, nowadays most often confida guidewire. Balloon-predilatation is almost always performed. The valve position is controlled with contrast in aorta + sometimes with echocardiography.

A.femoralis is closed with different devices: Proglide, Prostar or MANTA device.

There is no cardiopulmonary bypass machine in the operating room.

Pacemaker is left in place for 1-2 days depending on ECG changes.

TAVR Procedure LKPG

In Linköping, the procedure is by default performed in general anaesthesia (GA). Local anaesthesia is only employed in patients with high risks for general anaesthesia or in cases of staff/ICU bed shortage.

The procedure is performed by a cardiologist and a cardiothoracic surgeon.

Right ventricle (RV) electrode is placed through v.jugularis interna. An alternative is pacing through the guidewire in LV (usually in cases with Symetis valve) or RV pacing through the electrode inserted via femoral vein. The next step is ultrasound guided puncture of a.femoralis communis – one side only. Heparin is given with target Activated Clotting Time (ACT) of 250-350seconds. ACT check-up every 30 minutes.

 An introducer sheath is introduced into the common femoral artery. Secondly, a guidewire and the delivery system over the guidewire is introduced to the descending aorta. The valve is mounted on the balloon in the descending aorta, no guidewire is present in the ventricle at that moment to minimize the risk for ventricular rupture. TEE check-up is made to make sure no embolic material is engaged on the system.

TEE surveillance during the whole procedure is default when GA is the case. In local anaesthesia cases TTE is used. Intracardiac echocardiography (ICE) is also an option, although rarely used.

A soft tip guidewire (Advantage guidewire is default, Straight tip Terumo guidewire is an alternative) is steered through the valve under TEE guidance. Valve is placed into the anatomical position with TEE- and fluoro-guidance. Guidewire is pulled back into the system in order to prevent ventricular rupture, ventricular extra systole and damage to the mitral apparatus, as well as to harmonize the prosthesis/native valve movement. Under rapid ventricular pacing the valve is deployed. The TEE is used to evaluate valve function, paravalvular leak (PVL), ventricular function, coronary ostia patency and volume status.

In a case of PVL more than mild post-dilatation is done under rapid ventricular pacing.

The system is extracorporated and the femoral artery is closed with one Prostar XL or two Proglide vascular closure devices.

What is unique in Linköping is that no contrast media is the default way, no contralateral access is the default way, no stiff guidewire is present in LV during a prolonged period of time and no BAV is the default.

Cardiopulmonary bypass machine and perfusion technician are available in the operating room at all times.

TAVR Procedure NYP

At NYP the crew in the cath lab consists of around 11 people: a cardiothoracic surgeon, an interventional cardiologist, a cardiology resident, an anaesthesiologist + anaesthesiology resident, two cath lab nurses, a radiology technician, an angioplasty specialist (scrub technician), two people from Edwards/Medtronic preparing the valve. If the procedure is done under general anaesthesia, there is also an echo technician and an echo attending.

The procedural steps at NYP are as follows: Defibrillator pads are applied to anterior and posterior chest wall. Anaesthesia mask is applied if general anaesthesia case. Analgesia is administered by cardiac anaesthesiologist. Radial A-line is placed. Intubation if general anaesthesia. TEE probe – general anaesthesia cases/TTE for monitored anaesthesia care cases – Baseline echo evaluation. Central line placement. (Advance swan probe - for right heart pressures - select cases, usually general anaesthesia) Sterile field is set up.

2-3 access sites: large bore (14- 18F) arterial on one side, 6F arterial + 7F venous on opposite, right radial or brachial for Sentinel cerebral protection device in selected cases. Transvenous pacemaker, a test of pacemaker is made. Pigtail through the 6F arterial sheath for angiogram. Heparin given to achieve ACT > 250.

Introducer sheath for balloon expandable, in line sheath for self-expandable valves. Wire is inserted to cross the valve. When crossed - AL1/MB1 catheter across the valve. Wire is exchanged for either a Confida wire or Lunderquist wire. Balloon angioplasty under rapid pacing is next. Delivery system – valve positioned using aortography. New angiogram to position. Valve deployment under rapid ventricular pacing. Post deployment injection. TEE/TTE to assess valve function assess for any paravalvular leak and measure mean gradients. Removal of arterial sheaths, deployment of Perclose, haemostasis. Removal of venous sheaths, application of manual pressure. Transfer to ICU for routine post TAVR care.

Post-TAVR

Table 5 – Protocols post-TAVR – antiplatelet therapy & follow up visits

	NYP	GBG	LKPG
Antiplatelet therapy	Dual antiplatelets 6 months	Dual antiplatelets 3 months	Dual antiplatelets 6 months
If patient is already on anticoagulants for atrial fibrillation	Occasionally one antiplatelet is added	Occasionally one antiplatelet is added	No antiplatelet is added
Follow up visits and echocardiography	Cardiologist 2 weeks post TAVR. Surgeon 30 days post op. Echo at 30 days & 1 year	Cardiologist & echo at 30 days, 6 months, 1 year and yearly thereafter	Cardiologist & echo at 30 days, 6 months, 1 year and yearly thereafter

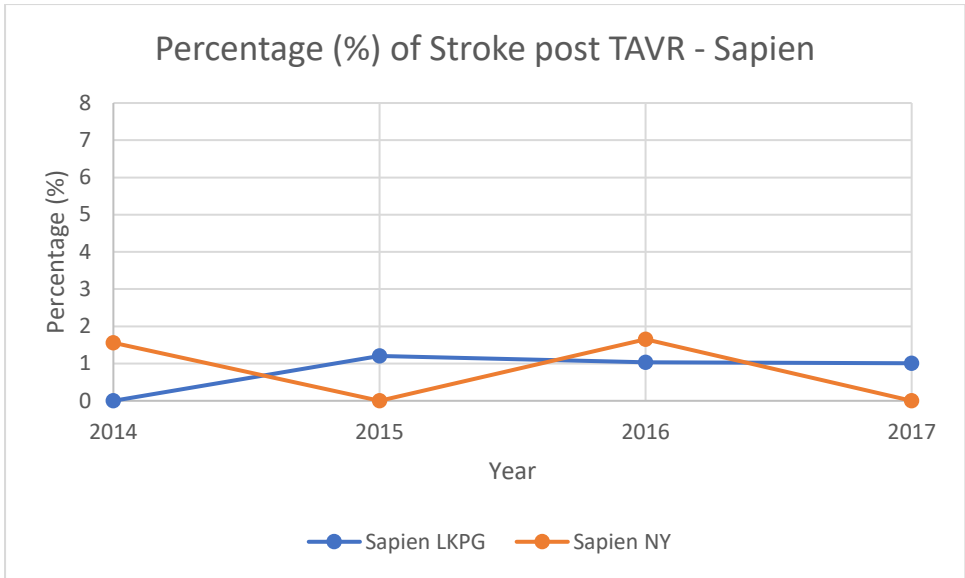**Outcomes - Complication Rates & Mortality**

Stroke:

Figure 7 – Proportion of stroke after TAVR in LKPG and NYP using Edwards valves

There was no statistically significant difference between stroke rates post TAVR with

SAPIEN valves in New York and Linköping.

3 out of 350 (0.86%) patients who underwent TAVR with a SAPIEN valve in Linköping

2014-2017 were reported with stroke as a complication. In New York, the number was 3 out
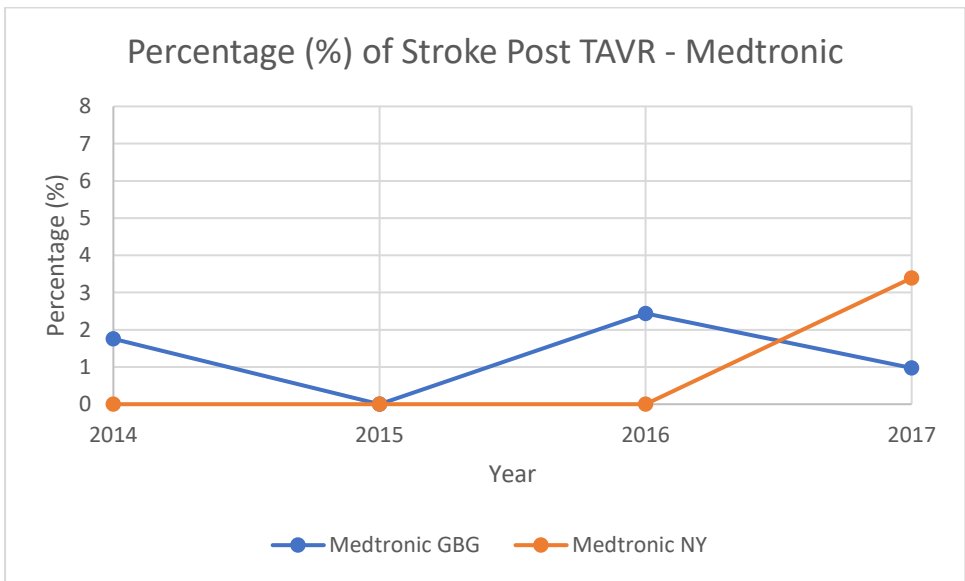
of 398 (0.75%) (p=0.8743).

Figure 8 – Proportion of stroke after TAVR in GBG and NYP using Medtronic valves

There was no statistically significant difference in stroke rates post TAVR with Medtronic valves in New York and Gothenburg 2014-2017 (*p*=0.8809).

In New York, 2 out of 149 (1.34%) patients experienced a stroke, in Gothenburg there were 3 out of 256 (1.17%) cases.
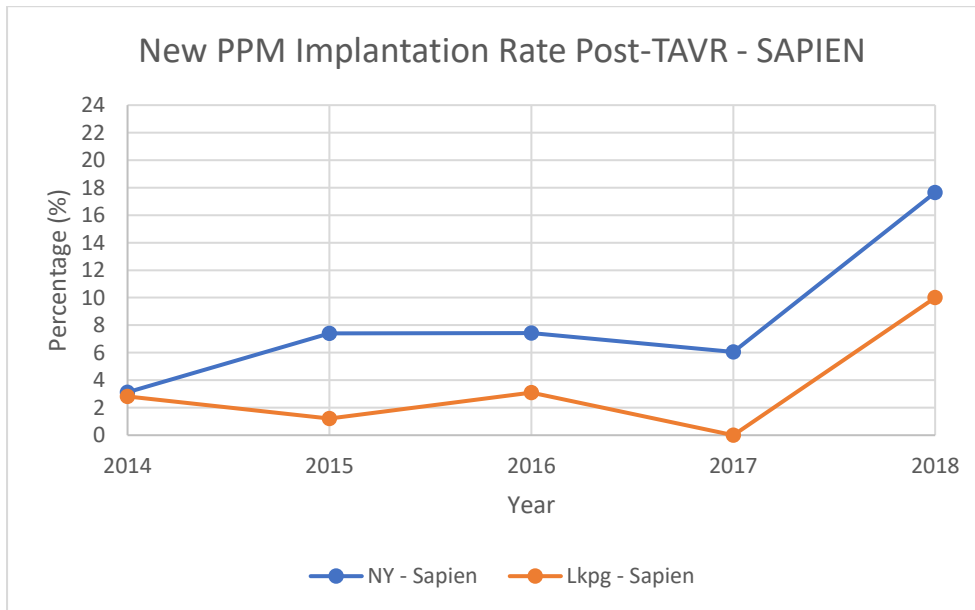
Pacemaker Results:

Figure 9 – Proportion of new PPM after TAVR in LKPG and NYP using Edwards valves

In total during the four-year period 2014-2017, there were 350 cases of SAPIEN valve implantation in Linköping University Hospital and 398 cases in New York Presbyterian Hospital. 6 patients (1.71%) in Linköping required a permanent pacemaker implantation after the procedure. 25 patients (6.28%) required a PPI in New York. The difference in PPM implantation rates post TAVR with Sapien valves was statistically significant (*p*=0.0032)
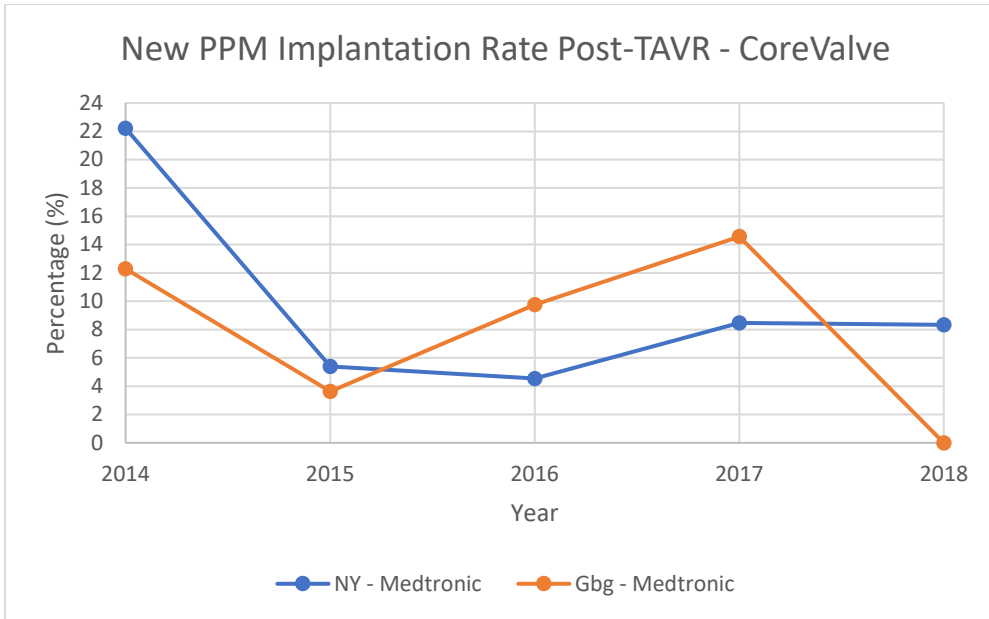
Figure 10 – Proportion of new PPM after TAVR in GBG and NYP using Medtronic valves

PPI was required in 11 of 149 (7.38%) patients post TAVR with Medtronic valves in New York 2014-2017 and 28 of 256 (10.94%) patients with Medtronic valves in Gothenburg. No statistically significant difference was found for proportion new permanent pacemaker post TAVR with Medtronic valves between New York and Gothenburg 2014-2017 (p=0.3198)
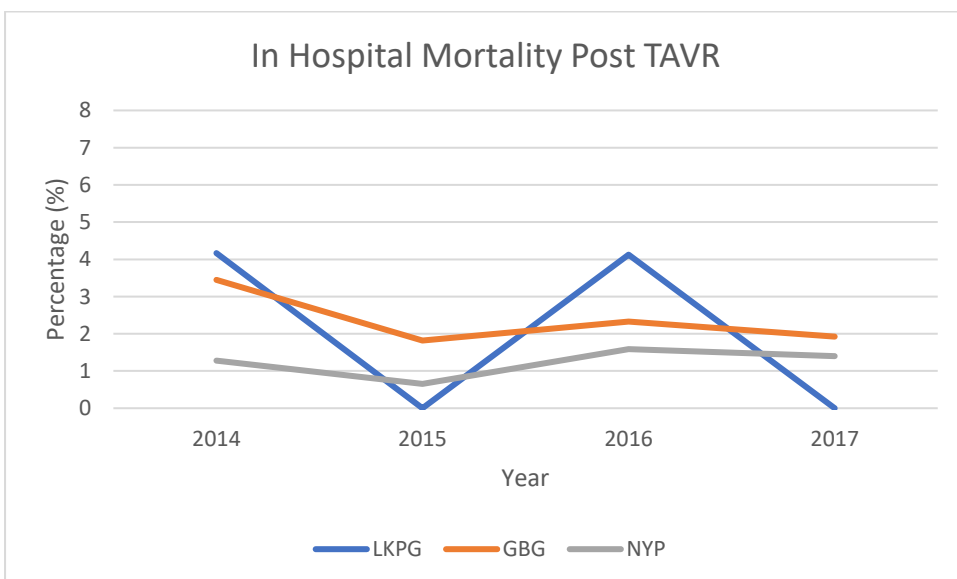

Figure 11 – Proportion of in-hospital-mortality following TAVR per year

In-hospital mortality was in total during 2014-2017 found to be 1.26% in NYP, 1.55% in Gothenburg and 1.99% in Linköping. There was no significant difference in mortality between the three hospitals (p-value 0.668).
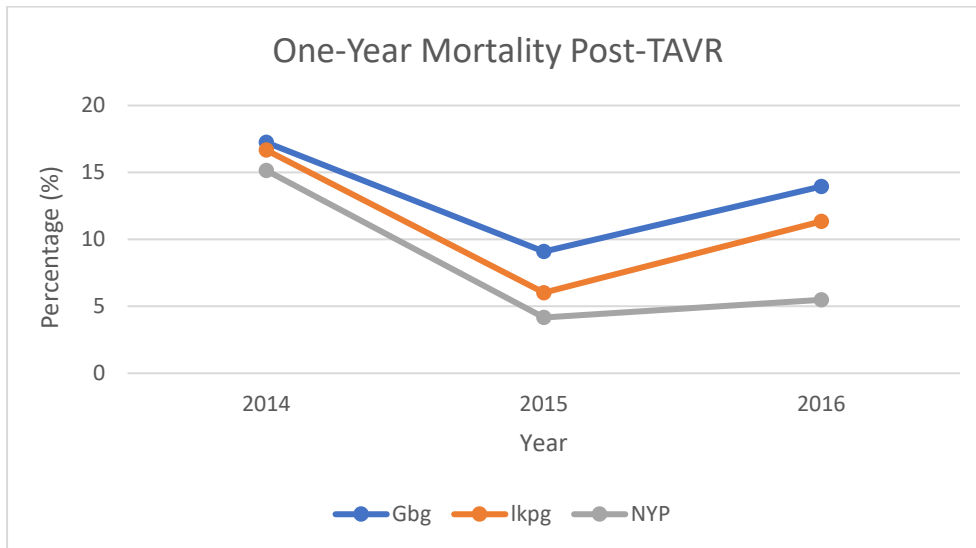

Figure 12 – One-year mortality after TAVR in GBG, LKPG and NYP over time

There was no data available in the registries regarding 1-year mortality from 2017 since the data was extracted in January 2018.

The mortality dates in Swedeheart and TVT registry are taken from national mortality registries and social security death index respectively.

25 of 368 (7%) of patients that data was available for regarding mortality 2014-2017 in NYP died within a year after TAVR. 28 of 252 (11%) died within a year in LKPG between 2014 and 2017 and 21 of 156 (13%) died within a year in GBG.

The difference in one-year mortality between the three institutions was significant (P=0.0347) The difference between LKPG and NYP was not significant (p=0.0814). LKPG – GBG was not significant (p=0.5802). NYP-GBG was significant (p=0.0216).

There was a big drop in mortality rates in all three hospitals between 2014 and 2015. As this was hypothesized to be explained by incorporating intermediate risk patients as opposed to

only operating high risk, the risk profiles were analysed as well. The risk score used in NYP is STS-score while the Swedish hospitals use Euroscore II. The percentage of non-high-risk patients was analysed. Non-high-risk were defined as Euroscore II <5% or Sts-score <8%. The table below shows the results:
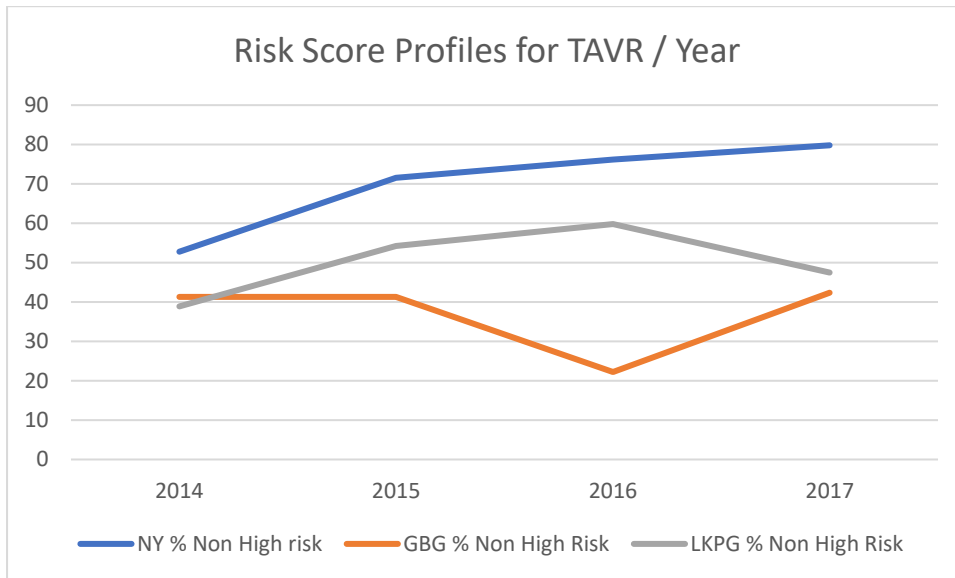
Figure 13 – Proportion of non-high-risk patients undergoing TAVR per year

Surprisingly the percentage of non-high-risk patients was highest in New York during the whole period 2014-2017. It was significantly higher in New York than in Linköping and Gothenburg ($p<0.0001$ for both).

Vascular complications were documented in very dissimilar ways in the different registries which made statistical comparison unfeasible. In any case, during the production of this project, the noted proportion of major vascular complications did seem to be relatively low.

Figure 14 – Proportion major vascular complications after TAVR at NYP over time

Discussion

1. Epidemiology

The baseline characteristics among patients in the three institutions were quite similar. The patients at NYP had significantly higher proportion of hypertension prior to the procedure and the proportion of men was higher in LKPG but as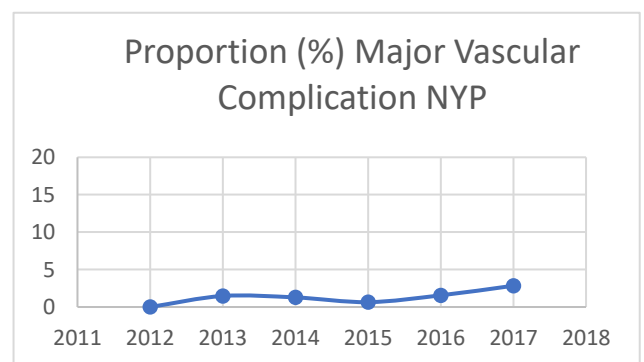ide from this, there were no differences in the populations. Mean ages at the time of the procedure were comparable as well. Proportion of myocardial infarction (MI) before TAVR was also analysed. However, due to dissimilar definitions in the registries – in Sweden, only MIs within 3 months before the procedure were recorded while NYP recorded all MIs, the results were not analogous. Of note, there was no significant difference in proportion of MIs between the Swedish hospitals.

2. Procedural differences

1. Anaesthesia type used for TAVR

Principal differences exist in the type of anaesthesia used for TAVR among institutions. While almost all cases in 2017 in Gothenburg were done under local anaesthesia (LA) without any sedation, almost all cases in Linköping were performed under general anaesthesia (GA). As for New York, there was a 1:1 ratio between GA and monitored anaesthesia care (MAC).

One could argue which approach is best. Arguments against GA include: no symptomatic feedback from the patient in case of vascular injury or a neurological complication; there could be a lack of physiological blood pressure recovery after rapid ventricular pacing (RVP) resulting in prolonged hypotension which can be followed by catecholamine induced hypertension; higher procedure cost; the involvement of more personnel compared to LA, high stress levels among patients regarding concerns about GA prior to a procedure.

On the other hand, GA brings the advantage of TEE use during the procedure which is one of the factors contributing to a low new PPM rate, better patient comfort due to the absence of groin pain during puncture and being asleep during RVP.

Another factor contributing to the higher frequency of GA in LKPG and NYC is the fact that all TA-TAVR are done under GA. The trans-apical approach is not utilized in GBG which contributes for the minimal use of GA as compared to the two other centres.

Analysing the dynamics over time, it was interesting to find that the general trend early on was toward LA, however with time LKPG reversed it back to GA.

GBG makes logistics associated with the procedure much simpler and more cost efficient thanks to the usage of local anaesthesia.

2. Procedure time

The shortest procedure time was in LKPG, followed by GBG and NYP, respectively. The fewer intraprocedural steps in LKPG perhaps accounted for the shortest procedural duration. Those fewer step included:

- o 1 arterial access
- o skipping over going through the valve with a catheter
- o skipping over the wire exchange for the delivery system
- o no pre-dilatation
- o hardly ever post-dilatation
- o all angiographic steps virtually absent

The way by which the three institutions define procedural times varies, which also could account for the difference seen in the results between Sweden and USA. NYP defines procedure time as the time from anaesthesia induction until the moment the patient leaves the

procedure room. Bed shortage in the ICUs lead to prolonged time in the procedure room which inaccurately reflects as a longer procedure time in the registry.

In LKPG and GBG the stop time of the procedure is defined as the time when the artery is closed. The start time in GBG and LKPG is defined as the time of insertion of pacemaker introducer in the neck vessel.

Since total time in the cath lab has been shown to be one of the significant procedural predictors (58), aiming for the shortest possible procedure time should be one of the goals for improving the safety of TAVR.

3. Fluoroscopy time

NYP reported the shortest fluoroscopy time.

The reasons for aiming for the shortest time possible is to minimize the exposure to radiation – both to the patient and the provider, as well as to make the procedure more cost effective.

4. Pre- and post-dilations

GBG and NYP have higher pre-dilation rates in comparison to LKPG. The probable explanation is they use a self-expanding valve and not a balloon mounted one. Self-expanding valves have lower radial strength and accordingly cannot open a highly calcified valve as well as their balloon mounted counterparts. BAV is employed to overcome this issue. Also, directly after valve deployment the self-expandable valves suffer from PVLs more often and post-dilation is needed to address them.

The possible disadvantages of BAV (listed below) are reasons why TAVR without BAV may be a better option:

        i. Rapid Pacing → Hypoperfusion (cerebral and myocardial).

     ii.   Stiff guidewire in the left ventricle → risk of perforation and

         arrhythmia.

    iii.   Passage nearby embolic sources at aortic arch with BAV system.

    iv.   Risk of major vascular complications

     v.   Contrast (if used for sizing or from balloon rupture).

    vi.   Longer procedure and fluoroscopy times, higher costs.

   vii.   Conduction disturbance is more likely with BAV. (59)

5. Contrast media volumes

What was unique in LKPG is that not using contrast was the default. TAVR patients are often sensitive to contrast administration due to:

- overt renal failure

- subclinical reduced glomerular filtration accompanying their increased age and low cardiac output

- medications (metformin, diuretics)

- recent contrast exposure during aortic and ilio-femoral CT screening and coronary angiography

Due to the risks mentioned above, patients become more prone to developing acute kidney injury (AKI), namely contrast induced nephropathy.(60)

The Source 3 Registry reported 27-32% renal insufficiency in baseline population characteristics.(61)

A meta-analysis of 5971 patients has shown that AKI leads to a 5-fold increase in 30-day mortality and 3-fold increase in 1-year mortality.(62) Therefore, efforts should be made to minimize the rate of AKI post-TAVR.

6. Intraprocedural echo-guidance is virtually used in all cases in LKPG, both for puncture and during the procedure, while in GBG it is used during the arterial puncture only. NYP alternates in its usage. Echo-guidance can be employed during following procedural steps:

During arterial puncture to ensure:

- Common femoral artery is punctured and not the superficial femoral

- Central luminal access

- Puncture area is free from calcified plaques on the anterior wall of the artery

- There is no transvenous puncture

- Lumen diameter is sufficient

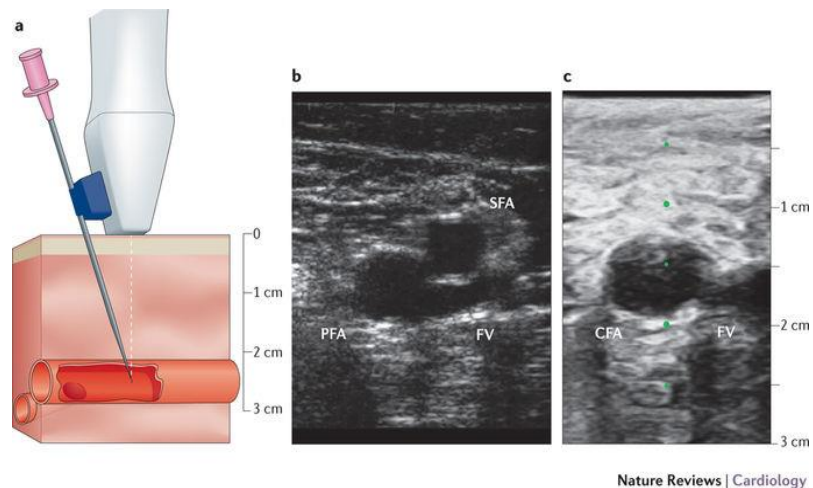**Figure 15** – Showing the concept of ultrasound guided arterial puncture. Courtesy of Nature Reviews, Cardiology

TEE during TAVR in LKPG is used for:

- guiding the system in the ascending aorta

- cusp alignment

- avoiding thromboembolism

- guiding valve crossing with guidewire and delivery system

- prevention of AV-block

- guiding the height of valve placement

- screening for a coronary artery occlusion

- monitoring ventricular function with regional wall movement abnormalities and volume status

- pericardial effusion and pleural effusion evaluation

- valve function and detecting para-valvular leakage

Nonetheless, most of these factors can be controlled by alternative methods such as angiography, the use of reference catheters or calcifications as landmarks, invasive pressure monitoring and the analysis of a combination of vital signs.

The extensive use of ultrasound in LKPG is part of a general approach in many procedures. The goal is to minimize the number of vascular access sites, minimize contrast amount and use more 3D imaging. This approach is more expensive and requires more personnel.

7. Number of arterial access sites

GBG and NYP use two arterial access sites per patient while LKPG uses one, as the echo-guidance technique is used for valve placement. The second access site is normally used for contrast injections and for a pigtail catheter insertion into the aortic root in order to get a landmark for appropriate valve placement. In LKPG the TOE operator shows the landmarks instead.

Reducing the number of access sites may reduce the risk of vascular complications and shorten procedural time.

Cost-effectiveness of this approach is not warranted because the cost of echo-operators and equipment counterbalances the savings on the catheter site.

There are two infrequent situations where a second arterial access may be needed in LKPG as well:

    a. Snare is needed for valve passage (valve in valve, bicuspid, dilation of the ascending aorta)

    b. For aorto-iliac or femoral artery balloon occlusion in case of a vascular complication

8. Cath Lab Team

The number of people in the cath lab along with the different categories of physicians performing the procedures differs considerably among the institutions. In GBG, solely interventional cardiologists perform the procedures, while in LKPG and NYP a collaboration exists between cardiothoracic surgeons and interventional cardiologists. LKPG's approach requires the most staff, followed by NYP, while GBG employs the smallest team.

In LKPG a thoracic surgeon and two cardiologists (one in training) are present in every case. Additionally, a TOE operator and an anaesthesiology team of three are also present. A vascular surgeon is on stand-by, as is a perfusionist.

GBG has no surgical presence in the cath lab but rely on a regular on-call back-up. Neither an echocardiographer nor a perfusionist are present, and the anaesthesiology team is minimalistic – 1 nurse.

NYP creates a balance between the abovementioned approaches.

9. Economy

As a result of staff-strategy GBG is a clear winner with regards to cost-effectiveness. Also, the valve product they use is less expensive than in NYP and LKPG. In addition, not having cardiopulmonary bypass on standby or extensive anaesthesiology equipment further contributes to the better economical outcome.

10. Creatinine changes

It was surprising that there was a decrease in creatinine levels after TAVR as compared to before. An administration of contrast was expected to increase the levels. The decrease could possibly be explained by that as TAVR treats the aortic stenosis, it also improves the flow of blood to the kidneys and therefore improves the kidney function as well.

Another interesting finding was that the percentage of patients with >25% increase in creatinine (definition of contrast induced nephropathy) was not significantly lower in LKPG than in GBG (p=0.86), although nearly no contrast is used during the procedure in LKPG. Eliminating contrast from the procedure was expected to significantly reduce contrast induced nephropathy. The insignificance suggests that it is the contrast administered during diagnostics before TAVR that is the main reason for contrast induced nephropathy in the setting of TAVR.

3. Outcomes

1-year Mortality

The difference in 1-year mortality was an interesting finding. The unexpected discovery of a larger proportion of non-high-risk patients in New York compared to Europe further added interest to this question.

The lower overall mortality in New York as compared to Linköping and Gothenburg could be

explained by a larger proportion of non-high-risk patients undergoing TAVR. Particularly the difference in mortality between Gothenburg and New York in 2016 when 76% of the patients in NYP were non-high-risk and only 22% were non-high-risk in GBG.

The higher 1-year mortality in Gothenburg in 2016 as compared to 2015 could be explained by the larger proportion of high-risk patients with more comorbidities undergoing TAVR in 2016.

The drop in mortality in New York between 2014 and 2015 could to some extent be explained by referring more non-high-risk patients for the procedure (53% vs 72%).

Also, the overlap in mortality rates and risk scores between Gothenburg and Linköping in 2014 strengthens the argument that the mortality correlates with the risk score to a certain degree, even if the risk scores are not considered to be perfect predictors of mortality in the setting of TAVR.

New PPM frequency

The significantly lower incidence of new PPM with Sapien valves in LKPG compared to NYP is also an interesting finding. The incidence was also much lower than what is reported in the literature.(17, 46) Procedural changes made by the cardiologists in LKPG could explain these findings. An effort is made to eliminate any contact between the tools used during TAVR and the conduction system of the heart. The aspects taken into consideration by the physicians performing TAVR in LKPG are:

1. Aiming for a very high valve position – not only the final position but also avoiding a low position at ANY point during the procedure.
2. Visualising the ventricular septum by TEE – this avoids the mechanical destruction of conduction tissues. The ventricular septum cannot be seen on fluoroscopy.

3. Fewer manipulations are made in proximity to the conduction system – eliminating balloon aortic valvuloplasty altogether and eliminating use of catheters.

All of these factors most likely contribute to lowering the frequency of new PPM after TAVR. Since most published data at this time shows a significantly higher frequency of new PPM after TAVR as compared to surgical AVR, finding that it is possible to lower the risk to <2% or even eliminate the risk for new PPM post TAVR completely, as was achieved in LKPG in 2017 is a striking finding. It is a new argument for the advantage of TAVR over sAVR adding value to predicting its bright future.

One of the aspects that could alter the results in a registry to a clinics' disadvantage is that some patients are diagnosed with conditions which are indications for a pacemaker during the evaluation for TAVR. Thus, they may have a pacemaker implanted within 30 days after TAVR procedure due to the conduction abnormalities discovered before the intervention. It is good to recognize the pacemaker indications before TAVR and provide a pacemaker accordingly. Otherwise, a patient may be recognized as a pacemaker candidate after TAVR and the pacemaker implantation may be falsely interpreted as TAVR complication. In LKPG efforts are made to provide the pacemakers to scheduled TAVR recipients before the TAVR procedure to avoid this misinterpretation. However, in most cases, waiting time for TAVR is shorter (30-60 days) than for elective NPPM implantation and pacemakers are implanted after TAVR accordingly.

Furthermore, valve sizing may play a role in the rates of new PPM. Some centres tend to oversize the prosthesis in order to prevent perivalvular aortic insufficiency which has been identified as a risk factor for reduced survival. Oversizing increases the risk for post TAVR AV-block. To oversize or not to oversize – that is the question. Should one prioritize less

insufficiency or less AV-block? More research is needed to compare the long-term effects of both complications.

Of note, the data was collected in the beginning of the year with few cases registered in 2018. Therefore, it may not show accurate numbers for 2018.

Stroke

There were no significant differences in stroke rates between the three institutions. Different approaches are utilized to minimize stroke rates in the three institutions, but they result in similar outcomes. Perhaps if all clinics combined the best parts of their approaches, the stroke rates could be even lower.

At NYP there is an emphasis on cerebral protection devices, e.g. SENTINEL whereas in LKPG the focus is on avoiding manoeuvres in proximity to the thromboembolic areas in the aorta through visualising them on TEE and minimizing the use of catheters and passages.

General discussion regarding strengths and weaknesses of the method:

The strengths of the study were: large number of patients, multi-center study, the registries used for data collection are of good quality with few values missing.

As for weaknesses, there were challenges coming with comparison of different types of registries with varying definitions of variables. For example, analysis of vascular complications was impossible, and rates of post-dilation were not recorded in the TVT registry.

Conclusion

Overall all three centres have low periprocedural, 30-day and 1-year mortality and morbidity rates. On average these results appear much better than those reported from high volume centres and multicentre studies reported in the literature.

TAVR results from the three centres are non-inferior and in many aspects superior to published surgical AVR series. These findings make a strong argument to extend TAVR indications to patients with lower perioperative risks.

It was also interesting to find out that similar results can be achieved using substantially different procedural protocols and perioperative logistics. The centres analysed put different priorities in their TAVR refinement programs. The outcomes of these actions achieved the desired results. While one centre has succeeded with providing the procedure at much lower cost, another one succeeded with excellent survival rates and the third one with impressive low rates of complications. This variability paves a way for finding additional enhancements in this rapidly expanding technology. Further research is needed to combine the best procedural practises for patients undergoing TAVR regardless of centre to develop the ultimate TAVR. The final goal being a cost-effective procedure with excellent short and long-term outcomes giving the TAVR recipients a long, high quality life seems to be just around the corner.

Populärvetenskaplig Sammanfattning

Titel: Förbättring av säkerheten vid aortaklaffbyte – jämförelse av svenska och amerikanska tillvägagångssätt

Aortastenos är en av de vanligaste hjärtsjukdomarna. Det som händer är att en av hjärtats klaffar (aortaklaffen) blir stel och öppnas sämre vilket leder till att blod inte kan flöda ut från hjärtat till kroppen som vanligt. Prognosen för de drabbade är mycket dålig utan behandling – över 50% av patienterna dör inom 2 år om klaffen inte byts ut. Förr var kirurgi det enda sättet för att byta ut den sjuka klaffen. Kirurgi är dock ett stort ingrepp med många risker och inte alla äldre personer kan genomgå detta. För 10 år sedan tillkom en ny metod som heter TAVR som gör att man kan leverera den nya klaffen via kärl, utan kirurgi. Endast ett stick i ljumsken behövs. Eftersom metoden är relativt ny utförs den på olika sätt på olika sjukhus och komplikationer associerade med den varierar.

Syftet med den här studien var att jämföra hur ingreppet utförs i Sverige och i USA, vilka förbättringar av grundprotokollet som har gjorts och hur de har påverkat komplikationsfrekvenser – stroke, nytillkommet behov av pacemaker och mortalitet.

Detta gjordes genom att data från nationella register samlades in, analyserades och intervjuer genomfördes med operatörerna på tre olika sjukhus – Universitetssjukhus i Göteborg, Linköping och Presbyterian Hospital i New York.

Analysen visade att det fanns många metodskillnader i de olika sjukhusen men resultaten var i alla fall mycket goda – bättre än de som finns rapporterade för samma metod i litteraturen och bättre än för kirurgi. Studien visade att det är möjligt att helt undvika stroke, nytillkommet behov av pacemaker och njurskador associerade med proceduren. De olika sjukhusen la fokus på olika saker för att förbättra metoden och de lyckades med respektive mål. Mortalitetsfrekvensen var lägst i New York, behov av pacemaker var lägst i Linköping

och metoden var mest kostnadseffektiv i Göteborg. Den här variabiliteten lägger grunden för att hitta det ultimata sättet att utföra TAVR på. Det slutgiltiga målet, vilket är en kostnadseffektiv procedur med utmärkta kort- och långtidsresultat verkar vara precis runt hörnet.

Acknowledgements:

It would not have been possible to write this thesis without the help and support of the kind people around me, to only some of whom it is possible to give particular mention here.

I would like to express my deepest appreciation to Prof. Arash Salemi at New York Presbyterian Hospital who made it possible to realize this international project. It was a great honour to work under his supervision.

I would like to thank my supervisors in Gothenburg, Dr Petur Petursson and Dr Oskar Angerås, and in Linköping – Prof. Henrik Ahn for their help and support along the way.

In addition, a thank you to Dr Geoffrey Bergman and Dr Patrick Looser at New York Presbyterian Hospital for their kindness and important inputs.

I would also like to express my gratitude to Dr Omar Al Hussein for his valuable opinions on the text and for making the writing of this thesis a pleasant experience.

Appendices:

Additional information about aortic stenosis:

Symptoms of Aortic Stenosis
The classic triad of symptoms in patients with aortic stenosis is: angina pectoris, syncope and shortness of breath.
Many patients are diagnosed before symptom onset, after a systolic murmur is found on physical examination. The diagnosis is then confirmed by echocardiography.
As the diagnosed patients are followed prospectively, they begin to present with a gradual decrease in exercise tolerance, fatigue or exertional dyspnea and ultimately one of the three classic symptoms described above.
Other symptoms include: atrial fibrillation, pulmonary hypertension, systemic venous hypertension (late finding), gastrointestinal bleeding (associated with vascular malformations and shear stress induced platelet aggregation which resolves after AVR), infective endocarditis (younger patients) and transient ischemic attack / stroke or embolization of calcium to other organs.

Patients with a bicuspid aortic valve develop symptoms earlier than those with a tricuspid valve - at age 50-70 years vs >70 years respectively.(63) Bicuspid aortic valve is often associated with dilatation of the ascending aorta that cannot be addressed by TAVR nowadays while it can be repaired with AVR. Due to this fact as well as because of the much longer valve prosthesis durability required, these patients are better suited for AVR than TAVR on most occasions.

Physical Examination
Auscultation: Ejection systolic murmur (crescendo decrescendo) with radiation to the carotids is typical for aortic stenosis.
Echocardiography: is the widely recognized primary method for evaluating aortic stenosis. It is used to define the anatomy of the valve: tricuspid vs bicuspid, the aetiology of stenosis (congenital, rheumatic or degenerative calcific), the grade of AS, the severity of valve calcification, systolic & diastolic LV function, LV hypertrophy, aortic root dimensions and other associated valve disease, for example aortic regurgitation which coexists in approximately 75% of patients. This is essential when considering a patient for TAVR vs sAVR. In most instances, surgical repair is more suited if multiple valve repairs are needed. The transaortic jet velocity, valve area and mean transaortic pressure gradient can be measured with Doppler echocardiography. These parameters are used to assess disease severity.(63) Also velocity time interval quotient and maximal flow velocity delay are helpful.

Special attention must be paid in cases with low LV-function. In these cases, due to low stroke volumes many echo-parameters can be falsely negative (max velocity, mean gradient) despite a severe grade of stenosis. This condition is named low flow/low gradient severe

aortic stenosis. In these cases, the VTI quotient and visual judgement of valve calcification, leaflet thickness and mobility are useful. In some cases, special diagnostic tools like stress echocardiography or calculation of calcification index from CT can be very helpful. An ultimate tool is balloon aortic valvuloplasty (BAV). This is a kind of TAVR rehearsal. Eventual clinical improvement after BAV paves way for a patient to be given TAVR that is a more long-term solution than BAV.

The European Association of Echocardiography and American Society of Echocardiography have published guidelines for the use of echocardiography in potential candidates for TAVR since it plays a critical role in the evaluation before the intervention.

ECG: Electrocardiography is generally performed as a part of the initial workup, even though it is not indicated for diagnosis of aortic stenosis. Left ventricular hypertrophy is the main electrocardiographic change, found in about 85% of patients with severe AS, followed by left atrial enlargement - 80%. Other common findings are ST segment depression and T wave inversion. Atrial fibrillation is present in 10-15%.(63) p.1474
ECG may also reveal indications for pacemaker that went unnoticed before the patient was considered a TAVR candidate. This is especially essential in patients with symptoms of syncope.
ECG also reveals the pre-TAVR risk factors for a post-TAVR PPM like AV-block I, RBBB, bifascicular block or A-fib with low ventricular rate, as well as cases overtreated with drugs causing bradyarrhythmia like betablockers.

Aspects to be considered by the Heart Team for the decision between SAVR and TAVR in patients at increased surgical risk:

	Favours TAVI	Favours SAVR
Clinical characteristics		
STS/EuroSCORE II <4% (logistic EuroSCORE I <10%)[a]		+
STS/EuroSCORE II ≥4% (logistic EuroSCORE I ≥10%)[a]	+	
Presence of severe comorbidity (not adequately reflected by scores)	+	
Age <75 years		+
Age ≥75 years	+	
Previous cardiac surgery	+	
Frailty[b]	+	
Restricted mobility and conditions that may affect the rehabilitation process after the procedure	+	
Suspicion of endocarditis		+
Anatomical and technical aspects		
Favourable access for transfemoral TAVI	+	
Unfavourable access (any) for TAVI		+
Sequelae of chest radiation	+	
Porcelain aorta	+	
Presence of intact coronary bypass grafts at risk when sternotomy is performed	+	
Expected patient–prosthesis mismatch	+	
Severe chest deformation or scoliosis	+	
Short distance between coronary ostia and aortic valve annulus		+
Size of aortic valve annulus out of range for TAVI		+
Aortic root morphology unfavourable for TAVI		+
Valve morphology (bicuspid, degree of calcification, calcification pattern) unfavourable for TAVI		+
Presence of thrombi in aorta or LV		+
Cardiac conditions in addition to aortic stenosis that require consideration for concomitant intervention		
Severe CAD requiring revascularization by CABG		+
Severe primary mitral valve disease, which could be treated surgically		+
Severe tricuspid valve disease		+
Aneurysm of the ascending aorta		+
Septal hypertrophy requiring myectomy		+

Figure 16 – Decision-making SAVR vs TAVR. Courtesy of European Society of Cardiology

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