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Reducing the risks of transcatheter aortic valve implantation

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Transcatheter aortic valve implantation (TAVI) was performed for the first time in 2002 in a patient who could not undergo surgical aortic valve replacement.[1] The next milestones were achieved in 2010, when TAVI showed to be superior with respect to mortality to conservative treatment in inoperable patients, and non-inferior to SAVR in patients at high surgical risk.[2,3] In the years thereafter, the number of TAVI procedures has grown tremendously around the world. Soon this procedure was proven to be at least as effective as SAVR in patients considered at intermediate risk[4,5] The indication of TAVI may further shift towards patients with a lower risk profile in the near future, with the results of the low risk TAVI trials in mind (TAVI was superior to SAVR in patients with a balloon-expandable prosthesis and non-inferior in patients with a self-expanding prosthesis).[6,7] Throughout the years, the outcomes have significantly improved with the arrival of newer prosthetic valves and delivery systems, increased operator skills, better patient selection, lower risk patients and improved vascular access management. However, there remains a chance of serious complications such as major vascular, bleeding and thromboembolic events, as well as frequently occurring paravalvular regurgitation (PAR) and the need for permanent pacemaker implantation.[4–13] Further reducing the risks of TAVI is therefore desired and even required when shifting the indication to younger patients with a lower risk profile. For these reasons, the main focus of this thesis is studying how to reduce the risk of TAVI by:

1. **PART I: Improving antithrombotic treatment in patients undergoing TAVI**
2. **PART II: Patient specific computer modelling and new imaging technologies for TAVI procedures**
3. **PART III: Evaluating individual outcomes of TAVI**

PART I: Improving antithrombotic treatment in patients undergoing TAVI

Although the outcomes of TAVI have improved throughout the years, bleeding and thromboembolic complications remain frequently observed.[9–16] As expected, both bleeding and thromboembolic risk are high in patients undergoing TAVI, due to the advanced age and many comorbidities in these elderly patients. Despite several trials studied the optimal antithrombotic therapy (ATT) after, the ideal regime to minimize both these risks is still unknown. Therefore, when starting this thesis, we provided an overview of the guidelines at that time and performed a review of available literature performed, with the intent of a more patient tailored ATT (**Chapter 2**).[17] At that time, both the European and American leading practice guidelines on ATT after TAVI, published in 2017, relied only on expert consensus and did not provide a clear strategy because of a lack of randomized evidence.[18,19] The rationale for the suggested ATT strategies in the guidelines were actually copied from the patient population undergoing elective percutaneous coronary intervention (PCI). Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, was shown to be effective in reducing thromboembolic risk (especially stent thrombosis) in the first period after PCI. However, a TAVI population is quite different from a PCI population, with a more advanced age and numerous comorbidities influencing the balance between thromboembolic and bleeding risks (see **Chapter 2**, Table 2). Patients undergoing TAVI are therefore more prone for bleeding complications, which suggests using a less intensified ATT in TAVI patients than in patients undergoing PCI.

Nevertheless, the 2017 ESC guidelines advised in patients, without a long-term indication for oral anticoagulation (OAC), to use DAPT using aspirin and clopidogrel for the first three to six months after TAVI followed by single antiplatelet therapy (SAPT), using lifelong aspirin or clopidogrel (see **Chapter 2,** Figure 1). There where however, several observational studies investigating SAPT versus DAPT post TAVI, reporting less bleeding events in patients on SAPT (mostly aspirin) and more importantly no increase in thromboembolic events with SAPT.[20–25] In addition, three small underpowered randomized clinical trials demonstrated similar results.[26–28] The largest one, the Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation trial randomized 222 patients and observed less major or life-threatening bleeding events at 3 months with SAPT using aspirin compared to DAPT (3.6% versus 10.8%) without a concomitant increase of thromboembolic events.[26]

Approximately a third of the TAVI patients has a long term indication for OAC, mostly for atrial fibrillation (AF).[4,5,29] In addition, around 10% of the patient undergoing TAVI develop AF after TAVI requiring OAC.[29,30] For

these patients, the 2017 guidelines recommended the use of a vitamin K-antagonist (VKA) with or without aspirin or clopidogrel lifelong (**Chapter 2,** Figure 1). At that time, only observational studies had examined the addition of an antiplatelet agent to VKA after TAVI. These studies suggested that additional antiplatelet therapy was associated with more bleeding events than a VKA alone strategy, while there was no decrease of thromboembolic events.[20,31,32]

At the conclusion of **Chapter 2**, we provide a flowchart with antithrombotic strategies for patients undergoing TAVI based on the available evidence at the start of this thesis (Figure 3). This was a prelude for the following chapters in this thesis in which we tried to further elucidate the optimal ATT in patients undergoing TAVI.

Additional antiplatelet therapy after TAVI

Additional antiplatelet therapy to aspirin after TAVI

Because there was a lack of evidence on the optimal ATT in TAVI, we designed the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular TAVI) trial.[33] The POPular TAVI trial is an investigator-initiated, parallel-group, international multicenter, open label, randomized clinical trial investigating the role of additional clopidogrel in patients undergoing TAVI and was divided into two cohorts: Cohort A consisting of patients without a long term indication for OAC and cohort B consisting of patients with a long-term indication for OAC. We hypothesized that the omission of clopidogrel, thus aspirin alone or OAC alone, are superior to aspirin or OAC with 3 months of additional clopidogrel with regard to bleeding events (primary outcome), while being non-inferior with regard to a composite of bleeding and thromboembolic events (first composite secondary outcome) and a composite of thromboembolic events (second composite secondary outcome).

In **Chapter** 3 we describe the results of cohort A of the POPular TAVI Trial, that randomized 690 patients to either aspirin alone or aspirin plus clopidogrel for 3 months after TAVI followed by aspirin alone.[34] Regarding the primary outcome all bleeding at 1 year, aspirin alone was superior to aspirin plus clopidogrel (15.1% versus 26.6%, risk ratio (RR) 0.57, P=0.001). Aspirin alone was also superior to aspirin plus clopidogrel on the composite of bleeding and thromboembolic complications (23.0% versus 31,1%, RR 0.74, P=0.04). More interestingly, aspirin alone, as compared to aspirin plus clopidogrel, did not lead to an increase in neither the composite of thromboembolic complications, including cardiovascular mortality, ischemic stroke or myocardial infarction (9.7% versus 9.9%, RR 0.98, P=0.004 for noninferiority), nor the individual components of this composite. However, the trial was not powered for this thromboembolic endpoint.

Because of underpowering for the thromboembolic endpoint in POPular TAVI (**Chapter** 4) we performed a systematic review and patient level meta-analysis (**Chapter 5**).[35] In the meta-analysis, we combined the patient-level data of the POPular TAVI trial with the other three randomized trials comparing aspirin alone versus DAPT (mostly aspirin alone versus aspirin with clopidogrel) after TAVI available to date.[26–28,34] A total of 1086 patient were included across the four eligible trials. The composite of all-cause mortality, major or life-threatening bleeding, stroke, or myocardial infarction occurred significantly less in patients receiving aspirin alone compared to patients receiving dual antiplatelet therapy at 30 days (10.3% versus 14.1%, p=0.034) and at 3 months (11.0% versus 16.5%, p=0.02). The occurrence of the same composite endpoint excluding bleeding (only thromboembolic events) did not differ between patients on aspirin alone and patients on dual antiplatelet therapy at 30 days (5.5% versus 6.6%, p=0.47) and at 3 months (6.9% versus 8.5%, p=0.39), respectively. Of most interest, major bleeding and the combination of major and life-threatening bleeding occurred significantly less in the aspirin alone group, while the individual thromboembolic outcomes were comparable between both groups. Based on the results of the POPular TAVI trial cohort A and this meta-analysis, we conclude that clopidogrel in addition to aspirin after TAVI leads to more bleeding events and does not prevent patients from thromboembolic complications such as stroke.

Additional antiplatelet therapy to OAC after TAVI

In **Chapter 6**, we present the results of cohort B of the POPular TAVI trial, including patient with a long term indication for OAC.[36] In total, we randomized 331 patients to either OAC alone or OAC plus clopidogrel for 3

months followed by OAC alone. The same primary and secondary outcome applied in this cohort of the trial as for cohort A. Similar to cohort A, OAC was proven to be superior to OAC plus clopidogrel regarding the primary outcome all bleeding at 1 year (21.7% versus 34.6%, RR 0.63, P=0.01). Monotherapy with OAC was also superior to OAC plus clopidogrel for the composite of bleeding and thromboembolic complications (31.2% versus 45.5%, RR 0.69) and importantly not leading to an increase in the composite of thromboembolic complications (13.4% versus 17.3%, respectively, RR 0.77 for non-inferiority) or the individual components.

Use of direct-acting oral anticoagulants after TAVI

In **Chapter 7**, we describe the data available at that time on the safety and efficacy of direct-acting oral anticoagulants (DOAC) after TAVI in an editorial.[37] Although the guidelines at the time of the POPular TAVI trial did not mention the use of DOAC after TAVI, we decided to include patients on either VKA or DOAC in cohort B of the POPular TAVI trial because of an increasing number of patients administered DOAC for AF. Subgroup analyses of these patients showed no difference in outcome in patients on DOAC as compared to VKA after TAVI for both the primary and secondary outcomes, however the patient numbers were too low to draw any definitive conclusion.

Multiple observational studies suggested that the use of DOAC after TAVI is as efficient as VKA. However, no randomized data was available at that time, leading us eagerly awaiting for the results of both the Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (ENVISAGE-TAVI AF) trial and the Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial.[38,39] The first one, the ENVISAGE-TAVI trial, demonstrated non-inferiority of edoxaban compared to VKA on a composite efficacy outcome including all-cause death, myocardial infarction, ischemic stroke systemic thromboembolism, valve thrombosis and major bleeding (17.3 versus 16.5 per 100 person-years, respectively, P=0.01).[40] However, the primary safety outcome major bleeding, was higher in the DOAC group as compared to the VKA group (9.7 versus 7.0 per 100-person-years, respectively, P=0.93 for non-inferiority), mainly caused by a difference in gastrointestinal bleeding. The results of the second trial, the ATLANTIS trial, investigated apixaban versus standard of care (VKA [stratum 1] or antiplatelet therapy [stratum 2] depending on whether there was an indication for OAC) after successful TAVI. The results were online presented at the American College of Cardiology Virtual Annual Scientific Session 2021.[41] Stratum 1 showed similar rates on both the combination and individual components of the primary outcome of death, stroke, myocardial infarction, systemic emboli, deep vein thrombosis or pulmonary embolism, or major bleedings between apixaban and VKA (21.9% versus 21.9% for the combined primary outcome). Based on these results, DOAC seems to be a feasible alternative to VKA in patients undergoing TAVI with an indication for long-term OAC. This will make the ATT in these patients less complicated, especially since DOAC is standard of care in patient with atrial fibrillation.[42] Subsequently, stratum 2 of the ATLANTIS trial including patients without an established indication for OAC, reported a negative trend of more (non-cardiovascular) death in the DOAC arm (in this trial apixaban) compared to standard of care.[41] In addition, the A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement (GALILEO) trial, studied the use of low dose rivaroxaban (10 mg) combined with aspirin for 3 months, than low dose rivaroxaban alone compared to DAPT for 3 months followed by aspirin alone in patients undergoing successful TAVI without an indication for OAC.[43] This trial was prematurely terminated for safety reasons, because the investigational arm (rivaroxaban in combination with aspirin) caused a higher risk of death or thromboembolic complications as well as a higher risk of bleeding events than DAPT post TAVI. These results resulted in a contraindication for rivaroxaban in combination with aspirin in patients without an indication for OAC in the updated American guidelines of November 2020.[44]

Heparin reversal using protamine at the conclusion of TAVI procedures

Chapter 8 describes our view on the need for heparin reversal using protamine at the conclusion of a TAVI procedure.[45] Little is known on this matter, resulting in the liberally use of protamine in patients at the end of a TAVI procedure to reverse the anticoagulant effect of heparin. Based on years of experience in the field of cardiac surgery,[46] protamine may also be beneficial in the field of TAVI, with its large-bore catheters in combination with population at risk for bleeding.[47] However, precaution is advised given the rare change of an anaphylactic reaction on protamine in some patients. One observational study observed lower rates of the

primary composite outcome of all-cause mortality and major and life-threatening bleeding at 30-days with the use of protamine compared to no heparin reversal (3.2% versus 8.7%, P=0.003).

Another aspect of ATT management is how to handle patients on DOAC, discontinue before the procedure or continue during TAVI? To study this interesting issue, we are performing the Periprocedural Continuation Versus Interruption of Oral Anticoagulant Drugs During Transcatheter Aortic Valve Implantation (POPular PAUSE) trial, within the same collaboration network of the POPular TAVI trial (NCT04437303). In this randomized controlled trial we investigate the effect of DOAC continuation versus discontinuation in 858 patients with an established indication for DOAC undergoing TAVI. We hypothesize that continuation of DOAC during TAVI may decrease thromboembolic complications without increasing bleeding complications at 30 days.

Conclusions of PART I: Antithrombotic treatment in patients undergoing TAVI

The main findings can be summarized as follows. For patients without a long-term indication for OAC, we showed evidence that an ATT without additional clopidogrel significantly reduced bleeding complication after TAVI without increasing thromboembolic complications. As a result, the European Society of Cardiology have updated their guideline on the management of valvular heart disease in August 2021.[48] In this renewed guideline single antiplatelet therapy is recommend lifelong in patients with no baseline indication for OAC (class I, level of evidence A). For patients with a long-term indication for OAC after TAVI we also found evidence that additional antiplatelet therapy with clopidogrel is associated with an increase of bleeding events, while the thromboembolic events were comparable. In the updated European guideline, OAC lifelong (no addition of antiplatelet therapy) is now recommended (class I, level of evidence B).[48] In this guideline, for patients with an indication for OAC, the use of DOAC is not routinely recommended after TAVI. Abovementioned results suggest that these DOACs can be used in patients with a clear indication for OAC.[44,48] However, edoxaban in the ENVISAGE-TAVI trial , comes at the cost of more bleeding for edoxaban compared to VKA. On the other hand, the use of DOACs in patients without a clear indication for OAC, has resulted in harm since rivaroxaban in the GALILEO trial showed an increase in death and bleeding and apixaban increased non-cardiovascular death as compared to antiplatelet therapy. Therefore, DOACs are contraindicated in patients without a clear indication for OAC after TAVI in the latest guidelines. Based on ENVISAGE-TAVI and ATLANTIS, apixaban may be the best alternative to VKA after TAVI.

PART II: Patient specific computer modelling and new imaging technologies for TAVI procedures

The performance and outcomes of TAVI procedures have become increasingly better over the years. This is largely due to fast development of the technique, devices, and operator skills. In addition, simplification of the TAVI procedure itself played also an important role. In the beginning of TAVI, procedures were performed with general anesthesia, surgical cut-down and even frequently heart lung machine standby. Nowadays, most procedures are performed in a cardiac catheterization laboratory under local anesthesia. The role of image technologies, in particularly the role of transesophageal echocardiography (TEE) has changed as well.
In **Chapter 9**, we present alternative image tools to TEE for the 'minimalistic' TAVI procedure, such as the use of transthoracic echocardiography, extended use of fluoroscopy, patient specific computer modeling and 3D MSCT fusion.[49] This chapter serves as a stepping stone to the other chapters of PART II, where the use of patient specific computer modelling and computed tomography fractional flow reserve (CT-FFR) will be described as tool to reduce the risk of TAVI.

Patient specific computer modeling using HEARTguide software

Patient specific computer modelling software is a new image modality based on the pre-procedural MSCT images and is specially developed to display the effects of pericprocedural device–host interaction, which is not possible with the MSCT images alone. For example the HEARTguide software (formerly TAVIGuide), developed by FEops (FEops, Ghent, Belgium), is able to derive a simulation of the TAVI procedure and can provide an overview of the best fitting valve size and implantation depth with corresponding PAR and influence on the conduction system[50,51].

Patients with bicuspid aortic valve stenosis undergoing TAVI

In **Chapter 10,** we retrospectively investigated the utility of HEARTguide software in a case series including 7 patients with BAV stenosis undergoing TAVI.[52] In two cases we were unable to successfully implant a TAVI device due to a too large annulus and an aortic root rupture. HEARTguide correctly predicted (retrospectively) the devastating outcome in these patients and displayed a severe PAR and an elliptical prosthetic valve morphology (in the case with an aortic annulus rupture). In the other five successful cases the software correctly predicted prosthetic valve morphology after implantation and the severity of PAR (in three of the five cases also the correct location of the PAR).

Second, in **Chapter 11** we retrospectively investigated the effect of optimal prosthetic valve sizing and implantation depth, advised by HEARTguide, on PAR post implantation.[53] In total 50 patients were included in this registry. Optimal prosthetic valve sizing and positioning was accomplished (prosthetic valve size and positioning with a predicted PAR <5ml/sec compared to the most optimal patient specific computer simulation) in 39 patients. These patients were compared with those without optimal prosthetic sizing and positioning (n=11) regarding severity of PAR and long-term survival. The severity of PAR was significantly lower in patients with optimal prosthetic valve sizing and positioning (P<0.001). Also, the long-term survival at two years was significantly better in patient with optimal prosthetic valve sizing and positioning (9.1% versus 34.5%, HR 6.23, P=0.02).

Despite the retrospective design and small number of included patients, both **Chapter 10** and **Chapter 11** showed the potential of additional HEARTguide patient specific computer modeling in patients with BAV stenosis undergoing TAVI. However, validation in a large prospective study is required.

Patients with challenging aortic annulus measurements

In **Chapter 12**, we tested the utility of the HEARTguide software in six complex TAVI cases.[54] We retrospectively tested whether the HEARTguide software was able to predict the complexity of the cases in terms of predicted PAR and prosthetic valve sizing and thus whether it was able to prevent patient-prosthesis mismatch. In two cases we have implanted the largest Evolut R 34mm device with a significant PAR despite several maneuvers or postdilatation, while in the other 6 cases we peri-procedurally switched to a larger prosthetic valve size. For the first two cases the computer model correctly predicted the outcome (severity of PAR including its location) and found no fitting prosthetic valve device. In the other cases were we switched to a larger device size during the procedure, the software correctly advised implantation a larger valve. Also, the severity and the location of the PAR was correctly predicted in three of the four cases.

In addition, in **Chapter 13** we display a multicenter retrospective study where we investigated the additional value of HEARTguide on prosthetic valve sizing (and consequently its effect on lowering moderate to severe PAR post implantation) in patients with a borderline aortic annulus size range (the 'grey zone').[55] A patient specific computer model was produced in 24 patients with borderline aortic annulus measurements and who were treated with a prosthesis size other than recommended by the specific valve matrix (thus operator decision). In 10 (41.7%) patients HEARTguide advised a different valve size than the standardized matrix. In 4 of these patients, HEARTguide concluded that the smaller device recommended by the matrix would result in moderate to severe PAR, while the larger device did not, which was correctly predicted.

The number of patients in both chapters remains limited for direct implantation of HEARTguide for this matter, in combination with a lack of randomized data. On the other hand, in case of a valve size dilemma, HEARTguide can provide additional arguments which may help to choose the best valve size in order to prevent significant PAR.

New imaging technologies

CT-FFR in TAVI patients

In **Chapter 14**, we assess the diagnostic performance of CT-FFR on top of coronary computed tomography angiography (CCTA) for the diagnosis of coronary artery disease (CAD) in the work-up for TAVI. We included

338 patients who routinely underwent MSCT and invasive coronary angiography (ICA) before TAVI and retrospectively assessed the diagnostic performance of CT-FFR on top of CTTA (using MSCT images) using ICA as reference. Significant CAD on ICA was found in 76 patients. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CT-FFR were 84.6%, 88.3%, 63.2%, 96.0% and 87.6%. Compared to CCTA, CT-FFR significantly improves the diagnostic accuracy (P=0.02) and could reduce the number of ICA in patients undergoing TAVI by 57.1% versus 43.6% using CCTA alone (P<0.001).

Previous meta-analysis already showed the potential of CCTA as a gatekeeper for ICA for detection CAD in TAVI patients, with a sensitivity and specificity of 95% and 65%, respectively.[56] However, CT-FFR on top of CCTA in the pre-workup for TAVI patients is not investigated before. Compared to the results of CT-FFR in patient with chest pain, we observed in TAVI patients a comparable sensitivity and slightly higher specificity of CT-FFR.[57] Although the complication rates are limited, ICA still is an invasive procedure with a risk of serious complications. With the frail TAVI population in mind, alternative strategies for the detection significant CAD requiring treatment may reduce the exposure of TAVI patients to risky procedures in the pre-TAVI workup. We showed that CT-FFR can be of significant use regarding this matter and it can be performed without additional testing. However, this technique is quite expensive and highly dependent on the quality of the CCTA images. Also, CT-FFR algorithms are not validated yet for patients with previous myocardial infarction, coronary artery stenting, coronary artery bypass grafting or valve surgery.

Image fusion models during TAVI procedures

First, in **Chapter 15.1** we were able to fully automatic fuse in real time the pre-procedural MSCT images with fluoroscopy using 3D transoesophageal echocardiography during the TAVI procedure.[58] We matched the MSCT images with the live fluoroscopy images to access more anatomical information (such as the aortic valve annulus and cusps) to optimize the implant location of the TAVI prosthesis. With this information is possible to guide the implantation of a TAVI prosthesis without using a contrast medium. Therefore, this technique makes it possible to perform a procedure without the use of a contrast medium, especially useful in patient with severe kidney impairment.

Second, in **Chapter 15.2**, we describe a case where we have added a patient specific computer simulation by HEARTguide to the fusion model described in **Chapter 15.1**.[59] In this case we managed to lie the simulation provide by HEARTguide over the live fluoroscopy images. We displayed during the TAVI procedure the most optimal valve size and implantation depth (based on predicted PAR and contact pressure), which can be used as an better referential marker for the operator during prosthetic valve deployment than in **Chapter 15.1**.

Conclusions of part II: Patient specific computer modelling and new imaging technologies for TAVI procedures

The main findings of this part can be summarized as follows. We showed that HEARTguide was retrospectively able to correctly predict the outcomes of TAVI in patients with BAV stenosis. We also found in a retrospective manner a significantly lower rate of severe PAR and consequently mortality in patients with optimal prosthetic valve sizing and positioning as advised by HEARTguide as compared to those without optimal sizing and positioning. Further validation in prospective and randomized trials is necessary to validate these results. Second, HEARTguide can provide additional information and help physicians to choose the best fitting valve in for patients undergoing TAVI with borderline aortic annulus measurements. The use of CT-FFR significantly improves the diagnostic accuracy of CCTA for diagnosing stable CAD requiring treatment and increases the proportion of patients in whom ICA is not needed. It has the potential to be integrated in the current clinical work-up for TAVI for diagnosing stable CAD requiring treatment.

PART III: Evaluating individual outcomes of TAVI

Outcomes of TAVI in a real world Dutch population

In the first chapter of **PART III (Chapter 16)**, we report the 30-days outcomes of TAVI procedures of a real world TAVI population in the Netherlands.[60] Since most randomized controlled trials include a selected patient

population, real world data provide a broader view of the everyday treated population. In this multicenter observational prospective registry, we included 1250 TAVI patients. In the first 30 days after TAVI, 30 (2.4%) patients died, 36 (2.9%) patients suffered from a stroke, 13 (1.0%) patients had a myocardial infarction, 66 (5.2%) patients had a major, life-threatening or disabling bleeding, 17 (1.3%) had a major non-bleeding vascular complication, and a permanent pacemaker implantation was required in 138 (11.0%) patients. Our results were quite comparable with other European, American and Asian real-world reports on complications following TAVI.[61–64] We observed that, although, thromboembolic complications such as stroke are most feared by patients, mortality was most often caused by a bleeding event. As mentioned earlier, POPular TAVI showed lower bleeding rates by omitting clopidogrel as addition to aspirin or OAC after TAVI, without increasing thromboembolic events. This strategy was adopted by the most recent European guideline.

Detection of kidney improvement early after TAVI

In **Chapter 17**, we describe the results of a prespecified substudy of the POPular TAVI where we investigated the early detection of kidney function worsening or improving after TAVI.[65] We measured the periprocedural course of proteinuria and renal function in the first 72 hours in 133 patients after TAVI, by collecting plasma and urine samples at 6, 24, 48 and 72 hours after TAVI. Serum creatinine and estimated glomerular filtration rate did not change over time, while the amount of proteinuria decreased in the early days after TAVI suggesting early signs of kidney function improvements. Whether these findings will result in further improvement of kidney function after 72 hours needs to be verified in a larger cohort with longer follow-up as well as its role as an early predictor of kidney improvement after TAVI.

The use of the Academic Research Consortium high bleeding risk criteria in TAVI patients

In **Chapter 18**, we try to validate Academic Research Consortium High Bleeding Risk (ARC-HBR) criteria, originally released for patients undergoing coronary artery stenting, in TAVI patients using the POPular TAVI trial cohort [66] The median ACR-HBR score of the 978 included patients was 3 [IQR 1-5] and 78.5% of the patients had a score of more than 2 (thus considered as high bleeding risk patients). As expected, both major (chronic OAC use) and minor criteria (≥75 years of age, 49% with moderate chronic kidney disease) were frequently observed, demonstrating the high bleeding risk profile of the TAVI population. As a result, the cut-off criteria for high bleeding risk (one major or two minor criteria) seems to be inappropriate to stratify high bleeding risk in TAVI population. An ARC-HBR score of six (two points per major and one point per minor criteria) seems to be a more effective cut off value for bleeding events (22.3% for below six versus 32.6% for six or more , p=0.04). However, in general, the clinical impact of the ARC-HBR criteria in TAVI may be limited to the periprocedural ATT, since the results of both cohorts of POPular TAVI (**Chapter 3 and Chapter 6**) strongly suggest monotherapy with aspirin or OAC in all patients after TAVI.

Early use of a novel collagen based vascular closure device

Chapter 19 demonstrates a single center experience of a novel collagen based vascular closure device, possibly leading to less periprocedural vascular and bleeding complications.[67] In this retrospective study we compared this new MANTA device (168 patients) with the Prostar XL device (198 patients) on safety and feasibility outcomes at 30-days. A successful closure was obtained in 98.8% of the patients receiving the MANTA and 98.5% of the patients receiving the Prostar XL. The MANTA device was associated with less vascular complications and minor bleeding compared to previously used Prostar XL device at 30-days (10.7% versus 18.8%, p=0.003 and 13.7% versus 19.7%, p=0.080, respectively), while there were no differences in major vascular and bleeding complications (0.6% versus 1.0%, P=0.661 and 0.6% versus 1.5% P=0.102, respectively). Based on our finding we consider the MANTA device as a safe and feasible option for vascular access closure in patients undergoing transfemoral TAVI. Also, the randomized MANTA vs. Suture-based vascular closure after transcatheter aortic valve replacement trial, observed no differences in vascular complications and significant bleeding events between MANTA and Proglide.[68] One of the main limitations of the MANTA device is that it is not suitable in all patients undergoing TAVI. For example, patients with a small femoral artery diameter in combination with a deep course of the femoral artery (i.e. in patients with obesity), are more at risk for vascular complications and vascular closure device failure.[69] Furthermore, in case of vascular closure device failure, the treatment strategy is more drastic (covered stent or surgical bailout and repair) than with the other vascular closure devices (use of an extra device).[68] Therefore, patient risk stratification is necessary when using the MANTA.

Prosthetic valve endocarditis after TAVI

In **Chapter 20,** we describe the incidence and outcome of prosthetic valve endocarditis (PVE) after TAVI in the Netherlands.[70] In this multicenter retrospective registry, we screened 3968 TAVI patients for PVE. During a mean follow-up of almost 3 years, 16 (0,4%) patients developed PVE, with an incidence rate of 0.13 event per 1000 person-years. The mean time to onset of PVE was 177 days. The (first-year) incidence of PVE in our study was lower compared to those of other national registries (1.4%[71] versus 2.3%[72] versus 0.24% in our study). Although rare, PVE is known for it's poor outcome and high mortality rate. Also in our cohort, mortality was high (31%), most likely caused by a more advanced age, frailty and presence of many co-morbidities in these TAVI patients. All patients with PVE were treated conservatively with antibiotics and even after a prolonged period of antibiotic therapy, no re-intervention was performed, possible due to high surgical risk. This may be changing in the near future, when TAVI indications shift towards lower risk patients.

Coronary artery stenting after TAVI

In **Chapter 21**, we present the results of an international multicenter retrospective study on the incidence and causes of unplanned percutaneous coronary intervention (PCI) after TAVI including more than 15325 patients.[73] The incidence of unplanned PCI is this cohort was 0.9% over a median follow-up of 191 days. Of interest, the main indication for PCI in the first two years after TAVI was an acute coronary syndrome, while afterwards chronic coronary syndrome became more prevalent as main reason for PCI. Patients were most at risk in the first two weeks after TAVI. The overall incidence might be underestimated given the relative short follow-up period and the fact that chronic coronary syndromes are an important reason for unplanned PCI at the long-term. In this cohort, the overall PCI success rate was 96.6%, even 100% in patients treated with a the balloon-expandable TAVI prosthesis (versus 94.9% when treated with a self-expandable prosthesis). In this light, coronary angiography can be more technical challenging in patients with self-expandable valves as the Evolut CoreValve, due to its narrow waist and its frame above the coronary ostia, than in patients with a balloon-expandable Sapien valve.[74] Further investigation on the timing of revascularization in patients with CAD undergoing TAVI remains relevant, also for the question how to deal with CAD after TAVI.

Conclusions of PART III: Evaluating individual outcomes of TAVI

The main findings can be summarized as follows. Important complications as bleeding and thromboembolic complications still occur quite often within the first 30-day after TAVI. Hopefully, further improvements in the devices in combination with the aspects described in PART I and PART II will enhance the safety and reducing the risks of TAVI procedures in future. Proteinuria seems to be a good marker for early signs of kidney improvement, while other measurements did not change in this period. However, no data was available after 72 hours after TAVI. The current ARC-HBR criteria cut off value is not useful to discriminate high from low bleeding risk in TAVI patients. On the other hand, using a score of 6 or more may discriminate the bleeding risk better in TAVI patients. These results need to be verified in a larger cohort of patients and other risk factors as von Willebrand disease may be of additional value. The novel MANTA device is a safe alternative for closing the access site after TAVI. On the other hand, the MANTA device is not suitable for all patients (i.e patients with small artery diameters or a deep course of the femoral artery) and thus patient selection is required for the best results. Prosthetic valve endocarditis after TAVI is rare but has severe consequences with high mortality rates. All patients we treated conservatively with antibiotics, most likely due to the high surgical risk for re-intervention. When treating lower risk TAVI patients, possibly reintervention for prosthetic valve endocarditis is an option. Last, we observed low incidences of PCI after TAVI. The main indication for PCI in the first two years was acute coronary syndrome, while chronic coronary syndrome was more prevalent after two years. Further research on the optimal timing of CAD before or after TAVI is desirable.

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