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Rikhard Björn

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To my dear wife Hanna, and our darling boy Klaus

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ABSTRACT

The only curative treatments for aortic valve defects are valve repair or valve replacement using either a mechanical or a biological prosthesis. An aortic valve replacement can be performed via transcatheter aortic valve implantation (TAVI) or open-heart surgery. Outcomes following a surgical aortic valve replacement (SAVR) are generally favorable; however, the procedure carries inherent risks.

Atrial fibrillation (AF) is the most common complication following SAVR, occurring in approximately 32.9% to 74.0% of patients during the index hospitalization and in 18.5% to 44.5% later postoperatively. Among patients undergoing a mechanical aortic valve replacement, stroke remains one of the most feared complications, with an estimated annual incidence ranging from 0.4% to 1.8%. Due to the thrombogenic nature of mechanical valves, lifelong anticoagulation therapy is required. However, this therapy increases the risk of major bleeding events.

This thesis investigated the complications following a bioprosthetic and a mechanical SAVR, with a focus on new-onset atrial fibrillation (NOAF), major stroke, and bleeding events, as well as their associations with antithrombotic therapy.

The findings indicate that NOAF occurs in a substantial proportion of patients after both a bioprosthetic and a mechanical SAVR. Furthermore, patients who develop NOAF during their initial hospitalization are at high risk of recurrent AF later in life and all-cause mortality in both bioprosthetic and mechanical SAVR cohorts.

In addition, the incidence of early postoperative major bleeding is significantly higher than that of a major stroke following a bioprosthetic and a mechanical SAVR. The risk of major bleeding remains higher during both early and late periods in patients with a mechanical aortic valve prosthesis, while in patients with bioprosthesis, the risks of stroke and bleeding are nearly equal.

In the future, the guidelines should account for bleeding risk in addition to thrombotic complications in patients undergoing SAVR.

KEYWORDS: surgical aortic valve replacement, atrial fibrillation, bleeding, stroke, antithrombotic medication

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TIIVISTELMÄ

Aorttaläpän vikojen ainoat parantavat hoitomuodot ovat läpän korjaus tai vaihto mekaaniseen tai biologiseen tekoläppään. Aorttaläppä voidaan vaihtaa joko katetriläppätoimenpiteellä (TAVI) tai avosydänleikkauksella. Kirurgisen aorttaläpän vaihdon tulokset ovat lähtökohtaisesti hyviä, mutta toimenpiteeseen liittyy merkittäviä riskejä. Yleisin komplikaatio avosydänleikkauksen jälkeen on eteisvärinä, jota esiintyy aiempien tutkimusten mukaan 32.9–74.0 %:lla potilaista sairaalahoidon aikana ja 18.5–44.5 %:lla myöhemmässä seurannassa. Näiden esiintymisen keskinäisestä suhteesta ja erityisesti pitkäaikaisseurannasta on kuitenkin rajallisesti tietoa. Mekaanisen aortan tekoläppäleikkauksen läpikäyneillä potilailla pelätyin komplikaatio on kuitenkin aivoinfarkti, jonka ilmaantuvuus on 0,4–1,8% vuodessa. Mekaanisten läppien trombogeenisyyden vuoksi potilaat tarvitsevat elinikäisen verenohennuslääkityksen, mikä puolestaan lisää vakavien verenvuotojen riskiä.

Tässä väitöskirjassa tutkittiin kirurgisen aortan tekoläppäleikkauksen komplikaatioita sekä sairaalahoitojakson aikana että pitkäaikaisseurannassa. Erityisesti tarkasteltiin uuden eteisvärinän, vakavien aivoinfarktien ja verenvuotojen esiintyvyyttä sekä niiden yhteyttä verenohennuslääkkeiden ja muiden veren hyytymistä estävien lääkkeiden käyttöön.

Tutkimuksen tulokset osoittavat, että uusi eteisvärinä on yleinen komplikaatio sekä biologisen että mekaanisen aortan tekoläppäleikkauksen jälkeen. Uuden eteisvärinän esiintyminen sairaalahoidon aikana ennustaa myöhempää eteisvärinän uusiutumista ja on yhteydessä kokonaiskuolleisuuteen molemmissa potilasryhmissä.

Molemmissa potilasryhmissä varhaisen leikkauksenjälkeisen vakavan verenvuodon ilmaantuvuus on merkittävästi korkeampi kuin vakavan aivohalvauksen. Pitkällä aikavälillä vakavan verenvuodon riski säilyy suurempana mekaanisen aorttaläppäproteesin saaneilla potilailla, kun taas bioproteesipotilailla aivohalvauksen ja verenvuodon riskit ovat lähes samansuuruiset.

Kansainvälisten hoitosuositusten tulisi jatkossa tarkemmin huomioida verenvuotoriski aortan tekoläppäleikkauksen läpikäyneillä potilailla.

AVAINSANAT: aortan tekoläppäleikkaus, eteisvärinä, verenvuoto, aivoinfarkti, hyytymisenestolääkkeet

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Abbreviations

ADP	adenosine-diphosphate receptor antagonists
AF	atrial fibrillation
ASA	acetylsalicylic acid
AVR	aortic valve replacement
BAV	bicuspid aortic valve
BMI	body mass index
CABG	coronary artery bypass grafting
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female)
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CRP	C-reactive protein
eGFR	estimated glomerular filtration rate
GI	gastrointestinal
HR	hazard ratio
INR	international normalized ratio
IQR	interquartile range
KNN	K-Nearest Neighbors
LA	left atrial
LVEF	left ventricular ejection fraction
LMWH	low-molecular-weight heparin
MR	mitral valve regurgitation
NOAC	novel oral anticoagulant
NOAF	new-onset atrial fibrillation
NYHA	New York Heart Association classification
OAC	oral anticoagulation
OHS	open heart surgery
PCI	percutaneous coronary intervention

PH	pulmonary hypertension
PPI	proton pump inhibitor
RCT	randomized controlled trial
ROS	reactive oxygen species
SAVR	surgical aortic valve replacement
SD	standard deviation
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TTR	time in therapeutic range
VKA	vitamin K antagonist

List of original publications

This dissertation is based on the following original publications, which are referred to in the text with Roman numerals:

I Björn R, Nissinen M, Lehto J, Malmberg M, Yannopoulos F, Airaksinen J, Hartikainen J, Nieminen T, Biancari F, Gunn J & Kiviniemi T. Late incidence and recurrence of new-onset atrial fibrillation after isolated surgical aortic valve replacement. *The Journal of Thoracic and Cardiovascular Surgery*, 2021;164 (6):1833 – 1843.

II Björn R, Lehto J, Malmberg M, Anttila V, Airaksinen J, Gunn J & Kiviniemi T. Antithrombotic Medication and Major Complications After Mechanical Aortic Valve Replacement. *The American Journal of Cardiology,* 2023; 204: 185-194.

III Björn R, Lehto J, Malmberg M, Anttila V, Gunn J, Nieminen T, Hartikainen J, Biancari F, Airaksinen J & Kiviniemi T. Major bleeding complications and antithrombotic treatment after isolated surgical bioprosthetic aortic valve replacement. *Manuscript.*

The use of the articles as sub-publications in the dissertation has been granted permission by the publishers.

1 Introduction

Aortic stenosis is the most common primary valvular lesion requiring surgical or transcatheter intervention worldwide (Praz et al., 2025). Another prevalent condition affecting the aortic valve is aortic regurgitation. Both pathologies result in progressive valve deterioration and, if left untreated, ultimately lead to death. The only curative treatment for aortic valve stenosis or regurgitation is valve repair or replacement using either a mechanical or a biological prosthesis. The aortic valve can be replaced with a prosthetic valve through a transcatheter aortic valve replacement (TAVI) or an open-heart surgery (OHS). The latest European guideline for the management of valvular heart disease (VHD) suggests that a bioprosthetic SAVR is recommended for 60 to 70-year-old patients, when the surgical risk is low. Furthermore, in patients younger than 60 years old requiring an aortic valve replacement (AVR), mechanical valves are preferred over biological ones (Praz et al., 2025).

Although a valve replacement is curative for valvular heart disease, it presents several challenges. AF is the most common complication following SAVR. The incidence of postoperative AF (POAF), typically referring to in-hospital or early AF episodes after surgery regardless of prior AF history, ranges from 25.0% to 74.0% (Attia et al., 2022; Helgadottir et al., 2012). Additionally, the term new-onset AF (NOAF) refers to AF occurring in-hospital, early, or late after surgery in patients without a prior history of AF. The reported incidence of an in-hospital NOAF following SAVR ranges from approximately 32.9% to 74.0%, while the incidence of a late AF ranges from 18.5% to 44.5% (Almassi et al., 1997; Helgadottir et al., 2012; Hørsted Thyregod et al., 2024; Ong et al., 2022). Despite its clinical significance, only a limited number of studies have investigated the relationship between an in-hospital NOAF and a subsequent AF recurrence or long-term mortality in SAVR patients. This knowledge gap is particularly evident in patients undergoing a mechanical SAVR, for whom data on AF recurrence remain scarce.

Mechanical valves generally provide lifelong durability. However, they are associated with an increased risk of thromboembolic events, necessitating lifelong anticoagulation therapy with a vitamin K antagonist (VKA), guided by the international normalized ratio (INR). In contrast, bioprosthetic valves are less thrombogenic and offer a durability of 10 to 18 years (Bourguignon et al., 2015; Fatima et al., 2019).

For patients without an initial indication for long-term oral anticoagulation (OAC), the current guidelines recommend treatment with low-dose acetylsalicylic acid (ASA) or VKAs for the first three months following a bioprosthetic SAVR. Because of the potential disabling and even fatal thromboembolic complications ensuing from inadequate anticoagulation, the focus of the VKA therapy has been on preventing thromboembolic events. However, it is important to recognize that the VKA therapy carries an increased risk of major bleeding events, which can pose serious threats to patient safety.

This thesis investigates the incidence and recurrence of NOAF following SAVR. Furthermore, it aims to clarify the incidence of major bleeding and stroke events after SAVR and to examine their association with antithrombotic therapy.

2 Review of literature

2.1 Surgical aortic valve replacement

Since the 1960s, SAVR has been the standard treatment for aortic valve disease (Harken et al., 1960). Initially, SAVR procedures were performed using mechanical aortic valves. However, within a few years, bioprosthetic valves were introduced to the market (Carpentier et al., 1969). Since then, artificial valve technology has advanced significantly, driven by improvements in materials and manufacturing techniques. Today, a wide variety of both mechanical and bioprosthetic aortic valve prostheses are available. Bioprosthetic valves are typically made from animal tissue, such as porcine aortic valves or bovine pericardium, and may be designed as stented, stentless, or sutureless. Mechanical valves are constructed from durable materials such as pyrolytic carbon or titanium. The main designs include bileaflet, tilting disc, and the older ball-in-cage models. Bileaflet valves are most commonly used today due to their superior hemodynamic performance and durability (Sellke, 2016). Both types of prosthetic valves are implanted via OHS. However, in 2002, the first TAVI using a bioprosthetic valve was successfully performed in humans (Cribier et al., 2002). Following the I-REVIVE and RECAST trials, the pioneering studies that demonstrated the feasibility of TAVI, this technique has become a mainstream therapeutic option, particularly for patients over 75 years of age (Blankenberg et al., 2024; Généreux et al., 2024).

The choice between TAVI and SAVR has recently become one of the most debated topics in cardiology. This has led to a surge in research, including several randomized controlled trials (RCTs) (Adams et al., 2014; Blankenberg et al., 2024; Hørsted Thyregod et al., 2024; Leon et al., 2016; Mack et al., 2019; Makkar et al., 2020; Popma et al., 2019; Reardon et al., 2017; Smith et al., 2011; Thyregod et al., 2019; Toff et al., 2022). A 2023 meta-analysis by Ahmad et al., which included eight RCTs and 8,698 patients, found no statistically significant difference in all-cause mortality between TAVI and SAVR in higher-risk patients during the weighted mean follow-up of 3.9 years (HR 0.96, 95% CI 0.96–1.13, p = 0.34) (Ahmad et al., 2023). However, in lower-risk patients, a significant early survival benefit was observed in favor of TAVI (RR 0.67, 95% CI 0.47–0.96, p = 0.031).

Due to the excellent outcomes associated with TAVI, current European guidelines recommend TAVI over surgery for high-risk patients, suitable moderate-risk patients, and individuals over 70 years of age. A bioprosthetic SAVR, however, remains the preferred option for patients aged 60 to 70 years and those at low surgical risk, primarily because the long-term durability of TAVI remains uncertain (Praz et al., 2025). While current recommendations support TAVI in patients over 70 years, it is important to note that the randomized trials informing these guidelines did not stratify patients based on the presence of bicuspid aortic valves (BAV), despite BAV being common in real-world populations (Jørgensen et al., 2024; Mehaffey et al., 2024). In contrast, mechanical aortic valves are well known for their long-term durability, making a mechanical SAVR the preferred choice for patients under 50 years of age and select patients between the ages of 50 and 60 years (Otto et al., 2021; Praz et al., 2025).

Consequently, TAVI may become a viable option for younger patient populations. However, the durability of mechanical prosthetic valves still surpasses that of TAVI valves, indicating that TAVI may not be appropriate for all patients, at least in the near future. Certain clinical conditions, such as infective endocarditis, remain contraindications for TAVI. Moreover, surgical intervention continues to be the preferred approach for patients with BAV, particularly those with complex anatomical features, younger age, or aortic root dilatation. These considerations underscore the ongoing relevance of both a bioprosthetic and a mechanical SAVR in contemporary clinical practice.

Mechanical prosthetic valves are typically constructed using a pyrolytic carbon orifice, a frame made from titanium or stainless steel, and a sewing ring. Unlike bioprosthetic valves, which are generally trileaflet, modern mechanical valves are bileaflet in design. While the overall function of both valve types is similar, subtle differences exist between models from different manufacturers. Bioprosthetic aortic valves are traditionally categorized into porcine and bovine types, depending on the source tissue. In addition to these conventional prostheses, alternative options such as homografts and autografts are also an option (Sellke, 2016). One notable example is the Ross procedure, in which the patient's diseased aortic valve is replaced with their own pulmonary valve (autograft), and the pulmonary valve is subsequently replaced with a homograft or xenograft. Compared to mechanical aortic prostheses, patients undergoing the Ross procedure typically do not require long-term anticoagulation, resulting in lower rates of bleeding and thromboembolic events. While the requirement for intermittent reinterventions may limit the overall benefit of the Ross procedure, it nevertheless represents an excellent therapeutic option for patients in whom the procedure is feasible (Mazine et al., 2018).

Both a bioprosthetic and a mechanical SAVR are performed via OHS, which is traditionally conducted through a median sternotomy. Once the heart is exposed,

systemic heparinization is administered, followed by cannulation of the ascending aorta and right atrium. Antegrade cardioplegia, delivered via the ascending aorta or coronary arteries, is commonly used to achieve myocardial protection. Cardiopulmonary bypass (CPB) is established by inserting aortic and venous cannulas. A vent is placed either in the ascending aorta or through the right superior pulmonary vein into the left ventricle to facilitate ventricular decompression. Following this, an aortotomy is performed, typically into the non-coronary sinus, after excision of the native valve. Commercial sizers are used to determine the appropriate prosthesis size. If necessary, annular enlargement is performed to accommodate a sufficiently large valve. The standard implantation technique involves the use of interrupted sutures. In this method, individual, evenly spaced sutures are placed through the annulus and the sewing ring of the prosthetic valve to ensure secure fixation, optimal hemostasis, and precise positioning. Once the prosthesis is parachuted into place and all the sutures are tied, the aortotomy is closed using polypropylene sutures. After closure, the aortic root vent is activated and the pulmonary vent temporarily paused to perform de-airing maneuvers, followed by removal of the aortic cross-clamp and reactivation of the pulmonary vent. Transesophageal echocardiography is used to assess for paravalvular leaks. The patient is gradually rewarmed, and epicardial atrial and ventricular pacing wires are placed due to the risk of atrioventricular block and other arrhythmias. During weaning from CPB, the venous and aortic cannulas are removed, heparin is reversed with protamine, and chest tubes are inserted into the posterior pericardium and anterior mediastinum. Finally, the surgical incisions are closed (Sellke, 2016).

2.2 Antithrombotic medication after SAVR

Patients undergoing SAVR are at an elevated risk of thromboembolic complications (Cannegieter et al., 1994; Heras et al., 1995). The risk of thromboembolic events is higher with mechanical than with bioprosthetic valves. The standard antithrombotic medication for mechanical prostheses has been VKA therapy, most commonly warfarin. To reduce the risk of thromboembolic events, patients with mechanical aortic valves require lifelong anticoagulation with warfarin, guided by the international normalized ratio (INR) (Praz et al., 2025). INR is calculated by comparing a patient's prothrombin time (PT) to a standardized PT(Loeliger, 1984). Warfarin therapy is typically initiated on the first postoperative day. Low molecular weight heparin (LMWH) is started on the day of the surgery and continued until the VKA treatment reaches therapeutic levels. In mechanical aortic valve prostheses, targeting a median INR value for each patient is recommended. The INR is determined based on valve thrombogenicity or patient-specific risk factors. In modern mechanical valve prostheses, the INR target for patients without additional risk factors is 2.5, with a

recommended range of 2.0 to 3.0 (Otto et al., 2021; Praz et al., 2025) However, for patients with mechanical aortic On-X valves, a target INR of 1.5 to 2.0, in conjunction with an ASA, is used (Gerdisch et al., 2022; Puskas et al., 2018). Nevertheless, maintaining such a narrow INR target is challenging, and even small deviations below the target can result in a thrombotic state. Additionally, combining VKA therapy with ASA increases bleeding rates and reduces the potential benefits associated with a lower INR target.

While novel oral anticoagulants (NOACs) have emerged as preferred agents in many clinical settings, they are not used in patients with mechanical valve prostheses. The first RCT investigating the use of NOACs in this population was the RE-ALIGN trial. This study was terminated early due to a higher incidence of strokes and myocardial infarctions in the dabigatran group compared to the warfarin group (Eikelboom et al., 2013). As a result of these unfavorable outcomes, only a limited number of RCTs have since been conducted on the use of other NOACs in patients with mechanical valves. In comparing apixaban and warfarin in patients with an On-X aortic valve by Wang et al., apixaban did not demonstrate noninferiority to warfarin, and the study was stopped prematurely because the apixaban group received significantly more thromboembolic complications(Wang et al., 2023). However, in the small pilot study by Duraes et al., patients with mechanical mitral or aortic valves receiving rivaroxaban experienced thromboembolic and bleeding events similar to those of warfarin patients (Duraes et al., 2021).Currently, VKAs remain the only approved oral anticoagulant therapy for patients with mechanical aortic valve prostheses (Otto et al., 2021; Praz et al., 2025).

Though lifelong warfarin therapy is recommended for mechanical AVR, the approach for bioprosthetic AVR remains controversial. Current recommendations are largely based on observational studies rather than RCTs. In the studies by Brennan et al. and Christersson et al., the use of warfarin compared to ASA decreased the risk of thromboembolic rates and increased the risk of bleeding. However, in the study by Brennan et al., the use of warfarin also decreased the risk of death. In contrast, in the study by Christensson et al., there were no differences between the groups (Brennan et al., 2012; Christersson et al., 2019).

Additionally, it has been shown that discontinuation of warfarin therapy within three months after a bioprosthetic SAVR is associated with a significantly increased risk of stroke, thromboembolic complications, and cardiovascular death. Furthermore, discontinuation of warfarin therapy beyond three months postoperatively has been linked to an increased risk of cardiovascular mortality (Mérie et al., 2012). However, in one of the few RCTs on this topic, Rafiq et al. found that patients receiving ASA therapy experienced fewer major bleeding events than those on OAC therapy, with ASA proving equally effective as warfarin in preventing thromboembolic events (Rafiq et al., 2017). A similar trend was observed in the meta-analysis

by Riaz et al., which included 6,431 patients. The study found that at three months, warfarin use was associated with a significantly increased risk of bleeding compared to ASA or placebo, without a corresponding increase in thromboembolic protection (Riaz et al., 2016). However, a more recent meta-analysis by Uimonen et al. reported the lowest 0 to 12-month mortality in patients treated with anticoagulation alone (2.0%, 95% CI 0.4–9.7%) or in combination with antiplatelet therapy (2.2%, 95% CI 0.9–5.5%). In contrast, the highest mortality was observed in patients who received no antithrombotic therapy (7.3%, 95% CI 3.6–14.2%), suggesting a potential benefit of continuing OAC beyond three months (Uimonen et al., 2024).

The American guidelines provide a Class IIb recommendation and the European guidelines provide a Class IIa recommendation for the use of Warfarin therapy for three months following a bioprosthetic SAVR, indicating that OAC may be considered. Additionally, the European guideline allows for the use of ASA instead of OAC in patients without another indication for anticoagulation. In addition, the American guidelines provide a Class IIa recommendation and the European guidelines provide a Class IIb recommendation to continue ASA if there is no indication for OAC therapy (Otto et al., 2021; Praz et al., 2025).

2.3 Complications after SAVR

SAVR is a pivotal procedure for patients with severe aortic valve disease, but it carries inherent risks that must be carefully considered. Both early and long-term complications, such as AF, bleeding, and a stroke, are significant concerns and will be discussed in detail later in this chapter. A study by Agarwal et al. reported an in-hospital mortality rate of approximately 3.0% following the procedure (Agarwal et al., 2015). However, a more recent study by Thourani et al., involving 234,556 patients undergoing SAVR, found a lower operative mortality rate of 1.54%. Additionally, the study highlighted that mortality rates are influenced by the annual procedural volume of the operating centers (Thourani et al., 2022). Dimagli et al. demonstrated that mortality and morbidity rates following SAVR have significantly improved over time, with the in-hospital mortality decreasing from 2.9% in 2000 to 2005 to 0.7% in 2012 to 2017 (Dimagli et al., 2020). Despite these improvements, overall life expectancy following SAVR remains lower than that of the general population, as noted by Glaser et al. (Glaser et al., 2021). Postoperative life expectancy is influenced by several factors, including patient age, surgical risk, and the type of valve implanted, an important consideration emphasized by Martinsson et al. (Martinsson et al., 2021). For example, the five-year survival rate after SAVR ranges from 81.6% to 90% (Kvidal et al., 2000; Sun et al., 2025; Viktorsson et al., 2019). When analyzing outcomes by prosthesis type, patients receiving mechanical valves generally exhibit lower mortality rates, largely due to their younger age at the time of

surgery. However, the relationship between age and mortality across different valve types is more complex than it may initially appear.

A meta-analysis and systematic review by Tasoudis et al. revealed that patients aged 50 to 70 years undergoing mechanical AVR experienced improved overall survival compared to those receiving bioprosthetic valves (HR 0.76, 95% CI 0.70–0.83, $P < 0.0001$) (Tasoudis et al., 2022). Notably, in patients under 50 years of age, no significant association was found between prosthesis type and mortality. Furthermore, subsequent studies by Ashwat et al. and Rodríguez-Caulo et al. suggested that patients under 65 years receiving bioprostheses had overall survival rates comparable to those with mechanical prostheses (Ashwat et al., 2024; Rodríguez-Caulo et al., 2023).

Moreover, the extensive retrospective multicenter study by Brennan et al, which included 39,199 patients undergoing an isolated SAVR, confirmed that long-term mortality rates were similar between patients receiving bioprosthetic and mechanical valves. However, the study highlighted that bioprostheses were associated with a higher long-term risk of reoperation and endocarditis (Brennan et al., 2013). Similarly, studies by Stassano et al. and Rodríguez-Caulo et al. reported an increased incidence of reoperation and structural valve deterioration in patients with bioprostheses (Rodríguez-Caulo et al., 2023; Stassano et al., 2009). This elevated risk of reoperation is primarily attributed to structural valve deterioration, which is more prevalent in bioprosthetic valves (Kostyunin et al., 2020). Previous studies comparing outcomes after bioprosthetic vs. mechanical SAVR have generally been retrospective, involving heterogeneous patient cohorts and potentially leading to selection bias. Moreover, follow-up durations in many of these analyses have been relatively short in relation to the long-term outcomes of interest. Consequently, the current evidence remains limited, and the comparative survival between bioprosthetic and mechanical valves should be interpreted cautiously.

In addition to structural concerns, patients may also experience non-structural valve deterioration, with endocarditis being one of the most serious complications. The incidence of endocarditis following SAVR ranges from 1.0% to 7.3% (Brennan et al., 2013; Kytö et al., 2020; Klautz et al., 2021; Slouha et al., 2023). Another significant concern is the potential need for permanent pacemaker implantation, which affects approximately 3.4% to 14% of patients postoperatively, with the majority requiring implantation within the first two weeks (Adams et al., 2014; Dawkins et al., 2008; Hørsted Thyregod et al., 2024; Leon et al., 2016; Mack et al., 2019; Ravaux et al., 2021; Smith et al., 2011). Preoperative conduction abnormalities have been identified as potential predictors for this postoperative requirement (Dawkins et al., 2008; Ravaux et al., 2021). In addition, superficial wound infections are a common complication after SAVR. Thus, deep wound infections significantly increase both short- and long-term mortality compared to patients without infection (Kaspersen et al., 2021).

Although not directly related to the surgical procedure itself, several postoperative complications after isolated SAVR may arise secondary to the systemic impact of perioperative hemodynamic instability, inflammation, and prolonged mechanical ventilation. Acute kidney injury, for instance, occurs in approximately 8.0–17.0% of patients and is thought to result primarily from ischemia–reperfusion injury, hypoperfusion, and the inflammatory response associated with extracorporeal circulation (Najjar et al., 2015; Wu et al., 2025). Postoperative pneumonia, including ventilator-associated infections, develops in about 2–3% of cases and is largely related to prolonged intubation, impaired respiratory mechanics, and systemic inflammatory stress (Barnett et al., 2024; Fischbach et al., 2024). In contrast, acute myocardial infarction after SAVR is uncommon, with an incidence below 1% within six months (Isogai et al., 2022).

Lastly, patients undergoing SAVR are also at risk of developing postpericardiotomy syndrome. In a real-world study conducted by Lehto et al., 11.2% of patients were diagnosed with this condition (Lehto et al., 2020).

2.3.1 New-onset atrial fibrillation

AF is the most common complication following SAVR. NOAF refers to a new-onset AF occurring after surgery in patients with no prior history of AF. NOAF can be classified as either an in-hospital NOAF, occurring during the index hospitalization, or a late AF, occurring after hospital discharge. The term POAF is used to describe AF that occurs after surgery, regardless of prior AF history (Ashwat et al., 2024; Iturra et al., 2014; Sumal et al., 2021). However, most studies using the term POAF have excluded patients with any history of AF (Banach et al., 2007; Bramer et al., 2011; Carter-Storch et al., 2019; Filardo et al., 2010; Helgadottir et al., 2012; Kalra et al., 2019; Kiviniemi et al., 2018; LaPar et al., 2014; Melduni et al., 2015; Park et al., 2017; Rezk et al., 2023; Saxena et al., 2013; Swinkels et al., 2017; Viktorsson et al., 2019). Although early POAF typically refers to in-hospital events, some studies include AF episodes occurring up to 30 days postoperatively under the same term (Banach et al., 2007; Bouhout et al., 2014; Carter-Storch et al., 2019; Melduni et al., 2015; Viktorsson et al., 2019). Therefore, an in-hospital POAF without a prior history of AF can be considered equivalent to an in-hospital NOAF. While in-hospital NOAF is frequently reported, its definition varies significantly across studies. These variations include differences in detection methods (e.g., 12-lead ECG vs. telemetry), arrhythmia duration thresholds, and whether symptoms or interventions are required for diagnosis (Almassi et al., 1997; Bramer et al., 2011; Filardo et al., 2010; Helgadottir et al., 2012; Huckaby et al., 2020; Kalra et al., 2019; Saxena et al., 2013; Swinkels et al., 2017; Tanawuttiwat et al., 2014). In contrast, less is known about the incidence and the clinical implications of late AF following SAVR. The quality of

data on this topic is generally lower, particularly when derived from registry-based studies (Attia et al., 2022).

2.3.1.1 Epidemiology

Due to the variation in the definitions of in-hospital NOAF, the reported incidences of this complication after SAVR have varied widely across studies. Additionally, most studies do not differentiate in-hospital NOAF incidence between a mechanical and a bioprosthetic SAVR. Overall, the incidence of in-hospital NOAF ranges from 32.9% to 74.0%(Almassi et al., 1997; Bramer et al., 2011; Filardo et al., 2010; Helgadottir et al., 2012; Huckaby et al., 2020; Kalra et al., 2019; Kiviniemi et al., 2018; Saxena et al., 2013; Swinkels et al., 2017; Tanawuttiwat et al., 2014). Among patients undergoing a bioprosthetic SAVR, in-hospital NOAF occurs in 36.2% to 60% of cases (Huckaby et al., 2020; Kiviniemi et al., 2018; Saxena et al., 2013; Tanawuttiwat et al., 2014). In contrast, data on in-hospital NOAF following a mechanical SAVR are limited. Available studies report an incidence ranging from 20.7% to 32.8% (Huckaby et al., 2020; Saxena et al., 2013). These findings suggest that an in-hospital NOAF is more common in patients undergoing a bioprosthetic SAVR.

In studies that include both mechanical and bioprosthetic SAVR patients within the same population, the reported incidences of late AF range from 4.5% to 44.5% (Carter-Storch et al., 2019; Melduni et al., 2015; Ong et al., 2022; Rezk et al., 2023). Notably, Ong et al. reported a particularly low incidence of 4.5%. However, the incidence is likely higher, as only 40% of patients underwent ECG monitoring in this study (Ong et al., 2022). Therefore, a more accurate estimate of the overall incidence of a late AF is likely between 18.5% and 44.5%. Following a bioprosthetic SAVR, the incidence of late AF has been reported to range from 25.1% to 38.3% (Adams et al., 2014; Ashwat et al., 2024; Attia et al., 2022; Hørsted Thyregod et al., 2024; Makkar et al., 2020; Popma et al., 2019; Smith et al., 2011; Watkins et al., 2025). In contrast, data on late AF following a mechanical SAVR are extremely limited. Nevertheless, the available evidence suggests a lower incidence compared to a bioprosthetic SAVR, ranging from 25.0% to 27.0% (Attia et al., 2022; Watkins et al., 2025). The higher incidence of AF observed in patients undergoing bioprosthetic SAVR is most likely attributable to their higher baseline risk profile rather than to factors directly related to the surgical procedure itself.

2.3.1.2 Risk factors

Numerous studies have investigated the risk factors associated with NOAF in patients undergoing OHS. However, data specifically addressing risk factors in patients undergoing a mechanical SAVR remain limited. Among the identified predictors,

age has consistently emerged as the most significant factor for an in-hospital NOAF (Almassi et al., 1997; Rostagno et al., 2010; Yagdi et al., 2003). Similar associations have been observed in patients undergoing SAVR, where age has also been shown to significantly influence the incidence of NOAF (Bramer et al., 2011; Filardo et al., 2010; Girerd et al., 2011; Kalra et al., 2019; Melduni et al., 2015; Yagdi et al., 2003). Furthermore, Ong et al. identified age as an independent risk factor for late AF following SAVR (Ong et al., 2022). In a study by Banach et al., age was also found to be a predictor of NOAF occurring within one week after a mechanical SAVR (Banach et al., 2007). Potential mechanisms underlying this association in elderly patients may include age-related alterations in atrial anatomy and changes in electrophysiological properties (Wasmer et al., 2017).

In addition to advanced age, several comorbid conditions, such as hypertension, have been associated with an increased risk of NOAF following SAVR (Almassi et al., 1997; Girerd et al., 2011). Hypertension can induce structural remodeling of the heart, leading to atrial enlargement and fibrosis and eventually to AF (Maesen et al., 2011). Additionally, Banach et al. reported that a history of systolic heart failure was significantly associated with NOAF occurring within one week postoperatively, a finding supported by Park et al. and Helgadottir et al. (Banach et al., 2007; Helgadottir et al., 2012; Park et al., 2017). Systolic heart failure can result from a variety of underlying conditions with diverse pathophysiological mechanisms. However, in patients with systolic heart failure, the development of AF is primarily driven by volume overload and consequent atrial dilatation. Diastolic heart failure has also been shown to be an independent predictor of NOAF within 30 days after surgery. One potential explanation for this could be the increased stretch in pulmonary vessels caused by the pressure increase in the left atrium (Melduni et al., 2015). Furthermore, chronic kidney disease has been recognized as a contributing factor to NOAF within the postoperative period (Girerd et al., 2011; Park et al., 2017), and similar associations have been observed with late AF (Ong et al., 2022). The mechanisms by which chronic kidney disease (CKD) contributes to the development of NOAF are not fully understood. However, patients with CKD often present with comorbid conditions such as hypertension, fluid overload, and heart failure, all of which are known to increase the risk of NOAF (Chua et al., 2015). Moreover, COPD has been linked to an increased incidence of in-hospital NOAF following OHS (Almassi et al., 1997; Saxena et al., 2013; Zacharias et al., 2005).

Obesity has also emerged as a significant determinant of in-hospital NOAF following cardiac surgery (Zacharias et al., 2005). In patients undergoing SAVR, a high body mass index (BMI) has been shown to be an independent predictor of in-hospital NOAF regardless of the patient's sex (Bramer et al., 2011). Interestingly, Banach et al. reported that a BMI below 21 kg/m² was associated with an increased risk of NOAF within one week after a mechanical SAVR (Banach et al., 2007). The

association between obesity and AF may be partially explained by the presence of pericardial fat, which has been linked to a heightened risk of arrhythmogenesis (Banach et al., 2007; Thanassoulis et al., 2010).

Furthermore, the occurrence of NOAF within 30 days after SAVR has been independently associated with an increased risk of developing a late AF (Melduni et al., 2015). Similar findings were reported by Park et al. in patients undergoing OHS (Park et al., 2017).

2.3.1.3 Structural- and procedural predictors

Echocardiography plays a crucial role in assessing the risk of AF in patients undergoing SAVR. Tanawuttiwat et al. demonstrated that an increased left atrial (LA) diameter was associated with a higher risk of developing an in-hospital NOAF following a bioprosthetic SAVR (Tanawuttiwat et al., 2014). Similar findings were reported by Park et al. in patients undergoing OHS, where a larger LA diameter was linked to NOAF occurring within 30 days postoperatively (Park et al., 2017). Additionally, Carter-Storch et al. identified an increased LA volume index as an independent risk factor for NOAF within one week after surgery (Carter-Storch et al., 2019). Beyond these conventional echocardiographic parameters, novel indices such as the peak atrial longitudinal strain index have emerged as promising predictors of an in-hospital NOAF risk after SAVR, as highlighted by the findings of Pernigo et al. (Pernigo et al., 2017).

The urgency of the surgical procedure also appears to influence the risk of postoperative arrhythmias. Urgent or emergent procedures are associated with an increased risk of developing a late AF (Ong et al., 2022). Patients undergoing an emergency or an urgent SAVR experience more hemodynamic stress, systemic inflammation, and atrial structural changes, all of which promote atrial electrical instability (Maesen et al., 2011). This risk is further compounded by prolonged stays in the intensive care unit and extended hospitalizations, which also correlate with a higher incidence of an in-hospital NOAF (Almassi et al., 2015).

2.3.1.4 Pathophysiology

The pathophysiology of NOAF is multifactorial and remains incompletely understood. Although several mechanisms have been proposed, the precise processes underlying its onset and persistence following a cardiac surgery are still being elucidated. NOAF is believed to arise from the interaction between transient triggers and a vulnerable atrial substrate, which is shaped by preoperative conditions and surgical remodeling. This environment facilitates two primary arrhythmogenic mechanisms:

ectopic firing due to triggered activity and re-entry, both of which disrupt normal cardiac electrical conduction (Maesen et al., 2011).

Ectopic firing primarily involves dysregulation of calcium (Ca^{2+}) channels. During action potential repolarization, elevated intracellular Ca^{2+} levels can activate the sodium-calcium exchanger, generating a depolarizing current. When combined with autonomic nervous system activation, this process can lead to afterdepolarizations and triggered activity (Andrade et al., 2014; Reilly et al., 2011). These ectopic impulses often originate near the pulmonary veins. While ectopic firing is typically responsible for NOAF in structurally normal atria, re-entry mechanisms are more likely in atria with conduction abnormalities. In such cases, NOAF is exacerbated by structural changes such as fibrosis and reduced conduction velocity, which may already be present before surgery (Gaudino et al., 2023).

Overall, no significant differences in macroscopic inflammation have been observed in the atrial tissue of patients with NOAF compared to those without the arrhythmia (Cosgrave et al., 2006; Garcia et al., 2012). However, patients who develop NOAF tend to exhibit higher preoperative and postoperative white blood cell counts than controls. Moreover, the temporal pattern of AF following cardiac surgery has been shown to correlate with fluctuations in the inflammatory markers (Abdelhadi et al., 2004; Maesen et al., 2011). Elevated preoperative plasma levels of the inflammatory cytokines, such as interleukin-2 and interleukin-6, have also been reported in some studies (Hak et al., 2009; Ucar et al., 2007). In patients undergoing OHS who develop NOAF, higher postoperative levels of high-sensitivity C-reactive protein (hs-CRP) have been observed (Park et al., 2017). Inflammatory mediators are believed to contribute to the development of NOAF by altering atrial electrical activity and promoting conditions favorable to re-entry mechanisms (Ishii et al., 2005). Additionally, the presence of mediastinal blood has been proposed as another potential trigger for NOAF (St-onge et al., 2018).

Elevated levels of reactive oxygen species (ROS) have been observed in the atrial tissue of patients at risk for developing NOAF, contributing to both ectopic activity and the formation of a re-entry substrate (Sovari and Dudley, 2012). ROS production has also been associated with cardiopulmonary bypass and cardioplegic arrest, both of which are known to induce cellular changes in atrial tissue that disrupt normal electrical conduction (Ferreira et al., 2023). Among the various mechanisms of atrial remodeling implicated in the pathogenesis of NOAF, the ROS-generating system, particularly nicotinamide adenine dinucleotide phosphate oxidase, has been identified as a key contributor (Kim et al., 2008).

Furthermore, atrial tissue is subjected to ischemia as a consequence of the surgical techniques employed during OHS. This ischemic stress contributes to mitochondrial dysfunction and increased production of ROS within the atrial myocardium (Jeong et al., 2012). This cascade of events is believed to induce preoperative

alterations in the atrial substrate, which may act as triggers for postoperative AF, ultimately contributing to the development of NOAF (Dobrev et al., 2019).

2.3.1.5 Treatment

The absence of a unified consensus on best practices for managing in-hospital NOAF following cardiac surgery has resulted in considerable variability in clinical approaches. The primary objective in managing in-hospital NOAF is prevention. Amiodarone has demonstrated efficacy in this regard, with several studies reporting favorable outcomes in reducing the incidence of in-hospital NOAF among patients undergoing OHS (Daoud et al., 1997; Yagdi et al., 2003). Consistent with these findings, both the ESC and the ACC guidelines recommend perioperative administration of amiodarone to mitigate the risk of NOAF (Joglar et al., 2024; Van Gelder et al., 2024).

Beta-blockers have also been shown to effectively reduce the incidence of in-hospital NOAF. Furthermore, the combination of beta-blockers with amiodarone has been associated with enhanced preventive efficacy, as demonstrated by Auer et al. (Auer et al., 2004). Alternative treatment strategies include steroids, colchicine, magnesium, and (bi)atrial pacing. However, the current ESC guideline does not recommend these methods because of the lack of scientific evidence for the prevention of NOAF (Van Gelder et al., 2024). Pharmacological therapy is not the only strategy available. A recent randomized controlled trial by Gaudino et al. investigated the impact of posterior left pericardiectomy on the incidence of in-hospital NOAF. The study revealed that this surgical intervention significantly reduced the occurrence of AF following OHS. Notably, among the 223 patients undergoing SAVR, the incidence of NOAF was 18% in those who received posterior left pericardiectomy, compared to 38% in those who did not (Joglar et al., 2024; Van Gelder et al., 2024). As a result, both the ESC and the ACC guidelines now advocate for the use of a concomitant posterior left pericardiotomy to further reduce the incidence of postoperative AF (Joglar et al., 2024; Van Gelder et al., 2024).

In contrast to preventive strategies, evidence suggests that cardioversion may not offer a significant advantage over rate control in the management of an in-hospital NOAF following OHS. Gillinov et al. found no meaningful difference in outcomes between cardioversion and rate control strategies (Gillinov et al., 2016). Furthermore, Kiviniemi et al. reported that patients undergoing SAVR who developed in-hospital NOAF experienced worse outcomes when rhythm control was pursued. Specifically, those treated with electrical cardioversion exhibited more than a two-fold increase in the risk of thromboembolic events and mortality (Kiviniemi et al., 2018). These findings suggest that cardioversion may not always be the most appropriate treatment strategy for in-hospital NOAF. According to the ACC guidelines,

the recommended approach for hemodynamically stable patients with in-hospital NOAF is rate control, with a target heart rate of less than 100 beats per minute. In cases where patients poorly tolerate NOAF, direct current cardioversion combined with antiarrhythmic drug therapy is considered a more appropriate intervention (Van Gelder et al., 2024). These insights underscore the need for a multifaceted treatment strategy that integrates both pharmacologic and surgical approaches to effectively prevent and manage in-hospital NOAF and optimize patient outcomes.

2.3.1.6 Prognosis

In-hospital NOAF has been recognized as an independent risk factor for increased mortality and morbidity following both OHS and SAVR (Filardo et al., 2010; Girerd et al., 2011; Helgadottir et al., 2012). Specifically, Filardo et al. reported that patients who developed an in-hospital NOAF after OHS had a 48% higher risk of mortality compared to those who did not. Moreover, Banach et al. demonstrated that among patients undergoing a mechanical SAVR, the occurrence of NOAF within the first postoperative week was associated with an elevated risk of early postoperative mortality (Banach et al., 2007). Furthermore, a large nationwide study by Kalra et al., which included 122,765 SAVR patients, confirmed that in-hospital NOAF significantly increases the risk of in-hospital mortality (Kalra et al., 2019).

Although the mechanisms by which NOAF contributes to adverse survival outcomes remain unclear, several hypotheses have been proposed to explain its association with late mortality. Patients with NOAF tend to be physiologically frailer. Additionally, NOAF is more frequently observed in sicker patients who have a higher risk of mortality. These conditions can lead to the increased mortality associated with NOAF, although no direct causality between NOAF and higher mortality is necessarily always present (Kalra et al., 2019). However, a study by Swinkels et al. found that among SAVR patients with a mean follow-up of 17.8 years, in-hospital NOAF did not emerge as an independent risk factor for reduced long-term survival (Swinkels et al., 2017). The discrepancy with other literature likely arises because Swinkels et al. studied a lower-risk, isolated SAVR population with very long-term follow-up, where the transient impact of NOAF may have been diminished, and their multivariable analysis may have adjusted away NOAF's independent prognostic significance.

In addition to its impact on mortality, in-hospital NOAF has been associated with other postoperative complications. NOAF is a significant risk factor for ischemic stroke. The risk varies depending on the context in which NOAF occurs, such as during critical illness, infection, or surgery. Though the incidence of NOAF is higher in cardiac surgeries, the relative risk of stroke is significantly more elevated in non-cardiac surgeries. (Lin et al., 2019; Rasmussen et al., 2022). NOAF can lead to

decreased cardiac output and hemodynamic compromise due to the acute loss of atrial systole and rapid ventricular rates. Hemodynamic problems can lead to delayed recovery, and NOAF is associated with prolonged hospital stays (Bosch et al., 2018; Stojadinović et al., 2022). In addition, NOAF has also been associated with an increased risk of ventricular arrhythmias in patients undergoing cardiac surgery, potentially due to shared underlying conditions, such as myocardial stress, inflammation, or autonomic imbalance (Yarlagadda et al., 2024). Patients who develop NOAF are more likely to experience gastrointestinal bleeding compared to those without the arrhythmia (Saxena et al., 2013). This increased risk may be attributed to the use of anticoagulant therapy, which predisposes patients to bleeding events. Moreover, Saxena et al. also observed that among patients undergoing an isolated SAVR, those with in-hospital NOAF had a twofold increased risk of developing new-onset renal failure compared to those without NOAF.

2.3.2 Bleeding

2.3.2.1 Epidemiology

The definition of bleeding has varied significantly across studies and clinical settings. The International Society on Thrombosis and Haemostasis provided an early standardized definition of major bleeding, which has been widely applied in anticoagulation and non-surgical trials (Schulman and Kearon, 2005). For cardiac surgery, the Universal Definition of Perioperative Bleeding was later developed to incorporate procedure-specific parameters, including postoperative chest-tube output, transfusion requirements, and the need for surgical re-exploration (Dyke et al., 2014). To harmonize bleeding endpoints in cardiovascular research, the Bleeding Academic Research Consortium (BARC) proposed a hierarchical classification system ranging from Type 0 (no bleeding) to Type 5 (fatal bleeding). In this system, Type 1 bleeding is minor and not actionable, while Type 2 bleeding is overt and clinically evident, requiring medical attention or hospitalization but not fulfilling criteria for higher grades. Type 3 bleeding is clinically significant and subdivided into 3a (overt bleeding with hemoglobin drop of 3–5g/dL or any transfusion with overt bleeding), 3b (hemoglobin drop > 5 g/dL, cardiac tamponade, bleeding requiring surgery or intravenous vasoactive support), and 3c (intracranial or intraocular bleeding compromising vision). Type 4 bleeding is defined as coronary artery bypass grafting (CABG)–related and includes, for example, reoperation for bleeding or chest-tube output ≥ 2 L within 24 hours. Type 5 refers to fatal bleeding, with 5a indicating probable and 5b definite fatal events confirmed by imaging or autopsy (Mehran et al., 2011). The BARC definition is now widely regarded as a strong and clinically relevant framework due to its clarity, reproducibility, and applicability across diverse

cardiovascular interventions. However, in the context of cardiac surgery, these categories may overlap, as re-operation is often indicated by the clinical presentation of tamponade rather than the quantitative amount of blood loss alone.

Bleeding is one of the most significant complications following SAVR. The incidence and prevalence of major bleeding events following SAVR are influenced by a variety of factors and show considerable variability across studies. Several large-scale studies, including RCTs, have compared a bioprosthetic SAVR with TAVI, providing valuable insights into bleeding outcomes (Adams et al., 2014; Hørsted Thyregod et al., 2024; Jørgensen et al., 2025; Leon et al., 2016; Mack et al., 2019; Makkar et al., 2020; Reardon et al., 2017; Smith et al., 2011; Toff et al., 2022). Additionally, multiple studies have compared mechanical and bioprosthetic aortic valves, reporting differences in bleeding incidence (Chiang et al., 2014; Glaser et al., 2016; Hirji et al., 2018; Kytö et al., 2020, 2019; Rück et al., 2021; Sun et al., 2025). Technical factors that influence bleeding incidence include the duration of follow-up, classification to minor or major bleeding, and whether the bleeding event is classified as short-term or long-term. Additionally, one of the most important factors influencing the incidence of bleeding events is the type of valve implanted, which significantly affects anticoagulation requirements and associated risks. The majority of bleeding events occur particularly among patients receiving anticoagulant or antiplatelet therapy. These medications, while essential for preventing thromboembolic events, substantially affect the risk of delayed bleeding complications.

Moreover, the accuracy of the data on bleeding can vary depending on the study design. Registry-based studies may underreport or inconsistently classify bleeding events, as they are not specifically designed to investigate this outcome. In contrast, RCTs typically define bleeding as a prespecified endpoint, allowing for more rigorous and systematic monitoring (Leon et al., 2016; Mack et al., 2019). Similarly, the retrospective CAREAVR study was explicitly designed to collect data on both stroke and major bleeding events (Lehto et al., 2018). Variability in the definitions and the classification criteria across studies has led to substantial discrepancies in reported findings, particularly with regard to incidence.

Most bleeding complications reported after SAVR are long-term in nature. Overall, the long-term incidence of bleeding following SAVR has been reported to range from 4.9% to 47.0% (Glaser et al., 2016; Leon et al., 2016). Although many of the reported rates are relatively high, recent studies suggest a downward trend in bleeding incidence over time (Daeter et al., 2024; Guimaron et al., 2021). In patients undergoing a bioprosthetic SAVR, early bleeding complications are more readily assessed due to the availability of numerous RCTs comparing early outcomes between a bioprosthetic SAVR and TAVI (Adams et al., 2014; Jørgensen et al., 2024; Leon et al., 2016; Popma et al., 2019; Reardon et al., 2017; Smith et al., 2011; Tchetche et al., 2025; Toff et al., 2022). In contrast, data on early bleeding complications

associated with modern mechanical valve prostheses remain extremely limited. The overall incidence of early major bleeding events in patients with mechanical valves has been addressed in two studies over the past few years (Bouhout et al., 2014; Kytö et al., 2019). No other recent studies have provided detailed information on early bleeding complications following a mechanical SAVR. However, due to methodological differences across studies, including variations in the follow-up duration, the patient populations, and the definitions of bleeding, the overall incidence may not be the most reliable or usable metric for accurately assessing bleeding risk. Since most studies on this topic provide accurate Kaplan-Meier curves for study endpoints, it is possible to estimate both the early risk of bleeding and the annual risk based on this information and graphs. This allows for meaningful comparisons between studies with different follow-up durations. Table 1 compares early and long-term major bleeding and ischemic stroke events after SAVR (Table 1).

In patients undergoing a mechanical SAVR, the risk of early major bleeding events ranges from 0.4% to 2.9% (Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Kytö et al., 2020, 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025). Notably, the risk of bleeding is highest during the initial days following the operation. For instance, in the study by Bouhout et al., approximately 5% of patients undergoing a mechanical SAVR experienced bleeding that necessitated reoperation within 48 hours postoperatively (Bouhout et al., 2014). Subsequently, after the early postoperative period, the risk of bleeding remains relatively stable. During long-term follow-up, the estimated annual incidence of major bleeding ranges from 0.6%/year to 3.8%/year (Bouhout et al., 2014; Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Hirji et al., 2018; Kytö et al., 2020, 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025).

In studies comparing a bioprosthetic and a mechanical SAVR, the risk of early major bleeding events in patients with bioprosthetic valves is similar to that in patients with mechanical prostheses, ranging from 0.4% to 2.9% (Chiang et al., 2014; Goldstone et al., 2017; Kytö et al., 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025). However, in RCTs, comparing SAVR with TAVI, the early bleeding risk in patients undergoing a bioprosthetic SAVR is significantly higher, ranging from 2.4% to 43.4% (Jørgensen et al., 2025, 2024; Leon et al., 2016; Mack et al., 2019). This discrepancy may be explained by the fact that patient populations in TAVI studies tend to be older and have a higher burden of comorbidities, which increases the likelihood of bleeding complications related to surgery. Nevertheless, despite differences in study design and methodology, the risk of major bleeding remains relatively constant after the perioperative period. During long-term follow-up, the estimated annual risk of major bleeding in patients undergoing a bioprosthetic SAVR ranges from 0.3%/year to 1.9%/year (Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Jørgensen et al., 2024; Kytö et al., 2020, 2019; Leon et al., 2016; Mack et

al., 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025; Tchetche et al., 2025). The risk of major bleeding is generally lower in patients with biological prostheses compared to patients with mechanical ones. This has also been consistently observed across multiple studies comparing outcomes between mechanical and bioprosthetic aortic valves, despite differences in study design and methodology (Chiang et al., 2014; Goldstone et al., 2017; Kytö et al., 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025).

While the incidence of bleeding after SAVR can be substantial, patients on long-term oral anticoagulation bear a higher overall risk of major bleeding. Yearly major bleeding rates vary by agent and patient risk, approximately 3.1–3.4% for warfarin and 2.1–3.6% for novel oral anticoagulants, with wider variation according to the CHA_2DS_2-VASc risk profile (Eikelboom et al., 2013; Giugliano et al., 2013; Granger et al., 2011; Patel et al., 2011)

2.3.2.2 Risk factors

Studies have consistently shown that patients who experience major bleeding events following both a mechanical and a bioprosthetic SAVR tend to be older (Bendayan et al., 2020; Goldstone et al., 2017; Hirji et al., 2018; Kytö et al., 2020, 2019; Labaf et al., 2016; Sun et al., 2025). One potential explanation is that older patients are often frailer, which may predispose them to bleeding complications. Bendayan et al. demonstrated that frailty, as measured by the Essential Frailty Toolset, was independently predictive of major bleeding, with an odds ratio (OR) of 1.68 per point (95% CI 1.36–2.09) (Bendayan et al., 2020). In addition, older patients are at increased risk of bleeding due to age-related physiological changes and a higher burden of comorbidities such as CKD. Moreover, polypharmacy is common in this population, and the concurrent use of anticoagulants, antiplatelet agents, and nonsteroidal anti-inflammatory drugs further predisposes them to bleeding complications. Preoperative anemia has also been identified as an independent risk factor for major bleeding in patients undergoing a bioprosthetic SAVR (Généreux et al., 2014). Furthermore, in a study by Labaf et al. involving patients with mechanical aortic valve prostheses, previous bleeding was associated with an increased risk of major bleeding in both univariable and multivariable analyses (Labaf et al., 2016).

Although the definitions of major bleeding events vary across studies (Chiang et al., 2014; Sun et al., 2025), only a limited number of investigations provide detailed reporting on the specific types of bleeding following SAVR. Existing research indicates that gastrointestinal (GI) bleeding is the most common form of major bleeding after SAVR (Bouhout et al., 2014; Brennan et al., 2012; Kytö et al., 2020, 2019; Labaf et al., 2016). Notably, studies by Kytö et al. and Bouhout et al. reported that 26.5% and 39.5% of major bleeding events following a mechanical SAVR,

respectively, were attributable to gastrointestinal bleeding(Bouhout et al., 2014; Kytö et al., 2019). The high prevalence of gastrointestinal (GI) bleeding following SAVR may be partially explained by Heyde's syndrome, a condition characterized by GI bleeding in patients with aortic stenosis (AS). This syndrome results from shear stress-induced degradation of von Willebrand factor (vWF), leading to impaired platelet function and bleeding from fragile angiodysplasia. Although SAVR typically restores vWF levels and reduces bleeding risk, some patients may continue to experience GI bleeding due to persistent angiodysplasia or the ongoing need for anticoagulation therapy (Loscalzo, 2012). Following GI bleeding, intracranial hemorrhage has been reported as the second most common type of major bleeding after SAVR (Bouhout et al., 2014; Kytö et al., 2020, 2019).

In addition, early major bleeding has been associated with significantly increased 1-year all-cause and cardiac mortality compared to patients without bleeding events (Généreux et al., 2014). Similarly, Chiang et al. reported a 30-day mortality rate of 13.2% among patients who experienced major bleeding after SAVR (Chiang et al., 2014). These findings underscore the clinical importance of recognizing and managing early bleeding complications following a bioprosthetic SAVR.

2.3.2.3 Effect of antithrombotics

Bleeding is a well-recognized complication in patients receiving antithrombotic therapy, with those on anticoagulation treatment being at particularly high risk (Wysowski et al., 2007). As previously discussed, lifelong anticoagulation therapy is required following a mechanical SAVR. In contrast, the use of antithrombotic medication after a bioprosthetic SAVR is more nuanced, primarily due to the associated risk of bleeding complications. Current guidelines typically recommend antithrombotic therapy for three months following bioprosthetic valve implantation.

In the study by Gryaznov et al., it was found that patients receiving either antiplatelet or anticoagulation therapy had a significantly higher risk of major bleeding compared to those who received no antithrombotic treatment. This increased risk was evident both during the early follow-up period (less than three months) and in the long-term follow-up. Notably, even monotherapy with either antiplatelet or anticoagulant agents substantially elevated the risk of bleeding (Gryaznov et al., 2020). When comparing various antithrombotic medications, warfarin has been consistently associated with a significantly increased risk of bleeding. In a study by Riaz et al., warfarin use was linked to a higher overall bleeding risk (OR 1.96, 95% CI 1.25–3.08, $p < 0.0001$) and an elevated risk of bleeding within the first three months postoperatively (OR 1.92, 95% CI 1.10–3.34, $p < 0.0001$), compared to aspirin or placebo(Riaz et al., 2016). Similarly, Christersson et al. found that warfarin exposure was associated with a higher incidence of hemorrhagic stroke (HR 1.94, 95% CI

1.07–3.51, p = 0.029) and major bleeding (HR 1.67, 95% CI 1.30–2.15, p < 0.0001) compared to single antiplatelet therapy (SAPT) (Christersson et al., 2019). In an RCT by Rafiq et al., warfarin use was significantly associated with major bleeding (OR 5.18, 95% CI 1.06–25.43, p = 0.043) (Rafiq et al., 2017). In contrast, Brennan et al. reported that warfarin monotherapy was not associated with a higher risk-adjusted incidence of hospital readmission for bleeding compared to aspirin alone. Moreover, the combination of warfarin and aspirin significantly increased bleeding risk (relative risk [RR] 2.80, 95% CI 2.18–3.60, p < 0.0001) (Brennan et al., 2012). Furthermore, Merie et al. observed that patients receiving warfarin therapy had a higher risk of major bleeding during the first three months following SAVR. However, from three to six months postoperatively, no significant difference in bleeding risk was observed between patients with and without anticoagulation therapy (Mérie et al., 2012).

A relatively recent meta-analysis by Uimonen et al. examining antithrombotic therapy following a bioprosthetic SAVR found that all antithrombotic regimens were associated with increased bleeding rates throughout the one-year follow-up period. Notably, between three and twelve months postoperatively, the risk of bleeding was nearly eight times higher in patients receiving combined antiplatelet and anticoagulation therapy compared to those not receiving any antithrombotic treatment (OR 7.76, 95% CI 1.42–42.4) (Uimonen et al., 2024). Although antithrombotic therapy increases the incidence of bleeding complications after a bioprosthetic SAVR, it has been shown that, in most cases of late major bleeding, the indication for antithrombotic treatment is primarily related to underlying comorbidities rather than prophylaxis following valve replacement (Klautz et al., 2021).

Patients undergoing a mechanical SAVR require lifelong anticoagulation therapy, most commonly with warfarin, which, as discussed above, significantly increases the risk of bleeding complications. Although the association between bleeding events and anticoagulation or antiplatelet therapy in patients with mechanical aortic valve prostheses has not been extensively studied, it remains a critical area of investigation. It is well established that elevated international normalized ratio (INR) levels predispose patients to bleeding. However, a study by Labaf et al. found no significant difference in the incidence of major bleeding when comparing different target INR ranges – specifically, 2.0 to 3.0, 2.5 to 3.5, and 2.0 to 4.0 (Labaf et al., 2016).

Further insights were provided by the LOWERING-IT trial, which demonstrated that in patients with mechanical aortic valves receiving coumarin therapy, a lower INR target range of 1.5 to 2.5 was associated with a similar risk of thromboembolic events but significantly reduced the incidence of all types of bleeding compared to conventional anticoagulation regimens (Torella et al., 2010). In addition, the On-X valve, a relatively novel mechanical aortic valve, enables the use of lower INR

targets. This was initially demonstrated in the PROACT trial, which found that the incidence of both major and minor bleeding events was significantly higher in patients with a mean INR target of 2.50 ± 0.63 compared to those with a lower mean INR target of 1.89 ± 0.49 (1.48% vs. 3.26%/patient-year, p = 0.047 for major bleeding, and 1.32% vs. 3.41%/patient-year, p = 0.021 for minor bleeding). Notably, all patients in the trial also received ASA (Puskas et al., 2018). Furthermore, a recent real-world study by Gerdisch et al. involving a five-year follow-up demonstrated improved outcomes in terms of major bleeding among patients maintained on a lower INR target of 1.5 t2.0 in combination with ASA, compared to the PROACT composite control group. These findings were consistent across various patient subgroups, including those managed in real-world settings, those utilizing home-monitoring, and high-risk individuals (Gerdisch et al., 2024). However, no long-term outcome data on this topic that extends beyond 10 years of follow-up are available. Although the results are encouraging, maintaining a lower narrow INR target is challenging. Additionally, when INR values fall outside the lowered therapeutic target, patients are likely to be at high thromboembolic risk.

The quality of the VKA treatment has a crucial role in patient safety. Previous studies have shown that patients with poor VKA treatment quality face significantly increased risks of both bleeding and thromboembolic complications (Grzymala-Lubanski et al., 2014; Havers-Borgersen et al., 2020). Moreover, Lehto et al.'s nationwide cohort study of 1,086 Finnish patients with AF who underwent a mechanical SAVR demonstrated that suboptimal anticoagulation quality, defined as a Time in Therapeutic Range (TTR) below 80% for a target INR of 2.0 to 3.5, was strongly associated with adverse clinical outcomes. Specifically, patients with TTR < 80% experienced nearly twice the risk of major bleeding (adjusted HR 1.97, 95% CI 1.39–2.79, p < 0.001), and patients with more INR drops under 2.0 were at higher stroke risk (adjusted HR/SD 1.22, 95% CI 1.01–1.46, p=0.035) (Lehto et al., 2025).

2.3.3 Ischemic stroke

Stroke following SAVR remains a significant concern, with the potential to profoundly affect patient outcomes and quality of life. Although SAVR is generally effective in alleviating symptoms and extending survival, the risk of stroke continues to be a critical consideration for healthcare providers after both a bioprosthetic and a mechanical SAVR. The incidence of a postoperative stroke varies and is influenced by several factors, including patient age and comorbidities. Due to the inherent thrombogenicity of mechanical valves, patients undergoing SAVR with mechanical prostheses are at an elevated thromboembolic risk. However, as previously discussed, this risk can be mitigated through an appropriate VKA therapy.

2.3.3.1 Epidemiology

The long-term incidence of major stroke following a bioprosthetic SAVR remains notably variable, ranging from 2.4% to 16.4% across studies (Smith et al., 2011; Mérie et al., 2012c; Leon et al., 2016; Mack et al., 2019; Popma et al., 2019; Makkar et al., 2020; Rück et al., 2021; Hørsted Thyregod et al., 2024). Although lifelong VKA treatment is standard of care following a mechanical SAVR, the risk of thromboembolic events persists, with reported long-term incidences of stroke ranging from 3.3% to 14.7% (Bouhout et al., 2014; Brennan et al., 2012; Goldstone et al., 2017; Kytö et al., 2020; Labaf et al., 2016; Rodríguez-Caulo et al., 2023; Sun et al., 2025; Vogt et al., 2022). Notably, Kytö et al. reported a particularly high 10-year ischemic stroke rate of 18.9% in a nationwide mechanical valve cohort(Kytö et al., 2019).

To better describe the stroke risk, it is essential to distinguish between early and long-term stroke incidence following SAVR, as the underlying risk factors and event rates differ substantially. In the early postoperative period, the incidence of ischemic stroke ranges from 0.4% to 6.1% after a bioprosthetic SAVR (Jørgensen et al., 2024; Kytö et al., 2019; Leon et al., 2016; Mack et al., 2019; Madhavan et al., 2023; Popma et al., 2019; Smith et al., 2011; Sun et al., 2025; Tchetche et al., 2025). In patients undergoing a mechanical SAVR, the risk of early ischemic stroke events ranges from 0.3% to 2.3% (Chiang et al., 2014; Glaser et al., 2016; Kytö et al., 2020, 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025). However, only a few studies have provided detailed insights into early stroke rates following a mechanical SAVR (Bouhout et al., 2014; Chiang et al., 2014; Kytö et al., 2019).

During long-term follow-up, the estimated annual risk of ischemic stroke in patients undergoing a bioprosthetic SAVR ranges from 0.3%/year to 2.2%/year (Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Jørgensen et al., 2025; Kytö et al., 2020, 2019; Leon et al., 2016; Mack et al., 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025; Tchetche et al., 2025). In addition, in patients undergoing a mechanical SAVR, the estimated annual incidence of ischemic stroke ranges from 0.4%/year to 1.8%/year (Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Hirji et al., 2018; Kytö et al., 2020, 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025). In addition, silent stroke is prevalent both after SAVR and TAVI. Postoperative MRI findings reveal new cerebral lesions in 38–61% of the patients undergoing SAVR (Grabert et al., 2016). After TAVI, the incidence is even higher, up to 77% (Wu et al., 2025)

The risk of ischemic stroke in patients on OAC therapy is not negligible, similar to the risk of bleeding. Yearly rates of major stroke differ depending on the specific anticoagulant used and the patient's underlying risk factors. For warfarin, the rates range from approximately 1.5% to 2.2%, whereas novel OACs exhibit rates between 1.2% and 1.7%. These rates can vary significantly based on the CHA_2DS_2-VASc risk

profile (Eikelboom et al., 2013; Giugliano et al., 2013; Granger et al., 2011; Patel et al., 2011).

Moreover, numerous studies addressing both a bioprosthetic and a mechanical SAVR provide valuable data on major bleeding in conjunction with major stroke complications. As discussed in this and previous chapters, the majority of available literature emphasizes long-term complications following a bioprosthetic SAVR, while data on early complications after a mechanical SAVR remain relatively limited. Nevertheless, in studies that report both major stroke and major bleeding within the same patient cohort, a consistent trend emerges: the incidence of major bleeding is significantly higher than that of major stroke. This pattern is observed across both mechanical and bioprosthetic valve recipients (Table 1).

While both a bioprosthetic and a mechanical SAVR remain integral to contemporary cardiac surgical practice, their associated risks, particularly those related to stroke and bleeding, require careful consideration to optimize patient outcomes.

Table 1. Comparison of early and long-term major bleeding and ischemic stroke events after SAVR. BIO: bioprosthetic SAVR; MECH: mechanical SAVR.

Reference	Prospective/ Retrospective	Biopros-thetic SAVR (+/-)	Mechanical SAVR(+/-)	Cohort size (n) (BIO/ MECH)	Follow-up time (BIO/MECH) (mean or median)	Annual risk of bleeding (%*) (BIO/MECH)	Annual risk of stroke (%*) (BIO/MECH)	Risk of early bleeding (%*) (BIO/MECH)	Risk of early stroke (%*) (BIO/MECH)	Defination of Major Stroke	Defination of Major Bleeding
Sun et al., 2024	Retro-spective	+	+	n=3508/ n=2254	7.8 years/ 11.0 years	1.2%/ 1.5%	0.5%/ 0.5%	2.3%/ 2.3%	0.7%/ 0.8%	Incident hemor-rhagic or ischemic stroke documented on medical records	Incidence of intracranial hemor-rhage, gastrointestinal bleeding, or hemoptysis during follow-up
Jørgen-sen et al., 2024	Prospec-tive	+	-	n=174/-	1 year/-	0.2%/-	0.1%/-	16.9%/-	1.6%/-	VARC-3	VARC-3
Rodri-guez-Caulo et al., 2021	Retro-spective	+	+	n=911/ n = 1822	8.1 years/ 8.5 years	0.3%/ 0.6%	0.3%/ 0.4%	0.9%/ 0.7%	0.3%/ 0.3%	NA	NA
Kytö et al., 2020	Retro-spective	+	+	n=576/ n=576	6.7 years/ 6.7 years	1.6%/ 2.1%	0.9%/ 1.2%	0.7%/ 0.4%	0.7%/ 0.5%	ICD-10 code I63	ICD-10 codes on intracranial, gas-trointestinal or other major bleeding
Kytö et al., 2019	Retro-spective	+	+	n=3931/ n=296	8.3 years/ 8.3 years	1.9%/ 3.8%	1.5%/ 1.8%	0.4%/ 0.4%	1.1%/ 0.5%	ICD-10 code I63	ICD-10 codes on intracranial, gas-trointestinal or other major bleeding
Popma et al., 2019	Prospec-tive	+	-	n=678/-	2 years/-	1.6%/-	2.8%/-	7.5%/-	1.7%/-	Modified Rankin scale	Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood, or causing hospitalization or permanent injury, or requiring sur-gery and does not meet criteria of life-threatening or disabling bleeding

Mack et al., 2019	Prospec-tive	+	-	n=454/-	1 year/-	1.6%/-	0.8%/-	24.3%/-	2.4%/-	Modified Rankin scale	VARC-2, BARC
Goldstone et al., 2017	Retro-spective	+	-	n=3845/ n=6097	5.0 years/ 8.2 years	1.6%/ 2.3%	2.1%/ 1.0%	2.9%/ 2.9%	2.1%/ 2.1%	IDC-9 codes on is-chemic, hemor-raghic and iatro-genic stroke	ICD-9 codes on intracerebral hem-orrhage, hemopericardium/tapmo-panade, gastrointestinal hemor-rhage,hemoptysis, epistaxis, hemar-throsis, retinal/choroidal hemor-rhage, blood transfusion
Leon et al., 2016	Prospec-tive	+	-	n=1021/-	2 years/-	1.9%/-	1.5%/-	43.4%/-	6.1%/-	At least 2 points on the modified Rankin scale	Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood or causing hospitalization or permanent injury, or requiring sur-gery and does not meet criteria of life-threatening or disabling bleeding
Glaser et al., 2015	Retro-spective	+	+	n=1832/ n=2713	5.0 years/ 8.8 years	0.6%/ 1.1%	0.8%/ 0.7%	0.4%/ 1.0%	0.7%/ 0.7%	ICD-10 codes I21 to I21.9	ICD-10 codes: D629, I60, I61, I62, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922, I312, I230, J942, K661, M250, N421, N501A, N938, N939, N950, R041, R042, R048, R049, R31
Chiang et al., 2014	Retro-spective	+	+	n=1466/ n=2787	10.6 years/ 10.9 years	0.4%/ 0.8%	0.4%/ 0.5%	0.5%/ 0.6%	1.9%/ 1.2%	ICD-9 codes includ-ing ischemic, hemor-raghic and iatrogenic stroke	ICD-9 codes on intracerebral hem-orrhage, hemopericardium or car-diac tamponade, gastrointestinal hemorrhage,hematu-ria, hemarthro-sis, hemoptysis
Brennan et al., 2013	Retro-spective	+	+	n=24410/ n=14789	12.6 years/ 13.2 years	1.0%/ 1.5%	0.8%/ 0.9%	NA/NA	NA/NA	NA	NA

BARC=Bleeding Academic Research Consortium; ICD=International Classification of Diseases; VARC=Valve Academic Research Consortium

2.3.3.2 Risk factors

Similar to major bleeding, advanced age and the presence of multiple comorbidities are key predictors of stroke following SAVR (Agarwal et al., 2015; Idrees et al., 2016). Although the risk of stroke increases significantly with advancing age (Idrees et al., 2016; Labaf et al., 2016), the risk is particularly high in patients over 85 years (Agarwal et al., 2015). This elevated risk is likely attributable to cumulative age-related vascular changes compounded by the burden of comorbid conditions.

Key pre-existing conditions that increase stroke risk after SAVR include diabetes mellitus, hypertension, renal failure, preoperative AF, and a history of prior stroke (Alwaqfi et al., 2024; Heras et al., 1995; Idrees et al., 2016; Labaf et al., 2016; Ruel et al., 2004; Thiagarajan et al., 2017; Udesh et al., 2017). In the study by Andreasen et al., patients who had a stroke within three months before undergoing SAVR faced a 14.7 times higher risk of experiencing a recurrent stroke compared to those without a prior stroke (Andreasen et al., 2018). Additionally, patients with a history of cerebrovascular disease, such as carotid stenosis or cerebral arterial occlusion, are at even greater risk of adverse neurological outcomes (Udesh et al., 2017). Although AF is a well-established risk factor for stroke, Labaf et al. found no significant association between AF and the incidence of stroke or thromboembolism following SAVR (Labaf et al., 2016).

Intraoperative factors also play a critical role in influencing stroke risk during SAVR. Prolonged cardiopulmonary bypass duration and extended aortic cross-clamping times yield a particular risk. Bypass times exceeding 90 minutes have been associated with an increased risk of microembolic events and systemic inflammation, both of which contribute to stroke. Similarly, longer aortic cross-clamping durations are linked to a higher incidence of neurological complications due to ischemia-reperfusion injury. The use of an intra-aortic balloon pump further signifies a heightened perioperative risk profile (Alwaqfi et al., 2024; Biancari et al., 2013). Emergency SAVR procedures are associated with a substantially greater risk of stroke compared to elective surgeries, likely due to limited preoperative optimization and increased hemodynamic instability, as demonstrated by Biancari et al. This study also reported that excessive bleeding requiring transfusion or surgical re-exploration is associated with an elevated stroke risk, potentially due to inflammatory responses and hemodynamic fluctuations (Biancari et al., 2013).

Finally, the CHA_2DS_2-VASc score, traditionally used to assess stroke risk in patients with AF, has demonstrated utility in predicting stroke risk among patients undergoing SAVR. Higher scores are associated with increased rates of stroke and transient ischemic attacks (TIAs), thereby aiding in the preoperative identification of high-risk individuals (Kiviniemi et al., 2019).

Patients who experience a perioperative stroke face nearly a fivefold increase in operative mortality (Thiagarajan et al., 2017). Furthermore, a stroke is associated

with significantly prolonged hospital stays and increased healthcare costs, reflecting the complexity of post-stroke management (Agarwal et al., 2015; Durko et al., 2018; Messé et al., 2014).

Both perioperative and postoperative strokes remain significant complications in patients undergoing SAVR; therefore, minimizing stroke risk is a critical component of perioperative care. Surgical closure of the left atrial appendage (LAAC) can help prevent strokes in patients with AF undergoing cardiac surgery. In a study by Whitlock et al. involving patients with AF who underwent cardiac surgery, LAAC was found to be associated with a 33% reduction in the risk of stroke or systemic embolism over a mean follow-up period of 3.8 years (Whitlock et al., 2021). The current ESC AF guideline recommends (IB) LAAC as an addition for patients with AF who are undergoing SAVR (Van Gelder et al., 2024). The American Heart Association recommends a structured, multidisciplinary approach to stroke prevention. This includes the preoperative assessment of individual risk factors such as advanced age, AF, prior stroke or TIA, and renal dysfunction. Intraoperatively, strategies should focus on maintaining adequate cerebral perfusion, minimizing aortic manipulation through imaging guidance, and ensuring optimal blood pressure and bleeding control. Postoperatively, an early neurological evaluation and prompt imaging are essential for timely stroke detection. Furthermore, immediate access to a multidisciplinary stroke team and the rapid initiation of acute interventions, such as thrombolysis or thrombectomy, are crucial for achieving optimal clinical outcomes (Gaudino et al., 2020).

3 Aims of the study

The main aims of the study were to:

1. Evaluate the incidence of an in-hospital NOAF and its association with the development of a late AF during long-term follow-up in patients undergoing an isolated bioprosthetic and a mechanical SAVR. (Study I)
2. Assess the impact of an in-hospital NOAF on all-cause mortality in patients with an isolated bioprosthetic and a mechanical SAVR. (Study I)
3. Compare the risk of major bleeding and major stroke following a bioprosthetic and a mechanical SAVR. (Study II and III)
4. Analyze antithrombotic treatment strategies and the effectiveness of VKA therapy at the time of major bleeding and thrombotic events, both during the perioperative period and throughout long-term follow-up, in patients with a bioprosthetic and a mechanical SAVR. (Study II and III)

4 Materials and methods

4.1 Study design and patient populations

All three studies (I, II, and III) were retrospective cohort studies conducted as part of the Consortium of Studies in the Field of Atrial Fibrillation, Stroke, and Bleeding in Patients Undergoing Aortic Valve Replacement (CAREAVR; ClinicalTrials.gov Identifier: NCT02626871). CAREAVR is a multicenter retrospective study involving 1073 patients who underwent an isolated SAVR at four Finnish University Hospitals (Helsinki, Turku, Oulu, and Kuopio) between 2002 and 2014 (in Helsinki, from 2006 to 2014). Patients undergoing any additional major cardiac procedures were excluded, including LAAC. In addition, follow-up data for mortality were complete for all patients, while data for other endpoints were available for 1,004 patients (93.6%). In the mechanical patient cohort, all patients were treated with permanent VKAs. However, among them, 22 patients received the On-X valve (CryoLife Inc., Kennesaw, Georgia) and were treated with VKA targeting an INR of 1.5 to 2.0, in combination with ASA 100 mg once daily.

Due to the lack of follow-up data on non-mortality outcomes, patients who underwent a mechanical SAVR at Oulu University Hospital were included only in the mortality analyses of Study I. In Study II, only patients from Turku University Hospital were included. In Study III, all four University Hospitals contributed to the long-term analyses. However, comprehensive data on early postoperative 30-day antithrombotic treatment were available only for patients who underwent an isolated bioprosthetic SAVR at Turku University Hospital. Consequently, other hospitals were excluded from the 30-day postoperative analysis in Study III due to the absence of perioperative antithrombotic treatment data.

The data used in all three studies were retrospectively collected from the electronic patient records of each study hospital. In order to obtain reliable and accurate follow-up data, only patients from the catchment area of each study hospital were included. Additionally, long-term follow-up data were collected directly from the patient records of Turku University Hospital. These records were reviewed using a standardized, structured data collection protocol to extract preoperative, perioperative, discharge, and long-term follow-up data, including NOAF, stroke, TIA, bleeding events, and mortality. To ensure data integrity, an independent, certified third-

party data monitor audited each study site. Data on causes and timing of death were obtained from Statistics Finland, a national authority that tracks mortality across regions, even if patients relocate. This enabled a longer and more complete follow-up for mortality compared to other endpoints. In Study I, the median follow-up time for mortality was 10.4 years (interquartile range [IQR] 6.7–12.5) in the mechanical cohort and 8.4 years (IQR 6.5–10.4) in the bioprosthetic cohort. For other outcomes in the combined cohort, the median follow-up was 5.4 years (IQR 3.4–8.4). In Study II, the median follow-up time for non-mortality outcomes was 7.3 years (IQR 4.2–10.9), and for mortality, 8.8 years (IQR 5.7–12.1). In Study III, the median follow-up time for other outcomes was 4.9 years (IQR 3.0–7.0).

After the exclusion of patients with a prior history of AF, the final cohort of Study I consisted of 529 patients in the bioprosthetic group and 253 in the mechanical valve group. Study II included 308 patients who underwent an isolated mechanical SAVR at the cardiac surgery unit of Turku University Hospital between 2002 and 2014. Study III comprised 721 patients who underwent an isolated bioprosthetic SAVR at four aforementioned Finnish University Hospitals during the same time period as in study II. A subgroup of 227 patients had detailed day-to-day data available on short-term antithrombotic therapy and was included in the analysis of postoperative outcomes during the 30-day perioperative period. In addition, the study populations of studies I–III are presented in Figure 1.

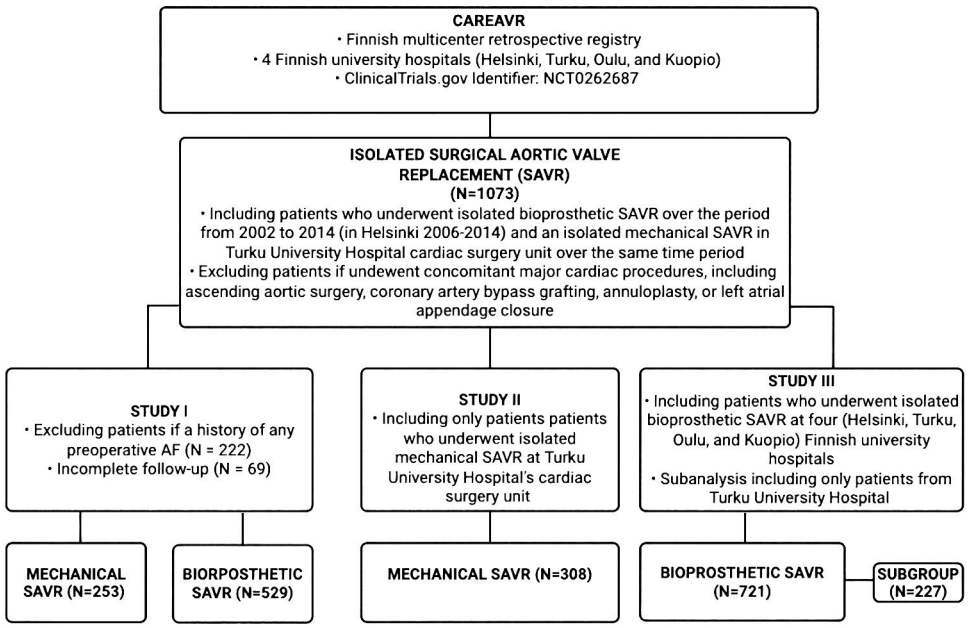

Figure 1. Study population flowchart for Studies I–III. Compiled by Rikhard Björn.

4.2 Outcomes

Study I

The primary outcomes of Study I were the incidence of NOAF during the index hospitalization and the occurrence of a late AF during long-term follow-up. Since the study was retrospective, no protocol-based ECG analysis was performed. Both an in-hospital and a late AF were diagnosed based on an incidental finding or symptoms combined with an ECG or telemonitoring confirming an AF episode. An in-hospital NOAF was diagnosed based on a 12-lead ECG recording or telemonitoring, confirming an AF episode lasting 10 minutes or longer. In-hospital NOAF refers specifically to AF diagnosed at the University Hospital where the SAVR was performed. A late AF was defined as any AF episode occurring after hospital discharge during follow-up, also confirmed by a 12-lead ECG or telemonitoring, with a minimum duration of 10 minutes. The AF episodes that began during the index hospitalization and persisted after discharge were not classified as late AF if sinus rhythm was restored, either spontaneously or through cardioversion, within three months of the index surgery. However, patients who remained in a new permanent AF beyond three months postoperatively were included in the late AF group and classified as having AF after discharge. In addition, atrial flutter was included in the NOAF category, as the general management principles and indications for anticoagulation are the same as for patients with AF. The secondary outcome was late mortality and its association with an in-hospital NOAF.

Studies II and III

The primary outcomes of Studies II and III were the incidence of in-hospital and late major bleeding or major stroke. A major bleeding event was defined as an overt, actionable sign of hemorrhage requiring diagnostic evaluation, hospitalization, or treatment by a healthcare professional, corresponding to BARC types 3 to 5 (Mehran et al., 2011). An ischemic stroke was defined as a permanent focal neurological deficit, adjudicated by a neurologist and confirmed by computed tomography. Major stroke was defined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, excluding lacunar strokes (<20 mm in diameter)(Adams et al., 1993). In addition, the secondary outcomes in Study II included all-cause mortality, as well as the incidence of in-hospital and late AF. The study outcomes of Studies I–III are presented in Figure 2.

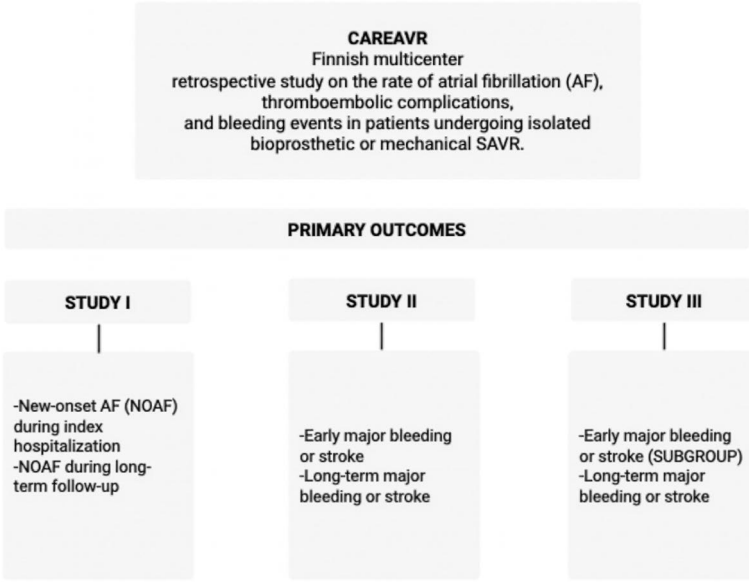

Figure 2. Flowchart of study outcomes in Studies I–III. Compiled by Rikhard Björn.

4.3 Statistical analysis

In Study I, the statistical analyses were performed using SPSS version 25.0 (IBM Corp., Albany, NY) and R statistical software version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). In Study II, all statistical analyses were conducted using R software version 4.1.2, and in Study III, analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). In all studies, continuous variables were reported as mean ± standard deviation for normally distributed data, and as median with interquartile range (25th–75th percentiles) for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test and visual inspection of distribution plots. Categorical variables were presented as absolute counts and percentages.

Study I

For univariable analyses of Study I, the Cox proportional hazards model, unpaired t-test, and Mann–Whitney test were employed, as appropriate. To identify baseline factors associated with AF after hospital discharge, least absolute shrinkage and selection operator Lasso–penalized Cox regression was applied using the R package glmnet (version 3.0-2). The Lasso model that yielded the minimal prediction error based on 10-fold cross-validation was selected. From this model, variables with

penalized β coefficients of ≥0.1 or ≤–0.1 were retained to identify the most relevant predictors.

K-nearest neighbors (KNN) imputation was applied to address missing data in the multivariable models, using all baseline variables as predictors (R package simputation, version 0.2.4). For variables with more than 15% missing data in one or more analysis subgroups, continuous variables were first converted to binary, and an additional factor level of "not applicable" was introduced to account for missingness. Multivariable multilevel Cox regression analyses were used to evaluate the association between AF during the index hospitalization and adverse outcomes (R package coxme, version 2.2-16). Research sites were modeled as separate levels by including the center number as a random effect. To account for differences in the year of study entry across centers, a three-level random intercept model was employed, incorporating the year of entry nested within each research site. The multivariable mixed-effects Cox regression models were adjusted for the following fixed effects: EuroSCORE II, age at the time of surgery, continuation of oral anticoagulation beyond three months postoperatively (in the combined and bioprosthetic cohorts), and prosthesis type (in the combined cohort). To reduce potential bias from perioperative mortality, patients who died within 30 days of surgery were excluded from the mortality analyses.

Study II

In Study II, Pearson's chi-square test and Fisher's exact test were used to analyze associations between preoperative and perioperative medications. Univariable analyses of the baseline characteristics and the operative data were conducted using the Cox proportional hazards model. The proportional hazards assumption for Cox regression was assessed using graphical methods. A multivariable competing risk analysis was performed by including variables with a p-value < 0.10 from the univariable analysis. A p-value < 0.05 was considered statistically significant. Due to the exploratory nature of the study, no corrections for multiple testing were applied.

Study III

To evaluate predictive factors for major complications during the early postoperative 30-day period in Study III, Pearson's chi-square test and Fisher's exact test were employed. For long-term bleeding risk, a multivariable mixed-effects Cox regression model was used, incorporating the site number as a random effect. The model was adjusted for the HAS-BLED score and age at the time of surgery, both treated as fixed effects. Statistical significance was defined as $p < 0.05$. The proportional

hazards assumption was assessed using Schoenfeld residuals. No corrections for multiple testing were applied due to the exploratory nature of the study.

4.4 Ethics

Studies I to III were conducted in accordance with the principles outlined in the Declaration of Helsinki, as revised in 2002. All studies received approval from the Hospital District of Southwest Finland and the Ethics Committee of the National Institute for Health and Welfare (Finland). As the studies were retrospective and observational in nature, informed consent was not required.

5 Results

5.1 Late incidence and recurrence of NOAF after an isolated SAVR (Study I)

In Study I, a total of 333 patients (42.6%) experienced an in-hospital NOAF, while 250 patients (32.0%) developed a late AF during follow-up. In the bioprosthetic cohort, 269 patients (50.9%) had an in-hospital NOAF, and 176 patients (33.3%) developed late AF, corresponding to an incidence rate of 8.82 per 100 person-years. In the mechanical cohort, 64 patients (25.3%) experienced an in-hospital NOAF, and 74 patients (29.2%) developed a late AF after hospital discharge, corresponding to an incidence rate of 5.05 per 100 person-years. Cumulative incidence estimates of late AF after a hospital discharge at 30 days, three months, one year, and five years were 16.8%, 21.4%, 24.6%, and 30.6% in the bioprosthetic cohort, and 12.3%, 15.9%, 17.5%, and 22.7% in the mechanical cohort, respectively. Among patients in the bioprosthetic cohort, a late AF occurred in 137 patients (50.6%) with an in-hospital NOAF (incidence rate 17.6 per 100 person-years) and in 39 patients (15.2%) without an in-hospital NOAF (3.23 per 100 person-years). In the mechanical cohort, a late AF occurred in 31 patients (48.4%) with an in-hospital NOAF (9.55 per 100 person-years) and in 43 patients (22.8%) without an in-hospital NOAF (3.77 per 100 person-years). The cumulative incidence of late AF after hospital discharge, stratified by the presence or absence of in-hospital NOAF, is illustrated in Figure 3 Baseline characteristics and operative data for patients in the combined cohort, stratified by the presence of late AF, are presented in Table 2.

Table 2. Baseline characteristics and operative data of patients who underwent isolated mechanical or bioprosthetic aortic valve replacement with and without atrial fibrillation after hospital discharge. Modified from the original publication I, Table 1.

	AF after discharge (n=250)	No AF (n=532)	HR (95% CI)	P-value
Age	73.0 (66.0–78.0)	70.0 (62.0–77.0)	1.03 (1.02–1.04)	<0.001
Females	125 (50.0%)	262 (49.2%)	1.11 (0.86–1.42)	0.421
Diabetes	30 (12.0%)	91 (17.1%)	0.81 (0.55–1.19)	0.284
Dyslipidemia	135 (54.4%)	259 (48.7%)	1.30 (1.01–1.68)	0.038
Hypertension	180 (72.0%)	330 (62.0%)	1.60 (1.22–2.12)	0.001
Peripheral artery disease	12 (4.8%)	19 (3.6%)	1.46 (0.82–2.61)	0.204
Coronary artery disease	57 (22.8%)	102 (19.2%)	1.34 (1.00–1.80)	0.052
Chronic lung disease	43 (17.3%)	67 (12.6%)	1.40 (1.01–1.95)	0.044
Active smoking	12 (6.1%)	57 (12.4%)	0.49 (0.28–0.89)	0.018
Active or ex-smoker	54 (28.4%)	164 (37.2%)	0.72 (0.52–0.98)	0.039
Body mass index (kg/m2)	27.5 (25.5–31.1)	27.6 (24.6–30.8)	0.99 (0.99–1.01)	0.870
Active endocarditis	8 (3.2%)	23 (4.3%)	0.69 (0.34–1.40)	0.304
Previous endocarditis	5 (2.0%)	15 (2.8%)	0.64 (0.26–1.56)	0.325
Previous venous thromboembolism	4 (1.6%)	9 (1.7%)	1.08 (0.40–2.91)	0.876
Previous stroke or TIA	32 (13.1%)	54 (10.4%)	1.36 (0.94–1.97)	0.106
Previous myocardial infarction	18 (7.2%)	20 (3.8%)	1.80 (1.11–2.92)	0.016
Previous percutaneous coronary intervention	12 (4.8%)	34 (6.4%)	0.87 (0.49–1.56)	0.639
Previous cardiac surgery	14 (5.6%)	29 (5.5%)	1.14 (0.66–1.95)	0.637
EuroSCORE II (%)	1.6 (1.0–2.5)	1.4 (0.9–2.1)	1.02 (1.00–1.05)	0.092
NYHA Class III or more	136 (54.4%)	226 (42.5%)	1.51 (1.18–1.94)	0.001
Left ventricular ejection fraction (%)	60.0 (51.0–69.0)	62.0 (54.0–70.0)	0.99 (0.98–1.01)	0.271
Left atrium diameter (mm)	43.0 (39.0–47.0)	41.0 (36.0–45.0)	1.04 (1.02–1.06)	0.001
Aortic valve peak pressure gradient (mmHg)	81.0 (68.5–99.5)	80.0 (66.0–99.0)	1.00 (0.99–1.01)	0.952
Aortic valve regurgitation	147 (61.0%)	304 (59.4%)	1.03 (0.79–1.33)	0.854
Aortic valve regurgitation degree*	1.0 (1.0–3.0)	1.0 (1.0–3.0)	0.99 (0.83–1.16)	0.812
Mitral valve regurgitation	125 (51.7%)	284 (44.1%)	1.39 (1.08–1.79)	0.011
Mitral valve regurgitation degree†	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.55 (1.19–2.00)	0.001
Pulmonary artery hypertension:				
Moderate to severe (systolic ≥ 31 mmHg)	38 (21.7%)	58 (14.1%)	1.28 (0.89–1.84)	0.184
Severe (systolic ≥ 51 mmHg)	7 (4.0%)	11 (2.7%)	1.02 (0.48–2.19)	0.953
Urgent, emergency or salvage procedure	17 (6.8%)	36 (6.8%)	1.15 (0.70–1.88)	0.588

Pulse	69.5 (61.0–78.0)	68.0 (61.0–77.0)	1.00 (0.99–1.01)	0.739
Valve prosthesis size (mm)	23.0 (21.0–25.0)	23.0 (21.0–25.0)	1.03 (0.97–1.11)	0.345
Preoperative laboratory values:				
EGFR (ml/min/1.73 m^2)	76.2 ± 20.3	79.6 ± 20.4	0.99 (0.99–1.00)	0.025
Postoperative laboratory values:				
EGFR (ml/min/1.73 m^2) minimum	75.3 (55.5–94.0)	78.0 (61.0–99.0)	0.99 (0.99-1.00)	0.004
CK-MB (µg/l) maximum	29.5 (21.0–41.4)	26.5 (19.9–38.9)	1.00 (1.00–1.00)	0.599
NOAF during index hospitalization	168 (67.2%)	167 (31.6%)	3.68 (2.82–4.81)	<0.001
Cardioversion during hospitalization	71 (28.4%)	59 (11.2%)	2.57 (1.95–3.39)	<0.001
Reoperation due to bleeding	21 (8.4%)	41 (7.7%)	1.18 (0.75–1.84)	0.478
Delayed ventilation	21 (8.4%)	45 (8.5%)	1.18 (0.75–1.84)	0.474
Acute de novo dialysis	2 (0.8%)	7 (1.3%)	0.82 (0.21–3.33)	0.790
In-hospital death	1 (0.4%)	11 (2.1%)	1.36 (0.19–9.73)	0.759
Length of hospital stay	9.0 (7.0–11.0)	8.0 (7.0–10.0)	0.99 (0.97–1.01)	0.182

Continuous variables are reported as median (interquartile range (IQR)) or mean ± standard deviation (SD). Values in parentheses are percentages. AF: atrial fibrillation; AVR: aortic valve replacement; CK-MB: Creatinine Kinase-MB; eGFR: Estimated Glomerular Filtration Rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; INR: International Normalized Ratio; NYHA: New York Heart Association; TIA: transient ischemic attack. * Within the patients with aortic valve regurgitation. † Within the patients with mitral valve regurgitation.

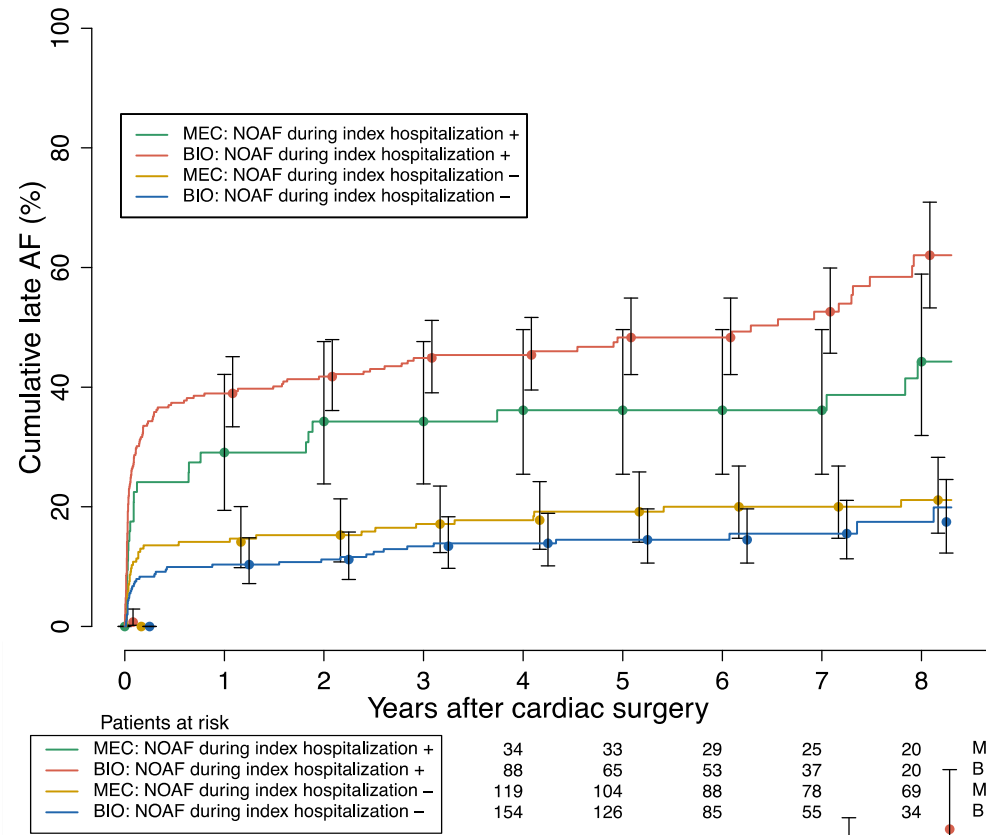

Figure 3. Cumulative incidence of late AF after hospital discharge in patients with and without NOAF during the index hospitalization undergoing isolated aortic valve replacement with a bioprosthesis (BIO) or a mechanical prosthesis (MEC). From the original publication I, Figure 3.

The stable predictors of AF after hospital discharge, identified by Lasso regression analysis with penalized β coefficients ≥ 0.1 or ≤ –0.1, are presented in Table 3 for the combined and separate mechanical and bioprosthetic patient cohorts. In the combined cohort, the multivariable model identified mitral valve regurgitation (MR) grade III or higher and in-hospital NOAF as independent predictors of late AF. Additionally, LA dilatation and moderate to severe renal impairment were associated with an increased risk of late AF in both the combined and bioprosthetic cohorts. Interestingly, smoking emerged as an independent protective factor against late AF in these same cohorts. In the mechanical and combined cohorts, a history of previous myocardial infarction was identified as an independent predictor of late AF. The predictors identified exclusively in the combined cohort included advanced age, hypertension, peripheral artery disease, chronic lung disease, previous stroke or TIA, and shorter hospital stay.

Table 3. The predictors of AF after hospital discharge. Modified from the original publication I, Table 2.

	Mechanical SAVR		Bioprosthetic SAVR		Both cohorts
	β*		β*		β*
Age	NS		NS		0.112
Hypertension	NS		NS		0.115
Peripheral artery disease	NS		NS		0.245
Chronic lung disease	NS		NS		0.153
Active smoking	NS		-0.157		-0.369
Previous stroke or TIA	NS		NS		0.168
Previous myocardial infarction	0.533		NS		0.290
Left atrium dilatation	NS		0.208		0.217
Mitral valve regurgitation degree III or more	0.234		0.490		0.776
Valve prosthesis size (mm)	0.151		NS		NS
Postoperative eGFR minimum <60 ml/min/1.73 m^2	NS		0.182		0.241
NOAF during index hospitalization	0.599		1.115		1.112
Length of hospital stay	NS		NS		-0.106

β, Penalized beta-coefficient; AF: atrial fibrillation; AVR: aortic valve replacement; NYHA: New York Heart Association. * All main effects and interactions with a penalized beta-coefficient ≥0.1 or ≤ –0.1 selected in Lasso regression analysis.

Paroxysmal NOAF during the index hospitalization was not significantly associated with a postoperative major stroke in the combined cohort (HR 1.60, 95% CI 0.99–2.59, p = 0.055), nor in the mechanical (HR 2.11, 95% CI 0.73–6.08, p = 0.168) or bioprosthetic (HR 1.21, 95% CI 0.70–2.08, p = 0.495) cohorts when analyzed separately. However, when evaluating the composite endpoint of a stroke or death, an in-hospital NOAF was significantly associated with an increased risk in the combined cohort (HR 2.40, 95% CI 1.80–3.20, p < 0.001), as well as in the mechanical (HR 1.98, 95% CI 1.07–3.64, p = 0.029) and bioprosthetic (HR 1.88, 95% CI 1.34–2.62, p < 0.001) cohorts, after excluding patients who died within 30 days postoperatively. This association remained significant after adjusting for EuroSCORE II, age at the time of surgery, continuation of oral anticoagulation beyond three months (in the combined and bioprosthetic cohorts), and prosthesis type (in the combined cohort), as well as for center number and year of surgery as random effects. In the adjusted models, the association persisted in the combined (HR 1.57, 95% CI 1.14–2.17, p = 0.006) and bioprosthetic (HR 1.57, 95% CI 1.08–2.28, p = 0.018) cohorts but did not reach statistical significance in the mechanical cohort (HR 1.82, 95% CI

0.95–3.47, p = 0.072). The cumulative incidence of major stroke after an isolated SAVR in patients with an in-hospital NOAF is illustrated in Figure 4.

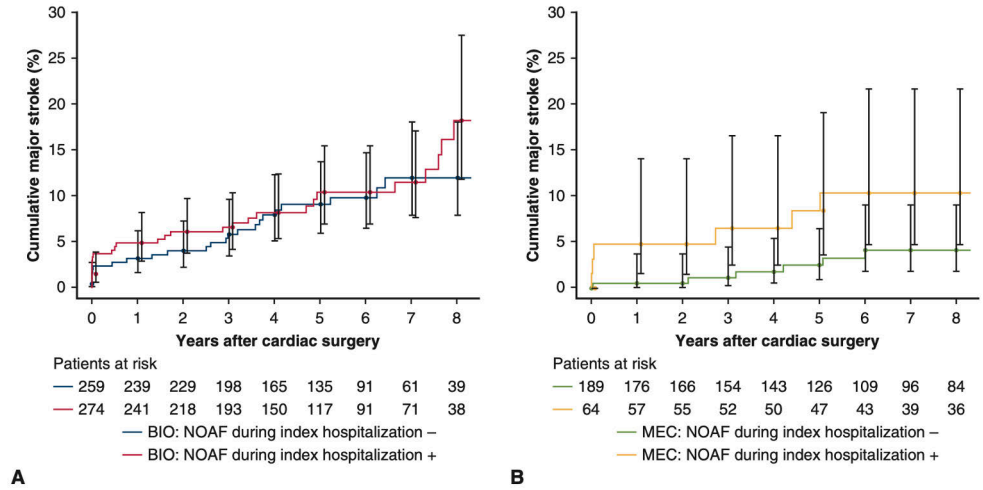

Figure 4. The cumulative incidence of major stroke after an isolated SAVR in patients undergoing (A) a bioprosthetic (BIO) and (B) a mechanical (MEC) valve procedure with no previous AF episodes stratified according to the appearance of NOAF during the index hospitalization. From the original publication I, Figure 2.

Patients who experienced an in-hospital NOAF episode had a significantly higher risk of mortality during follow-up in both the mechanical cohort (HR 2.29, 95% CI 1.26–4.15, p = 0.006) and the bioprosthetic cohort (HR 1.86, 95% CI 1.38–2.51, p < 0.001; Figure 5). This elevated mortality risk persisted in the combined cohort (HR 1.65, 95% CI 1.23–2.21, p < 0.001), as well as in each cohort analyzed separately (mechanical: HR 2.05, 95% CI 1.10–3.82, p = 0.025; bioprosthetic: HR 1.63, 95% CI 1.17–2.28, p = 0.004) even after adjustment for EuroSCORE II, age at the time of surgery, continuation of oral anticoagulation beyond three months postoperatively (in the combined and bioprosthetic cohorts), and prosthesis type (in the combined cohort), as well as for center number and year of index operation as random effects.

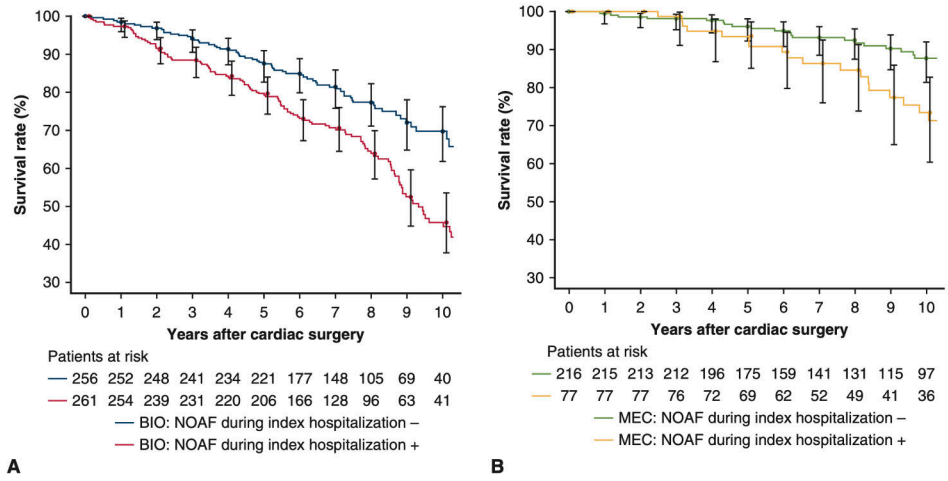

Figure 5. Survival after an isolated SAVR in patients undergoing (A) a bioprosthetic (BIO) and (B) a mechanical (MEC) valve procedure with no previous AF episodes stratified according to the appearance of NOAF during the index hospitalization. Patients alive 30 days after the surgery are included. From the original publication I, Figure 1.

5.2 The incidence of major bleeding and major stroke after an isolated SAVR (Study II, III)

In Study II, which included patients undergoing mechanical SAVR, 19 patients (6.2%) experienced major bleeding events, and four patients (1.3%) experienced major stroke events within the 30-day postoperative period. The median time to a perioperative major bleeding event was 1.0 days (IQR 1.0–11.0), while the median time to diagnose major stroke was 11.5 days (IQR 6.5–15.5) post-surgery. Notably, 78.9% of the perioperative bleeding events were classified as surgical bleedings that necessitated re-exploration. During long-term follow-up, 60 major bleeding events (20.9%) and 12 major strokes (4.0%) were recorded. The cumulative incidence of major bleeding at 30 days, and one, three, and five years, was 6.2%, 7.6%, 13.3%, and 17.3%, respectively. For a major stroke, the cumulative incidence at one, three, and five years was 1.3%, 2.0%, and 3.2%, respectively (Figure 6).

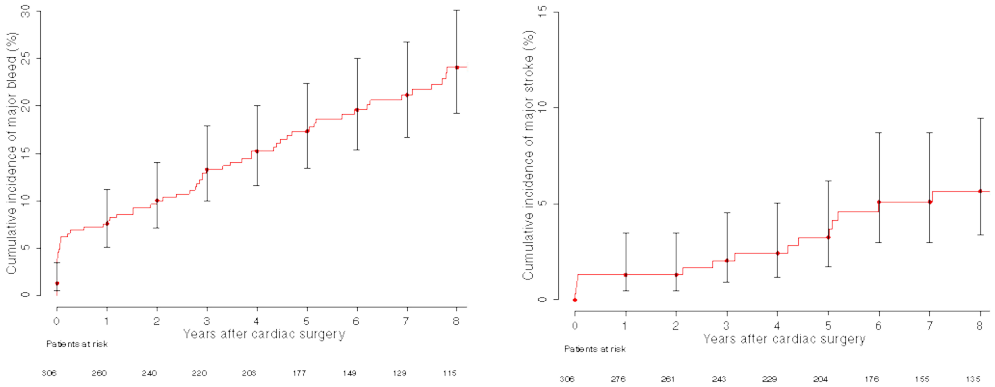

Figure 6. Cumulative incidence of major bleeding and major stroke after an isolated mechanical SAVR. From the original publication II, Figure 3.

After excluding perioperative major bleeding and stroke events occurring within 30 days after the index operation, the incidence rate was 3.1 per 100 patient-years for major bleeding and 0.5 per 100 patient-years for a major ischemic stroke. Notably, the ratio of major bleeding events to major strokes was highest among patients with a CHA2DSVASc score of 1 to 2 (Figure 7).

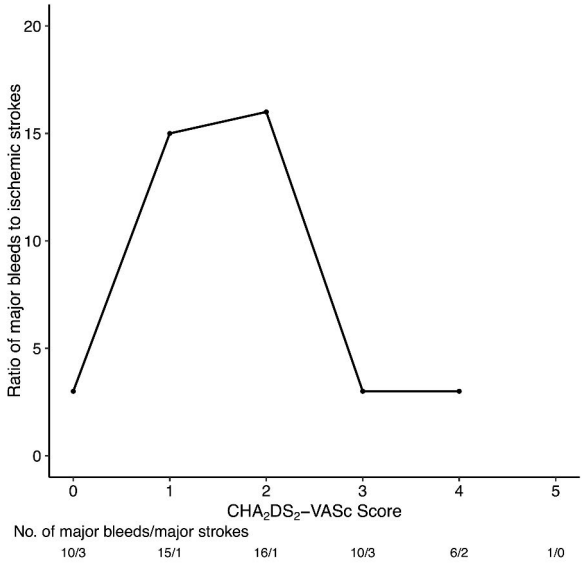

Figure 7. The ratio of major bleeding to major strokes during long-term follow-up in relation to CHA2DS2-VASc score. CHA2DS2-VASc = congestive heart failure; hypertension; age ≥75 (doubled); diabetes mellitus; previous stroke, transient ischemic attack or thromboembolism (doubled); vascular disease; age 65 to 74; sex category (female). From the original publication II, Figure 4.

Considering the other outcomes of Study II, a total of 26 patients (8.5%) received a pacemaker during long-term follow-up, with a median implantation time of 3.0 years after the index operation (IQR 116 days to 7.9 years). Notably, six of these implantations occurred within the first three postoperative days. During the follow-up period, 62 patients died. The survival rates at 30 days, and 1, 5, and 10 years were 96.1%, 95.5%, 91.5%, and 78.3%, respectively. The most common underlying causes of death were coronary artery disease (n = 10, 18.5%) and aortic valve stenosis (n = 10, 18.5%). Nontraumatic intracerebral hemorrhage accounted for one death, and stroke for three deaths. Additionally, seven patients (11.7%) died within 30 days following their first major bleeding event. Although patients who experienced major bleeding events tended to have lower survival rates compared to those who did not, the difference did not reach statistical significance (HR 1.49, 95% CI 0.88–2.50, p = 0.135). Reoperation for bleeding emerged as the sole independent predictor of a major stroke (HR 60.8, 95% CI 11.4–326.1, p < 0.001).

In Study III, which focused on patients undergoing a bioprosthetic SAVR, a subgroup of 227 patients was analyzed. Among them, 31 patients (13.7%) experienced major bleeding, and 13 patients (5.7%) suffered a major stroke within the 30-day postoperative period. Notably, 25 of the 31 bleeding events (80.6%) occurred within two days post-surgery. The median time to major bleeding event was zero days (IQR 0–1 days), while the median time to diagnose major stroke was three days (IQR 1–7 days).

During long-term follow-up, a total of 40 (5.5%) major bleeding events and 47 (6.5%) major stroke events were recorded. The event rates were 1.2 per 100 patient-years for major bleeding and 1.4 per 100 patient-years for major stroke. The cumulative incidence of major bleeding at three months, and one, two, and five years was 0.6%, 1.0%, 2.0%, and 4.4%, respectively.

When comparing risk factors for early versus long-term major bleeding in patients undergoing bioprosthetic SAVR, those who experienced early major bleeding had more frequent preoperative use of adenosine diphosphate (ADP) receptor inhibitors (p = 0.020). In addition, multivariable competing risk analyses in Studies II and III identified several independent predictors of major bleeding during long-term follow-up. In patients undergoing mechanical SAVR, a lower body mass index (BMI) was associated with increased risk (HR 0.93, 95% CI 0.87–0.99, p = 0.021). Among patients undergoing bioprosthetic SAVR, the following factors were associated with higher risk: preoperative hypertension (HR 3.75, 95% CI 1.26–11.3, p = 0.017), preoperative atrial fibrillation (AF) (HR 2.26, 95% CI 1.18–4.34, p = 0.014), previous percutaneous coronary intervention (PCI) (HR 3.03, 95% CI 1.26–7.28, p = 0.013), higher EuroSCORE II (HR 1.08, 95% CI 1.01–1.15, p = 0.019), greater severity of aortic valve regurgitation (HR 1.47, 95% CI 1.03–2.09, p = 0.032), greater severity of mitral regurgitation (MR) (HR 2.39, 95% CI 1.50–3.81, p < 0.001), pulmonary

hypertension (HR 2.90, 95% CI 1.43–5.89, p = 0.003), and longer index hospital stay (HR 1.04, 95% CI 1.01–1.07, p = 0.001). In both Studies II and III, GI bleeding was the most common site of major bleeding during long-term follow-up. Specifically, 25 events (41.7%) in Study II and 17 events (42.5%) in Study III were GI in origin. Additionally, intracranial bleeding accounted for 11 events (18.3%) in Study II and 14 events (35.0%) in Study III.

5.3 The relationship between antithrombotic treatment and major complications (study II, III)

Figures 8 and 9 present the 30-day perioperative anticoagulation treatment and timing of adverse events in patients from Studies II and III. In Study II, during major perioperative bleeding, 26% of patients were on triple antithrombotic therapy, consisting of enoxaparin 40 mg subcutaneously, VKA (mostly below the therapeutic range), and the tail effect of preoperative aspirin. Moreover, over half of the remaining patients were on dual anticoagulation with enoxaparin and VKA. The median INR at the time of major bleeding was 1.6 (1.4–2.4), and for a major stroke, 1.6 (1.2–2.3).

In Study III, within the subgroup of 227 patients with perioperative antithrombotic treatments available, 138 (60.7%) were on preoperative ASA. At the time of perioperative major bleeding events, 17 patients (54.8%) were receiving triple antithrombotic therapy. The median INR at the time of major bleeding was 1.5 (IQR 1.1–2.3), and at the time of a major stroke, 1.3 (IQR 1.0–1.8). Patients who experienced major bleeding were more frequently using adenosine-diphosphate (ADP) receptor inhibitors preoperatively (p = 0.020). The event rate for major bleeding was 3.4 per 100 patient-weeks in those with residual ASA effect during surgery, compared to 2.3 per 100 patient-weeks in those without. Additionally, patients who experienced a major stroke were more likely to have received a 60 mg perioperative dose of LMWH compared to a 40 mg dose (p = 0.002). At hospital discharge, they were also more likely to be on ASA (p = 0.045).

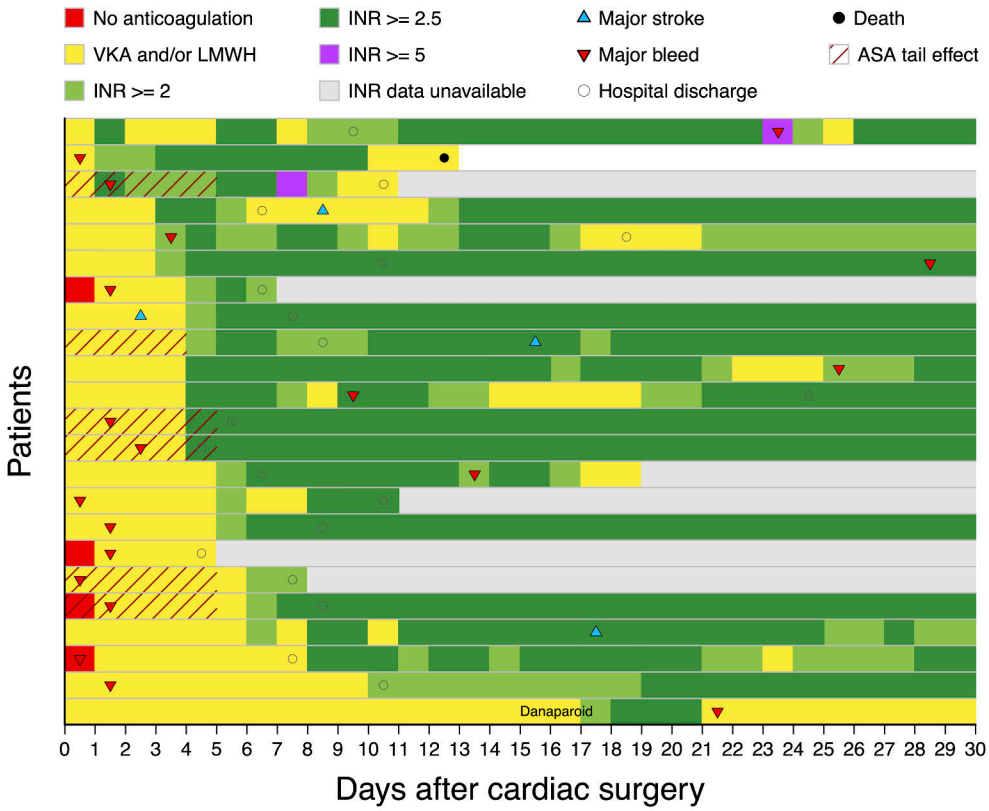

Figure 8. The perioperative antithrombotic treatment of patients experiencing a major stroke or major bleeding within 30 days after a mechanical isolated SAVR. ASA = acetylsalicylic acid; INR = international normalized ratio, LMWH = low molecular weight heparin. From the original publication II, Figure 1.

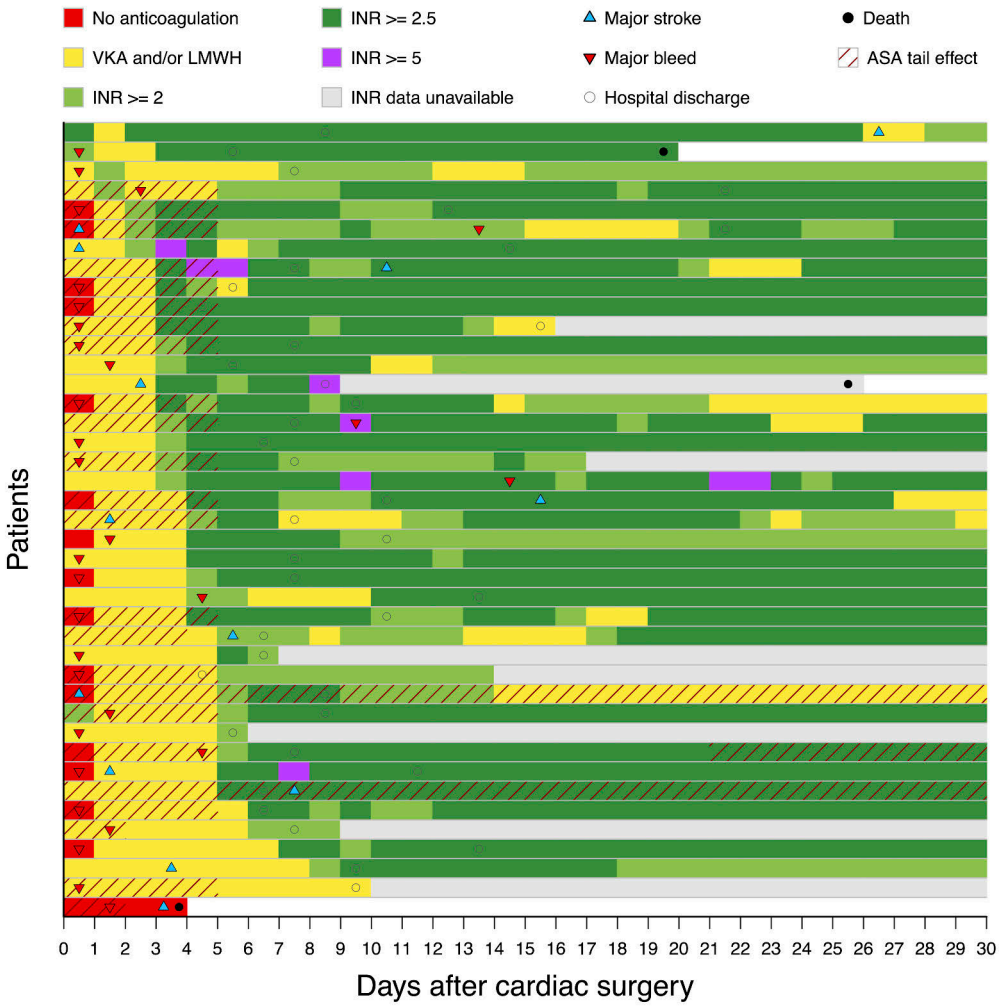

Figure 9. The perioperative antithrombotic treatment of patients experiencing a major stroke or major bleeding within 30 days after a bioprosthetic isolated SAVR. ASA = acetylsalicylic acid; INR = international normalized ratio; LMWH = low molecular weight heparin. From the original publication III, Figure 1.

During the long-term follow-up in Study II, which included 308 patients who underwent isolated mechanical AVR, the median INR at the time of the first major bleeding event was 3.2 (2.5–3.9), with 17 patients (35.4%) presenting an INR >3.5 during the episode. In contrast, the median INR at the time of the first major stroke was 2.1 (1.3–2.9); seven patients (58.3%) had an INR <2.5, and four patients (33.3%) had an INR <2.0. In Study III, most bleeding events occurred in patients receiving VKA treatment, although most of the patients had INR within the target range during the event. During long-term follow-up in Study III, among patients with permanent

OAC continued directly after the routine three-month treatment (n = 207), 23 (11.1%) experienced major bleeding. In contrast, OAC was discontinued after three months in 454 patients, and in 374 of these, it was not re-initiated during follow-up. Among patients without permanent OAC during follow-up, 15 (4.0%) patients experienced major bleeding. Additionally, among the 80 patients who re-initiated OAC after discontinuation at three months, three patients (3.8%) experienced major bleeding. The relationship between OAC and the cumulative incidence of major bleeding is illustrated in Figures 10 and 11. Furthermore, among patients who experienced a major stroke during long-term follow-up, 22 (46.8%) were on OAC at the time of the event.

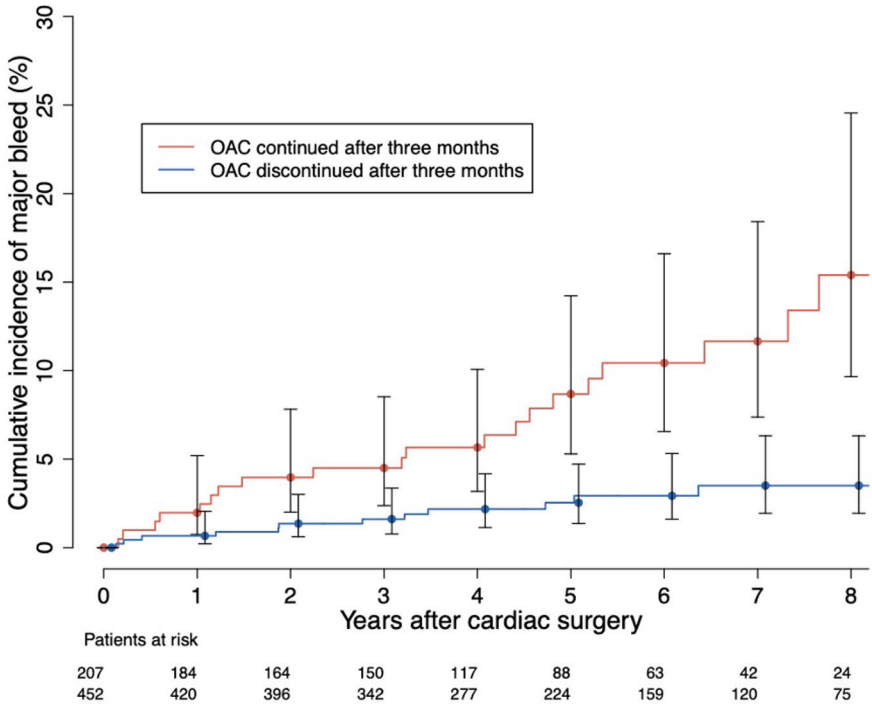

Figure 10. The relation of OAC on the cumulative incidence of major bleeding during the long-term follow-up after an isolated bioprosthetic SAVR. From the original study III, Figure 3.

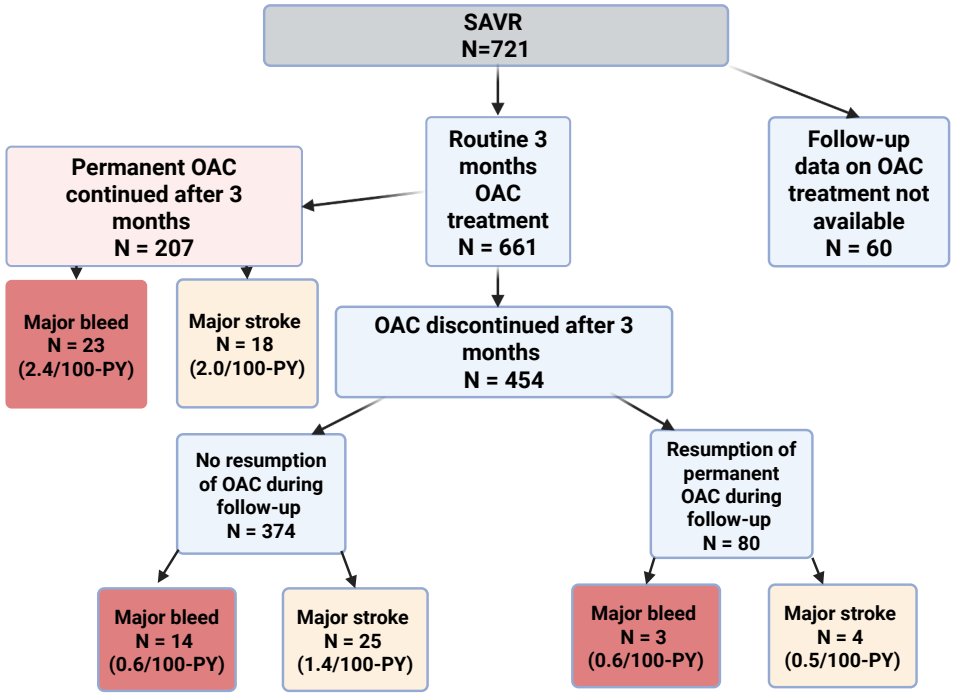

Figure 11. Flowchart of major bleeding events and their relations to OAC treatment after bioprosthetic SAVR. From the original study III, Figure 4.

6 Discussion

6.1 Incidence, recurrence, and prognosis of NOAF

One of the main findings of Study I was that an in-hospital NOAF was strongly associated with a late AF. Both in the bioprosthetic and mechanical patient cohorts, AF occurred in half of the patients with an in-hospital NOAF after hospital discharge. Furthermore, among patients who developed AF during the long-term and detailed follow-up of five years, nearly three-quarters in the bioprosthetic group and almost half of the patients in the mechanical patient group had also experienced NOAF during the index hospitalization. Thus, in both the mechanical and combined cohorts, an in-hospital NOAF appeared to be a strong biomarker of a later AF.

In the bioprosthetic group, the incidence of an in-hospital NOAF was higher than reported in most of the earlier studies (Huckaby et al., 2020; Saxena et al., 2013). However, the incidence of a late AF in this group was consistent with previous findings (Adams et al., 2014; Ashwat et al., 2024; Attia et al., 2022; Hørsted Thyregod et al., 2024; Leon et al., 2016; Makkar et al., 2020; Popma et al., 2019; Smith et al., 2011; Watkins et al., 2025). In the mechanical group, the incidence of an in-hospital NOAF was slightly lower than in earlier studies (Huckaby et al., 2020; Saxena et al., 2013), while the incidence of a late AF remained comparable (Attia et al., 2022; Watkins et al., 2025). Notably, the overall incidence of NOAF both during the index hospitalization and after discharge was high in our study, especially considering that none of the patients had a history of AF prior to surgery. Overall, the incidence of NOAF during the first three months after the surgery seems to be around 16% in patients undergoing a mechanical SAVR and 21% in patients with a bioprosthetic SAVR, respectively. After three months, the risk of NOAF stabilizes, and the estimated annual risk of NOAF in patients with mechanical aortic valve prostheses stays at 1.4%/year and in patients with bioprosthetic aortic valves at 2.0%/year.

Consistent with previous studies, both an in-hospital NOAF and a late AF were more frequent in patients undergoing a bioprosthetic SAVR. This may be attributed to older age and a higher prevalence of comorbidities such as hypertension, diabetes, and coronary artery disease. However, when stratified by the presence of NOAF during index hospitalization, no significant difference between the bioprosthetic and mechanical cohorts was observed (Figure 3). Moreover, the risk of a late AF

developing in patients without an in-hospital NOAF was similar across both groups, regardless of risk factors. This suggests that surgical trauma and the physical stress related to the cardiac surgery trigger NOAF by affecting a vulnerable atrial substrate (Maesen et al., 2011), thereby identifying patients at higher risk for late AF.

Although stroke is a well-known complication of AF, an in-hospital NOAF was not significantly associated with postoperative major stroke in either the combined cohort or the individual cohorts. This may reflect the effectiveness of the VKA therapy in the mechanical SAVR patients with AF, and the appropriate initiation of anticoagulation in the bioprosthetic valve patients upon AF recurrence. However, NOAF emerged as a strong biomarker of all-cause mortality following both a mechanical and a bioprosthetic SAVR. The relative increase in mortality risk was similar in both groups, despite the higher baseline risk in the bioprosthetic group as indicated by EuroSCORE II values. Therefore, an in-hospital NOAF identifies a subgroup of patients at increased long-term mortality risk, likely reflecting the underlying patient risk profile rather than a direct causal effect. This finding aligns with previous studies that have recognized an in-hospital NOAF as an independent predictor of overall mortality following SAVR (Filardo et al., 2010; Girerd et al., 2011; Helgadottir et al., 2012), although those studies included both SAVR and other OHS patients. Compared to these earlier studies, postoperative late mortality in Study I was notably higher. As demonstrated in our study, an in-hospital NOAF following SAVR is associated with an increased risk of both late AF and mortality. These findings underline the importance of identifying patients with NOAF after SAVR, as it indicates a higher overall risk.

Amiodarone and beta-blockers have shown efficacy in reducing the incidence of an in-hospital NOAF (Auer et al., 2004; Daoud et al., 1997; Yagdi et al., 2003). In addition, posterior left pericardiotomy during the operation has been seen to reduce the risk of NOAF (Gaudino et al., 2021). One potential preventive approach in patients undergoing an isolated SAVR is to administer amiodarone and/or beta-blockers to those identified as high-risk based on NOAF predictors. Thus, these patients may be suitable candidates for posterior left pericardiotomy. In addition, if NOAF occurs, it is crucial to ensure comprehensive and effective management and follow-up in these patients to prevent adverse clinical outcomes.

6.2 Predictors of a late AF

In Study I, within the combined patient cohort, increasing age, hypertension, chronic lung disease, previous stroke or TIA, previous myocardial infarction, LA dilatation, MR degree III or higher, postoperative eGFR minimum <60 mL/min/1.73 m², and in-hospital NOAF were identified as independent predictors of AF after hospital discharge. Aging, hypertension, chronic lung disease, LA dilatation, and impaired renal

function have been reported as predictors of NOAF following OHS or SAVR also in previous studies (Banach et al., 2007; Filardo et al., 2010; Girerd et al., 2011; Park et al., 2017; Tanawuttiwat et al., 2014). Additionally, myocardial infarction and MR are well-established risk factors for AF (Van Gelder et al., 2024). It is known that individual susceptibility, particularly genetic predisposition, plays a significant role in the development of AF following cardiac surgery. These genetic factors can trigger a complex cascade of pathophysiological changes within the atrial myocardium, promoting ectopic activity and conduction abnormalities, thereby increasing the likelihood of initiating or maintaining AF (Balouch et al., 2014; Oyen et al., 2012). Patients with other comorbidities, such as the ones mentioned above, are likely to be more vulnerable to these pathophysiological changes in the atrium, leading to the development of AF. As AF is a well-established risk factor for stroke or TIA, it is possible that patients with stroke or TIA may have experienced a paroxysmal undetected AF episode during the cerebrovascular event.

In the bioprosthetic cohort, independent predictors of late AF included LA dilatation, MR degree III or higher, postoperative eGFR minimum <60 mL/min/1.73 m², and in-hospital NOAF. In the mechanical cohort, previous MI, MR degree III or higher, in-hospital NOAF, and valve prosthesis size were identified as independent predictors of AF after discharge. Thus, an in-hospital NOAF was a consistent independent predictor of late AF across the bioprosthetic, mechanical, and combined cohorts. The effect of a larger valve prosthesis size refers most likely to the dilated aortic annulus, as larger prosthetic valves are generally implanted in patients with larger aortic annuli, which have been associated with increased atrial dimensions (Ergül et al., 2023). These anatomical characteristics may necessitate more extensive surgical manipulation and retraction during valve implantation, potentially leading to greater atrial trauma and inflammation.

Interestingly, in the combined cohort, longer hospital stay was identified as an independent protective factor against AF after discharge. Patients who remain hospitalized longer are more likely to be monitored continuously, allowing for early 'in-hospital' detection and treatment of arrhythmias before hospital discharge. However, patients with longer hospital stays may also have higher mortality, causing a potential source of bias. Moreover, in both the combined and bioprosthetic cohorts, active smoking was associated with a lower incidence of late AF. Similar findings have been reported in a few previous studies (Almassi et al., 2015; El-Chami et al., 2010; Mariscalco and Engström, 2009). One possible explanation is that patients predisposed to AF may have experienced smoking-induced paroxysms of AF prior to surgery, leading to their exclusion from Study I.

6.3 Incidence of major bleeding and stroke

Studies II and III demonstrated that the incidence of major bleeding following both a mechanical and a bioprosthetic SAVR was notably higher than that of a major stroke during the early postoperative period. The 30-day postoperative risk of major bleeding was approximately five times higher than that of a major stroke after a mechanical SAVR, and two times higher after a bioprosthetic SAVR. Consequently, approximately one in twenty patients experienced major bleeding within 30 days after a mechanical SAVR, and one in ten after a bioprosthetic SAVR.

As previously discussed, reports of early major bleeding complications following mechanical SAVR are limited, likely reflecting historical variability in definitions and reporting practices, rather than a complete lack of data. Earlier studies often emphasized outcomes such as tamponade or reoperation, and standardized bleeding criteria have only become more prevalent in TAVI vs SAVR comparisons. In the study by Bouhout et al., 5% of patients undergoing mechanical AVR experienced early major bleeding, and 2% experienced an early major stroke (Bouhout et al., 2014), findings that align with those of Study II. In contrast, Kytö et al. reported a cumulative 30-day incidence of 0.4% for major bleeding and 0.5% for a major stroke (Kytö et al., 2020), most likely reflecting the lower sensitivity for bleeding events in epidemiological settings.

More data are available on early bleeding complications after a bioprosthetic SAVR, largely due to randomized controlled trials comparing a bioprosthetic SAVR with TAVI. However, reported bleeding rates vary widely. For example, Kytö et al. reported an early major bleeding incidence as low as 0.4% (Kytö et al., 2019), whereas the PARTNER 2 trial reported a significantly higher 30-day incidence of life-threatening or disabling bleeding at 43.4% (Leon et al., 2016). Consistent with our findings in Study III, the incidence of early bleeding exceeded that of a major stroke in the studies by Popma et al. and Leon et al. (Leon et al., 2016; Popma et al., 2019). Conversely, Merie et al. observed a higher early stroke risk compared to bleeding (Mérie et al., 2012b).

These discrepancies in bleeding incidence are likely attributable to differences in patient populations and the definitions of major bleeding used across studies. Standardizing the definitions would facilitate more accurate comparisons of bleeding outcomes.

Study II showed that one in five patients experienced a major bleeding event during long-term follow-up after a mechanical SAVR. In previous studies, the reported incidence of major bleeding has varied considerably, largely due to differences in the definitions used and variable follow-up times. For example, Kytö et al. reported a 10-year bleeding event rate of 37.0% (Kytö et al., 2019), while Glaser et al. observed a 9.6% incidence over a median follow-up of 15.8 years (Glaser et al., 2016). Compared to Study II, the 5-year cumulative incidence of major bleeding reported

by Chiang et al. and Bouhout et al. was lower (5.0% to 7.9% vs. 17.3%) (Bouhout et al., 2014; Chiang et al., 2014). In contrast, the findings of Goldstone et al. were more consistent with Study II, with a 5-year cumulative incidence of approximately 18% (Goldstone et al., 2017).

Furthermore, in Study II, the rate of major bleeding events was five times higher than that of the major stroke events in mechanical SAVR patients. The ratio of major bleeding to major stroke was higher in Study II than in most previous studies. However, most prior studies have also reported a higher incidence of late bleeding compared to a major stroke. Only in the study by Bouhout et al. was the incidence of a late major stroke comparable to that of major bleeding (Bouhout et al., 2014). In patients undergoing a mechanical SAVR, the risk of early bleeding is slightly higher compared to the risk of an ischemic stroke: 0.4% to 2.9% vs. 0.3% to 2.3%. However, after the early postoperative period, the estimated annual bleeding risk is significantly higher compared to the estimated annual risk of an ischemic stroke: 0.6% to 3.8% per year vs. 0.4% to 1.8% per year (Brennan et al., 2013; Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Kytö et al., 2020, 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025). Although the number of ICHs was similar to that of major strokes in Study II, ICHs are typically weighted more heavily than strokes in net clinical benefit analyses of oral anticoagulation. Therefore, while an ischemic stroke is a well-recognized and feared complication following a mechanical SAVR, these findings suggest that major bleeding may be a more clinically significant concern during long-term follow-up.

In contrast to the findings from the mechanical SAVR population in Study II, Study III – focusing on patients undergoing a bioprosthetic SAVR – demonstrated that the long-term risk of major bleeding was nearly equivalent to that of a major stroke. Similar observations have been reported in previous studies (Chiang et al., 2014; Glaser et al., 2016; Lu et al., 2023; Mérie et al., 2012b), although many earlier reports have indicated a higher risk of bleeding compared to that of a stroke (Goldstone et al., 2017; Kytö et al., 2020; Leon et al., 2016; Mack et al., 2019; Smith et al., 2011; Sun et al., 2025). The reported incidence of bleeding during long-term follow-up has varied widely, ranging from 4.0% to 47.0% (Brennan et al., 2013; Leon et al., 2016; Lu et al., 2023; Mack et al., 2019; Sun et al., 2025), although many of these studies included 30-day bleeding events in their long-term data, potentially inflating the reported rates.

In Study III, approximately 1 in 20 patients experienced major bleeding during long-term follow-up after a bioprosthetic SAVR. Glaser et al. reported comparable findings, with a bleeding incidence of 4.9% and a stroke incidence of 6.1%, although their analysis excluded early postoperative events (Glaser et al., 2016). Overall, beyond the early postoperative period, the estimated annual risk of bleeding becomes more comparable to that of an ischemic stroke, with reported rates ranging from

0.2% to 1.9%/year for bleeding and 0.4% to 2.8%/year for stroke (Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Jørgensen et al., 2024; Kytö et al., 2020, 2019; Mack et al., 2019; Popma et al., 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025).

In the early postoperative phase, patients undergoing a bioprosthetic SAVR face a significantly higher risk of bleeding compared to that of an ischemic stroke, with reported rates ranging from 0.4% to 43.4% for bleeding and 0.4% to 6.1% for stroke. However, in studies directly comparing mechanical and bioprosthetic valves, these risks appear more balanced, with early bleeding rates of 0.4% to 2.9% and stroke rates of 0.3% to 2.1% (Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Kytö et al., 2020, 2019; Rodríguez-Caulo et al., 2023; Sun et al., 2025). The highest early bleeding risks have been reported in studies comparing TAVI with SAVR (Jørgensen et al., 2024; Leon et al., 2016; Mack et al., 2019; Popma et al., 2019).

Taken together with findings from Study II, the results suggest that patients with bioprosthetic aortic valves maintain a favorable long-term balance between major bleeding and stroke, with both complications occurring at relatively low rates.

When comparing Studies II and III, the incidence of major bleeding was higher among patients undergoing a mechanical SAVR. This observation aligns with prior studies that included both mechanical and bioprosthetic SAVR patients (Brennan et al., 2013; Chiang et al., 2014; Glaser et al., 2016; Goldstone et al., 2017; Kytö et al., 2020; Lu et al., 2023; Rodríguez-Caulo et al., 2023; Sun et al., 2025). Although mechanical SAVR patients are typically younger and have fewer comorbidities associated with bleeding risk, they still experience a higher incidence of bleeding complications, likely due to the requirement for lifelong anticoagulation therapy. A more detailed discussion on this topic is provided later in this chapter.

6.4 Predictors of major bleeding and stroke

The only independent predictor of major bleeding events identified in study II including mechanical SAVR patients, was a lower BMI. Prior studies have also reported improved outcomes after cardiac procedures for patients who are overweight or obese (Thourani et al., 2011; van Nieuwkerk et al., 2021). However, these studies primarily focused on coronary artery bypass grafting (CABG) and TAVI, resulting in a scarcity of data regarding the influence of obesity on postoperative bleeding after SAVR. For major strokes, the sole independent predictor was re-operation due to bleeding, explicitly referring to re-operations due to bleeding directly related to the surgical procedure itself, such as anastomotic or prosthetic-site leaks. It should be acknowledged that the term re-operation may also contain procedures performed for other cardiac indications, including coronary bypass surgery or aortic reconstruction. One potential explanation for the increased stroke rates associated with re-

operations is that the anticoagulation treatment for these patients is often paused, leading to an imbalance in the coagulation system that may predispose them to stroke events. In addition, patients undergoing reoperation after SAVR may be more exposed to procedural factors such as prolonged cardiopulmonary bypass and extensive tissue manipulation, which are known to be associated with increased stroke risk in SAVR populations (Alwaqfi et al., 2024).

In study III, the preoperative use of ADP receptor inhibitors was identified as a predictor of early postoperative bleeding following a bioprosthetic SAVR. ADP receptor inhibitors are well-recognized risk factors for major bleeding (Serebruany et al., 2004). In patients receiving proton-pump inhibitors (PPIs), the increased risk of bleeding is likely related to previous postoperative bleeding events; PPIs are often initiated to prevent the recurrence of GI bleeding events. Furthermore, patients who experienced an early postoperative major stroke received higher doses of perioperative LMWH and were more likely to be on ASA therapy at the time of discharge. These differences likely reflect treatment adjustments following the early cerebrovascular event rather than a predisposition to such events. The independent predictors of major bleeding events during long-term follow-up included preoperative hypertension, preoperative AF, prior PCI, higher EuroSCORE II, greater degrees of AR and MR, pulmonary hypertension, and a longer index hospital stay. Hypertension, VKA treatment, and pulmonary hypertension are commonly recognized predictors of bleeding (Opitz et al., 2009; Wysowski et al., 2007). The effect of preoperative AF is likely due to the ongoing requirement for OAC therapy. Although patients with aortic stenosis are known to have a higher risk of bleeding due to Heyde's syndrome (Loscalzo, 2012), no direct association between AR or MR and bleeding has been previously established. One potential explanation for this finding is that heart failure is relatively common in patients with AR or MR, and it is known to increase the risk of bleeding (Ducrocq et al., 2010). Moreover, heart failure is also a prevalent risk factor for AF (Anter et al., 2009).

6.5 Antithrombotic medication and its relation to major complications

As discussed earlier, information regarding complications and their relationship to antithrombotic medication after a mechanical SAVR has been limited. Additionally, despite numerous reports on the occurrence of postoperative complications following a bioprosthetic SAVR, there is a lack of data concerning the timing of antithrombotic treatment in relation to these complications. Study II provided a novel illustration of major complications during the 30-day perioperative period after an isolated mechanical SAVR (Figure 8), which was later followed by a similar illustration in bioprosthetic SAVR patients in study III (Figure 9). As shown in Figure 8, the

majority of early bleeding events after a mechanical SAVR were frequently associated with triple antithrombotic therapy, consisting of enoxaparin 40 mg subcutaneously, oral subtherapeutic VKA, and the residual effect of preoperative exposure to aspirin. Although the patient populations differed between study II and study III, similar findings were observed in the latter with bioprosthetic patients. Furthermore, in study II, a nonsignificant trend was noted correlating the residual effect of aspirin during surgery with perioperative bleeding events. The tail effect of aspirin is known to last from five to seven days (Awtry and Loscalzo, 2000). Without adequate preoperative interruption of aspirin therapy, the residual tail effect may predispose patients to early postoperative surgical site bleeding, which may lead to an increase in major bleeding events and the need for re-exploration. Therefore, properly discontinuing preoperative ASA could potentially lower the risk of early perioperative bleeding. However, these results need to be validated in a larger study, preferably within a prospective randomized framework that incorporates current anticoagulation strategies.

Patients undergoing mechanical AVR require lifelong treatment with VKAs guided by INR. It has been established that in patients receiving VKAs, the risk of bleeding increases exponentially when the INR exceeds 4.5 (Crowther et al., 2009). The most recent international guidelines for managing VHDs recommend targeting a median INR value rather than adhering to a specific therapeutic range. Based on the thrombogenicity of the prosthesis and patient-related risk factors, the recommended median target value for a mechanical aortic valve prosthesis can vary between 2.5 and 3.5 (Otto et al., 2021; Praz et al., 2025).

Previous studies concerning lower target INR therapeutic ranges have consistently demonstrated that a lower target INR is associated with reduced bleeding rates, while the risk of thromboembolic events remains comparable. (Gerdisch et al., 2024; Torella et al., 2010). However, study II revealed that only one-third of bleeding events during long-term follow-up occurred when the INR was higher than the defined therapeutic range. Additionally, most stroke events occurred when the INR was within or above the therapeutic range. Consequently, only a fraction of adverse events could theoretically be prevented through modifications to VKA treatment. Given the exceptionally high occurrence of bleeding, it is evident that the VKA treatment is not the sole contributor to the increased bleeding risk in patients with mechanical aortic valves. For example, Heyde's syndrome, characterized by gastrointestinal bleeding due to angiodysplasia in the context of aortic stenosis, may persist or recur even after a mechanical SAVR, thereby contributing to ongoing bleeding complications (Loscalzo, 2012). However, in a recent study by Lehto et al., a TTR of less than 80% with an INR target of 2.0 to 3.5 was associated with an increased risk of bleeding, while increased time in subtherapeutic INR levels (INR < 2) was linked to a higher incidence of stroke (Lehto et al., 2025). Therefore, the quality of

the VKA treatment undoubtedly plays a role in the development of both bleeding and ischemic events and the quality of the VKA treatment should be of high priority after a mechanical SAVR.

In study III, the majority of major bleeding events during long-term follow-up occurred while patients were undergoing OAC treatment, which was primarily implemented with VKA. The high proportion of VKA use can be attributed to the limited application of NOACs at the time of the study. Although the bleeding risk is likely lower with NOACs (Adeboyeje et al., 2017), it is noteworthy that most major bleeding events in patients treated with VKA occurred when the INR was within the therapeutic range. The current ESC guidelines recommend that after a bioprosthetic SAVR in patients with no indications for OAC, routine treatment with three months of VKA or low-dose ASA should be administered (Praz et al., 2025). Following this three-month period, the use of OACs is contingent upon other clinical indications, such as AF. In patients with AF, NOACs are preferred over VKAs. In the current study, OAC was discontinued after the routine three-month treatment in two-thirds of patients. Among those who continued permanent OAC immediately after this period, 1 in 10 experienced major bleeding, compared to fewer than 1 in 20 among patients who had their OAC discontinued after three months.

While OAC therapy is crucial when there is a clear indication for anticoagulation, these findings underscore the need to avoid anticoagulation of bioprosthetic SAVR patients in borderline indications, such as perioperative or subclinical AF, due to the heightened bleeding risk in this population. Potential preventive strategies, such as long-term PPI therapy, may offer greater benefit to this patient population and should be better investigated and exploited. Moreover, the use of NOACs instead of VKAs is likely to be beneficial also in this patient population. In the mechanical SAVR patients, the prevention of bleeding complications would be of even greater importance. The primary objective of anticoagulation therapy following mechanical valve replacement has been to prevent thromboembolic complications. This focus is evident in European and American guidelines, which, beyond addressing prosthesis selection, surgical technique, and periprocedural antithrombotic strategies, do not provide specific recommendations for preventing major bleeding events (Otto et al., 2021; Praz et al., 2025). Although current antithrombotic regimens are generally effective in minimizing stroke risk when correctly managed, there remains a clear unmet need for strategies aimed at reducing the substantial incidence of severe bleeding. Future guidelines should also focus on assessing bleeding risk in patients with a mechanical SAVR.

Although TAVI is currently the first-line treatment for older patients with aortic valve disease, and its use is expanding among younger populations, mechanical valves remain the preferred option in some instances due to their superior durability compared to biological prostheses. Therefore, biological valve prostheses or TAVI

are not yet suitable for all patient groups. Furthermore, conditions such as infective endocarditis continue to contraindicate TAVI.

6.6 Limitations and strengths

Several factors need to be considered when interpreting the findings of this thesis. The main limitation of studies I–III is the retrospective nature of the CAREAVR data. In Study I, a significant limitation of the study is its single-center setting for outcomes other than mortality. The small size of the patient cohorts is another limitation of this thesis; therefore, these findings should be considered hypothesis-generating. In the study, an important limitation is that the detection of AF after hospital discharge was not based on continuous ECG recording (e.g., Holter or implantable rhythm recorders) but on ECG recordings during the 3- and 12-month follow-up visits and ECGs of symptomatic or otherwise detected AF episodes. Thus, the actual AF occurrence after the surgery is likely higher because some of the asymptomatic AF episodes were most likely missed. In addition, there is a lack of external validation when addressing the predictors of AF after hospital discharge. However, in Study I, the analyses were performed in the combined patient cohort as well as in bioprosthetic and mechanical patient cohorts separately, allowing the critical evaluation of the identified predictors. The additional factors possibly affecting the risk of AF and arising during the follow-up period were unavailable, and therefore, these factors potentially modifying the results could not be analyzed. The baseline differences between the two patient cohorts were inevitable, underlining that the study aimed to compare the effect of NOAF on late AF in selected patients undergoing a mechanical or a biological aortic valve replacement rather than comparing the two valve types.

Although the studies were retrospective, the data were collected from electronic patient records, and data on the baseline, operation, and major outcomes are reported in detail. Only patients from the hospitals' catchment areas were included in the studies to obtain reliable and accurate follow-up data. Also, the patient populations were from regional catchment areas where AF episodes and cerebrovascular events are treated exclusively at the participating centers. In addition, a professional third party monitored the data as quality control of the CAREAVR database. Moreover, data on late mortality were obtained from Statistics Finland, ensuring the quality of survival data of the patients.

7 Conclusions

The following conclusions can be drawn from the present study:

The incidence of NOAF during the index hospitalization and a late AF after a bioprosthetic and a mechanical SAVR is notably high. An in-hospital NOAF is a significant biomarker of late AF after a mechanical and a bioprosthetic SAVR. Additionally, an in-hospital NOAF is associated with increased long-term mortality in both patient cohorts. Patients undergoing SAVR require effective strategies to prevent the onset of NOAF during hospitalization. However, if NOAF develops, it is essential to ensure comprehensive and effective management and follow-up in these patients.

The risk for major bleeding after a mechanical SAVR is fivefold compared to the risk of a major stroke both in the early and long-term follow-up. After a bioprosthetic SAVR, the occurrence of early major bleeding is twofold higher compared to the occurrence of an early major stroke. However, the long-term risk of stroke and bleeding rates are similar after a bioprosthetic SAVR, with bleeding often occurring on OAC. The early postoperative bleeding events often occur in patients with the ASA tail effect present.

The present results suggest that while carefully selected bioprosthetic SAVR patients with NOAF and risk factors for stroke are likely to benefit from permanent OAC, the anticoagulation treatment results in significantly increased bleeding risk. Therefore, while OAC therapy is essential when there is a clear indication for anticoagulation, these findings support the view that OAC use should be avoided in borderline indications, such as subclinical AF, due to the population's high bleeding risk. In mechanical SAVR patients, effective methods to mitigate bleeding risk need to be identified, and future guidelines should better address the prevention of bleeding episodes. Additionally, discontinuing ASA early enough prior to the SAVR is suggested to reduce the risk of early bleeding events, but the benefit of such a protocol needs to be confirmed in randomized settings.

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