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Risks factors for dofetilide-associated torsades de pointes among hospitalized patients with atrial fibrillation

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Background: Significant variation in the approach to the initiation and dose adjustment of dofetilide during hospitalization for atrial fibrillation (AF) has been noted. Certain patients may be at increased risk of excessive QT prolongation which could predispose to Torsades de pointes (TdP).
Purpose: To examine for potentially modifiable risk factors of TdP in patients receiving dofetilide for AF.
Methods: We utilized a case-control cohort with 31 AF patients on dofetilide with subsequent TdP or excessive QTc prolongation (TdP cases). Our controls were selected in a random fashion from our hospital database and matched (1:1) according to age, gender, and dofetilide dose (n=31). We evaluated clinical variables known to pose risk of TdP: 1) QTc interval exceeding recommendations (baseline QTc >440 ms or >500 ms if QRS >120 ms, and subsequent QTc >500 ms or >550 ms if QRS >120 ms); 2) underlying AF with rapid ventricular rate response at the time of drug initiation which potentially obscures accurate QT measurement; 3) bradycardia <50 bpm; 4) potential drug-drug interactions; 5) concomitant QT-prolonging drugs; 6) electrolytes abnormalities; and 7) active diuretic therapy for treatment of heart failure. Multivariate regression analysis was performed to examine for an independent association between these pre-determined risks and TdP.
Results: Age, gender, baseline creatinine clearance, left ventricular ejection fraction and dofetilide dose were well matched between TdP cases and controls. In comparison to the control group, TdP cases were likely to be in AF at the time of dofetilide initiation (72.7% vs. 25.0%), had a longer baseline QTc interval (472±41ms vs. 441±32ms), tended to receive concomitant digoxin and amiodarone (25.8% vs. 3.2%), and were more likely to be on active diuretic therapy (32.3% vs. 9.7%). In multivariate regression analysis of patients admitted for dofetilide initiation (n=50), QTc exceeding recommendations (adjusted odd ratio [AOR] 6.79, 95% confidence interval [CI] 1.48–30.84; P=0.013) and underlying AF with rapid ventricular rate (AOR 14.26, 95% CI 2.05–99.15; P=0.007) were independent risk factors for TdP. In the entire study cohort, including new and long-term dofetilide users (N=62), administration of diuretics (AOR 6.60, 95% CI 1.04–41.93; P=0.046) was independently associated with an increased risk of TdP.
Conclusions: Excessive QTc prolongation and AF with rapid ventricular rate at the time of drug initiation, as well as active diuretic therapy are risk factors for dofetilide-related TdP. This data provides insight into how to develop preventive strategies that could be adapted for safety protocols among hospitalized patients on dofetilide.

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Faster heart rate is associated with significantly higher risk of death and hospitalization due to heart failure in patients with persistent or permanent atrial fibrillation: insights from ARISTOTLE

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Background: Rate-control is a front-line therapy in patients with persistent or permanent atrial fibrillation (AF). However, the independent association of heart rate with patient outcomes and the optimal level of heart rate control are still unknown, including for patients who have AF and heart failure (HF).
Purpose: To assess the relationship between heart rate (ventricular response in AF) and clinical outcomes in patients with persistent or permanent AF, with and without HF.
Methods: We included in this post-hoc analysis all patients enrolled in the ARISTOTLE trial with persistent or permanent AF (n=15,365). Heart rate was measured by electrocardiogram at baseline. Socio-demographic and clinical characteristics, including medications and selected biomarkers (NT-proBNP, troponin I and T, GDF-15), were compared according to the level of heart rate (categorized as <80 bpm, 80–119 bpm, and ≥120 bpm). Relationships between heart rate (as a continuous variable) and clinical endpoints were assessed using Cox regression models. Adjusted hazard ratios (HR) and 95% confidence intervals (CIs) were calculated. The analysis was performed in the overall population and in those with HF.
Results: Patients with faster heart rate (≥120 bpm [n=1094]) were younger and more likely to have a history of HF or reduced ejection fraction than patients with heart rates of either 80–119 bpm (n=6409) or <80 bpm (n=7862). They were also more likely to be on beta-blockers (69%), digoxin (42%), amiodarone (14%), or verapamil (6%). All biomarkers were lower in the group of patients with controlled heart rate (80–119 bpm) as compared with patients with heart rate <80 bpm and those with heart rate ≥120 bpm. In the overall population, increase in heart rate (per 10 beats per minute) was associated with a higher risk of death (HR 1.04, 95% CI [1.01–1.07]) and HF hospitalizations (HR 1.06, 95% CI [1.01–1.10]) in the adjusted analysis (p≤0.01). In patients with HF, increase in heart rate was associated with a high risk of HF hospitalizations (HR 1.06, 95% CI [1.01–1.11]) in the adjusted analysis (p=0.02), but not death.
Conclusion: In patients with persistent or permanent AF, a faster heart rate is associated with a modest but significant increase in death and HF hospitalizations in the overall population, and with an increase in HF hospitalizations in patients with HF. More randomized trials are needed to determine whether, how, and among whom heart rate should be more aggressively managed in patients with AF.
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Antiarrhythmic drugs increase the risk of fall-related injuries and syncope in patients with atrial fibrillation - a nationwide cohort study

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Introduction: Rate management in atrial fibrillation (AF) with anti-arrhythmic drugs (AAD) and rate-lowering drugs (RLD) can cause bradyarrhythmia that could lead to fall-related injuries and syncope especially in the elderly AF population.
Purpose: To investigate whether use of AADs and RLDs or in combination of both increase the risk of fall-related injuries and syncope in patients with AF and aged ≥65 years.
Methods: Through the Danish nationwide registries all patients with AF between 2000 and 2014 and aged above ≥65 years were included on the date of their first prescription for an AAD defined as amiodarone and class-1C or a RLD defined as a beta blocker, digoxin, or class-IV drug. Outcomes were hospitalized fall-related injuries, syncope, and both as composite endpoints. The incidence rate ratio (IRR) was calculated using time-varying Poisson regression in four exposure groups; mono-therapy RLD, monotherapy AAD, dual therapy RLDs, and dual therapy with a RLD and an AAD. Sub analyses were also performed for each specific drug and combinations of two drugs.
Results: A total of 100,935 patients with AF were included in the study; 53,481 (53.0%) were women and a median age of 78 years (interquartile range [IQR]: 72–84). During a median follow-up of 2.5 years (IQR 1.0–5.0), 19,773 (19.6%) had a diagnosis of fall-related injury and 6,636 (6.6%) had a diagnosis of syncope. Compared to RLD monotherapy, for fall-related injury and syncope on dual RLD the IRR was 0.88 (95% confidence interval [CI]; 0.85–0.91), on AAD monotherapy it was 1.36 (1.24–1.49), and on dual therapy with AAD and RLD it was 1.48 (1.37–1.60) (Figure 1). Similar when analyzing specific drugs, compared to beta blocker treatmen amiodarone increased the risk of fall-related injuries and syncope; amiodaron monotherapy; IRR: 1.48; (1.34–1.63), amiodarone & beta-blocker; IRR: 1.64 (1.48–1.81), amiodarone & digoxin; IRR: 1.86 (1.56–2.22), amiodarone & class IV IRR; 1.71 (1.22–2.38).

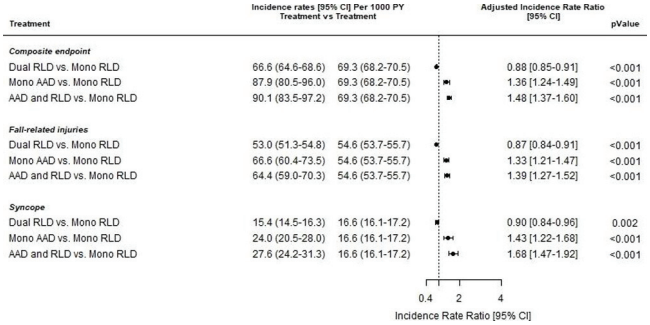

Figure 1. Incidence rate ratios and 95% confidence intervals for fall-related injuries, syncope and composite endpoint by combinations of rate lowering and anti-arrhythmic drugs. The model was adjusted for age, sex, calendar year, ischemic heart disease, heart failure, chronic pulmonary obstruction disease, diabetes, valvular AF, ablation for AF, ablation for other (ventricular tachycardia, supraventricular tachycardia, and HIS-ablation). Abbreviations: AF; atrial fibrillation, AAD; anti-arrhythmic drug, IRR; incidence rates rate, PY; person years,

Conclusion: In elderly patients with AF, AAD treatment was associated with increased risk of fall-related injuries and syncope. The highest risk was found for AAD combined with RLD and specifically amiodarone was associated with increased risk for both outcomes.
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The relationships between heart rate variability, inflammation and fibrosis markers in patients with atrial fibrillation

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Background: Atrial fibrillation (AF) is the most frequent arrhythmia found in clinical practice. It is assumed that the autonomic nervous system, more specifically,

a deviation of dynamic balance between the sympathetic and parasympathetic influences, plays the essential role in the development of AF. An important criterion in the evaluation of the interaction of the autonomic nervous system and circadian rhythms of physiological functions of the heart is heart rate variability (HRV). HRV parameters have a prognostic value for the occurrence and development of various clinical forms of AF. Moreover, inflammation and fibrosis are the important and leading mechanisms of AF. The aim of this study is to evaluate relationships between inflammation, fibrosis markers and parameters of HRV including the impact of this relationship on clinical presentation and outcome of AF patients.

Methods: 145 patients with nonvalvular AF (mean age 62.6±7.5) were enrolled in this study. After the enrollment, the echocardiography examination and 24-hour ambulatory Holter monitoring ECG have been registered in each patient. Estimated time-domain parameters of HRV were SDNN, RMSSD and frequency-domain parameters were LF and HF. We have measured plasma indexes of inflammation (CRP, IL-6) and fibrosis (TGF-β1) in all the observed patients with AF and 42 healthy control subjects. All of blood tests in plasma have been determined by ELISA on the analyzer "Stat Fax 303 Plus" using commercial kits "BioSource". Studies have been conducted on the basis of simple randomized open label protocols, using the universal statistical packages SPSS 13.0 and EXCEL-2007.

Results: The obtained results showed that compared with the control group, AF patients had higher levels of HRV: time-domain parameters (SDNN p=0.001; RMSSD p=0.025) and frequency-domain parameters (LF p=0.005; HF p=0.05). AF patients had higher levels of inflammation and fibrosis markers: IL-6 (p=0.033), CRP (p=0.002), TGF-β1 (p=0.001). Plasma CRP and TGF-β1 levels, as well as HRV time domain parameters were higher among AF patients at "high" risk of stroke (p=0.003). Moreover, levels of these parameters were markedly elevated in patients with dilated left atrium and longer duration of AF.

Conclusions: AF is associated with inflammation and fibrosis, as well as the increase of HRV parameters, which demonstrate sympathetic and parasympathetic influences on the heart. The link between HRV, inflammation and fibrosis can represent a prognostic value in maintaining of AF.

ATRIAL FIBRILLATION – STROKE PREVENTION

P5796

Prevalence and correlates of left atrial enlargement based on left atrial volume index in korean patients with non-valvular atrial fibrillation: data from comparison study of drugs for symptom control

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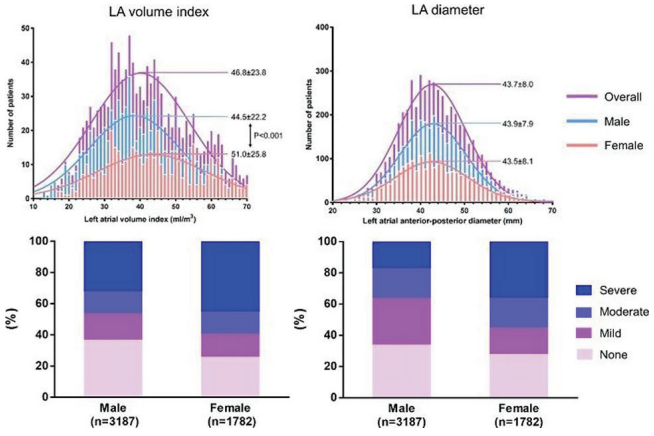
Background: Left atrial enlargement (LAE) was known to be associated with increased cardiovascular events. Prevalence and correlates of LAE based on left atrial volume index (LAVI) in non-valvular atrial fibrillation (NVAF) patients was not well evaluated.

Purpose: To find out the prevalence and correlates of LAE based on LAVI in NVAF patients

Methods: A total of 4,969 NVAF patients enrolled in the COmparison study of Drugs for symptom control and complication prEvention of AF (CODE-AF) registry were evaluated (mean 67.6 years, 64.1% male). LAE was classified as mild (≥34 mL/m^3), moderate (≥42 mL/m^3), and severe (≥48 mL/m^3).

Results: Mean LAVI in overall population was 46.8±23.8 mL/m^3 and was larger in female compared to male (51.0±25.8 vs. 44.5±22,2 mL/m, p<0.001). LAE was diagnosed in 3334 (67.1%) patients (mild, 16.3%; moderate, 13.8%; severe, 36.9%). Moderate-severe LAE was noted in 27.3% and 37.1% of patients with CHA2DS2-VASc score of 0 and 1, respectively. In the multivariable analysis, type of AF (OR 3.16 95% CI 2.78–3.60 for persistent; OR 7.44, 95% CI 4.53–12.98 for permanent) was at highest odds of moderate-severe LAE. The other correlates were age, females, lean body mass, CHA2DS2-VASc score, chronic kidney disease, valvular heart disease (other than mitral stenosis), intracardiac devices, high left atrial filling pressure. Whereas prior AF ablation and symptomatic AF showed lower odds. There was weak correlation between left atrial diameter and LAVI (kappa 0.369, p<0.001). The classification based on LA diameter rendered 17.5% of overestimation and 29.1% of underestimation.

Conclusion: LAE was common echocardiographic finding in NVAF and was associated with various factors. There was considerable discrepancy between LAVI and LA diameter for diagnosis of LAE



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ECG holter monitoring and survival of patients with atrial fibrillation

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Background: The importance of duration and number of ventricular pauses in the patients with atrial fibrillation is insufficiently known.

Purpose: The aim of the study was to assess the clinical importance of ventricular pauses in patients with atrial fibrillation during 24-hours Holter monitoring.

Methods: The study group consisted of 271 consecutive patients admitted to cardiology outpatient clinic in years 2004–2017 who had 24-hours ECG Holter and during the whole monitoring period had atrial fibrillation.

The retrospective analysis of the following data from the medical recordings: age, gender, concomitant diseases: diabetes, arterial hypertension, previous myocardial infarction, stroke, percutaneous coronary interventions or coronary artery bypass graft (PCI/CABG), permanent cardiac pacing, history of atrial fibrillation was performed. Moreover, the mean, maximum and minimum heart rate, the duration of the longest ventricular pause, the number of ventricular pauses longer than 2 seconds were assessed.

The personal identification numbers (PESEL) of the patients were used to obtain survival data.

The group of 71 patients who died were compared to 200 patients who survived till December 1-st 2017.

Multivariate Cox regression analysis was performed to find factors related to prognosis.

Results: The maximal, mean and minimal value of heart rate were similar in the two groups of patients. Multivariate Cox regression analysis revealed that the following variables were related to the increased mortality: longer history of atrial fibrillation (OR 1.04 95% CI 1.01–1.08; p=0.023), PCI/CABG in medical history (OR 4.01, 95% CI 1.77–9.08; p<0.001), higher number of ventricular pauses lasting at least 2 s (OR 1.003 95% CI 1.001–1.005; p<0,001). Contrary the patients with longer duration of the longest ventricular pauses had better survival (OR 0.34 95% CI 0.20–0.59; p<0.001).

Conclusion(s): 1. Both the lack of ventricular pauses and the high number of ventricular pauses during 24 hours ECG Holter monitoring is related to increased mortality in patients with atrial fibrillation.

2. The mean, maximal and minimal value of heart rate do not distinguish patients in term of survival.

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Prevalence of interatrial block and its association with specific coronary arteries in patients with ST- segment elevated myocardial infarction

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Introduction: Interatrial block (IAB), defined as P wave duration greater than 120 milliseconds (ms), is strongly associated with recurrence of atrial fibrillation (AF) in different clinical scenarios. Ischemia is considered as one of the mechanisms underlying the pathogenesis of IAB by contributing atrial fibrosis.

Purpose: The aim of this study is to investigate the correlation between culprit coronary artery lesion with the presence of IAB and newly detected AF at 12 months.

Abstract P5797 – Table 1. Clinical and ECG characteristics

	Male gender (%)	Age (years)	CHF (%)	PCI/CABG (%)	The longest pause ≥3s (%)	The longest pause 2–2.9s (%)	The longest pause <2s (%)	Heart rate mean / max / min	Atrial fibrillation history (years)	DM (%)	Pernament pacing (%)
Died (N=71)	55	75	33	25	10	30	60	76 / 134 / 46	5 (1–10)	32	10
Survived (N=200)	58	71	21	13	19	43	38	76 / 144 / 44	4 (1.5–9)	22	4
p	NS	0.001	0.054	0.015	0.08	0.054	0.001	NS	NS	0.066	0.06

CHF: congestive heart failure; DM: diabetes mellitus; PCI/CABG: Percutaneous coronary intervention/Coronary artery bypass graft.