Atrial Fibrillation

Primary prevention with statin therapy

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1. Bang CN, Greve AM, Boman K, Egstrup K, Gohlke-Baerwolf C, Køber L, Nienaber CA, Ray S, Rossebø AB, Wachtell K. Effect of Lipid Lowering on New-Onset Atrial Fibrillation in Patients with Asymptomatic Aortic Stenosis. The Simvastatin and Ezetimibe in Aortic Stenosis Study. Am Heart J 2012;163:690-6.

2. Bang CN, Gislason GH, Køber L, Torp-Pedersen C, Greve AM, Wachtell K. Statins Reduce New-Onset AF in a First Time Myocardial Infarctions Population – A Nationwide Propensity Score Matched Study. Eur J Prev Cardiol. [Epub ahead of print].

3. Bang CN, Greve AM, Abdulla J, Køber L, Gislason GH, Wachtell K. The preventive effect of statin therapy on new-onset and recurrent atrial fibrillation in patients not undergoing invasive procedures - A systematic review and meta-analysis. Int J Cardiol. 2013 Aug 10;167(3):624-30.

INTRODUCTION

Prevalence and impact of atrial fibrillation

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation resulting in inadequate atrial mechanical function.1 It is characterized by the replacement of regular P waves by rapid irregular fibrillatory waves that varies in amplitude and shape associated with unsystematic frequent ventricular response if the atrioventricular conduction is intact.1 AF is the most common sustained cardiac arrhythmia affecting 0.4 to 1% of the general population, increasing with comorbidity to more than 9% in patients with aortic stenosis (AS) and increasing with age to more than 8% in those over 80 years of age.1-9 Furthermore, AF is the most frequent complication to cardiac surgery, affecting up to 30% after coronary artery bypass grafting (CABG) and 41-60% after aorta valve surgery.10-12 The degree of AF burden is independently predictive of poor prognosis including increased risk of non-hemorrhagic stroke and maybe death.1-9 AF can be classified according to duration of AF in paroxysmal, persistent and permanent, where permanent AF implies the most advanced stage of heart disease that is associated with more chronic structural changes in the heart such as enlargement of the atrium and development of fibrosis in the atrial myocardium that maintains the disease and makes it more treatment resistant.1, 13

Etiology of atrial fibrillation

AF is associated with both non-cardiac and cardiac diseases. Examples of the first are volume changes as fever, hyperthyroidism, alcohol intake, as well as pulmonary embolism, adverse effects of medical treatment and metabolic disorders or without known underlying disease known as familiar or lone AF. Despite the high incidence and impact morbidity and mortality the etiology and pathophysiology of AF are not completely understood. One of the more accepted theories is that AF results from complex pathophysiological processes that promote triggers of the arrhythmia and prompts formation of the structural, cellular and electrical remodeling. All of these changes are closely related and serves as the substrate and/or trigger for AF. The structural remodeling represents atrial and pulmonary vein dilatation, atrial myocardial fibrosis and reduced contractility, due to myocyte loss and fibrotic tissue formation, characterized by the deposition of collagen and fibronectin, which leads to separation of and impaired conduction between atrial myocytes.1, 14, 15 The cellular remodeling may occur by apoptosis, myolysis and channel expression changes in the atrial myocardium.1 The electrical remodeling represents shortening of the atrial effective refractory period, loss of rate adaptation, and prolongation of atrial conductivity.16-18 Underlying heart and vascular diseases as hypertension, coronary disease, heart failure and valvular disease contribute to these changes. AF alone also begets AF. After onset of AF several mechanisms contributes to the maintenance and worsening of the arrhythmia. The rapid atrial rates induces stretch and ischemia leading to the atrial myopathy also known as the “tachycardia remodeling”.19 These changes result in multiple conduction blocks in the muscle tissue generating multiple wavelets and irregular re-entrant activity, contributing to arrhythmogenesis.20, 21 The tachycardia remodeling further contains mechanisms as shortening of effective refractory period, calcium channel down regulation and changed sympathetic innervations.22

The pathophysiological mechanism seems to depend on whether the AF is associated with surgery or not. Several causal factors related to the development of post-surgical AF have been suggested, including myocardial ischemia, electrolyte disorders, cardiac valve abnormalities, and sudden withdrawal of medication.23-25 Other potentially factors during the surgical dissection and manipulations are; local inflammation with or without pericarditis, elevations in atrial pressure from postoperative ventricular stunning, chemical stimulation during perioperative support with catecholamines and other inotropic agents, reflex sympathetic activation from volume loss, anemia or pain, parasympathetic activation, fever from atelectasis or infection arisen during the operation.26-28 The pathophysiological mechanism of AF unrelated to surgery, is believed to be factors such as increased angiotensin II, inflammation, dilatation and fibrosis of the left atrial tissue in different combinations.14, 15, 29-32 Whether the largest contributor to AF unrelated to surgery is caused by one of these factors or other unknown factors remains unclear.

Atrial fibrillation and myocardial infarction

AF is a common complication after myocardial infarction (MI) and new-onset AF has been demonstrated to be associated with adverse outcome and mortality in this setting even if AF is transient.33-36 Therefore, AF should not be regarded as a benign complication to MI, but it remains to be shown whether prevention of AF in this setting is beneficial with regards to improved outcome.

The mechanisms that promote the development of AF in the MI setting are complex and multi-factorial, and the understanding of the pathophysiology remains incomplete. AF in MI patients has been associated with several clinical factors including increased age, history of hypertension and diabetes, renal dysfunction, and, in particular, the presence of heart failure symptoms and left ventricular (LV) dysfunction.37-39 Interestingly, there is evidence that suggest AF to be associated with impairment in endothelial function even in the absence of heart failure or hypertension which could explain the increased incidence of AF associated to ischemia-reperfusion injury after MI.40

Increased atrial pressure often occurs in relation to MI.39, 41 Studies report atrial ischemia42, 43 and sudden increase in atrial pressure44 to promote AF in MI patients without chronic alterations in the atrial function and structure. In addition, inflammation seems to be important not only in AF but also in MI pathophysiology. C-reactive protein (CRP) has been showed to reduce nitric oxide production in the endothelial cells and increase endothelial expression of adhesion molecules.45 CRP may also be a marker of chemotaxis of monocytes and foam cell formation in atherosclerotic plaques and enhances vasoreactivity of unstable plaques.45

Atrial fibrillation and aortic stenosis

Several lines of recent evidence suggest that development of AS involves an inflammatory process with histopathological changes in the valve leaflets that are similar to those in other atherosclerotic diseases.46, 47 As mentioned in the previously numerous clinical studies report that inflammation are important for the initiation and maintenance of AF. Inflammation could therefore explain why AF may be associated with AS. Another, more likely explanation is that LV becomes hypertrophic as an adaptation to increased afterload caused by LV outlet obstruction.48 This results in an increase in LV filling pressure to maintain a normal stroke volume that is transferred through an open mitral valve to the left atria (LA).48 The increased atrial pressure gradually causes atrial enlargement and stress to the myocardial tissue along with the progress of the stenosis.49

Avoiding AF in AS patients seems very important, because of the rapid worsening in many cases and the risk of sudden death after symptom onset.9, 48 Symptomatic patients are also at significant risk while awaiting surgery,48 and preoperative AF seems to increase late morbidity and maybe also mortality.8, 50, 51 There is evidence that suggest that AF should be seen as an adverse prognostic sign that reflects underlying cardiovascular diseases.52 This is supported by a recently published paper which showed that intensive observation and treatment of AF patients can increased the prognosis of these patients.53

Management of atrial fibrillation

Management of patients with AF involves rate and rhythm control defined as controlling the ventricular rhythm and restoring and maintaining sinus rhythm respectively.1 Symptomatic AF with palpitations, hypotension and dyspnoea often requires rhythm control by termination of AF with electrical or medical cardioversion; or rate control by medical treatment. Rate or rhythm control, antithrombotic therapy can be considered depending on the type of AF, the severity, symptoms, side effects and the patient preference and age. The same factors also determine which strategy of treatment should be used for AF. Catheter and surgical ablation is another recommended treatment that are effective for both rate and rhythm control. However, usually drugs and cardioversion are first and LA ablation the secondary options and only used in the more persistent types of AF.
Management of AF in AS patients follows conventional guidelines, although a rate control strategy is usually adopted because of the low likelihood of maintaining sinus rhythm in the long term. In addition, oral anticoagulation is recommended to patients with AF and underlying structural disease including AS.1

Statins

Inhibitors of 3-hydroxy-3-methylglutaryl co-enzyme- A (HMG-CoA), or statins, have the liver as target organ and works by inhibiting the HMG-CoA-reductase, an enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor.54 Additionally, mevalonic acid has shown to be a precursor in many other non-steroidal isoprenoid compounds and inhibition of these enzymes may result in pleiotropic effects in a variety of cell types.40, 54 Experimental evidence suggest that inhibition of Rho isoprenylation mediates many of the cholesterol-independent effects of statins including regulation of cell shape, motility, secretion, proliferation, and gene expression.55, 56 These changes results in modulation of endothelial and myocardial function, oxidative stress, plaque stability, inflammation, thrombosis, and stroke.55

Statins increase endothelial nitric oxide (NO) production by stimulating and up-regulating endothelial synthase resulting in improved endothelial function independently of the cholesterol level.55, 57 In addition, statins increase the expression of tissue-type plasminogen activator and inhibit the expression of the potent mitogen and vasoconstrictor the endothelin-1.58 Furthermore, statins decrease the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase and release of superoxides in cardiac myocytes and reduces cardiac hypertrophy.59-62

Importantly, statin treatment has shown to decrease CRP, the number of inflammatory cells and inhibit adhesion molecules.55, 63, 64 The T-lymphocytes and the inflammatory response are impeded by statins inhibition of major histocompatibility complex class II that are expressed in endothelial cells and monocyte/macrophages and thereby repressing major histocompatibility complex (MHC)-II–mediated T-cell activation.64 Finally, statins have been shown to decrease CD40-expression and CD40-related activation of vascular cells, as well as to reduce tumor necrosis factor α and interferon γ in stimulated T-lymphocytes.65, 66

Angiotensin II mediates a cascade of processes that results in myocyte hypertrophy, fibroblast proliferation, accumulation of collagen and apoptosis.67 In addition, angiotensin II modifies atrial electrophysiology by indirect effects on ion channels, by increasing calcium influx, promoting inflammation, and possibly also causing gap junction remodeling, which in turn impairs cell-to-cell coupling.67 There is evidence that statins provide neurohormonal effect by decreasing the stretch induced release of angiotensin II from the atrial myocardium through lowering angiotensin II type 1 receptors.29 Furthermore, statins desensitize cultured cardiac myocytes to β-adrenergic stimulation, which lower the stimulus of the atria and maybe the incidence of AF.68

OBJECTIVES AND HYPOTHESES

Numerous studies have reported a preventive effect of statin treatment on AF, many good causal mechanisms have been suggested and statins are now recommended as documentation level IIa in patients undergoing cardiac surgery to prevent AF.69 In addition, studies have suggested dose and type dependent effect on statins although the patient sample was limited in these studies. Conversely, some studies have not been able to show a positive effect of statins. However, only a small proportion of the previous studies have specified the type and stage of AF examined in the respective study. Interestingly, AS and AF seem to share some pathophysiological mechanisms that might be prevented by statin treatment. Better management of AF in MI setting is warranted, because of increased morbidity and mortality when developing AF. Therefore, the hypotheses of this PhD thesis were:

1) Statin treatment in combination with ezetimibe would be associated with a reduction in new-onset AF in AS patients.

2) Statin treatment would be associated with a reduction in new-onset AF in a large first-time MI population and higher dose would be more effective than low dose. In addition, the preventive effect would be different according to the statin type.

3) Statin treatment in patients that did not undergo cardiac intervention would prevent the onset and recurrence of AF.

Thus the aim of this thesis was to analyze the preventive effect of statin treatment in: 1) patients with AS, 2) in a large sample of MI patients and to further analyze the effect of different statin dosage and different statin types, and 3) a non-operative setting by conducting a large meta-analysis on all the published articles examining the effect of statin treatment on new-onset and recurrent AF.

MATERIAL AND METHODS

Study populations

This PhD thesis included three different patient samples.

I. The first sample consisted of 1,873 patients with mild to moderate AS from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, a randomized, multicenter, double-blind, placebo-controlled study where patients were treated with intensive lipid lowering with simvastatin plus ezetimibe or placebo and were followed for a mean of 4.3 years .70, 71 Patients with previous AF or AF at baseline were excluded.
II. The second sample consisted of 89,703 patients with first-time acute MI between 1997 and 2009 in Denmark and claimed prescriptions of statins after discharge. They were identified from the Danish National Patient Registry and the Danish Registry of Medicinal Product Statistics.
III. The third patient sample consisted of 235,945 patients from all published studies into beginning of July 2011 who examined patients treated with a statin vs. a control group unrelated to invasive cardiac interventions.

Electrocardiograms

In Paper I, new-onset AF was identified from annual in-study electrocardiograms and electrocardiograms recorded in case of referral for aortic valve replacement. All electrocardiograms (n=7,302) underwent Minnesota coding by a physician blinded to the randomization and all clinical data at the SEAS electrocardiographic core reading center in Copenhagen.72 Patients with a history or baseline AF was excluded.

Echocardiograms

For paper I, Echocardiographic study protocol, reading procedures, and reproducibility have been published.73 Briefly all echocardiograms were read blinded at the SEAS Echocardiographic Core Laboratory, Haukeland University Hospital, Bergen, Norway. Aortic valve area indexed by body surface area was calculated by applying the continuity equation74 in accordance with recent recommendations.75 LV dimensions and wall thicknesses were measured on 2-dimensional images according to American Society of Echocardiography guidelines using an anatomically validated formula. LV ejection fraction and LV mass were determined by standard 2D-echocardiography.76

Registers

To examine the effect of statins in MI setting and in large scale, we included patients from the Danish National Patient Registry. The Danish National Patient Registry has since 1978 registered all hospital admissions in Denmark. Each admission is registered with one primary diagnosis and one or more secondary diagnoses according to the International Classification of Diseases (ICD), until 1994 the ICD-8 and from 1994 the ICD-10. To get information about the concomitant medicine we used The Danish Registry of Medical Product Statistics (national prescription registry). This registry has since 1995 kept records of every drug prescription dispensed from pharmacies in Denmark. Each medication is classified by the international Anatomical Therapeutical Chemical system, and the registry also includes information about the date of dispensing, formulation, strength, and quantity dispensed. Information on patients' vital status (dead or alive) was obtained

from the civil registration system through Statistics Denmark. In Denmark, every resident is provided with a permanent and unique civil registration number that enables linkage between these administrative registries.

Statistics

PAPER I

The free statistical software program R version 2.10.1. and SAS statistical software package version 9.2 for PC (SAS Institute Inc, Cary, NC) were used for statistical analysis. Continuous variables are presented as mean±standard deviation (SD) and categorical as percentages. Variables not normally distributed were log transformed as appropriate and expressed as mean with 5 and 95 percentiles. Differences in categorical variables were evaluated by Chi-square tests and in continuous variables by the Student's t-test. Baseline clinical, demographic and laboratory data were assessed for association with new-onset AF by univariate and multivariable analysis using Cox proportional hazard analysis to estimate hazards ratios (HR) and confidence interval (CI). Cholesterol, high-sensitivity CRP (hsCRP) and systolic blood pressure were inserted as time-depending variables by choosing the last measurement before AF onset. Variables without univariate effect on new-onset AF were eliminated ($p<0.05$) before making multivariable models with the exception of randomized treatment (simvastatin and ezetimibe) that was always forced into the models. The predictive value of new-onset AF was assessed by Cox based delayed-entry statistics (i.e. counting the time from new-onset AF to censoring or event provided that the primary endpoint had not occurred prior to new-onset AF). Proportionality was tested by cumulative residuals. A cumulative incidence-rate plot of new-onset AF occurrence was evaluated in respect to treatment group with death as a competing event.77 To account for difference in all-cause mortality, odds ratio were determined by multivariable logit-link model for competing risks,78 where a regression analysis of the cumulative incidence probabilities was calculated adjusted for gender and age. The effect of treatment on the combined endpoint of new-onset AF and death was evaluated using same method as used for new-onset AF. To test if AVR influenced the result we performed additional analyses stratifying by AVR. However, this did not significantly alter the results. A two-tailed p-value <0.05 was regarded as statistically significant.

PAPER II

SAS statistical software package version 9.1 for UNIX servers (SAS Institute Inc, Cary, NC) were used for statistical analysis. Descriptive data was reported as mean ± standard deviation (SD), median with Interquartile Range or frequencies expressed as percentages. Differences in categorical variables were evaluated using Chi-square test and continuous variables using t-test or the Wilcoxon ranked sum test. Risk of new-onset AF according to statin treatment was evaluated by multivariable time-dependent Cox proportional-hazard model adjusted for age, sex, calendar year, concomitant pharmacotherapy and comorbidity. The proportional-hazard assumption, linearity of continuous variables and lack of interactions was tested and found normal unless otherwise reported. Additionally, we carried out a propensity-score matched Cox proportional hazard analysis. We quantified a propensity-score for the likelihood of receiving statin treatment within the first year from discharge by multivariate logistic regression analysis conditional on baseline covariates (see Table 2). Using the Greedy matching macro downloaded at: http://mayoresearch.mayo.edu/mayo/research/biostat/upload/gmatch.sas, we matched each case to one control on the basis of the propensity score. Use of statins during follow-up was again included as a time dependent covariate. Furthermore, we evaluated if risk of new-onset AF was modified by statin dosage (dose-response relationship) or type of statin therapy by linear hypothesis testing. Finally, we evaluated if compliance with statin treatment affected risk of new-onset AF, by dividing patients in two groups defined as good compliance (≥ 80% proportion of days covered with statins) or poor compliance (< 80% proportion of days covered with statins). A cumulative incidence-rate plot of new-onset AF occurrence was evaluated in respect to statin compliance with death as a competing event and adjusted for aforementioned comorbidity 77. A two-tailed p-value <0.05 was regarded as statistically significant in all calculations.

PAPER III

Meta-analysis package of the statistic software program STATA version 10 (STATA Corporation, Lakeway Drive, College Station, Texas, USA) was used for all analysis. The reported numbers of AF (and flutter if reported) in statin treated groups compared with numbers of no-statin groups were pooled together. The overall risk ratio (RR) with 95% CI for the risk of AF in statin groups were estimated. We used fixed or random effects model for data combination depending on data heterogeneity. Heterogeneity was tested using Chi-square method (with a p-value below 0.05 considered significant) and I2 statistic. The I2 (measured as 0-100%) indicates the percentage of variation in the study results attributed to between-study heterogeneity rather than sampling error. A value of I2 above 20% was considered significant. For the estimated overall RR, a p-value below 0.05 and Z score above 2 was considered significant. Sub-analyses comparing different study groups were performed by analyzing study groups (randomized vs. observational trials, MI vs. non-MI trials, or trials classified according to types of statins) as class variables and repeating the analyses as mentioned above. To assess statin-type effect, statins were divided into 3 groups: atorvastatin, simvastatin and "mixed statins". The mixed statins group was defined as any other type of statin than atorvastatin, simvastatin or if no type of statin was defined. All of the parameters were weighted with respect to number of patients in the respective studies.

To demonstrate the agreement or disagreement in the magnitude of the estimated treatment effect between the included randomized controlled trials (RCTs) and observational studies, we constructed a meta-analytic model by comparing 10 pairs of suitable RCTs (only one RCT was excluded due to its very small size) versus 10 observational trials. Each pair consisted of a RCT versus its corresponding observational study of comparable size. We run the analysis using the afore-mentioned meta-analytic methods. To identify potential sources of bias in the reported events of AF among the RCTs (according to the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group) sequence generation, concealment of allocation sequence, blinding, incomplete outcome data, selective outcome reporting, and any other potential sources of bias was considered. Risk of bias at the individual trial level and across the RCTs was categorized into low or high.

RESULTS

New-onset of atrial fibrillation and effect of statin treatment in patients with aortic stenosis (Paper I)

A total of 1,421 patients included in this study; 716 patients receiving simvastatin and ezetimibe and 705 placebo. New-onset AF

occurred in 85 (6%) patients during average follow-up time of 4.3 ± 0.8 years, 44 (14.6 per 1,000 person-years of follow-up) in the treatment group and 41 in the placebo group (13.7 per 1,000 person-years of follow-up). There was no difference in median time to new-onset AF between treatment groups (simvastatin and ezetimibe: 1,566 ± 356 days and placebo: 1,578 ± 333 days, p = 0.515). Cumulative incidence curves and multivariable "logit"-competing risk calculations with death as competing event showed no effect of treatment with simvastatin and ezetimibe on the incidence of new-onset AF (Figure 2, OR: 0.89 [95%CI: 0.57-1.97], p=0.717). In univariate and multivariable Cox models treatment combination of simvastatin and ezetimibe was not associated with less new-onset AF (HR: 0.96 [95% CI: 0.63-1.47], p = 0.86, and HR: 0.97 [95%CI: 0.62-1.51], p = 0.88, respectively).

Stratifying after AVR, there were 63 with new-onset AF before AVR (9 among the simvastatin and ezetimibe and 13 in the placebo group, respectively) and 22 with new-onset AF before AVR. In multivariable Cox analysis adjusted for age and gender, treatmant with simvastatin and ezetimibe was not associated with lower risk of new-onset AF before or after AVR (p for interaction = 0.285, HR: 1.20 [95% CI: 0.73-1.97], p = 0.481, and HR: 0.61 [95%CI: 0.26-1.42], p = 0.256, respectively).

In additional analyses testing for differences in rate of all-cause mortality, there were 207 patients with the combined endpoint new-onset AF and death. Treatment with the combination of ezetimibe and simvastatin was not associated with this combined endpoint either (HR: 0.96 [95%CI: 0.73-1.26], p = 0.76). When stratifying the effect of simvastatin and ezetimibe treatment in respect whether the patient had and AVR or not, we found no different effect on the combined endpoint (p = 0.289 and 0.298 respectively).

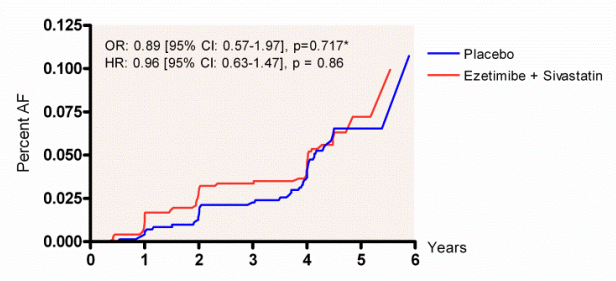

Figure 1
Estimated Probability of New-onset Atrial Fibrillation According to Treatment in Patients with Aortic Stenosis
AF, Atrial Fibrillation; CI, Confidence Interval; HR, Hazard Ratio; OR, Odds Ratio; *Evaluated by "logit-link" multivariabel competing risk calculations with death as competing event

New-onset of atrial fibrillation and effect of statin treatment in myocardial infarction (Paper II)

A total of 97,499 patients were admitted with first-time MI in the period from 1997–2009; 89,703 (92.0%) were alive at discharge and included in the study. After discharge, 56,044 patients (62.5%) claimed at least one prescription of statin therapy. New-onset AF was registered in 5,698 (10%) and in 5,010 (15%) among patients receiving and not receiving statin treatment, respectively. In multivariable Cox model adjusted for age, gender, year, concomitant medical treatment and comorbidity; statin treatment was associated with reduced incident of new-onset AF (HR:0.85 [95%CI: 0.81-0.89], p<0.001). The propensity-score matched analysis yielded nearly identical results (HR: 0.82 [95%CI: 0.78-0.85], Figure 2).

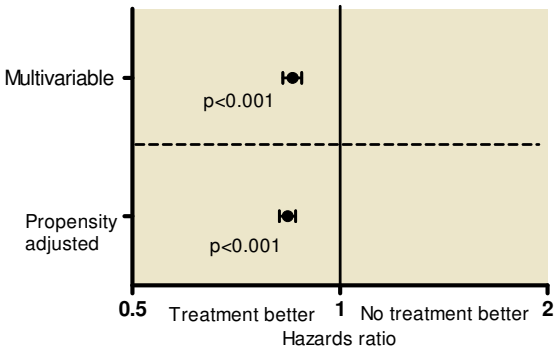

Figure 2
Preventive Effect Of Statins On New-Onset Atrial Fibrillation After Myocardial Infarction In Multivariable And Propensity-Score Matched Cox Regression Analysis
Hazard Ratio and 95% Confidence Interval

Statin type dependent effect (Paper II & III)

In multivariable Cox model, both atorvastatin and simvastatin in MI setting was associated with reduced incident of new-onset AF (HR: 0.81[0.73-0.90], P<0.001 and HR: 0.82[0.78-0.86], p<0.001, respectively), whereas pravastatin was not (HR: 0.96[0.87-1.06], p=0.381). The effect of both atorvastatin (p=0.014) and simvastatin (p=0.003) were significant larger than pravastatin (Figure 3). Both high and low dose atorvastatin and simvastatin had effect on new-onset AF (all p<0.01). The meta-analysis showed no significant effect when trying to analyze the statins individually.

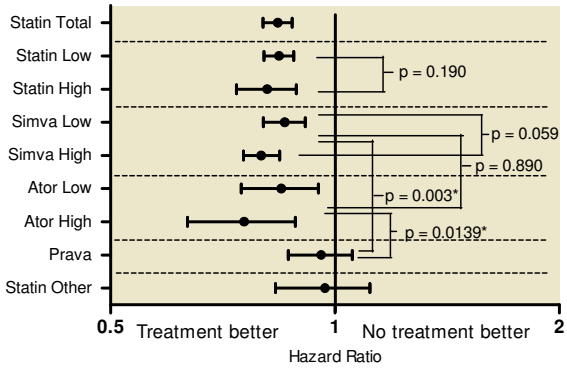

Figure 3
Statins Brand and Dose Preventive Effect on New-onset Atrial Fibrillation
Hazard Ratio and 95% Confidence Interval
Ator: Atorvastatin, Prava: Pravastatin, Simva: Simvastatin

Statin dose dependent effect (Paper II)

When comparing dosage of statins, high dose of statin treatment was associated with a trend to less new-onset AF compared with low dose statin treatment. High dose simvastatin compared to low dose simvastatin nearly reached statistically significance (p=0.059). However, there were no significant effect of high and low dosage atorvastatin (p = 0.240) or high and low dosage statins in general (p = 0.190).

Statin compliance (Paper II)

Furthermore, in multivariable adjusted Cox model, a high compliance to statin therapy (≥80% of days covered with statins) was

significantly associated with a reduction in new-onset AF compared to low compliance (<80% of days covered with statins) (HR:0.83 [95%CI: 0.80-0.87], Figure 4).

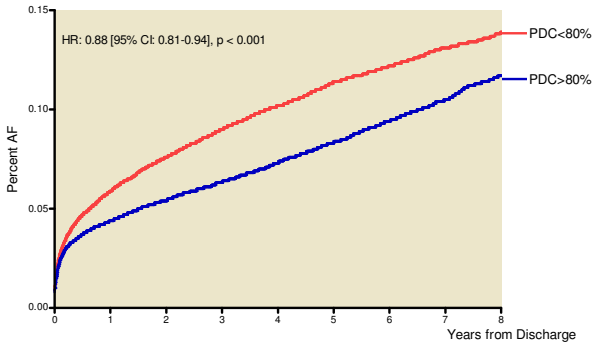

Figure 4
Cumulative Incidence of New-Onset Atrial Fibrillation after First-Time Myocardial Infarction Stratified by Statins Compliance
CI: Confidence interval, HR: Hazards ratio, PDC: Proportion of days covered

New-onset and recurrent atrial fibrillation and effect of statin treatment in patients not undergoing invasive cardiac interventions (Paper III)

A total of 235,945 patients were included in this meta-analysis; 106,640 patients received statin therapy vs. 129,305 who served as controls. New-onset AF occurred in 11.9% versus 19.7% in patients treated with statin therapy compared to controls. Recurrent AF occurred in 7.8% vs. 9.1%, respectively. The overall use of statins was associated with a significant overall risk reduction of AF (RR: 0.81 [95% CI: 0.80-0.83], p<0.0001). The studies were significantly heterogeneous (I2=82.1% and p< 0.001, Figure 5). Analysis of statins effect on new-onset and recurrent AF in the observational studies showed a significant risk reduction (RR: 0.88 [95% CI: 0.85-0.91], p<0.001) and (RR: 0.75 [95% CI: 0.72-0.77], p<0.001) respectively (Figure 5).

Assessing exclusively the RCTs, statin treatment showed a non-significant risk reduction of new-onset and recurrent AF (RR: 1.00 [95% CI: 0.91-1.10], p=0.991) and (RR: 0.88 [95% CI: 0.75-1.02], p=0.091) respectively. Meta-analyses of the 11 RCTs showed non-significant heterogeneity for new-onset and recurrent AF, (I2=31.4% and p=0.20) and (I2=31.1% and p=0.20) respectively. Combining the results of RCTs on new-onset and recurrent AF showed no significant benefit from statins (RR: 0.97 [95% CI: 0.90-1.05], p=0.509). The studies were homogeneous (I2=31% and p=0.14 for heterogeneity).

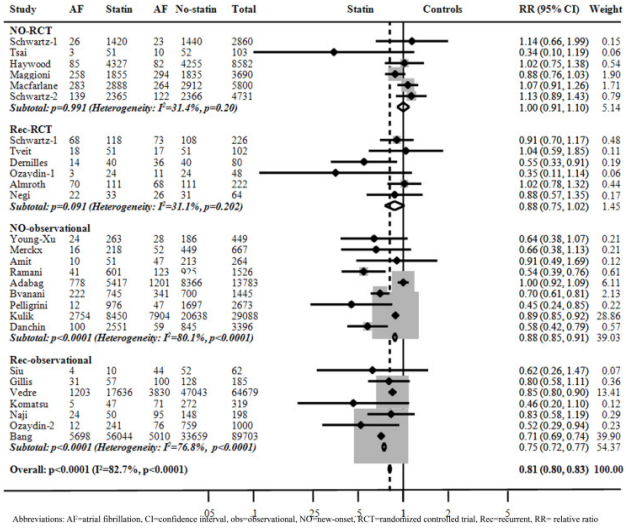

Figure 5
Results of the Meta-analysis According to Classification of Atrial Fibrillation and Study Design

DISCUSSION

This PhD thesis on the preventive effect of statins on AF has five new observations. First, treatment with a combination of 40 mg simvastatin and ezetimibe 10 mg did not prevent new-onset AF in patients with mild to moderate AS. Second, statin treatment was associated with less AF development in first-time MI patients. Third, atorvastatin and simvastatin were associated with a more potent reduction of new-onset AF than pravastatin. Fourth, patients with good compliance to statin treatment were associated with a greater reduction in AF than those with poor compliance. Finally, in a systematic review and meta-analysis of the published literature, statins was associated with a preventive effect on both new-onset and recurrent AF in non-operative trials, however, this preventive effect was not supported by RCTs.

Etiology of atrial fibrillation

As mentioned previously in this thesis, the pathophysiological changes associated with the development of AF are complex, multifactorial and may also be affected if surgery is involved.23, 40, 79-82 Statin treatment has been shown to significantly decrease CRP-levels, reduce pericardial fibrosis and the prevalence of AF, supporting the theory that AF may be partially caused by an inflammatory process and that statin-treatment may counteract this inflammatory process.63, 64 Other mechanisms could be statins reducing nitric oxide produced by statins resulting in decrease of diastolic wall stress and spontaneous activity in the pulmonary veins.83 The majority of human trials are observational and they have showed that statins are associated with a beneficial effect on AF.84-86 A recently published meta-analysis based on published and unpublished randomized trials87 showed that statins reduced risk of AF in short- but not long-term statin treatment. However, the authors did not differentiate between AF types which are important because permanent AF implies a more advanced stage associated with more chronic changes and making AF more resistant to treatment.1, 13 The implication is that the preventive effect of statins maybe greater in “healthier” patients with less substrate and structural remodeling of the atria. This was supported by Reilly et al.,88 who showed that up-regulation of atrial NADPH oxidases, a factor reversed by statins, was an early but transient event in the natural history of AF. In all

the papers included in this thesis, we therefore primarily assessed new-onset AF.

Statins preventive effect on atrial fibrillation

The efficacy of statins, in reducing morbidity and mortality in patients with documented CAD or those at increased risk of CAD has been well demonstrated.89, 90 In addition, studies have shown that statin treatment may prevent AF.85, 86, 91-93 The first study in this thesis, did not show any effect of treatment with simvastatin and ezetimibe, neither on the incidence nor time to occurrence of AF in patients with asymptomatic mild to moderate AS. An explanation of our negative results may be that the AS patients represent a more advanced stage of disease with irreversible substrate remodeling of the left atria due to chronic pressure overload prior to start of statin treatment. This is supported by the association of more severe AS with rate of new-onset AF in the first study. The mechanisms may involve that increased LV filling pressure contributes to atrial fibrosis and dilatation, which results in increased atrial remodeling involving altered connexin expression, marked conduction abnormalities that are all important determinants in initiating AF.1, 94-96 However, these processes are counteracted by some of the other mechanisms that statins possesses; decreasing in stretch-induced release of angiotensin II from the atrial myocardium through lowering angiotensin II type 1 receptors,29 preventing myocyte hypertrophy, fibroblast proliferation, accumulation of collagen and apoptosis,67 modification of atrial electrophysiology by indirect effects on ion channels, by increasing calcium influx, promoting inflammation, and by causing gap junction remodeling, which in turn impairs cell-to-cell coupling.67

Notwithstanding, there are studies that have failed to show an association between statin treatment and AF.97-100 The clinical evidence for the efficacy of statins is primarily provided by observational and retrospective analyses as shown in Paper III. The aforementioned mechanisms are all assumptions that only partly explain a possible mechanism of AF prevention by statins. No causal pathophysiological mechanism that fully explain the observed association have been found.22

Numerous studies on patients undergoing CABG have shown that the use of statins may prevent post-operative AF. This finding has been summarized in recently published large scale meta-analyses.85, 86, 91-93, 101 Thus, statins are recommended as a class IIa recommendation for prevention of new-onset AF after CABG.69 The results of the third paper included in this thesis showed no convincing effect of statins effect on new-onset AF in a non-operative population, indicating that the effect of statins is very dependent upon differences in pathobiology between various cardiovascular diseases and interventions.

There are data suggesting that high cholesterol levels have beneficial effects including prevention of AF. This controversial effect also known as “the cholesterol paradox”,102-105 might be another explanation for the lack of positive effect especially in the first paper, where ezetimibe was given together with statins. There is no evidence that ezetimibe possess a pleiotropic effect that prevents AF and subsequently the only contribution was lipid lowering which may counteract the anti-inflammatory, autonomic modulation and anti-oxidant activity effect of statins. Two retrospective observational studies have demonstrated a dose-dependent response of statin therapy on AF.106, 107 Therefore, another explanation to the lack of effect of simvastatin and ezetimibe treatment could be that the average dose of statin was too small to have an effect on new-onset AF.

AF after discharge from MI is a frequent event and is associated with increased morbidity and mortality.36, 52, 108, 109 Whether atrial ischemia promotes AF in MI patients is controversial.41-43 A recently published study of 2,460 patients with acute MI showed that CAD affecting the atrial branches was an independent predictor for the development of AF after MI. This finding has been supported by other investigators.42, 43, 52 Previous in this thesis, other potential contributing factors has been mentioned including inflammation, pressure overload and impairment of endothelial function. This putative increased risk has been hypothesized to reflect the fact that AF is target organ damage that may precede or be caused by elevated filling pressures, atrial volume overload and heart failure.110 Some studies have reported that this association is seemingly independent of age, heart failure, and ventricular dysfunction.111 Others have argued that AF is merely a risk marker of death, and not a causal mediator of MI.112, 113

There are still gaps in the knowledge regarding AF in the post-MI setting: what are the optimal surveillance for AF after MI, are there other clinical risk markers or biomarkers for AF after MI, what are the optimal therapeutic regime and are there other therapies that would diminish AF after MI?114 This thesis tried to answer some of these questions by analyzing if statins could prevent new-onset AF after MI. In concordance with other studies we demonstrated in a large MI cohort that statin treatment was associated with reduced incidence of new-onset AF after MI and that a higher dose tended to reduce AF more than low dose of statins. Previously Danchin et al.115 showed in 3,396 patients from the French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) register that early start of statins after acute MI was associated with a 40% lower onset of AF and that high dose statin was related to AF reduction compared to conventional dose. A Canadian study found that statin treatment lowered short- and long-term mortality in MI patients that developed post-operational AF.116 However, there was no effect of statin treatment in patients without post-operational AF. In addition, they revealed post-operational AF was associated with both short- and long-term mortality. This could imply that statin treatment is important to prevent AF onset in post-MI setting. Whether this effect is due to statins modulation of endothelial and myocardial function, oxidative stress, inflammation, or due to decrease in ischemic burden caused by statins effect on plaque stability and thrombosis is not well described in the literature. CRP reduces endothelial cells nitric oxide production and expression of adhesions molecules; plays an important role in chemotaxis of monocytes and foam cell formation in atherosclerotic plaques; and promotes tissue factor release and potentiates the effect of killer T-cells on endothelial cells.45 Therefore, it is challenging to differentiate whether statins effect in MI setting is caused by lowering of the ischemic burden or one of the more direct factors as described. Probably both factors contribute to the preventive effect on AF, which is in concordance with previous studies showing preventive effect on AF in other subgroups than MI patients.117-119 However, the fact that no clear cause-specific explanation and that only very few RCT have shown a preventive effect of statins questions whether the observed effect of statins may be caused by bias. Imbalances in baseline characteristics might have confounded the results; e.g. more patients on statin treatment used B-blockers and ACE-inhibitors,

which could account for some of the preventive effect of the statins.

Compliance
Previous studies suggest that patients' compliance to medical treatment is important after MI and that a focused effort would appear to provide long-term benefit.120, 121 According to previous literature, this has only been shown for all-cause mortality in respect to statins compliance. In the second paper in this thesis, we revealed that a good compliance to statin treatment was associated to prevention of late AF after discharge from MI. This finding could be important in the light of AF after MI being associated with adverse outcome and mortality in this setting even though the AF might be transient.33-36

Statin type depending effect
Data suggest that there is a difference in the potency between the various types of statins.122 To our knowledge, only few studies have examined the effect of statin types on AF. Naji et al.123 demonstrated that atorvastatin had larger effect than simvastatin on recurrence rate of AF after success full electrical conversion. This thesis showed that atorvastatin and simvastatin were associated with prevention of new-onset AF in MI setting compared to pravastatin. An explanation could be that pravastatin is a hydrophilic statin hindering the penetration of the cell membrane compared to the lipophilic simvastatin and atorvastatin.124-126 This could also explain that atorvastatin is the least potent of these statins to lower blood cholesterol. No difference in effect were seen between simvastatin and atorvastatin in the MI setting. However, in the meta-analysis (Paper 3) no significant effect was detected in observational or RCTs when analyzing the preventive effect in respect to statin type. This was may be due to the small number of studies and the fact that no effect was seen when analyzing RCT. The preventive effect detected in the mixed group of statins is based on observational studies, which is limited by the observational nature. To explore this observational effect further would require a large scale RCT.

STRENGTHS AND LIMITATIONS
The results of this thesis should be interpreted with caution outside of the study populations, and especially in patients without AS and MI, since the hemodynamic consequences of AS or the ischemic burden in MI patients may have influenced the results. However, the systematically review and meta-analysis in this thesis tried to investigate statins preventive effect in a wider perspective which was a strength to this PhD thesis.

Another strength to this PhD thesis was that all of the included studies examined new-onset AF. Permanent AF implies a more advanced stage that is associated with more chronic structural changes in the heart such as enlargement of the atria and development of fibrosis in the atrial myocardium that maintains the disease and makes it more treatment resistant.1, 13

Detection of AF can be a challenge because the arrhythmia can be self-limiting and do not always cause symptoms. Therefore the optimal method to detect the arrhythmia would have been continuous monitoring. In the first study included in this thesis, AF onset, whether paroxysmal or persistent, was identified from annual in-study electrocardiograms and electrocardiograms in case of hospital admission for aortic valve replacement. This method may be unable to detect episodes of paroxysmal AF without need of hospital admission. Thus our method may have underestimated AF occurrence and primarily detected symptomatic AF. Though all electrocardiograms (n=7,302) underwent Minnesota coding by a physician blinded to all clinical data at the SEAS electrocardiographic core reading center in Copenhagen which was a strength in the first study.

The second study in this thesis is inherently limited due to the retrospective, non-randomized, observational data design. However, the completeness of data, which enabled comprehensive follow-up for 10 years, is strength to this study. The Danish National Patient Registry as well as the National Prescription Registry have both been shown to be accurate.127, 128 Furthermore the second paper was based on registries that did not include clinical data. Thus, no data were available on echocardiographic parameters as well as precise indications and contraindications to statin treatment (e.g., information on cholesterol level, which often is used to determine the statin dose). Another limitation was that we did not have data on some comorbid status, most importantly; hypertension and heart failure which are all known to be associated with risk of developing AF. In addition, imbalances in baseline characteristics might have confounded the results; e.g. more patients on statin treatment used beta-blockers and angiotensin converting enzyme-inhibitors, which could account for some of the preventive effect of the statins. The "healthy adherer effect" was an important confounder when assessing compliance. Patients that are adherent are also more adherent to other medication and often have a more healthy lifestyle.129 Only a randomized, controlled trial can remove this bias. However, we have tried to address issues of potential bias and baseline imbalances between the groups, by performing 3 different sensitivity analyses; 1) a multivariable model adjusting for potential confounders; 2) time-dependent variable analysis; and 3) a propensity score-matched analysis. The propensity matched analysis has been shown to eliminate as much as 90% of bias in observational studies.130 New-onset AF, whether paroxysmal or persistent, was identified from the National Patient Registry. AF diagnosis is in this registry based on admission for AF or AF recorded during hospital admission for other reasons. This method leaves episodes of paroxysmal AF without need of hospital admission undetected. Thus, our method may have underestimated AF occurrence and primarily detected symptomatic AF. Another limitation was that we were not able to differentiate whether the observed preventive effect of statins on AF was due to pleiotropic effect e.g. anti-inflammatory or the effect simply was due to statins effect to lower the ischemic burden. However, the multivariable Cox analyses was adjusted for in-study re-infarction and no difference on in-study re-infarction was seen in the propensity matched analyses.

In our meta-analysis (paper 3) the effect of statins was limited to the observational studies which most likely associated with some bias. In particular, the heterogeneity and the significant differences in baseline characteristics with regard to age, hypertension and use of beta-blocker therapy among the observational studies might have contributed to bias. Additionally, the observational studies tended to overestimate the effect when compared to RCTs. The comparison of the estimates of statin effect between the RCTs and observational trials was limited to ten studies from each category, which might have been influenced by chance and selection bias. Only 11 RCTs met the inclusion criteria for this meta-analysis. Therefore the meta-analysis, in particular the subanalysis, is underpowered to make safe recommendations. Fur-

thermore, the RCTs were relatively of smaller size, had high potential risk of bias, provided retrospective data analyses and were not designed to test the preventive effect of statins on AF as a primary endpoint. In addition, the main part of both the observational and the RCTs were based on electrocardiograms.

CONCLUSIONS AND PERSPECTIVES

The results from the RCT in asymptomatic AS patients (paper 1) showed that statins had no preventive effect of the incidence of new-onset of AF. The second paper, a large scale observational trial showed that statins had a preventive effect on new-onset AF in patients after MI. On the contrary, the meta-analysis in this PhD thesis showed that a preventive effect was only present in the observational studies but was absent in the RCTs. Based on this PhD thesis, although there might be an effect in MI patients, primary statin treatment to prevent new-onset AF cannot be recommended in AS patients or in patients not undergoing cardiac surgery.

SUMMARY

Atrial fibrillation (AF) is a common complication after myocardial infarction (MI) and new-onset AF has been demonstrated to be associated with adverse outcome and a large excess risk of death in both MI and aortic stenosis (AS) patients. Prevention of new-onset AF is therefore a potential therapeutic target in AS and MI patients. Lipid-lowering drugs, particularly statins, have anti-inflammatory and antioxidant properties that may prevent AF. Accordingly, statins are recommended as a class IIa recommendation for prevention of new-onset AF after coronary artery bypass grafting (CABG). However, this preventive effect has not been investigated on new-onset AF in asymptomatic patients with AS or a large scale first-time MI patient sample and data in patients not undergoing invasive cardiac interventions are limited.
This PhD thesis was conducted at the Heart Centre, Rigshospitalet, Denmark with the aim to investigate the three aforementioned questions and to add to the existing evidence of AF prevention with statins. This was done using three different settings: 1) a randomized patients sample of 1,873 from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, 2) a register patient sample of 97,499 with first-time MI, and 3) all published studies until beginning of June 2011 examining statin treatment on new-onset and recurrent AF in patients not undergoing cardiac surgery.

This thesis revealed that statins did not lower the incidence or the time to new-onset AF in patients with asymptomatic AS. However, statin treatment showed an independently preventive effect on new-onset AF, including type-dependent effect and a trend to dosage-dependent effect. In addition, this thesis showed that good compliance to statin treatment was important to prevent new-onset AF. Finally, the meta-analysis in this PhD thesis showed a preventive effect in the observational studies but although this effect was absent in the randomized controlled trials. Based on this PhD thesis, although there might be an effect in MI patients, primary statin treatment to prevent new-onset AF cannot be recommended in AS patients or in patients not undergoing cardiac surgery.

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