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Focus on Left Atrial Appendage Closure and Cardiac Troponin Release in Clinical Practice

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To my family

UNIVERSITY OF TURKU
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ABSTRACT

Oral anticoagulation (OAC) is to date the most effective treatment for ischaemic stroke prevention in atrial fibrillation (AF). However, percutaneous left atrial appendage closure (LAAC) is an emerging alternative for patients with contraindications to OAC, yet the optimal postprocedural antithrombotic treatment and patient selection criteria for LAAC are uncertain. Furthermore, the diagnostic utility of cardiac troponins (cTn) for myocardial infarction is often limited by mildly elevated cTns in AF, but the determinants of cTn release in AF remain incompletely understood. The aim of this thesis was to investigate single antiplatelet therapy after LAAC in patients at high bleeding risk (I), the feasibility of LAAC in AF patients with prior intracranial bleeding and thromboembolism (II), and the impact of heart rate on cTn levels in patients presenting to the emergency department primarily with AF (III).

Percutaneous LAAC followed by single APT was associated with a 73% lower-than-predicted rate of thromboembolism (2.7 per 100 patient-years) than in historical controls. Individually tailored short-term (< 6 months) and long-term single antiplatelet therapy – based on cardiovascular risks – provided similar outcomes in terms of thromboembolism and intracranial bleeding (I). The results also suggest that similar conservative approach was safe in patients with prior intracranial bleeding and thromboembolism (II). Furthermore, high ventricular rate on admission was associated with mildly elevated peak cTn T levels in symptomatic AF patients (III). The association between heart rate and cTn T level was nonlinear and became prominent after exceeding an admission heart rate of 125 beats per minute. Additionally, new-onset AF, the absence of palpitations, old age, low haemoglobin level, decreased kidney function, diabetes, and heart failure were independently associated with cTn T level.

In conclusion, LAAC followed by individually tailored and minimized single APT seems a reasonable strategy for AF patients who have contraindications to OAC, and also for high-risk AF patients with both prior intracranial bleeding and thromboembolism. High ventricular rate in AF should be taken into account when evaluating the diagnostic value of cTn elevation in the emergency department.

KEYWORDS: atrial fibrillation, cardiac troponin, intracranial bleeding, left atrial appendage closure, thromboembolism

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TIIVISTELMÄ

Antikoagulaatiohoito on tehokkain tapa vähentää eteisvärinäpotilaiden aivoinfarktiriskiä. Vasemman eteiskorvakkeen katetrisulku on lupaava hoitovaihtoehto potilaille, joilla antikoagulaatiohoitoa ei voida käyttää. Toistaiseksi on vähän tietoa, miten antitromboottinen hoito optimoidaan eteiskorvakkeen sulun jälkeen ja millaiset eteisvärinäpotilaat hyötyvät eniten toimenpiteestä. Eteisvärinäpotilailla usein havaitut lievästi kohonnet troponiinipitoisuudet sydänlihasvaurion merkkiaineina häiritsevät sydäninfarktidiagnostiikkaa, mutta troponiiniarvoja nostavat tekijät ovat huonosti tunnettuja. Tämän väitöskirjan tavoitteina oli arvioida yhdellä verihiutale-estäjällä toteutetun hoidon turvallisuutta eteiskorvakkeen katetrisulun jälkeen suuren verenvuotoriskin eteisvärinäpotilailla (I) sekä katetrisulkua potilailla, jotka olivat sairastaneet sekä kallonsisäisen verenvuodon että tromboembolisen komplikaation ennen toimenpidettä (II), ja tarkastella syketaajuuden vaikutusta troponiinitasoon eteisvärinän vuoksi päivystykseen hakeutuneilla oireisilla potilailla (III).

Eteiskorvakkeen katetrisulkuun ja yhden verihiutale-estäjän jatkohoitoon liittyi 73 % ennustettua alhaisempi tromboembolisten tapahtumien ilmaantuvuus (2.7/100 potilasvuotta) verrattuna historiallisiin verrokkeihin. Yksilöllisesti sydän- ja verisuonitautiriskien perusteella suunniteltu lyhytaikainen (alle 6 kuukauden) ja pitkäaikainen verihiutale-estohoito tuottivat samanlaiset seurantatulokset tromboembolisten komplikaatioiden ja kallonsisäisten verenvuotojen osalta (I). Tämäntyyppinen yksilöllisesti kevennetty hoitotapa osoittautui myös turvalliseksi eteisvärinäpotilailla, jotka olivat toipuneet aiemmasta kallonsisäisestä verenvuodosta ja tromboembolisesta komplikaatiosta (II). Päivystykseen hakeutuneilla potilailla nopea eteisvärinän kammiovaste oli yhteydessä lievästi kohonneisiin troponiini T:n pitoisuuksiin (III). Sykkeen ja troponiini T:n välinen yhteys oli epälineaarinen ja sykkeen troponiinitasoa nostava vaikutus tuli selkeimmin esiin vasta kammiovasteen ylittäessä 125/min.

Eteiskorvakkeen katetrisulku yhdessä yksilöllisesti suunnitellun verihiutale-estohoidon kanssa vaikuttaa järkevältä hoitovaihtoehdolta potilaille, joilla on vasta-aiheita antikoagulaatiohoidolle ja ovat erityisen korkeassa tromboembolisten komplikaatioiden riskissä. Eteisvärinän nopea kammiovaste tulisi ottaa huomioon arvioitaessa troponiinipäästön diagnostista merkitystä päivystyksessä.

AVAINSANAT: eteisvärinä, tromboembolia, troponiini, kallonsisäinen vuoto, eteiskorvakkeen sulku

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Abbreviations

AF	atrial fibrillation
APT	antiplatelet therapy
ASA	acetylsalicylic acid, or aspirin
bpm	beats per minute
$CHADS_2$	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischaemic attack
CHA_2DS_2-VASc	congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack or thromboembolism, vascular disease, age 65–74 years, and sex category (female)
CI	confidence interval
cTn	cardiac troponin
DRT	device-related thrombus
ECG	electrocardiogram
HAS-BLED	hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs and/or alcohol concomitantly
HR	hazard ratio
hs-cTn	high-sensitivity cardiac troponin
ICD-10	International Classification of Diseases, Tenth Revision
IQR	interquartile range
LAA	left atrial appendage
LAAC	left atrial appendage closure
NOAC	non-vitamin K antagonist oral anticoagulant
OAC	oral anticoagulation
TIA	transient ischaemic attack
VKA	vitamin K antagonist

List of Original Publications

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

I Pouru, J.-P., Jaakkola, S., Lund, J., Biancari, F., Saraste, A., & Airaksinen, K. E. J. (2019). Effectiveness of only aspirin or clopidogrel following percutaneous left atrial appendage closure. *The American Journal of Cardiology*, 124(12), 1894–1899. DOI: 10.1016/j.amjcard.2019.08.050

II Pouru, J.-P., Lund, J., Jaakkola, S., Vasankari, T., Biancari, F., Saraste, A., & Airaksinen, K. E. J. (2020). Percutaneous left atrial appendage closure in patients with prior intracranial bleeding and thromboembolism. *Heart Rhythm*, 17(6), 915–921. DOI: 10.1016/j.hrthm.2020.01.028

III Pouru, J.-P., Jaakkola, S., Biancari, F., Kiviniemi, T. O., Nuotio, I., & Airaksinen, K. E. J. (2020). Association of heart rate with troponin levels among patients with symptomatic atrial fibrillation. *JAMA Network Open*, 3(9), e2016880. DOI: 10.1001/jamanetworkopen.2020.16880

1 Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting one in three older adults during their lifetime (Weng et al., 2018). The arrhythmia is not usually acutely life threatening, yet it is a treacherous disease associated with an increased risk of ischaemic stroke, impaired quality of life, frequent hospitalizations, and excess mortality (Hindricks et al., 2021). An even greater burden of AF and its complications on healthcare resources is expected given the number of individuals with AF is projected to more than double in the first half of the 21st century in the US and Europe (Go et al., 2001; Krijthe et al., 2013). Therefore, there is an increasing demand for effective management of AF patients.

Oral anticoagulation (OAC) reduces the risk of ischaemic stroke by approximately two-thirds and is the cornerstone of AF treatment (Hindricks et al., 2021). However, AF patients at high risk of bleeding, such as those with a recent intracranial bleeding, are frequently without adequate thromboprophylaxis (Pennlert et al., 2015), or receive anticoagulants at the possible cost of excess bleeding (Majeed et al., 2010). According to the current guidelines, percutaneous left atrial appendage closure (LAAC) may be considered for the prevention of thromboembolic events in AF patients with contraindications for long-term anticoagulation, although randomized data in these patients are lacking (January et al., 2019; Hindricks et al., 2021). Moreover, the optimal antithrombotic treatment strategy following LAAC for these high-risk patients is undefined (Glikson et al., 2020).

Cardiac troponins (cTn) are the biomarkers of choice in the rule-in and rule-out diagnosis of acute myocardial infarction (Collet et al., 2021). However, elevated cTn levels are frequently observed in patients presenting primarily with AF to the emergency room (Parwani et al., 2013; Gupta et al., 2014; Kaura et al., 2020). Considering that symptomatic episodes of AF are a common cause of emergency department visits and subsequent hospitalization (Rozen et al., 2018), the differential diagnosis of elevated troponin levels in AF is clinically important. However, determinants of cTn release in AF are largely unknown.

In order to further improve the current practises, a better understanding of the pitfalls and challenges in AF treatment and management is necessary. Therefore, this

thesis focuses on several special present-day challenges in the management of AF. First, as the optimal postprocedural antithrombotic treatment after LAAC has not been established, this study investigated abbreviated single antiplatelet therapy (APT) post-LAAC in AF patients at high risk of bleeding. Second, this study examined the clinical outcome after LAAC in AF patients with a previous intracranial bleeding and thromboembolic event. Third, patients presenting to the emergency department with a primary diagnosis of AF were studied to assess the interplay between heart rate and troponin release in AF.

2 Review of the Literature

2.1 Atrial fibrillation

2.1.1 Diagnosis and classification

AF is a supraventricular tachyarrhythmia which is characterized by rapid and uncoordinated atrial activity. The chaotic atrial activity results in a loss of atrioventricular synchrony, and thus, irregular and rapid ventricular contractions. A standard 12-lead electrocardiogram (ECG) documentation is the golden standard in the diagnosis of AF. Uncoordinated atrial electrical activations result in the following distinctive and diagnostic features of AF: (1) absence of distinct P waves; (2) irregular atrial activity; and (3) irregularly irregular RR intervals. The European Society of Cardiology recommends either a single-lead ECG of at least 30 seconds or a standard 12-lead ECG recording to establish the clinical diagnosis of AF. (Kirchhof et al., 2016; Hindricks et al., 2021)

The classification of AF is based on its clinical presentation (January et al., 2014; Kirchhof et al., 2016; Hindricks et al., 2021). Over the course of time, AF progresses from short to longer and from odd to frequent episodes, and annually approximately 7 % of patients with paroxysmal AF develop persistent or permanent AF (Blum et al., 2019). By definition, paroxysmal episodes terminate within 7 days while persistent episodes last over 7 days. In permanent AF, restoration of sinus rhythm is not pursued. Table 1 summarizes the current nomenclature adapted from the American and European AF guidelines.

Clinically AF can present with a wide range of symptoms or even with no symptoms at all. The most common symptoms include palpitations, chest discomfort, fatigue, dizziness, dyspnoea, and exercise intolerance (Nabauer et al., 2009; Freeman et al., 2015). However, almost half of the patients with diagnosed AF are asymptomatic (Akao et al., 2013; Boriani et al., 2015; Freeman et al., 2015), or up to 90% of patients with new-onset atrial high rate episodes (Diederichsen et al., 2019). Moreover, among symptomatic patients, asymptomatic episodes of paroxysmal AF may occur (Page et al., 1994; Israel et al., 2004; Verma et al., 2013).

Table 1. Clinical classification of atrial fibrillation (AF) according to the AHA/ACC/HRS and ESC guidelines.

Term	Definition
First diagnosed AF	New-onset AF that has not been previously diagnosed
Paroxysmal AF	AF that terminates within 7 days with or without intervention
Persistent AF	AF that lasts longer than 7 days
Long-standing persistent AF	AF sustained over 12 months
Permanent AF	AF is accepted and no interventions are pursued to restore sinus rhythm

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society. Modified from (January et al., 2014; Hindricks et al., 2021).

However, regardless of symptoms, patients with AF are at an increased risk of adverse events, in particular ischaemic stroke (Martinez et al., 2014; Jaakkola et al., 2016). As the severity of these symptoms varies, the European Heart Rhythm Association has introduced a scale to quantify symptoms and to aid physicians in choosing strategies to alleviate symptoms (Table 2) (Wynn et al., 2014).

The differential diagnosis of AF includes other supraventricular arrhythmias, such as atrial flutter and atrial tachycardia. Atrial flutter merits a brief mention as it shares predisposing factors with AF and often coexists with or precedes AF. However, the electrophysiological mechanism of atrial flutter is distinct from AF, and usually involves a macro re-entrant circuit with an atrial rate of 240–300 beats per minute (bpm). Nevertheless, atrial flutter is also associated with an increased risk of ischaemic stroke, and therefore, the recommendations for ischaemic stroke prevention in patients with AF are also applicable in atrial flutter (January et al., 2014; Hindricks et al., 2021).

Table 2. The modified EHRA classification of symptoms related to atrial fibrillation.

EHRA score	Symptoms	Description
1	None	No symptoms
2a	Mild	Normal daily activities not affected, not troubled by symptoms
2b	Moderate	Normal daily activities not affected, troubled by symptoms
3	Severe	Normal daily activities affected
4	Disabling	Normal daily activities discontinued

Abbreviation: EHRA, European Heart Rhythm Association. Modified from (Wynn et al., 2014).

2.1.2 Epidemiology, burden, and impact of atrial fibrillation

The prevalence of AF is higher among men than women and increases substantially with advancing age. In 2019, the global prevalence of atrial fibrillation (AF) and flutter was estimated to be 59.7 million or 0.7% of the total population (Vos et al., 2020). In a German cohort of 8.3 million individuals, the prevalence of AF was 2.4% in men and 1.9% in women, and increased from < 0.5% in individuals aged under 50 years to > 10% in those age 75 years or older (Wilke et al., 2013). Figure 1 illustrates the relationship between age and AF prevalence in selected studies (Go et al., 2001; Jeong, 2005; Heeringa et al., 2006; Stefansdottir et al., 2011; Wilke et al., 2013).

The prevalence of AF has been increasing drastically, and in the last decade alone, the estimated global prevalence of AF and atrial flutter increased by approximately 30% (Vos et al., 2020). The trend is expected to continue for decades to come, possibly owing to ageing of the population, better recognition of AF, and rising life expectancy by virtue of enhanced management of cardiovascular and other comorbidities (Stefansdottir et al., 2011; Chugh et al., 2014; Schnabel et al., 2015). In Europe, the number of adults aged 55 years and older with AF is expected to more than double from 8.8 million in 2010 to 17.9 million by 2060 (Krijthe et al., 2013). Likewise, in the US, the number is projected to increase from 2.3 million in 2000 to 5.6 million by 2050 (Go et al., 2001).

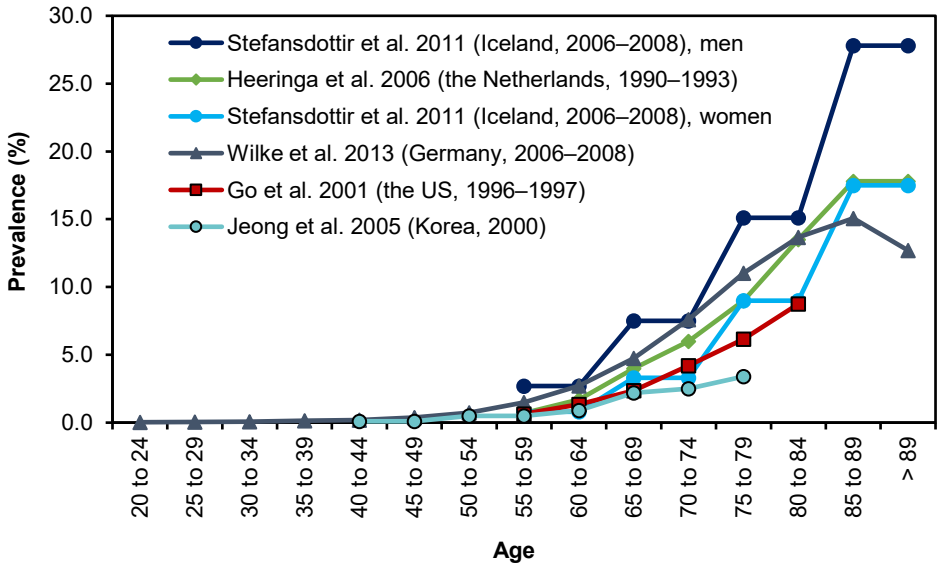


Figure 1. The prevalence of atrial fibrillation stratified by age-groups in selected epidemiological studies. Data from (Go et al., 2001; Jeong, 2005; Heeringa et al., 2006; Stefansdottir et al., 2011; Wilke et al., 2013).

The incidence of AF also increases with age and is higher among men than women. The estimated global incidence of AF is approximately 40–70 per 100 000 person-years translating into an estimated 3–5 million new cases annually (Chugh et al., 2014; Vos et al., 2020; Lippi et al., 2021). To keep things in perspective, the lifetime risk of developing AF is estimated to be 1 in 3 to 4 adults older than 40–55 years of age (Lloyd-Jones et al., 2004; Heeringa et al., 2006; Weng et al., 2018). In a German study, the overall incidence of AF per 1000 person-years was 4.4 in men and 3.9 in women (Wilke et al., 2013). In the Rotterdam Study, a Dutch prospective cohort study, the incidence rate per 1000 person-years was 11.5 in men and 8.9 in women aged 55 and older (Heeringa et al., 2006). Figure 2 illustrates the relationship between age and AF incidence in selected studies (Heeringa et al., 2006; Stefansdottir et al., 2011; Piccini et al., 2012; Wilke et al., 2013).

The estimated global incidence of AF has increased from 1.8 million cases in 1997 to 4.7 million cases in 2019 (James et al., 2018; Vos et al., 2020; Lippi et al., 2021), with more than twice as high incidence in developed than in developing countries (Chugh et al., 2014). Among US Medicare beneficiaries aged 65 and older, AF incidence remained relatively stable from 1993 to 2007 (0.2% annual change) and was 33.9 per 1000 person-years in men and 24.7 per 1000 person-years in women in 2007 (Piccini et al., 2012). In the Framingham Heart Study, an ongoing American cohort study, the age-adjusted incidence of AF per 1000 person-years increased from 3.7 to 13.4 in men, and from 2.5 to 8.6 in women aged 50 and older, over the course of 50 years (Schnabel et al., 2015). However, when analyses were

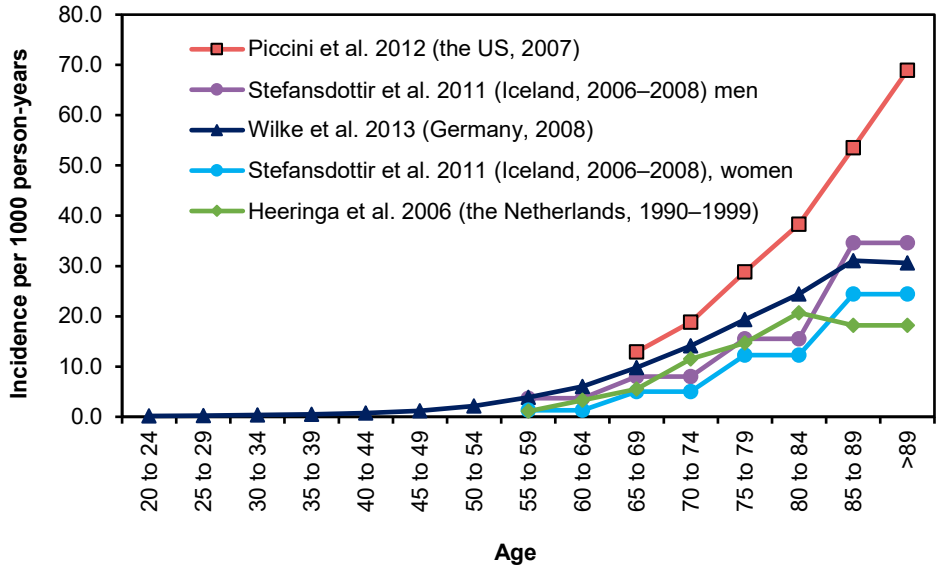


Figure 2. The incidence of atrial fibrillation stratified by age-groups in selected epidemiological studies. Data from (Heeringa et al., 2006; Stefansdottir et al., 2011; Piccini et al., 2012; Wilke et al., 2013).

restricted to the cases confirmed by ECG during scheduled clinical visits, the trend was no longer significant (Schnabel et al., 2015). Therefore, besides population ageing, improvements in recognition and surveillance of AF could contribute to the observed trend.

The most prevalent concomitant diseases in AF patients include hypertension, heart failure, valvular heart disease, coronary artery disease, and diabetes, to name a few (Nieuwlaat et al., 2005; Nabauer et al., 2009; Steinberg et al., 2017). Evidence from prospective cohort studies have identified several risk factors for AF development, such as older age, male sex, hypertension, and prevalent cardiovascular disease (Schnabel et al., 2015; Kirchhof et al., 2016). In a prospective US cohort of middle-aged adults, elevated blood pressure was the most important determinant of incident AF with a population attributable factor of 17–27% (Huxley et al., 2011). Moreover, 57% of incident AF could be explained by hypertension, overweight, smoking, pre-existing cardiac disease and diabetes (Huxley et al., 2011). In addition, genetic factors explain a certain degree of AF susceptibility (Christophersen et al., 2009; Choi et al., 2020). Notably, many risk factors predisposing to incident AF are also associated with AF-related complications, namely ischaemic stroke and heart failure, and therefore, the management of cardiovascular risk factors and AF-associated comorbidities is an integral part of the comprehensive treatment of AF (Hindricks et al., 2021).

The association between AF and the risk of cardiovascular and all-cause mortality is well established. Approximately 1 in 4 older adults (median age 80) with incident AF die within a year after the diagnosis (Piccini et al., 2012). In a Swedish cohort study, AF was associated with a 1.6-fold increase in all-cause mortality, a 2.4-fold increase in death from myocardial infarction, and a 2.6-fold increase in death from heart failure compared with the general population (Friberg et al., 2007). In a large meta-analysis of over 4.3 million individuals, AF was significantly associated with a 1.7-fold increased risk of all-cause mortality in women, and a 1.5-fold increased risk in men (Emdin et al., 2016).

Furthermore, AF is a common cause for emergency department visits, and is also associated with cardiovascular as well as non-cardiovascular hospitalizations. In the US, 60–70% of patients visiting the emergency department for AF are eventually admitted to the hospital (Rozen et al., 2018). Overall, 1 in 3 AF patients have at least 1 hospitalization annually (Kim et al., 2011; Christiansen et al., 2013; Steinberg et al., 2014). A nationwide cohort study from Denmark found a 8.6-fold increased risk for cardiovascular hospitalization in patients with AF, including a 11-fold higher risk for heart failure and a 6.8-fold higher risk for ischaemic heart disease admissions (Christiansen et al., 2013). Likewise, in a US-based study of approximately 90 000 AF patients, the rate of all-cause hospitalizations was 2 times higher (37.5% vs. 17.5%) and the rate of cardiovascular hospitalizations was 4 times higher (21.3% vs.

5.4%) over 12 months in patients with AF compared to matched controls (Kim et al., 2011).

The healthcare expenditures of AF are mostly driven by the costs of AF-related complications and hospitalizations. In Sweden, the direct and indirect costs of AF-related complications (stroke and heart failure) were estimated to be 59% of the total annual costs of AF in 2007 (€708 million) (Ericson et al., 2011). In Finland, the estimated first-year direct healthcare costs of incident ischaemic stroke were on average $29 576 per patient ($31 723 in AF patients) in 2007 (Meretoja et al., 2011). Moreover, the estimated lifetime costs of incident ischaemic stroke were $131 000 (Meretoja et al., 2011). In Denmark, over a 3-year period after AF diagnosis, the costs were estimated to be almost 3-fold higher among the individuals with than those without ischaemic stroke within the first year after AF diagnosis (€89 510 vs. €30 066) (Johnsen et al., 2017). Moreover, the estimated costs attributable to AF were 1.3–1.7% of the total healthcare costs in Denmark (Johnsen et al., 2017). Considering the current trends and projections, the public health burden of AF is substantial, and thus, there is an urge to improve strategies to prevent AF development and its adverse consequences.

2.1.3 Thrombogenesis in atrial fibrillation

Thromboembolism is the most serious consequence of AF. A 2018 meta-analysis including nearly 130 000 ischaemic strokes in unselected patients found that approximately 20–23% of all ischaemic strokes were of cardioembolic aetiology (21–25% were due to large artery atherosclerosis, 21–24% were due to small artery occlusion, and 24–28% were of undetermined aetiology) (Ornello et al., 2018). However, thromboembolism is considered the primary aetiology of ischaemic stroke in patients with AF and only approximately one-third of ischaemic strokes are considered non-cardioembolic (Katsi et al., 2019). Moreover, the clinical significance of thromboembolism in AF is underscored by the observations that ischaemic strokes associated with AF are more fatal (~20% mortality at 1 month) and lead to greater disability and prolonged hospital stays than in those without the arrhythmia (Lin et al., 1996; Kaarisalo et al., 1997; Lamassa et al., 2001; Gattellari et al., 2011).

Thrombosis in the left atrial appendage (LAA) is considered the major cause of cardioembolic and ischaemic stroke in AF (January et al., 2014; Hindricks et al., 2021). The thrombus in the LAA – comprised mainly of fibrin and acellular debris (Wysokinski et al., 2004) – can fragment, dislodge and embolize to the cerebral or peripheral arteries causing serious ischaemic complications. In AF, over 90% of the cardiac thrombi are located in the LAA, whereas other locations (e.g., left atrial cavity, and right atrial appendage) are uncommon (Blackshear & Odell, 1996;

Mahajan et al., 2012; Cresti et al., 2019). However, in the presence of coexisting mitral stenosis, thrombi are located in the left atrial cavity in up to 50% of cases (Blackshear & Odell, 1996; Mahajan et al., 2012). The prevailing framework for understanding thrombogenesis in AF includes abnormal blood stasis, endothelial dysfunction, and hypercoagulability (Watson et al., 2009). These requirements for thrombus formation are also summarized in Virchow's triad (Figure 3), named after a German physician Rudolf Virchow (Watson et al., 2009).

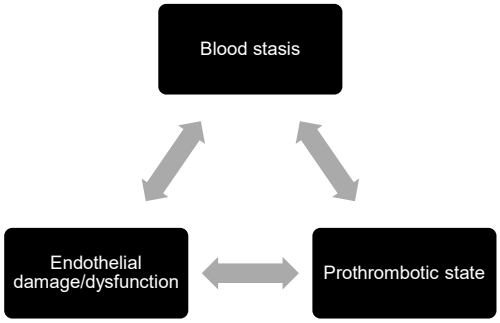


Figure 3. Virchow's triad of thrombogenesis in atrial fibrillation. Reference: (Watson et al., 2009).

The LAA is a vestige of the embryonic left atrium, but still has a few known physiological functions, such as maintenance of blood pressure via the activation of stretch-receptors and secretion of atrial natriuretic peptide and B-type natriuretic peptide (Romero et al., 2014; Yaghi et al., 2015). In AF, unsynchronized atrial contractions, and the subsequent loss of atrial systole, lead to a decrease in contractility and blood flow within the LAA (Beigel et al., 2014). Anatomically, the LAA is a pouch-like extension to the left atrial wall with distinctive orifice, neck and body sections, although there is considerable variations in its morphology, shape and size (Beigel et al., 2014). The LAA is usually comprised of two lobes, with an increasing number of lobes and more complex morphology predisposing to blood stagnation and thrombus formation (Yamamoto et al., 2014). Four broad morphological types are identified as "chicken wing", "cactus", "windsock", and "cauliflower", of which the chicken wing subtype is the most prevalent and the least associated with thromboembolism (Di Biase et al., 2012). In addition to shape, also atrial fibrosis (Daccarett et al., 2011), and extensive trabeculations in the LAA (Khurram et al., 2013), have been associated with ischaemic stroke. However, the evidence on the significance of LAA orifice area is mixed (Khurram et al., 2013; Lee et al., 2015). Besides anatomical considerations, independent parameters of LAA function, such as spontaneous echo contrast (i.e., an echocardiographic finding of the echogenicity of blood under

low-shear conditions) and reduced flow velocities, are associated with thrombus formation and thromboembolic events (Romero et al., 2014; Yaghi et al., 2015). Moreover, left atrial enlargement (e.g., due to long-term AF, mitral valve stenosis, or heart failure) aggravates blood stasis and is associated with thromboembolic stroke in AF (Daniel et al., 1988; Benjamin et al., 1995).

Prothrombotic state in AF is a concurrent finding with abnormal flow dynamics and stasis in the LAA (Watson et al., 2009). The generalized prothrombotic state in AF is supported by observational findings of abnormal biomarker levels of coagulation (e.g., D-dimer, fibrinogen, thrombin-antithrombin complex, antithrombin III, and prothrombin fragments 1 and 2) and platelet activation (e.g., platelet factor 4, β-thromboglobulin, and P-selectin) in patients with AF (Wu et al., 2015). For example, increased D-dimer (i.e., a degradation product of cross-linked fibrin) concentration reflects active fibrinolysis, and thus, D-dimer is considered an indirect biomarker of ongoing coagulation and thrombosis. Indeed, increased D-dimer levels independently predict LAA thrombi (Habara et al., 2007), and thromboembolic events even in anticoagulated AF patients (Sadanaga et al., 2010; Christersson et al., 2014).

There is also evidence for impaired fibrinolytic function in AF (Watson et al., 2009). Two indices of fibrinolysis – tissue plasminogen activator antigen and plasminogen activator inhibitor-1 – have been shown to be increased in AF patients compared to controls (Wu et al., 2015). High tissue plasminogen activator antigen levels predict major adverse cardiovascular events and all-cause mortality in AF patients (Freynhofer et al., 2013), and future thromboembolic stroke in healthy subjects (Ridker et al., 1994). In a study of 269 AF patients, the risk for major adverse events and all-cause mortality was increased by 2.5-fold in patients with above-median levels of tissue plasminogen activator antigen (Freynhofer et al., 2013). The precise mechanism by which the fibrinolytic function is altered remains uncertain, but endothelial dysfunction and systemic inflammation are hypothesized to be involved in the pathogenesis (Watson et al., 2009).

Platelets have a major physiological role in primary haemostasis as they rapidly bind to the site of vascular and endothelial injury. Increased circulating levels of platelet activation markers – such as platelet factor 4, β-thromboglobulin, and P-selectin – have been detected in AF patients (Wu et al., 2015). However, the potential role of platelets in the prothrombotic state of AF remains controversial (Watson et al., 2009). A 2007 case-control study found higher levels of platelet microparticles and P-selectin in AF patients compared to healthy subjects (Choudhury et al., 2007). However, there was no significant difference between AF and disease-matched patients, which lead the authors to conclude that the platelet activation was probably related to underlying cardiovascular diseases (Choudhury et al., 2007). On the other hand, a 2011 case-control study found significantly higher P-selectin levels in AF

patients under 60 years of age and without underlying cardiovascular disease when compared to age-matched controls (Fu et al., 2011). Meanwhile, a 2018 study by Wysokinski et al. demonstrated that elevated P-selectin level was associated with the intensity of spontaneous echo contrast in AF patients (Wysokinski et al., 2018). However, in the absence of severe spontaneous echo contrast, P-selectin levels were similar in AF patients and controls (Wysokinski et al., 2018), suggesting a close relationship between blood stasis and thrombotic abnormalities. Furthermore, in a 2013 Australian study, 55 AF patients in sinus rhythm undergoing catheter ablation were studied. Rapid atrial pacing (150 bpm) and induced AF for 15 minutes were sufficient to cause increased platelet activation and thrombin generation in the left atrium, suggested by increased P-selectin and thrombin-antithrombin III levels (Lim et al., 2013).

The third aspect of Virchow's triad – endothelial damage – is also present in AF. Von Willebrand factor is a plasma glycoprotein which, among other functions, mediates platelet binding to exposed subendothelial tissue in primary haemostasis. Von Willebrand factor is recognized as a biomarker of endothelial injury and dysfunction (Watson et al., 2009), and significantly elevated von Willebrand factor levels are found in AF patients (Wu et al., 2015). Von Willebrand factor is not only independently associated with left atrial thrombosis (Heppell et al., 1997), but also an independent risk factor for major adverse events, stroke, bleeding, and death in AF patients (Ye et al., 2020). Also, immunohistochemical evidence suggest a direct role of von Willebrand factor in atrial thrombogenesis irrespective of the presence of AF (Fukuchi et al., 2001). In addition to von Willebrand factor, a high level of E-selectin – another index of endothelial activation – has been shown to independently predict ischaemic stroke, myocardial infarction, and all-cause mortality (Krishnamoorthy et al., 2013).

In summary, there is mounting evidence for the complex thrombogenic mechanisms that are associated with thromboembolic events in AF. Potential mechanisms that might promote the prothrombotic state include inflammation, release of growth factors, atrial remodelling, reduced nitric oxide synthesis and altered renin-angiotensin-aldosterone system (Watson et al., 2009). Nonetheless, oral anticoagulants significantly reduce circulating coagulation markers (Siegbahn et al., 2016; Christersson et al., 2019) and the risk of thromboembolism (Hart et al., 2007; Ruff et al., 2014), and are the mainstay of the ischaemic stroke prevention in AF.

2.2 Management of atrial fibrillation

The optimal management of AF integrates strategies to diminish the risk of ischaemic stroke (A), to alleviate patients' symptoms (B), and to reduce the burden of the associated cardiovascular comorbidities (C). These strategies are incorporated in the Atrial Fibrillation Better Care pathway, a patient-centred approach to AF management, which is recommended by the European Society of Cardiology in their latest 2020 AF guidelines (Hindricks et al., 2021).

Rate and rhythm control strategies primarily aim to alleviate AF-related symptoms (e.g., exercise intolerance, dyspnoea, fatigue, and palpitations) which relate to impaired quality of life (Hindricks et al., 2021). Although previous trials did not show survival advantage of rhythm control over rate control (Van Gelder et al., 2002; Wyse et al., 2002), recent evidence suggests that early rhythm control in patients with newly diagnosed AF is associated with a lower risk of adverse cardiovascular events (Kirchhof et al., 2020). Furthermore, in patients with AF and heart failure with reduced ejection fraction, catheter ablation is associated with a reduced risk of all-cause mortality and hospitalization for heart failure (Marrouche et al., 2018). Moreover, in case of emergency, acute rate and rhythm control may be needed in haemodynamically unstable AF patients.

First-line options for rate control include pharmacological agents that slow conduction in the atrioventricular node (e.g., β-blockers, diltiazem, verapamil, and digoxin). If pharmacological rate control is ineffective, pacemaker implantation and atrioventricular node ablation and may be considered. Rhythm control strategies, in general, aim to restore and maintain sinus rhythm in symptomatic AF patients. Rhythm control options include electrical cardioversion, pharmacological cardioversion, antiarrhythmic drugs, and pulmonary vein isolation via catheter ablation in selected AF patients. In general, AF catheter ablation is recommended after the failure of antiarrhythmic drug therapy, and in patients with left ventricular dysfunction related to AF-induced cardiomyopathy (Hindricks et al., 2021). Additionally, recent research shows that catheter ablation for AF as the first-line treatment significantly improves the quality of life and reduces the use of healthcare resources without increasing the risk of adverse events (Andrade et al., 2021).

2.2.1 Prevention of thromboembolism in atrial fibrillation

The prevention of thromboembolism, and especially ischaemic stroke, plays a fundamental part in AF management, and is essential to avoid unnecessary loss of life and quality of life. Long-term OAC is the first-line therapy and the primary means to reduce the risk of thromboembolic complications in AF. In clinical practice, patients who are at increased risk of thromboembolism often share risk factors for bleeding complications. However, in most cases, the overall risk for thromboembolism outweighs the increased risk of bleeding. (Hindricks et al., 2021)

In the subsequent chapters, risk factors and clinical risk assessment for thromboembolism and bleeding complications, and the clinical challenges in managing anticoagulation are described.

2.2.1.1 Risk factors for ischaemic stroke in atrial fibrillation

Approximately 10–30% of ischaemic strokes are associated with AF (Friberg et al., 2014; Kishore et al., 2014; Jaakkola et al., 2016), although covert AF or atrial high rate episodes might not necessarily imply a causal relationship in all cases (Ntaios, 2020; Svendsen et al., 2021). Nonetheless, the overall risk of ischaemic stroke is increased by 4–5-fold in AF patients, while the absolute risk ranges from 0.2%/year to over 10%/year depending on the individual risk burden (Wolf et al., 1991; Kannel et al., 1998; Friberg et al., 2012a; Van Den Ham et al., 2015). In the Framingham Heart Study, the proportion of strokes (of which 12% were haemorrhagic) attributable to AF increased from 1.5% to 23.5% for ages 50–59 years to 80–89 years, respectively (Wolf et al., 1991). In a Swedish registry study of over 90 000 patients with ischaemic stroke, the likelihood of underlying AF was significantly elevated (30–70%) if risk factors for incident AF and AF-related thromboembolism – such as older age, heart failure, and hypertension – were present (Friberg et al., 2014).

Age

Increasing age is a major risk factor for ischaemic stroke in patients with AF (Van Walraven et al., 2009; Marinigh et al., 2010). The relative risk is increased approximately 40–45% every 10-year age increment (Van Walraven et al., 2009; Marinigh et al., 2010). In the Swedish Atrial Fibrillation cohort, patients 65–74 years of age had a 3.1 times higher risk, and patients 75 years of age and older had a 5.5 times higher risk of ischaemic stroke in comparison with those 65 years old and younger (Friberg et al., 2012a). In the historical randomized trials, among 426 patients (mostly Caucasian) with AF but no other risk factors (including previous stroke/TIA, hypertension, heart failure, diabetes, or vascular disease), the annual risk of stroke was ~0% for patients < 60 years of age, 1.6% for patients 60–69 years of

age, 2.1% for patients 70–79 years of age, and 3.0% for patients 80 years of age or older (Atrial Fibrillation Investigators, 1994). Meanwhile, in Korean patients without other known risk factors, the annual rate of ischaemic stroke was 1.9% for patients 55–59 years old, and 2.9% for patients 60–64 years old (Kim et al., 2018).

Previous ischaemic stroke or transient ischaemic attack

Overwhelming evidence suggest that previous ischaemic stroke and transient ischaemic attack (TIA) are strong risk factors for recurrent events (Pisters et al., 2012; Noubiap et al., 2021). In the historical randomized clinical trials (Atrial Fibrillation Investigators, 1994), previous stroke/TIA was the strongest predictor of future stroke (a 2.5-fold increased risk) and was associated with high event rates (11.7%/year in controls and 5.1%/year in warfarin-treated patients). Also, in a Swedish cohort of over 90 0000 AF patient without anticoagulation, prior ischaemic stroke was associated with a 3.1-fold greater risk of recurrent event (Friberg et al., 2012a).

Previous intracranial bleeding

Previous intracranial bleeding is associated with a 1.5–3-fold increased risk of ischaemic stroke in AF patients (Friberg et al., 2012a; Lerario et al., 2015; Nielsen et al., 2015a; Murthy et al., 2020), especially during the first months after intracerebral bleeding when the risk is increased up to 6-fold (Nielsen et al., 2015a; Murthy et al., 2020). In a large US cohort study of over 2 million AF patients, the 1-year rate of ischaemic stroke was 8.1% after intracerebral bleeding, 3.9% after subdural bleeding, and 2.0% in patients without intracranial bleeding, and the adjusted risk of ischaemic stroke was increased by 2.8-fold and 1.6-fold after intracerebral and subdural bleeding, respectively (Lerario et al., 2015).

Hypertension

Hypertension is highly prevalent, reported in up to 80% of AF patients (Steinberg et al., 2017). Moreover, hypertension is associated with incident AF (O'Neal et al., 2015), and ischaemic stroke in AF (Friberg et al., 2012a; Pisters et al., 2012; Noubiap et al., 2021). In a large cohort of 1.25 million patients initially free from cardiovascular disease, a 20 mmHg increment in systolic blood pressure was associated with a 1.35-fold increased risk of ischaemic stroke (Rapsomaniki et al., 2014). In a meta-analysis of over 1.4 million AF patients, hypertension was the most prevalent cardiovascular risk factor (~60%) and associated with a 1.6-fold increased risk of stroke or systemic embolism (Noubiap et al., 2021).

Heart failure

Heart failure and AF share common risk factors, frequently coexist, and together are associated with increased mortality (Wang et al., 2003). Heart failure is

independently associated with a 1.5–2.1-fold increased long-term risk of ischaemic stroke (Adelborg et al., 2017), although its role as an independent risk factor in patients with AF is uncertain (Friberg et al., 2012a; Olesen et al., 2012a; Pisters et al., 2012).

Valvular heart disease

Valvular heart disease is present in approximately 20% of elderly AF patients, with mitral regurgitation and aortic stenosis being the most common valvular pathologies (Banerjee et al., 2019). Moreover, left-sided valvular heart disease in patients with AF is associated with increased risk of thromboembolism (Philippart et al., 2015; Banerjee et al., 2019; Melgaard et al., 2020). A 2015 French study observed a higher risk of thromboembolism in patients with AF and valve disease (excluding rheumatic mitral stenosis and valvular prosthesis) but the risk was likely explained by other common risk factors for thromboembolism (Philippart et al., 2015). In a 2019 UK study of over 76 000 individuals with AF, mitral stenosis, aortic stenosis and mechanical valve replacement were associated with a 13–27% higher risk of stroke, systemic embolism, and all-cause mortality (Banerjee et al., 2019).

Sex differences

Female sex has been considered as an independent risk factor for thromboembolism (Fang et al., 2005; Dagres et al., 2007), although the findings are inconsistent (Pisters et al., 2012). A meta-analysis of over 1.6 million AF patients found a 1.18-fold increased risk of stroke or systemic embolism in females, driven by a greater risk in studies outside Asia (Noubiap et al., 2021). However, observational data suggest that female sex is an age-dependant risk modifier rather than an independent risk factor per se (Friberg et al., 2012b; Mikkelsen et al., 2012; Nielsen et al., 2018; Wu et al., 2020). In a Swedish registry study, the risk of stroke was similar between females (0.7%/year) and males (0.5%/year) with AF, aged < 65 years and without vascular disease (Friberg et al., 2012b). Likewise, in a Danish registry study of over 87 000 patients, female sex was found to be an independent risk factor for thromboembolic events only for AF patients aged ≥ 75 years (Mikkelsen et al., 2012). Moreover, in a Taiwanese study, the risk of ischaemic stroke was lower in females aged < 65 years compared to males (Wu et al., 2020).

Other clinical risk factors

Other contributing risk factors for thromboembolism in AF include diabetes (Van Staa et al., 2011; Friberg et al., 2012a), peripheral vascular disease (Olesen et al., 2012b), chronic kidney disease (Zeng et al., 2015), obstructive sleep apnoea (Yaranov et al., 2015), and Asian ethnicity (Kim et al., 2018). Moreover, various haemostatic indices and echocardiographic markers (discussed in Chapter 2.1.3), and

elevated B-type natriuretic peptide and cTn levels (Sadanaga et al., 2011; Hijazi et al., 2012) have been associated with thromboembolic events in AF.

Non-adherence to oral anticoagulation

A systematic review of over half a million AF patients found that nearly one-third of patients are non-adherent to OAC (Salmasi et al., 2020). One-year adherence ranged from 41% to 95%, and non-adherence was associated with ischaemic stroke (50% to 2-fold increased risk), higher mortality, and greater healthcare costs (Salmasi et al., 2020). Moreover, a 2021 population study of over 100 000 AF patients from the UK and Denmark found that discontinuation of OAC was associated with a 2–3 fold increased risk of ischaemic stroke compared to patients who maintain OAC (García Rodríguez et al., 2021).

2.2.1.2 Clinical risk stratification of thromboembolism

CHA_2DS_2-VASc score (Table 3) has emerged as a widely used risk assessment tool for predicting ischaemic stroke in patients with AF (Lip et al., 2010; Hindricks et al., 2021). In general, all current risk scores schemes have modest predictive ability (c-statistics 0.6–0.7) for ischaemic stroke (Van Staa et al., 2011; Van Den Ham et al., 2015). However, the CHA_2DS_2-VASc score – outperforming its predecessor, the $CHADS_2$ scheme – identifies patients at low risk of thromboembolism who would not benefit from anticoagulation (Lip et al., 2010). In previous observational studies, a CHA_2DS_2-VASc score of 0 in untreated patients with AF was associated with a 0.2–0.5%/year rate of ischaemic stroke (Van Staa et al., 2011; Friberg et al., 2012a; Van Den Ham et al., 2015; Allan et al., 2017).

As for the female population with AF, the risk of ischaemic stroke is similar to males when no other stroke risk factors are present (CHA_2DS_2-VASc score of 0 in males, and 1 in females) but greater after addition of 2 or more non-sex-related stroke risk factors (Nielsen et al., 2018). In a Danish nationwide cohort study, non-anticoagulated AF patients without traditional stroke risk factors (i.e., a CHA_2DS_2-VASc score of 0 in males, or 1 in females) had a low ischaemic stroke rate which increased from 0.43%/year to 1.5%/year with the addition of 1 risk factor (Lip et al., 2015). Thus, the European Society of Cardiology and the American College of Cardiology/American Heart Association/Heart Rhythm Society recommend abstaining from anticoagulant treatment for AF patients with a CHA_2DS_2-VASc score 0 in males, or 1 in females (January et al., 2019; Hindricks et al., 2021). As for AF patients at moderate stroke risk (i.e., a CHA_2DS_2-VASc score of 1 in males, or 2 in females), the American guidelines state that OAC may be considered for these patients (January et al., 2019), and the European guidelines state that OAC should

be considered after individual risk assessment and based on patient preferences (Hindricks et al., 2021).

The risk of ischaemic stroke increases drastically with increasing CHA_2DS_2-VASc score (Figure 4) (Friberg et al., 2012a; Van Den Ham et al., 2015; Allan et al., 2017), and randomized trials have provided robust evidence of benefit from OAC in AF patients at high risk of ischaemic stroke (Hart et al., 2007; Ruff et al., 2014). Therefore, OAC is strongly recommended for AF patients with CHA_2DS_2-VASc score ≥ 2 in males, or ≥ 3 in females (January et al., 2019; Hindricks et al., 2021), for most of whom there is a significant net clinical benefit of anticoagulation (i.e., the risk of ischaemic stroke without anticoagulation outweighs the risks of bleeding on anticoagulation) (Allan et al., 2017; Jaakkola et al., 2018).

Understandably, other clinical risk factors exist beyond those incorporated in the CHA_2DS_2-VASc scheme. For example, ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study risk score includes proteinuria and renal dysfunction as predictors of ischaemic stroke, and it slightly outperforms the CHA_2DS_2-VASc score and more accurately identifies patients at low risk (Van Den Ham et al., 2015). Also, a novel ABC-AF (Age, Biomarkers, Clinical history) stroke risk score incorporates age, prior stroke/TIA and levels of 3 biomarkers (high-sensitivity cTn [hs-cTn], N-terminal prohormone of brain natriuretic peptide) as predictors, and is superior to the CHA_2DS_2-VASc score for the annual stroke risk prediction (Benz et al., 2021).

Table 3. Risk factors for thromboembolism included in the **CHA_2DS_2-VASc** risk score.

Risk factors	Points
Congestive heart failure	1
Hypertension	1
Age 75 years or older	2
Diabetes mellitus	1
Stroke, transient ischaemic attack, or systemic embolism	2
Vascular disease	1
Age 65 to 74 years	1
Sex **c**ategory, female	1

The acronym CHA_2DS_2-VASc stands for congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischaemic attack or thromboembolism, vascular disease (e.g., prior myocardial infarction, peripheral artery disease, aortic plaque), age 65–74 years, and sex category (female). Modified from (Lip et al., 2010).

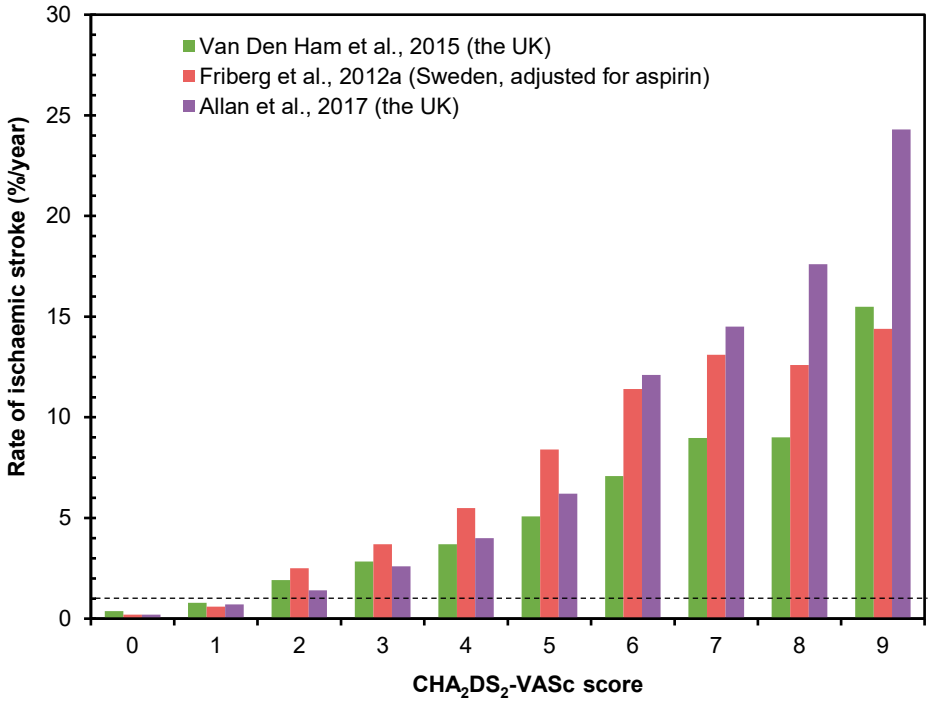


Figure 4. Annual rate of ischaemic stroke in patients with atrial fibrillation and without anticoagulation treatment. Selected studies with a total of 15 070 ischaemic strokes in 191 233 patients. Data from (Friberg et al., 2012a; Van Den Ham et al., 2015; Allan et al., 2017).

2.2.1.3 Anticoagulation therapy for ischaemic stroke prevention

Oral anticoagulants are the mainstay of therapy for ischaemic stroke prevention in AF. Warfarin is among the most widely used vitamin K antagonists (VKAs) and it inhibits the enzymatic activation of coagulation factors II, VII, IX, and X in the liver. It reduced the risk of ischaemic stroke by 65% and all-cause mortality by 26% compared with placebo or no treatment in the earliest randomized clinical trials (Hart et al., 2007). Limitations and disadvantages of warfarin usage are its narrow therapeutic window, numerous interactions with other drugs and dietary intake of vitamin K, and unpredictable pharmacokinetics, and thus, its usage requires frequent monitoring and constant individually tailored dose adjustments.

Novel, non-VKA oral anticoagulants (NOACs) are currently preferred over warfarin for ischaemic stroke prevention in most AF patients (January et al., 2019; Hindricks et al., 2021), and they directly inhibit specific pathways of coagulation cascade. The most commonly used NOACs include direct inhibitors of factor Xa (e.g., rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (e.g., dabigatran) which are as efficacious as warfarin in ischaemic stroke prevention (Ruff et al., 2014). Moreover, NOACs are associated with a ~50% reduced risk of intracranial bleeding and a ~10% reduced risk of mortality but with a ~25% increased risk of gastrointestinal bleeding compared to warfarin (Ruff et al., 2014). Real-world evidence complements the data from the pivotal NOAC trials (RE-LY[a], ROCKET-AF[b], ARISTOTLE[c], and ENGAGE AF-TIMI 48[d]) indicating broadly similar results in terms of efficacy and safety (Coleman et al., 2019; de Groot et al., 2021). Other notable advantages of NOACs over VKAs are a standard dosing regimen (once or twice daily), and no need for continuous laboratory monitoring. Moreover, the persistence to anticoagulation treatment is higher among AF patients treated with NOACs compared to those treated with VKAs (Zalesak et al., 2013; Beyer-Westendorf et al., 2016). While NOACs are contraindicated in patients with mechanical heart valves (Eikelboom et al., 2013) and are not recommended in patients with a concomitant moderate-to-severe mitral stenosis (Hindricks et al., 2021), NOACs seem safe and effective in the presence of other valvular heart disease

[a] RE-LY [dabigatran], Randomized Evaluation of Long Term Anticoagulation Therapy
[b] ROCKET-AF [rivaroxaban], Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
[c] ARISTOTLE [apixaban], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
[d] ENGAGE AF-TIMI 48 [edoxaban], Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48

(Renda et al., 2017), and following bioprosthetic valve replacement (Carnicelli et al., 2017; Guimarães et al., 2019).

APT was previously considered a recommended choice for patients with a low risk of thromboembolism but contraindications to VKAs (Fuster et al., 2006). However, the prescription of antiplatelet agents in patients with AF to prevent thromboembolism is an outdated practice and advised against in the current guidelines (Hindricks et al., 2021). Aspirin, also known as acetylsalicylic acid (ASA), is associated with a modest, but nonsignificant, 21% risk reduction in ischaemic stroke compared with placebo (Hart et al., 2007). However, compared with aspirin, apixaban demonstrates superior efficacy in preventing ischaemic stroke in AF, with a comparable bleeding risk (Connolly et al., 2011). Moreover, although addition of clopidogrel to aspirin is superior to aspirin monotherapy (Connolly et al., 2009a), it is associated with about half the efficacy of warfarin for ischaemic stroke prevention while carrying an equal risk of major bleeding with warfarin (ACTIVE Writing Group of the ACTIVE Investigators et al., 2006).

2.2.1.4 Bleeding risk assessment

An essential part of OAC-based thromboprophylaxis is bleeding risk assessment before, and reassessment during, anticoagulation therapy. Many risk factors for thromboembolism are also risk factors for major bleeding events, and vice versa. When weighting the benefits of OAC against the increased risk of bleeding, the net clinical benefit favours anticoagulation in most AF patients (Friberg et al., 2012c; Allan et al., 2017; Jaakkola et al., 2018). Thus, rather than justifying withholding anticoagulation, bleeding risk scores help identifying modifiable risk characteristics and informing patients and physicians about the perceived risks and benefits of OAC therapy (Hindricks et al., 2021). Overall, several bleeding risk scores have been developed and validated in AF cohorts treated with OACs, mostly VKAs, which all demonstrate limited risk discrimination ability (c-statistics ranging from 0.5 to 0.8) (Borre et al., 2018). The HAS-BLED score (Table 4) is a bleeding assessment tool currently recommended in the European guidelines (Hindricks et al., 2021). The annual rate of major bleeding increases from 0.5–1.5% in patients with a HAS-BLED score ≤ 1 to 3.5–16% in patients with a HAS-BLED score ≥ 4 (Pisters et al., 2010; Friberg et al., 2012a; Lip et al., 2018).

Table 4. Risk factors for major bleeding in the **HAS-BLED** risk score.

Risk factors	Points
Hypertension	1
Abnormal renal and/or liver function	1–2
Stroke	2
Bleeding predisposition or tendency	1
Labile international normalized ratio	2
Elderly (age > 65 years)	1
Drugs (antiplatelet agents/NSAIDs) and/or excess alcohol usage	1–2

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs. Modified from (Pisters et al., 2010).

The HAS-BLED risk score was originally derived in prospective cohort of AF patients treated with VKAs to predict for major bleeding (intracranial, hospitalization, a haemoglobin level decrease > 2 g/L, and/or requiring blood transfusion) (Pisters et al., 2010). In the derivation and validation studies, predictors of major bleeding were concomitant use of antiplatelet drugs, previous major bleeding, old age, severe renal impairment, diabetes, and left ventricular dysfunction (Pisters et al., 2010; Lip et al., 2011). Additional clinical risk factors incorporated in other bleeding risk scores include anaemia, low platelet count, previous stroke, and malignancy, to name a few (Borre et al., 2018). More recently, ABC bleeding score (Age, Biomarkers, and Clinical history) was introduced – including hs-cTn T, haemoglobin, and growth differentiation factor 15 as predictive biomarkers – and validated in AF patients treated with warfarin, apixaban, or dabigatran (Hijazi et al., 2016). Additionally, the HAS-BLED score has been shown to predict incident and recurrent intracranial bleeding (Apostolakis et al., 2012; Friberg et al., 2012a; Chan et al., 2014; Chao et al., 2018), although contradictory results exist in NOAC-treated patients (Yao et al., 2017; Paciaroni et al., 2021).

2.2.1.5 The dilemma of intracranial bleeding

Oral anticoagulants are effective in reducing the risk of thromboembolic stroke in AF but come at the price of increased risk of bleeding. Haemorrhagic stroke accounts for roughly 10–20% of all strokes in NOAC-treated AF patients, and up to 30% in warfarin-treated patients (Connolly et al., 2009b; Granger et al., 2011; Patel et al., 2011; Giugliano et al., 2013). Most intracranial bleedings in OAC-treated patients are intracerebral (Figure 5), and the risk of intracranial bleeding is increased up to 7–10-fold in warfarin users, or to approximately 1%/year (Hart et al., 1995). Moreover, although the risk is reduced by half in NOAC-treated patients (Ruff et al., 2014; Katsanos et al., 2018), NOACs are still associated with an elevated risk of intracranial bleeding comparable to aspirin (Connolly et al., 2011; Huang et al., 2018).

Intracranial bleeding in OAC-treated patients is a tragic manifestation associated with poor prognosis, disability and high early mortality (Hart et al., 1995; Huhtakangas et al., 2011; Katsanos et al., 2018). In the NOAC versus warfarin trials, case fatality rates ranged approximately from 30% to 50% and were similar irrespective of the assigned treatment (Hart et al., 2012; Hankey et al., 2014; Lopes et al., 2017; Nelson et al., 2021). Older age, previous stroke or TIA, randomization to warfarin, aspirin usage at randomization, and Asian ethnicity were common independent predictors of intracranial bleeding in these trials (Hart et al., 2012; Hankey et al., 2014; Lopes et al., 2017; Nelson et al., 2021).

From the clinician's and patient's perspective, the major concern is the recurrence of intracranial bleeding after OAC reinstitution that must be balanced against the risk of thromboembolism in AF. A 2017 US study of over 43 000 OAC-naïve patients with AF found a 12% incidence of ischaemic stroke and a 20% incidence of haemorrhagic stroke in patients with prior intracranial bleeding (Redfors et al., 2017). Meanwhile, other previous observational studies in survivors

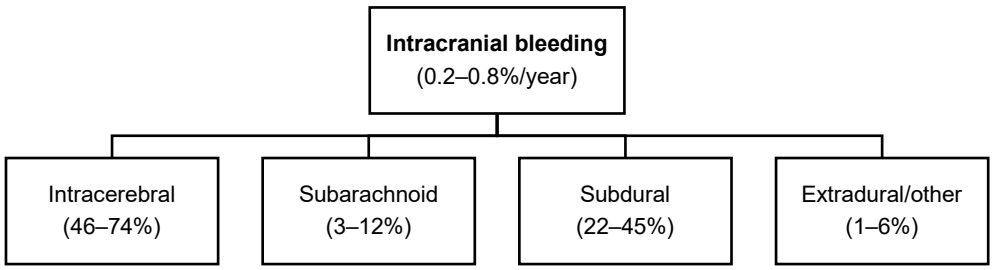


Figure 5. The main subtypes of intracranial bleeds in patients with atrial fibrillation and treated with novel oral anticoagulants (apixaban, dabigatran, edoxaban, or rivaroxaban) or warfarin in the randomized trials. References: (Hart et al., 2012; Hankey et al., 2014; Lopes et al., 2017; Nelson et al., 2021).

of intracranial bleeding with AF have demonstrated a high rate of recurrent intracranial bleeding (4–9%/year) irrespective of OAC resumption (Kuramatsu et al., 2015; Nielsen et al., 2015b), although some studies indicate an up to 5-fold increased risk of recurrent bleeding in OAC-treated patients (Majeed et al., 2010; Chao et al., 2016; Nielsen et al., 2017). Nevertheless, the rate of thromboembolism is consistently higher in patients without OAC (6–15%/year) than in OAC-treated patients (2–5%/year) (Kuramatsu et al., 2015; Nielsen et al., 2015b, 2017; Chao et al., 2016; Pennlert et al., 2017; Redfors et al., 2017). Furthermore, despite the high risk of thromboembolism, many AF patients lack adequate thromboprophylaxis after surviving intracranial bleeding as only ~10–20% of these patients are prescribed OAC over the first year after bleeding (Kuramatsu et al., 2015; Pennlert et al., 2015; Vestergaard et al., 2016).

The risk for recurrent intracranial bleeding is high during the early phases of intracranial bleeding (Majeed et al., 2010; Nielsen et al., 2015b), but so is the risk of ischaemic stroke in AF patients (Nielsen et al., 2015a; Murthy et al., 2020). Previous intracerebral bleeding, especially lobar and cerebral amyloid angiopathy-related intracerebral bleeding, and multiple cerebral microbleeds are important non-modifiable predictors of recurrent bleeding (Bailey et al., 2001; Charidimou et al., 2017). A 2017 meta-analysis found a higher recurrence rate in patients with (7.4%/year) than without (1.1%/year) prior cerebral amyloid angiopathy-related intracerebral bleeding (Charidimou et al., 2017). Also, a 2021 UK study demonstrated a higher rate of recurrent bleeding after lobar (5.1 per 100 patient-years) than non-lobar intracerebral bleeding (1.8 per 100 patient-years) (Li et al., 2021). Other factors that have been associated with recurrent intracranial or intracerebral bleeding include older age (Vermeer et al., 2002), arterial hypertension (Biffi et al., 2015), previous ischaemic stroke (Huhtakangas et al., 2013), ε2 and ε4 alleles of the apolipoprotein E gene (O'Donnell et al., 2000), diabetes mellitus, and vascular disease (Chao et al., 2016).

The recent results from two, relatively small, randomized trials remain inconclusive regarding the benefit of restarting anticoagulation after intracranial bleeding. APACHE-AF (Apixaban After Anticoagulation-Associated Intracerebral Hemorrhage in Patients With Atrial Fibrillation) randomized 101 AF patients with CHA_2DS_2-VASc score ≥ 2 to NOAC (apixaban) and to avoid OAC (51% received APT) 7–90 days after intracerebral bleeding. At a median follow-up of 1.9 years, the annual rate of non-fatal stroke or vascular death was around 12% irrespective of anticoagulation (Schreuder et al., 2021). Likewise, SoSTART (Start or Stop Anticoagulants Randomised Trial) randomized 203 AF patients on average 4 months after intracranial bleeding to start OAC (98% on NOACs) and avoid OAC (31% on APT) (Salman et al., 2021a). Although the cumulative incidence of ischaemic stroke at 2 years was 9 times higher in the avoid-OAC group (27.9%) than in the start-OAC

group (3.1%), the trial was unable to demonstrate the non-inferiority of OAC for avoiding recurrent intracranial bleeding (the cumulative incidence of intracranial bleeding 10.7% in the NOAC group, and 8.1% in the avoid-OAC group at 2 years) (Salman et al., 2021a). On-going large randomized trials, such as ENRICH-AF (ClinicalTrials.gov Identifier: NCT03950076), ASPIRE (NCT03907046) and PRESTIGE-AF (NCT03996772), are expected to provide more information on the safety and efficacy of anticoagulation and avoiding anticoagulation in AF patients with intracranial or intracerebral bleeding (Katsanos et al., 2020).

Observational studies have projected a period from 7–8 weeks to 10–30 weeks for OAC initiation to be associated with a positive clinical outcome (i.e., the lowest combined risk of adverse events) in patients with AF surviving intracranial bleeding (Majeed et al., 2010; Pennlert et al., 2017). The current guidelines from the European Society of Cardiology, and the American Heart Association and American Stroke Association suggest delaying initiation of anticoagulation at least 2–4 weeks after intracranial bleeding based on available observational data (Hemphill et al., 2015; Hindricks et al., 2021), and considering percutaneous closure of the LAA if contraindications for long-term anticoagulation are present (January et al., 2019; Hindricks et al., 2021).

Given the knowledge gaps regarding the ischaemic stroke prevention in AF after intracranial bleeding, the question remains whether OAC initiation is safe after intracranial bleeding, and if so when should OAC be initiated. However, considering the high rates of thromboembolism in AF patients who do not receive OAC, percutaneous LAAC has emerged as an appealing alternative to OAC in the prevention of thromboembolism after intracranial bleeding and in patients with high risk of bleeding. The rationale for LAAC and related questions are reviewed in the following chapters.

2.2.2 Left atrial appendage closure

The LAA is susceptible to thrombus formation, probably owing to blood stasis and flow abnormalities accompanied by endothelial dysfunction and abnormal changes in coagulation (Watson et al., 2009). In AF, over 90% of thrombi are located in the LAA in the absence of concomitant valvular disease (Blackshear & Odell, 1996; Mahajan et al., 2012; Cresti et al., 2019). Therefore, techniques to isolate and occlude the LAA have been introduced in an attempt to reduce the risk of thromboembolic stroke.

2.2.2.1 Surgical left atrial appendage closure

Surgical left atrial appendectomy was first described in human by Dr John L. Madden over 70 years ago, well before anticoagulation with warfarin emerged as the preventive strategy for thromboembolism. In 1949, Madden wrote: "Since a thrombus is the precursor of every arterial embolus, the ideal prophylaxis for recurrent arterial emboli should be the removal of the thrombus together with its site of origin" (Madden, 1949). Contemporary surgical LAAC techniques include, inter alia, excision, epicardial stapling, clip application, and endocardial suture closure, which are performed during open heart surgery, surgical AF ablation, or as a stand-alone thoracoscopic procedure. Success rates with varying surgical LAAC techniques range from 40% to 100% (Tsai et al., 2015), and incomplete surgical LAAC has been associated with thrombus formation (Kanderian et al., 2008), and thromboembolic events (Aryana et al., 2015).

In AF patients undergoing cardiac surgery, surgical LAA closure for stroke prevention may be considered according to the current guidelines (Hindricks et al., 2021). This recommendation is based on limited observational and randomized data indicating significant reduction in stroke incidence and all-cause mortality (Tsai et al., 2015; Hindricks et al., 2021). Recently, in the largest randomized trial to date of surgical LAAC in 4811 AF patients undergoing cardiac surgery for other indications, surgical LAA occlusion provided additional benefit and reduced the risk of thromboembolism by approximately one-third when added to long-term OAC (Whitlock et al., 2021). However, surgical LAAC has not yet been compared to OAC for ischaemic stroke prevention or in patients with contraindications to OAC.

2.2.2.2 Percutaneous left atrial appendage closure devices

Percutaneous LAAC was first introduced at the beginning of the 21st century as a less invasive alternative to surgical LAAC, and with a rationale of preventing ischaemic stroke in patients with contraindications to VKA treatment (Sievert et al., 2002). In 2001, PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion; ev3 Inc., Plymouth, Minnesota, USA) system, invented by Michael Lesh, was the first-in-human LAAC device implanted via a catheter-based delivery system and using transseptal catheterization (Sievert et al., 2002; Ostermayer et al., 2005). The implant consisted of a self-expanding nitinol frame coated with expanded polytetrafluoroethylene to minimize thrombogenicity and facilitate neo-endothelialization (i.e., formation of a non-thrombogenic luminal surface of endothelium) (Sievert et al., 2002; Ostermayer et al., 2005). Early feasibility studies reported promising results although procedure-related serious adverse events (e.g., cardiac tamponade, and haemothorax) were recognized (Ostermayer et al., 2005). The PLAATO device was eventually removed from the market in 2005 for financial reasons and is no longer available, but other devices were already in development by then (Meier et al., 2014).

The currently available percutaneous LAAC techniques include endovascular implantation of nitinol-based LAAC devices, and percutaneous suture ligation using an endo- and epicardial approach (Glikson et al., 2020). Endovascular LAAC devices are either plugs with a single lobe obstructing the LAA orifice, or pacifiers with a proximal disc sealing the LAA orifice and a distal plug anchoring to the LAA. Implantation procedures are typically performed via femoral venous access and transseptal puncture and with transoesophageal echocardiographic and fluoroscopic guidance under general anaesthesia, or even local anaesthesia (Glikson et al., 2020).

The most commonly used LAAC devices include the Watchman and Watchman FLX devices (both by Boston Scientific, Marlborough, Massachusetts, USA) featuring a polyethylene terephthalate coated plug, and the Amplatzer Cardiac Plug and Amplatzer Amulet devices (both by Abbott Vascular, Santa Clara, California, USA) featuring a pacifier filled with polyester fabric (Glikson et al., 2020). The Watchman device is the first LAAC device studied in randomized trials and the first LAAC device approved by the US Food and Drug Administration in 2015 for stroke prevention in AF (Reddy et al., 2017; Glikson et al., 2020). An upgraded design has been introduced in the Watchman FLX device, and early results suggest improved performance and safety (Kar et al., 2021). In 2021, the Amplatzer Amulet device received the US Food and Drug Administration approval after randomized clinical trial data demonstrated that the Amulet was non-inferior for stroke prevention compared with the Watchman device (Lakkireddy et al., 2021).

Several other LAAC devices have been developed and are commercially available in Europe, including WaveCrest device (Biosense Webster, Diamond Bar,

California, USA) featuring a single plug with an expanded polytetrafluoroethylene coating, Ultraseal device (Cardia, Inc., Eagan, Minnesota, USA) featuring a pacifier with a polyvinyl alcohol foam and polyester fabric covered disc, and LAmbre device (Lifetech, Shenzhen, China) featuring a pacifier with a polyethylene terephthalate filled disc (Glikson et al., 2020). The LARIAT device (SentreHEART, Redwood City, California, USA) combines epi- and endocardial approaches to deploy an epicardial suture at the base of the LAA, and thereby leaving no foreign material inside the LAA. Although complete closure with the LARIAT device has demonstrated a low rate of thromboembolism, residual leaks are common and associated with thromboembolic events (Mohanty et al., 2020).

In the following chapters, percutaneous LAAC for ischaemic stroke prevention in AF is reviewed with reference to the available evidence regarding the most common contemporary LAAC devices (the Watchman and Amplatzer devices).

2.2.2.3 Randomized trial data on the efficacy and safety of percutaneous left atrial appendage closure

To date, three completed randomized trials have compared percutaneous LAAC with OAC: **PROTECT AF** (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation), **PREVAIL** (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), and **PRAGUE-17** (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation). The findings of these trials are discussed below and summarized in Table 5.

Between years 2005 and 2008, the PROTECT AF trial enrolled 707 AF patients at high risk of ischaemic stroke ($CHADS_2$ score ≥ 1) and randomized patients in a 2:1 ratio to LAAC with the Watchman device or warfarin treatment. In the intervention arm, following Watchman device implantation, patients were treated with warfarin plus aspirin 81 mg for 45 days, then aspirin 325 mg plus clopidogrel 75 mg until 6 months, followed by aspirin 325 mg indefinitely (Holmes et al., 2009). After 1065 patient-years of follow up (mean follow-up of 18 months), the Watchman device was non-inferior to warfarin therapy for the primary outcome (composite of any stroke, systemic embolism, and cardiovascular or unexplained death) (Holmes et al., 2009). However, PROTECT AF trial was unable to prove non-inferiority of the Watchman device for ischaemic stroke prevention, and ischaemic stroke rate was even slightly higher in the LAAC group (2.2 per 100 patient-years) compared to the warfarin arm (1.6 per 100 patient-years). Moreover, LAAC was associated with early serious and procedure-related adverse events (e.g., device embolization in 0.6%, pericardial effusion requiring surgical or percutaneous drainage in 4.8%, and ischaemic stroke in 1.1% of patients) (Holmes et al., 2009).

Due to the periprocedural complication rates and safety concerns raised by the US Food and Drug Administration, a second randomized controlled trial was mandated and conducted. The PREVAIL trial randomized additional 407 AF patients in a similar 2:1 fashion to Watchman device (postprocedural antithrombotic treatment identical with PROTECT AF) or warfarin treatment. There was a significant decrease in early procedure-related complications from 8.7% in PROTECT AF to 4.2% in PREVAIL (Holmes et al., 2014). However, in contrary to PROTECT AF, the Watchman device was not non-inferior to warfarin for the primary outcome in the PREVAIL trial, mainly because of lower-than-expected event rates in the warfarin group. Nevertheless, LAAC met non-inferiority for postprocedural (i.e., events occurring beyond 7 days) ischaemic stroke or systemic embolism in the primary and final analyses, although the 18-month event rates were consistently higher in the Watchman arm (rate ratio, 1.6–2.8) (Reddy et al., 2017). A combined analysis of the PROTECT AF and PREVAIL trials found a significantly lower rate of haemorrhagic stroke in the LAAC group compared to warfarin group (0.17%/year vs. 0.87%/year, $p = 0.0022$), although there was a non-significant 71% higher thromboembolism rate in the LAAC group (1.6%/year vs. 0.95%/year, $p = 0.08$) (Reddy et al., 2017).

A 2020 study by Osmancik and colleagues was the first to compare LAAC with NOACs in a randomized controlled setting (Osmancik et al., 2020). The PRAGUE-17 trial enrolled 402 AF patients who were randomized in a 1:1 ratio to LAAC or NOACs. Overall, patients presented with risk factors for major bleeding (mean HAS-BLED score, 3.1 ± 0.9), and nearly half of the patients had a history of bleeding requiring intervention or hospitalization (Osmancik et al., 2020). However, high bleeding risk was not the only inclusion criteria. In the LAAC group, patients received either the Amplatzer Amulet (61%) or the Watchman/Watchman FLX device (39%), and most patients (82%) were discharged on dual APT (the recommended treatment regimen was aspirin 100 mg plus clopidogrel 75 mg for 3 months, followed by aspirin indefinitely). In the NOAC group, most patients were treated with apixaban 5 mg twice daily (79%) or apixaban 2.5 mg twice daily (16%). After mean follow-up of 21 months, percutaneous LAAC was non-inferior to NOACs for the primary composite endpoint (all stroke or TIA, systemic embolism, clinically significant bleeding, cardiovascular death, and significant procedure-related complications) (Osmancik et al., 2020). Meanwhile, the annual rate of ischaemic stroke or TIA was 2.6% in the LAAC group and 2.3% in the NOAC group. However, as the trial was limited by sample size and relatively short follow-up, any meaningful comparisons of individual endpoints were hindered. The authors estimated that a trial of approximately 7000 patients would be required to establish non-inferiority of LAAC versus NOAC for the composite endpoint of stroke, TIA, or systemic embolism alone (Osmancik et al., 2020). Nonetheless, at the median

follow-up of 3.5 years, LAAC remained non-inferior to NOACs for the primary endpoint, and moreover, LAAC was associated with a significantly reduced clinically relevant non-procedure-related bleeding (3.4%/year vs. 5.9%/year) (Osmancik et al., 2022). However, haemorrhagic strokes remained infrequent, occurring only in 3 (0.7%) patients (Osmancik et al., 2022).

Randomized comparison of the two most common LAAC devices has been lacking until recently. The recent randomized Amulet IDE (Amplatzer Amulet Left Atrial Appendage Occluder IDE Trial) trial demonstrated non-inferiority of the Amplatzer Amulet device compared to the Watchman device for safety (procedure-related complications, all-cause death, or major bleeding) and effectiveness (ischaemic stroke or systemic embolism) (Lakkireddy et al., 2021). A total of 1878 AF patients with a $CHADS_2$ score ≥2 or a CHA_2DS_2-VASc score of ≥3 were randomized, and around 20% of these patients were deemed to be at high risk of bleeding. Implantation was successful in 98.4% and 96.4% of patients with the Amulet and Watchman devices, respectively. Most patients with the Watchman device were discharged on warfarin plus aspirin, and most patients with the Amulet device received aspirin plus clopidogrel at discharge, and from 9 months on, most patients were on single APT alone. At 18 months, the rates of ischaemic stroke and major bleeding were similar in the Amulet group (1.7% for ischaemic stroke, and 11.6% for major bleeding), and in the Watchman group (1.9% for ischaemic stroke, and 12.3% for major bleeding).

In summary, randomized controlled trials have demonstrated that the composite outcome of percutaneous LAAC is comparable to warfarin, and more recently NOACs (primarily apixaban) (Table 5), although early potentially life-threatening procedure-related complications (e.g., device embolization, pericardial effusion, cardiac tamponade, and vascular access-related complications) are not negligible, ranging from 3% to 5% in the latest trials (Osmancik et al., 2020; Lakkireddy et al., 2021). Furthermore, randomized data are not yet available to establish superiority of LAAC over NOACs in AF patients at high bleeding risk, or to address the postprocedural antithrombotic treatment in these patients. In the following two chapters, the rationale and contemporary evidence for postprocedural antithrombotic treatment is outlined, and recent real-world observational studies on LAAC in AF patients at high bleeding risk and with previous intracranial bleeding are presented.

Table 5. Summary of randomized controlled trials comparing percutaneous left atrial appendage closure (LAAC) with oral anticoagulation (OAC).

	PROTECT AF		**PREVAIL**		**PRAGUE-17**	
Site (enrolment)	The United States and Europe (2005–2008)		The United States (2010–2012)		Czech Republic (2015–2019)	
Population	$CHADS_2$ ≥1. Exclusion criteria included contraindications to warfarin.		$CHADS_2$ ≥2 (or ≥1 with an additional risk factor). Additionally, excluded patients with indication for long-term clopidogrel.		Prior bleeding requiring hospitalization or intervention (~50%), or thromboembolism while on anticoagulation, or CHA_2DS_2-VASc ≥ 3 and HAS-BLED ≥ 2.	
Treatment arms	**LAAC** (Watchman) and warfarin + ASA for 45 days → DAPT until 6 months → lifelong SAPT	**Warfarin**	**LAAC** (Watchman) and warfarin + ASA for 45 days → DAPT until 6 months → lifelong SAPT	**Warfarin**	**LAAC** (Amulet or Watchman) and DAPT for 3 months → lifelong SAPT	**NOAC** (primarily apixaban)
No. of participants (CHA_2DS_2-VASc)	463 (3.4 ± 1.5)	244 (3.7 ± 1.6)	269 (4.0 ± 1.2)	138 (4.1 ± 1.2)	201 (4.7 ± 1.5)	201 (4.7 ± 1.5)
Age	71.7 ± 8.8	72.7 ± 9.2	74.0 ± 7.4	74.9 ± 7.2	73.4 ± 6.7	73.2 ± 7.2
Implant success	90.9% (408/449)	N/A	95.1% (252/265)	N/A	96.8% (181/187)	N/A
Follow-up	47.6 ± 21.3 months (2717 patient-years)		47.9 ± 19.4 months (1626 patient-years)		3.5 years (IQR, 2.6–4.3) (1354 patient-years)	
All 7-day procedure-related complications	8.7%, incl. pericardial effusion requiring intervention (4.0%)	N/A	4.5%, incl. pericardial effusion requiring intervention (1.9%)	N/A	2.1%	N/A
Ischaemic stroke	1.3%/y	1.1%/y	1.7%/y	0.7%/y	2.1%/y (all-stroke)	1.8%/y (all-stroke)
Haemorrhagic stroke	0.16%/y	1.06%/y	0.18%/y	0.54%/y	1 (0.5%)	2 (1%)
Cardiovascular or unexplained death	1.0%/y	2.3%/y	1.8%/y	2.0%/y	3.0%/y	4.4%/y
Key findings	The Watchman device was noninferior for prevention of the primary endpoint (composite of ischaemic or haemorrhagic stroke, systemic embolism, and cardiovascular or unexplained death) (2.2%/y vs. 3.7%/y).		The Watchman device was noninferior to warfarin for ischaemic stroke prevention or systemic embolism > 7 days post-procedure at 18 months, but statistical non-inferiority was not achieved for the primary endpoint (6.4% vs. 6.3%).		LAAC was noninferior to NOAC for prevention of the primary endpoint (composite of all-cause stroke, systemic embolism, cardiovascular death, clinically significant bleeding, or procedure-/device-related complications) (8.6%/y vs. 11.9%/y). Moreover, at median of 3.5 years, LAAC was associated with significantly reduced non-procedural bleeding.	
	At 5 years, the Watchman device was associated with significant reductions in haemorrhagic stroke, disabling/fatal stroke, cardiovascular and all-cause mortality, but no significant reduction in ischaemic stroke was found.					

Abbreviations: ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; N/A, not applicable; SAPT, single antiplatelet therapy. References: (Holmes et al., 2009, 2014; Reddy et al., 2017; Osmancik et al., 2020, 2022).

2.2.2.4 Postprocedural antithrombotic therapy

In current clinical practice, percutaneous LAAC is mainly performed in AF patients with contraindications to OAC and at high bleeding risk (Landmesser et al., 2018; Boersma et al., 2019), in accordance with the present AF guidelines (January et al., 2019; Hindricks et al., 2021). Although the objective of LAAC is to substitute for long-term OAC, antithrombotic treatment is recommended following endovascular LAAC to prevent thrombus formation until complete endothelialization of the implanted device (Glikson et al., 2020). Currently, dual APT is recommended for 1–6 months in this patient population based on observational data and prior experience with other endovascular devices (Glikson et al., 2020). However, in real-world practice, treatment strategies are considerably heterogeneous (Landmesser et al., 2018; Boersma et al., 2019). Nevertheless, most patients are treated with dual APT for 1–12 months post-LAAC, followed by indefinite single APT (Landmesser et al., 2018; Boersma et al., 2019). However, the optimal intensity, duration, and type of postprocedural antithrombotic strategies after LAAC remain controversial and empirical in the absence of randomized head-to-head comparison. Figure 6 illustrates various postprocedural treatment strategies.

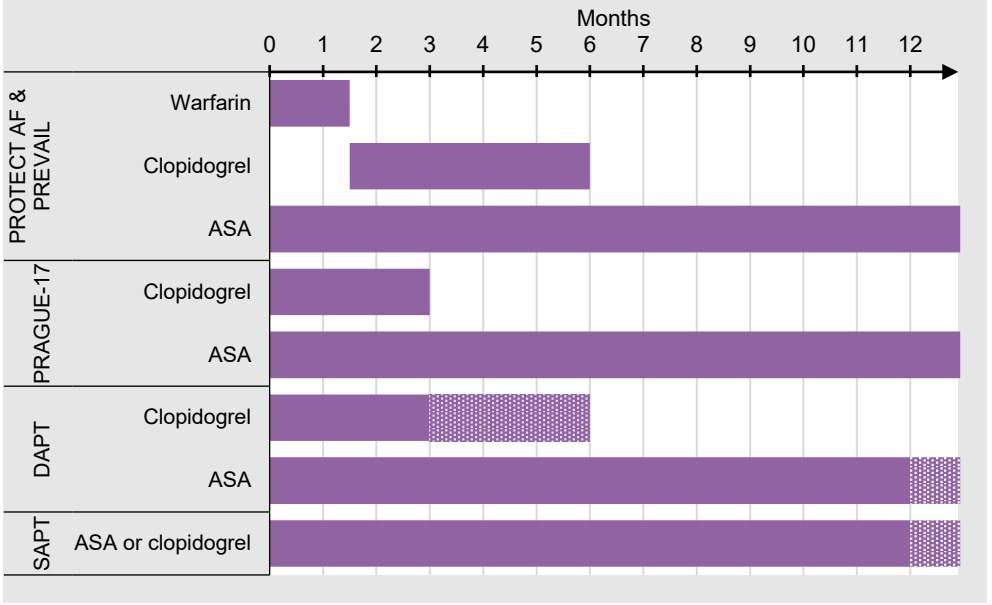


Figure 6. Illustration of various postprocedural antithrombotic strategies in the PROTECT AF, PREVAIL and PRAGUE-17 trials and real-world registries. The light colour indicates alternation in therapy duration. ASA denotes acetylsalicylic acid; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy. References: (Holmes et al., 2009, 2014; Landmesser et al., 2018; Boersma et al., 2019; Osmancik et al., 2020)

Device-related thrombus

Although the healing process is not fully understood, neo-endothelization of the device surface is desired for its antithrombotic properties. Pre-clinical studies in dogs indicate complete endothelialization in 1–3 months post LAAC (Schwartz et al., 2010; Kar et al., 2014). However, the biological healing process and time required for endothelialization cannot be directly extrapolated to diseased human hearts. For example, several surgical case reports show inadequate endothelialization from 10 months up to 2 years after LAAC (Massarenti & Yilmaz, 2012; Schiettekatte et al., 2014; Sharma et al., 2018). Also, recently device-related thrombus (DRT) associated with incomplete endothelialization has also been directly visualized in two cases 2–4 months post LAAC despite intensive postprocedural regimen of warfarin plus aspirin was administered (Abe et al., 2020; Nakamura et al., 2020). Additionally, Lindner et al. used computed tomography angiography to assess incomplete endothelialization, defined as contrast enhancement inside the LAA in the absence of any peri-device leak (Lindner et al., 2021). Six months post-LAAC, 20 (56%) of 36 consecutive patients without peri-device leak demonstrated incomplete endothelialization (Lindner et al., 2021). Thus, further studies are warranted to elucidate the significance and predictors of incomplete neo-endothelialization.

Thrombus formation on the LAAC device is an unfortunate complication occurring in approximately 2–4% of patients after LAAC, probably owing to incomplete device endothelialization (Alkhouli et al., 2018; Dukkipati et al., 2018; Aminian et al., 2019; Sedaghat et al., 2021). The risk of thromboembolic events is increased by 3–5-fold in the presence of DRT, with observed ischaemic event rates of 6.3–18.3% and 1.6–3.8% in patients with and without DRT, respectively (Alkhouli et al., 2018; Dukkipati et al., 2018; Aminian et al., 2019). Therefore, antithrombotic treatment is often switched to OAC until complete resolution of DRT (Glikson et al., 2020). Several known predictors of DRT include older age, previous ischaemic stroke, permanent AF, larger LAA ostium width, decreased left ventricular ejection fraction, and deep device implantation (Dukkipati et al., 2018; Fauchier et al., 2018; Aminian et al., 2019). However, although DRT is associated with higher thromboembolism rates, approximately up to 90% of ischaemic events after LAAC still occur in patients without DRT (Dukkipati et al., 2018; Aminian et al., 2019).

Antiplatelet therapy

The choice of postprocedural antithrombotic treatment in the prevention of DRT and residual burden of thromboembolism remains a matter of debate. In the PROTECT AF and PREVAIL trials, the intensive postprocedural treatment of warfarin plus aspirin for 6 weeks, followed by dual APT until 6 months, was largely based on prior animal data on endothelialization and empirical evidence from the early experience in human (Sick et al., 2007; Holmes et al., 2018). A 2019 study compared short-term OAC strategy (mainly similar to the PROTECT AF and PREVAIL trial protocols) with APT (mainly dual APT). At 6 months, there was no significant difference in thromboembolism or major bleeding between these strategies, although DRT was significantly more frequent in patients receiving APT (3.1%) than those receiving OAC (1.4%) (Søndergaard et al., 2019). Similarly, a recent meta-analysis of over 12 000 patients found no difference in all-cause stroke and major bleeding between OAC and APT (mainly dual APT) strategies after mean follow-up of 14 months (Osman et al., 2020). However, there was no significant difference in the incidence of DRT (3.0% vs. 2.0%, for APT and OAC strategies, respectively) and only 9% of patients received single APT (Osman et al., 2020).

Dual APT for 1–6 months, followed by indefinite single APT, is recommended for most patients after LAAC (Glikson et al., 2020). However, dual APT has been associated with a similar major bleeding risk compared to warfarin (ACTIVE Writing Group of the ACTIVE Investigators et al., 2006). Moreover, warfarin increased the risk of major bleeding by 57% (2.0%/year vs. 1.3%/year) and the risk of intracranial bleeding by 87% (0.4%/year vs. 0.2%/year) compared to single APT (aspirin) in the ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) A trial (Connolly et al., 2009a).

Long-term single APT is used in 60–70% of patients after LAAC in the real-world practice, while all antithrombotic treatments are discontinued only in 8–20% of patients within 1–2 years (Boersma et al., 2019; Hildick-Smith et al., 2020). Besides device-related indications for antithrombotic therapy, other indications may exist in real-life clinical practice, such as previous percutaneous coronary intervention or the secondary prevention of atherosclerotic cardiovascular disease (Collins et al., 2009). Nonetheless, aspirin monotherapy increases the risk of major bleeding by ~50–70% and the risk of intracranial bleeding by ~30–65% compared with no antithrombotic treatment (McQuaid & Laine, 2006; Abdelaziz et al., 2019; Hald et al., 2021). However, minimizing the postprocedural antithrombotic regimen to single APT at discharge has been evaluated only in a few studies (Table 6).

Table 6. Summary of recent studies investigating single antiplatelet therapy following percutaneous left atrial appendage closure (LAAC).

Country, number of subjects (Reference)	Age, years	CHA_2DS_2-VASc; HAS-BLED	Baseline characteristics	Device(s) for LAAC	Antithrombotic treatment post-LAAC	Follow-up	Outcome (% or %/year)
Canada N = 31 (Rodriguez-Gabella et al., 2016)	76 ± 7	5.5 ± 1.6; 4.5 ± 0.9	Previous intracranial bleeding (39%), gastrointestinal bleeding (39%)	ACP/Amulet 97%), Watchman (3%)	ASA 80–100 mg (71%), or clopidogrel 75 mg (29%) indefinitely	19 months (IQR, 12–24)	TEC: 0 Major bleeding: 1 (3.2%) Intracranial bleeding: 0 All-cause mortality: 5 (16%) DRT: 1 (3.3%) at 45 days
France N = 76 (Jalal et al., 2017)	73 ± 8	4.4 ± 1.3; 3.4 ± 1.0	Previous intracranial bleeding (66%), and stroke or TIA (52%)	ACP (80%), Amulet (20%)	ASA 80–325 mg (93%), or clopidogrel 75 mg (4%) for at least 12 months	13 ± 3 months, 75 patient-years	TEC: 3 (4.0%/y) IS: 2 (2.6%/y) Major bleeding: 1 (1.3%/y) Intracranial bleeding: 1 (1.3%/y) All-cause mortality: 2 (2.6%/y) DRT: 5/66 (6.8%) at 12 weeks
Denmark N = 110 (Korsholm et al., 2017)	73 ± 10	4.4 ± 1.6; 4.1 ± 1.1	Previous haemorrhagic stroke (70%), and bleeding event (82%)	ACP (67%), Amulet (33%)	ASA 75 mg (85%), or clopidogrel 75 mg (3%) for at least 6 months, DAPT (12%)	2.3 years (IQR, 1.6–3.2), 265 patient-years	IS: 6 (2.3%/y) Major bleeding: 10 (3.8%/y) Intracranial bleeding: 3 (2.8%) All-cause mortality: 20 (7.5%/y) DRT: 2 (1.9%)
Italy N = 280 (Patti et al., 2020)	76 ± 7	4.3 ± 1.5; 3.4 ± 0.9	Previous stroke (39%), major bleeding (56%), chronic renal failure (56%)	ACP/Amulet (77%), Watchman/other device (23%)	Low-dose ASA (95%) or clopidogrel (5%) up to 1 year	12 months	TEC: 5 (1.8%) Major bleeding: 8 (2.9%) Intracranial bleeding: 0 Cardiovascular mortality: 17 (6%) DRT: 4 (0.7%)

Values are number (%), mean ± standard deviation, or median (IQR) unless otherwise indicated. Abbreviations: ACP, Amplatzer Cardiac Plug; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; DRT, device-related thrombus; IS, ischaemic stroke; IQR, interquartile range; LAAC, left atrial appendage closure; TEC, thromboembolic complication; TIA, transient ischaemic attack.

2.2.2.5 Percutaneous left atrial appendage closure in patients with contraindications to oral anticoagulation

The PROTECT AF and PREVAIL trials found LAAC with the Watchman device to be comparable to warfarin treatment (Reddy et al., 2017). However, these trials excluded the very patients for whom LAAC could be considered according to the current guidelines, namely AF patients with contraindications to long-term OAC treatment (January et al., 2019; Hindricks et al., 2021). While NOACs with a more favourable safety profile and efficacy have emerged as the first-line OAC treatment for most patients with AF (Ruff et al., 2014), the PRAGUE-17 trial was the first to describe similar outcome in patients treated with LAAC and NOACs (Osmancik et al., 2020, 2022).

Retrospective, real-world studies indicate that percutaneous LAAC is effective in reducing thromboembolic events also in AF patients with contraindications to OAC (Boersma et al., 2019; Hildick-Smith et al., 2020). In 2 recent real-world studies with a total of over 2000 patients undergoing LAAC with the Watchman or Amplatzer Amulet device, 31–72% of patients had a history of major bleeding, and most patients were discharged on dual APT (58–60%) or short-term anticoagulation (18–27%) while less than one-fifth received single APT (7–22%) (Boersma et al., 2019; Hildick-Smith et al., 2020). At 2 years, the annual rate of ischaemic stroke was 1.3–2.2%, and the annual rate of major bleeding was 2.7–7.2% (Boersma et al., 2019; Hildick-Smith et al., 2020). Moreover, in patients with a prior major bleeding, the annual rate of major bleeding was 4.5–8.7% (Boersma et al., 2019; Hildick-Smith et al., 2020). Despite differences in study participants and postprocedural antithrombotic treatment, the real-world data in this high-risk population is comparable to the randomized trials in terms of ischaemic stroke rate (Table 5).

Furthermore, reflecting on the evidence from the randomized trials that excluded patients with contraindications to OAC, there is an indication that LAAC could reduce the risk of clinically relevant bleeding events. A 2017 patient-level meta-analysis of the PROTECT AF and PREVAIL trials found a 80% reduced risk of haemorrhagic stroke (a total of 18 events per 4343 patient-years) in the LAAC group (0.17%/year) compared to the warfarin group (0.87%/year) (Reddy et al., 2017). Also, the PRAGUE-17 found a significantly reduced rate of clinically relevant non-procedure-related bleeding in the LAAC group, treated with mainly single APT in long-term, compared to the NOAC group, treated with mainly apixaban (Osmancik et al., 2022).

However, the safety and efficacy of either LAAC or NOACs in patient at high bleeding risk have not yet been well-examined in randomized trials. The ASAP-TOO (ClinicalTrials.gov identifier: NCT02928497) trial is an ongoing randomized clinical trial that will compare the Watchman device to single APT or no therapy in up to 888 AF patients who are deemed unsuitable for long-term OAC but have an

indication for thromboprophylaxis (i.e., a CHA_2DS_2-VASc score ≥ 2) (Holmes et al., 2017). Moreover, in CLOSURE-AF (ClinicalTrials.gov identifier: NCT03463317), the clinical benefit of LAAC followed by APT is being compared with OAC (NOACs or VKAs) in AF patients at high bleeding risk (Glikson et al., 2020).

The clinical dilemma of intracranial bleeding (reviewed in more detail in Chapter 2.2.1.5) has been addressed by only a handful of LAAC studies (Table 7). However, in these observational studies, the delay from prior intracranial bleeding to LAAC has ranged on average from 7 months to 2.5 years, and the postprocedural treatment has been heterogeneous, including single APT, dual APT and OAC (Table 7). Besides the randomized trials assessing OAC versus avoiding OAC after intracranial bleeding (e.g., the ENRICH-AF, ASPIRE and PRESTIGE-AF trials), the STROKECLOSE (ClinicalTrials.gov identifier: NCT02830152) and A3ICH (ClinicalTrials.gov identifier: NCT03243175) trials are ongoing randomized trials aiming at assessing the efficacy and safety of LAAC after intracerebral bleeding (Glikson et al., 2020; Schreuder et al., 2021). The A3ICH trial aims to assess the net clinical benefit of NOAC (apixaban) compared to LAAC or avoiding OAC in 300 patients with AF and a spontaneous intracerebral bleeding no earlier than 14 days before randomization. The STROKECLOSE trial is another ongoing trial with a target of 750 AF patients, with a recent intracerebral bleeding from 4 weeks to 6 months prior to the enrolment, randomized to LAAC with the Amplatzer Amulet device or conventional therapy (OAC/APT/no therapy) (Glikson et al., 2020).

Table 7. Summary of recent studies investigating endovascular left atrial appendage closure (LAAC) in patients with prior intracranial bleeding.

Country Number of subjects (Reference)	**Age, years**	**CHA_2DS_2-VASc; HAS-BLED**	**Types of intracranial bleeding**	**Delay from bleeding to LAAC**	**Device(s) for LAAC**	**Postprocedural antithrombotic treatment**	**Follow-up**	**Outcome (% or %/year)**
Germany N = 20 (Horstmann et al., 2014)	72.6 ± 5.8	4.5 ± 1.4; 4.7 ± 1.0	ICH (75%), SDH (20%), SAH (5%)	23.1 ± 28.6 months	ACP (100%)	ASA and clopidogrel for 3 months, then ASA indefinitely	13.6 ± 8.2 months	TEC: 0 Major bleeding: 0 All-cause mortality: N/A
Canada N = 26 (Fahmy et al., 2016)	76 ± 7.0	4.9 ± 1.7; 4.4 ± 0.6	N/A (intraocular, 8%)	30 ± 48 months	ACP (46%), Watchman (35%), Amulet (19%)	ASA and clopidogrel (92%) for 1–3 months, then ASA for ≥ 6 months	11.9 ± 13.3 months	TEC: 1 TIA (3.8%) Major bleeding: 0 All-cause mortality: 1 (3.8%)
France N = 46 (Renou et al., 2017)	73.7 ± 8.4	5.2 ± 1.1; 4.0 ± 1.0	ICH (100%): lobar (54%), CAA-related (6%), deep (40%)	7 ± 4 months	ACP/Amulet (87%), Watchman (13%)	ASA (94%) ≥ 6 months (56% lifelong), ASA and clopidogrel (2%)	12.6 ± 7 months	TEC: 2 IS (4.35%/y) Major bleeding: 4.35%/y, 1 ICH All-cause mortality: 3 (6.5%)
Multiple countries* N = 198 (Tzikas et al., 2017a)	73.7 ± 7.9	4.5 ± 1.5 3.5 ± 1.1	N/A	N/A	ACP (100%)	SAPT (48%), DAPT (11%), various combinations	18.4 ± 12.0 months	TEC: 1.4%/y (stroke/TIA) Major bleeding: 0.7%/y, 1 ICH (0.5%) All-cause mortality: N/A
Spain N = 9 (Fayos-Vidal et al., 2017)	72.7 ± 8.2	4 (IQR, 2.5); 3 (IQR, 0)	ICH (8: 7 deep, 1 lobar), SDH (1)	<1 month (5); 12 ± 16 months	Amulet (7), ACP (2)	ASA or clopidogrel for 6 months (5) and indefinitely (4)	15 months (range, 0.25–2 years)	TEC: 0 Major bleeding: 0 All-cause mortality: 0
Spain N = 47 (Cruz-González et al., 2017)	80 ± 6	5 ± 1; 4 ± 1	ICH (72%), SDH (21%), SAH (4%)	median 8 months (range, 3–20)	Watchman (51%), Amulet (45%), ACP (4%),	ASA and clopidogrel (81%), ASA or clopidogrel alone (11%)	28 months (IQR, 15–48 months)	TEC: 1 IS (0.86%/y) Major bleeding: 1 SAH (0.86%/y) All-cause mortality: N/A

Table 7. (Continued)

Country Number of subjects (Reference)	**Age, years**	**CHA_2DS_2-VASc; HAS-BLED**	**Types of intracranial bleeding**	**Delay from bleeding to LAAC**	**Device(s) for LAAC**	**Postprocedural antithrombotic treatment**	**Follow-up**	**Outcome (% or %/year)**
Denmark, Finland, Sweden N = 151 (Nielsen-Kudsk et al., 2017)	71.9 ± 8.7	3.9 ± 1.5; 4.2 ± 0.8	ICH (100%)	6 months (IQR, 3–32)	ACP/Amulet (100%)	ASA and/or clopidogrel (93%)	6 months (IQR, 3–12)	TEC: 2 IS (1.7%/y) Major bleeding: 3.5%/y, 1 ICH (0.9%/y) All-cause mortality: 2 (1.7%/y)
United States N = 38 (Hutt et al., 2019)	73.2 ± 7	5.0 ± 1.3; 4.2 ± 1.0	ICH (60%), SDH (24%), SAH (16%)	21 months (IQR, 4–25)	Watchman (100%)	OAC and ASA for 45 days, then DAPT until 6 months, then lifelong ASA	13.5 months (IQR, 8–19)	TEC: 0 Major bleeding: 0 All-cause mortality: 0
United States N = 16 (Ajmal et al., 2020)	74.6 ± 5.8	4.5 (IQR, 3); 4 (IQR, 1)	ICH (43.7%), SDH (43.7%), SAH (12.5%)	≥ 8 weeks	Watchman (100%)	OAC and ASA for 45 days, then DAPT until 6 months, then lifelong ASA	27 months	TEC: 0 Major bleeding: 0 All-cause mortality: 0
United States N = 63 (Hucker et al., 2020)	75.3 ± 6.0	4.9 ± 1.7; 3.5 ± 1.1	ICH (57%), SDH (29%), SAH (10%)	7 months (IQR, 3–18)	Watchman (100%)	OAC and ASA (43%), DAPT (19%)	6 months	TEC: 0 IS Major bleeding: 2 (3.2%) All-cause mortality: 3 (4.8%)
Italy N = 32 (Barocelli et al., 2020)	75.4 ± 9	4.4 ± 1.7; 3.2 ± 0.9	ICH (68%), SDH (19%), SAH (13%)	N/A	ACP/Amulet (100%)	DAPT (81%), SAPT (19%)	24 ± 15 months	TEC: 4.8%/y, 2 IS (3.2%/y) Major bleeding: 1 (1.6%/y) All-cause mortality: 1 (1.6%/y)
Italy N = 110 (Casu et al., 2021)	74 ± 8.6	4.16 ± 0.46; 3.56 ± 1.02	ICH (75%), SDH (17%), SAH (8%)	N/A	Watchman (45%), ACP (18%), Amulet (34%)	DAPT (54%), SAPT (30%)	12 months	TEC: 3 IS (2.7%), 1 TIA Major bleeding: 4 ICH (3.6%) All-cause mortality: 4 (3.6%)

Abbreviations: ACP, Amplatzer Cardiac Plug; ASA, acetylsalicylic acid; CAA, cerebral amyloid angiopathy; DAPT, dual antiplatelet therapy; ICH, intracerebral haemorrhage; IS, ischaemic stroke; IQR, interquartile range; LAAC, left atrial appendage closure; N/A, not available or not available; SAH, subarachnoid haemorrhage; SAPT, single antiplatelet therapy; SDH, subdural haemorrhage; TEC, thromboembolic complication; TIA, transient ischaemic attack. *Belgium, Switzerland, Germany, the United Kingdom, Italy, and Portugal.

2.3 Cardiac troponins and the diagnosis of acute myocardial infarction in atrial fibrillation

2.3.1 Cardiac troponins, myocardial injury and infarction

Troponins are regulatory proteins of striated muscle contraction, essential for skeletal and cardiac muscle contraction. The basic contractile unit for striated muscle cell is the sarcomere, composed mainly of actin and myosin filaments. Troponin complex and tropomyosin, distributed alongside actin filaments, regulate the calcium-dependent interaction between the myofilaments. According to the sliding filament theory, muscle contraction and force generation are the result of these myofilaments sliding relative to each other (Parmacek & Solaro, 2004). The troponin complex consists of three subunits, of which troponin C (~18 kDa) binds to calcium, troponin I (~23 kDa) inhibits contraction in the absence of calcium, and troponin T (~35 kDa) binds the complex to tropomyosin (Parmacek & Solaro, 2004). Cardiac troponin (cTn) C is expressed in both cardiac and slow-twitched skeletal muscle, while cTn I and cTn T are encoded by unique genes and are almost exclusively expressed in cardiomyocytes (Parmacek & Solaro, 2004), although increase cTn T, but not cTn I, levels may be detected in patients with skeletal muscle injury and myopathy (Thygesen et al., 2019).

Myocardial infarction is characterized by cardiomyocyte death due to prolonged myocardial ischaemia, resulting in concurrent cTn release in proportion to the extent of myocardial injury. Type 1 myocardial infarction is due to an acute atherothrombotic event attributable to coronary artery disease, and usually requires urgent revascularization and antithrombotic strategies (Collet et al., 2021). On the other hand, type 2 myocardial infarction is caused by an imbalance in myocardial oxygen supply and demand without acute atherothrombosis (Collet et al., 2021). In current clinical practice, cTn I and T are the biomarkers of choice for the differential diagnosis of acute non-ST-segment elevation myocardial infarction (Table 8), and other less specific and less sensitive biomarkers (e.g., creatine kinase myocardial band, myoglobin, and lactate dehydrogenase) have been superseded by troponin testing (Thygesen et al., 2019).

Table 8. Summary of the key definitions in the 4th Universal Definition of Myocardial Infarction.

Term	Criteria	Description
Myocardial injury	▪ ≥ 1 elevated cTn value above the 99th percentile of the levels detected in a healthy reference population (i.e., 99th percentile upper reference limit). A rising and/or falling pattern indicates an acute myocardial injury.	Any injury to myocardial cells that causes an elevation in circulating cTn above normal levels.
Type 1 myocardial infarction	▪ ≥ 1 elevated cTn value with a rising and/or falling pattern and ▪ ≥ 1 of the following: symptoms of acute myocardial ischaemia, new ischaemic ECG changes, pathological Q wave development, imaging evidence of loss of viable myocardium or ischaemic regional wall motion abnormality, or identification of a coronary thrombus.	Acute atherothrombotic event that is caused by underlying coronary artery disease and plaque rupture/erosion.
Type 2 myocardial infarction	▪ ≥ 1 elevated cTn value with a rising and/or falling pattern and ▪ a mismatch between oxygen supply and demand unrelated to acute atherothrombotic coronary event and ▪ ≥ 1 of the following: symptoms of acute myocardial ischaemia, new ischaemic ECG changes, pathological Q wave development, or imaging evidence of loss of viable myocardium or ischaemic regional wall motion abnormality.	Acute myocardial injury that results from an imbalance in myocardial oxygen supply and demand but is not caused by rupture/erosion of atherosclerotic plaque.

Clinical classification of myocardial infarction includes also types 3–5 (fatal myocardial infarction occurring before blood sampling, myocardial infarction related to percutaneous coronary intervention, and myocardial infarction related to coronary artery bypass grafting, respectively). Abbreviations: cTn, cardiac troponin; ECG, electrocardiogram. Reference: (Thygesen et al., 2019).

However, differentiating type 1 myocardial infarction from other causes of cTn elevation poses a clinical challenge. High-sensitivity cTn (hs-cTn) assays can detect circulating cTn in the majority of healthy individuals and enable precise detection of abnormal cTn levels (Thygesen et al., 2019). Thus, high negative predictive value of normal hs-cTn level allows a rapid rule-out strategy of myocardial infarction (Collet et al., 2021). However, the interpretation of elevated cTn levels is complicated by numerous conditions other than type 1 myocardial infarction (Table 9), especially in patients with mild cTn elevations (Boeddinghaus et al., 2017), and in unselected patient populations (Shah et al., 2017).

Table 9. Various acute and chronic conditions associated with elevated cardiac troponin level apart from type 1 myocardial infarction.

Cardiac conditions	Systemic and non-cardiac conditions
Cardiac procedures	Anaemia
Cardiomyopathy	Aortic dissection
Coronary artery spasm/embolism/dissection	Critical illness, sepsis, hypotension
Heart failure	Infiltrative disease
Myocarditis	Pulmonary embolism
Tachyarrhythmia	Renal disease
Takotsubo cardiomyopathy	Strenuous exercise

References: (Thygesen et al., 2019; Collet et al., 2021).

2.3.2 Prevalence and prognostic value of elevated cardiac troponins in atrial fibrillation

Elevated cTn levels (i.e., above the 99th percentile upper reference limit) are frequently observed in patients with AF in both acute and stable settings. Increased basal cTn levels were found in approximately 5–25% of stable AF patients in the biomarker substudies of ARISTOTLE, RE-LY and ENGAGE AF-TIMI 48 trials (Hijazi et al., 2012, 2014a; Ruff et al., 2016). In the emergency department, cTns are routinely measured in up to 90% of patients presenting with AF, and 14–56% of these patients have elevated cTn levels (Meshkat et al., 2011; Van Den Bos et al., 2011; Augusto et al., 2017; Stoyanov et al., 2018). However, only one-fifth of AF patients with elevated cTns are diagnosed with acute coronary syndrome and four in five patients have an alternative diagnosis (Augusto et al., 2017; Stoyanov et al., 2018). From another perspective, elevated cTn levels are found in 15–44% of patients who are hospitalized primarily due to AF (Parwani et al., 2013; Gupta et al., 2014; Kaura et al., 2020). In a Portuguese study of 383 AF patients, cTn was measured in 91% of hospitalized patients (Augusto et al., 2017). Notably, among patients with mildly elevated cTn value, acute coronary syndrome was an infrequent diagnosis, occurring only in 5% of patients compared to 68% of patients with markedly elevated cTn level (i.e., >10 times above the upper limit of normal) (Augusto et al., 2017). Similarly, in a German study of nearly 3000 AF patients admitted to the emergency department, the majority (88%) had detectable and 56% had elevated hs-cTn T levels (Stoyanov et al., 2018). Elevated cTn levels were found in 34% of patients with the main admission diagnosis of AF. However, myocardial infarctions comprised only 14% of admission diagnoses in patients with elevated cTn levels (Stoyanov et al., 2018).

The prognostic significance of cTn levels is widely recognized, and in the general population, greater basal hs-cTn levels have been associated with developing cardiovascular disease, including coronary artery disease and stroke (Willeit et al.,

2017), heart failure (Evans et al., 2018), and incident AF (Filion et al., 2015; Zhu et al., 2018). In AF patients, increased basal hs-cTn levels, even in concentrations below the 99th percentile upper reference limit, predict future adverse events, including stroke, thromboembolism, cardiac death and major bleeding (Hijazi et al., 2012, 2014a; Ruff et al., 2016; Broersen et al., 2020). Moreover, in hospitalized AF patients, elevated cTn levels have been independently associated with increased risk of myocardial infarction (Gupta et al., 2014), heart failure hospitalization (Quesada et al., 2021), and all-cause mortality (Van Den Bos et al., 2011; Stoyanov et al., 2018; Kaura et al., 2020; Paana et al., 2021).

2.3.3 Pathophysiological mechanisms of cardiac troponin release

Cardiomyocyte necrosis is considered the principal mechanism for cTn release secondary to myocardial infarction (White, 2011; Mair et al., 2018). An immunohistochemical study by Fishbein and colleagues demonstrated that, following permanent or temporary coronary occlusion in 50 experimental animals, cTn was lost solely from necrotic cardiomyocytes (Fishbein et al., 2003). However, release of cTn from cardiomyocytes occurs in response to a range of insults, including transient myocardial ischaemia, trauma, inflammation, and toxins (Jeremias & Gibson, 2005; White, 2011). The prevailing assumption is that majority of cTns are structurally bound to actin filaments in the contractile apparatus, whilst small amounts (3–8%) of cTns are loosely bound and constitute rapidly releasable pools (Katus et al., 1991; Adams et al., 1994; Mair et al., 1996; Bleier et al., 1998). Myocardial infarction results in a characteristic pattern of circulating cTn with an initial rise followed by a sustained release lasting up to 7–14 days (Adams et al., 1994; Mair et al., 1996). The sustained increase in cTn level has been presumed to be caused by gradual degradation of structurally bound myofibrils, and changes in the plasma flow through the damaged myocardium (Starnberg et al., 2014).

However, clinical conditions other than acute myocardial infarction can be associated with an increase in circulating cTn levels, which suggests alternative and multifactorial mechanisms besides myocardial necrosis (White, 2011; Mair et al., 2018). Circulating cTn levels may increase as a result of abnormal cardiac stress, as is seen in supraventricular tachycardia (Redfearn et al., 2005; Sayadnik et al., 2017), rapid atrial pacing (Turer et al., 2011), and strenuous exercise (Shave et al., 2010; Paana et al., 2019). Moreover, rapid atrial pacing may induce cTn release even in the absence of clinical signs of myocardial ischaemia (Turer et al., 2011), and positive stress test alone (i.e., inducible myocardial ischaemia on ECG) does not correlate with increased cTn levels (Samaha et al., 2019). Overall, potential pathophysiological mechanisms include necrosis, apoptosis, release of membranous

blebs and proteolytic degradation products, increased cell membrane permeability, and cardiomyocyte renewal (White, 2011; Mair et al., 2018).

A mismatch between myocardial oxygen demand and supply (i.e., demand ischaemia) could predispose to cTn release in AF. The irregular ventricular rhythm during acute AF is associated with impaired diastolic coronary flow dynamics and unmet myocardial oxygen demand (Kochiadakis et al., 2002), and the impairment appears to be accentuated with high ventricular rates (Scarsoglio et al., 2019). Moreover, rapid atrial pacing is associated with ventricular oxidative stress that is mediated by angiotensin II type 1 receptor signalling, and subsequently associated with impaired microvascular blood flow and cTn release (Goette et al., 2009). Transient myocardial ischaemia induced by stress testing is associated with modest albeit quantifiable cTn release in proportion to the degree of ischaemia on nuclear imaging (Sabatine et al., 2009). Similarly, in a recent pioneering clinical study, balloon-induced ischaemia for 30–90 seconds was sufficient to cause an increase in hs-cTn levels (Árnadóttir et al., 2021), while myocardial necrosis seems unlikely after such a brief ischaemia (Weil et al., 2017). In a porcine model, Weil and colleagues demonstrated that brief ischaemia was associated with cTn release without any histopathological evidence of necrosis but instead with evidence of focal myocyte apoptosis (Weil et al., 2017), although there is controversy regarding the methods to detect apoptosis (Hammarsten et al., 2018). Another ischaemia-induced mechanism was proposed by Hickman et al. who suggested that cTn could be released by the formation of membranous blebs from intact plasma membrane and without irreversible cardiomyocyte death (Hickman et al., 2010). It has also been suggested that cTn could be released via cell wounds (i.e., pores in the plasma membrane) under ischaemia, beta-adrenergic stimulation or mechanical stretching (Hammarsten et al., 2018). Moreover, intrinsic repair mechanisms seem to protect against cell death after such membrane injury, and impairment of cell wound repairment could hypothetically result in persistent cTn elevations (Hammarsten et al., 2018).

Furthermore, myocardial strain (i.e., deformation of myocardial structure under excessive wall tension) is a potential non-ischaemic cause of cTn release (Jeremias & Gibson, 2005). Preload-induced mechanical stretch may induce proteolytic cTn degradation (Feng et al., 2001), increase cell membrane permeability (Hammarsten et al., 2018), and induce apoptosis (Weil et al., 2018). Hessel et al. demonstrated that stimulation of stretch-responsive integrins *in vitro* results in the release of cTn I without irreversible cell death (Hessel et al., 2008). Meanwhile, Weil and colleagues demonstrated in a porcine model that increased left ventricular end-diastolic pressure, produced by intravenous phenylephrine infusion, was associated with cTn I release and cardiomyocyte apoptosis in the absence of myocardial ischaemia and cardiomyocyte necrosis (Weil et al., 2018). Moreover, cardiomyocyte renewal rate

is approximately 0.5–2% per year in healthy human hearts (Eschenhagen et al., 2017), which could explain some degree of detectable basal hs-cTn levels in healthy subjects as well as AF patients. Additionally, cardiomyocyte renewal rate could be accelerated after myocardial injury (Eschenhagen et al., 2017).

2.3.4 Rapid ventricular rate and tachycardia-induced cardiomyopathy in atrial fibrillation

AF can cause AF-induced and tachycardia-induced cardiomyopathy that are characterized by a potentially reversible left ventricular dysfunction. Tachycardia-induced cardiomyopathy results from high ventricular rates, usually due to supraventricular tachyarrhythmias, whereas AF-induced cardiomyopathy develops despite adequate rate control (Huizar et al., 2019). In these conditions, chronic high ventricular rates and recurrent arrhythmias are considered to eventually result in rapid deterioration in ventricular function as heart failure sets in, and arrhythmia control is required for recovery (Huizar et al., 2019). Moreover, the diagnosis requires exclusion of other irreversible and reversible causes of cardiomyopathy (Huizar et al., 2019). However, the prevalence of AF- and tachycardia-induced cardiomyopathy in patients with AF is unclear. A recent retrospective study of 482 patients with paroxysmal AF, and previously normal left ventricular ejection fraction in sinus rhythm, found that heart rate was an independent predictor of reduced left ventricular systolic function during AF (Marcusohn et al., 2021). Of 482 patients, 80 (17%) patients had reduced left ventricular ejection fraction during AF and a higher median heart rate (120 beats/min minute vs. 103 beats/min) than those with preserved ejection fraction (Marcusohn et al., 2021).

In experimental animal models, rapid atrial or ventricular pacing causes left ventricular systolic and diastolic dysfunction to a degree that is dependent on the duration and rate of tachycardia (Coleman et al., 1971; Damiano et al., 1987; Spinale et al., 1990; Shinbane et al., 1997). During chronic tachycardia cardiac output and left ventricular ejection fraction begin to decline as heart failure sets in (Shinbane et al., 1997). However, after termination of rapid pacing, ejection fraction usually normalized within 1–2 weeks, but end-diastolic volumes remain persistently elevated beyond 12 weeks (Damiano et al., 1987). Besides the haemodynamic changes, chronic tachycardia produces structural changes that result in dilated cardiomyopathy but without significant hypertrophy or increased ventricular mass (Shinbane et al., 1997). However, during recovery phase after cessation of tachycardia, left ventricular hypertrophy and diffuse interstitial fibrosis may develop (Spinale et al., 1991; Shinbane et al., 1997). At the cellular level, chronic rapid pacing is associated with depletion of myocardial energy stores, cardiomyocyte loss, cellular elongation, and disruption of basement membrane attachment and

surrounding extracellular matrix (Shinbane et al., 1997; Gupta & Figueredo, 2014). Additionally, angiotensin II type 1 receptor-mediated oxidative stress, impaired myocardial blood flow and cTn I release have been associated with rapid atrial pacing in animal model (Goette et al., 2009).

Rate and rhythm control strategies are currently primarily indicated to reduce AF-related symptoms (Hindricks et al., 2021). In permanent AF, lenient (< 100 beats/min at rest) and strict (< 80 beats/min at rest) rate control strategies are associated with a similar rate of major cardiovascular events (Van Gelder et al., 2010), a comparable impact on quality of life (Groenveld et al., 2011), and no difference in adverse atrial or ventricular remodelling (Smit et al., 2011). However, recent evidence suggests that early rhythm control strategy, including mainly antiarrhythmic drugs, in patients with newly diagnosed AF is associated with a lower risk of adverse cardiovascular events compared with rate control strategy (Kirchhof et al., 2020; Kim et al., 2021). Moreover, catheter ablation for AF as the initial rhythm control strategy significantly improves quality of life and reduces hospitalization without increasing the risk of adverse events (Andrade et al., 2021).

The restoration of sinus rhythm with AF ablation compared with pharmacological rate control in patients with idiopathic cardiomyopathy and systolic dysfunction (i.e., a left ventricular ejection fraction ≤ 45%) is associated with a significantly improved left ventricular function (Prabhu et al., 2017), and partly reversible fibrosis (Prabhu et al., 2018), suggesting that structural changes in AF-induced cardiomyopathy are not completely reversible. Therefore, catheter ablation for pulmonary vein isolation is recommended in patients with highly probable AF-induced cardiomyopathy (Hindricks et al., 2021).

In recent randomized trials, catheter ablation for AF compared with standard pharmacological rate and/or rhythm control was associated with a significantly reduced risk of death and heart failure hospitalization in patients with a left ventricular ejection fraction ≤ 35% (Marrouche et al., 2018), but also a significantly reduced risk of death or cardiovascular hospitalization in AF patients, of whom only ~5% had an ejection fraction ≤ 35% (Packer et al., 2019). In addition to AF ablation, a rate control strategy of atrioventricular node ablation and biventricular pacing in AF patients with heart failure was shown to be superior to pharmacological rate control in improving quality of life and reducing heart failure hospitalization (Brignole et al., 2018), and more recently, reducing all-cause mortality (Brignole et al., 2021).

3 Aims

The principal aim of this research was to address contemporary challenges in the management of AF. The specific aims of the studies were as follows:

1. To evaluate the outcome of AF patients at high bleeding risk receiving abbreviated or long-term single APT following LAAC (Study I).
2. To investigate the outcome of AF patients with previous intracranial bleeding and thromboembolism undergoing LAAC (Study II).
3. To identify factors associated with hs-cTn T release in patients presenting to the emergency department with symptomatic AF, and to assess the impact of ventricular rate on circulating hs-cTn T levels (Study III).

4 Materials and Methods

4.1 Study subjects and design

4.1.1 Prospective registry on percutaneous left atrial appendage closure (Studies I and II)

Subjects

Studies I and II were observational cohort studies based on a prospectively maintained single-centre registry on AF patients undergoing percutaneous LAAC device implantation in Turku University Hospital, Finland. All consecutive adult patients with contraindications to OAC (i.e., high bleeding risk or prior major bleeding event) undergoing LAAC between February 2009 and August 2018 were invited to participate in the registry. During the study period, 172 patients were recruited, and of those 165 (95.9%) patients were discharged from the hospital following successful LAAC and had follow-up available.

Procedure

Percutaneous LAAC procedure was performed under general anaesthesia and using a femoral vein catheterization by experienced operators. Fluoroscopic guidance and continuous transoesophageal echocardiography were used throughout the implantation procedure. The LAAC device was delivered in the LAA using transseptal approach. Adequate device position was verified before the LAAC device was released from the delivery system. Devices used for LAAC were the Amplatzer Cardiac Plug (Abbott Vascular, Santa Clara, California, USA), the Amulet device (Abbott Vascular, Santa Clara, California, USA), and the Watchman device (Boston Scientific, Marlborough, Massachusetts, USA). Prior to discharge from the hospital, adequate device position was confirmed, and pericardial effusion was excluded. The postprocedural antithrombotic regimen were chosen individually at operators' discretion after assessment of perceived risks for bleeding and thromboembolic complications.

Design

In Study I, AF patients with contraindications to OAC treated with single APT alone following successful LAAC were included, and patients who were discharged on anticoagulation therapy were excluded. The monotherapies were predominantly aspirin (ASA, acetylsalicylic acid) 100 mg per day, or clopidogrel 75 mg per day. According to the duration of postprocedural APT, two groups were formed to describe patients treated with short-term (i.e., ≤ 6 months) and long-term (i.e., lifelong) single APT strategies.

In Study II, patients with a history of intracranial bleeding undergoing successful LAAC were included, and patients were assigned into two groups according to whether they had a history of thromboembolic event or not. In Study II, previous intracranial bleeding events were retrospectively reviewed from electronic patient records and further classified based on the ICD-10 codes (International Classification of Diseases, Tenth Revision). The date of prior intracranial bleeding was retrieved to evaluate time from the bleeding event to LAAC procedure. If the exact date was unavailable, the date was approximated to the last date of the month/year or listed as a missing value. A flow chart and Venn diagram of the study participants is shown in Figure 7.

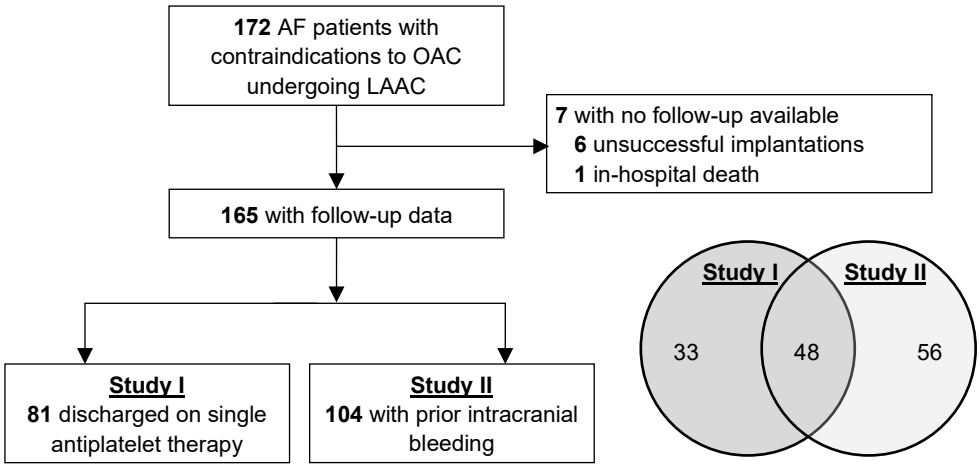


Figure 7. Flow chart and Venn diagram of the study population in Studies I and II. AF denotes atrial fibrillation, LAAC, left atrial appendage closure, and OAC, oral anticoagulation.

To gather and record data on patient characteristics, procedure, antithrombotic medications, in-hospital and follow-up complications, a prespecified electronic case report form was used. Patients were prospectively followed up to 5 years, and then patient records were retrospectively reviewed until April 26, 2019. First clinical follow-up was scheduled 1–3 months post-procedure, and thereafter patients were followed annually through phone calls or clinic visits.

Recorded in-hospital and procedure-related complications included ischaemic cerebrovascular events, myocardial infarction, cardiac tamponade, device embolization and bleeding events. The primary outcomes were thromboembolic events (ischaemic stroke, TIA, or systemic embolism) and intracranial bleeding. The secondary outcomes were major bleeding and all-cause mortality. Causes of death were obtained from the Causes of Death Registry, Statistics Finland, and electronic patient records. All endpoint events were recorded and reviewed retrospectively. Thromboembolic events were recorded as diagnosed by the treating neurologist, and defined according to the Munich consensus document (Tzikas et al., 2017b). Major bleeding was defined as overt bleeding with a decrease in haemoglobin of 20 g/L or more, requiring the transfusion of 2 or more units of blood, occurring in a critical site, or contributing to death, according to the International Society on Thrombosis classification (Schulman & Kesron, 2005).

4.1.2 Troponin release in symptomatic atrial fibrillation (Study III)

Subjects

Study III was a retrospective cohort study based on data from Tropo-AF study (Minor Troponin Elevations in Patients With Atrial Fibrillation, ClinicalTrials.gov Identifier: NCT03683836). The Tropo-AF study aimed to identify aetiological factors associated with minor cTn T elevations in AF patients visiting the emergency department of the Turku University Hospital, Finland. Between March 2013 and April 2016, the Tropo-AF study included a total of 2911 adult patients with AF. Of the 2911 patients, 501 (17%) fulfilled the following inclusion criteria for Study III:

(a) at least two hs-cTn T samples obtained within 72 hours,

(b) serial measures of hs-cTn T not exceeding 100 ng/L,

(c) AF confirmed by a 12-lead ECG on admission, and

(d) AF designated as the principal discharge diagnosis.

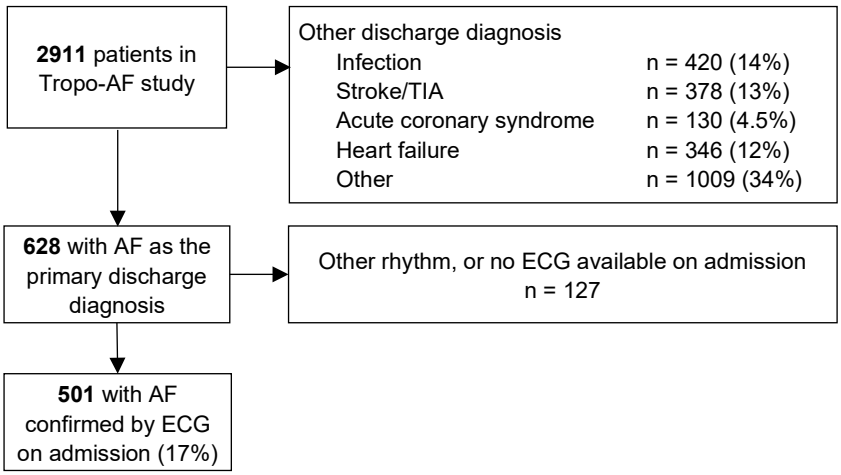


Figure 8. Flow chart of the study population in Study III. AF denotes atrial fibrillation, ECG, electrocardiogram, and TIA, transient ischaemic attack.

Patients aged < 18 years or residing outside the catchment area of Turku University Hospital were excluded from this study. Moreover, in patients with multiple emergency department admissions during the study period, only the first one was considered for this analysis. The flow chart of the study is shown in Figure 8.

Design

In Study III, a prespecified electronic case report form was used to manually gather comprehensive clinical data on baseline characteristics and 12-month follow-up of all-cause mortality, myocardial infarctions, and ischaemic strokes. Laboratory data were collected through computerized search of the laboratory database provided by Turku University Hospital laboratory service. The primary outcome was the peak hs-cTn T level within 72 hours of the emergency department admission. Throughout the study period, hs-cTn T was measured in the hospital laboratory using a commercial hs-cTn T assay (Elecsys Troponin T-high sensitive, Roche Diagnostics GmbH, Mannheim, Germany) and standard methods. The limit of detection for the assay was 5 ng/L, and an upper reference limit of 14 ng/L was used. The admission heart rate was derived from the first 12-lead ECG obtained during the index admission. Dynamic hs-cTn T change was defined as the absolute value of the difference between the peak and minimum hs-cTn T values divided by the minimum hs-cTn T value.

4.2 Statistical analysis

The statistical analyses were performed using SPSS Statistics for Windows, version 25.0 (IBM Corporation, Armonk, New York, USA), and R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). The SPSS software was used for analyses in all of the studies (I–III), and additionally, the R software was used for analyses in Studies II and III.

Categorical variables were reported as counts (n) and percentages (%). In Studies I and II, categorical variables were compared using the chi-square test, or Fisher's exact test when the expected values was less than 5. In Study III, Fisher's exact test or Mantel-Haenszel linear-by-linear association test for trend were used.

Continuous variables were reported as mean and standard deviation (SD), or median and interquartile range (IQR), and compared between groups using independent sample t-test or Mann-Whitney U-test, as appropriate. Normality of data was visually assessed using Q-Q plots and histograms, or Shapiro-Wilk test. A 2-sided p value < 0.05 was considered significant. Comprehensive statistical methods for the studies are described below.

Studies I and II

Incidence rate was calculated as number of events divided by the observation time in years and expressed per 100 patient-years. Patient-years were estimated from the index procedure until the event of interest or censoring. The predicted annual rates of thromboembolism and major bleeding were based on the median CHA_2DS_2-VASc and HAS-BLED scores and corresponding incidence rates in historical controls as appropriate (Pisters et al., 2010; Friberg et al., 2012a). The HAS-BLED score was modified to exclude labile international normalized ratio and alcohol abuse in the lack of adequately reported data.

In Study I, The Kaplan-Meier method was used to illustrate the timing of events. A landmark analysis was performed including patients free from endpoint of interest at the 6-month landmark. The log rank test was used to compare Kaplan-Meier estimated survival across the groups. Multivariable analyses were not conducted due to the small sample size.

In Study II, R package, epitools (version 0.5-10), was used to calculate event rates with 95% confidence intervals (exact method) and unadjusted incidence rate ratios with 95% confidence intervals (mid-p exact method). Cumulative incidence function was used to estimate the incidence of thromboembolism, and intracranial bleeding. The cumulative incidence function accounts for the competing risk of death prior to the primary event of interest.

Study III

In Study III, multivariable linear regression analysis was performed to evaluate the association between admission heart rate and peak hs-cTn T level. All relevant variables with p value < 0.1 in univariate analysis were entered into a multivariable regression model using a backward procedure (p value > 0.1 for exclusion and p value < 0.05 for model inclusion). In multivariable regression models, variance inflation factors were < 1.6 ensuring lack of multicollinearity between variables.

Secondly, generalized additive model (Hastie & Tibshirani, 1986) with scaled t distribution and identity link was used to explore nonlinear relationships between admission heart rate (as thin-plate spline) and peak hs-cTn T (response variable) using *gam* in the *mgcv* package for R. Adjustments were made for age, haemoglobin, estimated glomerular filtration rate, diabetes mellitus, congestive heart failure, new-onset AF and palpitation symptoms. For smoothing selection, the restricted maximum likelihood criterion was applied. The model was visualized with 95% confidence intervals using a Bayesian approach. The Akaike information criterion (AIC) was then used to assess the performance of linear regression and generalized additive models.

In addition, 5 equal-sized groups were formed based on patients' admission heart rates (rounded to the nearest 5 bpm): < 90, 90–109, 110–124, 125–139, and ≥ 140 bpm. Multivariable logistic regression analysis was used to evaluate association between the groups and elevated hs-cTn T level (> 14 ng/L). Adjustments were made for age, haemoglobin, estimated glomerular filtration rate, diabetes mellitus, congestive heart failure, new-onset AF, and palpitation symptoms. Subjects with hs-cTn T level below the limit of detection (< 5 ng/L) were assigned a value of 4 ng/L for statistical testing (17 patients).

4.3 Ethical aspects

The Ethics Committee of the Hospital District of Southwest Finland approved the study protocols, and the studies were conducted in accordance with the Declaration of Helsinki. All participants in Studies I and II provided written informed consent for the prospective follow-up. No written informed consent was required for Study III due to the retrospective nature of the study.

5 Results

5.1 Single antiplatelet therapy after percutaneous left atrial appendage closure (Study I)

Eighty-one (49%) of the 165 patients discharged following successful LAAC were discharged on either aspirin (n = 77, 95%) or clopidogrel (n = 4, 5%) monotherapy. The mean age of these patients was 75 years and 44% were female. The primary contraindication to OAC therapy was a prior major bleeding: intracranial bleeding in 48 (59%) patients and other major bleeding in 16 (10%) patients. The Amplatzer Cardiac Plug was implanted in 18 (22%) patients and the Amplatzer Amulet in 63 (78%) patients. Overall, 6 (7%) patients experienced non-fatal in-hospital complications, none of which were cerebrovascular. Four access site bleedings and 1 cardiac tamponade fulfilled the definition for major bleeding. One patient received a new LAAC device following device embolization a few months earlier.

The baseline characteristics of the study participants are presented in Table 10. Most patients (n = 61, 75%) received short-term single APT for 6 months or less, while 20 (25%) patients were prescribed long-term single APT. The mean CHA_2DS_2-VASc score was significantly higher among patients assigned for long-term single APT (5.5 ± 1.4) than those assigned for short-term single APT (4.5 ± 1.3, p = 0.006) driven by higher prevalence of vascular disease (70% vs. 16%, p < 0.001) and heart failure (35% vs. 11%, p = 0.016).

The median duration of follow-up was 2.5 years (interquartile range [IQR], 1.2–4.1 years) with a total follow-up of 234 patient-years. The effectiveness of LAAC with postprocedural single APT in reducing thromboembolic events and major bleeding in comparison to historical controls is illustrated in Figure 9. Overall, there were 6 thromboembolic events (2.7 per 100 patient-years), of which 4 were ischaemic strokes (1.7 per 100 patient-years). Major bleeding events occurred in 8 patients (3.6 per 100 patient-years). Four patients had intracranial bleedings (1.7 per 100 patient-years), all with a fatal outcome within 1 month. The early and overall follow-up outcome is presented in Table 11, and the individual characteristics of those with thromboembolic or intracranial bleeding events are summarized in Table 12.

Table 10. Baseline characteristics of Study I participants stratified by duration of single antiplatelet therapy (n = 81). Modified from the original publication I, Table 1.

Variable	Short-term (≤ 6 months; n = 61)	Long-term (Lifelong; n = 20)	p value
Age (years)	74 ± 7	75 ± 8	0.932
Female	28 (46%)	8 (40%)	0.645
Permanent atrial fibrillation	28 (46%)	9 (45%)	0.944
CHA_2DS_2-VASc score	4.5 ± 1.3	5.5 ± 1.4	0.006
Heart failure	7 (11%)	7 (35%)	0.016
Hypertension	44 (72%)	14 (70%)	0.854
Diabetes mellitus	12 (20%)	9 (45%)	0.025
Stroke/transient ischaemic attack/thromboembolism	44 (72%)	14 (70%)	0.854
Intracranial bleeding	40 (65%)	8 (40%)	0.043
Vascular disease*	10 (16%)	14 (70%)	<0.001
HAS-BLED score†	3.1 ± 0.8	3.5 ± 1.0	0.142
Liver disease	1 (2%)	2 (10%)	0.149
Estimated glomerular filtration rate‡ (ml/min/1.73 m^2)	64.7 ± 18.4	55.8 ± 22.5	0.080
<30	3 (5%)	3 (15%)	0.135
Prior drug usage predisposing to bleeding	18 (30%)	9 (45%)	0.202
Anaemia§	13 (21%)	11 (55%)	0.004
Device			0.538
Amplatzer Amulet	46 (75%)	17 (85%)	
Amplatzer Cardiac Plug	15 (25%)	3 (15%)	
Device size (mm)	25 (22–28)	26 (25–28)	0.060
≥26	22 (36%)	11 (55%)	0.135

Values are number (%), mean ± standard deviation, or median (interquartile range).
*Vascular disease was defined as diagnosed coronary artery disease, or peripheral artery disease. †Modified HAS-BLED score was calculated with no points for labile international normalized ratio and alcohol abuse. ‡Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. §Anaemia was defined as haemoglobin concentration of < 130 g/L for men and < 120 g/dL for women.

Table 11. Early and overall follow-up outcome after left atrial appendage closure in Study I (n = 81). Modified from the original publication I, Table 2.

Variable	0–6 months		During entire follow-up	
Endpoints	**No. (%)**	**Rate (95% CI)**	**No. (%)**	**Rate (95% CI)**
Death	5 (6%)	12.8 (5.6–29.0)	15 (19%)	6.4 (3.9–10.5)
Cardiovascular	4 (5%)	10.2 (4.0–25.9)	9 (11%)	3.8 (2.0–7.3)
Thromboembolic events	3 (4%)	7.7 (2.6–22.9)	6 (7%)	2.7 (1.2–5.9)
Ischaemic stroke	3 (4%)	7.7 (2.6–22.9)	4 (5%)	1.7 (0.7–4.6)
Transient ischaemic attack	0	-	2 (2%)	0.9 (0.2–3.5)
Systemic embolism	0	-	0	-
Major bleeding events	5 (6%)	13.1 (5.8–29.7)	8 (10%)	3.6 (1.8–7.1)
Intracerebral bleeding*	2 (2%)	5.1 (1.3–19.7)	4 (5%)	1.7 (0.6–4.5)

Incidence rates are expressed as number of events per 100 patient-years of follow-up. Abbreviations: CI, confidence interval. *One patient had a haemorrhagic transformation of an ischaemic stroke.

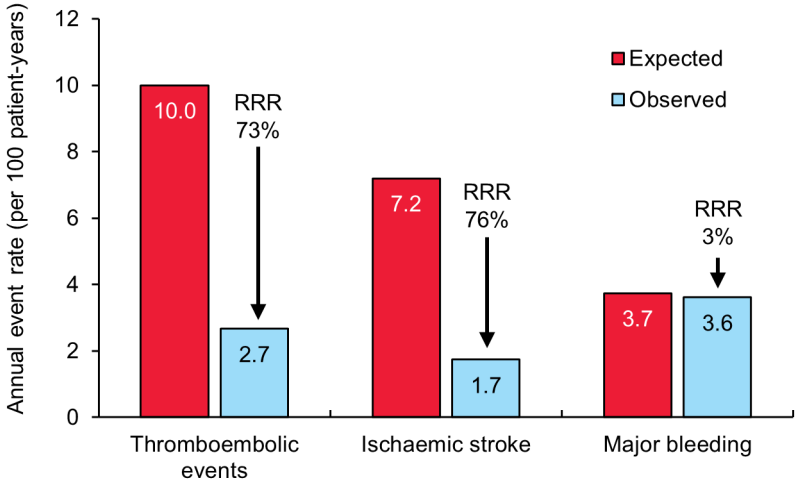


Figure 9. Effectiveness of left atrial appendage closure followed by single antiplatelet therapy in patients with contraindications to oral anticoagulation. The predicted annual rates of thromboembolic and major bleeding events are estimated from historical controls based on the median CHA_2DS_2-VASc and HAS-BLED scores (Pisters et al., 2010; Friberg et al., 2012a). Modified from the original publication I, Figure 1. RRR denotes relative risk reduction.

Table 12. Individual characteristics of patients with thromboembolic or intracranial bleeding events during follow-up in Study I. Modified from the original publication I, Table 3.

Age (years), sex	Type of atrial fibrillation	Contraindication to OAC	CHA_2DS_2-VASc / HAS-BLED scores	Device (size, mm)	Event	Antithrombotic therapy at the time of the event	Timing post-procedure (days)	Carotid plaque
55 (M)	Paroxysmal	Major bleeding	4 / 3	Amulet (25)	Transient ischaemic attack	Aspirin, 100 mg	654	N/A
62 (M)	Permanent	Intracranial bleeding	2 / 3	ACP (18)	Intracerebral bleeding*	None	624	N/A
68 (M)	Paroxysmal	Intracranial bleeding	2 / 3	Amulet (25)	Intracerebral bleeding*	Aspirin, 100 mg	33	Yes
70 (M)	Persistent	Intracranial bleeding	4 / 3	Amulet (31)	Ischaemic stroke*	Aspirin, 100 mg	148	Yes
72 (F)	Paroxysmal	Intracranial bleeding	3 / 3	Amulet (22)	Ischaemic stroke*†	Aspirin, 100 mg	30	N/A
78 (M)	Permanent	Intracranial bleeding	2 / 3	Amulet (31)	Ischaemic stroke	None	619	N/A
80 (F)	Paroxysmal	Intracranial bleeding	6 / 4	ACP (30)	Transient ischaemic attack	None	734	Yes
80 (M)	Paroxysmal	High bleeding risk	4 / 4	Amulet (28)	Ischaemic stroke	Aspirin, 100 mg	107	Yes
86 (F)	Paroxysmal	Major bleeding	6 / 4	ACP (26)	Intracerebral bleeding*	Aspirin, 100 mg	430	N/A

Abbreviations: ACP, Amplatzer Cardiac Plug; F, female; M, male; N/A, not available; OAC, oral anticoagulation. *Fatal event within 30 days. †Patient had a subsequent haemorrhagic transformation of an ischaemic stroke.

Table 13. Follow-up outcome past the 6-month landmark grouped by short-term (≤ 6 months) and long-term (lifelong) single antiplatelet therapy (SAPT) strategies (n = 72). Modified from the original publication I, Supplementary Table 3.

Variable	Short-term SAPT (n = 55)	Long-term SAPT (n = 17)
Median follow-up (years)	2.6 (1.7–4.5)	2.6 (1.7–4.4)
Total follow-up years	178.7	39.7
Number of events (per 100 patient-years)		
All-cause death	5 (2.8)	12 (30.2)
Thromboembolic events	2 (1.2)	1 (2.6)
Ischaemic stroke	1 (0.6)	0 (0)
Transient ischaemic attack	1 (0.6)	1 (2.6)
Major bleeding	2 (1.1)	1 (2.5)
Intracranial bleeding	1 (0.6)	1 (2.5)

Six-month landmark analysis in 72 (89%) patients showed that the all-cause mortality was higher in patients receiving long-term single APT ($p = 0.012$ for log-rank test). No statistically significant difference in freedom from thromboembolism (95.1% vs. 88.9% at 3 years), intracranial bleeding (97.6% vs. 91.7% at 3 years), or major bleeding (95.1% vs. 91.7% at 3 years) was detected between patients assigned to short-term single APT and long-term single APT strategies.

5.2 Percutaneous left atrial appendage closure following prior intracranial bleeding (Study II)

In Study II, 104 patients with prior intracranial bleeding underwent successful LAAC. The median time from the intracranial bleeding event to LAAC was 7 months (IQR, 4–38 months). The mean age was 73 years and the median CHA_2DS_2-VASc score was 5 (IQR, 4–6). Prior intracranial bleedings were classified as intracerebral in 69 (66%), subdural in 21 (20%), and subarachnoid in 11 (11%) patients. Of these, 8 subdural and 2 subarachnoid bleedings were considered traumatic. Seventy-one (68%) patients were on anticoagulation therapy at the time of intracranial bleeding. Moreover, 39 (38%) patients had a history of thromboembolism, including 29 (28%) with a prior ischaemic stroke. The baseline characteristics in patients with and without prior thromboembolism are detailed in Table 14.

Table 14. The baseline characteristics of the study population, and patients with and without prior thromboembolism. Modified from the original publication II, Table 1.

Clinical variables	Overall (N = 104)	Prior thrombo-embolism (n = 39)	No prior thrombo-embolism (n = 65)	p value
Age (years)	73.0 ± 7.4	73.3 ± 7.6	72.9 ± 7.3	0.769
Female	31 (30)	16 (41)	15 (23)	0.076
Persistent atrial fibrillation	60 (58)	19 (49)	41 (63)	0.159
Type of intracranial bleeding*				0.079
Intracerebral	69 (66)	24 (62)	45 (69)	0.521
Subarachnoid	11 (11)	8 (21)	3 (5)	0.018
Subdural	21 (20)	6 (15)	15 (23)	0.452
Time from intracranial bleeding to LAAC†				
Median (months)	7 (4–38)	5 (4–21)	7 (4–56)	0.156
>12 months	40 (38)	13 (34)	27 (42)	0.530
Congestive heart failure	19 (18)	6 (15)	13 (20)	0.611
Hypertension	78 (75)	28 (72)	50 (77)	0.642
Diabetes mellitus	23 (22)	7 (18)	16 (25)	0.474
Vascular disease	28 (27)	7 (18)	21 (32)	0.170
CHA_2DS_2-VASc score				
Mean	4.7 ± 1.4	4.8 ± 1.2	4.6 ± 1.5	0.487
Median	5 (4–6)	5 (4–6)	5 (4–6)	0.558
HAS-BLED score‡				
Mean	3.3 ± 0.9	3.5 ± 0.9	3.2 ± 0.8	0.214
Median	3 (3–4)	4 (3–4)	3 (3–4)	0.128
Liver disease	1 (1)	0 (0)	1 (2)	1.000
eGFR§ (ml/min/1.73 m^2)				
Mean	66.0 ± 17.9	67.7 ± 17.8	65.0 ± 18.1	0.455
<60	44 (42)	15 (38)	29 (45)	0.682
Anaemia¶	21 (20)	10 (26)	11 (17)	0.313
Devices				0.579
Amplatzer Cardiac Plug	42 (40)	18 (46)	24 (37)	0.411
Amplatzer Amulet	60 (58)	20 (51)	40 (62)	0.315
Watchman	2 (2)	1 (3)	1 (2)	1.000
Median size (mm)	25 (22–28)	25 (22–27)	25 (22–28)	0.638

Values are presented as n (%), mean ± standard deviation and/or median (interquartile range). Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; LAAC, left atrial appendage closure. *Data on the exact type of intracranial bleeding missing in 3 patients. †Data missing in 2 patients. ‡Modified HAS-BLED score was estimated without considering labile international normalized ratio and alcohol abuse. §Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (data missing for 1 patient). ¶Anaemia was defined as a haemoglobin level < 120 g/L in women and < 130 g/L in men.

Postprocedural antithrombotic treatment was heterogeneous at discharge (Table 15), and most patients were assigned to discontinue antithrombotic treatment by 6 months. Aspirin was prescribed for short-term (≤ 6 months in duration) in 62 (60%), 12 months in 1 (1%), and lifelong in 31 (30%) patients (missing data on duration in 1 patient). Clopidogrel, as monotherapy or in combination, was prescribed for ≤ 1 month in 21 (20%) patients. Of note, 48 (46%) patients received aspirin or clopidogrel monotherapy. Thirty-four (34%) patients received anticoagulation which was prescribed for ≤ 14 days in 17 of 34 patients (50%), and for ≤1 month in 31 of 34 (91%) patients. Patients with prior thromboembolism were more often, than those without, prescribed combination of antiplatelet agents and anticoagulants (41% vs. 20%, p = 0.025). No difference was observed in the prescription of short-term (≤ 6 months) antithrombotic treatment between these two groups. Notably, 32 (31%) patients assigned for long-term (> 6 months) antithrombotic treatment had higher prevalence of vascular disease (66% vs. 10%, p < 0.001 and heart failure (34% vs. 11%, p = 0.011) than those with ≤ 6 months regimen.

Table 15. Antithrombotic treatment strategies assigned at discharge. Modified from the original publication II, Table 2.

Variable	Overall (N = 104)	Prior thromboembolism (n = 39)	No prior thromboembolism (n = 65)	p value
At discharge				
Antiplatelet agents	99 (95)	36 (92)	63 (97)	0.361
Aspirin	72 (69)	30 (77)	42 (65)	0.272
Clopidogrel	4 (4)	2 (5)	2 (3)	0.630
Aspirin + clopidogrel	19 (18)	1 (3)	18 (28)	0.001
Aspirin + dipyridamole	2 (2)	1 (3)	1 (2)	1.000
Aspirin + clopidogrel + dipyridamole	2 (2)	2 (5)	0 (0)	0.138
Anticoagulants	34 (32)	19 (49)	15 (23)	0.010
Warfarin	1 (1)	1 (3)	0 (0)	0.375
NOAC	10 (10)	4 (10)	6 (9)	1.000
LMWH	23 (22)	14 (36)	9 (14)	0.014
Antiplatelet agents + anticoagulants	29 (28)	16 (41)	13 (20)	0.025
Beyond 6 months				
Antiplatelet agents	32 (31)	12 (31)	20 (31)	1.000
Aspirin	28 (27)	9 (23)	19 (29)	0.649
Aspirin + dipyridamole	4 (4)	3 (8)	1 (2)	0.147
Anticoagulants	0	0	0	

Values are presented as n (%). Abbreviations: LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant.

The overall follow-up outcome is detailed in Table 16. The median follow-up was 3.6 years (IQR, 1.9–5.0 years) with 137 and 250 patient-years of follow-up in patients with and without prior thromboembolism, respectively. The rate of thromboembolism was 3.1 per 100 patient-years (95% CI, 0.8–7.9) in patients with prior thromboembolism and 3.6 per 100 patient-years (95% CI, 1.5–7.0) in patients without prior thromboembolism. Recurrent intracranial bleeding occurred with a rate of 2.3 per 100 patient-years (95% CI, 0.5–6.8) and 1.6 per 100 patient-years (95% CI, 0.4–4.1), respectively. Figure 10 illustrates the relative risk reduction of thromboembolic and bleeding events in patients with and without prior thromboembolism.

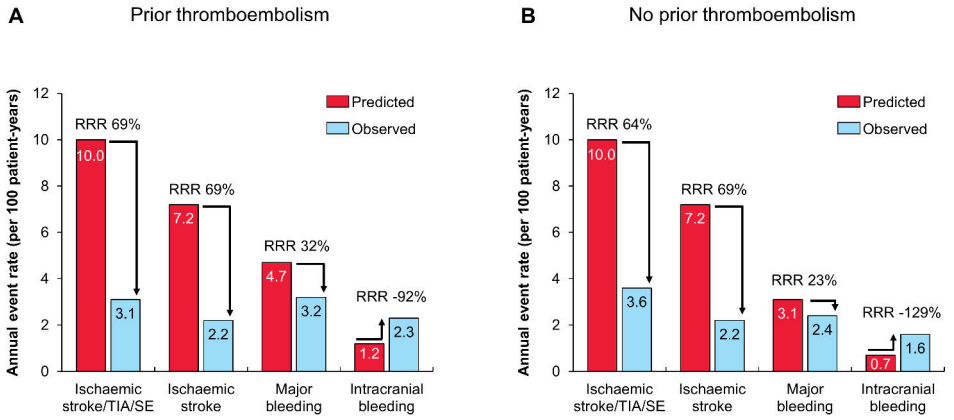


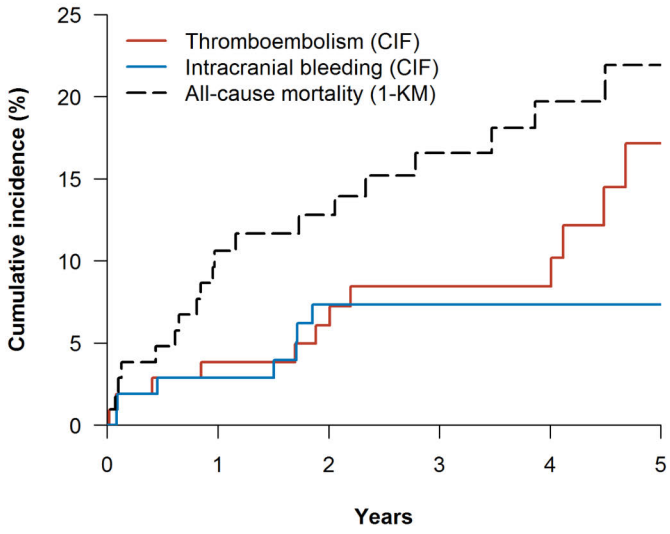
Figure 10. Effectiveness of left atrial appendage closure in patients with previous intracranial bleeding and with (A) and without prior thromboembolism (B). The predicted annual rates of thromboembolic and bleeding events are estimated from historical controls based on the median CHA_2DS_2-VASc and HAS-BLED scores (Friberg et al., 2012a). From the original publication II, Figure 1. RRR denotes relative risk reduction.

Table 16. Follow-up outcome after percutaneous left atrial appendage closure in patients with a history of intracranial bleeding. Modified from the original publication II, Table 3.

Endpoint	Overall (N = 104)		Prior thromboembolism (n = 39)		No prior thromboembolism (n = 65)		
	n (%)	%/year (95% CI)	n (%)	%/year (95% CI)	n (%)	%/year (95% CI)	Unadjusted IRR (95% CI)
All-cause mortality	22 (21.2)	5.7 (3.6–8.6)	7 (17.9)	5.1 (2.1–10.5)	15 (23.1)	6.0 (3.4–9.9)	0.86 (0.32–2.06)
Thromboembolism	12 (11.5)	3.4 (1.8–5.9)	4 (10.3)	3.1 (0.8–7.9)	8 (12.3)	3.6 (1.5–7.0)	0.88 (0.23–2.87)
Ischaemic stroke	8 (7.7)	2.2 (0.9–4.3)	3 (7.7)	2.2 (0.5–6.5)	5 (7.7)	2.2 (0.7–5.0)	1.06 (0.20–4.50)
Transient ischaemic attack	4 (3.8)	1.1 (0.3–2.7)	1 (2.6)	0.8 (0.0–4.2)	3 (4.6)	1.2 (0.3–3.6)	0.66 (0.02–5.72)
Major bleeding	10 (9.6)	2.7 (1.3–4.9)	4 (10.3)	3.2 (0.9–8.2)	6 (9.2)	2.4 (0.9–5.3)	1.34 (0.33–4.84)
Intracranial bleeding	7 (6.7)	1.9 (0.7–3.8)	3 (7.7)	2.3 (0.5–6.8)	4 (6.2)	1.6 (0.4–4.1)	1.47 (0.27–7.05)
Composite of thromboembolism, or intracranial bleeding*	17 (16.3)	4.9 (2.9–7.9)	7 (17.9)	5.8 (2.3–12)	10 (15.4)	4.5 (2.1–8.2)	1.31 (0.47–3.46)

Values are presented as n (%), incidence rate (95% CI) or incidence rate ratio (95% CI). Abbreviations: CI, confidence interval, IRR, incidence rate ratio.
*2 patients had both thromboembolic and intracranial bleeding events.

The overall rates of thromboembolism and intracranial bleeding were 3.4 per 100 patient-years (95% CI, 1.8–5.9) and 1.9 per 100 patient-years (95% CI, 0.7–3.8), respectively. Accounting for the competing risk of death, the thromboembolism rate was 3.8% at 1 year, 6.1% at 2 years, and 8.5% at 3 years, and the intracranial bleeding rate was 2.9% at 1 year, 7.3% at 2 years, and 7.3% at 3 years (Figure 11). Notably, most thromboembolic events and intracranial bleedings occurred in patients on antithrombotic therapy (Table 17). At 1 year, the Kaplan-Meier estimate of all-cause mortality was 10.6% (95% CI, 4.5–16.3). Overall, 22 (21%) patients died with a rate of 5.7 per 100 patient-years (95% CI, 0.7–3.8).



Number at risk						
Thromboembolism	104	86	73	56	44	21
Intracranial bleeding	104	87	73	57	45	27
All-cause mortality	104	88	77	60	47	28

Figure 11. The cumulative incidences of thromboembolism, intracranial bleeding, and all-cause mortality. To account for competing risk of death, the cumulative incidence function (CIF) method was applied for thromboembolism and intracranial bleeding. The Kaplan-Meier (KM) estimate was used to illustrate all-cause mortality. From the original publication II, Figure 2.

Table 17. Individual characteristics of patients with primary outcomes (thromboembolism, or intracranial bleeding) after LAAC. Modified from the original publication II, Supplementary Tables 1 and 2.

Age (sex), years	CHA_2DS_2-VASc / HAS-BLED scores	Type of prior intracranial bleeding	Time from bleeding to LAAC, months	Device (size, mm)	Endpoint(s)	Time from LAAC, months	Antithrombotic therapy at the time of the event	Carotid plaque
Patients with prior thromboembolism (n = 7/39)								
69 (M)	5 / 3	SAH	2	Amulet (22)	Intracranial bleeding (traumatic SAH)	18	Aspirin, 100 mg	N/A
70 (M)	4 / 3	ICH	5	Amulet (31)	Ischaemic stroke	5*	Aspirin, 100 mg	Yes
71 (M)	4 / 4	ICH	3	Amulet (31)	Intracranial bleeding (ICH)	22	Rivaroxaban, 20 mg	Yes
71 (M)	5 / 4	ICH	6	Watchman (33)	Ischaemic stroke	48	Aspirin, 100 mg	Yes
75 (F)	5 / 3	ICH	5	ACP (24)	Intracranial bleeding (ICH)	5	Aspirin, 100 mg	N/A
75 (M)	4 / 4	ICH	4	ACP (26)	Ischaemic stroke	56	N/A	N/A
79 (F)	6 / 4	ICH	>24	ACP (30)	TIA	24	None	Yes
Patients without prior thromboembolism (n = 10/65)								
62 (M)	4 / 3	ICH	2	ACP (18)	Intracranial bleeding (ICH)	21*	N/A	N/A
68 (F)	7 / 4	ICH	18	ACP (24)	Ischaemic stroke	10	None	N/A
68 (M)	4 / 3	ICH	7	Amulet (25)	Intracranial bleeding (ICH)	1*	Aspirin, 100 mg	Yes
72 (F)	5 / 3	ICH	12	Amulet (22)	Ischaemic stroke, Intracranial bleeding (ICH)	1*	Aspirin, 100 mg	N/A
72 (M)	6 / 5	ICH	7	ACP (28)	Intracranial bleeding (ICH), TIA	21	None	N/A
76 (M)	4 / 4	SDH	>24	ACP (26)	TIA	26	Aspirin, 100 mg	Yes
78 (M)	2 / 3	SDH	3	Amulet (31)	Ischaemic stroke	20	Aspirin, 100 mg	N/A
78 (M)	4 / 3	ICH	>24	ACP (26)	TIA	49	Aspirin, 100 mg	Yes
79 (F)	8 / 3	ICH	3	Amulet (34)	Ischaemic stroke	6 days	Enoxaparin, 20 mg	Yes
81 (F)	7 / 4	SAH	>24	ACP (22)	Ischaemic stroke	54	Aspirin, 100 mg	No

Abbreviations: ACP, Amplatzer Cardiac Plug; F, female; ICH, intracerebral haemorrhage; LAAC, left atrial appendage closure; M, male; N/A, not available; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage; TIA, transient ischaemic attack. * Fatal event within 30 days.

5.3 Impact of heart rate on cardiac troponin T levels in atrial fibrillation (Study III)

In Study III, a total of 501 patients admitted to the emergency department primarily for AF were included. The peak hs-cTn T (mean, 27.5 ± 20.7 ng/L) was below the limit of detection (< 5 ng/L) in 17 (3.4%) patients and considered elevated (> 14 ng/L) in 326 (65%) patients. The mean heart rate at admission was 114 ± 28 bpm (median, 116 bpm; IQR, 95–135 bpm). At 1 year, 41 (8.2%) patients had died, myocardial infarction occurred in 4 (0.8%) patients, and ischaemic stroke in 4 (0.8%) patients. No significant differences were found in these endpoints between patients with heart rates < 125 bpm and ≥ 125 bpm. Table 18 summarizes the baseline characteristics of Study III.

In the multivariable linear regression analysis, an increase in peak hs-cTn T level was independently associated with a higher heart rate (β [standardized coefficient] = 0.194, $p < 0.001$). Older age, lower haemoglobin level, decreased estimated glomerular filtration rate, diabetes mellitus, congestive heart failure, new-onset AF, and absence of palpitation symptoms were the other independent predictors of peak hs-cTn T in the multivariable model. The simple and multiple linear regression results of factors associated with hs-cTn T level are detailed in Table 19.

Table 18. The baseline characteristics of the Study III population. Modified from the original publication III, Table 1.

Variable	Overall (N = 501)	< 125 bpm (n = 299)	≥ 125 bpm (n = 202)	p value
Age, years	75.6 (66.6–82.3)	76.0 (66.7–82.4)	75.0 (66.3–82.1)	0.41
Female	262 (52.3)	142 (47.5)	120 (59.4)	0.01
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)	3 (2–4)	0.43
Congestive heart failure	45 (9.0)	29 (9.7)	16 (7.9)	0.53
Hypertension	318 (63.5)	192 (64.2)	126 (62.4)	0.71
Diabetes mellitus	93 (18.6)	60 (20.1)	33 (16.3)	0.35
Prior stroke/TIA	60 (12.0)	37 (12.4)	23 (11.4)	0.78
Coronary artery disease*	131 (26.1)	85 (28.4)	46 (22.8)	0.18
Prior myocardial infarction	67 (13.4)	42 (14.0)	25 (12.4)	0.69
Prior PCI or CABG	66 (13.2)	37 (12.4)	29 (14.4)	0.59
Hypercholesterolaemia	193 (38.5)	119 (39.8)	74 (36.6)	0.51
Current smoker	28 (5.6)	13 (4.3)	15 (7.4)	0.17
Active malignancy	26 (5.2)	14 (4.7)	12 (5.9)	0.54
Type of atrial fibrillation				
Permanent or persistent	91 (18.2)	69 (23.1)	22 (10.9)	0.001
Paroxysmal	280 (55.9)	165 (55.2)	115 (56.9)	0.72
New-onset	130 (25.9)	65 (21.7)	65 (32.2)	0.01

Table 18. (Continued)

Variable	Overall (N = 501)	< 125 bpm (n = 299)	≥ 125 bpm (n = 202)	p value
Antiplatelet therapy	120 (24.0)	74 (24.7)	46 (22.8)	0.67
Acetylsalicylic acid	108 (21.6)	70 (23.4)	38 (18.8)	0.23
Clopidogrel	14 (2.8)	5 (1.7)	9 (4.5)	0.10
Anticoagulation	269 (53.7)	173 (57.9)	96 (47.5)	0.03
Antiarrhythmic agents	341 (68.1)	219 (73.2)	122 (60.4)	0.003
β blockers	332 (66.3)	214 (71.6)	118 (58.4)	0.003
Symptoms				
Chest pain	99 (19.8)	57 (19.1)	42 (20.8)	0.65
Dyspnoea	133 (26.5)	79 (26.4)	54 (26.7)	>0.99
Palpitations	250 (49.9)	148 (49.5)	102 (50.5)	0.86
Heart rate at admission, bpm†	116 (95–135)	98 (83–113)	138 (131–146)	<0.001
Laboratory variables				
Peak hs-cTn T at 72 h, ng/L	20.0 (12.0–38.0)	18.0 (11.0–31.5)	25.5 (14.2–44.8)	<0.001
SBP, mm Hg‡	136 (120–150)	136 (121–152)	135 (118–149)	0.29
Haemoglobin, g/L	138 (125–148)	138 (125–149)	137 (126–147)	0.68
C-reactive protein, mg/L§	3 (2–10)	3 (2–8)	4 (2–11)	0.01
eGFR, mL/min/1.73m^2 ¶	66.6 (51.3–82.4)	66.1 (50.5–80.6)	67.8 (53.7–84.1)	0.24
< 60	186 (37.1)	115 (38.5)	71 (35.1)	0.51

Values are presented as n (%), or median (interquartile range). Abbreviations: bpm, beats per minute; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; hs-cTn, high-sensitivity cardiac troponin; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischaemic attack. *Coronary artery disease was defined as a diagnosis of coronary disease, history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery. †Heart rate was determined from the first 12-lead electrocardiogram obtained during the emergency department visit. ‡ Missing data on systolic blood pressure in 60 (12%) patients. §Missing data on C-reactive protein in 85 (17%) patients. ¶Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Table 19. Simple and multiple linear regression analyses of factors associated with high-sensitivity cardiac troponin (hs-cTn) T level. Unpublished data from Study III.

		Univariable analysis		Multivariable analysis*		
Variable	N	β	p value	Unstandardized coefficient (95% CI)	β	p value
Heart rate, bpm, per 10-unit	501	0.154	0.001	1.414 (0.842, 1.987)	0.194	< 0.001
Age, years, per 10-unit	501	0.308	< 0.001	2.766 (0.891, 4.642)	0.141	0.004
Haemoglobin, g/L, per 10-unit	500	-0.290	< 0.001	-1.698 (-2.72, -0.676)	-0.142	0.001
eGFR†, mL/min/1.73 m^2, per 10-unit	501	-0.244	< 0.001	-1.346 (-2.257, -0.434)	-0.130	0.004
Diabetes mellitus	501	0.140	0.002	6.885 (2.786, 10.985)	0.129	0.001
Congestive heart failure	501	0.177	< 0.001	8.955 (3.211, 14.699)	0.124	0.002
New-onset atrial fibrillation	501	0.216	< 0.001	7.332 (3.53, 11.134)	0.155	< 0.001
Palpitations	501	-0.251	< 0.001	-6.274 (-9.629, -2.919)	-0.152	< 0.001
Coronary artery disease	501	0.143	0.001			
Antiarrhythmic drugs	501	0.101	0.024			
Female sex	501	-0.003	0.950			
Active malignancy	501	0.042	0.347			
Hypertension	501	0.079	0.079			
Chest pain	501	0.075	0.095			
Dyspnoea	501	0.036	0.421			
Systolic blood pressure	441	0.010	0.838			
Model statistics						
R^2				0.258		
Adjusted R^2				0.246		
AIC				4319.44		

Abbreviations: AIC, Akaike information criterion; β, standardized coefficient; bpm, beats per minute; eGFR, estimated glomerular filtration rate; R^2, coefficient of determination. *Variables associated with hs-cTn T level ($p < 0.10$) in univariable analysis were included in multivariable analysis using backward elimination procedure. $F(8, 491 = 21.327)$, $p < 0.001$. †eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

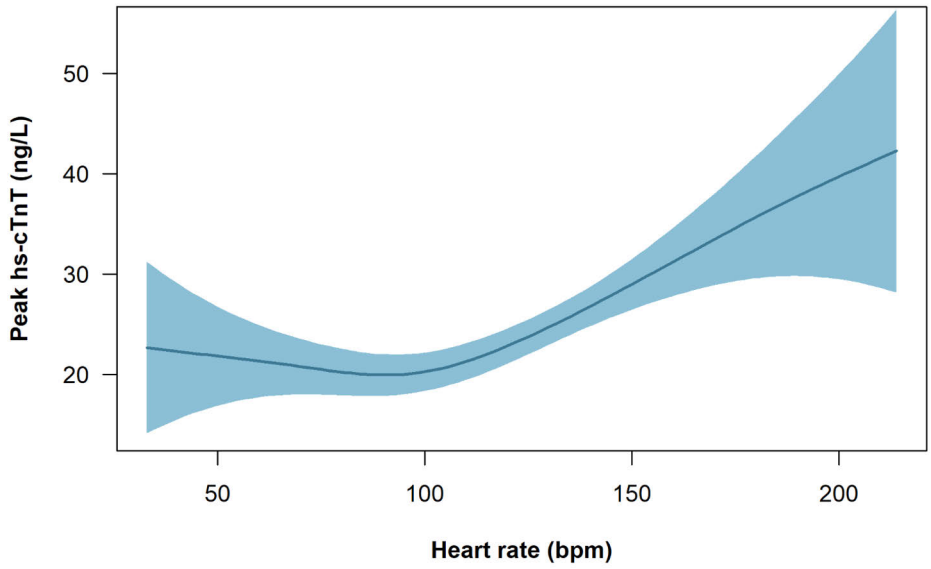


Figure 12. Generalized additive model and the relationship between admission heart rate and peak high-sensitivity cardiac troponin (hs-cTn) T (adjusted R^2 = 0.249; Akaike information criterion, 4232.21; estimated degrees of freedom, 3.04, p < 0.001). Adjusted for age, haemoglobin, estimated glomerular filtration rate, diabetes mellitus, congestive heart failure, new-onset atrial fibrillation, and palpitation symptoms. Shaded region indicates 95% confidence intervals of the smooth function (continuous line) with the uncertainty of the overall mean. Modified from the original publication III, Figure A.

Moreover, multiple logistic regression revealed that the impact of heart rate on elevated hs-cTn T level (> 14 ng/L) was limited to patients in the two groups with the highest heart rates (heart rate, 125–139 bpm: adjusted odds ratio, 2.03; 95% CI, 1.05–3.90; p = 0.03; heart rate ≥ 140 bpm: adjusted odds ratio, 4.05; 95% CI, 1.80–9.12; p = 0.001) compared to those with admission heart rate < 90 bpm. The generalized additive model confirmed a nonlinear association between peak hs-cTn T and admission heart rate (Figure 12). The predicted impacts of older age, lower haemoglobin level, and decreased glomerulus filtration rate on peak hs-cTn T were additive as illustrated in Figure 13 (unpublished).

Of 501 patients, 131 (26%) had known coronary artery disease and presented with slightly higher peak hs-cTn T levels (median, 24 ng/L; IQR, 14–45 ng/L) compared to those without known coronary artery disease (median, 19 ng/L; IQR, 11–35 ng/L; p = 0.001). In the multiple linear regression, the peak hs-cTn T level was independently associated with higher heart rate in patients with (β = 0.168, p = 0.04) and those without known coronary artery disease (β = 0.205, p < 0.001; p for interaction = 0.66). Considering the multiple comorbidities included in the CHA_2DS_2-VASc score, 80% (68/85) of patients with a CHA_2DS_2-VASc score ≥ 4

and heart rate ≥ 125 bpm had elevated hs-cTn T levels, while only 35% (17/48) of patients with a CHA_2DS_2-VASc ≤ 1 and heart rate < 125 bpm had elevated hs-cTn T levels (Figure 14).

Furthermore, 69 (14%) patients had a greater than 50% change in hs-cTn T levels (i.e., between the peak and minimum hs-cTn T value) with a significant positive association with admission heart rate (Figure 15). Multiple logistic regression analysis revealed that heart rate ≥ 140 bpm remained significantly associated with a > 50% change in hs-cTn T levels (adjusted odds ratio, 4.61; 95% CI, 1.62–13.14; p = 0.004; heart rate < 90 bpm as reference) after the multivariable adjustments.

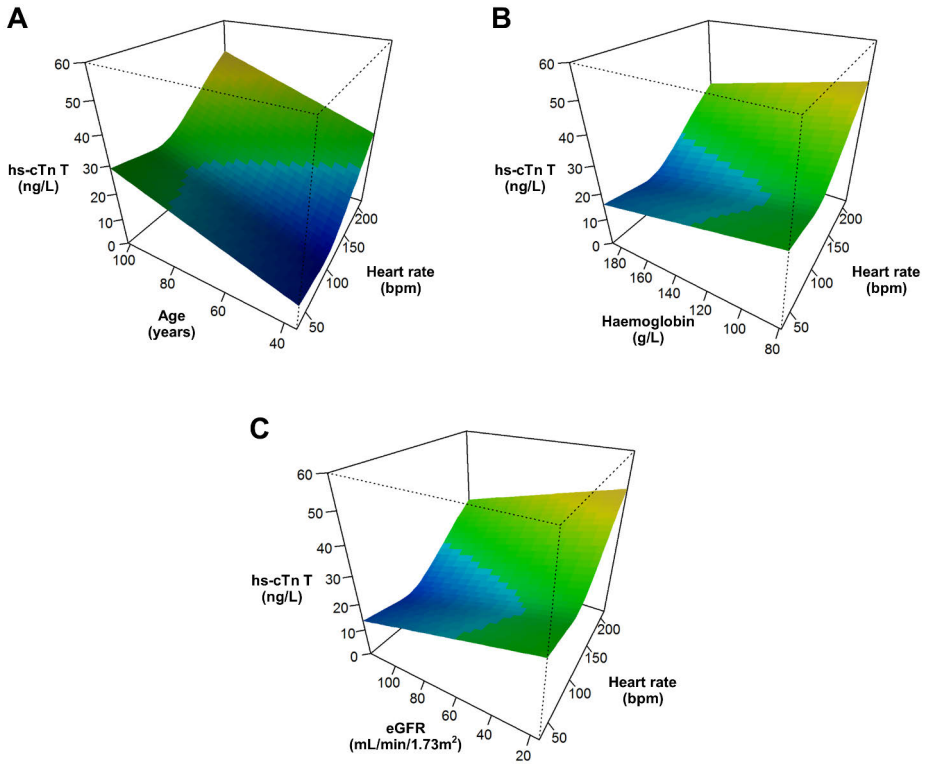


Figure 13. Three-dimensional graphs illustrating the summed effects of admission heart rate and age (A), haemoglobin (B), and estimated glomerular filtration rate (eGFR) (C) on the peak high-sensitivity troponin (hs-cTn) T level in the generalized additive model. Unpublished data from Study III.

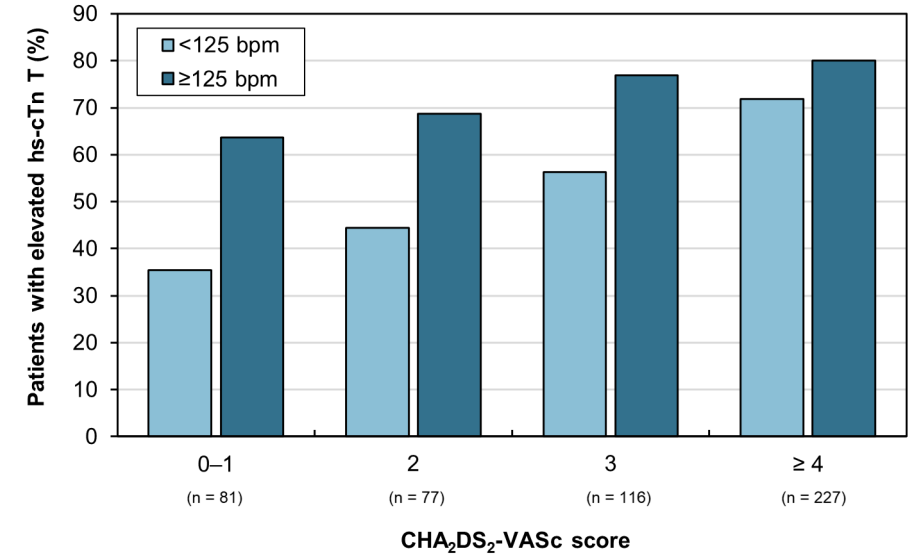


Figure 14. Proportion of patients with high-sensitivity cardiac troponin (hs-cTn) T level elevation (> 14 ng/L) stratified by CHA_2DS_2-VASc score and heart rate (p for overall trend < 0.001). Modified from the original publication III, Figure B. bpm denotes beats per minute.

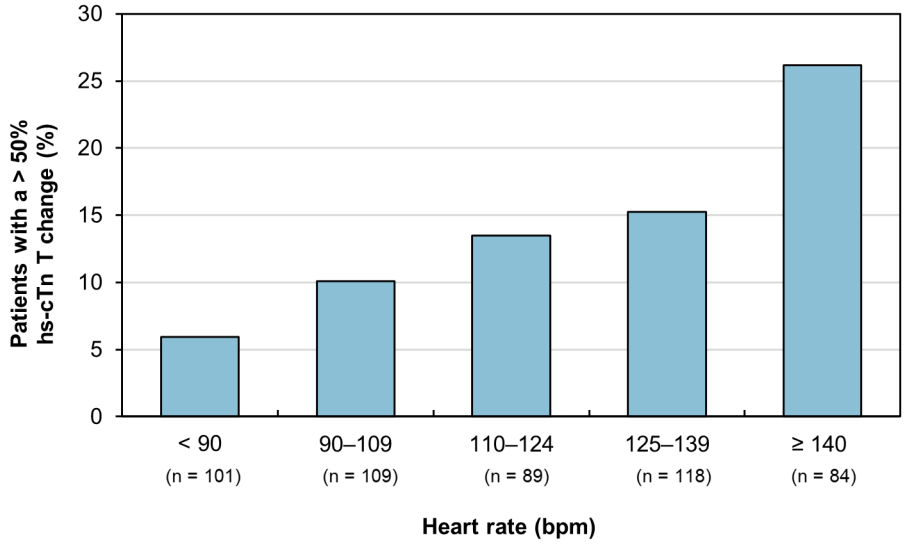


Figure 15. Proportion of patients with a dynamic high-sensitivity troponin (hs-cTn) T level change of more than 50% stratified by admission heart rate (p for trend < 0.001). bpm denotes beats per minute. Unpublished data from Study III.

6 Discussion

6.1 Single antiplatelet treatment following percutaneous left atrial appendage closure

The main finding of Study I was that percutaneous LAAC followed by individually tailored single APT was associated with a relatively low rate of ischaemic stroke (1.7 per 100 patient-years) and major bleeding events (3.6 per 100 patient-years). In comparison to historical controls, the rate of ischaemic stroke was 76% lower than predicted based on the median CHA_2DS_2-VASc score (Friberg et al., 2012a). Meanwhile, the rate of major bleeding was comparable to the observed rate in AF patients treated with OAC (Pisters et al., 2010), despite minimizing the postprocedural antithrombotic treatment to short-term single APT in most patients.

The findings of Study I suggest that individually tailored single APT strategy might be a safe and feasible option after LAAC for AF patients at very high risk of severe bleeding complications. Long-term (i.e., indefinite) single APT was mainly prescribed to patients with more prevalent vascular disease (i.e., coronary artery disease, or peripheral artery disease) and other cardiovascular morbidities, such as diabetes mellitus and heart failure, compared to patients prescribed short-term (i.e., for a maximum of 6 months) single APT. Therefore, the significantly higher mortality in the long-term single APT group could be related to the greater burden of pre-existing cardiovascular disease. Nevertheless, the overall mortality in Study I was comparable to that in large "real world" registries (8–10% at 1 year, and 15–16% at 2 years) when mostly dual APT at discharge followed by single APT was used after LAAC (Boersma et al., 2017, 2019; Landmesser et al., 2018; Hildick-Smith et al., 2020).

The rates of ischaemic stroke (1.7%/year) and major bleeding (3.6%/year) in Study I, were also similar to those reported in these large registry studies on LAAC (1.3–2.2%/year for ischaemic stroke, and 2.7–7.2%/year for major bleeding) (Boersma et al., 2019; Hildick-Smith et al., 2020). The present results also extend the previous findings by Jalal et al., Korsholm et al., and Rodriguez-Gabella et al. on single APT following LAAC. The previous studies found a 0–4.0%/year thromboembolism rate and a 1.3–3.8%/year rate of major bleeding but were limited

by small sample size (31–94 patients) and relatively short follow-up (1–2 years). (Rodriguez-Gabella et al., 2016; Jalal et al., 2017; Korsholm et al., 2017).

In Study I, single APT was discontinued within 6 months in most patients who presented with a more favourable cardiovascular risk profile (e.g., lower prevalence of coronary artery disease, and diabetes). However, in spite of this conservative approach, one patient with no antithrombotic therapy suffered a fatal intracerebral bleeding almost 2 years post-procedure. On the other hand, late cerebrovascular ischaemic events were rare in patients with no long-term antithrombotic treatment, but carotid disease was an anecdotal finding in these patients with late events. Therefore, antithrombotic treatment in these patients warrants future research, since carotid atherosclerosis and stenosis have been associated with ischaemic cerebrovascular events and mortality even in anticoagulated AF patients (Lehtola et al., 2017; Becattini et al., 2018), and there is a close relationship between carotid atherosclerosis and coronary artery disease (Sillesen et al., 2012; Jashari et al., 2013). Nevertheless, indefinite single APT seems justified in many patients with high risk of atherosclerotic cardiovascular disease and in the secondary prevention of vascular events (e.g., coronary events, and ischaemic stroke) (Collins et al., 2009), even after surviving intracerebral bleeding (Salman et al., 2019, 2021b).

Taken together these findings reinforce the notion that a residual burden of ischaemic cerebrovascular events and bleeding complications exists even after successfully occluding the LAA and avoiding OAC. Moreover, it is necessary not to overlook the fact that a residual burden of ischaemic stroke persists in adequately anticoagulated AF patients (Ruff et al., 2014). In fact, in warfarin-treated AF patients, more than half of ischaemic strokes are deemed non-cardioembolic (Hart et al., 2000), and anticoagulation seems to have a limited effectiveness in prevention of non-cardioembolic stroke and its recurrence compared to APT (Hart et al., 2000; Sandercock et al., 2009; De Schryver et al., 2012).

Considering that the principle of LAAC is to prevent thrombus formation in the LAA and subsequent thromboembolism, it should not be surprising that a residual risk of ischaemic stroke persists. First, thrombosis and occlusion of cerebral arteries may also be due to large artery atherosclerosis and cerebral small vessel disease, which share multiple risk factors with ischaemic stroke in AF (Friberg et al., 2012a). Second, cardioembolic stroke may still occur, although thrombosis is a rare phenomenon outside the LAA (Blackshear & Odell, 1996; Mahajan et al., 2012; Cresti et al., 2019), due to the persisting stasis in the left atrial cavity (Shively et al., 1996), and the occult prothrombotic state (Watson et al., 2009). Third, the risk of ischaemic stroke in patients with DRT cannot be ignored, although vast majority (~90%) of ischaemic strokes still occur in patients without DRT (Alkhouli et al., 2018; Dukkipati et al., 2018; Aminian et al., 2019). Therefore, anticoagulation is recommended to treat patients with detected DRT until thrombus resolution is

confirmed (Glikson et al., 2020), which is yet another clinical dilemma and exposes patients to an increased risk of bleeding. Therefore, optimizing antithrombotic strategy following LAAC remains a complex clinical challenge since the increased bleeding risk must be weighed against underlying risks of ischaemic events.

In the randomized PROTECT-AF and PREVAIL trials, warfarin therapy was continued for 45 days post-implantation, followed by dual APT up to 6 months and lifelong aspirin from then on (Reddy et al., 2017). It is obvious that this regimen is not applicable to patients with contraindications to OAC. The current guidelines recommend dual APT strategy for high bleeding risk patients during the first 1–6 post-operative months (Hindricks et al., 2021), although this regimen remains empirical and almost doubles the risk of intracranial bleeding compared to single APT alone (Connolly et al., 2009a). Moreover, from the standpoint of bleeding risk, it would seem reasonable to abbreviate dual APT from 6 months to 1 month if possible (Valgimigli et al., 2021).

Therefore, it is questionable, whether dual APT would deliver any additional benefit in patients at high bleeding risk. In Study I, the early months following LAAC presented the highest risk for thromboembolic events as 3 out of 4 observed ischaemic strokes occurred within the first 6 months. Therefore, dual APT and OAC might provide more effective ischaemic stroke prevention. However, the margin for more effective antithrombotic treatment seems to be restricted since 2 out of 4 observed intracranial bleedings, all which were fatal, occurred within the first 6 months. Additionally, a recent propensity score-matched analysis of 514 AF patients treated with single or dual APT (generally for less than 6 months, then aspirin alone) following LAAC is in support of this view (Patti et al., 2020). At 1 year, the rate of major bleeding was significantly lower in the single APT group (2.3% vs. 7.0%), while the rate of thromboembolism was similar (1.8% vs. 2.1%) compared to the dual APT group (Patti et al., 2020).

In the light of recent evidence and upcoming trials, the current postprocedural regimen might have to be revised. First, there is indirect evidence of significant activation of coagulation system peaking at 1 week post-LAAC but persisting up to 6 months (Rodés-Cabau et al., 2017), while OAC significantly attenuates this activation compared to APT (Asmarats et al., 2020; Duthoit et al., 2020). Second, the majority of DRT events are observed during APT and after discontinuation of short-term OAC (Dukkipati et al., 2018; Lakkireddy et al., 2021). Third, in a recent study of 198 AF patients treated with long-term half-dose NOAC after LAAC, no DRT and only 1 TIA (0.5%/year) was observed at median follow-up of 13 months (Della Rocca et al., 2021). Notably, a recent pilot study by Lindner et al. revealed that neo-endothelialization of LAAC devices (the Amplatzer Amulet and Watchman devices) was still incomplete at 6 months in the majority (20 of 36 patients) (Lindner et al., 2021). However, whether incomplete neo-endothelialization is associated with

DRT and thromboembolic complications, and to what extent, remains to be determined in large-scale prospective studies. Taken together, these findings might imply that 6-week OAC is not sufficient to prevent DRT and DRT-associated thromboembolic complications in long-term. However, most ischaemic strokes still occur in patients without DRT. In fact, the rate of thromboembolism was similar in patients who received 45-day OAC (followed by APT) or dual APT in a propensity-matched analysis, although DRT was associated with APT (Søndergaard et al., 2019). Nonetheless, in patients at high bleeding risk, the utilization of more intensive antithrombotic treatment is of concern, especially in patients with recent intracranial bleeding (Study II). Considering that NOACs are associated with similar rates of major bleeding and intracranial bleeding compared to low-dose aspirin (Connolly et al., 2011; Huang et al., 2018), it would be of great interest to compare short-term single APT, assessed in Study I, to short-term NOAC in patients with no other indication for APT.

In summary, rigorously conducted randomized clinical trials are warranted to assess the optimal choice and duration of antithrombotic treatment. According to the findings of Study I, short-term single APT after LAAC seems to be a reasonable option for selected AF patients at high bleeding risk and no other indications for APT. The results from ongoing randomized trials comparing NOACs and dual APT (ANDES and FADE-DRT trials), and short-term APT to long-term single APT (ASPIRIN-LAAO), are likely to provide valuable insight into the quest for the optimal postprocedural antithrombotic treatment (Table 20).

Table 20. Several randomized clinical trials registered in ClinicalTrials.gov evaluating antithrombotic treatment following percutaneous left atrial appendage closure*

Study name	Interventions (estimated enrolment)	Primary outcome	Estimated completion
Comparison of different postprocedural antithrombotic treatments			
APPENDAGE NCT04796714	Aspirin vs. aspirin plus clopidogrel (n = 60)	Ischaemic brain lesions at 3 months	2022
ANDES NCT03568890	NOACs vs. aspirin plus clopidogrel for 8 weeks (n = 350)	Device thrombosis at 2 months	2025
FADE-DRT NCT04502017	Half-dose NOACs vs. OAC for 6 weeks, then dual APT until 6 months (or aspirin plus NOAC for clopidogrel non-responders), then aspirin alone (n = 360)	Stroke, systemic embolism, device-related thrombosis, and major bleeding at 1 year	2023
The optimal duration of postprocedural antithrombotic treatment			
SAFE-LAAC NCT03445949	30 days vs. 6 months dual APT (randomized); discontinuation of antithrombotic treatment at 6 months vs. long-term single APT (nonrandomized). (n = 160)	Stroke, systemic embolism, nonfatal myocardial infarction, cardiovascular and all-cause mortality, moderate-to-severe bleeding, and LAA thrombus at 17 months	2022
ASPIRIN-LAAO NCT03821883	Aspirin vs. placebo from 6 months onwards. Excludes patients with indication for long-term aspirin therapy (e.g., coronary artery disease, prior myocardial infarction). (n = 1120)	Stroke, systemic embolism, cardiovascular or unexplained death, acute coronary syndrome, revascularization, and major bleeding at 2 years	2024

Abbreviations: ANDES, Short-Term Anticoagulation Versus Antiplatelet Therapy for Preventing Device Thrombosis Following Left Atrial Appendage Closure; APPENDAGE, AntiPlatelet theraPy stratEgy followiNg Left Atrial appenDAGe closurE; APT, antiplatelet therapy; ASPIRIN-LAAO, Aspirin Discontinuation After Left Atrial Appendage Occlusion in Atrial Fibrillation; FADE-DRT, Efficacy of Different Anti-Thrombotic Strategies on Device-Related Thrombosis Prevention After Percutaneous Left Atrial Appendage Occlusion; LAA, left atrial appendage; NOAC, novel oral anticoagulant; OAC, oral anticoagulation; SAFE-LAAC, Optimal Antiplatelet Therapy Following Left Atrial Appendage Closure. *Data accessed January 10, 2022.

6.2 Percutaneous left atrial appendage closure in patients with prior intracranial bleeding and thromboembolism

The findings of Study II indicate that percutaneous LAAC might be a reasonable treatment option in AF patients with prior intracranial bleeding, and especially in those high-risk patients additionally having suffered prior thromboembolic event. The overall incidence of thromboembolism was 3.4%, diminishing the risk by approximately two-thirds in relation to the expected rates in historical controls (Friberg et al., 2012a). The rate of ischaemic stroke (2.2%/year) was identical between patients with and without prior thromboembolism, and quite comparable to the rate of stroke or systemic embolism (1.5%/year) in apixaban-treated patients with a CHA_2DS_2-VASc score of 3 or more in the ARISTOTLE trial (Lopes et al., 2012).

The current guidelines recognize the uncertainty of optimal timing to resume OAC in intracerebral bleeding survivors, and delaying the re-administration of anticoagulants for at least 4 weeks is advised (Hemphill et al., 2015; Hindricks et al., 2021). In clinical practice, however, only approximately 10% of AF patients are on OAC 6 months after intracranial bleeding (Pennlert et al., 2015), undoubtably exposing these patients to an unnecessary high risk of ischaemic stroke. Therefore, percutaneous LAAC would seem a reasonable option in such circumstances while the safety and optimal timing for OAC initiation after intracranial bleeding remains unknown.

The time interval from intracranial bleeding to LAAC device implantation is a crucial factor when identifying a reasonable patient population for the procedure. In fact, recurrent intracranial bleeds seem to occur early even without any antithrombotic treatment being administered (Nielsen et al., 2015b). Nevertheless, anticoagulation in these patients is obviously associated with higher rates of recurrent bleeding as was demonstrated by the recent results from SoSTART and APACHE-AF trials (Salman et al., 2021a; Schreuder et al., 2021).

In small studies with a relatively long treatment delay from intracranial bleeding to LAAC (21–30 months), no recurrent intracranial bleedings and only very few adverse events have been reported (Horstmann et al., 2014; Fahmy et al., 2016; Hutt et al., 2019). Moreover, in these studies, patients received either dual APT or OAC following LAAC. On the contrary, in Study II, the median time interval was 7 months which is similar with only a few recent studies on LAAC after intracranial bleeding (Nielsen-Kudsk et al., 2017; Renou et al., 2017; Hucker et al., 2020). In all of these studies except one (Hucker et al., 2020), ischaemic strokes and recurrent intracranial bleeding events were observed (Korsholm et al., 2017; Renou et al., 2017). In the study by Hucker et al., 63 patients were discharged on NOACs, dual APT, and 1/3 of patients even on OAC plus aspirin following LAAC with the Watchman device. Despite this intensive postprocedural antithrombotic treatment,

no recurrent intracranial bleedings were reported. However, 9 (14%) patients with a intracranial bleeding less than 60 days before LAAC were treated with dual APT, the study population was small, and the follow-up was limited to 6 months (Hucker et al., 2020).

The results of Study II complement the previous findings on LAAC after intracranial bleeding (Nielsen-Kudsk et al., 2017; Renou et al., 2017), especially when comparing these results to intracranial survivors with AF but without adequate thromboprophylaxis (Kuramatsu et al., 2015; Salman et al., 2021a) (Figure 16). In the SoSTART trial (Salman et al., 2021a), 203 AF patients were randomly assigned median 4 months (IQR, 2–9 months) after intracranial bleeding to start OAC (98% received NOACs) or avoid OAC (31% received aspirin or clopidogrel monotherapy). Moreover, SoSTART trial patients were at high risk of ischaemic stroke (the median CHA_2DS_2-VASc score was 4, and 21% of patients had a history of ischaemic stroke).

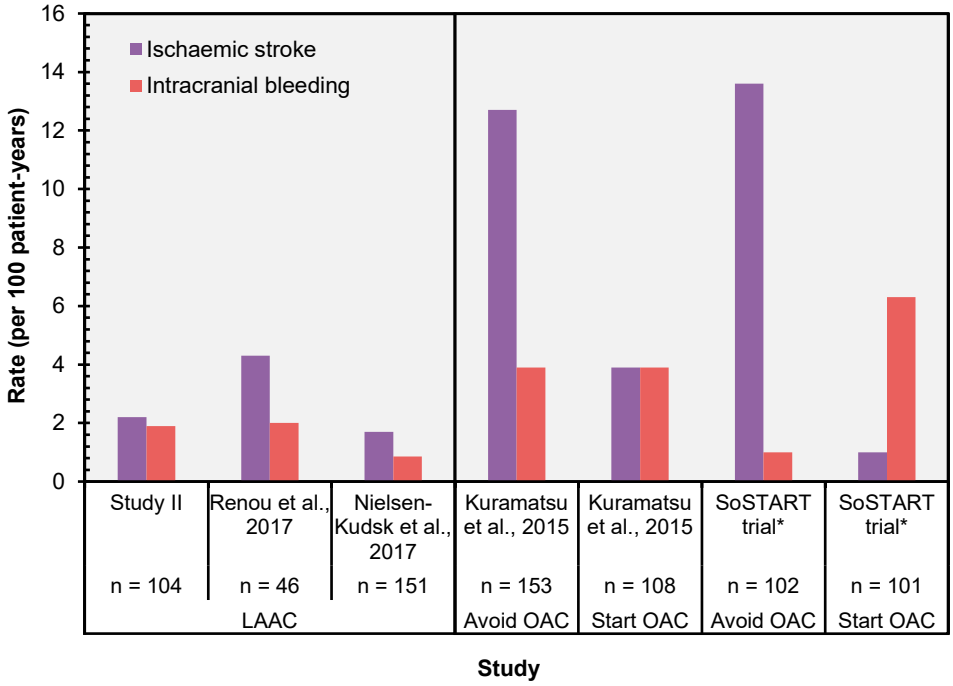


Figure 16. The rate of ischaemic stroke and recurrent intracranial bleeding in AF patients with prior intracranial bleeding. In the selected studies on left atrial appendage closure (LAAC) (Nielsen-Kudsk et al., 2017; Renou et al., 2017), the procedure was performed on average approximately 7 months after intracranial bleeding In. the propensity-score matched sample by Kuramatsu et al., the follow-up started from the index intracerebral bleeding (Kuramatsu et al., 2015). In SoSTART (Start or STop Anticoagulants Randomised Trial), 203 patients were randomly allocated to avoid or start oral anticoagulation (OAC) at a median of 3.8 months after intracranial bleeding. *The rate is cumulative event rate at 1 year.

In the avoid-OAC group, the recurrence rate of intracranial bleeding was only 1.0% (95% CI, 0.1–6.9), but the rate of ischaemic stroke was 13.6% (95% CI, 8.1–22.2) at 1 year (Salman et al., 2021a). Meanwhile, in the start-OAC group, the rate of ischaemic stroke was low at 1.0% (95% CI, 0.1–6.9), but the recurrence rate of intracranial bleeding was 6.3% (95% CI, 2.9–13.6) at 1 year (Salman et al., 2021a).

In Study II, LAAC in AF patients with previous intracranial bleeding demonstrated favourable outcomes (i.e., balanced risk of ischaemic stroke and recurrent intracranial bleeding) irrespective of history of thromboembolism. Therefore, given that patients with prior ischaemic stroke or TIA are at increased risk of recurrent events, an ongoing Nordic multicentre randomized controlled trial will shed light on the feasibility of LAAC for secondary prevention. The Occlusion-AF trial (ClinicalTrials.gov Identifier: NCT03642509), will compare LAAC followed by single APT to NOAC therapy in up to 750 AF patients with a recent ischaemic stroke or TIA (Korsholm et al., 2022). Moreover, considering the high rates of ischaemic events in AF patients assigned to avoid OAC after recent intracranial bleeding (Kuramatsu et al., 2015; Salman et al., 2021a; Schreuder et al., 2021) and a high proportion (~80–90%) of patients who lack adequate thromboprophylaxis in the real-world setting (Pennlert et al., 2015; Vestergaard et al., 2016), the results from randomized STROKECLOSE (ClinicalTrials.gov Identifier: NCT02830152) and A3ICH (ClinicalTrials.gov Identifier: NCT03243175) trials assessing the efficacy and safety of LAAC in these high-risk patients are eagerly awaited.

In summary, it is clear from the above mentioned, and from the present results of Study II, that AF patients with previous intracranial bleedings and thromboembolic events pose a therapeutic challenge to balance the risk of recurrent events. Therefore, percutaneous LAAC with minimized and individually tailored antithrombotic treatment (i.e., aiming for short-term single APT) would seem a reasonable alternative to OAC in these selected patients.

6.3 Impact of ventricular rate on cardiac troponin release in atrial fibrillation

The main finding of Study III was that high ventricular rate was significantly associated with elevated hs-cTn T level in patients presenting primarily with AF to the emergency department. Moreover, the association of heart rate on hs-cTn T release appeared non-linear and became more pronounced when the admission heart rate exceeded the threshold of 125 bpm. Notably, more than two thirds of patients with high ventricular rate (> 125 bpm) had elevated hs-cTn T level, but minor troponin elevations were not infrequent in patients with adequate rate control either, especially in the presence of co-morbidities.

Abnormal, mildly elevated troponin level is a common finding in patients with AF (Hijazi et al., 2012, 2014a; Ruff et al., 2016), and minor troponin release in AF patients seems to be rarely caused by type 1 myocardial infarction (Augusto et al., 2017; Stoyanov et al., 2018; Jaakkola et al., 2019). Considering that the use of cTns is at the heart of the diagnosis of non-ST-segment elevation myocardial infarction (Collet et al., 2021), it is not surprising that elevated troponin levels are an everyday challenge in AF patients presenting to the emergency department with chest discomfort, dyspnoea or other acute symptoms. In Study III, besides high ventricular rate, the peak hs-cTn T level was also associated with several clinical characteristics including new-onset AF, the absence of palpitations, old age, low haemoglobin level, decreased kidney function, diabetes, and heart failure. However, the magnitude of troponin release was not independently associated with known coronary artery disease, and patients with troponin elevation were not at high cardiovascular risk at 1 year after hospitalization. Moreover, the troponin release was often dynamic (i.e., a rising/falling pattern in cTn levels) in tachycardic patients suggesting that dynamic change in hs-cTn level has limited value in the diagnostic algorithms of acute coronary syndrome in this patient population.

The aetiopathogenesis of the sustained cTn elevation in AF patients remains unclear and is likely multifactorial. Normal ageing, and subclinical coronary artery disease, its risk factors and left ventricular dysfunction are also known to be associated with minor increase in troponin levels (DeFilippi et al., 2010). In Study III, older age and multiple co-morbidities (e.g., chronic kidney disease and anaemia) increased the odds of minor hs-cTn T level elevations also in these selected patients presenting primarily with AF to the emergency department.

Chronically elevated troponin concentrations, even below the 99th percentile, predict cardiovascular events in patients with AF and in apparently healthy general population (Hijazi et al., 2014b; Willeit et al., 2017). Moreover, a mild elevation of hs-cTn T has been associated with incident heart failure, and it has been linked to progressive changes in the cardiac structure, an increased left ventricular mass, and both non-ischaemic and ischaemic fibrosis (DeFilippi et al., 2010; Seliger et al.,

2017). Considering that elevated troponin levels are also associated with incident AF (Filion et al., 2015; Zhu et al., 2018), the sustained elevation of troponins might also reflect the presence of atrial cardiomyopathy behind AF (Avitall et al., 2008; Goette et al., 2016), or an incipient AF-induced cardiomyopathy (Huizar et al., 2019). Moreover, lower levels of cTn T before catheter ablation of AF or atrial flutter predict improvement in left ventricular systolic function in patients with a reduced left ventricular ejection fraction (Aoyama et al., 2020). Considering that the improvement in left ventricular systolic function is also associated with partly reversible fibrosis in these patients (Prabhu et al., 2018), persistently elevated cTn levels might indicate advanced or irreversible ventricular remodelling.

Interestingly, hypertension treatment with amlodipine, and the intensification of lenient ventricular rate control with β-blockers and calcium antagonists in AF seem to have a modest effect on troponin release in patients with stable AF (Hoshide et al., 2013; Ulimoen et al., 2014). Therefore, the findings of Study III might suggest that many AF patients have inadequate ventricular rate control in the acute setting, and the transient troponin release in these patients is dependent on a certain heart rate threshold, in addition to the aforementioned chronic contributing conditions.

Transient troponin release has been previously observed in conditions associated with high heart rate, such as paroxysms of supraventricular tachycardia (Redfearn et al., 2005; Sayadnik et al., 2017), rapid atrial pacing (Turer et al., 2011), and strenuous exercise (Shave et al., 2010; Paana et al., 2019). Moreover, exercise-induced troponin release seems to correlate with heart rate, and to be dependent on a minimum heart rate and duration of tachycardia above this critical threshold (Bjørkavoll-Bergseth et al., 2020). The findings of Study III might indicate, that in AF, there is also a critical threshold in ventricular rate at 120–130 bpm, over which the baseline troponin release is augmented (i.e., acute-on-chronic effect). Moreover, in Study III, the lack of palpitation symptoms was associated with elevated cTn T levels. This observation may indirectly suggest longer duration of acute arrhythmia before seeking for medical care. Moreover, the highest cTn T levels were observed in patients with new-onset AF, but unfortunately no data on the duration of the index AF episode was available.

The pathophysiology of tachycardia-induced troponin elevation in AF remains incompletely understood. Rapid ventricular response in AF may cause a mismatch between myocardial oxygen supply and demand (Kochiadakis et al., 2002; Scarsoglio et al., 2019), and subsequent transient myocardial ischaemia could result in the release of cTn into the circulation (Sabatine et al., 2009; Weil et al., 2017; Árnadóttir et al., 2021). However, myocardial ischaemia is not the prerequisite of cTn release (Samaha et al., 2019), and previous studies have demonstrated that troponin elevations can be observed after paroxysms of supraventricular tachycardia or rapid atrial pacing also in patients with normal coronary arteries and even without

biochemical evidence of myocardial ischemia (Redfearn et al., 2005; Miranda et al., 2006; Patanè et al., 2009; Turer et al., 2011; Yedder et al., 2011). Meanwhile, other potential tachycardia-induced mechanisms include reversible cell injury causing a temporary increase in membrane permeability and release of loosely bound troponin molecules into the extracellular space and bloodstream (Jeremias & Gibson, 2005; Hickman et al., 2010; Hammarsten et al., 2018). Finally, high ventricular rate is not without consequences because prolonged tachycardia accelerates progression of myocardial fibrosis in experimental AF model (Ling et al., 2012), and may lead to tachycardia-induced cardiomyopathy (Huizar et al., 2019), and also increase susceptibility to the progression of AF (Avitall et al., 2008).

In summary, high ventricular rate (> 125/min) was a significant modifier of cTn release in symptomatic AF patients. Prospective studies are warranted to confirm and investigate the clinical impact of this phenomenon. Nevertheless, this finding is of clinical relevance when evaluating the differential diagnosis of mild cTn elevation in symptomatic AF patients. Moreover, considering the prognostic significance of chronically elevated cTn levels, it is important to elucidate the precise pathophysiological mechanism of cTn release in future studies.

6.4 Strengths and limitations

The present research has its strengths and limitations that must be acknowledged. The major limitations of this research are the single-centre design, the retrospective nature of data review, and the relatively small sample size in all the studies (I–III). However, the follow-up data in Studies I and II were prospectively collected up to 5 years, data were collected from comprehensive electronic patient records, and structured case report forms were used to ensure the uniformity of reporting.

In Studies I and II, investigated endovascular LAAC devices included mainly the Amplatzer devices (Amplatzer Cardiac Plug and Amulet), and only a few Watchman devices were implanted during the study period. Although the different device designs might have an impact on the outcome, recent findings suggest comparable safety and efficacy between these LAAC devices (Lakkireddy et al., 2021). Nonetheless, these LAAC devices used in this study are among the most common devices in current practice. Moreover, in Studies I and II, the expected annual ischaemic stroke and major bleeding rates were estimated from historical controls based on the CHA_2DS_2-VASc and HAS-BLED scores, and thus, comparisons to the observed rates should be made with caution. Furthermore, the modified HAS-BLED score was estimated without including labile international normalized ratio and alcohol usage, which might underestimate the risk of bleeding events. Also, in Study II, the individual tailoring of discharge medication did not allow comparisons between various early postprocedural antithrombotic regimen.

The findings of Study III should not be interpreted without considering the following limitations. First, patients with hs-cTn T level > 100 ng/L were excluded, and therefore, the findings of this study should not be generalized to AF patients with markedly elevated cTn levels. Second, admission heart rates were collected only from a single admission ECG recording. Multiple ECG recordings or telemetry data could have provided an average estimate of the admission heart rate. Third, only patients with multiple hs-cTn T samples were included in this analysis, and thus the study is susceptible to selection bias. Nevertheless, Study III is representative of real-world clinical practice in which serial hs-cTn measurements are routinely performed in the emergency department and mildly elevated cTn levels are frequently encountered in symptomatic AF patients.

6.5 Future perspectives

The optimal strategy for preventing ischaemic stroke in AF patients with contraindications to OAC, such as recent intracranial bleeding, remains an unresolved issue. Although percutaneous LAAC followed by short-term single APT seems a sensible alternative to OAC in these selected patients, the choice and duration of postprocedural antithrombotic treatment remains practically empirical. The postprocedural antithrombotic treatment should not be excessively intensive nor extended for longer than is necessary, especially in high bleeding risk patients. Nonetheless, robust data from adequately powered clinical trials are needed to optimize treatment in these fragile patients. Moreover, a special focus should be given to reducing the residual burden of ischaemic cerebrovascular events that persists after successful LAAC but also in OAC-treated patients.

Mildly elevated cTn level in symptomatic AF patients presents a clinical challenge to distinguish acute coronary event requiring urgent revascularization from other conditions causing an acute or sustained cTn release. In the present study, high ventricular rate was associated with cTn release in patients admitted to the emergency department primarily for AF. Whether this phenomenon is related to inadequate ventricular rate control and has any prognostic significance, requires further studies. Implantable loop recorders and other means of heart rhythm monitoring might provide a convenient way to assess the frequency of high ventricular rate episodes, and thereby the long-term impact of inadequate ventricular rate control.

7 Conclusions

The findings from this research expand the understanding of specific contemporary issues in AF management. This thesis describes the unique challenge in the prevention of ischaemic stroke in AF patients who have contraindications to OAC and undergo percutaneous LAAC. Furthermore, this research also addresses the differential diagnosis of mild cTn elevation in symptomatic AF patients. The following are the main conclusions of this dissertation:

1. Percutaneous LAAC followed by abbreviated postprocedural single APT is a reasonable treatment strategy for AF patients with strict contraindications to OAC when no other indication for long-term APT is present.
2. Percutaneous LAAC with minimized antithrombotic treatment is a feasible treatment option in AF patients with a history of both intracranial bleeding and thromboembolism to balance the risk of recurrent events.
3. High ventricular response in AF is associated with increased hs-cTn T levels, and therefore should be taken into account, among other clinical factors, when evaluating the diagnostic value of minor troponin elevation in the emergency department.

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References

Abdelaziz, H. K., Saad, M., Pothineni, N. V. K., et al. 2019. Aspirin for primary prevention of cardiovascular events. *Journal of the American College of Cardiology*. 73(23):2915–2929. https://doi.org/10.1016/j.jacc.2019.03.501.

Abe, R., Takamisawa, I., Saji, M., et al. 2020. Small thrombi and incomplete endothelialization detected by cardiac endoscopy after left atrial appendage closure using Watchman device. *European Heart Journal - Case Reports*. 4(5):1–2. https://doi.org/10.1093/ehjcr/ytaa279.

ACTIVE Writing Group of the ACTIVE Investigators, Connolly, S., Pogue, J., et al. 2006. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *The Lancet*. 367(9526):1903–1912. https://doi.org/10.1016/s0140-6736(06)68845-4.

Adams, J. E., Schechtman, K. B., Landt, Y., et al. 1994. Comparable detection of acute myocardial infarction by creatine kinase MB isoenzyme and cardiac troponin I. *Clinical Chemistry*. 40(7 I):1291–1295. https://doi.org/10.1093/clinchem/40.7.1291.

Adelborg, K., Szépligeti, S., Sundbøll, J., et al. 2017. Risk of stroke in patients with heart failure: A population-based 30-year cohort study. *Stroke*. 48(5):1161–1168. https://doi.org/10.1161/strokeaha.116.016022.

Ajmal, M., Naik, H. & Kocheril, A. 2020. Left atrial appendage closure in patients with intracranial hemorrhage and nonvalvular atrial fibrillation. *Journal of Stroke and Cerebrovascular Diseases*. 29(4):104685. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104685.

Akao, M., Chun, Y. H., Wada, H., et al. 2013. Current status of clinical background of patients with atrial fibrillation in a community-based survey: The Fushimi AF Registry. *Journal of Cardiology*. 61(4):260–266. https://doi.org/10.1016/j.jjcc.2012.12.002.

Alkhouli, M., Busu, T., Shah, K., et al. 2018. Incidence and clinical impact of device-related thrombus following percutaneous left atrial appendage occlusion: A meta-analysis. *JACC: Clinical Electrophysiology*. 4(12):1629–1637. https://doi.org/10.1016/j.jacep.2018.09.007.

Allan, V., Banerjee, A., Shah, A. D., et al. 2017. Net clinical benefit of warfarin in individuals with atrial fibrillation across stroke risk and across primary and secondary care. *Heart*. 103(3):210–218. https://doi.org/10.1136/heartjnl-2016-309910.

Aminian, A., Schmidt, B., Mazzone, P., et al. 2019. Incidence, characterization, and clinical impact of device-related thrombus following left atrial appendage occlusion in the prospective global AMPLATZER Amulet Observational Study. *JACC: Cardiovascular Interventions*. 12(11):1003–1014. https://doi.org/10.1016/j.jcin.2019.02.003.

Andrade, J. G., Wazni, O. M., Kuniss, M., et al. 2021. Cryoballoon ablation as initial treatment for atrial fibrillation: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*. 78(9):914–930. https://doi.org/10.1016/j.jacc.2021.06.038.

Aoyama, D., Miyazaki, S., Hasegawa, K., et al. 2020. Preprocedural troponin T levels predict the improvement in the left ventricular ejection fraction after catheter ablation of atrial fibrillation/flutter. *Journal of the American Heart Association*. 9(7):e015126. https://doi.org/10.1161/jaha.119.015126.

Apostolakis, S., Lane, D. A., Guo, Y., et al. 2012. Performance of the HEMORR2HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation. *Journal of the American College of Cardiology*. 60(9):861–867. https://doi.org/10.1016/j.jacc.2012.06.019.

Árnadóttir, Á., Pedersen, S., Bo Hasselbalch, R., et al. 2021. Temporal release of high-sensitivity cardiac troponin T and I and copeptin after brief induced coronary artery balloon occlusion in humans. *Circulation*. 143(11):1095–1104. https://doi.org/10.1161/circulationaha.120.046574.

Aryana, A., Singh, S. K., Singh, S. M., et al. 2015. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm*. 12(7):1431–1437. https://doi.org/10.1016/j.hrthm.2015.03.028.

Asmarats, L., O'Hara, G., Champagne, J., et al. 2020. Short-term oral anticoagulation versus antiplatelet therapy following transcatheter left atrial appendage closure. *Circulation: Cardiovascular Interventions*. 13(8):e009039. https://doi.org/10.1161/circinterventions.120.009039.

Atrial Fibrillation Investigators. 1994. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: Analysis of pooled data from five randomized controlled trials. *Archives of Internal Medicine*. 154(13):1449–1457. https://doi.org/10.1001/archinte.1994.00420130036007.

Augusto, J., Borges Santos, M., Roque, D., et al. 2017. Mild troponin elevation in patients admitted to the emergency department with atrial fibrillation: 30-day post-discharge prognostic significance. *Internal and Emergency Medicine*. 13(3):333–341. https://doi.org/10.1007/s11739-017-1777-7.

Avitall, B., Bi, J., Mykytsey, A., et al. 2008. Atrial and ventricular fibrosis induced by atrial fibrillation: Evidence to support early rhythm control. *Heart Rhythm*. 5(6):839–845. https://doi.org/10.1016/j.hrthm.2008.02.042.

Bailey, R. D., Hart, R. G., Benavente, O., et al. 2001. Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. *Neurology*. 56(6):773–777. https://doi.org/10.1212/wnl.56.6.773.

Banerjee, A., Allan, V., Denaxas, S., et al. 2019. Subtypes of atrial fibrillation with concomitant valvular heart disease derived from electronic health records: Phenotypes, population prevalence, trends and prognosis. *Europace*. 21(12):1776–1784. https://doi.org/10.1093/europace/euz220.

Barocelli, F., Coli, S., Crocamo, A., et al. 2020. Left atrial appendage occlusion in patients with atrial fibrillation and large prevalence of prior intracranial bleeding. *Journal of Cardiovascular Medicine*. 21(8):583–591. https://doi.org/10.2459/jcm.0000000000000976.

Becattini, C., Dentali, F., Camporese, G., et al. 2018. Carotid atherosclerosis and risk for ischemic stroke in patients with atrial fibrillation on oral anticoagulant treatment. *Atherosclerosis*. 271:177–181. https://doi.org/10.1016/j.atherosclerosis.2018.02.004.

Beigel, R., Wunderlich, N. C., Ho, S. Y., et al. 2014. The left atrial appendage: Anatomy, function, and noninvasive evaluation. *JACC: Cardiovascular Imaging*. 7(12):1251–1265. https://doi.org/10.1016/j.jcmg.2014.08.009.

Benjamin, E. J., D'Agostino, R. B., Belanger, A. J., et al. 1995. Left atrial size and the risk of stroke and death: The Framingham Heart Study. *Circulation*. 92(4):835–841. https://doi.org/10.1161/01.cir.92.4.835.

Benz, A. P., Hijazi, Z., Lindbäck, J., et al. 2021. Biomarker-based risk prediction with the ABC-AF scores in patients with atrial fibrillation not receiving oral anticoagulation. *Circulation*. 143:1863–1873. https://doi.org/10.1161/circulationaha.120.053100.

Beyer-Westendorf, J., Ehlken, B. & Evers, T. 2016. Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. *Europace*. 18(8):1150–1157. https://doi.org/10.1093/europace/euv421.

Di Biase, L., Santangeli, P., Anselmino, M., et al. 2012. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *Journal of the American College of Cardiology*. 60(6):531–538. https://doi.org/10.1016/j.jacc.2012.04.032.

Biffi, A., Anderson, C. D., Battey, T. W. K., et al. 2015. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA*. 314(9):904–912. https://doi.org/10.1001/jama.2015.10082.

Bjørkavoll-Bergseth, M., Kleiven, Ø., Auestad, B., et al. 2020. Duration of elevated heart rate is an important predictor of exercise-induced troponin elevation. *Journal of the American Heart Association*. 9(4):e014408. https://doi.org/10.1161/jaha.119.014408.

Blackshear, J. L. & Odell, J. A. 1996. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *The Annals of Thoracic Surgery*. 61(2):755–759. https://doi.org/10.1016/0003-4975(95)00887-x.

Bleier, J., Vorderwinkler, K. P., Falkensammer, J., et al. 1998. Different intracellular compartmentations of cardiac troponins and myosin heavy chains: A causal connection to their different early release after myocardial damage. *Clinical Chemistry*. 44(9):1912–1918. https://doi.org/10.1093/clinchem/44.9.1912.

Blum, S., Meyre, P., Aeschbacher, S., et al. 2019. Incidence and predictors of atrial fibrillation progression: A systematic review and meta-analysis. *Heart Rhythm*. 16(4):502–510. https://doi.org/10.1016/j.hrthm.2018.10.022.

Boeddinghaus, J., Reichlin, T., Nestelberger, T., et al. 2017. Early diagnosis of acute myocardial infarction in patients with mild elevations of cardiac troponin. *Clinical Research in Cardiology*. 106(6):457–467. https://doi.org/10.1007/s00392-016-1075-9.

Boersma, L. V., Ince, H., Kische, S., et al. 2017. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm*. 14(9):1302–1308. https://doi.org/10.1016/j.hrthm.2017.05.038.

Boersma, L. V., Ince, H., Kische, S., et al. 2019. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: Final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circulation: Arrhythmia and Electrophysiology*. 12(4):e006841. https://doi.org/10.1161/circep.118.006841.

Boriani, G., Laroche, C., Diemberger, I., et al. 2015. Asymptomatic atrial fibrillation: Clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. *American Journal of Medicine*. 128(5):509-518.e2. https://doi.org/10.1016/j.amjmed.2014.11.026.

Borre, E. D., Goode, A., Raitz, G., et al. 2018. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: A systematic review. *Thrombosis and Haemostasis*. 118(12):2171–2187. https://doi.org/10.1055/s-0038-1675400.

Van Den Bos, E. J., Constantinescu, A. A., Van Domburg, R. T., et al. 2011. Minor elevations in troponin I are associated with mortality and adverse cardiac events in patients with atrial fibrillation. *European Heart Journal*. 32(5):611–617. https://doi.org/10.1093/eurheartj/ehq491.

Brignole, M., Pokushalov, E., Pentimalli, F., et al. 2018. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *European Heart Journal*. 39(45):3999–4008. https://doi.org/10.1093/eurheartj/ehy555.

Brignole, M., Pentimalli, F., Palmisano, P., et al. 2021. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: The APAF-CRT mortality trial. *European Heart Journal*. 42(46):4731–4739. https://doi.org/10.1093/eurheartj/ehab569.

Broersen, L. H. A., Stengl, H., Nolte, C. H., et al. 2020. Association between high-sensitivity cardiac troponin and risk of stroke in 96 702 individuals: A meta-analysis. *Stroke*. 51(4):1085–1093. https://doi.org/10.1161/strokeaha.119.028323.

Carnicelli, A. P., De Caterina, R., Halperin, J. L., et al. 2017. Edoxaban for the prevention of thromboembolism in patients with atrial fibrillation and bioprosthetic valves. *Circulation*. 135(13):1273–1275. https://doi.org/10.1161/circulationaha.116.026714.

Casu, G., D'Angelo, G., Ugo, F., et al. 2021. Left atrial appendage occlusion in atrial fibrillation patients with previous intracranial bleeding: A national multicenter study. *International Journal of Cardiology*. 328:75–80. https://doi.org/10.1016/j.ijcard.2020.11.045.

Chan, K. H., Ka-Kit Leung, G., Lau, K. K., et al. 2014. Predictive value of the HAS-BLED score for the risk of recurrent intracranial hemorrhage after first spontaneous intracranial hemorrhage. *World Neurosurgery*. 82(1–2):e219–e223. https://doi.org/10.1016/j.wneu.2013.02.070.

Chao, T. F., Liu, C. J., Liao, J. N., et al. 2016. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. *Circulation*. 133(16):1540–1547. https://doi.org/10.1161/circulationaha.115.019794.

Chao, T. F., Lip, G. Y. H., Lin, Y. J., et al. 2018. Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: Attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study. *International Journal of Cardiology*. 254:157–161. https://doi.org/10.1016/j.ijcard.2017.11.025.

Charidimou, A., Karayiannis, C., Song, T. J., et al. 2017. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. *Neurology*. 89(23):2317–2326. https://doi.org/10.1212/wnl.0000000000004704.

Choi, S. H., Jurgens, S. J., Weng, L.-C., et al. 2020. Monogenic and polygenic contributions to atrial fibrillation risk: Results from a national biobank. *Circulation research*. 126(2):200–209. https://doi.org/10.1161/circresaha.119.315686.

Choudhury, A., Chung, I., Blann, A. D., et al. 2007. Elevated platelet microparticle levels in nonvalvular atrial fibrillation: Relationship to P-selectin and antithrombotic therapy. *Chest*. 131(3):809–815. https://doi.org/10.1378/chest.06-2039.

Christersson, C., Wallentin, L., Andersson, U., et al. 2014. D-dimer and risk of thromboembolic and bleeding events in patients with atrial fibrillation - observations from the ARISTOTLE trial. *Journal of Thrombosis and Haemostasis*. 12(9):1401–1412. https://doi.org/10.1111/jth.12638.

Christersson, C., Wallentin, L., Andersson, U., et al. 2019. Effect of apixaban compared with warfarin on coagulation markers in atrial fibrillation. *Heart*. 105(3):235–242. https://doi.org/10.1136/heartjnl-2018-313351.

Christiansen, C. B., Olesen, J. B., Gislason, G., et al. 2013. Cardiovascular and non-cardiovascular hospital admissions associated with atrial fibrillation: A Danish nationwide, retrospective cohort study. *BMJ Open*. 3(1):e001800. https://doi.org/10.1136/bmjopen-2012-001800.

Christophersen, I. E., Ravn, L. S., Budtz-Joergensen, E., et al. 2009. Familial aggregation of atrial fibrillation: A study in Danish twins. *Circulation: Arrhythmia and Electrophysiology*. 2(4):378–383. https://doi.org/10.1161/circep.108.786665.

Chugh, S. S., Havmoeller, R., Narayanan, K., et al. 2014. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. *Circulation*. 129(8):837–847. https://doi.org/10.1161/circulationaha.113.005119.

Coleman, C. I., Briere, J.-B., Fauchier, L., et al. 2019. Meta-analysis of real-world evidence comparing non-vitamin K antagonist oral anticoagulants with vitamin K antagonists for the treatment of patients with non-valvular atrial fibrillation. *Journal of Market Access & Health Policy*. 7(1):1574541. https://doi.org/10.1080/20016689.2019.1574541.

Coleman, H. N., Taylor, R. R., Pool, P. E., et al. 1971. Congestive heart failure following chronic tachycardia. *American Heart Journal*. 81(6):790–798. https://doi.org/10.1016/0002-8703(71)90083-4.

Collet, J. P., Thiele, H., Barbato, E., et al. 2021. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal*. 42(14):1289–1367. https://doi.org/10.1093/eurheartj/ehaa575.

Collins, R., Peto, R., Hennekens, C., et al. 2009. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *The Lancet*. 373(9678):1849–1860. https://doi.org/10.1016/s0140-6736(09)60503-1.

Connolly, S. J., Pogue, J., Hart, R. G., et al. 2009a. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *New England Journal of Medicine*. 360(20):2066–2078. https://doi.org/10.1056/nejmoa0901301.

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., et al. 2009b. Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*. 361(12):1139–1151. https://doi.org/10.1056/nejmoa0905561.

Connolly, S. J., Eikelboom, J., Joyner, C., et al. 2011. Apixaban in patients with atrial fibrillation. *New England Journal of Medicine*. 364(9):806–817. https://doi.org/10.1056/nejmoa1007432.

Cresti, A., García-Fernández, M. A., Sievert, H., et al. 2019. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study. *EuroIntervention*. 15(3):e225–e230. https://doi.org/10.4244/eij-d-19-00128.

Cruz-González, I., Rama-Merchan, J. C., Martínez-Peralta, S., et al. 2017. Safety and effectiveness of percutaneous closure of left atrial appendage in patients with intracranial hemorrhage. *Revista Española de Cardiología*. 70(1):58–60. https://doi.org/10.1016/j.rec.2016.08.010.

Daccarett, M., Badger, T. J., Akoum, N., et al. 2011. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *Journal of the American College of Cardiology*. 57(7):831–838. https://doi.org/10.1016/j.jacc.2010.09.049.

Dagres, N., Nieuwlaat, R., Vardas, P. E., et al. 2007. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: A report from the Euro Heart Survey on Atrial Fibrillation. *Journal of the American College of Cardiology*. 49(5):572–577. https://doi.org/10.1016/j.jacc.2006.10.047.

Damiano, R. J., Tripp, H. F., Asano, T., et al. 1987. Left ventricular dysfunction and dilatation resulting from chronic supraventricular tachycardia. *Journal of Thoracic and Cardiovascular Surgery*. 94(1):135–143. https://doi.org/10.1016/s0022-5223(19)36329-9.

Daniel, W. G., Nellessen, U., Schröder, E., et al. 1988. Left atrial spontaneous echo contrast in mitral valve disease: An indicator for an increased thromboembolic risk. *Journal of the American College of Cardiology*. 11(6):1204–1211. https://doi.org/10.1016/0735-1097(88)90283-5.

DeFilippi, C. R., De Lemos, J. A., Christenson, R. H., et al. 2010. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA*. 304(22):2494–2502. https://doi.org/10.1001/jama.2010.1708.

Diederichsen, S. Z., Haugan, K. J., Brandes, A., et al. 2019. Natural history of subclinical atrial fibrillation detected by implanted loop recorders. *Journal of the American College of Cardiology*. 74(22):2771–2781. https://doi.org/10.1016/j.jacc.2019.09.050.

Dukkipati, S. R., Kar, S., Holmes, D. R., et al. 2018. Device-related thrombus after left atrial appendage closure: Incidence, predictors, and outcomes. *Circulation*. 138(9):874–885. https://doi.org/10.1161/circulationaha.118.035090.

Duthoit, G., Silvain, J., Marijon, E., et al. 2020. Reduced rivaroxaban dose versus dual antiplatelet therapy after left atrial appendage closure: ADRIFT a randomized pilot study. *Circulation: Cardiovascular Interventions*. 13(7):e008481. https://doi.org/10.1161/circinterventions.119.008481.

Eikelboom, J. W., Connolly, S. J., Brueckmann, M., et al. 2013. Dabigatran versus warfarin in patients with mechanical heart valves. *New England Journal of Medicine*. 369(13):1206–1214. https://doi.org/10.1056/nejmoa1300615.

Emdin, C. A., Wong, C. X., Hsiao, A. J., et al. 2016. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ*. 352:h7013. https://doi.org/10.1136/bmj.h7013.

Ericson, L., Bergfeldt, L. & Björholt, I. 2011. Atrial fibrillation: The cost of illness in Sweden. *European Journal of Health Economics*. 12(5):479–487. https://doi.org/10.1007/s10198-010-0261-3.

Eschenhagen, T., Bolli, R., Braun, T., et al. 2017. Cardiomyocyte regeneration: A consensus statement. *Circulation*. 136(7):680–686. https://doi.org/10.1161/circulationaha.117.029343.

Evans, J. D. W., Dobbin, S. J. H., Pettit, S. J., et al. 2018. High-sensitivity cardiac troponin and new-onset heart failure: A systematic review and meta-analysis of 67,063 patients with 4,165 incident heart failure events. *JACC: Heart Failure*. 6(3):187–197. https://doi.org/10.1016/j.jchf.2017.11.003.

Fahmy, P., Spencer, R., Tsang, M., et al. 2016. Left atrial appendage closure for atrial fibrillation is safe and effective after intracranial or intraocular hemorrhage. *Canadian Journal of Cardiology*. 32(3):349–354. https://doi.org/10.1016/j.cjca.2015.07.723.

Fang, M. C., Singer, D. E., Chang, Y., et al. 2005. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: The AnTicoagulation and Risk factors in Atrial fibrillation (ATRIA) study. *Circulation*. 112(12):1687–1691. https://doi.org/10.1161/circulationaha.105.553438.

Fauchier, L., Cinaud, A., Brigadeau, F., et al. 2018. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *Journal of the American College of Cardiology*. 71(14):1528–1536. https://doi.org/10.1016/j.jacc.2018.01.076.

Fayos-Vidal, F., Arzamendi-Aizpurua, D., Millán-Álvarez, X., et al. 2017. Left atrial appendage closure in patients with intracranial haemorrhage and atrial fibrillation. *Neurologia*. 17(pii: S0213-4853):30242–30246. https://doi.org/10.1016/j.nrl.2017.05.013.

Feng, J., Schaus, B. J., Fallavollita, J. A., et al. 2001. Preload induces troponin I degradation independently of myocardial ischemia. *Circulation*. 103(16):2035–2037. https://doi.org/10.1161/01.cir.103.16.2035.

Filion, K. B., Agarwal, S. K., Ballantyne, C. M., et al. 2015. High-sensitivity cardiac troponin T and the risk of incident atrial fibrillation: The Atherosclerosis Risk in Communities (ARIC) study. *American Heart Journal*. 169(1):31-38.e3. https://doi.org/10.1016/j.ahj.2014.10.005.

Fishbein, M. C., Wang, T., Matijasevic, M., et al. 2003. Myocardial tissue troponins T and I: An immunohistochemical study in experimental models of myocardial ischemia. *Cardiovascular Pathology*. 12(2):65–71. https://doi.org/10.1016/s1054-8807(02)00188-6.

Freeman, J. V., Simon, D. N., Go, A. S., et al. 2015. Association between atrial fibrillation symptoms, quality of life, and patient outcomes: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation: Cardiovascular Quality and Outcomes*. 8(4):393–402. https://doi.org/10.1161/circoutcomes.114.001303.

Freynhofer, M. K., Draxler, D. F., Gruber, S. C., et al. 2013. Endogenous t-PA-antigen is an independent predictor of adverse cardiovascular events and all-cause death in patients with atrial fibrillation. *Journal of Thrombosis and Haemostasis*. 11(6):1069–1077. https://doi.org/10.1111/jth.12213.

Friberg, L., Hammar, N., Pettersson, H., et al. 2007. Increased mortality in paroxysmal atrial fibrillation: Report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *European Heart Journal*. 28(19):2346–2353. https://doi.org/10.1093/eurheartj/ehm308.

Friberg, L., Rosenqvist, M. & Lip, G. Y. H. 2012a. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: The Swedish Atrial Fibrillation cohort study. *European Heart Journal*. 33(12):1500–1510. https://doi.org/10.1093/eurheartj/ehr488.

Friberg, L., Benson, L., Rosenqvist, M., et al. 2012b. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: Nationwide retrospective cohort study. *BMJ*. 344(7862):e3522–e3522. https://doi.org/10.1136/bmj.e3522.

Friberg, L., Rosenqvist, M. & Lip, G. Y. H. 2012c. Net clinical benefit of warfarin in patients with atrial fibrillation: A report from the Swedish Atrial Fibrillation Cohort Study. *Circulation*. 125(19):2298–2307. https://doi.org/10.1161/circulationaha.111.055079.

Friberg, L., Rosenqvist, M., Lindgren, A., et al. 2014. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke*. 45(9):2599–2605. https://doi.org/10.1161/strokeaha.114.006070.

Fu, R., Wu, S., Wu, P., et al. 2011. A study of blood soluble P-selectin, fibrinogen, and von Willebrand factor levels in idiopathic and lone atrial fibrillation. *Europace*. 13(1):31–36. https://doi.org/10.1093/europace/euq346.

Fukuchi, M., Watanabe, J., Kumagai, K., et al. 2001. Increased von Willebrand factor in the endocardium as a local predisposing factor for thrombogenesis in overloaded human atrial appendage. *Journal of the American College of Cardiology*. 37(5):1436–1442. https://doi.org/10.1016/s0735-1097(01)01125-1.

Fuster, V., Rydén, L. E., Cannom, D. S., et al. 2006. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: A report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice. *Europace*. 8(9):651–745. https://doi.org/10.1093/europace/eul097.

García Rodríguez, L. A., Cea Soriano, L., Munk Hald, S., et al. 2021. Discontinuation of oral anticoagulation in atrial fibrillation and risk of ischaemic stroke. *Heart*. 107(7):542–548. https://doi.org/10.1136/heartjnl-2020-317887.

Gattellari, M., Goumas, C., Aitken, R., et al. 2011. Outcomes for patients with ischaemic stroke and atrial fibrillation: The PRISM study (a Program of research informing stroke management). *Cerebrovascular Diseases*. 32(4):370–382. https://doi.org/10.1159/000330637.

Van Gelder, I. C., Hagens, V. E., Bosker, H. A., et al. 2002. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *New England Journal of Medicine*. 347(23):1834–1840. https://doi.org/10.1056/nejmoa021375.

Van Gelder, I. C., Groenveld, H. F., Crijns, H. J. G. M., et al. 2010. Lenient versus strict rate control in patients with atrial fibrillation. *New England Journal of Medicine*. 362(15):1363–1373. https://doi.org/10.1056/nejmoa1001337.

Giugliano, R. P., Ruff, C. T., Braunwald, E., et al. 2013. Edoxaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*. 369(22):2093–2104. https://doi.org/10.1056/nejmoa1310907.

Glikson, M., Wolff, R., Hindricks, G., et al. 2020. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - An update. *Europace*. 22(2):184. https://doi.org/10.1093/europace/euz258.

Go, A. S., Hylek, E. M., Phillips, K. A., et al. 2001. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA*. 285(18):2370–2375. https://doi.org/10.1001/jama.285.18.2370.

Goette, A., Bukowska, A., Dobrev, D., et al. 2009. Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles. *European Heart Journal*. 30(11):1411–1420. https://doi.org/10.1093/eurheartj/ehp046.

Goette, A., Kalman, J. M., Aguinaga, L., et al. 2016. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. *Europace*. 18(10):1455–1490. https://doi.org/10.1093/europace/euw161.

Granger, C. B., Alexander, J. H., McMurray, J. J. V., et al. 2011. Apixaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*. 365(11):981–992. https://doi.org/10.1056/nejmoa1107039.

Groenveld, H. F., Crijns, H. J. G. M., Van Den Berg, M. P., et al. 2011. The effect of rate control on quality of life in patients with permanent atrial fibrillation: Data from the race II (Rate Control

Efficacy in Permanent Atrial Fibrillation II) study. *Journal of the American College of Cardiology*. 58(17):1795–1803. https://doi.org/10.1016/j.jacc.2011.06.055.

de Groot, J. R., Weiss, T. W., Kelly, P., et al. 2021. Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: 1-year follow-up of the prospective observational ETNA-AF-Europe study. *European Heart Journal - Cardiovascular Pharmacotherapy*. 7(FI1):f30–f39. https://doi.org/10.1093/ehjcvp/pvaa079.

Guimarães, P. O., Pokorney, S. D., Lopes, R. D., et al. 2019. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: Insights from the ARISTOTLE trial. *Clinical Cardiology*. 42(5):568–571. https://doi.org/10.1002/clc.23178.

Gupta, S. & Figueredo, V. M. 2014. Tachycardia mediated cardiomyopathy: Pathophysiology, mechanisms, clinical features and management. *International Journal of Cardiology*. 172(1):40–46. https://doi.org/10.1016/j.ijcard.2013.12.180.

Gupta, K., Pillarisetti, J., Biria, M., et al. 2014. Clinical utility and prognostic significance of measuring troponin I levels in patients presenting to the emergency room with atrial fibrillation. *Clinical Cardiology*. 37(6):343–349. https://doi.org/10.1002/clc.22251.

Habara, S., Dote, K., Kato, M., et al. 2007. Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation. *European Heart Journal*. 28(18):2217–2222. https://doi.org/10.1093/eurheartj/ehm356.

Hald, S. M., Möller, S., García Rodríguez, L. A., et al. 2021. Trends in incidence of intracerebral hemorrhage and association with antithrombotic drug use in Denmark, 2005-2018. *JAMA Network Open*. 4(5):e218380. https://doi.org/10.1001/jamanetworkopen.2021.8380.

Van Den Ham, H. A., Klungel, O. H., Singer, D. E., et al. 2015. Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke in patients with atrial fibrillation: Results from a national primary care database. *Journal of the American College of Cardiology*. 66(17):1851–1859. https://doi.org/10.1016/j.jacc.2015.08.033.

Hammarsten, O., Mair, J., Möckel, M., et al. 2018. Possible mechanisms behind cardiac troponin elevations. *Biomarkers*. 23(8):725–734. https://doi.org/10.1080/1354750x.2018.1490969.

Hankey, G. J., Stevens, S. R., Piccini, J. P., et al. 2014. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: The Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in At. *Stroke*. 45(5):1304–1312. https://doi.org/10.1161/strokeaha.113.004506.

Hart, R. G., Boop, B. S. & Anderson, D. C. 1995. Oral anticoagulants and intracranial hemorrhage. Facts and hypotheses. *Stroke*. 26(8):1471–1477. https://doi.org/10.1161/01.str.26.8.1471.

Hart, R. G., Pearce, L. A., Miller, V. T., et al. 2000. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: Frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. *Cerebrovascular Diseases*. 10(1):39–43. https://doi.org/10.1159/000016023.

Hart, R. G., Pearce, L. A. & Aguilar, M. I. 2007. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of Internal Medicine*. 146(12):857–867. https://doi.org/10.7326/0003-4819-146-12-200706190-00007.

Hart, R. G., Diener, H. C., Yang, S., et al. 2012. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: The RE-LY trial. *Stroke*. 43(6):1511–1517. https://doi.org/10.1161/strokeaha.112.650614.

Hastie, T. & Tibshirani, R. 1986. Generalized additive models. *Statistical Science*. 1(3):297–310. https://doi.org/10.1214/ss/1177013604.

Heeringa, J., Van Der Kuip, D. A. M., Hofman, A., et al. 2006. Prevalence, incidence and lifetime risk of atrial fibrillation: The Rotterdam study. *European Heart Journal*. 27(8):949–953. https://doi.org/10.1093/eurheartj/ehi825.

Hemphill, J. C., Greenberg, S. M., Anderson, C. S., et al. 2015. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American

Heart Association/American Stroke Association. *Stroke*. 46(7):2032–2060. https://doi.org/10.1161/str.0000000000000069.

Heppell, R. M., Berkin, K. E., McLenachan, J. M., et al. 1997. Haemostatic and haemodynamic abnormalities associated with left atrial thrombosis in non-rheumatic atrial fibrillation. *Heart*. 77(5):407–411. https://doi.org/10.1136/hrt.77.5.407.

Hessel, M. H. M., Atsma, D. E., Van Der Valk, E. J. M., et al. 2008. Release of cardiac troponin I from viable cardiomyocytes is mediated by integrin stimulation. *Pflugers Archiv European Journal of Physiology*. 455(6):979–986. https://doi.org/10.1007/s00424-007-0354-8.

Hickman, P. E., Potter, J. M., Aroney, C., et al. 2010. Cardiac troponin may be released by ischemia alone, without necrosis. *Clinica Chimica Acta*. 411(5–6):318–323. https://doi.org/10.1016/j.cca.2009.12.009.

Hijazi, Z., Oldgren, J., Andersson, U., et al. 2012. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: A randomized evaluation of long-term anticoagulation therapy (RE-LY) substudy. *Circulation*. 125(13):1605–1616. https://doi.org/10.1161/circulationaha.111.038729.

Hijazi, Z., Siegbahn, A., Andersson, U., et al. 2014a. High-sensitivity troponin I for risk assessment in patients with atrial fibrillation: Insights from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. *Circulation*. 129(6):625–634. https://doi.org/10.1161/circulationaha.113.006286.

Hijazi, Z., Wallentin, L., Siegbahn, A., et al. 2014b. High-sensitivity troponin T and risk stratification in patients with atrial fibrillation during treatment with apixaban or warfarin. *Journal of the American College of Cardiology*. 63(1):52–61. https://doi.org/10.1016/j.jacc.2013.07.093.

Hijazi, Z., Oldgren, J., Lindbäck, J., et al. 2016. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: A derivation and validation study. *The Lancet*. 387(10035):2302–2311. https://doi.org/10.1016/s0140-6736(16)00741-8.

Hildick-Smith, D., Landmesser, U., John Camm, A., et al. 2020. Left atrial appendage occlusion with the AmplatzerTM AmuletTM device: Full results of the prospective global observational study. *European Heart Journal*. 41(28):2894–2901. https://doi.org/10.1093/eurheartj/ehaa169.

Hindricks, G., Potpara, T., Dagres, N., et al. 2021. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *European heart journal*. 42(5):373–498. https://doi.org/10.1093/eurheartj/ehaa612.

Holmes, D. R., Reddy, V. Y., Turi, Z. G., et al. 2009. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomised non-inferiority trial. *The Lancet*. 374(9689):534–542. https://doi.org/10.1016/s0140-6736(09)61343-x.

Holmes, D. R., Kar, S., Price, M. J., et al. 2014. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: The PREVAIL trial. *Journal of the American College of Cardiology*. 64(1):1–12. https://doi.org/10.1016/j.jacc.2014.04.029.

Holmes, D. R., Reddy, V. Y., Buchbinder, M., et al. 2017. The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial. *American Heart Journal*. 189:68–74. https://doi.org/10.1016/j.ahj.2017.03.007.

Holmes, D. R., Schwartz, R. S., Latus, G. G., et al. 2018. A history of left atrial appendage occlusion. *Interventional Cardiology Clinics*. 7(2):143–150. https://doi.org/10.1016/j.iccl.2017.12.005.

Horstmann, S., Zugck, C., Krumsdorf, U., et al. 2014. Left atrial appendage occlusion in atrial fibrillation after intracranial hemorrhage. *Neurology*. 82(2):135–138. https://doi.org/10.1212/wnl.0000000000000022.

Hoshide, S., Fukutomi, M., Eguchi, K., et al. 2013. Change in high-sensitive cardiac troponin T on hypertensive treatment. *Clinical and Experimental Hypertension*. 35(1):40–44. https://doi.org/10.3109/10641963.2012.689044.

Huang, W. Y., Singer, D. E., Wu, Y. L., et al. 2018. Association of intracranial hemorrhage risk with non-vitamin K antagonist oral anticoagulant use vs aspirin use: A systematic review and meta-analysis. *JAMA Neurology*. 75(12):1511–1518. https://doi.org/10.1001/jamaneurol.2018.2215.

Hucker, W. J., Cohen, J. A., Gurol, M. E., et al. 2020. WATCHMAN implantation in patients with a history of atrial fibrillation and intracranial hemorrhage. *Journal of Interventional Cardiac Electrophysiology*. 59(2):415–421. https://doi.org/10.1007/s10840-019-00678-w.

Huhtakangas, J., Tetri, S., Juvela, S., et al. 2011. Effect of increased warfarin use on warfarin-related cerebral hemorrhage: A longitudinal population-based study. *Stroke*. 42(9):2431–2435. https://doi.org/10.1161/strokeaha.111.615260.

Huhtakangas, J., Löppönen, P., Tetri, S., et al. 2013. Predictors for recurrent primary intracerebral hemorrhage: A retrospective population-based study. *Stroke*. 44(3):585–590. https://doi.org/10.1161/strokeaha.112.671230.

Huizar, J. F., Ellenbogen, K. A., Tan, A. Y., et al. 2019. Arrhythmia-induced cardiomyopathy: JACC State-of-the-Art Review. *Journal of the American College of Cardiology*. 73(18):2328–2344. https://doi.org/10.1016/j.jacc.2019.02.045.

Hutt, E., Wazni, O. M., Saliba, W. I., et al. 2019. Left atrial appendage closure device implantation in patients with prior intracranial hemorrhage. *Heart Rhythm*. 16(5):663–668. https://doi.org/10.1016/j.hrthm.2018.11.022.

Huxley, R. R., Lopez, F. L., Folsom, A. R., et al. 2011. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: The atherosclerosis risk in communities (ARIC) study. *Circulation*. 123(14):1501–1508. https://doi.org/10.1161/circulationaha.110.009035.

Israel, C. W., Grönefeld, G., Ehrlich, J. R., et al. 2004. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: Implications for optimal patient care. *Journal of the American College of Cardiology*. 43(1):47–52. https://doi.org/10.1016/j.jacc.2003.08.027.

Jaakkola, J., Mustonen, P., Kiviniemi, T., et al. 2016. Stroke as the first manifestation of atrial fibrillation. *PLoS ONE*. 11(12). https://doi.org/10.1371/journal.pone.0168010.

Jaakkola, S., Kiviniemi, T. O., Nuotio, I., et al. 2018. Usefulness of the CHA2DS2-VASc and HAS-BLED scores in predicting the risk of stroke versus intracranial bleeding in patients with atrial fibrillation (from the FibStroke Study). *American Journal of Cardiology*. 121(10):1182–1186. https://doi.org/10.1016/j.amjcard.2018.01.038.

Jaakkola, S., Paana, T., Nuotio, I., et al. 2019. Etiology of minor troponin elevations in patients with atrial fibrillation at emergency department–Tropo-AF Study. *Journal of Clinical Medicine*. 8(11):1963. https://doi.org/10.3390/jcm8111963.

Jalal, Z., Dinet, M. Lou, Combes, N., et al. 2017. Percutaneous left atrial appendage closure followed by single antiplatelet therapy: Short- and mid-term outcomes. *Archives of Cardiovascular Diseases*. 110(4):242–249. https://doi.org/10.1016/j.acvd.2016.09.006.

James, S. L., Abate, D., Abate, K. H., et al. 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 392(10159):1789–1858. https://doi.org/10.1016/s0140-6736(18)32279-7.

January, C. T., Wann, L. S., Alpert, J. S., et al. 2014. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 130(23):e199–e267. https://doi.org/10.1161/cir.0000000000000041.

January, C. T., Wann, L. S., Calkins, H., et al. 2019. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart R. *Circulation*. 140(2):e125–e151. https://doi.org/10.1161/cir.0000000000000665.

Jashari, F., Ibrahimi, P., Nicoll, R., et al. 2013. Coronary and carotid atherosclerosis: Similarities and differences. *Atherosclerosis*. 227(2):193–200. https://doi.org/10.1016/j.atherosclerosis.2012.11.008.

Jeong, J. H. 2005. Prevalence of and risk factors for atrial fibrillation in Korean adults older than 40 years. *Journal of Korean Medical Science*. 20(1):26–30. https://doi.org/10.3346/jkms.2005.20.1.26.

Jeremias, A. & Gibson, C. M. 2005. Narrative review: Alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Annals of Internal Medicine*. 142(9):786–791. https://doi.org/10.7326/0003-4819-142-9-200505030-00015.

Johnsen, S. P., Dalby, L. W., Täckström, T., et al. 2017. Cost of illness of atrial fibrillation: A nationwide study of societal impact. *BMC Health Services Research*. 17(1):714. https://doi.org/10.1186/s12913-017-2652-y.

Kaarisalo, M. M., Immonen-Räihä, P., Marttila, R. J., et al. 1997. Atrial fibrillation and stroke: Mortality and causes of death after the first acute ischemic stroke. *Stroke*. 28(2):311–315. https://doi.org/10.1161/01.str.28.2.311.

Kanderian, A. S., Gillinov, A. M., Pettersson, G. B., et al. 2008. Success of surgical left atrial appendage closure. Assessment by transesophageal echocardiography. *Journal of the American College of Cardiology*. 52(11):924–929. https://doi.org/10.1016/j.jacc.2008.03.067.

Kannel, W. B., Wolf, P. A., Benjamin, E. J., et al. 1998. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. *American Journal of Cardiology*. 82(7 A):2N-9N. https://doi.org/10.1016/s0002-9149(98)00583-9.

Kar, S., Hou, D., Jones, R., et al. 2014. Impact of Watchman and Amplatzer devices on left atrial appendage adjacent structures and healing response in a canine model. *JACC: Cardiovascular Interventions*. 7(7):801–809. https://doi.org/10.1016/j.jcin.2014.03.003.

Kar, S., Doshi, S. K., Sadhu, A., et al. 2021. Primary outcome evaluation of a next-generation left atrial appendage closure device: Results from the PINNACLE FLX trial. *Circulation*. 143(18):1754–1762. https://doi.org/10.1161/circulationaha.120.050117.

Katsanos, A. H., Schellinger, P. D., Köhrmann, M., et al. 2018. Fatal oral anticoagulant-related intracranial hemorrhage: a systematic review and meta-analysis. *European Journal of Neurology*. 25(10):1299–1302. https://doi.org/10.1111/ene.13742.

Katsanos, A. H., Kamel, H., Healey, J. S., et al. 2020. Stroke prevention in atrial fibrillation: Looking forward. *Circulation*. 142:2371–2388. https://doi.org/10.1161/circulationaha.120.049768.

Katsi, V., Georgiopoulos, G., Skafida, A., et al. 2019. Noncardioembolic stroke in patients with atrial fibrillation. *Angiology*. 70(4):299–304. https://doi.org/10.1177/0003319718791711.

Katus, H. A., Remppis, A., Scheffold, T., et al. 1991. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *American Journal of Cardiology*. 67(16):1360–1367. https://doi.org/10.1016/0002-9149(91)90466-x.

Kaura, A., Arnold, A. D., Panoulas, V., et al. 2020. Prognostic significance of troponin level in 3121 patients presenting with atrial fibrillation (The NIHR Health Informatics Collaborative TROP-AF study). *Journal of the American Heart Association*. 9(7):e013684. https://doi.org/10.1161/jaha.119.013684.

Khurram, I. M., Dewire, J., Mager, M., et al. 2013. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. *Heart Rhythm*. 10(12):1843–1849. https://doi.org/10.1016/j.hrthm.2013.09.065.

Kim, D., Yang, P.-S., You, S. C., et al. 2021. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: Nationwide cohort study. *BMJ*. 373:n991. https://doi.org/10.1136/bmj.n991.

Kim, M. H., Johnston, S. S., Chu, B. C., et al. 2011. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circulation: Cardiovascular Quality and Outcomes*. 4(3):313–320. https://doi.org/10.1161/circoutcomes.110.958165.

Kim, T. H., Yang, P. S., Yu, H. T., et al. 2018. Age threshold for ischemic stroke risk in atrial fibrillation cohort data covering the entire Korean population. *Stroke*. 49(8):1872–1879. https://doi.org/10.1161/strokeaha.118.021047.

Kirchhof, P., Benussi, S., Kotecha, D., et al. 2016. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal*. 37(38):2893–2962. https://doi.org/10.1093/eurheartj/ehw210.

Kirchhof, P., Camm, A. J., Goette, A., et al. 2020. Early rhythm-control therapy in patients with atrial fibrillation. *New England Journal of Medicine*. 383(14):1305–1316. https://doi.org/10.1056/nejmoa2019422.

Kishore, A., Vail, A., Majid, A., et al. 2014. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: A systematic review and meta-analysis. *Stroke*. 45(2):520–526. https://doi.org/10.1161/strokeaha.113.003433.

Kochiadakis, G. E., Skalidis, E. I., Kalebubas, M. D., et al. 2002. Effect of acute atrial fibrillation on phasic coronary blood flow pattern and flow reserve in humans. *European Heart Journal*. 23(9):734–741. https://doi.org/10.1053/euhj.2001.2894.

Korsholm, K., Nielsen, K. M., Jensen, J. M., et al. 2017. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. *EuroIntervention*. 12(17):2075–2082. https://doi.org/10.4244/eij-d-16-00726.

Korsholm, K., Damgaard, D., Valentin, J. B., et al. 2022. Left atrial appendage occlusion vs novel oral anticoagulation for stroke prevention in atrial fibrillation: Rationale and design of the multicenter randomized occlusion-AF trial. *American Heart Journal*. 243:28–38. https://doi.org/10.1016/j.ahj.2021.08.020.

Krijthe, B. P., Kunst, A., Benjamin, E. J., et al. 2013. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *European Heart Journal*. 34(35):2746–2751. https://doi.org/10.1093/eurheartj/eht280.

Krishnamoorthy, S., Khoo, C. W., Lim, H. S., et al. 2013. Prognostic role of plasma von Willebrand factor and soluble E-selectin levels for future cardiovascular events in a “real-world” community cohort of patients with atrial fibrillation. *European Journal of Clinical Investigation*. 43(10):1032–1038. https://doi.org/10.1111/eci.12140.

Kuramatsu, J. B., Gerner, S. T., Schellinger, P. D., et al. 2015. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 313(8):824–836. https://doi.org/10.1001/jama.2015.0846.

Lakkireddy, D., Thaler, D., Ellis, C. R., et al. 2021. Amplatzer Amulet left atrial appendage occluder versus Watchman device for stroke prophylaxis (Amulet IDE): A randomized, controlled trial. *Circulation*. 144(19):1543–1552. https://doi.org/10.1161/circulationaha.121.057063.

Lamassa, M., Di Carlo, A., Pracucci, G., et al. 2001. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: Data from a multicenter multinational hospital-based registry (the European community stroke project). *Stroke*. 32(2):392–398. https://doi.org/10.1161/01.str.32.2.392.

Landmesser, U., Tondo, C., Camm, J., et al. 2018. Left atrial appendage occlusion with the AMPLATZER Amulet device: One-year follow-up from the prospective global Amulet observational registry. *EuroIntervention*. 14(5):e590–e597. https://doi.org/10.4244/eij-d-18-00344.

Lee, J. M., Seo, J., Uhm, J. S., et al. 2015. Why is left atrial appendage morphology related to strokes? an analysis of the flow velocity and orifice size of the left atrial appendage. *Journal of Cardiovascular Electrophysiology*. 26(9):922–927. https://doi.org/10.1111/jce.12710.

Lehtola, H., Airaksinen, K. E. J., Hartikainen, P., et al. 2017. Stroke recurrence in patients with atrial fibrillation: concomitant carotid artery stenosis doubles the risk. *European Journal of Neurology*. 24(5):719–725. https://doi.org/10.1111/ene.13280.

Lerario, M. P., Gialdini, G., Lapidus, D. M., et al. 2015. Risk of ischemic stroke after intracranial hemorrhage in patients with atrial fibrillation. *PLoS ONE*. 10(12):e0145579. https://doi.org/10.1371/journal.pone.0145579.

Li, L., Poon, M. T. C., Samarasekera, N. E., et al. 2021. Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *The Lancet Neurology*. 20(6):437–447. https://doi.org/10.1016/s1474-4422(21)00075-2.

Lim, H. S., Willoughby, S. R., Schultz, C., et al. 2013. Effect of atrial fibrillation on atrial thrombogenesis in humans: Impact of rate and rhythm. *Journal of the American College of Cardiology*. 61(8):852–860. https://doi.org/10.1016/j.jacc.2012.11.046.

Lin, H. J., Wolf, P. A., Kelly-Hayes, M., et al. 1996. Stroke severity in atrial fibrillation: The Framingham study. *Stroke*. 27(10):1760–1764. https://doi.org/10.1161/01.str.27.10.1760.

Lindner, S., Behnes, M., Wenke, A., et al. 2021. Incomplete neo-endothelialization of left atrial appendage closure devices is frequent after 6 months: A pilot imaging study. *International Journal of Cardiovascular Imaging*. 37(7):2291–2298. https://doi.org/10.1007/s10554-021-02192-5.

Ling, L. H., Kistler, P. M., Ellims, A. H., et al. 2012. Diffuse ventricular fibrosis in atrial fibrillation: Noninvasive evaluation and relationships with aging and systolic dysfunction. *Journal of the American College of Cardiology*. 60(23):2402–2408. https://doi.org/10.1016/j.jacc.2012.07.065.

Lip, G. Y. H., Nieuwlaat, R., Pisters, R., et al. 2010. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. *Chest*. 137(2):263–272. https://doi.org/10.1378/chest.09-1584.

Lip, G. Y. H., Frison, L., Halperin, J. L., et al. 2011. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drug. *Journal of the American College of Cardiology*. 57(2):173–180. https://doi.org/10.1016/j.jacc.2010.09.024.

Lip, G. Y. H., Skjøth, F., Rasmussen, L. H., et al. 2015. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *Journal of the American College of Cardiology*. 65(14):1385–1394. https://doi.org/10.1016/j.jacc.2015.01.044.

Lip, G. Y. H., Skjøth, F., Nielsen, P. B., et al. 2018. The HAS-BLED, ATRIA, and ORBIT bleeding scores in atrial fibrillation patients using non-vitamin K antagonist oral anticoagulants. *American Journal of Medicine*. 131(5):574e13–574e27. https://doi.org/10.1016/j.amjmed.2017.11.046.

Lippi, G., Sanchis-Gomar, F. & Cervellin, G. 2021. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. *International Journal of Stroke*. 16(2):217–221. https://doi.org/10.1177/1747493019897870.

Lloyd-Jones, D. M., Wang, T. J., Leip, E. P., et al. 2004. Lifetime risk for development of atrial fibrillation: The Framingham Heart Study. *Circulation*. 110(9):1042–1046. https://doi.org/10.1161/01.cir.0000140263.20897.42.

Lopes, R. D., Al-Khatib, S. M., Wallentin, L., et al. 2012. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: A secondary analysis of a randomised controlled trial. *The Lancet*. 380(9855):1749–1758. https://doi.org/10.1016/s0140-6736(12)60986-6.

Lopes, R. D., Guimarães, P. O., Kolls, B. J., et al. 2017. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. *Blood*. 129(22):2980–2987. https://doi.org/10.1182/blood-2016-08-731638.

Madden, J. L. 1949. Resection of the left auricular appendix: A prophylaxis for recurrent arterial emboli. *JAMA*. 140(9):769–772. https://doi.org/10.1001/jama.1949.02900440011003.

Mahajan, R., Brooks, A. G., Sullivan, T., et al. 2012. Importance of the underlying substrate in determining thrombus location in atrial fibrillation: Implications for left atrial appendage closure. *Heart*. 98(15):1120–1126. https://doi.org/10.1136/heartjnl-2012-301799.

Mair, J., Genser, N., Morandell, D., et al. 1996. Cardiac troponin I in the diagnosis of myocardial injury and infarction. *Clinica Chimica Acta*. 245(1):19–38. https://doi.org/10.1016/0009-8981(95)06168-1.

Mair, J., Lindahl, B., Hammarsten, O., et al. 2018. How is cardiac troponin released from injured myocardium? *European Heart Journal: Acute Cardiovascular Care*. 7(6):553–560. https://doi.org/10.1177/2048872617748553.

Majeed, A., Kim, Y. K., Roberts, R. S., et al. 2010. Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke*. 41(12):2860–2866. https://doi.org/10.1161/strokeaha.110.593087.

Marcusohn, E., Kobo, O., Postnikov, M., et al. 2021. Left ventricular systolic dysfunction due to atrial fibrillation: Clinical and echocardiographic predictors. *Cardiac Failure Review*. 7(e16). https://doi.org/10.15420/cfr.2021.17.

Marinigh, R., Lip, G. Y. H., Fiotti, N., et al. 2010. Age as a risk factor for stroke in atrial fibrillation patients: Implications for thromboprophylaxis. *Journal of the American College of Cardiology*. 56(11):827–837. https://doi.org/10.1016/j.jacc.2010.05.028.

Marrouche, N. F., Brachmann, J., Andresen, D., et al. 2018. Catheter ablation for atrial fibrillation with heart failure. *New England Journal of Medicine*. 378(5):417–427. https://doi.org/10.1056/nejmoa1707855.

Martinez, C., Katholing, A. & Freedman, S. B. 2014. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. *Thrombosis and Haemostasis*. 112(2):276–286. https://doi.org/10.1160/th4-04-0383.

Massarenti, L. & Yilmaz, A. 2012. Incomplete endothelialization of left atrial appendage occlusion device 10 months after implantation. *Journal of Cardiovascular Electrophysiology*. 23(12):1384–1385. https://doi.org/10.1111/j.1540-8167.2012.02360.x.

McQuaid, K. R. & Laine, L. 2006. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *American Journal of Medicine*. 119(8):624–638. https://doi.org/10.1016/j.amjmed.2005.10.039.

Meier, B., Blaauw, Y., Khattab, A. A., et al. 2014. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace*. 16(10):1397–1416. https://doi.org/10.1093/europace/euu174.

Melgaard, L., Overvad, T. F., Jensen, M., et al. 2020. Thromboembolic risk in nonanticoagulated patients with atrial fibrillation and valvular heart disease. *JACC: Clinical Electrophysiology*. 6(13):1672–1682. https://doi.org/10.1016/j.jacep.2020.07.005.

Meretoja, A., Kaste, M., Roine, R. O., et al. 2011. Direct costs of patients with stroke can be continuously monitored on a national level: Performance, effectiveness, and costs of treatment episodes in stroke (PERFECT stroke) database in Finland. *Stroke*. 42(7):2007–2012. https://doi.org/10.1161/strokeaha.110.612119.

Meshkat, N., Austin, E., Moineddin, R., et al. 2011. Troponin utilization in patients presenting with atrial fibrillation/flutter to the emergency department: Retrospective chart review. *International Journal of Emergency Medicine*. 4(1):1–5. https://doi.org/10.1186/1865-1380-4-25.

Mikkelsen, A. P., Lindhardsen, J., Lip, G. Y. H., et al. 2012. Female sex as a risk factor for stroke in atrial fibrillation: A nationwide cohort study. *Journal of Thrombosis and Haemostasis*. 10(9):1745–1751. https://doi.org/10.1111/j.1538-7836.2012.04853.x.

Miranda, R. C., Machado, M. D. N., Takakura, I. T., et al. 2006. Elevated troponin levels after prolonged supraventricular tachycardia in patient with normal coronary angiography. *Cardiology*. 106(1):10–13. https://doi.org/10.1159/000092449.

Mohanty, S., Gianni, C., Trivedi, C., et al. 2020. Risk of thromboembolic events after percutaneous left atrial appendage ligation in patients with atrial fibrillation: Long-term results of a multicenter study. *Heart Rhythm*. 17(2):175–181. https://doi.org/10.1016/j.hrthm.2019.08.003.

Murthy, S. B., Diaz, I., Wu, X., et al. 2020. Risk of arterial ischemic events after intracerebral hemorrhage. *Stroke*. 51(1):137–142. https://doi.org/10.1161/strokeaha.119.026207.

Nabauer, M., Gerth, A., Limbourg, T., et al. 2009. The Registry of the German Competence NETwork on Atrial Fibrillation: Patient characteristics and initial management. *Europace*. 11(4):423–434. https://doi.org/10.1093/europace/eun369.

Nakamura, K., Hara, H., Hashimoto, H., et al. 2020. Endoscopy for incomplete endothelialization and left atrial appendage occlusion with the watchman device. *JACC: Cardiovascular Interventions*. 13(3):391–393. https://doi.org/10.1016/j.jcin.2019.09.023.

Nelson, S. E., Giugliano, R. P., Antman, E. M., et al. 2021. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation with warfarin or edoxaban: An in-depth analysis from the ENGAGE AF-TIMI 48 randomized trial. *Journal of Clinical Neuroscience*. 86:294–300. https://doi.org/10.1016/j.jocn.2020.10.036.

Nielsen-Kudsk, J. E., Johnsen, S. P., Wester, P., et al. 2017. Left atrial appendage occlusion versus standard medical care in patients with atrial fibrillation and intracerebral haemorrhage: a propensity score-matched follow-up study. *EuroIntervention*. 13(3):371–378. https://doi.org/10.4244/eij-d-17-00201.

Nielsen, P. B., Larsen, T. B., Gorst-Rasmussen, A., et al. 2015a. Intracranial hemorrhage and subsequent ischemic stroke in patients with atrial fibrillation: A nationwide cohort study. *Chest*. 147(6):1651–1658. https://doi.org/10.1378/chest.14-2099.

Nielsen, P. B., Larsen, T. B., Skjøth, F., et al. 2015b. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: A nationwide cohort study. *Circulation*. 132(6):517–525. https://doi.org/10.1161/circulationaha.115.015735.

Nielsen, P. B., Larsen, T. B., Skjøth, F., et al. 2017. Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation. *JAMA Internal Medicine*. 177(4):563–570. https://doi.org/10.1001/jamainternmed.2016.9369.

Nielsen, P. B., Skjøth, F., Overvad, T. F., et al. 2018. Female sex is a risk modifer rather than a risk factor for stroke in atrial fibrillation: Should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? *Circulation*. 137(8):832–840. https://doi.org/10.1161/circulationaha.117.029081.

Nieuwlaat, R., Capucci, A., Camm, A. J., et al. 2005. Atrial fibrillation management: A prospective survey in ESC Member Countries - The Euro Heart Survey on atrial fibrillation. *European Heart Journal*. 26(22):2422–2434. https://doi.org/10.1093/eurheartj/ehi505.

Noubiap, J. J., Feteh, V. F., Middeldorp, M. E., et al. 2021. A meta-analysis of clinical risk factors for stroke in anticoagulant-naïve patients with atrial fibrillation. *Europace*. 23(10):1528–1538. https://doi.org/10.1093/europace/euab087.

Ntaios, G. 2020. Embolic stroke of undetermined source: JACC Review Topic of the Week. *Journal of the American College of Cardiology*. 75(3):333–340. https://doi.org/10.1016/j.jacc.2019.11.024.

O'Donnell, H. C., Rosand, J., Knudsen, K. A., et al. 2000. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. *New England Journal of Medicine*. 342(4):240–245. https://doi.org/10.1056/nejm200001273420403.

O'Neal, W. T., Soliman, E. Z., Qureshi, W., et al. 2015. Sustained pre-hypertensive blood pressure and incident atrial fibrillation: The Multi-Ethnic Study of Atherosclerosis. *Journal of the American Society of Hypertension*. 9(3):191–196. https://doi.org/10.1016/j.jash.2015.01.001.

Olesen, J. B., Fauchier, L., Lane, D. A., et al. 2012a. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: The Loire Valley Atrial Fibrillation Project. *Chest*. 141(1):147–153. https://doi.org/10.1378/chest.11-0862.

Olesen, J. B., Gislason, G. H., Torp-Pedersen, C., et al. 2012b. Atrial fibrillation and vascular disease-A bad combination. *Clinical Cardiology*. 35(Suppl 1):15–20. https://doi.org/10.1002/clc.20955.

Ornello, R., Degan, D., Tiseo, C., et al. 2018. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes a systematic review and meta-analysis. *Stroke*. 49(4):814–819. https://doi.org/10.1161/strokeaha.117.020031.

Osman, M., Busu, T., Osman, K., et al. 2020. Short-term antiplatelet versus anticoagulant therapy after left atrial appendage occlusion: A systematic review and meta-analysis. *JACC: Clinical Electrophysiology*. 6(5):494–506. https://doi.org/10.1016/j.jacep.2019.11.009.

Osmancik, P., Herman, D., Neuzil, P., et al. 2020. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *Journal of the American College of Cardiology*. 75(25):3122–3135. https://doi.org/10.1016/j.jacc.2020.04.067.

Osmancik, P., Herman, D., Neuzil, P., et al. 2022. 4-year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation. *Journal of the American College of Cardiology*. 79(1):1–14. https://doi.org/10.1016/j.jacc.2021.10.023.

Ostermayer, S. H., Reisman, M., Kramer, P. H., et al. 2005. Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO System) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: Results from the international multi-center feasibility trials. *Journal of the American College of Cardiology*. 46(1):9–14. https://doi.org/10.1016/j.jacc.2005.03.042.

Paana, T., Jaakkola, S., Bamberg, K., et al. 2019. Cardiac troponin elevations in marathon runners. Role of coronary atherosclerosis and skeletal muscle injury. The MaraCat Study. *International Journal of Cardiology*. 295:25–28. https://doi.org/10.1016/j.ijcard.2019.08.019.

Paana, T., Jaakkola, S., Biancari, F., et al. 2021. Minor troponin T elevation and mortality in patients with atrial fibrillation presenting to the emergency department. *European Journal of Clinical Investigation*. 51(11):e13590. https://doi.org/10.1111/eci.13590.

Paciaroni, M., Agnelli, G., Giustozzi, M., et al. 2021. Risk factors for intracerebral hemorrhage in patients with atrial fibrillation on non-vitamin K antagonist oral anticoagulants for stroke prevention. *Stroke*. 52:1450–1454. https://doi.org/10.1161/strokeaha.120.031827.

Packer, D. L., Mark, D. B., Robb, R. A., et al. 2019. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 321(13):1261–1274. https://doi.org/10.1001/jama.2019.0693.

Page, R. L., Wilkinson, W. E., Clair, W. K., et al. 1994. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation*. 89(1):224–227. https://doi.org/10.1161/01.cir.89.1.224.

Parmacek, M. S. & Solaro, R. J. 2004. Biology of the troponin complex in cardiac myocytes. *Progress in Cardiovascular Diseases*. 47(3):159–176. https://doi.org/10.1016/j.pcad.2004.07.003.

Parwani, A. S., Boldt, L. H., Huemer, M., et al. 2013. Atrial fibrillation-induced cardiac troponin I release. *International Journal of Cardiology*. 168(3):2734–2737. https://doi.org/10.1016/j.ijcard.2013.03.087.

Patanè, S., Marte, F. & Di Bella, G. 2009. Abnormal troponin I levels after supraventricular tachycardia. *International Journal of Cardiology*. 132(2):e57–e59. https://doi.org/10.1016/j.ijcard.2007.07.120.

Patel, M. R., Mahaffey, K. W., Garg, J., et al. 2011. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New England Journal of Medicine*. 365(10):883–891. https://doi.org/10.1056/nejmoa1009638.

Patti, G., Sticchi, A., Verolino, G., et al. 2020. Safety and efficacy of single versus dual antiplatelet therapy after left atrial appendage occlusion. *American Journal of Cardiology*. 134:83–90. https://doi.org/10.1016/j.amjcard.2020.08.013.

Pennlert, J., Asplund, K., Carlberg, B., et al. 2015. Antithrombotic treatment following intracerebral hemorrhage in patients with and without atrial fibrillation. *Stroke*. 46(8):2094–2099. https://doi.org/10.1161/strokeaha.115.009087.

Pennlert, J., Overholser, R., Asplund, K., et al. 2017. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. *Stroke*. 48(2):314–320. https://doi.org/10.1161/strokeaha.116.014643.

Philippart, R., Brunet-Bernard, A., Clementy, N., et al. 2015. Prognostic value of CHA2DS2-VASc score in patients with “non-valvular atrial fibrillation” and valvular heart disease: The Loire Valley

Atrial Fibrillation Project. *European Heart Journal*. 36(28):1822–1830. https://doi.org/10.1093/eurheartj/ehv163.

Piccini, J. P., Hammill, B. G., Sinner, M. F., et al. 2012. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries: 1993-2007. *Circulation: Cardiovascular Quality and Outcomes*. 5(1):85–93. https://doi.org/10.1161/circoutcomes.111.962688.

Pisters, R., Lane, D. A., Nieuwlaat, R., et al. 2010. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. *Chest*. 138(5):1093–1100. https://doi.org/10.1378/chest.10-0134.

Pisters, R., Lane, D. A., Marin, F., et al. 2012. Stroke and thromboembolism in atrial fibrillation. *Circulation Journal*. 76(10):2289–2304. https://doi.org/10.1253/circj.cj-12-1036.

Prabhu, S., Taylor, A. J., Costello, B. T., et al. 2017. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: The CAMERA-MRI study. *Journal of the American College of Cardiology*. 70(16):1949–1961. https://doi.org/10.1016/j.jacc.2017.08.041.

Prabhu, S., Costello, B. T., Taylor, A. J., et al. 2018. Regression of diffuse ventricular fibrosis following restoration of sinus rhythm with catheter ablation in patients with atrial fibrillation and systolic dysfunction: A substudy of the CAMERA MRI trial. *JACC: Clinical Electrophysiology*. 4(8):999–1007. https://doi.org/10.1016/j.jacep.2018.04.013.

Quesada, A., López-Valero, L., Marcaida-Benito, G., et al. 2021. Prognostic value of troponin I in atrial fibrillation. *Progress in Cardiovascular Diseases*. 67:80–88. https://doi.org/10.1016/j.pcad.2021.02.012.

Rapsomaniki, E., Timmis, A., George, J., et al. 2014. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *The Lancet*. 383(9932):1899–1911. https://doi.org/10.1016/s0140-6736(14)60685-1.

Reddy, V. Y., Doshi, S. K., Kar, S., et al. 2017. 5-year outcomes after left atrial appendage closure: From the PREVAIL and PROTECT AF trials. *Journal of the American College of Cardiology*. 70(24):2964–2975. https://doi.org/10.1016/j.jacc.2017.10.021.

Redfearn, D. P., Ratib, K., Marshall, H. J., et al. 2005. Supraventricular tachycardia promotes release of troponin I in patients with normal coronary arteries. *International Journal of Cardiology*. 102(3):521–522. https://doi.org/10.1016/j.ijcard.2004.05.076.

Redfors, B., Gray, W. A., Lee, R. J., et al. 2017. Patients with atrial fibrillation who are not on anticoagulant treatment due to increased bleeding risk are common and have a high risk of stroke. *JACC: Clinical Electrophysiology*. 3(12):1369–1376. https://doi.org/10.1016/j.jacep.2017.04.024.

Renda, G., Ricci, F., Giugliano, R. P., et al. 2017. Non–vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *Journal of the American College of Cardiology*. 69(11):1363–1371. https://doi.org/10.1016/j.jacc.2016.12.038.

Renou, P., Thambo, J.-B., Iriart, X., et al. 2017. Left atrial appendage closure in patients with atrial fibrillation and previous intracerebral hemorrhage. *Journal of Stroke and Cerebrovascular Diseases*. 26(3):545–551. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.11.126.

Ridker, P. M., Hennekens, C. H., Manson, J. E., et al. 1994. Prospective study of endogenous tissue plasminogen activator and risk of stroke. *The Lancet*. 343(8903):940–943. https://doi.org/10.1016/s0140-6736(94)90064-7.

Della Rocca, D. G., Magnocavallo, M., Di Biase, L., et al. 2021. Half-dose direct oral anticoagulation versus standard antithrombotic therapy after left atrial appendage occlusion. *JACC: Cardiovascular Interventions*. 14(21):2353–2364. https://doi.org/10.1016/j.jcin.2021.07.031.

Rodés-Cabau, J., O'Hara, G., Paradis, J. M., et al. 2017. Changes in coagulation and platelet activation markers following transcatheter left atrial appendage closure. *American Journal of Cardiology*. 120(1):87–91. https://doi.org/10.1016/j.amjcard.2017.03.253.

Rodriguez-Gabella, T., Nombela-Franco, L., Regueiro, A., et al. 2016. Single antiplatelet therapy following left atrial appendage closure in patients with contraindication to anticoagulation. *Journal of the American College of Cardiology*. 68(17):1920–1921. https://doi.org/10.1016/j.jacc.2016.08.016.

Romero, J., Cao, J. J., Garcia, M. J., et al. 2014. Cardiac imaging for assessment of left atrial appendage stasis and thrombosis. *Nature Reviews Cardiology*. 11(8):470–480. https://doi.org/10.1038/nrcardio.2014.77.

Rozen, G., Hosseini, S. M., Kaadan, M. I., et al. 2018. Emergency department visits for atrial fibrillation in the United States: Trends in admission rates and economic burden from 2007 to 2014. *Journal of the American Heart Association*. 7(15):e00902. https://doi.org/10.1161/jaha.118.009024.

Ruff, C. T., Giugliano, R. P., Braunwald, E., et al. 2014. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *The Lancet*. 383(9921):955–962. https://doi.org/10.1016/s0140-6736(13)62343-0.

Ruff, C. T., Giugliano, R. P., Braunwald, E., et al. 2016. Cardiovascular biomarker score and clinical outcomes in patients with atrial fibrillation: A subanalysis of the ENGAGE AF-TIMI 48 randomized clinical trial. *JAMA Cardiology*. 1(9):999–1006. https://doi.org/10.1001/jamacardio.2016.3311.

Sabatine, M. S., Morrow, D. A., De Lemos, J. A., et al. 2009. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: Results from TIMI 35. *European Heart Journal*. 30(2):162–169. https://doi.org/10.1093/eurheartj/ehn504.

Sadanaga, T., Sadanaga, M. & Ogawa, S. 2010. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. *Journal of the American College of Cardiology*. 55(20):2225–2231. https://doi.org/10.1016/j.jacc.2009.12.049.

Sadanaga, T., Kohsaka, S., Mitamura, H., et al. 2011. Elevated B-type natriuretic peptide level as a marker of subsequent thromboembolic events in patients with atrial fibrillation. *Heart and Vessels*. 26(5):530–535. https://doi.org/10.1007/s00380-010-0084-2.

Salman, R. A.-S., Dennis, M., Sandercock, P., et al. 2019. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): A randomised, open-label trial. *The Lancet*. 393(10191):2613–2623. https://doi.org/10.1016/s0140-6736(19)30840-2.

Salman, R. A.-S., Keerie, C., Stephen, J., et al. 2021a. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: A randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. *The Lancet Neurology*. 20(10):842–853. https://doi.org/10.1016/s1474-4422(21)00264-7.

Salman, R. A.-S., Dennis, M. S., Sandercock, P. A. G., et al. 2021b. Effects of antiplatelet therapy after stroke caused by intracerebral hemorrhage: Extended follow-up of the RESTART randomized clinical trial. *JAMA Neurology*. 78(10):1179–1186. https://doi.org/10.1001/jamaneurol.2021.2956.

Salmasi, S., Loewen, P. S., Tandun, R., et al. 2020. Adherence to oral anticoagulants among patients with atrial fibrillation: A systematic review and meta-analysis of observational studies. *BMJ Open*. 10(4):34778. https://doi.org/10.1136/bmjopen-2019-034778.

Samaha, E., Avila, A., Helwani, M. A., et al. 2019. High-sensitivity cardiac troponin after cardiac stress test: A systematic review and meta-analysis. *Journal of the American Heart Association*. 8(6):e008626. https://doi.org/10.1161/jaha.118.008626.

Sandercock, P. A. G., Gibson, L. M. & Liu, M. 2009. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. *Cochrane Database of Systematic Reviews*. 2009(2). https://doi.org/10.1002/14651858.cd000248.pub2.

Sayadnik, M., Shafiee, A., Jenab, Y., et al. 2017. Predictors of high-sensitivity cardiac troponin T elevation: In patients with acute paroxysmal supraventricular tachycardia and ischemic heart disease. *Texas Heart Institute Journal*. 44(5):306–311. https://doi.org/10.14503/thij-15-5338.

Scarsoglio, S., Gallo, C., Saglietto, A., et al. 2019. Impaired coronary blood flow at higher heart rates during atrial fibrillation: Investigation via multiscale modelling. *Computer Methods and Programs in Biomedicine*. 175:95–102. https://doi.org/10.1016/j.cmpb.2019.04.009.

Schiettekatte, S., Czapla, J., Nijs, J., et al. 2014. Unmasking a naked left atrial appendage closure device: A case of a silent embolic threat. *Heart Rhythm*. 11(12):2314–2315. https://doi.org/10.1016/j.hrthm.2014.10.015.

Schnabel, R. B., Yin, X., Gona, P., et al. 2015. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: A cohort study. *The Lancet*. 386(9989):154–162. https://doi.org/10.1016/s0140-6736(14)61774-8.

Schreuder, F. H. B. M., van Nieuwenhuizen, K. M., Hofmeijer, J., et al. 2021. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): A randomised, open-label, phase 2 trial. *The Lancet Neurology*. 20(11):907–916. https://doi.org/10.1016/s1474-4422(21)00298-2.

De Schryver, E. L., Algra, A., Kappelle, L. J., et al. 2012. Vitamin K antagonists versus antiplatelet therapy after transient ischaemic attack or minor ischaemic stroke of presumed arterial origin. *Cochrane Database of Systematic Reviews*. (9). https://doi.org/10.1002/14651858.cd001342.pub3.

Schulman, S. & Kesron, C. 2005. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*. 3(4):692–694. https://doi.org/10.1111/j.1538-7836.2005.01204.x.

Schwartz, R. S., Holmes, D. R., Van Tassel, R. A., et al. 2010. Left atrial appendage obliteration: Mechanisms of healing and intracardiac integration. *JACC: Cardiovascular Interventions*. 3(8):870–877. https://doi.org/10.1016/j.jcin.2010.04.017.

Sedaghat, A., Nickenig, G., Schrickel, J. W., et al. 2021. Incidence, predictors and outcomes of device-related thrombus after left atrial appendage closure with the WATCHMAN device—Insights from the EWOLUTION real world registry. *Catheterization and Cardiovascular Interventions*. 97(7):E1019–E1024. https://doi.org/10.1002/ccd.29458.

Seliger, S. L., Hong, S. N., Christenson, R. H., et al. 2017. High-sensitive cardiac troponin T as an early biochemical signature for clinical and subclinical heart failure: MESA (Multi-Ethnic Study of Atherosclerosis). *Circulation*. 135(16):1494–1505. https://doi.org/10.1161/circulationaha.116.025505.

Shah, A. S. V., Sandoval, Y., Noaman, A., et al. 2017. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. *BMJ*. 359:j4788. https://doi.org/10.1136/bmj.j4788.

Sharma, S. P., Singh, D., Nakamura, D., et al. 2018. Incomplete endothelialization of Watchman TM device: Predictors and implications from two cases. *Journal of Atrial Fibrillation*. 10(5). https://doi.org/10.4022/jafib.2162.

Shave, R., Baggish, A., George, K., et al. 2010. Exercise-induced cardiac troponin elevation: Evidence, mechanisms, and implications. *Journal of the American College of Cardiology*. 56(3):169–176. https://doi.org/10.1016/j.jacc.2010.03.037.

Shinbane, J. S., Wood, M. A., Jensen, D. N., et al. 1997. Tachycardia-induced cardiomyopathy: A review of animal models and clinical studies. *Journal of the American College of Cardiology*. 29(4):709–715. https://doi.org/10.1016/s0735-1097(96)00592-x.

Shively, B. K., Gelgand, E. A. & Crawford, M. H. 1996. Regional left atrial stasis during atrial fibrillation and flutter: Determinants and relation to stroke. *Journal of the American College of Cardiology*. 27(7):1722–1729. https://doi.org/10.1016/0735-1097(96)00049-6.

Sick, P. B., Schuler, G., Hauptmann, K. E., et al. 2007. Initial worldwide experience with the WATCHMAN Left Atrial Appendage System for stroke prevention in atrial fibrillation. *Journal of the American College of Cardiology*. 49(13):1490–1495. https://doi.org/10.1016/j.jacc.2007.02.035.

Siegbahn, A., Oldgren, J., Andersson, U., et al. 2016. D-dimer and factor VIIa in atrial fibrillation – Prognostic values for cardiovascular events and effects of anticoagulation therapy: A RE-LY substudy. *Thrombosis and Haemostasis*. 115(5):921–930. https://doi.org/10.1160/th15-07-0529.

Sievert, H., Lesh, M. D., Trepels, T., et al. 2002. Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: Early clinical experience. *Circulation*. 105(16):1887–1889. https://doi.org/10.1161/01.cir.0000015698.54752.6d.

Sillesen, H., Muntendam, P., Adourian, A., et al. 2012. Carotid plaque burden as a measure of subclinical atherosclerosis: Comparison with other tests for subclinical arterial disease in the high risk plaque bioimage study. *JACC: Cardiovascular Imaging*. 5(7):681–689. https://doi.org/10.1016/j.jcmg.2012.03.013.

Smit, M. D., Crijns, H. J. G. M., Tijssen, J. G. P., et al. 2011. Effect of lenient versus strict rate control on cardiac remodeling in patients with atrial fibrillation: Data of the RACE II (RAte Control Efficacy in permanent atrial fibrillation II) study. *Journal of the American College of Cardiology*. 58(9):942–949. https://doi.org/10.1016/j.jacc.2011.04.030.

Søndergaard, L., Wong, Y. H., Reddy, V. Y., et al. 2019. Propensity-matched comparison of oral anticoagulation versus antiplatelet therapy after left atrial appendage closure with WATCHMAN. *JACC: Cardiovascular Interventions*. 12(11):1055–1063. https://doi.org/10.1016/j.jcin.2019.04.004.

Spinale, F. G., Hendrick, D. A., Crawford, F. A., et al. 1990. Chronic supraventricular tachycardia causes ventricular dysfunction and subendocardial injury in swine. *American Journal of Physiology - Heart and Circulatory Physiology*. 259(1):H218–H229. https://doi.org/10.1152/ajpheart.1990.259.1.h218.

Spinale, F. G., Tomita, M., Zellner, J. L., et al. 1991. Collagen remodeling and changes in LV function during development and recovery from supraventricular tachycardia. *American Journal of Physiology - Heart and Circulatory Physiology*. 261(2):H308–H318. https://doi.org/10.1152/ajpheart.1991.261.2.h308.

Van Staa, T. P., Setakis, E., Di Tanna, G. L., et al. 2011. A comparison of risk stratification schemes for stroke in 79 884 atrial fibrillation patients in general practice. *Journal of Thrombosis and Haemostasis*. 9(1):39–48. https://doi.org/10.1111/j.1538-7836.2010.04085.x.

Starnberg, K., Jeppsson, A., Lindahl, B., et al. 2014. Revision of the troponin T release mechanism from damaged human myocardium. *Clinical Chemistry*. 60(8):1098–1104. https://doi.org/10.1373/clinchem.2013.217943.

Stefansdottir, H., Aspelund, T., Gudnason, V., et al. 2011. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. *Europace*. 13(8):1110–1117. https://doi.org/10.1093/europace/eur132.

Steinberg, B. A., Kim, S., Fonarow, G. C., et al. 2014. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *American Heart Journal*. 167(5):735-742.e2. https://doi.org/10.1016/j.ahj.2014.02.003.

Steinberg, B. A., Gao, H., Shrader, P., et al. 2017. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. *American Heart Journal*. 194:132–140. https://doi.org/10.1016/j.ahj.2017.08.011.

Stoyanov, K. M., Giannitsis, E., Biener, M., et al. 2018. Prognostic value of elevated high-sensitivity cardiac troponin T in patients admitted to an emergency department with atrial fibrillation. *Europace*. 20(4):582–588. https://doi.org/10.1093/europace/eux063.

Svendsen, J. H., Diederichsen, S. Z., Højberg, S., et al. 2021. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): A randomised controlled trial. *The Lancet*. 398(10310):1507–1516. https://doi.org/10.1016/s0140-6736(21)01698-6.

Thygesen, K., Alpert, J. S., Jaffe, A. S., et al. 2019. Fourth universal definition of myocardial infarction (2018). *European Heart Journal*. 40(3):237–269. https://doi.org/10.1093/eurheartj/ehy462.

Tsai, Y. C., Phan, K., Munkholm-larsen, S., et al. 2015. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: A meta-analysis. *European Journal of Cardio-thoracic Surgery*. 47(5):847–854. https://doi.org/10.1093/ejcts/ezu291.

Turer, A. T., Addo, T. A., Martin, J. L., et al. 2011. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: Insights from a coronary sinus sampling study. *Journal of the American College of Cardiology*. 57(24):2398–2405. https://doi.org/10.1016/j.jacc.2010.11.066.

Tzikas, A., Freixa, X., Llull, L., et al. 2017a. Patients with intracranial bleeding and atrial fibrillation treated with left atrial appendage occlusion: Results from the Amplatzer Cardiac Plug registry. *International Journal of Cardiology*. 236:232–236. https://doi.org/10.1016/j.ijcard.2017.02.042.

Tzikas, A., Holmes, D. R., Gafoor, S., et al. 2017b. Percutaneous left atrial appendage occlusion: The Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace*. 19(1):4–15. https://doi.org/10.1093/europace/euw141.

Ulimoen, S. R., Enger, S., Norseth, J., et al. 2014. Improved rate control reduces cardiac troponin T levels in permanent atrial fibrillation. *Clinical Cardiology*. 37(7):422–427. https://doi.org/10.1002/clc.22281.

Valgimigli, M., Frigoli, E., Heg, D., et al. 2021. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *New England Journal of Medicine*. 385(18):1643–1655. https://doi.org/10.1056/nejmoa2108749.

Verma, A., Champagne, J., Sapp, J., et al. 2013. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): A prospective, multicenter study. *JAMA Internal Medicine*. 173(2):149–156. https://doi.org/10.1001/jamainternmed.2013.1561.

Vermeer, S. E., Algra, A., Franke, C. L., et al. 2002. Long-term prognosis after recovery from primary intracerebral hemorrhage. *Neurology*. 59(2):205–209. https://doi.org/10.1212/wnl.59.2.205.

Vestergaard, A. S., Skjøth, F., Lip, G. Y. H., et al. 2016. Effect of anticoagulation on hospitalization costs after intracranial hemorrhage in atrial fibrillation a registry study. *Stroke*. 47(4):979–985. https://doi.org/10.1161/strokeaha.115.012338.

Vos, T., Lim, S. S., Abbafati, C., et al. 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 396(10258):1204–1222. https://doi.org/10.1016/s0140-6736(20)30925-9.

Van Walraven, C., Hart, R. G., Connolly, S., et al. 2009. Effect of age on stroke prevention therapy in patients with atrial fibrillation: The Atrial Fibrillation Investigators. *Stroke*. 40(4):1410–1416. https://doi.org/10.1161/strokeaha.108.526988.

Wang, T. J., Larson, M. G., Levy, D., et al. 2003. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. *Circulation*. 107(23):2920–2925. https://doi.org/10.1161/01.cir.0000072767.89944.6e.

Watson, T., Shantsila, E. & Lip, G. Y. 2009. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *The Lancet*. 373(9658):155–166. https://doi.org/10.1016/s0140-6736(09)60040-4.

Weil, B. R., Young, R. F., Shen, X., et al. 2017. Brief myocardial ischemia produces cardiac troponin I release and focal myocyte apoptosis in the absence of pathological infarction in swine. *JACC: Basic to Translational Science*. 2(2):105–114. https://doi.org/10.1016/j.jacbts.2017.01.006.

Weil, B. R., Suzuki, G., Young, R. F., et al. 2018. Troponin release and reversible left ventricular dysfunction after transient pressure overload. *Journal of the American College of Cardiology*. 71(25):2906–2916. https://doi.org/10.1016/j.jacc.2018.04.029.

Weng, L. C., Preis, S. R., Hulme, O. L., et al. 2018. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. *Circulation*. 137(10):1027–1038. https://doi.org/10.1161/circulationaha.117.031431.

White, H. D. 2011. Pathobiology of troponin elevations. *Journal of the American College of Cardiology*. 57(24):2406–2408. https://doi.org/10.1016/j.jacc.2011.01.029.

Whitlock, R. P., Belley-Cote, E. P., Paparella, D., et al. 2021. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *New England Journal of Medicine*. 384(22):2081–2091. https://doi.org/10.1056/nejmoa2101897.

Wilke, T., Groth, A., Mueller, S., et al. 2013. Incidence and prevalence of atrial fibrillation: An analysis based on 8.3 million patients. *Europace*. 15(4):486–493. https://doi.org/10.1093/europace/eus333.

Willeit, P., Welsh, P., Evans, J. D. W., et al. 2017. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. *Journal of the American College of Cardiology*. 70(5):558–568. https://doi.org/10.1016/j.jacc.2017.05.062.

Wolf, P. A., Abbott, R. D. & Kannel, W. B. 1991. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke*. 22(8):983–988. https://doi.org/10.1161/01.str.22.8.983.

Wu, N., Tong, S., Xiang, Y., et al. 2015. Association of hemostatic markers with atrial fibrillation: A meta-analysis and meta-regression. *PLoS ONE*. 10(4):e0124716. https://doi.org/10.1371/journal.pone.0124716.

Wu, V. C. C., Wu, M., Aboyans, V., et al. 2020. Female sex as a risk factor for ischaemic stroke varies with age in patients with atrial fibrillation. *Heart*. 106(7):534–540. https://doi.org/10.1136/heartjnl-2019-315065.

Wynn, G. J., Todd, D. M., Webber, M., et al. 2014. The European Heart Rhythm Association symptom classification for atrial fibrillation: Validation and improvement through a simple modification. *Europace*. 16(7):965–972. https://doi.org/10.1093/europace/eut395.

Wyse, D., Waldo, A., DiMarco, J., et al. 2002. A comparison of rate control and rhythm control in patients with atrial fibrillation. *New England Journal of Medicine*. 347(23):1825–1833. https://doi.org/10.1056/nejmoa021328.

Wysokinski, W. E., Owen, S. G., Fass, D. N., et al. 2004. Atrial fibrillation and thrombosis: immunohistochemical differences between in situ and embolized thrombi. *Journal of Thrombosis and Haemostasis*. 2(9):1637–1644. https://doi.org/10.1111/j.1538-7836.2004.00899.x.

Wysokinski, W. E., Cohoon, K. P., Melduni, R. M., et al. 2018. Association between P-selectin levels and left atrial blood stasis in patients with nonvalvular atrial fibrillation. *Thrombosis Research*. 172:4–8. https://doi.org/10.1016/j.thromres.2018.10.009.

Yaghi, S., Song, C., Gray, W. A., et al. 2015. Left atrial appendage function and stroke risk. *Stroke*. 46(12):3554–3559. https://doi.org/10.1161/strokeaha.115.011273.

Yamamoto, M., Seo, Y., Kawamatsu, N., et al. 2014. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. *Circulation: Cardiovascular Imaging*. 7(2):337–343. https://doi.org/10.1161/circimaging.113.001317.

Yao, X., Gersh, B. J., Sangaralingham, L. R., et al. 2017. Comparison of the CHA2DS2-VASc, CHADS2, HAS-BLED, ORBIT, and ATRIA risk scores in predicting non–vitamin K antagonist oral anticoagulants-associated bleeding in patients with atrial fibrillation. *American Journal of Cardiology*. 120(9):1549–1556. https://doi.org/10.1016/j.amjcard.2017.07.051.

Yaranov, D. M., Smyrlis, A., Usatii, N., et al. 2015. Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. *American Journal of Cardiology*. 115(4):461–465. https://doi.org/10.1016/j.amjcard.2014.11.027.

Ye, Y. Z., Chang, Y. F., Wang, B. Z., et al. 2020. Prognostic value of von Willebrand factor for patients with atrial fibrillation: A meta-analysis of prospective cohort studies. *Postgraduate Medical Journal*. 96(1135):267–276. https://doi.org/10.1136/postgradmedj-2019-136842.

Yedder, N. Ben, Roux, J. F. & Paredes, F. A. 2011. Troponin elevation in supraventricular tachycardia: Primary dependence on heart rate. *Canadian Journal of Cardiology*. 27(1):105–109. https://doi.org/10.1016/j.cjca.2010.12.004.

Zalesak, M., Siu, K., Francis, K., et al. 2013. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. *Circulation: Cardiovascular Quality and Outcomes*. 6(5):567–574. https://doi.org/10.1161/circoutcomes.113.000192.

Zeng, W. T., Sun, X. T., Tang, K., et al. 2015. Risk of thromboembolic events in atrial fibrillation with chronic kidney disease. *Stroke*. 46(1):157–163. https://doi.org/10.1161/strokeaha.114.006881.

Zhu, K., Hung, J., Divitini, M., et al. 2018. High-sensitivity cardiac troponin I and risk of incident atrial fibrillation hospitalisation in an Australian community-based cohort: The Busselton health study. *Clinical Biochemistry*. 58:20–25. https://doi.org/10.1016/j.clinbiochem.2018.05.003.

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