From the Department of Clinical Science and Education,
Södersjukhuset

Karolinska Institutet, Stockholm, Sweden

RISKS AND RISK MONITORING IN SOTALOL THERAPY FOR ATRIAL FIBRILLATION

Hanna Lenhoff

Karolinska Institutet

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Risks and risk monitoring in sotalol therapy for atrial fibrillation

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By

Hanna Lenhoff

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Principal Supervisor:
Associate Professor Mats Frick, M.D., Ph.D.
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset
Division of Cardiology

Co-supervisor(s):
Börje Darpö, M.D., Ph.D.

Professor Per Tornvall, M.D., Ph.D.
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset
Division of Cardiology

Opponent:
Professor Pyotr Platonov, M.D., Ph.D.
Lund University
Department of Clinical Sciences, Lund University Hospital
Division of Cardiology

Examination Board:
Professor Jonas Oldgren, M.D., Ph.D.
Uppsala University
Department of Medical Sciences
Division of Cardiology

Associate Professor Christina Christersson, M.D., Ph.D.
Uppsala University
Department of Medical Sciences
Division of Cardiology

Associate Professor Anders Englund, M.D., Ph.D.
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset

Nog finns det mål och mening med vår färd - men det är vägen, som är mödan värd

Karin Boye

To Lars, Signe, Klara, and Ida

Popular science summary of the thesis

Atrial fibrillation (AF) stands as the most common sustained cardiac arrhythmia significantly impacting patients' health and quality of life. The healthcare expenditures associated with AF are substantial, with approximately 3-4% of all Swedes living with the diagnosis of AF. Maintenance of sinus rhythm can alleviate symptoms and potentially enhance prognosis.

Sotalol is one of the recommended antiarrhythmic drugs to prevent AF recurrence. Its mechanism of action is that of a beta-blocker with antiarrhythmic properties, influencing the heart's electrical signal propagation, thus suppressing AF episodes. However, it also increases the risk of potentially fatal ventricular arrhythmias. Therefore, it is crucial to carefully consider and monitor these risks before and during sotalol treatment. The primary objective of this thesis was to examine the risks associated with sotalol treatment following cardioversion (CV) of AF in Sweden. Additionally, we aimed to expand our understanding of the most common risk marker in sotalol treatment: the prolongation of the QT interval, a distance measured on the electrocardiogram (ECG).

Two of the studies in this thesis focused on measuring the QT interval. The first used the standard 12-lead ECG, while the second study utilized continuous 12-lead Holter monitoring for 24 hours. The results revealed a reduction in the QT interval during the first week after CV to sinus rhythm in patients treated with sotalol. This was not observed in patients treated with a common beta-blocker. Additionally, the QT interval showed a diurnal variation, with some sotalol-treated patients experiencing significant QT interval prolongation. Despite this, no dangerous arrhythmias were observed during this short follow-up period. Whether these individual patients are at an increased risk of ventricular arrhythmias remains uncertain. Innovative technologies may offer opportunities for enhanced risk monitoring in the future.

The third study included a nationwide cohort of Swedish patients after CV of AF. No increase in mortality or ventricular arrhythmias was found among patients treated with sotalol when compared to those treated with beta-blockers. The prevalence of heart failure was uncommon, indicating that these patients probably were well selected for sotalol treatment.

Populärvetenskaplig sammanfattning

Förmaksflimmer är den vanligaste formen av rytmstörning i hjärtat och kan ge följder som stroke och hjärtsvikt. Åtminstone 3-4% av svenskar lever med diagnosen förmaksflimmer i Sverige idag, med stor påverkan på sjukvårdskonsumtionen som följd. Bibehållande av sinusrytm kan minska symtom och möjligen även förbättra prognosen.

Ofta behövs elkonvertering för att återställa hjärtats rytm. För att förhindra återfall av förmaksflimmer ges ofta även ett antiarytmikum som påverkar hjärtats elektriska signaler. Sotalol är ett av de rekommenderade läkemedlen. Tyvärr är sotalol behäftat med risk för allvarlig rytmstörning, kammartakykardier som kan leda till hjärtstopp. Syftet med denna avhandling var att undersöka risker vid sotalol-behandling efter elkonvertering av förmaksflimmer. Dessutom ville vi öka kunskapen om en av de vanligaste riskmarkörerna vid sotalol-behandling: förlängning av QT-tiden på EKG.

I delarbete I och II undersöktes QT-intervallet, först på det traditionella sätt med EKG som sker i klinisk vardag, sedan med dygnsregistrering av 12-avlednings EKG. Patienter inkluderades i samband med elkonvertering på hjärtintensiven på Södersjukhuset. Som kontrollgrupp till sotalol-behandling inkluderades patienter med betablockad-behandling. Resultaten visade att QT-intervallet minskar under den första veckan efter elkonvertering hos patienter behandlade med sotalol, ett fenomen som inte sågs i kontrollgruppen. Dessutom uppvisade QT-intervallet en dygnsvariation, där vissa samtliga sotalol-behandlade patienter hade tydlig QT-förlängning, särskilt nattetid. Detta till trots observerades inga farliga rytmstörningar under den korta uppföljningen. Om dessa individer har ökad risk för kammararytmier är oklart.

Delarbete III är en registerstudie med svenska patienter som elkonverterats för förmaksflimmer och är behandlade med sotalol eller betablockad. Sotalol-behandlade patienter (n=4953) uppvisade ingen ökad dödlighet eller diagnos av allvarlig hjärtrytmrubbning, jämfört matchade betablockad-behandlade patienter. Förekomsten av hjärtsvikt var låg, vilket indikerar att de som fick sotalol var väl selekterade.

Abstract

Background

Atrial fibrillation (AF) stands as the most prevalent arrhythmia, significantly impacting both the prognosis and symptomatology of affected individuals. Healthcare expenditures associated with AF treatment and its related complications, in terms of morbidity and mortality, are substantial. In symptomatic AF, or in AF-induced left ventricular dysfunction, the primary treatment objective is to restore sinus rhythm. Earlier studies suggested equivalence between rate and rhythm control, but contemporary research points toward rhythm control being associated with lower rates of cardiovascular hospitalization and events. Cardioversion (CV) is often necessitated and is most effective when combined with an antiarrhythmic drug. Sotalol, a potent Ikr blocker, is one of the recommended drugs to prevent AF relapse. However, sotalol carries an inherent risk of proarrhythmias and sudden death. The proarrhythmic risk associated with sotalol in guideline-selected patients undergoing contemporary management remains unknown. Prolongation of the QT interval, measured on ECG, is considered the most reliable risk marker for ventricular arrhythmias in sotalol treatment. The dynamicity of the QT interval in patients receiving Ikr blocking drugs is poorly studied. The thesis aimed to 1) evaluate the QT interval in patients after CV of AF with sotalol treatment and 2) compare mortality and the incidence of ventricular arrhythmias in patients following CV of AF who receive sotalol or beta-blockers.

Methods and results

Study I: Triplicate ECGs were recorded one hour after CV and one week later in 208 patients receiving a steady dose of sotalol or beta-blocker (metoprolol) treatment. In sotalol-treated patients, the mean QTc interval (QT corrected for heart rate) decreased during the week after CV (-20.3 ±24 ms), whereas no significant change was observed in metoprolol-treated patients (-2.5 ±18 ms). Longer QTc interval after CV and better renal function were associated with the reduction in QTc.

Study II: Twenty-four hour, 12-lead Holter recordings were conducted after CV in 50 patients treated with sotalol or metoprolol. Diurnal analysis of QTc revealed that 22% of sotalol-treated patients had >20% of all heartbeats with prolonged

QTc >500 ms, primarily occurring during nighttime, compared to no patients treated with metoprolol. Diurnal variations were observed in both HR and QTc.

Study III: A nationwide register-based cohort study involving all Swedish AF patients included after their second CV from 2006 to 2017. Patients receiving sotalol (n=4,987) and cardioselective beta-blocker-treated patients (n=27,078), were followed for an average of 458 days. A diagnosis of heart failure was found in 14% of patients. All-cause mortality was lower in sotalol-treated patients, a difference that persisted in the propensity-matched comparison (n=4,953 in each group) with an incidence rate (IR) of 1.19 (0.93-1.49) vs. 2.01 (1.67-2.39) deaths per 100 patient years, and IRR of 0.59 (0.44-0.79). No differences were observed in ventricular arrhythmias with an IR of 1.38 (1.10-1.71) vs. 1.26 (1.00-1.57) events per 100 patient years, and an IRR of 1.59 (0.85-2.99).

Conclusions and summary

In AF patients after CV, selected for sotalol treatment after 2006, mortality or ventricular arrhythmias were not increased compared to patients treated with a cardioselective beta-blocker (Study III). The QTc interval significantly decreased during the week following CV to sinus rhythm in sotalol-treated patients (Study 1). Patients on sotalol exhibited a substantial number of heartbeats with prolonged QTc over 24 hours, particularly at night. QT dynamicity over 24 hours was evident in sotalol-treated patients, although the impact of the HR correction formula remains unclear (Study II). These findings could provide insight into the increased risk of proarrhythmias immediately after CV and indicate that the QT interval is a dynamic measure. Careful patient selection and the avoidance of congestive heart failure likely minimize the risks associated with sotalol treatment.

List of scientific papers

I. Lenhoff H, Darpö B, Ferber G, Rosenqvist M & Frick M. Reduction over time of QTc prolongation in patients with sotalol after cardioversion of atrial fibrillation. Heart Rhythm. 2016 Mar;13(3):661-8.

II. Lenhoff H, Darpö B, Page A, Couderc JP, Tornvall P & Frick M. Diurnal QT analysis in patients with sotalol after cardioversion of atrial fibrillation. Ann Noninvasive Electrocardiol. 2021 Jul 26(4): e12834.

III. Lenhoff H, Jarnbert-Petersson H, Darpo B, Tornvall P & Frick M. (2023). Mortality and ventricular arrhythmias in patients on d,l-sotalol for rhythm control of atrial fibrillation - A nationwide cohort study. Heart Rhythm. 2023 Aug 18; S1547-5271(23)02589-4. https://doi.org/10.1016/j.hrthm.2023.08.019.

CONTENTS

List of abbreviations

AAD	Anti-Arrhyhtmic Drug
AERP	Atrial Effective Refractory Period
AF	Atrial Fibrillation
AHRE	Atrial High Rate Episode
APD	Action potential duration
AV	Atrioventricular
Ca^{2+}	Calcium
CHA_2DS_2–VASc	Risk score for predicting risk of stroke in AF, containing CHF, hypertension, age, diabetes, vascular disease, and female sex.
CI	Confidence Interval
CV	Electrical Cardioversion
CHF	Congestive Heart Failure
ECG	Electrocardiogram
EF	Ejection Fraction
EHRA	European Heart Rhythm Association
ERP	Effective Refractory Period
ESC	European Society of Cardiology
HR	Heart Rate
Ikr	Rapidly activated potassium ion channel
Iks	Slowly activated potassium channel
K^+	Potassium
J	Joule
Na^+	Sodium

SR	Sinus Rhythm
SD	Standard Deviation
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia

Introduction

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia, exerting significant impact on both morbidity and mortality among individuals, and imposing a considerable burden on healthcare systems. Despite considerable advancements in various facets of AF management over the past decade, including techniques such as ablation, risk factor mitigation, and stroke prevention strategies, the emergence of novel pharmacological agents for antiarrhythmic therapy remains limited.

Upon the initial diagnosis of AF, numerous considerations must be taken into account, encompassing risk factors, lifestyle aspects, occupation, symptoms, coexisting medical conditions, family history, presence of structural heart abnormalities, indication for the restoration of sinus rhythm (SR), prospects of electrical cardioversion (CV), pulmonary vein ablation, stroke risk assessment, and more. The demand for information is underscored by the extensive volume of studies in PubMed, where AF stands as one of the most extensively investigated cardiovascular diseases, garnering over 10,700 citations as of August 2023. Nonetheless, unresolved aspects remain concerning AF management and prevention. Questions persist about the impact of sustaining SR, beyond symptoms alleviation on prognosis, the enduring effects of pulmonary vein isolation on prognosis, and the optimal strategies for preventing AF.

For symptomatic AF cases, the primary treatment objective involves the restoration of SR. Antiarrhythmic drugs (AADs) can be used to prevent relapse of AF. The efficacy of the majority of AADs was established approximately two decades ago, lacking contemporary patient selection and treatment. Existing AADs carry the risk of several significant adverse effects, including unpredictable and concerning pro-arrhythmias. It remains unclear to what extent modern treatment modalities, follow-up procedures, novel techniques, and monitoring have influenced the risks associated with AAD therapy.

This research project commenced in the clinical context of the cardiac intensive care unit during CV of patients undergoing sotalol treatment. This context raised several questions concerning QT dynamicity and safety with sotalol, which this thesis aims to address.

1 Literature review

1.1 Prevalence and prognosis

AF is the most common sustained arrhythmia, with an estimated prevalence of 2.9–4.0% among adults in Swedish society[1,2]. The future risk of AF is projected to be more than 1 in 3 for individuals with a risk factor, when investigated at the age of 55 years[3]. The burden of AF amplifies with age, and combined with enhanced diagnostic capabilities, the prevalence is likely to rise, thereby augmenting the economic burden on society[4,5].

AF is associated with increased mortality and morbidity, although prior studies have presented conflicting outcomes regarding the degree of mortality elevation. In the 1990s, the Framingham study indicated a twofold increase in mortality among women with AF and a 1.5-fold increase among men[6], though mortality rates had declined by 25% in the 2015 follow-up[7]. This observation was supported by a meta-analysis that predicted mortality ratios of 1.7 for men and 1.6 for women in AF cases[5]. Registry-based Swedish data from 2002 revealed a several-fold rise in mortality among AF patients, with hazard ratios ranging from 1.7 to 4.9 in different age groups: a correlation that remained even after adjusting for concurrent cardiovascular, pulmonary and neoplastic diseases[8]. The risk of AF in young patients without risk factors, previously called "lone AF", is even less established, though shown to be significantly less elevated compared to patients with risk factors[9,10].

Stroke has long been a dreaded consequence of AF. Stroke is the third-leading cause of death in Sweden, except for the year 2020 during the Covid-19 pandemic[11]. AF is associated with 20–30% of all strokes[12]. The occurrence of AF-related stroke and death can largely be prevented with anticoagulants, at least by two-thirds[13]. With the introduction of direct oral anticoagulants after 2010, the bleeding risk has declined, and the use of anticoagulants have increased[14]. The usefulness of AF screening is a topic of debate, and several trials have investigated the issue[15,16]. Recent data from a study involving 2,536 patients with two points on CHA_2DS_2–VASc showed an increased bleeding risk and only moderate stroke prevention when initiating the direct anticoagulant edoxaban in patients with short duration AF, specifically atrial high rate episodes (AHRE ≥6 minutes) detected by implantable devices[17]. For now, the importance of ECG diagnosis in decisions about stroke prevention remains.

The other major cardiovascular consequence of AF is heart failure stemming from the tachyarrhythmia. AF and heart failure share numerous risk factors and frequently coexist, thereby complicating the differentiation of causal pathways to the tachycardiomyopathy[18,19]. Nevertheless, heart failure is documented as the predominant cause of death in AF cases[19,20]. Moreover, AF has been associated with increased mortality in myocardial infarction[21], although the causal relationship is unclear. AF is also a suspected risk factor for dementia, cognitive decline, and white matter lesion in the brain[22].

In summation, AF's prevalence is substantial and probably increasing due to global population aging and the potential impact of sedentary lifestyle if unchanged. Prevention of morbidity and mortality following AF will need careful management.

1.2 Diagnosis and clinical classification of AF

AF is a supraventricular arrhythmia originating within the atria of the heart and results in uncoordinated atrial activation, leading to the deterioration of their function. AF is diagnosed by ECG visualizing the lack of discernible p-waves. Instead, oscillations or fibrillatory waves manifest, accompanied by an irregular ventricular response and heart rhythm (HR) (Figure 1). The diagnosis is made either by a full 12-lead ECG or by Holter monitoring, where 30 seconds is demanded for diagnosis[10,23].

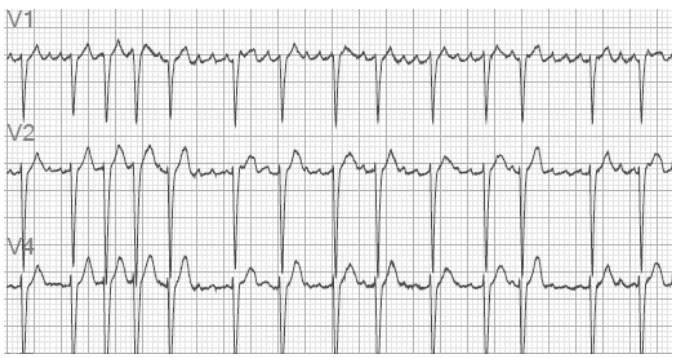

Figure 1 Three ECG chest-leads showing AF.

In most patients, the AF disease is a continuum, starting with short, perhaps silent episodes, then progression to longer, symptomatic episodes, and eventually to longer, non-self-terminating sustained arrhythmia. Due to its heterogenous presentation, several different classifications of AF have been proposed over the years. According to the European Society of Cardiology (ESC)

in 2020, *paroxysmal* AF is classified as AF that terminates spontaneously or with intervention within 7 days of onset, while *persistent* AF sustains beyond 7 days and often needs CV to terminate AF. *Permanent* AF is when a decision not to restore SR is taken, while *long-standing persistent* AF still targets rhythm control. In *first diagnosed* AF, the duration of AF is not always obvious[10].

1.3 Pathogenesis and electrical and structural remodeling

In normal SR, the initiation of a heartbeat originates from the sinus node when the action potential propagates through the atria to the ventricles via the atrioventricular (AV) node, introducing a controlled delay. The ventricular response and therefore HR, both in SR and AF, result from the inherent electrophysiological characteristics of the AV node. This is further influenced by sympathetic and vagal tone affecting the AV node, and the effects of drugs.

However, in AF, rapid and focal electrical activity originates from muscular sleeves extending into the pulmonary veins within the left atrium, spreading chaotically through the atria. This disorganized electrical activity, which includes ectopic beats and triggered activity, initiates, and likely sustains episodes of AF, leading to irregular atrial depolarizations without effective atrial contraction[24,25] .

The process of electrical remodeling was observed by Wijfells et al. who in 1994 demonstrated on 12 awake goats that AF leads to a shortening of the atrial effective refractory period (AERP), enhancing the stability and inducibility of the arrhythmia[26]. Two years later, pacing in dogs revealed that rapid pacing can induce AF that perpetuates itself[27,28]. As knowledge expanded on the importance of ion currents in the myocyte, it was found that during each heartbeat, calcium ions enter myocytes. This calcium influx is heightened during tachycardia when the AERP and repolarization shorten. Consequently, more calcium is released from the sarcoplasmic reticulum within the myocyte, further elevating calcium levels. This partially arrhythmic and partially sympathetic-driven increase in calcium is believed to contribute to electrical remodeling. The shortening of AERP is associated with calcium imbalance, but also with altered expression in other ion channels, leading to an increase in myocyte size and myolysis[29,30]. In paroxysmal AF, 90% is driven from the pulmonary veins, while the atria undergo remodeling as the disease progresses to more persistent AF[31]. The restoration of SR has been shown to at least partially reverse this process[26]. This forms the basis for the progression of AF, how "AF begets AF".

Several factors are recognized to contribute to structural remodeling of the cardiac atria, eventually resulting in atrial enlargement detectable by echocardiography. This enlargement is primarily attributed to a complex process of fibrosis development[32]. Fibrosis arises from a combination of electrical remodeling and systemic factors. As myocytes undergo electrical remodeling, calcium deposits change, resulting in reduced contractility and atrial enlargement. Additional factors contributing to atrial fibrosis include advanced age, structural heart disease, and hypertension[29]. Chronic inflammation may also play a role through various cellular mechanisms, leading to fibrosis, myocyte hypertrophy, fatty infiltration, connective tissue deposition and fibroblast activation, all of which have been observed in patients with AF[33,34]. This structural remodeling disrupts the alignment of muscle bundles, impacting the sarcoplasmic reticulum and causing alterations in electrical conduction of the action potential and further shortening of the AERP. This creates a pathway for re-entry and arrhythmias[26,29].

An improved understanding of electrical regulation through ion currents responsible for the action potential propagation throughout the heart provides insight into the actions of AADs. Recognizing the central role of the pulmonary veins in AF has led to development of ablation techniques.

1.4 The cardiac action potential and the QT interval

The electrical signaling within the heart, creating heartbeats, emerges from the movement of ions across cardiomyocyte membranes via ion channels, giving rise to an action potential. These ion channels exhibit different expression patterns throughout the heart, contributing to the modulation of action potential duration (APD). Ventricular myocytes, for instance, demonstrate prolonged APD, rendering them susceptible to arrhythmias[35].

The initiation of voltage change, propagated from pacemaker cells in the sinus node through bundle branches to all myocytes, serves as the essential driver of cardiac contraction. This elicits a shift in membrane potential, initiating a cascade of events constituting the action potential. The action potential curve is heavily influenced by diverse ion currents, prominently involving sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}), and the ion channels involved, driven by voltage changes, exhibit varying affinities for the ions (Figure 2).

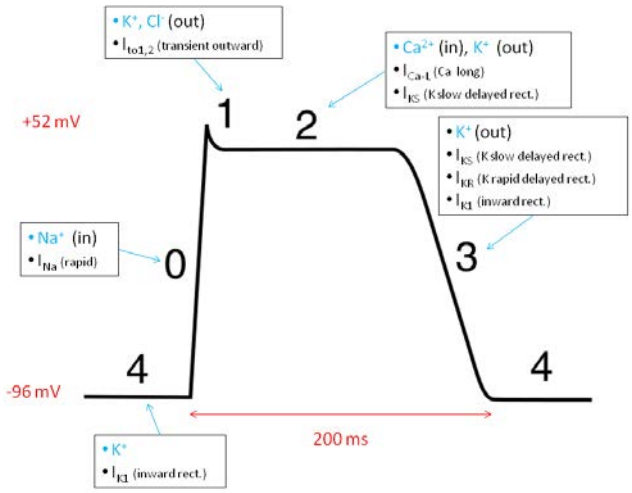

Figure 2 Simplified illustration of the action potential in a myocyte. The APD here is 200 ms; in humans it is longer, depending on heart rate. Reprinted with permission from Wikimedia (2023-08-23), CC BT-SA 3.0 DEED.
https://commons.wikimedia.org/wiki/File:Action_potential_ventr_myocyte.gif#filelinks

The major current that influences the duration of the repolarization is the delayed rectifier potassium current, with both a rapid and a slow component. The rapidly activating component of the potassium channel, known as Ikr, is pivotal, encoded by the KCNH2 gene, also referred to as hERG (human-ether-a-go-go-related gene)[36], functions alongside another element of potassium flow, Iks (the slowly activating potassium channel), which operates less rapidly. The ion channels responsible for Ikr are more abundant in ventricular than atrial myocytes, and the blocking of these channels reduces K^+ ions outflow, prolonging repolarization. Simultaneously, the Na-K ATPase contributes by facilitating sodium efflux and potassium influx, restoring the membrane potential and thereby priming the initiation of the next action potential cycle[30]. This, along with calcium-flow over the membrane, gives rise to the APD, discernible on the surface ECG as the QT interval[37]. It is notable that the Ikr component not only reacts swiftly but deactivates gradually, resulting in a continuous efflux of potassium even after the APD. In instances of tachycardia or extrasystoles, this can contribute to the reduction of the next APD[38]. Early afterdepolarizations (EAD) is a way of describing changes in ion flows and action potential at the terminal part of repolarization, causing oscillatory upstrokes in voltage, which may trigger (Figure 3)[39]. However, while the depolarization mirrors the QRS on the ECG and the repolarization phase mirrors the QT-interval on the ECG, subtle

disparities across the myocardium can lead to variations between the actual APD and the QT interval.

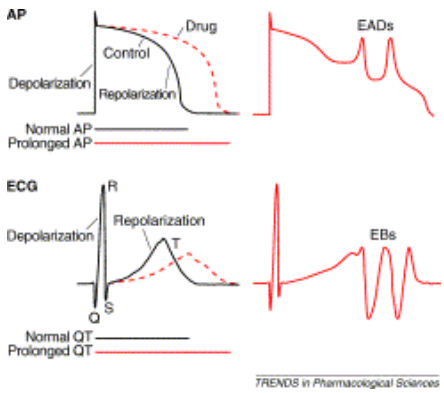

Figure 3 The action potentials in ventricular myocytes and ECG. Increase in AP duration prolongs the QT interval, as in the presence of a drug (e.g. sotalol). Reproduced with permission from Belardinelli et al. Assessing predictors of drug induced torsade de pointes. Trends in Pharmacological Sciences, Vol.24, Issue 12, 2003, Copyright ©2003, Elsevier.

This delicately calibrated system is susceptible to an array of disruptions, not only in ion channels alone, including hormones, genetic expression, environmental milieu and cardiac diseases affecting contractility[40,41]. Prolonged QT intervals, signifying prolonged APD and repolarization, are vulnerable to disturbances that can trigger life-threatening arrhythmias[42]. The term "repolarization reserve" was introduced by Roden to elucidate why not all individuals with QT prolongation developed arrhythmias[43-45]. Instead, it is a multifactorial interplay involving intrinsic and extrinsic factors such as innervation, vagal tone, structural heart disease, electrolyte balance, gap junction functionality, dispersion in the myocardium, where each component can affect arrhythmia development [36,46-49]. Despite progress, several aspects of cardiac electrophysiological function and modulation remain unknown. This includes other risk markers for ventricular arrhythmias, encompassing ECG details, autonomous nervous system changes, and genetics, all of which warrant further exploration[30,35,50].

1.5 Electrocardiographic measurements: QT and QTc intervals

The ECG provides a graphical representation of summation of ion currents in the heart, illustrating the relationship between voltage and time.

Quantification of the QT interval commences from the onset of the QRS interval and extends to the end of the T-wave, demarcated by the T-wave's return to baseline. U-waves are excluded from QT interval measurements[51,52]. To standardize and facilitate comparison of the QT interval with varying HR, correction of the QT interval for HR is essential. In 1920, Bazett proposed a standardized HR correction formula, where RR is determined in the preceding RR interval ($QTcB = QT/RR^{1/2}$)[53]. Following, diverse regression models have been proposed, often employing $QTc = QT/RR^{\alpha}$, where α assumes distinct values. QTcB has, however, been the clinical standard.

QT formulas for HR correction		
Bazett	$QTc_B = QT/RR^{1/2}$	$QTcB = \frac{QT}{RR\frac{1}{2}}$
Fridericia	$QTc_F = QT/RR^{1/3}$	$QTcF = \frac{QT}{RR\frac{1}{3}}$
Bundle branch block	$QT_m = QT_{BBB} - 50\%QRS_{BBB}$ (then apply HR correction formula)	
Abbreviations: HR, heart rate; QT in milliseconds, RR in seconds, RR=60000/HR		

However, several studies have demonstrated that QTcB leads to an inadequate HR correction, and new algorithms have been explored to optimize HR, each possessing its own limitations (Figure 4)[54–58].

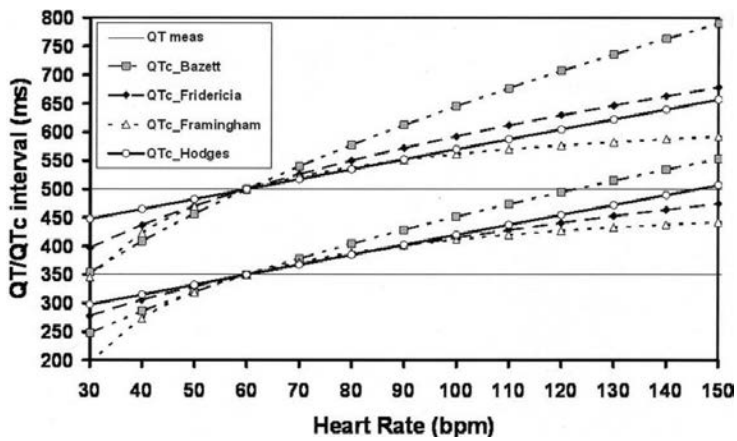

Figure 4 "A comparison of 4 different QTc formulae based on two values of QT, namely 350 ms and 500 ms. This clearly shows that the Bazett formula produces much higher values of QTc above 60 bpm compared to other formula and generally lower values below 60 bpm, with the exception of the Framingham formula." Reproduced with permission from Dr. Shen Luo. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. J Electrocardiol 2004; 37. Copyright ©2004, Sciencedirect.

Studies involving marginal HR fluctuations tend to yield more robust QTc measurements. Particularly, when HR variations fall within the range of 50-70 bpm, and changes remain below 10 beats per minute, a generalized formula, such as Fridericia's, can be employed for correction[55,57,59]. Many group-level studies recommend using the Fridericia ($QTcF = QT/RR^{1/3}$) formula[60,61], and this area is continuously evolving. In bundle branch blocks and paced heart beats the QTc estimation is challenging. The bundle branch block creates prolonged depolarization and QRS width, i.e. the JT interval reflects the depolarization. A formula subtracting the QT with half of the QRS width has been proposed[62]. The spline function is another formula that holds promise for paced heartbeats, where previous corrections proved challenging[63]. However, its application necessitates validation across broader patient populations. QTc measurement in AF present challenges; averaging over several beats is often recommended[64]. Online platforms provide QT correction calculations based on various formulas, such as www.QTcalculator.org[65], or the QT conversion - NHANES spline (shinyapps.io)[63].

The QTc interval is influenced by changes in electrolyte levels, ischemia, fever, circadian rhythm, and central nervous and hormonal status[66,67]. QTc studies have encountered criticism due to the substantial impact of multifaceted variables on measurements, encompassing technical measurement intricacies and individual-specific factors. New technology offers more automated measurements, increasing the ECG segment analysis, yet discussions persist on the optimal methodology for QTc comparisons and investigations[65,68,69].

1.6 QT diurnal variation

In clinical practice, measuring QTc is typically performed using a single ECG, providing a one-point prevalence measurement. However, it is well-established that 24-hour rhythms exist within various cardiac electrophysiological parameters, including HR and the QT interval[70]. The QT interval is longest during the night, and the most significant change in QTc occurs in the morning[71,72] . This diurnal variation has been associated with ventricular arrhythmias and sudden cardiac death, which tend to have an increased incidence in the morning, after awakening[73]. Nonetheless, the timing aspect is often overlooked in QT and ECG investigations[74].

The term "circadian" is sometimes used interchangeably to "diurnal" and reflects the intrinsic clock in the heart. Diurnal cardiac electrophysiology is influenced by

both the central suprachiasmatic nucleus, which acts via the autonomous nervous system, and a local cardiac clock within the heart. In 1986, Bexton et al. demonstrated that this diurnal variation was blunted in transplanted and diabetic hearts, suggesting the influence of vagal tone and catecholamines[72,75]. The intrinsic cardiac clock drives ion channel remodeling and function, as shown in transgenic mice where disruption of the diurnal rhythm leads to depression of the repolarizing current Ikr via the hERG channel, increasing susceptibility to ventricular arrhythmias[76,77]. However, it is not yet definitively established whether diurnal variation predicts ventricular arrhythmias in humans.

Evidence supporting the impact of diurnal variation in humans can be found in patients with inherited long QT syndromes (LQTS), which result from pathogenic variants in genes regulating ion channels. Specifically, LQTS 1-3 are associated with mutations in KCNQ1 (LQT1), KCNH2 (LQT2), or SCN5A (LQT3) genes. The two former code for proteins within the voltage-gated potassium channel, while the latter is a sodium channel subunit. The incidence of cardiac events in LQTS patients follows a circadian pattern specific to each LTQS subtype, with LQTS 1 events occurring in the afternoon, LQTS 2 events in the morning, and LQTS 3 events during the night[74].

Many factors have been identified as affecting the diurnal variation, including autonomic tone, feeding and activity levels, gender, HR, and the choice of HR correction formula[78-80]. The impact of structural heart disease on diurnal variation is less clear. In patients with recent myocardial infarction, QTc was prolonged, and the diurnal variation reduced post-infarction. Treatment with a beta-blocker normalized diurnal variation compared to no treatment and to healthy controls. However, it's worth noting that QTc correction was performed using the Bazett formula, which inadequately corrects for the bradycardic effect of a beta-blocker and has been shown to mask the diurnal variation[54,80].

The effects of QT-prolonging drugs on diurnality have yielded somewhat conflicting results. For example, moxifloxacin, a broad-spectrum fluoroquinolone antibiotic known for constant QT-prolongation, has retained diurnality compared to placebo. However, the response to meals-shortened QTc was exaggerated in patients on moxifloxacin[79]. In contrast, in 22 Covid-19 patients treated with hydroxychloroquine and azithromycin, QTc prolongation was constant and less variable under drug treatment, while the control group exhibited a more normal diurnal rhythm[81]. The diverse results of drugs affecting the diurnal QTc variation

have been debated, and it remains unclear whether this effect is more of a "regression towards the mean". However, due to the visualization of QT diurnal variation, recommendations have arisen to standardize ECG measurements by taking them at the same time of day to enable accurate comparison or using Holter recordings[82].

1.7 Current treatment strategies in AF

Modern evidence-based management of AF encompasses a multifaceted approach, including symptom alleviation, stroke risk assessment, prognostic indicators, and concurrent medical conditions and risk factors. The evaluation of symptoms is crucial in guiding treatment and is categorized in alignment with the EHRA scale[10], spanning from 1-4. *EHRA 1* indicates an absence of symptoms, while *EHRA 4* denotes the presence of debilitating symptoms. *EHRA 2* is probably most common, causing mild symptoms, with *EHRA 2b* affecting the patient negatively, with symptoms mostly in effort. These symptoms encompass palpitations, fatigue, dizziness, dyspnoea, chest pain, and anxiety during AF.

Managing AF symptoms entails two approaches: rate or rhythm control. Paroxysmal AF is commonly perceived as more symptomatic[83]. Rate control aims to modulate ventricular heart rate to alleviate symptoms and prevent tachycardia-induced cardiomyopathy, i.e. heart failure caused by high heart rate. Rhythm control seeks to reinstate and sustain SR.

Regardless of the chosen rhythm- or rate-based approach, stroke risk assessment is essential for all AF patients, with higher risk in the elderly[12,84]. The decision on thromboembolic prophylaxis hinges on clinical parameters determined by the CHA_2DS_2-VASc score, along with an evaluation of bleeding risk[10]. This score incorporates congestive heart failure (CHF), hypertension, diabetes, and stroke/transient ischemic attack according to the patient's age and sex, along with the presence of vascular disease, including peripheral arterial disease, prior myocardial infarction, and aortic atheroma. Scores range from 0 to 9, with higher scores reflecting elevated risk. Novel and refined scoring systems are presently under evaluation[85].

Irrespective of rate or rhythm strategy, addressing precipitating factors, often termed "upstream factors", within underlying cardiovascular conditions and unfavourable lifestyle patterns has demonstrated efficacy in reducing AF episodes in paroxysmal AF and enhancing life expectancy[10,86]. Minimizing alcohol

consumption, controlling hypertension, managing sleep apnoea, reducing obesity, and optimizing heart failure management are all crucial steps[10,87,88].

In summary, optimizing AF symptoms and prognosis involves a comprehensive approach encompassing lifestyle modifications, diagnostic assessments, and pharmacological and surgical interventions.

1.7.1 Rate control

Rate control in AF plays a crucial role in managing symptoms and reducing the risk of adverse cardiac events, such as tachycardia-induced cardiomyopathy and heart failure[89,90]. Various medications are available to achieve rate control and reduce ventricular HR in AF, with the most evidence supporting the use of beta-blockers, calcium channel blockers, amiodarone, and digoxin. However, current data on the comparative safety and effectiveness of these medications for ventricular rate control and symptoms alleviation are somewhat inconclusive[10,90–93].

Beta-blocker therapy is commonly the first-line treatment option for rate control in AF[90]. Calcium channel blockers can also be considered for primary rate control when left ventricular function is not compromised, and they can both be used in combination with digoxin[10]. Digoxin alone is a similar option [94], sometimes underused in solo therapy but limited by risk of accumulation in renal failure. Digoxin works by increasing vagal influence on the AV node, with its effects being less pronounced during exercise. Amiodarone is another potential option[95], but its side effects make it less favourable for long-term use. Nevertheless, the evidence supporting the selection of the most effective drug strategy for rate control is not robust[91]. When rate control efficacy is insufficient, or side effects pronounced, AV-node ablation is the final option, rendering the patient pacemaker-dependent.

1.7.2 Beta-blockers

Both cardioselective and non-cardioselective beta-blockers work by antagonizing beta-receptors, thereby reducing the effects of adrenaline and noradrenaline. They generally hinder the stimulation and elevation of intracellular cAMP levels due to beta-adrenergic stimulation, thereby decreasing HR by prolonging AV-nodal refractoriness, preventing ventricular arrhythmias, but also reducing contractility. The most used beta-blockers are cardioselective, such as metoprolol or bisoprolol, which have a 20 times higher affinity for beta1-

receptors in the heart, compared to beta2-receptors[96]. Elimination mostly occurs through the renal route after metabolization in the liver, primarily via the cytochrome P450 system. Beta-blockers have been shown to reduce mortality in CHF and to prevent new-onset AF in CHF[97-99]. Fortunately, cardioselective beta-blockers have not been shown to have negative respiratory effects, which has been a concern given that many patients with AF also suffer from chronic obstructive pulmonary disease[100].

In conclusion, achieving rate control in AF is essential for symptom relief and preventing cardiac complications. While there is still need for knowledge concerning the optimal drug strategy in different patients, in many circumstances beta-blockers are effective and tolerated.

1.7.3 Rhythm control

Rhythm control, aiming at maintaining the patient in SR, can, to some extent, be achieved by beta-blockers and calcium channel blockers, as well as AADs that prevent AF relapse while possessing a pharmacological cardioversion effect or facilitating electrical cardioversion (CV). While CV requires fasting and sedation of the patient, AADs come with their own limitations. Most AADs carry a risk of pro-arrhythmic effects or organ-specific toxicities. Furthermore, catheter ablation of pulmonary veins can be performed, albeit with its own risk of intraprocedural complications and varying degrees of success.

The AF preventive effect of beta-blockers is considered moderate to low[10]. As demonstrated by Kuhlkamp et al., when comparing beta-blockers to placebo, 96 patients on metoprolol experienced a 49% relapse into AF compared to 65% on placebo at 6 months[101]. Similarly, Nergårdh et al. showed a 54% relapse into AF with metoprolol treatment after six months, compared to 74% on placebo[102]. The mean dose of metoprolol was 100 mg and 169 mg respectively and the highest effective dose, along with additional CV, improved the maintenance of SR.

In summary, beta-blockers are well tolerated, improve prognosis in several diseases and have a low-moderate effect in preventing AF recurrences.

1.7.4 Cardioversion

Many patients with paroxysmal AF spontaneously convert to SR within the first 24 hours[103]. A longer duration of AF reduces the likelihood of spontaneous conversion.

Electrical CV can effectively restore SR with a high success rate (85-95%)[104,105]. CV is performed under sedation, requiring the patient to fast at least 6 hours. The electric shock causes a simultaneous depolarization of all myocytes and must be synchronized with the R-wave on the ECG to avoid inducing ventricular fibrillation. Factors enhancing the procedure include high voltage and manual pressure with handheld paddles, which increases the success rate, especially in obese patients[106]. In elective situations, patients can be optimized by alcohol withdrawal and treatment of hypokalaemia and hypertension, all which aids in maintaining SR[89,107]. Despite the high success rate of the CV procedure, relapse into AF is common, and after 12 months, nearly 75% of patients have relapsed, if not treated with an AAD[89,108].

1.7.5 Pharmacological cardioversion

Several AADs possess varying degrees of cardioverting efficacy, with the most established being infusion with vernakalant[109-112]. However, its efficacy is modest, with 43-52% of patients treated achieving SR after 24 hours. Sotalol has demonstrated a cardioversion effect of 26% in persistent AF[113]. In summary, pharmacological cardioversion exhibits modest efficacy, often necessitating electrical CV as a potential rescue option.

1.7.6 Pulmonary vein ablation

Pulmonary vein ablation has been used for rhythm control since the late 1990s and is now considered a prioritized treatment strategy[10,24,114]. However, ablation is an invasive procedure associated with a complication rate of 1-7% for serious adverse events and is not suitable for every patient[10,115-117]. Unfavourable factors for ablation include obesity, high bleeding or stroke risk, extensively remodelled atria, advanced age, and impaired kidney function.

The success rate of pulmonary vein ablation ranges from 66-85%[23,118,119], with continuous refinement and evolution of the technique[120]. Various studies, although lacking sham control, have demonstrated superior efficacy of ablation compared to AADs in maintaining SR and alleviating AF symptoms post-ablation[121,122]. ESC guidelines from 2016 recommended ablation when symptoms persist despite AAD treatment or when AADs are intolerable[123].

In recent years, a prognostic gain has been shown with ablation in comparison to drug treatment in patients with AF and CHF in the CASTLE AF, the AMICA and the CASTLE -HTx[124-126]. However, other studies, such as the CABANA trial, where only

15% had CHF, and the RAFT-AF did not show clear beneficial effects of ablation in AF patients[116,127]. In patients with paroxysmal AF, without CHF, several trials have proven the efficacy of ablation in symptom relief[128,129] and subsequently, the role of ablation in AF is strengthened in the ESC guidelines from 2020[10]. However, it's worth noting that AADs are required in 23-29% of patients even following ablation[116,124,127]. For patients unsuitable for or unwilling to undergo ablation, and for the one-third that experience relapse of AF, AADs remain a necessary therapeutic option.

1.7.7 Rhythm or rate control for prognosis

A rhythm-control strategy is favoured in symptomatic patients and might be warranted even in asymptomatic individuals when AF carries a risk of worsening heart failure or prognosis. The question of whether rhythm control leads to decreased morbidity and mortality remains contentious. The ambiguity persists whether AF primarily serves as a cardiovascular risk marker or if preserving SR influences prognosis beyond mere symptom alleviation.

The AFFIRM trial demonstrated no disparity in mortality among 4,060 patients randomized to rate or rhythm control over an average follow-up of 3.5 years[130]. Rhythm control was determined by the physician, with amiodarone (63%) or sotalol (41%) being the predominant choices. The crossover rate was 37.5% to rate control at 5 years. In the rhythm control group, twelve patients (0.8%) experienced the ventricular tachycardia Torsades de Pointes (TdP), compared to two in the rate control group. Reduced left ventricular EF was present in 27% of patients. Furthermore, a trend towards increased hospitalizations with AADs was shown[131], which may be explained by the need for repeated CV. However, improved prognosis was apparent in those patients who remained in SR[132]. The main findings from AFFIRM was consistent with those from the RACE trial, including 522 patients[89]. In the RACE trial, only 39% of patients in the rhythm control group had SR after two years, highlighting a substantial uncertainty regarding the use of sustaining SR.

Other studies have shown beneficial results with rhythm control. In the EAST AFNET 4 trial, 2,789 patients with recent-onset AF (<1 year) were randomized to early rhythm control or standard care[133]. The composite outcome of cardiovascular death, stroke, and cardiovascular hospitalization occurred at rates of 3.9 vs. 5/100 person-years (p=0.005), favoring rhythm control with a median follow-up of 5 years. Although ablation was used relatively infrequently

in the rhythm control group (19.4% by two years), a substantial proportion (86%) maintained SR at 1 year, compared to 66% in the standard group ($p<0.001$), indicating patients with paroxysmal AF with a lower risk for AF recurrence. Adverse events were noted in 4.9% of rhythm control patients, primarily related to AAD use, mostly bradycardia, but one case of TdP occurred, in contrast to a total of adverse events of 1.6% in the standard care group. Notably, the presence of SR at the 1-year follow-up emerged as a pivotal determinant of reduced outcomes in the rhythm control group[134]. The protracted inclusion period in this trial indicates a selected patient cohort. However, the positive effect of rhythm control has been demonstrated also in other analyses[135–137]. Yet, important questions remain, including defining the parameters of "early" and "successful" rhythm control, as well as determining the optimal timing and selection criteria for AAD or ablation.

1.8 Pharmacological rhythm control: Antiarrhythmic drugs with focus on sotalol

1.8.1 Background and classification

With the advent of clinical use of continuous Holter recordings in the 1960s, ventricular arrhythmias were recognized as causes of death in patients with myocardial infarctions and small cardiac scars observed during autopsy. This realization prompted the development of drugs targeting cardiac arrhythmias. The AADs were classified based on their primary effects on Na^+, K^+ and Ca^{2+} channels, which influence the action potential in cardiac myocytes. The original classification, proposed by Miles Vaughan Williams in 1970[138,139], is still in use, although it has been updated over time as the understanding of the various actions AADs have on multiple ion channels and their regulation has advanced[140,141].

The Vaughan Williams classification[139,140] includes:

1. *Class 1. Na^+-channel blocking agents:* Subclassified based on their degree of Na^+-channel block: *1a* (moderate blocking effect), *1b* (weak), and *1c* (marked). These agents reduce the slope of the action potential phase 0 while affecting the effective refractory period (ERP), subsequently elevating the electrical threshold. They also have K^+-blocking effects. They are generally avoided in ischemic heart disease.
2. *Class II. Beta-adrenergic inhibitors:* Nonselective or selective beta1-adrenergic receptor inhibitors. These agents reduce sinus node pacing rates and slow atrioventricular node conduction. They also reduce myocyte automaticity and triggered activity.
3. *Class III. K^+-channel blockers:* They prolong the action potential repolarization and lengthen ERP by blocking repolarizing currents, thereby prolonging the refractory period in the myocardium.
4. *Class IV. Ca^{2+} channel blockers:* These agents reduce heart rate and conduction, particularly within the atrioventricular node but also sinus node.

1.8.2 Antiarrhythmic therapy with focus on sotalol

Sotalol was initially described in 1965 and entered clinical use in the 1980s[142]. Originally employed as a pure beta-blocker, its effects were studied in rodents and guinea pigs. However, Vaughan Williams reclassified it as a Class III AAD in 1970 upon observing repolarization prolongation[143,144]. Sotalol is a racemic mixture of two isomers, where the l-isomer has a non-selective beta-blocking effect, and has been shown, in animal models, to exert effects typical of beta-blockers[145]. The d-isomer of sotalol impacts Ikr in a suppressive way and has demonstrated efficacy in terminating AF by prolonging the AERP and the wavelength for reentry in canine models[146,147]. It is important to note that sotalol is a drug with reverse use dependence, meaning that sotalol's Ikr-blocking effect is most pronounced at slow HR[148]. The mechanism remains unclear, but a potential accumulation of Iks may occur at slower HR, increasing risk of ventricular arrhythmias[149].

1.8.3 Sotalol in prevention of AF recurrence

All AADs have preventive effects on AF recurrence, however, the proportion of AF relapse after CV is high even in patients with AAD treatment. Most comparative studies on the efficacy of sotalol in patients with AF were conducted 15-25 years ago.

The initial studies on sotalol treatment demonstrated a modest AF preventive effect and proved its dose-dependency. In 1991, Benditt et al. published a trial involving patients with paroxysmal AF treated with sotalol or placebo[150]. A total of 184 patients received sotalol in doses ranging from 80-160 mg twice daily, and the time to the first recurrence was 25 days on placebo compared to 111, 226, and 172 days depending on the dose of sotalol, illustrating the dose-dependent effect of sotalol. In 2001, in a comparison between sotalol and bisoprolol, Plewan et al. found a similar rate of AF recurrence after CV (41% vs. 42%, ns) at one year[151]. The doses of bisoprolol (5 mg/day) and sotalol (160 mg/day) were modest in this unselected population. Since doses above 160 mg per day are usually needed to achieve sotalol´s class III effect, this could have contributed to the similar efficacy to the pure beta-blocker[152]. In the same year, Bellandi et al. demonstrated less AF recurrence at one year on sotalol compared to placebo (27% vs. 67% on placebo)[153]. Expectations were optimistic for the new AAD.

During the following years, 2004-2006, a couple of randomized studies were published, comparing sotalol to different AADs and placebo, and relatively soon they were included in a high-impact meta-analysis that revealed the moderate effectiveness of AADs in preventing the recurrence of AF after CV[154]. Pooled recurrence rates at one year were 71-84% in controls and reduced to 38-68% with AADs[154,155]. The efficacy was similar between different AADs except for amiodarone, which is more effective in preventing AF relapse, although its frequent side effects can reduce compliance to as low as 31%[156-159]. In the case of reduced EF, amiodarone is the only viable option[10].

When looking at sotalol studies in detail, encompassing 33-383 patients overall, they have different endpoints concerning AF recurrence, compromising comparisons between the studies (Table 1). Some trials had the time to first mean or median recurrence as endpoint, ranging from as short as 28 days to 74 days, whereas mean follow-up was 254 days in the SOPAT trial (Table 2). Higher recurrence rates were observed in those trials where AF was persistent at inclusion[158,160]. The comparator was placebo in all studies, but AADs such as quinidine and verapamil (the PAFAC and the SOPAT trial)[161,162] , azimilide (the A-COMET II trial)[160] and amiodarone (SAFE-T and Vijayalaksmi et al.)[157,158] were also used for comparison. Compared to the other AADs, sotalol was consistently better than placebo, indifferent, or superior to all AADs except amiodarone. Today, recommended AADs according to European and American guidelines for

rhythm control are dronedarone, propafenone, flecainide, or sotalol in absence of structural heart disease[10,163].

Table 1 Recurrence of AF in sotalol studies included in a meta-analysis.

	A COMET II 2006	**PAFAC 2004**	**SAFE-T 2005**	**SOPAT 2004**	**Vijayalakshmi 2006**
Sotalol/placebo n	223/224	383/88	261/132	264/251	33/23
Sotalol dosage mg	160 x 2	160 x 2	160 x 2	160 x 2	160 x 2 7 patients: 80 x 2
Median days to relapse of AF Sotalol/placebo	28/12	102/16	74/6 (ITT) 209/13 (PP)	162/58	NA
Total AF recurrence or discontinuation within 12 months Sotalol/placebo (%)	6 months only: 62/84	67/83	68/87	60/84	6 months only: 61/84
Abbreviations: AF, atrial fibrillation; n, number of patients; mg, milligram; ITT, intention to treat; PP, per protocol; NA, not available.					

1.8.4 Mortality and adverse events in sotalol trials

The isomer d-sotalol, acting purely as a potassium-channel blocker without clinically significant beta-blocking activity, demonstrated increased mortality in heart failure patients post-acute myocardial infarction[164]. The d,l-isomer of sotalol, which possesses a beta-blocking activity as well as a Ikr-blocking effect, has exhibited fewer associations with ventricular arrhythmias and mortality. Its use was established in 1982, when d,l-sotalol was compared to placebo in 1456 patients post-myocardial infarction patients. After one year, the mortality rate was 18% lower in the sotalol group, a difference not deemed significant. However, re-infarction rates were significantly lower, 41% ($p<0.05$), an effect that was attributed to the beta-blockade[165].

Mortality data regarding sotalol in patients with AF primarily relies on the meta-analyses described above performed in patients after CV. While mortality was not significantly increased in sotalol patients compared to placebo in the individual studies, the meta-analysis demonstrated an elevated risk of death (Figure 5). The meta-analysis included a total of 1,164 AF patients under sotalol treatment, and mortality was increased with a relative risk (RR) of 2.23 (95% CI 1.03-4.81) compared to placebo (Table 2)[154]. Trials by Benditt, Bellandi and Plewan were excluded from the meta-analysis due to patients not undergoing CV, short follow-up duration, unclear treatment allocation, and non-blinding in the Plewan trial. These initial individual studies did not indicate an increase in mortality. The

meta-analysis underwent updates in 2012, 2015, and 2019, incorporating new studies on dronedarone but not on sotalol[166–168].

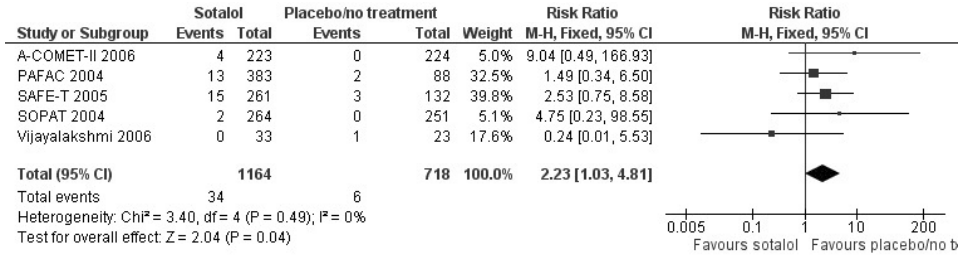

Figure 5 Mortality in studies on sotalol included in a meta-analysis. Published with permission from Lafuente-Lafuente, Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. Cochrane Database of Systematic Reviews. Copyright ©2016, John Wiley and Sons.

However, it is important to note that the trials included were designed to assess AF recurrence outcomes, not mortality. The control groups were smaller than the AAD groups in four out of five trials, and since most trials followed patients until AF recurrence, the follow-up duration was shorter in the control groups, resulting in shortened surveillance time[150,151]. Furthermore, both control and sotalol groups included patients with CHF (Table 2).

Table 2 Details of mortality/serious adverse events/prevalence of congestive heart failure and follow-up duration in sotalol studies

		A COMET II 2006	PAFAC 2004	SAFE-T 2005	SOPAT 2004	Vijayalakshmi 2006	Total
Sotalol	Dead/total (%)	4/223 (1.8)	13/383 (3.4)	15/261 (5.7)	2/264 (0.8)	0/33 (0)	34/1164 (2.9)
Placebo	Dead/total (%)	0/224 (0)	2/88 (2.3)	3/132 (0.8)	0/251 (0)	2/23 (8.6)	7/718 (1.0)
Serious adverse events of interest n (% sotalol)		TdP 0	TdP 9 (2.3) Syncope 3 (0.8)	TdP 1 (0.4)	TdP 0 Syncope 2 (0.8)	TdP 0 Syncope 0	TdP 10/1164 (0.9) Syncope 5/1164 (0.4)
NYHA Class included		NYHA I-III	NYHA I-III	NYHA I-II	NYHA I-III	NYHA I-II	
CHF % of all patients		48%	60%	27.6%	6.2% had EF<45%	3 %	
LV function		27% had EF<40%	FS: 30 ± 12%	EF: 0.52 (± 0.12)	EF: 0.62 (± 0.11)	EF: 0.40	
Follow-up duration Sotalol/Placebo		6 months completed by 33/15 %	Median: 102/16 days	12 months completed by 85/80 % Total patient-years: 298/106	Mean: 254/197 Continuation 12 months: 57/41%	6 months completed by 53/42 %	

Abbreviations: n, number of patients; CHF, Congestive heart failure; LV, Left ventricular; FS, Functional shortening (normal range> 25%); EF, Ejection fraction (normal range >55%)

In detail, follow-up duration was notably short in the PAFAC trial. The median follow-up time was 102 days for sotalol patients (n=383) and 16 days for the placebo group (n=88). In this time, mortality was 3.4% in sotalol-treated patients compared to 2.3%. Notably, 3.8% of sotalol patients (10 out of 383) experienced TdP. Among the sotalol patients, 59% had CHF, with NYHA IV being the only exclusion criterion[161]. In the A-COMET study, three deaths were classified as arrhythmic, although no TdP was found in the sotalol group. There were no deaths in the placebo group. However, the follow-up was brief, with only 15% in the placebo group completing the 26-week study period. Within the sotalol group, 48% had CHF, and 10% had EF below 40%[160]. Similarly, the SAFE T study reported 15 deaths in the sotalol group compared to three deaths in the placebo group. Among the patients who actually received their assigned study drug, there were 10 deaths in the sotalol group. After adjusting for the duration of the follow-up, the mortality ratio was 1.8 in the sotalol group compared to the placebo group (p=0.11). Among sotalol patients 27.6% of patients had CHF[156]. In contrast, in the SOPAT study, there were two deaths in the sotalol group. However, these were not considered related to the treatment. The only exclusion criterion was NYHA class IV, and among sotalol patients, 6.2% had an EF below 45%[162].

In summary, heart failure was present in many patients in these randomized sotalol trials. The extent to which mortality is increased in sotalol treatment for AF in patients with structurally healthy hearts remains not fully understood.

1.8.5 Comparisons between sotalol and other AADs

Contemporary comparisons between sotalol and other AADs are limited. Prospective, randomized studies focusing on AF patients with mortality outcome are lacking. However, register-based data have shown similar mortality rates between patients selected for different AADs without an increase compared to no AAD[169,170]. In August 2023, Pundi et al. published a retrospective comparison involving 11,296 American patients with AF, of which 8,190 commenced sotalol treatment[171]. In comparison to dronedarone, mortality and cardiovascular hospitalization rates were similar, but proarrhythmias, defined as a diagnosis of ventricular arrhythmia or cardiac arrest, were more common among sotalol-treated patients.

Due to a lack of data with class IC AADs, an evaluation of mortality risk was not included in the meta-analysis[168,172]. Dronedarone is the most studied AAD,

represented by 3,283 patients in the meta-analysis, without increased mortality[167]. However, the ANDROMEDA trial, including patients with CHF (n=310 on dronedarone)[173], including one-fourth with AF, as well as the PALLAS trial, including patients with permanent AF (n=1619 on dronedarone)[174], both showed increased mortality with dronedarone treatment. In PALLAS, 70% of patients had a history of CHF. These two studies, ANDROMEDA and the PALLAS, were not included in the meta-analysis since they did not study the recurrence rate of AF after CV.

In summary, comparative studies between AADs are limited, primarily powered to assess AF recurrence prevention rather than mortality. Underlying structural heart disease and CHF seem to result in increased mortality. Comparisons of mortality to placebo are less valid due to substantial differences in follow-up time. Randomized comparative studies with mortality outcome are lacking. The general recommendation for AADs, except amiodarone, is to use them in patients with structural healthy hearts.

1.8.6 Sotalol use in recent decades

The mortality signal observed in the abovementioned studies prompted changes in treatment guidelines. In Sweden, the National Board of Health and Welfare (Socialstyrelsen) revised their national guidelines in 2015, downgrading the recommendation for sotalol treatment to "not recommended" (Class 9)[114]. Notably, even before this policy change, a significant decrease in the prescription of sotalol in Sweden was evident (Figure 6). In contrast, the updated American guidelines in 2019 did not introduce any new recommendations regarding sotalol treatment compared to 2014. However, they underscored that eligible patients should have no underlying health issues[163,175]. Within the ESC guidelines, sotalol continues to be one of the recommended AADs[10].

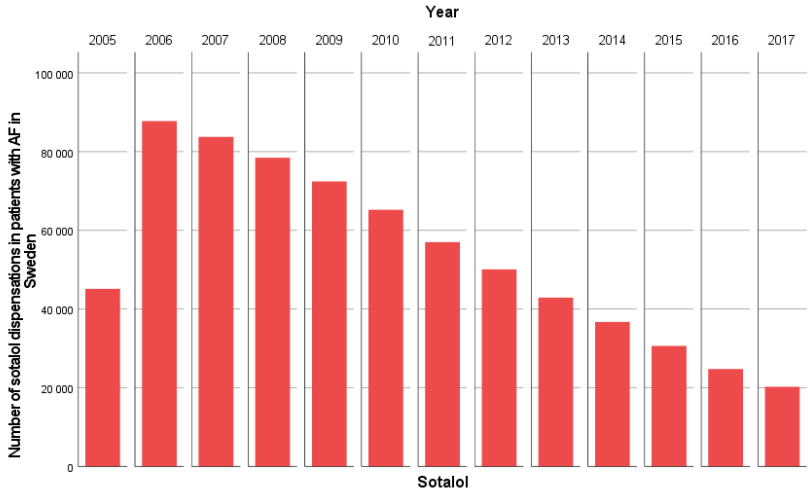

Figure 6 Number of sotalol dispensations in Sweden from 2005 to 2017 in patients with AF. Data from the Drug Prescription Register, held by the Swedish National Board of Health and Welfare.

On a global scale, sotalol remains frequently prescribed for AF prevention[171,176]. A register-based study conducted in the USA between 2014 and 2018, involving 21,921 patients, revealed that amiodarone was the most prescribed AAD (38%), followed by sotalol (23.2%) and dofetilide (19.2%). Less commonly prescribed was flecainide (9.8%) or propafenone (4.8%)[177]. In the USA, sotalol is often initiated in the hospital setting, contributing to increased healthcare expenditures[178]. Flecainide and amiodarone are the most prescribed AADs in large parts of Europe[14,176,179], despite scarce long-term mortality data on the former.

1.9 Torsades de Pointes and sotalol

The most feared adverse event associated with class III AADs, and potentially fatal, is the ventricular arrhythmia known as Torsades de Pointes (TdP), a polymorphic ventricular tachycardia (Figure 7). The French cardiologist Dessertenne first described it in 1966 as TdP, or "twisting of the points", and made a probable connection to QT prolongation[180].

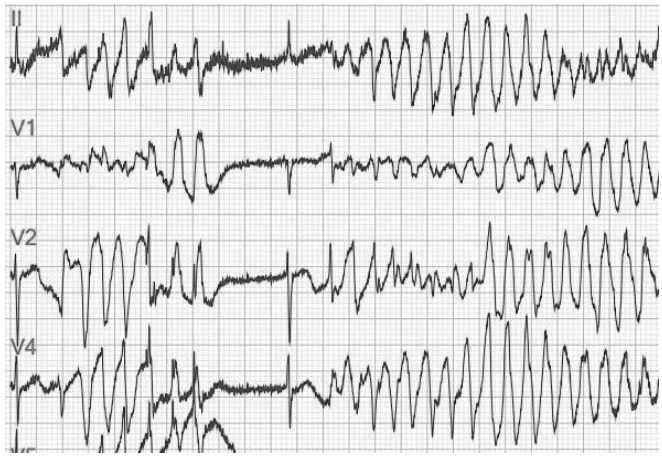

Figure 7 ECG showing TdP

For the individual, prediction of TdP is still difficult. Prolongation of the QTc is the most well-established risk marker for TdP. Even modest QT prolongation may serve as an early marker for serious cardiovascular events and has been proposed for use as one of the parameters in patient triage[181,182]. However, QT prolongation is time-dependent, affecting its sensitivity as a risk marker. ECGs at different time-points reveal varying QTc intervals[183].

In drug-induced TdP, the risk increases for every 10 ms increase in QTc >500 ms, and also if there is a sudden change of QTc >50-60 ms[184]. A distinct range of QTc interval that consistently predicts TdP or sudden death does not exist[185]. Although QTc-prolongation is common in TdP, TdP is uncommon without the influence of other risk factors such as bradycardia, hypokalemia, hypomagnesemia, structural heart disease, high drug concentrations, or concomitant medication with other QT prolonging drugs or loop diuretics[45,48,186,187]. Females and those with renal failure are at higher risk for developing TdP[188,189]. Advanced age is commonly recognized as a risk factor, given its association with QT prolongation; however, the evidence supporting its role in TdP risk is less robust[189–192]. Even after eliminating risk factors, TdP may occur after extended treatment[45,193,194]. Darbar et al. showed that the restoration of SR increases the risk of TdP in patients with persistent AF, although the mechanism remains unknown, and the authors speculated about the role of transmural dispersion of repolarization[195].

The true incidence of ventricular arrhythmias during treatment with AADs remains uncertain for several reasons: the incidence is low, studies are often

small, follow-up periods short, and it can manifest as syncope or sudden cardiac death, and recording the event, even when it occurs, can be challenging. It has been estimated that 10-20% of all sudden cardiac deaths are without structural heart disease[196,197], but the burden of arrhythmic death is unknown. This makes it difficult to estimate the true risk for a given patient.

TdP associated with sotalol treatment was first described in 1979, and since then, the estimated incidence of induced TdP ranges from 1.9% to 4.1%[184,189,194,198]. In a registry-based study of all Swedish AF patients from 2010 to 2015, Friberg identified an increased risk of a composite outcome of death, ICD placement, or ventricular arrhythmia in patients on sotalol compared to dronedarone. There were 107 diagnoses of ventricular arrhythmias recorded in 16,137 patients (0.23 per 100 person years) on sotalol compared to 16 in 8,254 patients on dronedarone (0.16 per 100 person years)[199]. In the more contemporary EAST-AFNET study, one patient out of 1,395 on AADs experienced TdP, with no specification of the given AAD[14].

It remains uncertain whether improved patient selection and control have reduced risks associated with AAD treatment. Clinical risk stratifications schemes have been proposed, possibly in combination with genetic screening and AI generated wearable ECG analysis in the future[186,200].

1.10 QTc diurnality in sotalol treatment

The investigation of QTc diurnal variation during sotalol treatment is relatively underexplored. Hohnloser et al. conducted a study in 1,993 involving 28 patients with previous ventricular tachycardia and administered sotalol. Reduced cardiac function was common, with 13 patients having EF <40%. Two-channel Holter recordings revealed the expected QT prolongation and a retained diurnal variation of QTc in patients on sotalol[201]. Another study by Du Pre et al. retrospectively examined QTc diurnality, measured as a peak-average on a cosine curve, in 39 patients with CHF and previous myocardial infarction. They found increased diurnality in patients with previous ventricular arrhythmias and suggested that the hERG channel was responsible. In addition, they showed a dose-dependent increase in QT diurnality when administering sotalol to nine patients, even when QTc was corrected with the Bazett formula[202]. Altogether, the clinical significance of Ikr blocking on QTc diurnality in patients without CHF remains largely unknown, as well as the potential arrhythmic risk with changes in diurnality.

2 Research aims

This project aimed to enhance the understanding of risks associated with sotalol treatment in patients with a rhythm control strategy for AF.

The specific aims were:

Study I To study if prolongation of QTc diminishes after CV in patients receiving sotalol.

Study II To study if Holter monitoring of QTc following CV can improve the detection of risks in patients treated with sotalol.

Study III To compare death and ventricular arrhythmias among Swedish patients with AF who undergo CV and receive sotalol treatment or beta-blockers.

3 Materials and methods

3.1 Overview of the studies

	Pilot study I	Study I	Study II	Study III
Design	Observational retrospective study	Prospective non-randomized observational study	Prospective non-randomized study	Observational Retrospective nationwide cohort study
Hypothesis	Feasibility, hypothesis generating	QTc is reduced after CV in sotalol-treated patients	Explorative on diurnal variation in sotalol therapy Effects of longer QTc-monitoring	Excess mortality in sotalol-treated patients
Data sources	Medical records	Patient inclusion, medical records	Patient inclusion, medical records	NPR CDR DPR
Patient population	N=65	N=208	N=56	N=32 065
Sotalol treated	N=18	N=104	N=27	N=4 987
Years	2009	2009-2013	2013-2014	2005-2018
Inclusion criteria	Persistent AF, elective CV	Persistent AF, elective CV, SR sotalol/metoprolol therapy		AF, second CV and sotalol/beta-blocker therapy
Statistical methods	Power calculation	Descriptive -Student t test -Pearson's chi-squared test Correlation analysis Linear regression	Descriptive -Student t test and Mann Whitney U -Fishers exact test	Kaplan Meijer and log-rank test Incidence rates Uni- and multivariable regression Propensity score matching
Outcomes	Feasibility, change in QTc	Reduction in QTc	QTc-prolongation and diurnal variation	All-cause mortality
Major bias	Measurement accuracy Lack of control group	Non-randomized No plasma-concentrations	Non-randomized Selection bias	Confounding Selection bias
Conclusion	Feasible, triplicate ECGs better	Sotalol-treated patient's QTc reduced after CV to SR.	One in five patients on sotalol had >20% of heartbeats with QTc>500 ms	No excess mortality in sotalol-treated patients compared to beta-blocker-treated.

Table 3 Overview of study design, population, data sources, bias and outcomes in the studies included in the thesis. Abbreviations: CV, electric cardioversion; N, number of patients; NPR, National Patient Register; CDR, Cause of Death Register; DPR, Drug Prescription Register; SR, sinus rhythm

3.2 Study I and II

3.2.1 Patients

Every year, the cardiology clinic at Stockholm South hospital performs approximately 350 elective CV and 300 acute CV. In 2010, when this research project was initiated, 25% of the scheduled CV patients received sotalol treatment. A local guideline was implemented, mandating ECG monitoring one week after CV to detect early relapse, enabling prompt scheduling of a new CV and reduction in the duration of AF episodes, as well as a thorough QTc surveillance. During these weekly follow-up visits, we observed a shortened QTc interval in some patients on sotalol. These patients exhibited a significantly prolonged QTc interval after CV, which should have led to a dose reduction. Surprisingly, despite no change in dosage, the QT interval had diminished by the following week.

In Study I, our objective was to investigate the QT interval in patients following CV and compare it with measurements taken one week later. The study specifically compared the QT interval in patients on sotalol at two different time points. Additionally, a control group was included, consisting of individuals receiving the most frequently used beta-blocker, metoprolol. Before initiating Study 1, a pilot study was conducted, including the 65 most recent patients who underwent CV, irrespective of their treatment, to determine the feasibility and ECG measurement procedures.

Eligible patients were patients with persistent, symptomatic AF scheduled for elective CV. They were monitored in our out-patient clinic before and after the CV, with a scheduled visit one-week post-CV. Patients were titrated to the highest tolerable dose of sotalol or metoprolol, respectively before CV. To be included in the study, the dose had to remain unchanged during the week before and after CV. The initial sotalol dose was 40 or 80 mg twice daily, with an increase to a maximum of 160 mg twice daily, after control of heart rate, QTc interval and blood pressure. For metoprolol, the target dose was 200 mg. If necessary for rate regulation, digoxin could be added during the titration period, always separated after successful CV. All patients were properly anticoagulated at least four weeks before the CV.

CV was performed in our intensive care unit under sedation with propofol, using up to three biphasic synchronized direct current shocks. Delivering of shocks began at 120-200 J, with an increase to at least two attempts at 200 J if

unsuccessful. Patients were fasted and instructed to take their medication with a mouthful of water in the morning. Only patients who converted to SR and remained in SR when recording a 12-lead ECG one hour after were included in the studies. In Study I, a total of 208 patients were prospectively included between December 2009 and January 2013 at Stockholm South Hospital, Sweden.

Study II extended the QT surveillance after CV with a 24 hour 12-lead Holter recorder. Patients in study II were recruited likewise prospectively, with inclusion starting in August 2013 and concluding in October 2014. Patients on sotalol were included continuously but could only be included when the author or supervisor was on duty and a 12-lead Holter recorder was available. The control group was included similarly, with the additional criterion that patients treated with sotalol were given priority. Inclusion was limited every week due to the availability of two recorders. Patients with QTc exceeding 520 ms post-CV were excluded from participation, as we recommended dose adjustment. In total 56 patients were included in Study II; however, two patients were excluded due to noise and four patients had relapse of AF the first 24 hours, keeping 50 for analysis (Figure 8).

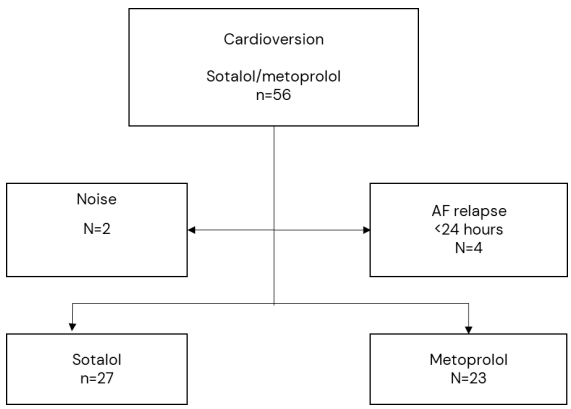

Figure 8 Flowchart of patient inclusion in Study II.

3.2.2 Measurement of QT

In Study I, triplicate standard 12-lead ECG recordings were taken after CV in the intensive care unit and one week later in the outpatient clinic. ECGs were recorded at a paper speed of 50 mm/s and a gain of 10 mm/mV. They were measured manually with calipers, and automized measurements were also utilized for review. All beats were measured in the three ECGs, and mean QT and RR interval were estimated. Interobserver variability of measurements were

investigated after the conclusion of study inclusion by Christer Wredlert, an experienced electrophysiologist assistant, who was blinded for treatment. Intraobserver variability was investigated through blinded re-measurement of ECGs from 45 patients.

The QT interval was measured as previously described (Figure 9)[65]. The longest QT interval with a distinct T-wave was used, usually lead II or V5. The same lead was used at baseline and follow-up in the individual patient. Heart rate correction was performed according to the Fridericia and Bazett formulas.

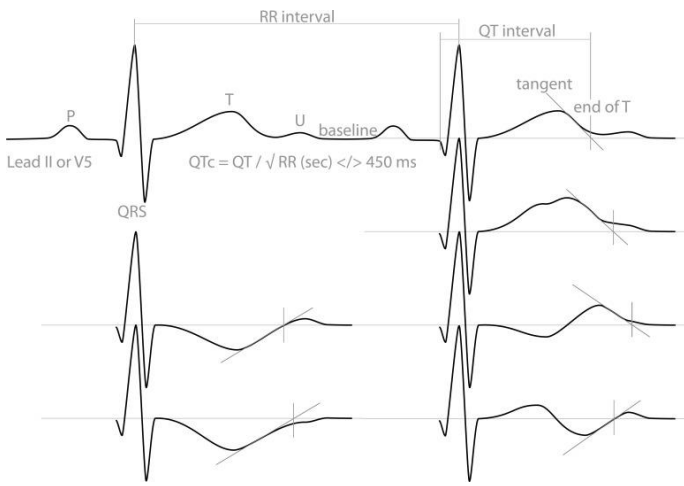

Figure 9 Description of QT measurements, start at the Q or R-wave and end where the tangent crosses the baseline, at the end of the T-wave in normal and abnormal TU morphologies. Published with permission from Vink et al. Determination and Interpretation of the QT interval. Circulation 2018 Nov 20;138(21). Copyright ©, 2018 Wolters Kluwer Health, Inc.

Patients with relapse of AF during the first week after CV were excluded since QT measurements in AF are challenging due to the varying RR-intervals, and the statistical variability would be substantial[64]. Initially, 131 patients with sotalol were included, with a 21% dropout rate due to AF relapse or dose adjustments, resulting in a retention of 104 patients. Metoprolol patients were subsequently enrolled until a similar sample size was achieved.

In Study II, 12-lead Holter ECG recordings were obtained with a continuous 12-lead digital Holter recorder. The recorder was hooked up one hour after CV with 12 electrodes connected to it, creating ECG data for 22-24 hours in every patient, stored on a memory card in the recorder. The measurements were more automized in the iCOMPAS software, automatically creating RR and QT intervals from every heartbeat (Figure 10). The ECGs and annotations were manually

overlooked, and more in detail when there were noise or alerts of arrhythmias. The big amount of raw data, in total 5,583,100 heartbeats, demanded less manual measurement. All heartbeats, except for obvious ectopic beats or noise, were measured regarding RR and QT-interval, as well as extended measurements of the peak and end of p-wave and t-wave.

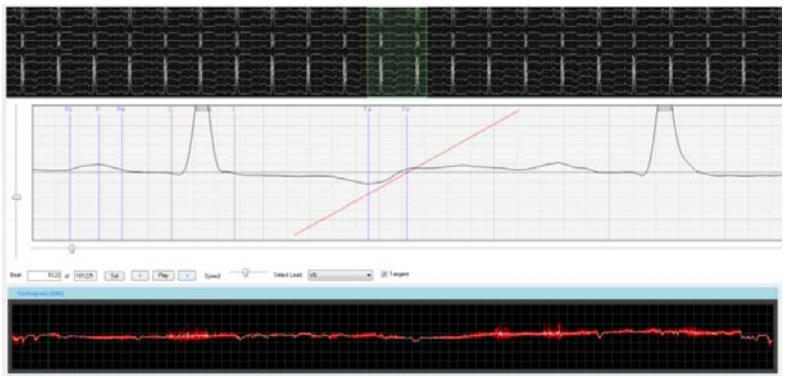

Figure 10 Example of automized QT measurement in Icompas

3.2.3 QT clocks

To achieve effective management and interpretation of the large volumes of data from the Holter recordings, we used a new method, created by Alex Page: the QT clocks[203]. The QT clock presents the QTc values plotted around a 24-hour clock. This visualization technique offers an immediate overview of the QT interval variation in individual patients or groups of patients throughout the day and night (Figure 11).

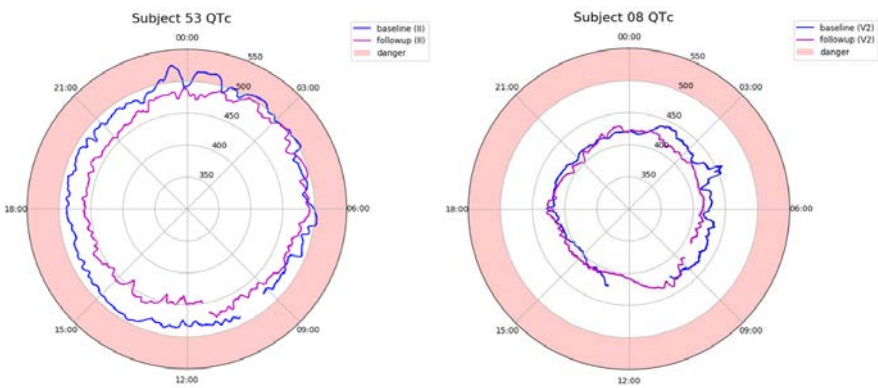

Figure 11 Example of QT clock in two individual patients with two recordings each. Notice the 24-hour clock.

3.2.4 Power calculations

Study I

Before conducting this study, a retrospective pilot study was performed. 65 patients who had undergone CV with routine ECG recording were retrospectively examined. QTc measurements were obtained from a single recorded ECG and from the ECG taken in the outpatient clinic one week later. Eighteen out of 65 patients were treated with sotalol (Figure 12). Among these, six out of ten patients had prolonged QTc after CV that had reduced by more than 30 ms one week later.

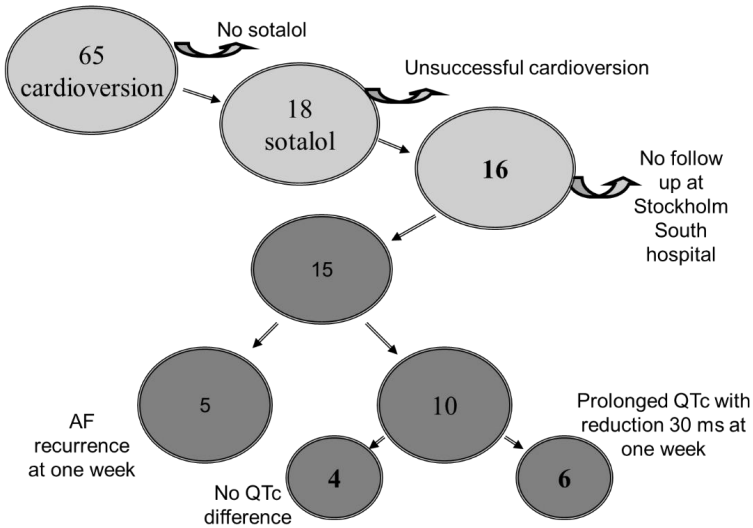

Figure 12 Pilot study to Study I. Flow chart of patients cardioverted on sotalol treatment.

The pilot study formed the basis for the power calculation, including prediction that 25% of patients would relapse into AF during the first week and be excluded. To achieve 80% power and a significance level of 0.05, we needed to include 120 patients in the study to observe a difference in QTc exceeding 30 ms in 25% of patients on sotalol, while this difference would only be seen in the 5% of the control group. Since it was unknown if QTc would be reduced also in the control group, we decided to include 120 patients in this group also.

Study II

No formal power calculation was conducted for Study II, as it was more exploratory in nature. The primary objective was to investigate the QT interval in

detail after CV using innovative techniques that allowed for comprehensive measurements over a 24-hour period, and to compare this to conventional ECGs.

3.3 Study III

The aim of this study was to compare mortality and incidence of ventricular arrhythmias in patients with a rhythm control strategy for AF and sotalol or beta-blocker treatment.

3.3.1 Cohort creation

The cohort for this study comprised Swedish patients with AF who underwent their second CV and received treatment with sotalol or one of the most prescribed beta-blockers in Sweden: metoprolol or bisoprolol, in conjunction with the CV. Data for this population-based cohort were collected from nationwide registries covering the period from 2006 to 2017. To identify patients with a true rhythm control strategy, only those who underwent a second CV were included. In Sweden, it is common practice to offer patients a first CV, typically while being treated with a cardioselective beta-blocker, even with very mild symptoms. In this study, we aimed to include patients for whom the treating physician identified patients with relapse of AF and indication for a second CV to achieve SR. As controls, the most used beta-blockers, metoprolol and bisoprolol, were selected. The choice of control drug for the study was based on the clinical decision-making process of the physician, and the fact that beta-blockers have no known increased mortality risk. Patients with implantable cardioverter defibrillator (ICD), a diagnosis of ventricular arrhythmias, or a history of resuscitation were excluded to ensure that patients with another cause for sotalol treatment, such as the prevention of ventricular arrhythmias, were not included in the cohort.

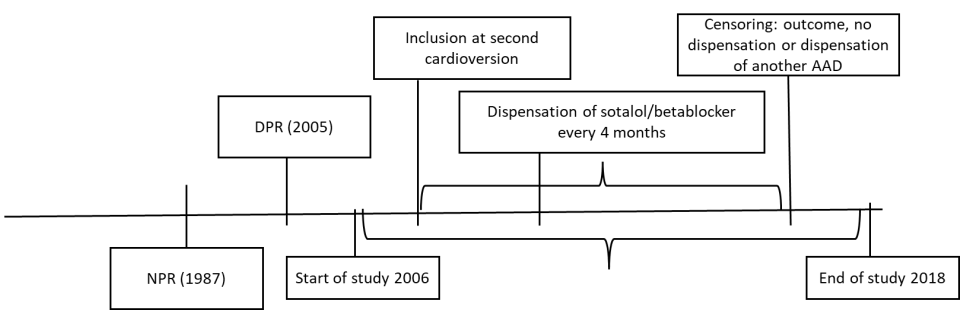

Figure 13 Flowchart of Study III.

3.3.2 Outcome

The primary outcome of this study was all-cause mortality during the treatment with sotalol or beta-blocker. The follow-up period began from the second CV and extended if the patient had regular dispensations of sotalol or beta-blocker. Censoring events included mortality, prescription of another AAD, crossover to the other treatment, or reaching 120 days after the last dispensation of the drug (Figure 13).

The secondary outcomes in this study were twofold. Firstly, a composite arrhythmic outcome was assessed, which included cardiac arrest, resuscitation, sudden death, and ventricular arrhythmias. Secondly, all the individual diagnoses within the composite arrhythmic outcome were analyzed separately.

3.3.3 The registers

Background characteristics and outcomes for Study III were obtained from the National Patient Register (NPR), while the patients' drug dispensations were obtained from the Drug Prescription Register (DPR) as a proxy for drug use (Table 4-5). The NPR contains diagnosis data from all Swedish hospitals, including both inpatient and outpatient clinics, dating back to 1987, while the DPR provides drug information starting from 2005. However, it is important to note that primary care diagnoses are not included in NPR. All diagnoses before index were collected, along with drug use information from the 12 months preceding the index date. After index, outcome diagnoses were used as well as drug consumption.

The gain further insights into the cause of death, the Cause of Death Register (CDR) was utilized. These registers, including the NPR, DPR and CDR, are managed by the Swedish National Board of Health and Welfare (www.socialstyrelsen.se), which links these registers together using unique civic identification numbers assigned to all permanent residents in Sweden.

Table 4 ICD-codes

		ICD-10 or procedural code beginning with:
Main arrhythmic outcome	Sudden cardiac death Cardiac arrest, unspecified	I461 I469
	CPR	DF028, I460
	Ventricular fibrillation or ventricular tachycardia	I490, I470, I472
	ICD-10 or procedural code beginning with:	
Cardioversion (CV)	DFO10, DF026, DF027	
Paroxysmal atrial fibrillation	I480	
Ventricular arrythmias	I490, I470, I472	
Ablation	FPB, DF003	
Covariates in multivariable regression and for background characteristics before index:		
Peripheral arterial disease	I70-73	
Intracranial hemorrhage (ICH)	I60, I61, I62, I690, I691	
Gastrointestinal bleeding	K226, K290, K625, K661, K920-2, I850, I983, K25-28	
Urogenital bleeding	N02, R319, N939, N950, N501A	
Bleeding: composite of ICH, Gastrointestinal and Urogenital		
Ischemic stroke or TIA	I63, I64, I693, I694, G45	
Emboli	I74, I26, I801, I802	
Heart failure (CHF) and valvular disease	I50, I05, I34-I39, Q232, Z952-3	
Hypertension (HT)	I10-15	
Ischemic heart disease (IHD including myocardial infarction)	I20-I25	
Diabetes	E10-14	

Table 4 ICD-codes continued

Alcohol	E244, F10, G312, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Liver disease	K70-77, JJB, JJC
Chronic kidney disease (CKD)	N17, N19, DR016, DR024, KAS00, KAS10, KAS20
Chronic obstructive pulmonary disease (COPD)	J43-44
Thyroid disease	E00-07, E890
Pacemaker and ICD	Z450, Z950, FPE, FPG, DF016 (Only FPG for new implanted ICD)
Dementia	O00-O03
Depression, anxiety	F32, F41
Sleep apnea	G473
Abbreviations: ICD, international classification of diseases, 10th revision.	

Table 5 ATC-codes

	ATC-code beginning with:
Study drugs	C07AA07: Sotalol C07ABO2. Metoprolol C07AB07: Bisoprolol
Other beta-blockers, digoxin and antiarrhythmic drugs:	C07AA05: propranolol CO7AG02: Carvedilol C07AB03: atenolol C07FB: Beta-blocker in combination with calcium channel blocker C07AG02 C01A: Digoxin C01BA03: Durbis, disopyramide C01BC04: Flecainide C01BD01: Amiodarone C01BD07: Dronedarone C08D: Verapamil, cardizem
Antihypertensive drugs including diuretics:	C02D: Old antihypertensive drugs, seldom used. C02CA: alfadil C02DE: Calcium channel blockers (old) C02L, C02N: Anti hypertensive combinations, seldom used. Diuretics: C03AA, C03AB, C03C, C03DA01-04 Calcium channel blockers: C08CA: amlodipine, felodipine
ACE-inhibitors, ARBs	C09A, C09C, C09B, C09D, C09DX04
Lipid lowering	C10
Antidiabetics	A10
Anticoagulants: DOAC and Warfarin	B01AE07, B01AF01, B01AF02, B01AF03, B01AA03
Platelet inhibitors including aspirin	B01AC06, B01AC
ATC: anatomical therapeutic chemical; ARBs: angiotensin receptor blockers; DOAC: Direct oral anticoagulants.	

Statistics

3.3.4 Study I-III

Continuous, patient-related variables were expressed as mean ± standard deviation (SD) if normally distributed, otherwise as median with interquartile range (IQR). Students' t-test was used to test the differences between groups after assessing statistical normality using a combination of visual inspection of histograms and the Kolmogorov-Smirnov test, while the Mann-Whitney U/Wilcoxon test was used if criteria for normality distribution were not met, typically in age and several ECG-parameters. Categorical variables were expressed as absolute and relative frequencies and compared using Pearson's chi-square in Study I and III, while the Fisher exact test was used in Study II. A two-sided p-value less than 0.05 was considered significant. Multivariable linear regression was used to test the association between baseline characteristics and the reduction in QTc in Study I. After exclusion of patients with missing values, 199 patients remained, and a modified Akaike Information Criterion was used to select variables predictive of the reduction in QTc.

Most analysis were performed using SPSS version 22 and 25 (IBM, Corp, Armonk, NY). In Study I, Pearson correlation was used to estimate the similarity between different ECG measurements, and this was done in Excel. The regression analysis in study I was done by the R-package MASS.

3.3.5 Study III

To find comparable patient groups chosen for treatment with sotalol or beta-blocker, a propensity score was calculated. The propensity score included all available variables that were believed to influence the likelihood of receiving sotalol or beta-blocker treatment. Patient age, gender, diagnosis of comorbidities and cardiovascular drugs prescriptions were included (Table 4-5). The propensity score was estimated as the predicted probability of treatment based on a logistic regression model. A one-to-one matching was employed, where pairs of one sotalol-treated and one beta-blocker-treated patient were formed. The matching process aimed to ensure that matched subjects had similar propensity score values, using a strict caliper of 0.001 or less. The matched pairs were then used for subsequent analysis.

In addition to absolute results, incidence rates (IR) and the comparative incidence rate ratios (IRR) were calculated for mortality and secondary endpoints. The sum of the patient's time of follow-up was used as denominator.

To analyze the outcomes in both overall cohort and in the propensity score matched cohort, we used two models: (1) a crude model to study the association between treatment (sotalol and beta-blocker) and time to mortality and (2) an adjusted model using Cox regression, where we adjusted for age, gender, comorbidities before index, and cardiovascular drugs used before index. We calculated hazard ratios for mortality and secondary outcomes. Testing for the assumption of proportional hazards was done and the assumptions were not violated. Both models were also used in subgroup analysis, with the addition of an interaction variable to test if the association between treatment and mortality was the same within the subgroup. Sensitivity analyses were performed to test the robustness of the results with and without patients with congestive heart failure and with different calipers for the propensity score matching, without significant impact on results. Most analyses were done in IBM SPSS Statistics (Version 28.0.0.1), while the propensity score matching and figures for Study III were done using R Studio 2022.0.3.

3.4 Ethical considerations

This research project emerged from a clinical inquiry regarding the safety of AF treatment, particularly during a period when sotalol was prevalent in use. The possible benefit of this project was to provide new evidence regarding sotalol's risk in AF treatment and the significance of the QT interval as a risk marker in clinical practice. While guidelines, which evolved during this project, acknowledge the arrhythmic risk following sotalol treatment, the drug is still used worldwide[171,177]. All treatment options for symptomatic AF, including ablations and other AADs, inhibit adverse events and risks. Increased understanding of risks with sotalol treatment would benefit patients and contribute to averting potential harm.

In Study I and II, the recruited patients received oral and written information. They could withdraw from the study at any point. All patients were treated equally, and patients were asked to participate regardless of sex, age, religion, or other personal matters. Patients who did not want to participate were monitored according to routine. Participation only required extended monitoring; all other healthcare provided was according to routine. The data in both studies was de-

identified as early as possible, immediately after the ECG recordings were collected and the data entered the clinical research form.

In the registry-based Study III, no individual information was given to the individuals in the nationwide cohort of AF patients. This was a retrospective trial of epidemiological nature, and all data were de-identified. All patients in Sweden, without deselection, are included in the used registries that adheres to privacy regulations and maintains the anonymity of the individuals involved.

The studies included in this thesis were conducted in accordance with the Declaration of Helsinki[204] and approval was obtained by the Ethics Committee in Stockholm. We intended from the start to publish our results in scientific papers regardless of the results and the syntaxes conducted can be accessed by reasonable request. Overall, we considered the risks of participating in these trials very low and exceeded by the possible benefits of expanded knowledge.

4 Results

4.1 Study I

The 208 patients included in this study did not differ in terms of mean age; 66 years in sotalol-treated patients vs. 65 years in beta-blocker-treated patients, gender distribution (73 vs. 74%) or prevalence of ischemic heart disease (14 vs. 15%). However, there was a notable difference in ejection fraction, with sotalol-treated patients having a mean ejection fraction of 52% compared to 47% in beta-blocker-treated patients. Mean dose of sotalol was 247±74 mg and of metoprolol 158±58 mg.

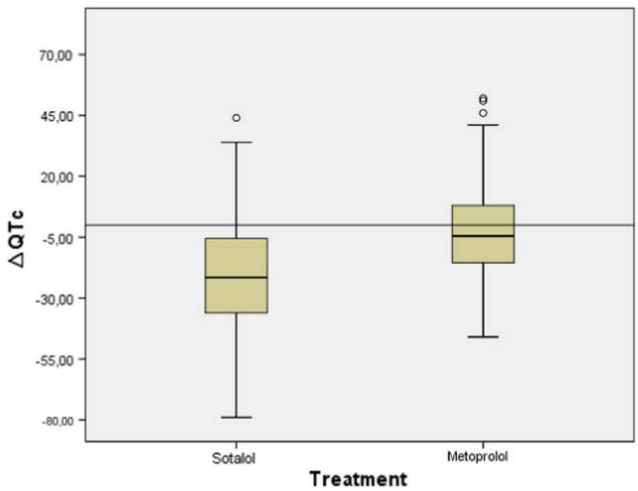

Figure 14 Change in corrected QT interval (ΔQTc) between 1 hour and 1 week after CV of atrial fibrillation. The reduction in the QTc interval from 1 hour to 1 week after CV was more pronounced in patients on sotalol despite unchanged dose and similar heart rate than in patients on metoprolol. Lenhoff et al.[205] Published with permission, Copyright © 2016 Heart Rhythm Society. Published by Elsevier Inc. All rights reserved.

The mean QTc interval was reduced in sotalol-treated patients during the week after CV (-20.3 ±24 ms), whereas no significant change was observed in metoprolol-treated patients (-2,5 ±18 ms) (Figure 14). Among patients treated with sotalol 25% exhibited a QTc >480 ms after CV, in contrast to 2% of patients treated with metoprolol. Prolonged QTc after CV was associated with greater reduction in QTc. An association was also observed between better renal function and a more substantial reduction in QTc. This relationship was stronger when calculated via the MDRD formula, which incorporates age, gender, race, and creatinine, compared to using creatinine alone (Figure 15). However, no

correlation was evident between renal function and the absolute prolongation of QTc after CV. Due to the absence of information regarding sotalol concentrations, the timing of ECGs was employed as a surrogate, without any correlation to changes in QTc.

While the HR remained unchanged within groups over the week, sotalol-treated patients exhibited an overall lower HR compared to metoprolol-treated patients (55 vs 58 bpm after CV and 56 vs. 59 bpm at one week). No ventricular arrhythmias were detected in the recorded ECGs.

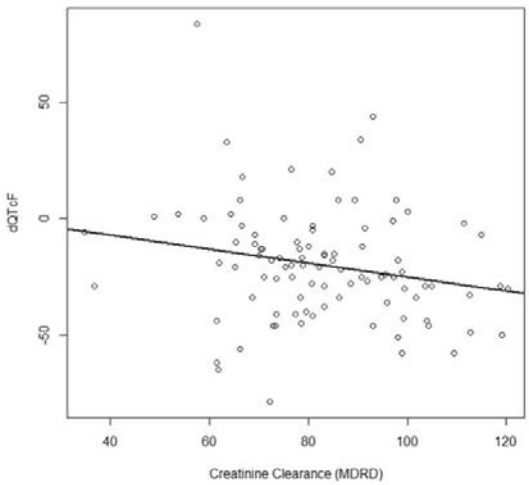

Figure 15 Change in the QTc interval correlated to creatinine clearance in patients treated with sotalol. Creatinine clearance was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Lenhoff et al.[205] Published with permission. Copyright © 2016 Heart Rhythm Society. Published by Elsevier Inc. All rights reserved.

In summary, the QTc interval was reduced during the week after CV in patients on sotalol, despite a consistent sotalol dosage and similar HR.

4.2 Study II

Fifty patients were enrolled in this non-randomized prospective study. In this study population, no significant differences were found in sotalol-treated patients vs. beta-blocker-treated patients in terms of gender distribution (26 vs. 30%), duration of AF (2.8 vs. 2.9 months), IHD prevalence (4 vs. 17%) or BMI (29 vs. 28 kg/m^2). However, notable differences were observed in ejection fraction (54 vs. 48%) and the diagnosis of CHF (0 vs. 30%), with CHF less common in patients receiving sotalol. Additionally, the patients treated with sotalol were younger (65 vs. 69 years).

Heart rate and QTc analysis

HR during AF prior to CV did not differ between sotalol-treated and beta-blocker-treated patients, with mean HR 82 (±16) vs. 83 (±14) bpm, p=0.36. Following CV, as measured on standard 12-lead ECGs, the QTc interval was wider in the sotalol group with mean 452 (±29) ms vs. 419 (±34) ms, while there was no significant difference in HR between the groups immediately after CV [57.3 (±8) vs. 53.2 (±9) bpm, p=0.16].

In the analysis of the Holter recordings, the mean HR over 24 hours was higher in sotalol-treated patients, with mean 61 (±6) bpm vs. 56 (±7) in beta-blocker-treated patients, p=0.04. Both groups exhibited diurnal variations in both HR and QTc (Figure 16). The lowest mean HR occurred during the early morning hours and was higher in patients treated with sotalol [56 bpm (90 % CI 52-60)], compared to beta-blockers [53 bpm (90% CI 50-56)].

The diurnal variation in QTc was most evident in sotalol-treated patients, with the longest mean QTc intervals observed during the night and early morning hours, followed by a subsequent increase until noon (Figure 16, Panel B). This pattern was less pronounced in patients receiving beta-blockers. The maximum mean QTc interval, calculated in two-hour time windows for sotalol-treated patients, was 461 ms (90% CI, 451–472 ms) between 02:00-03:39. In contrast, patients treated with beta-blockers exhibited their longest, but shorter QTc interval during the night [6:00–7:59 (433; 90% CI 419–447 ms)] and early evening [18:00–19:59 (435; 90% CI 423–447 ms)].

Six out of 27 patients (22%) treated with sotalol had >20% of all heartbeats with prolonged QTc >500 ms, occurring predominantly during nighttime, compared to no patient treated with metoprolol. Eight patients treated with sotalol had QTc > 500 ms in any 2-hour time window. Of these patients, two were identified with prolonged QTc by routine ECG after CV.

No sustained ventricular arrhythmias exceeding three heartbeats were observed during the recordings.

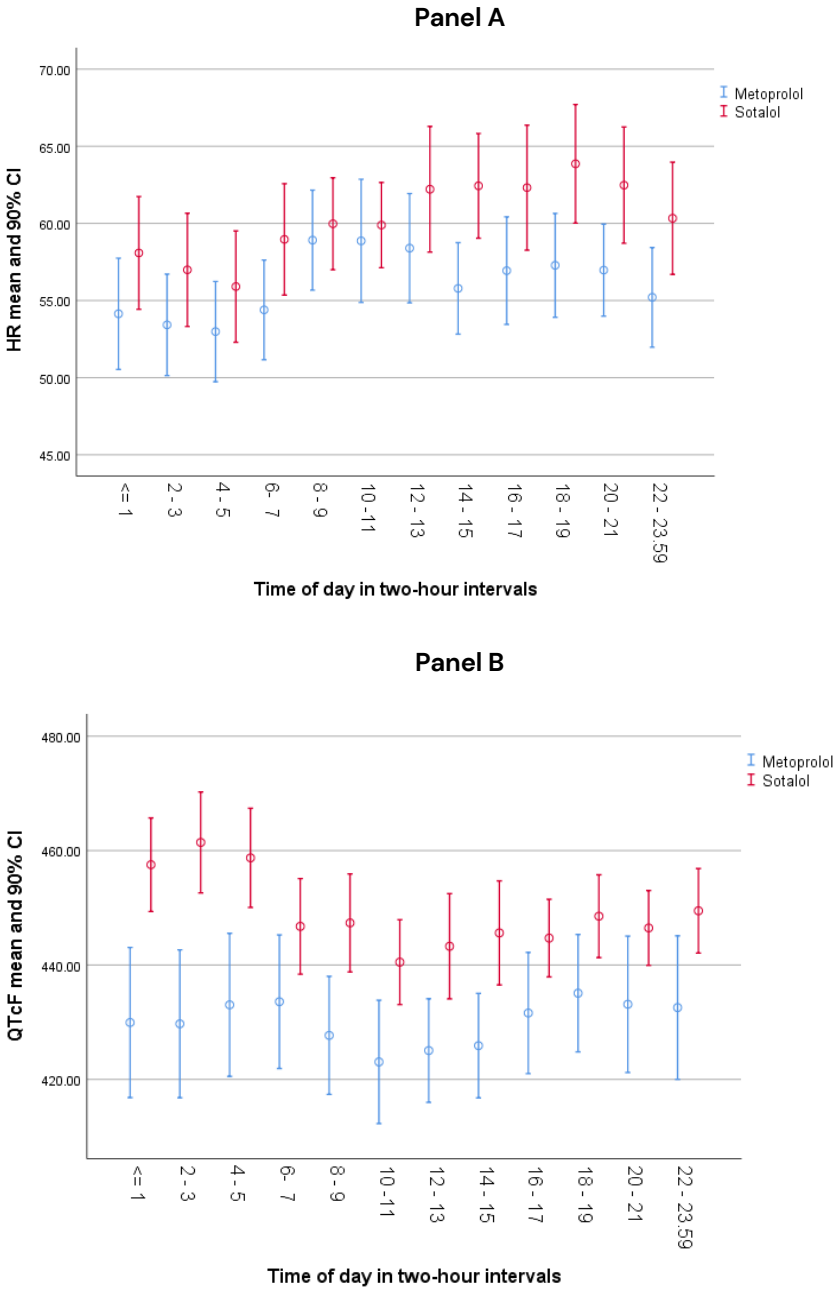

Figure 16 Panel A: Mean HR and 90% CI in two-hour intervals in patients on sotalol (red) and metoprolol (blue) in 24 hours Holter recordings after CV.
Panel B: Mean QTc and 90% CI in two-hour intervals in patients on sotalol (red) and metoprolol (blue) in 24 hours Holter recordings after CV. Published with permission. Copyright © 2021 Lenhoff et al.[206] *Annals of Noninvasive Electrocardiology* published by Wiley Periodicals LLC.

In summary, the 24-hour Holter recordings with QT-measurement immediately after CV demonstrated that QT-prolongation in patients treated with sotalol was frequent. The use of QT clocks provides a convenient visual representation of the individual overview of individual patients' overview of QTc intervals (Figure 17).

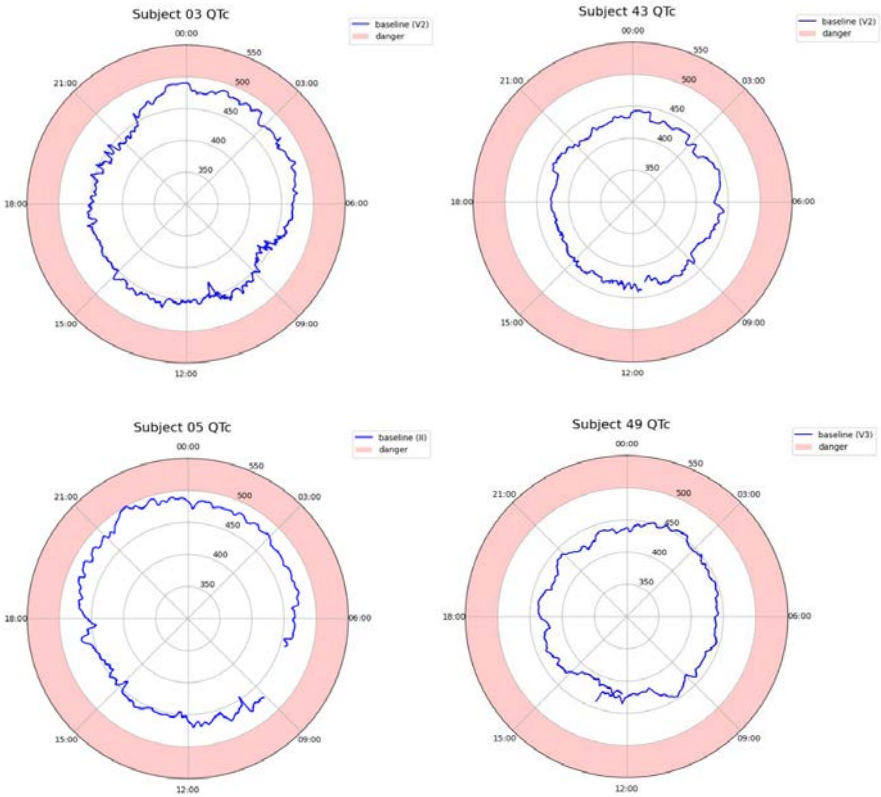

Figure 17 Example of QT clocks. Median QTc in individual patients treated with sotalol (left panel) or metoprolol (right panel) from 24-hour Holter recordings started immediately after CV. Danger zone is marked as QTc>500 ms in this "24-hour" clock.

4.3 Study III

Mortality analysis was conducted using the entire cohort, which comprised 4,987 patients receiving sotalol and 27,078 patients receiving beta-blocker. However, due to noncomparability between the two groups, two propensity score-matched cohorts were established, each containing 4,953 patients. The characteristics of these matched cohorts are summarized in Table 6. The groups were balanced across most categories; however, some differences persisted. Patients receiving sotalol treatment demonstrated a higher incidence of ischemic heart disease (IHD), whereas patients receiving beta-blocker treatment

had a greater prevalence of chronic kidney disease, sleep apnea, and chronic obstructive pulmonary disorder. ACE inhibitors and diuretics were slightly more prevalent in the beta-blocker-treated group, with no difference in the diagnosis of CHF.

Table 6 Background characteristics in propensity score matched cohorts.

	Sotalol	**Beta-blocker**	P value *
	(n=4 953)	(n=4 953)	
Age, years (mean; SD)	67.46 (9.82)	67.68 (9.48)	0.25
Women	1537 (31.0)	1542 (31.1)	0.91
CHA_2DS_2-VaSc score (mean;	2.37 (1.94)	2.37 (1.91)	0.41
Ischemic stroke, TIA	406 (8.2)	374 (7.6)	0.23
Ischemic heart disease	983 (19.8)	879 (17.7)	0.007
CHF	677 (13.7)	702 (14.2)	0.47
Hypertension	2713 (54.8	2742 (55.4)	0.56
Diabetes mellitus	533 (10.7)	505 (10.1)	0.38
OSAS	283 (5.7)	325 (6.6)	0.043
Chronic kidney disease	61 (1.2)	100 (2.0)	0.002
COPD	131 (2.6)	197 (4.0)	0.001
Pacemaker	156 (3.1)	136 (2.7)	0.26
Thyroid disease	329 (6.6)	332 (6.7)	0.90
Malignancy	635 (12.4)	592 (12.0)	0.19
Dementia	7 (0.1)	5 (0.1)	0.77
ACE-inhibitors/ARB	2547 (51.4)	2755 (55.6)	0.001
Digoxin	868 (17.5)	846 (17.1)	0.58
Diuretics	1294 (26.1)	1572 (31.7)	0.001
Statins	1795 (36.2)	1622 (32.7)	0.001
NOAC or Warfarin	3905 (78.8)	4202 (85.6)	0.001
Antidiabetics	432 (8.7)	423 (8.5)	0.75
Aspirin or platelet inhibitors	1902 (38.4)	1405 (28.4)	0.001
N (%) if not otherwise stated. * All p values derived from students´ t-test or chi2 test. Drugs dispensed within 12 months before index. Abbreviations: ARB: Angiotensin receptor blocker; CHF: Congestive heart failure; COPD: Chronic Obstructive Pulmonary Disease; NOAC: Novel oral anticoagulants; OSAS: Obstructive sleep apnea, SD: Standard deviation, TIA: Transient ischemic attack.			

The initial dispensed dose of sotalol was 40 or 80 mg twice daily for 96% of patients. The targeted sotalol dose was 80 mg twice daily in 64% of patients,

while 12% were administered 120-160 mg bid. Nearly 23% received 40 mg twice daily.

During a median follow-up of 173 (IQR 56-589) days, 73 deaths occurred among sotalol-treated patients, while 124 deaths were recorded in beta-blocker-treated patients. This translated to a mortality rate of 1.19 deaths per 100 person-years (95% CI 0.93-1.49) for sotalol-treated patients and 2.01 deaths per 100 person-years (95% CI 1.67-2.39) for beta-blocker-treated patients within the propensity matched cohorts (Figure 18, Table 7). Cardiovascular causes constituted the most frequent reason for death in both treatment groups, with malignancies being the second most common cause. The crude hazard ratio for overall mortality was 0.63 (0.47-0.85) in favor of sotalol treatment (Table 8).

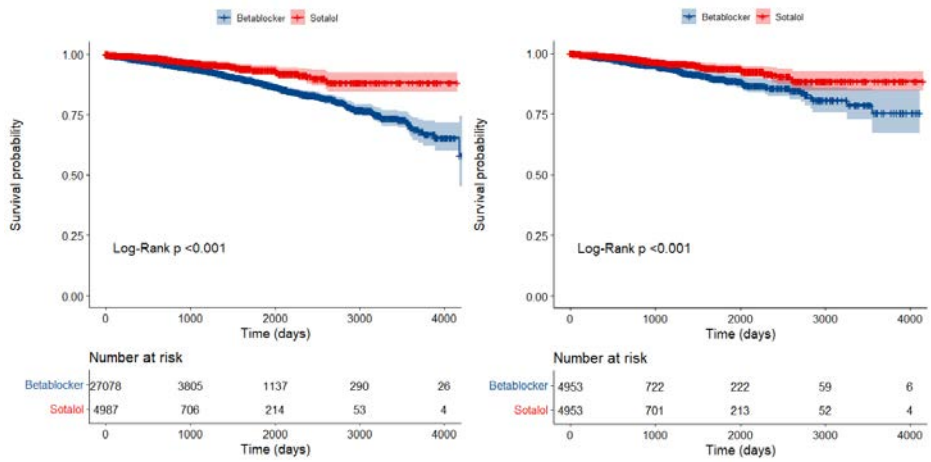

Figure 18 Kaplan-Meier curves with 95% confidence interval for all-cause mortality in patients treated with sotalol or beta-blockers following a 2nd CV of AF. The graphs show that the survival probability is higher for patients treated with sotalol (left), but the difference diminishes when comparing similar patients based on propensity score (right). Panel A: Total cohort (left). Panel B: Propensity-score matched cohorts (right). Lenhoff H et al.[207] Published with permission. © 2023 Published by Elsevier Inc. on behalf of Heart Rhythm Society.

Table 7 Mortality and secondary outcomes. Incidence rates (IR) per 100 person-years.

Total cohort ***Sotalol n=4 987 Beta-blocker n=27 078***			
	Sotalol	Beta-blocker	
	Events per 100 years at risk (IR)		IRR
Mortality	1.21 (0.95-1.52)	2.42 (2.26-2.60)	0.50 (0.39-0.63)
Composite arrhythmic outcome†	2.16 (1.81-2.56)	2.10 (1.95-2.26)	1.03 (0.86-1.23)
Ventricular arrhythmias	1.37 (1.10-1.70)	1.32 (1.20-1.45)	1.04 (0.83-1.31)
Cardiac arrest/death	0.60 (0.42-0.82)	0.69 (0.60-0.78)	0.87 (0.61-1.23)
Survived CPR	0.42 (0.27-0.61)	0.27 (0.22-0.34)	1.53 (0.99-2.37)
Propensity score matched cohort ***Sotalol n=4 953 Beta-blocker n=4 953***			
Mortality	1.19 (0.93-1.49)	2.01 (1.67-2.39)	0.59 (0.44-0.79)
Composite arrhythmic outcome[a]	2.13 (1.78-2.52)	2.07 (1.73-2.53)	1.03 (0.81-1.31)
Ventricular arrhythmias	1.38 (1.10-1.71)	1.26 (1.00-1.57)	1.10 (0.81-1.49)
Cardiac arrest/death	0.55 (0.38-0.77)	0.72 (0.52-0.96)	0.77 (0.49-1.20)
Survived CPR	0.41 (0.26-0.60)	0.25 (0.15-0.41)	1.59 (0.85-2.99)
IR: incidence rate (95% confidence intervals); IRR: Incidence rate ratio, sotalol vs. beta-blocker: [a]Composite of cardiac arrest and sudden cardiac death, ventricular arrhythmias, and survived resuscitation. CPR: cardiopulmonary resuscitation.			

Table 8 Comparisons of outcomes in patients with atrial fibrillation, included at second cardioversion, treated with sotalol or beta-blocker. Crude and adjusted measures are provided.

	Sotalol	Beta-blocker		Univariable (crude measures)		Multivariable (adjusted for all diagnosis, sex, age, and drugs)	
Total cohort Sotalol n=4 987 Beta-blocker n=27 078							
	N (%)	N (%)	p-value	HR	95% CI	aHR[a]	95% CI
Mortality	75 (1.5)	816 (3.0)	0.001	0.50	0.39-0.63	0.66	0.52-0.83
Composite arrhythmic	134 (2.7)	706 (2.6)	0.75	1.03	0.86-1.24	1.10	0.91-1.33
Ventricular arrhythmias	85 (1.7)	443 (1.6)	0.72	1.04	0.83-1.32	1.08	0.85-1.37
Cardiac arrest/death	37 (0.7)	231 (0.9)	0.50	0.87	0.61-1.23	0.99	0.70-1.41
Survived CPR	26 (0.5)	92 (0.3)	0.052	1.54	0.99-2.38	1.79	1.10-2.68
Propensity score matched cohort Sotalol n=4 953 Beta-blocker n=4 953							
Mortality	73 (1.5)	126 (2.5)	0.001	0.59	0.44-0.79	0.63	0.47-0.85
Composite arrhythmic outcome[b]	131 (2.6)	130 (2.6)	0.95	1.02	0.80-1.31	1.01	0.78-1.29
Ventricular arrhythmias	85 (1.7)	79 (1.6)	0.64	1.10	0.81-1.49	1.05	0.76-1.43
Cardiac arrest/death	34 (0.7)	45 (0.9)	0.22	0.76	0.49-1.19	0.77	0.49-1.21
Survived CPR	25 (0.5)	16 (0.3)	0.21	1.59	0.85-2.98	1.74	0.91-3.33

HR: Hazard ratios are reporting sotalol vs. beta-blocker; aHR: adjusted HR, multivariable cox regression; [b] : Composite of cardiac arrest and sudden cardiac death, ventricular arrhythmias, and survived resuscitation; VA: Ventricular arrhythmias; CPR: cardiopulmonary resuscitation.

Concerning the composite arrhythmic outcome, no significant differences emerged between the two treatment groups, each displaying an incidence rate of 2.1 events per 100 person-years (Table 7). Similarly, no significant distinctions were detected when analyzing the separate diagnosis within the secondary endpoint.

As part of the sensitivity analysis, additional assessments were performed. Firstly, the all-cause mortality was evaluated excluding patients diagnosed with CHF, yielding outcomes akin to the main analysis, with a hazard ratio of 0.64 (0.46-0.89). Secondly, a separate analysis was executed on sotalol-treated

patients who were not included in the propensity score matching. Among these 34 patients, a solitary death occurred during the study period. Subsequently, another sensitivity analysis was conducted, comparing propensity score matched cohorts using a less stringent caliper of 0.01. This encompassed all patients receiving sotalol from the entire cohort, matching them with counterparts receiving beta-blocker treatment (n=4,987 in each group). This analysis yielded comparable results, with a hazard ratio for mortality of 0.60 (0.45-0.80).

5 Discussion

This thesis explores the risks and risk markers associated with sotalol treatment for AF after CV, encompassing various clinical aspects from ECG risk factors to long-term safety outcomes. The investigative journey commenced with a study of the ECG and QT interval following CV, focusing on the ECG monitoring already in use in clinical practice. We found a reduction in the QTc interval during the week after CV in sotalol-treated patients, but not in beta-blocker-treated patients. Subsequently, our investigation extended to a continuous analysis of the QT interval through 24-hour ambulatory monitoring after CV, capturing a patient's complete daily life. We observed a high incidence of prolonged QTc interval and a diurnal variation in the QT interval, pronounced in patients on sotalol compared to patients on metoprolol. Thereafter, in the absence of a randomized longitudinal trial on risks with sotalol treatment, we planned a national study utilizing Swedish registries, focusing on mortality outcomes. Despite global variations in sotalol usage that intrigued us, the Swedish registries proved to be a valuable resource. We found, in AF patients after CV, no increase in mortality or ventricular arrhythmias in sotalol-treated patients compared to patients treated with a cardioselective beta-blocker.

5.1 Risk monitoring in sotalol treatment

In this thesis, two studies were devoted to evaluating the QTc interval after CV. Notably were the findings of QTc dynamics following CV, which were most pronounced in patients treated with sotalol. These dynamics appeared to be directly linked to sotalol-induced QTc prolongation, and not to the CV procedure or anesthesia, as they were not observed to the same extent in patients treated with metoprolol.

5.1.1 QT prolongation after CV

The QT-prolonging effect of sotalol is well-established. An increased proarrhythmic risk after conversion to SR, in contrast to persistent AF, have been demonstrated[195,208]. Small studies had suggested that when Ikr-blocking AADs are used for AF, QT prolongation and TdP often occur shortly after SR is restored[209,210]. Previous studies on class III AADs had shown that infusion of almokalant[211], an investigational pure Ikr blocker, induced TdP shortly after conversion to SR, and the extensive QT prolongation was most apparent in SR. Another trial with a pure Ikr blocker, dofetilide, confirmed the increased QT

prolongation in SR hypothesis[209]. This phenomenon was especially notable in patients with bradycardia, and associated with an increased dispersion of repolarization in SR. The mechanisms underlying the QTc prolongation post-CV are still unclear. Different mechanisms have been suggested: increased susceptibility to Ikr inhibition in SR, changes in nervous activity or neurohormonal levels[212], alterations in gene expressions regulating ion channels in the heart of patients with persistent AF[213], increased disparity of repolarization in SR, variations in QTc correction formulas, or their inability to adjust to sudden changes in QTc after a period of tachycardia[40,64]. In Study I, mean QTc after CV was 465±25 ms, supporting previous studies that the immediate period after CV may represent a time of increased proarrhythmic susceptibility due to pronounced QT prolongation.

5.1.2 QT dynamicity after CV

We found a reduction in the observed QTc interval the week post-CV in sotalol-treated patients of approximately 20 ms, compared to 2.5 ms in metoprolol-treated patients in Study I. Patients with the longest QTc interval after CV had the largest reduction, implying that regression towards the mean may have occurred. Interestingly, we found a correlation between normal renal function and a larger reduction in QTc over the following week, although patients with renal impairment were few. However, we did not find a correlation between the difference in QTc and the time of day for ECG, as a surrogate for plasma concentrations. It can be hypothesized that some time in normal SR adjusts the tachycardia-induced changes in repolarization reserve, perhaps via the autonomic nervous system, and normalizes currents of repolarization, thus reducing the susceptibility to sotalol.

Given these findings, we aimed to further investigate this phenomenon using Holter monitoring. The superior capabilities of Holter monitoring in detecting clinically significant QTc prolongation compared to conventional ECGs have been subsequently affirmed by Younis et al., in patients on amiodarone or flecainide, using three-lead Holter recorders[214]. They found that concomitant treatment with beta-blockers predicted longer QTc, perhaps due to bradycardia. The effect of beta-blockers on QTc are somewhat disparate. In inherited LQT patients, beta-blockers have been shown to shorten QTc at higher HR and lengthen it in bradycardia[215]. In our study, with beta-blocking effect due to metoprolol or sotalol, low HR proved the beta-blocking effect in both treatment

groups. However, HR within treatment groups was similar during the week and would not explain the reduction in QTc in sotalol-treated patients.

We observed a more pronounced diurnal variation in QTc intervals among patients on sotalol compared to those on metoprolol. Additionally, patients treated with sotalol had a higher percentage of heartbeats with prolonged QTc, frequently surpassing 500 ms, particularly during the night. This could, at least in part, be explained by sotalol's reverse use dependence. However, the combination of low HR and pronounced prolongation of QTc could potentially predispose susceptible patients to TdP. Recent recommendations have advocated Holter monitoring or repeated ECGs for 48 hours post-CV in patients with risk for QTc prolongation[74,214]. The emergence of wearables and various devices for QT interval measurement is expected to contribute to QT data generation. Tools like QT clocks offer valuable insight into the temporal patterns of QT intervals. Moreover, the potential of artificial intelligence in analyzing ECG or 24-hour monitors for predicting AF and CHF has been demonstrated[200,216,217]. However, its use in QT measurements requires further investigation. Furthermore, the clinical implications of diurnal variation and nocturnal QTc prolongation in sotalol treatment necessitates further research, including longer follow-up periods.

5.1.3 Comparison of Study I and II

A comparative analysis between patients in Study I and II, both undergoing sotalol treatment, revealed that the baseline QTc interval was longer in patients from Study I when compared to those in Study II, despite the latter group receiving a higher sotalol dose (Table 9). This difference may be attributed to the older age of women in Study I, resulting in longer QTc interval. This correlation aligns with previous research indicating an elevated risk of QT prolongation in elderly women, particularly in the presence of renal impairment[189]. Additionally, in Study II, patients with a QTc exceeding 520 ms were excluded in accordance with the study protocol, and dose adjustments were recommended. During the study period, there was an increased focus on monitoring the QTc interval at our clinic, likely raising awareness regarding QTc prolongation.

Table 9 Comparison of patients in Study I and II

	Study I	**Study II**
Sotalol (n)	104	27
HR in AF, bpm (median; IQR)	NA	82 (19)
HR in SR, bpm	55 +8	56 +8
QTc in SR, ms	465 +25	452 +30
Dose of sotalol, mg	247 +74	270 +50
QTc >500 ms (n; %)	12 (11.5)	2 (7.4)
Women, %	27	26
Age in women	70.4 +7	66.6 +6
>70 y old n sotalol (n; %)	30 (29)	7 (26)
QTc in sotalol patients>70 y	473 (27)	479 (29)
Mean; SD if not otherwise stated; n, number; y, years		

Risks with sotalol treatment

In the nationwide cohort in Study III, focusing on AF patients pursuing a rhythm control strategy, we discovered that patients using sotalol, when compared with cardio-selective beta-blockers, did not face a higher risk of mortality or ventricular arrhythmias. Despite the clear reduction in sotalol use observed in Sweden, sotalol remains widely utilized globally as an AAD for AF [170,177].

Due to the mechanism of action in APD prolongation due to Ikr block, as seen on ECG as QTc prolongation, sotalol may trigger the potentially lethal ventricular arrhythmia, TdP. Aggregated data from various cohorts, including patients with structural heart disease, have estimated the incidence of sotalol-induced TdP to be as high as 4.1%[155,184,198]. In more contemporary Swedish and American register-based cohorts, the diagnosis of ventricular arrhythmias was set at 0.23 and 3.4 per 100 patient-years, respectively[171,199], as compared to 1.38 (95% CI 1.10-1.71) per 100 patient-years in our findings. Our results show a lower incidence compared to previous meta-analyses, where 5.1% suffered from pro-arrhythmias, although that endpoint also included QT prolongation and bradyarrhythmia[166,168]. However, assessing these different incidences is complicated, particularly in registry-based studies, as the diagnosis of ventricular arrhythmias can vary, ranging from three consecutive ventricular heartbeats on a Holter recording to a hemodynamically unstable situation. Moreover, increased awareness may have led to extended monitoring for patients with known Ikr blocking drugs. In the USA, sotalol is usually initiated in the hospital, where patients with low risk for further treatment are selected. In an attempt to reduce the length of hospital stay,

intravenous sotalol with a loading dose of 125-135 mg have been tested in combination with mobile outpatient telemetry for 72 hours[218,219]. In this surveilled upload phase, approximately 20% of patients underwent dose adjustments for sotalol, most often due to bradycardia. In the larger study, including 240 patients of which 20% had CHF, one patient in the control group receiving per oral sotalol loading dose experienced QTc prolongation resulting in TdP. Additionally, three patients, two of whom received intravenous loading, had non-sustained ventricular tachycardia. This led to dose reduction in two cases and discontinuation of sotalol in one[219]. This illustrates the need for effective monitoring of the QTc interval in clinical practice.

CHF increases the risk of ventricular arrhythmias and is now a contraindication to sotalol treatment. However, in our study, patients demonstrated a relatively low frequency of CHF at 13.7%. The diagnosis of CHF in AF patients encompasses a wide spectrum. AF leads to a reduction in cardiac output by approximately 15-20%, coupled with diminished atrial contraction and irregular HR[10,220,221]. Consequently, CHF is diagnosed in some AF patients without evident structural heart disease. Unfortunately, data on EF are not included in the registries. As a result, the diagnosis of CHF in AF is challenging, potentially both underestimated and overestimated. However, the sensitivity analysis excluding patients with CHF in Study III did not yield significant alterations in the overall results. In Sweden, sotalol is typically initiated in the outpatient clinic. In our nationwide study, the incidence of ventricular arrhythmias was relatively low, comprising a total of 1.7% of all sotalol patients and without a difference to those treated with beta-blockers (1.6%). This finding suggests a highly selected population, likely excluding predominantly symptomatic and hemodynamic ventricular arrhythmias, given the absence of standardized telemetry. In these selectively chosen patients, outpatient initiation seems reasonably safe.

Female gender is a recognized risk factor for TdP, and in our study, only 31 % of participants were female. Advanced age has been considered a potential risk factor, often in combination with other precautionary factors. However, we did not observe advanced age as a risk factor for mortality or ventricular arrhythmias. Despite including 1,204 patients (24%) over the age of 75 and with a median age of 69 (IQR 62-74) years, our findings did not indicate an increased risk. In Studies I and II, we did observe that elderly patients had an increased QTc, aligning with other data showing QTc increases during adulthood[222,223]. The extent to which elderly patients chosen for treatment with sotalol were healthier

remains uncertain. Previous recommendations have discouraged the use of sotalol in patients older than 75 years.

Previous meta-analyses have demonstrated an increase in mortality among patients with sotalol treatment for AF after CV[155,166,167]. However, while sotalol has been the subject of numerous randomized trials, these were primarily designed to assess efficacy and monitor AF relapse rather than mortality. The comparison between the studies is limited due to differences in the control group's follow-up length and size. A high proportion of patients with CHF, up to 60%, were included[161]. The risk associated with AAD treatment in patients with CHF and structural heart disease is elevated[164,192,224], and this combination has been acknowledged in guidelines, now discouraging almost all AAD use except for amiodarone in patients with CHF[10,163]. In the absence of prospective, randomized trials with mortality outcomes in sotalol-treated patients without structural heart disease, various register-based trials have demonstrated somewhat differing results. For instance, in a comparison by Friberg of Swedish AF patients undergoing AAD treatment, lower all-cause mortality was found with flecainide compared to sotalol (HR 0.44 95% CI 0.33-0.57), with no difference with sotalol compared to dronedarone (HR 0.86 95% CI 0.63-1.17) in the propensity matched comparison[199]. All AADs, including sotalol, demonstrated lower mortality rates compared to a non-treated AF population, where 63% were on beta-blockers. The IR of mortality was 2.1 per 100 patient-years on sotalol treatment compared to 10.12 per 100 patient-years in the control group, indicating a highly selected group of younger patients. Another register-based comparison between sotalol and dronedarone, by Pundi et al., showed similar mortality rates for the two drugs, with an IR at 3.0 (95% CI 2.4-3.8) in sotalol-treated and 3.4 (95% CI 2.8-4.2) in dronedarone-treated patients[171]. In our study, we observed lower mortality among sotalol-treated patients, with an IR of 1.19 (95% CI 0.93-1.49). The different results are likely explained by a more selected population in our study. To our knowledge, no randomized study designed for mortality outcome with guideline-directed patient selection between AADs exists.

The recurrence rate of AF is unknown in our cohort. The extent to which an increased rate of SR might have contributed to reduced mortality is uncertain. While the efficacy of sotalol at a group level is modest, it can still be a viable option for certain individuals. Our results are derived from real-life data and could be a result of improved adherence to guidelines and increased awareness of risk factors in sotalol treatment. For physicians considering sotalol treatment,

adherence to specific guidelines, such as those outlined in Table 10, is recommended. However, establishing a precise age cutoff for recommending sotalol treatment remains a subject of ongoing debate. Notably, sotalol clearance is diminished by at least 29% in patients older than 70[225]. As a precautionary measure, we recommend initiating sotalol at a 50% reduced dosage compared to younger individuals and a combination of several precautionary factors should be avoided.

Table 10 Sotalol outpatient initiation

Contraindicated	**Should be used with precaution**
Severe AV conduction disturbances	With QT prolonging concomitant drugs
	If electrolyte disturbances (potassium, magnesium)
Severe sinus node dysfunction	
Left ventricular ejection fraction <40%	In long-term use of diuretics
QTc >450 ms in men, >460 ms in women	In bradycardia
Renal impairment: CrCl <60 mg/ml	In female gender
	Age >75 years
Left ventricular hypertrophy ≥15 mm	**Patient information:** Pausing sotalol if gastroenteritis/diarrhea. Add **alert** in patient chart: use of QT prolonging drugs
Follow-up:	One day and one-two weeks after dose titration check ECG: QTc >500 ms or increase >60 ms -> terminate sotalol.
Cardiologist follow-up at 6-12 months:	•Clinical evaluation including symptoms, syncope and heart rate •Laboratory investigation including creatinine and potassium •ECG: if bradycardia and/or QTc prolongation –> dose adjustment

At present, there remains uncertainty whether mortality rates are positively impacted by rhythm control. Future studies are crucial to confirm that the chosen treatment strategy, ablation or AAD treatment, does not increase mortality. The necessity for different treatment options persists since the primary goal of pursuing rhythm control for most patients is to alleviate symptoms. It is worth noting that symptoms may present mildly, often linked to anxiety, and can be eased through thorough information and assessment of

stroke risk. The selection of the most suitable treatment approach should be guided by careful evaluation of the individual patient's circumstances and comprehensive assessment.

5.2 Strengths and limitations

Considerable time has passed since the inception of this project, during which the landscape AF treatment has evolved significantly. There has been a notable shift in focus towards ablation, and stroke prevention and risk factor management have improved. Considering the increased understanding of AF, the following section will discuss the rationale behind methodological choices and highlights some related strengths and limitations.

5.2.1 Methodological considerations

All the studies conducted were observational, entailing certain inherent disadvantages. Firstly, they establish associations rather than proving causality. Accordingly, our results should not be construed as implying that sotalol leads to decreased mortality or that the QT interval decreases in all patients post-CV with sotalol treatment. Secondly, the non-randomized group allocation introduces several biases since patient groups inherently differ at baseline. Selection bias is intrinsic in patients selected for sotalol or beta-blocker treatment. Moreover, performance bias, potentially affecting sotalol patients more favorably due to careful patient care, is a possibility. In the register-based Study III, we used both multivariable regression and propensity score methods to mitigate baseline group differences. Nevertheless, it is important to acknowledge that it is not feasible to include all factors influencing a doctor's treatment decision in the analysis, thus confounding remains a concern.

Random error, or the role of chance, could also have influenced the results, particularly in studies with small sample sizes. In Study II, although the number of patients was small (n=50), the number of heartbeats was large. However, careful consideration of the clinical relevance of the findings rather than relying solely on statistical significance is necessary.

5.2.2 Study I-II

These studies were single-center investigation, which could potentially impact their external validity. However, the procedures of CV of AF patients and ECG recording are standardized. Patients receiving sotalol had previously been treated with a beta-blocker and experienced a relapse into AF; consequently,

prior CV was more common in sotalol-treated patients. Nonetheless, patients in both treatment groups were monitored in a similar manner and were relatively well matched, despite not being randomized. The diagnosis of CHF was more prevalent, and left ventricular EF was reduced in beta-blocker-treated patients, aligning with guidelines.

Given the nature of these studies, it was not possible to control differences in HR, rendering the results dependent on the rigor of the correction formulas. Various correction formulas were tested, yielding similar overall results. Plasma concentrations of sotalol or metoprolol were not measured, but all patients had reached a steady state at least one week before inclusion, and their renal function was normal.

In Study I, all measurements were performed manually, and it is well known that QT measurement accuracy is imperfect[226]. However, all patients were measured by averaging three ECGs. A blinded electrophysiologist assistant's measurements were used to test variability, but it is likely that some measurement inaccuracies remain. Since measurements were blinded for treatment, this bias would be randomly distributed to some extent.

In Study II, the sample size is small, but it encompassed a wide range of heartbeats. The internal validity in Study II was affected by a lack of information on external factors, such as sleep, mealtimes, the incidence of sleep apnea, or activity levels that might affect the QT interval. Additionally, ambulatory recordings in an outpatient setting generated a considerable amount of noise that needed to be filtered out, resulting in fewer valid heartbeats for analysis.

Regarding QT diurnal variation, evidence has been conflicting. The QT interval had not previously been investigated in patients taking sotalol after CV, revealing dynamicity in QTc that probably needs to be acknowledged in clinical practice.

5.2.3 Study III

In Study III, thus nationwide, encompassing all eligible patients undergoing their second CV with sotalol or beta-blocker treatment. This approach enhanced the study's external validity. However, the generalizability of the results is limited to countries with healthcare standards like Sweden. Data quality is a critical ethical consideration in register-based studies. Our results are dependent on the quality of the data in the registers; hence, we selected indisputable mortality as the primary endpoint. It is worth mentioning that after 2010, less than 20% of the

diagnosis in CDR are based on autopsy results[227]. Consequently, the cause of death is often determined through a probability diagnosis. In contrast, the DPR demonstrates high validity, although treatment duration calculation can vary with different dispensation intervals. Sensitivity analyses were performed to assess the impact of data quality on study results, including different dispensation intervals, yielding overall similar results.

The registries may contain errors and incomplete data, and certain diagnosis may have broad definitions. We endeavored to be stringent, engaged in forward planning, constantly checking examples, and conducted sensitivity analysis on CHF and IHD. We have tried to stratify analysis by subgroups to cover differences in population and equity. AF is a diagnosis with high validity in the registers, boasting a positive predictive value of 98%, and almost 100% coverage of all hospital care[228,229]. However, it is important to acknowledge that many other diagnoses in the registries may have varying degrees of validation and broad definitions. CHF in AF is typically a diagnosis with a wide spectrum, ranging from mild AF dyspnea symptoms or slightly elevated NT-proBNP to severely reduced left ventricular EF. Ventricular arrhythmias is another. The registers lack clinical parameters such as presence of SR, blood pressure, weight, laboratory results, or echocardiographic parameters.

One methodological concern was the selection of the control group. It could be argued that a fairer comparison would have been between sotalol and another AAD with the same indication. However, dronedarone, the nowadays most-used AAD in Sweden to prevent relapse, was shown to increase mortality in two studies[173,174]. Another comparison could have been with flecainide, an AAD with very few mortality studies[230,231]. In Sweden, these are the alternatives used as AADs, in addition to amiodarone. Amiodarone, although the most efficient AAD, has several serious toxicities, making it a last resort in most circumstances. We chose to compare sotalol with common beta-blockers, which have not been shown to increase mortality. In retrospect, the analysis could have been extended by the addition of a falsification endpoint.

Despite these limitations, we believe it is reasonable to claim that our results reflect real-life outcomes. To our knowledge, no other nationwide study on sotalol use after CV exists.

6 Conclusions

This thesis has examined the most established risk marker in sotalol treatment: the QT interval and the risk of adverse events in patients treated with sotalol after CV.

The specific conclusions were:

Study I

The QTc interval was reduced during the week following CV of AF in patients treated with sotalol. This was not seen in the control group of patients treated with metoprolol.

Study II

24-hour Holter recordings with QT-measurements identified more patients with QT prolongation after CV than conventional ECGs. QT prolongation at night was frequent in patients treated with sotalol. These results indicate that the QT interval is a dynamic measure that requires careful consideration in patients treated with sotalol.

Study III

In patients selected for sotalol treatment after 2006, mortality or ventricular arrhythmias were not increased following CV compared to patients treated with a cardioselective beta-blocker. These results indicate that careful patient selection and the avoidance of CHF can minimize the risks associated with sotalol treatment.

7 Points of perspective

On risks:

Sotalol can both induce and prevent ventricular arrhythmias and is well-established in the treatment of ventricular arrhythmias in patients with ICDs[232]. If mortality is increased due to sotalol treatment, the cause ought to be TdP leading to sudden cardiac death. However, the real incidence of ventricular arrhythmias in sotalol treatment is largely unknown, due to the lack of ECG surveillance and diagnosis. The cause of death in both register-based and prospective randomized studies is usually unknown and not based on autopsy results or ECG monitoring. Future research could, in prospective trials, increase knowledge on the occurrence of ventricular arrhythmias in sotalol treatment by using repeated Holters, implantable loop recorders, or wearables with arrhythmia diagnostics to capture the true incidence.

In our studies, the rates of ventricular arrhythmias were quite low. It must be stated, however, that the true incidence in all studies remains unknown due to non-continuous monitoring. Our findings of QT dynamicity need to be repeated and prolonged, and the immediate post-CV period could be of extra interest. It would be interesting to compare our findings in the selected cohort of patients after CV to patients internationally, especially in those countries where sotalol is frequently used.

More extensive and larger studies are needed to understand the prognostic relevance of treatment options in AF, particularly concerning long-term follow-up. Further research on comparative efficacy and risks of AADs is needed. Additionally, understanding how to tailor AF treatment for different patient groups, considering individualization, age, and gender differences, as well as optimal dosages of AADs, indications for CV, requires thorough investigation, optimally in randomized trials. Considering sotalol as treatment for AF can only be justified if the risk is very low, since symptom alleviation is the primary goal. It may still be an option for individuals. Exploring whether sotalol could be useful in patients with little structural remodeling, making risk factor interventions possible during a limited time period, as well as delaying or hindering ablation, is interesting. It is a concept that would need randomized comparisons. However, the optimal approach would be shifting the focus at a population level towards risk factor modification and AF prevention, rather than primarily relying on ablations or AADs.

On risk monitoring:

The value of QTc as a risk marker for ventricular arrhythmias in sotalol treatment is well established. However, as this thesis has illustrated, relying solely on one QTc value for risk evaluation is inadequate. Our studies emphasize the dynamic nature of the QT interval and the intricacies involved in its precise measurement. Whether this dynamic aspect holds prognostic value in predicting ventricular arrhythmias or mortality needs assessment in larger studies. Our findings need to be repeated and the burden of QT prolongation as a risk marker needs to be evaluated in prospective studies with hard endpoints, such as burden of ventricular arrhythmias or mortality.

Patients with initial QTc prolongation and sotalol treatment require extensive monitoring of ECG. Longer-term follow-up with repeat Holter monitors or implantable loop recorders is already available and could be studied. Innovative techniques, such as wearables or loop recorders with QT analysis, hold promise in refining QT measurements, but their integration and efficacy need further exploration. Additionally, other potential risk markers, encompassing both ECG risk markers, as T-wave changes and QT interval form instead of relying on interval length, as well as genetic susceptibility, may offer advantages and require further research, ideally in studies with proper outcomes such as ventricular arrhythmias, mortality, or syncope.

Sotalol, and other AAD patients, could be included in a clinical patient register, demanding repeated ECG monitoring, including alerts for potassium, creatinine levels, QTc prolongation and concomitant medications, which could aid in follow-up safety of sotalol-treated patients. The integration of computerized tools holds promise in aiding risk factor management in sotalol treatment, especially in avoiding polypharmacy in cases of QT prolongation and renal failure. This would also enable further research; however, its use needs to be properly evaluated.

The data on the arrhythmic vulnerability and increased ventricular arrhythmias in the immediate post-CV period rely on small studies. The mechanism behind QT prolongation observed remains unknown, and a possible change in ion balance can be explored, perhaps initially suggested in animal studies.

In this thesis, we have seen an example of dynamicity in a risk marker like the QT interval. Also, in other areas of medicine, trends and patterns of biomarkers are gaining attention. Whether this diurnal variation/QT change can be used to

assess an individual's risk for arrhythmias in sotalol treatment, to identify patients that would benefit from intervention/dose adjustments, with technical progress and genetic generated risk profiles in combination with clinical factors and risk profiles, is unknown. Further research is needed to see if this could create individualized risk profiles.

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