Screening, complications and outcome of aortic valve implantation
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Chapter 11

Summary
Patients with symptomatic aortic valve stenosis have an increased mortality risk and disease symptoms tremendously affect the quality of life. No pharmacotherapeutic measurements have proven to delay disease progression. Traditionally, surgical aortic valve replacement was the only treatment left for symptomatic patients. However, over the last years, transcatheter aortic valve implantation (TAVI) has been fully integrated as a therapeutic option for patients with aortic valve stenosis. Studies have reported good mid-term outcomes and current guidelines include TAVI as the preferred treatment for inoperable patients and as a good, less invasive, alternative for surgical aortic valve replacement in patients with high to intermediate surgical risk.

**SECTION I PATIENT SCREENING**

Computed tomography angiography (CTA) has become the clinical standard to assess the anatomy prior to TAVI. Intravenous contrast media are necessary to obtain images for this purpose. Historically it is believed that the contrast media may cause acute kidney injury. Although mostly the renal function returns to normal, there is an association between acute and permanent kidney injury and increased mortality. The risk of permanent injury is especially high for patients that already have an impaired renal function. To mitigate the effects of contrast media in these patients, guidelines recommend intravenous hydration with sodium chloride before and after contrast administration. In patients with aortic valve stenosis, this hydration takes 24 hours with an average volume of 1.5 to 2.0 liter. Volumes like this might increase the risk for acute heart failure, especially in the TAVI population. In Chapter 2 we report the findings of the randomized controlled trial (RCT) performed to analyze if short 1-hour, low-volume hydration with sodium bicarbonate was non-inferior to conventional 24-hour sodium chloride hydration to avoid a decline in renal function after CTA. All included patients had an impaired renal function (estimated glomular filtration rate (eGFR) <60 ml/min/1.73m2). We found that short hydration was non-inferior to conventional hydration and did not result in clinically significant renal dysfunction. In addition, more patients treated with conventional hydration reported increased dyspnea (16% versus 3% in short hydration). However, even though the absolute between group difference was 13%, this was non-significant (p=0.09).

Analysis of CTA in the old and frail TAVI population frequently reveals pathology not directly relevant for the procedure: potentially malignant incidental findings. As it is mostly unknown how these incidental findings influence survival, they often pose the TAVI team for dilemmas. Chapter 3 is a retrospective analysis of all CTAs performed in the Academic Medical Center in TAVI screening between 2009 and 2014. Of all patients that underwent TAVI, 20% had a potentially malignant incidental finding.
requiring (further) action after the procedure, including treatment, additional diagnostic testing, or follow-up. We demonstrated that patients with incidental findings had a worse prognosis than patients without such finding; at 5 years after TAVI, the risk of death from any cause was 65% in patients with incidental findings versus 49% in patients without findings. The presence of incidental findings on CTA that required (further) action after TAVI was an independent predictor of all-cause mortality. Moreover, it was a predictor of non-cardiovascular, but not of cardiovascular mortality.

SECTION II PERIPROCEDURAL COMPLICATIONS

The occurrence of a thromboembolic event is a major complication of TAVI with an incidence of 3%. The occurrence in half of these events within one week suggests a procedure related origin. In Chapter 4 we report the clinical course and outcome of three patients treated by TAVI, complicated by a thromboembolic event. All cases were followed by mechanical thrombectomy, which created the opportunity to perform a histopathologic analysis of the retrieved material. We demonstrated that manipulation of the aortic valve and vessel wall may cause embolization. In addition, the prosthesis implantation itself may induce platelet aggregation, activating of coagulation pathways, ultimately leading to thromboembolic events during or shortly after TAVI.

Vascular complications have been reported from the beginning of TAVI. Studies on these complications have been conducted with older generation prostheses. Technical refinements to these prostheses have been made and resulted in the latest generation balloon-expandable SAPIEN 3 (Edwards Lifesciences, Irvine, California, USA). The delivery system used for SAPIEN 3 implantation is smaller and more advanced compared to older generation devices, which potentially lowers complication rates. Therefore, in Chapter 5 we analyze the current incidence, predictors and impact of vascular complications after transfemoral TAVI with the SAPIEN 3. We found that also with this new prosthesis type, vascular complications remain an issue and their occurrence is difficult to predict. We found a relative low incidence of 5.8% for major vascular complications as compared to older generation prosthesis. Nevertheless major vascular complications were associated with an increased 30-day mortality risk. After these first 30 days vascular complications were not of influence on survival anymore.
SECTION III CLINICAL OUTCOME

For a long time surgical aortic valve replacement was the only available treatment for patients with severe symptomatic aortic valve stenosis. Surgical valve replacement can be performed with various prostheses types. In Chapter 6, the hemodynamic performance of two types of surgical implanted prostheses is evaluated: the stented and stentless bioprosthesis. One year after surgery 4D flow magnetic resonance imaging (MRI) was conducted in 28 patients with either prostheses type. We found that velocity, wall shear stress and energy loss were comparable when assessed for averaged values in the ascending aorta. However, the flow profile described with local analysis for stentless prosthesis was potentially favorable with a significant higher central velocity profile and lower values in the outer lumen.

With a shift in TAVI population to patients with lower surgical risks, prosthesis performance and longer-term outcome become of great importance. Over the years refinements of existing prostheses have been made. Adjustments of the balloon-expandable SAPIEN prosthesis first resulted in the SAPIEN XT and then in the SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA). In Chapter 7 we performed a retrospective analysis of patients with low to intermediate surgical risk to compare the outcome after transfemoral TAVI with the SAPIEN XT and SAPIEN 3. We demonstrated favorable procedural and mid-term outcomes of the SAPIEN 3, with more device success, less paravalvular leakage and less major bleeding complications. For both prostheses we demonstrated a low rate of vascular complications, low rate of permanent pacemaker implantations and above all, excellent 3-year survival. In Chapter 8 we gained insight in the trends in patient-, procedural characteristics and clinical outcome after TAVI from 2009 onwards, in a large consecutive real-world population of more than 1000 patients. Over the 8-year period we describe a clear shift towards a lower-risk TAVI population and improved clinical outcome including more symptom relief and lower complication rates. Mortality after TAVI declined impressively, mainly as a consequence of improved 30-day mortality for which the risk declined by 72% in the most recent time interval compared to the early years (2015-2016 vs. 2009-2013). It could be suggested that the shift towards a lower risk population was the explanation for the decline in complication and mortality rates. But although this could have been of influence, with an adjusted analysis, correcting for patient characteristics, we demonstrated that this shift was certainly not the only explanation for the observed decline. Most likely the improved outcome is strongly influenced by the increased operator and center experience combined with procedure- and device-related changes. Chapter 9 is an overview of autopsy findings in patients with TAVI in their medical history.
We used 72 cases of autopsy from 8 European centers and divided them according to the time interval of death after TAVI. We found different patterns in the causes of death among different time-intervals. Cardiogenic and especially hemorrhagic shock occurred less frequently as time after the procedure passed. On the contrary, respiratory failure and sepsis only occurred after 72 hours. Among patients who died after 72 hours, a high incidence of prosthetic valve endocarditis was present. Moreover, the study revealed a substantial added value of autopsy to the solely clinical determined cause of death as clinically relevant extra findings were found at autopsy in 60% of the patients, which completely changed the perception on the cause of death in more than 25% of all patients.