Suomen Kardiologinen Seura

Finnish Cardiac Society

49th Progress Report Meeting

April 26, 2023, Tampere

Contents

49th Progress Report Meeting Programme

Sopraano. Session 1. 49th Progress Report Meeting – YIAC

Chairman Tuomas Kiviniemi, Finnish Cardiac Society

Meeting is supported by unrestricted educational grant from Boehringer Ingelheim

11.00–11.05	Opening remarks. Tuomas Kiviniemi, Finnish Cardiac Society
11.05–11.13	Risk factors for ischemic sudden cardiac death in women. Ida Hookana (MD), Research Unit of Internal Medicine, MRC Oulu
11.13–11.21	Outcome of transcatheter atrial septal defect closure in a nationwide cohort. Valtteri Muroke (MD), Department of Cardiology, Helsinki University Hospital
11.21–11.29	Wall shear stress predicts pathological and biomechanical changes in thoracic aortic aneurysm. Miika Kiema (Doctoral Researcher), A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland
11.29–11.37	Apelin and apela for therapy of myocardial fibrosis and heart failure. Anna Kemppi (MSc, Doctoral Researcher), Research Unit of Biomedicine and Internal Medicine, University of Oulu, Faculty of Medicine
11.37–11.45	Cardiac ischemia on-a-chip: Antiarrhythmic effect of levosimendan on ischemic human-induced pluripotent stem cell-derived cardiomyocytes. Mahmoud Gaballa (PhD Student), Faculty of Medicine and Health Technology, Tampere University
11.45–11.53	Prognostic significance of beat-to-beat variability of spatial heterogeneity of repolarization analyzed from 5-minute resting electrocardiogram in coronary artery disease. Janne Rahola (MD), MRC Oulu, Cardiology Research Group, University of Oulu
11.53–12.01	Validation of novel electrocardiographic classification for stroke prediction in patients with atrial fibrillation undergoing cardioversion. Arto Relander (MD), Heart Center, Turku University Hospital and University of Turku
12.01–12.09	Transcatheter aortic valve implantation in nonagenarians. Matti Riihiniemi (BM), Department of Cardiology, University of Oulu and Oulu University Hospital
12.09–12.17	Major complications after mechanical aortic valve replacement. Rikhard Björn (MD), Heart Center, Turku University Hospital and University of Turku
12.17–12.25	Novel genetic variants associated with sudden cardiac death due to primary myocardial fibrosis. Anne Doedens (MSc), Research unit of Biomedicine and Internal Medicine, University of Oulu and Oulu University Hospital
12.25–12.30	Closing remarks

History of the Progress Report Meetings

Progress Report Meeting is organized by Finnish Cardiac Society to present opportunity for young investigators to report results of their studies. An important point is also training in presenting scientific papers to criticism of senior colleagues.

Boehringer Ingelheim has supported organizing the meeting from the beginning, 1975 by helping in practi-cal matters and presenting grants to the best of speakers.

Winners of the Boehringer Ingelheim grants

From year 2007 onwards the competition has had two categories instead of 1st and 2nd prize. However, if less than three eligible abstracts have been received to either category, the organizers reserve the right to combine the categories.

Year	1st Prize	2nd Prize
1975	Erkki Pesonen	–
1976	Heikki Karppanen	Markku S. Nieminen
1977	Matti Halinen	Ulla Korhonen
1978	Ilkka Torstila	Markku S. Nieminen
1979	Olli Meretoja	Aila Rissanen
1980	Jorma Viikari	Jouko Jalonen
1981	Markku Kupari	Irma Koivula
1982	Heikki Huikuri	Markku Kupari
1983	Seppo Hietakorpi	Kari Niemelä
1984	Markku Laakso	Heikki Huikuri
1985	Jukka Räisänen	Kari Niemelä
1986	Pekka Koskinen	Juha Mustonen
1987	Kimmo Mattila	Silja Majahalme
1988	Heikki Tikkanen	Paula Rämö
1989	Hannu Näveri	Keijo Peuhkurinen
1990	Markku Mäkijärvi	Juhani Valkama
1991	Eero Mervaala	Paavo Uusimaa
1992	Eero Mervaala	Anne Remes
1993	Juha Hartikainen	Helena Kovanen
1994	Kai Kiilavuori	Juha Perkiömäki
1995	Sirkku Pikkujämsä	Pasi Tavi
1996	Jorma Kokkonen	Timo Mäkikallio
1997	Pekka Raatikainen	Marja Laitinen
1998	Marja Laitinen	Antti Ylitalo, 3rd Prize Timo Mäkikallio
1999	Mika Laine	Timo Mäkikallio
2000	Saila Vikman	Antti Kivelä
2001	Jari Tapanainen	Pertti Jääskeläinen
2002	Tuomas Rissanen	Markku Pentikäinen
2003	Juhani Junttila	Markus Leskinen
2004	Jere Paavola	Tuomas Rissanen
2005	Mikko Mäyränpää	Satu Helske
2006	Olli Tenhunen	Johan Lassus

Year	Basic Science category	Clinical Research category
2007	Satu Helske	Ville Kytö
2008	Mirella Hietaniemi	Minna Kylmälä
2009	Johanna Lähteenvuo o.s. Markkanen	Annukka Marjamaa
2010	1st Prize Jani Tikkanen 2nd Prize Riina Kandolin	the categories were combined
2011	Markku Lähteenvuo	Aapo Aro
2012	1st Prize Kirsi Kujala 2nd Prize Maija Bry	the categories were combined
2013	Suvi Syväranta	Toni Grönberg
2014	1st Prize Leena Kaikkonen 2nd Prize Heli Tolppanen	the categories were combined
2015	1st Prize Aissa Bah 1st Prize Markus Räsänen	the categories were combined
2016	1st Prize Heli Tolppanen 1st Prize Kaj Ekström	the categories were combined
2017	Tarja Alakoski	Samuli Jaakkola
2018	Maija Ruuth	Tero Penttilä
2019	Annakaisa Tirronen	Anette Haukilahti
2020	1st Prize, Tiia Istolahti 1st Prize, Henna Korpela	2nd Prize, Vilbert Sikorski
2021	1st Prize Aleksi Leikas	2nd Prize Minna Koivunen
2022	1st Prize Markus Ritvos	2nd Prize Kristiina Harju

Ida Hookana (MD)
Research Unit of Internal Medicine, MRC Oulu

Risk factors for ischemic sudden cardiac death in women

Lauri Holmström, MRC Oulu, Oulu, Finland, Anette Haukilahti, MRC Oulu, Oulu, Finland, Antti Kiviniemi, MRC Oulu, Oulu, Finland, Tuomas Kenttä, MRC Oulu, Oulu, Finland, Juha Vähätalo, MRC Oulu, Oulu, Finland, Mikko Tulppo, MRC Oulu, Oulu, Finland, Samuli Lepojärvi, MRC Oulu, Oulu, Finland, Juha Perkiömäki, MRC Oulu, Oulu, Finland, Heikki Huikuri, MRC Oulu, Oulu, Finland, Juhani Junttila, MRC Oulu, Oulu, Finland

Aim

Sudden cardiac death (SCD) is a significant cause of death accounting for 15-20 % of all deaths in Western countries. Coronary artery disease (CAD) is the most common cause of SCD in both genders and SCD is often the first manifestation of underlying CAD among women. The aim of this case-control study was to determine factors associated to SCD due to CAD in women.

Methods

The study group consists of women with ischemic SCD (N=888) derived from the Fingesture study conducted in Northern Finland from 1998 to 2017. All SCDs were autopsy verified. The control group consisted of women with angiographically verified CAD without SCD occurring during the 5-year-follow-up (N=610) from the Artemis study. To perform comparison between these groups, we utilized medical records, autopsy findings, echocardiograms, and ECGs.

Results

Subjects with SCD were older (73.2±11.3 vs. 68.8±8.0 $p < 0.001$) and were more likely to be smokers or ex-smokers (37.1% vs. 27.6%, $p = 0.045$) compared to alive CAD patients. The proportion of subjects with prior myocardial infarction (MI) was higher in controls (46.9% vs. 41.4% in SCD subjects, $p = 0.037$), but in contrast, SCD subjects were more likely to have underlying silent MI (25.6% vs. 2.4% in CAD controls, $p < 0.001$). Decreased left ventricular ejection fraction (LVEF 35-55 %) was more common finding in SCD subjects than in CAD controls (33.1% vs. 8.7%, $p < 0.001$, respectively) as well as LV hypertrophy (70.9% vs. 55.1%, $p < 0.001$, respectively). Various ECG-abnormalities were more common in SCD subjects including higher heart rate, prolonged QTc-interval, wide or fragmented QRS-complex and early repolarization. The prevalence of Q-waves and T-inversions did not differ between these groups.

Conclusions

Underlying LVH and previous MI with myocardial scarring are common and often undiagnosed in women with ischemic SCD. These results suggest that untreated CAD with concomitant myocardial disease carries a high risk of SCD among women.

Figure 1. Flow chart of the study population selection

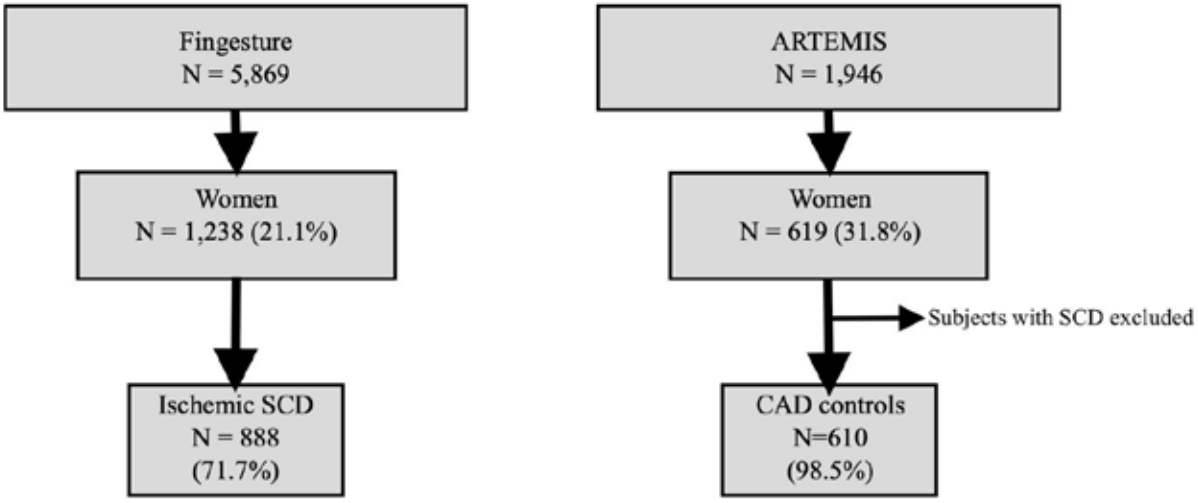
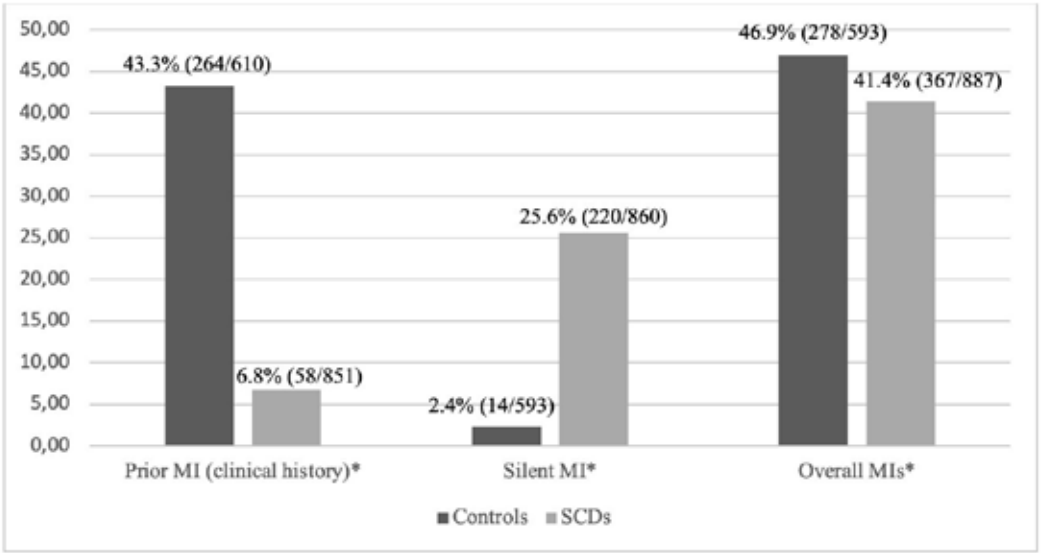
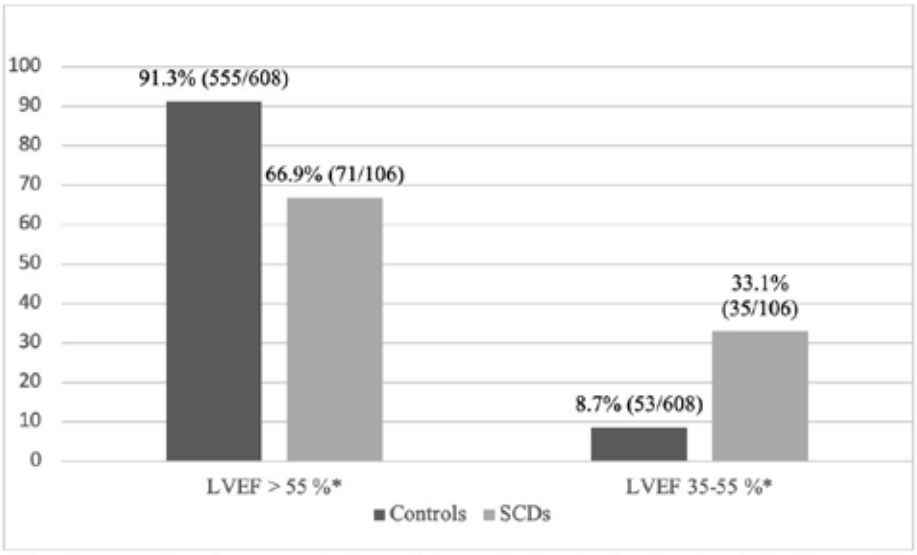


Figure 2. Prior MIs among SCD subjects and CAD controls



All subjects are females. MI indicates myocardial infarction. Prior MI: clinical history of MI. Silent MI: findings related to infarction scar with no MI/CAD history. Overall MIs: reported MIs, silent MIs and infarction scars discovered at the autopsy. *Significant difference ($p < 0.05$) between groups.

Figure 3. Left ventricular ejection fraction among SCD subjects and alive CAD controls



All subjects are females. LVEF indicates left ventricular ejection fraction. *Significant difference between groups ($p < 0.05$).

Table 1. Characteristics of ischemic SCD victims and alive CAD controls

	SCDs (N=888)	Controls (N=610)	p-value
Continuous variables, mean ± SD			
Age (y)*	73.2±11.3	68.8±8.0	p < 0.001
BMI (kg/m²)*	27.4±6.4	28.6 ± 5.0	p < 0.001
Categorical variables, prevalence, % (n/N)			
BMI			
BMI < 18.5*	5.5 % (39/703)	0.3 % (2/610)	p < 0.001
BMI > 30*	29.0 % (204/703)	37.0 % (226/610)	p = 0.002
Current smoker*	30.2 % (35/116)	6.3 % (38/608)	p < 0.001
Prior smoker*	6.9 % (8/116)	21.4 % (130/608)	p < 0.001
Current or prior smoker*	37.1 % (43/116)	27.6 % (168/608)	p = 0.045

All subjects are females. BMI indicates body mass index. *Significant difference between groups ($p < 0.05$)

Table 2. Prevalence of LVH among subjects with SCD and alive CAD controls

	SCDs (N=887)	Controls (N=610)	p-value
Continuous variables			
Heart weight (g), mean ± SD	404.1±95.6		
LVM (g), median, interquartile range		164.5 (142.5, 199.4)	
Categorical variables, prevalence, % (n/N)			
LVH	70.9 (629/887)	55.1 (336/610)	p < 0.001
LVH or prior MI	80.0 (710/888)	73.5 (443/603)	p = 0.004

All subjects are females. LVM indicates left ventricular mass. LVH= left ventricular hypertrophy. MI=myocardial infarction. *=Significant difference between groups ($p < 0.05$)

Table 3. Prevalence of electrocardiographic risk markers among SCD subjects and alive CAD controls

	SCDs (N = 171)	Controls (N = 595)	p-value
Continuous variables, mean ± SD			
QTc (ms)*	437.3±37.3	429.0±24.3	0.006
JTc (ms)*	342.0±35.7	335.9±21.8	0.036
PR (ms)*	164.7±35.5	172.9±28.9	0.007
Heart rate*	76.3±15.7	67.3±8.61	< 0.001
Categorical variables, prevalence, % (n/N)			
LVH (Sokolov-Lyon)	4.1 (7/171)	4.7 (28/595)	0.838
LVH (Cornell)	18.7 (32/171)	18.0 (107/595)	0.910
QTc > 460 ms*	25.7 (44/171)	11.1 (66/595)	< 0.001
QRS > 110 ms* *BBBs excluded*	9.5 (15/158)	2.7 (15/555)	< 0.001
QRS > 100 ms* *BBBs excluded*	15.2 (24/158)	9.4 (52/555)	0.041
PR < 120 ms *AFs & AFLs excluded*	3.4 (5/146)	1.6 (9/579)	0.172
PR > 200 ms *AFs & AFLs excluded*	14.4 (21/146)	14.9 (86/579)	0.898
Early repolarization* *BBBs excluded*	24.1 (38/158)	16.6 (92/554)	0.036
Lateral	14.6 (23/158)	9.6 (53/554)	0.080
Anterior	0.6 (1/158)	0 (0/554)	0.222
Inferior	9.5 (15/158)	7.6 (42/554)	0.506
Q-waves	9.4 (16/171)	6.2 (37/595)	0.171
Lateral	0.6 (1/171)	0.3 (2/595)	1.000
Anterior	2.3 (4/171)	1.0 (6/595)	0.243
Inferior	6.4 (11/171)	5.2 (31/595)	0.568
T-inversions	19.3 (33/171)	23.9 (142/594)	0.217
Lateral	13.5 (23/171)	13.8 (82/594)	1.000
Anterior*	5.3 (9/171)	11.1 (66/594)	0.028
Inferior	6.4 (11/171)	5.2 (31/594)	0.568
Fragmented QRS* *BBBs excluded*	42.4 (67/158)	23.8 (132/554)	< 0.001
Lateral*	14.6 (23/158)	2.3 (12/554)	< 0.001
Anterior*	10.8 (17/158)	3.2 (18/554)	< 0.001
Inferior*	36.1 (57/158)	20.0 (111/554)	< 0.001

All subjects are females. LVH indicates left ventricular hypertrophy. BBB=bundle branch block. AF = Atrial fibrillation. AFL = atrial flutter.
*Significant difference between groups (p < 0.05)

Valtteri Muroke (MD)
Department of Cardiology, Helsinki University Hospital

Outcome of transcatheter atrial septal defect closure in a nationwide cohort

Mikko Jalanko, Helsinki University Hospital, Helsinki, Finland, Jari Haukka, University of Helsinki, Helsinki, Finland, Juha Hartikainen, Kuopio University Hospital, Kuopio, Finland, Anna Tahvanainen, Tampere Uni-versity Hospital, Tampere, Finland, Heikki Ukkonen, Turku University Hospital, Turku, Finland, Kari Ylitalo, Oulu University Hospital, Oulu, Finland, Jaana Pihkala, New Childrens Hospital, Helsinki, Finland, Juha Sinisalo, Helsinki University Hospital, Helsinki, Finland

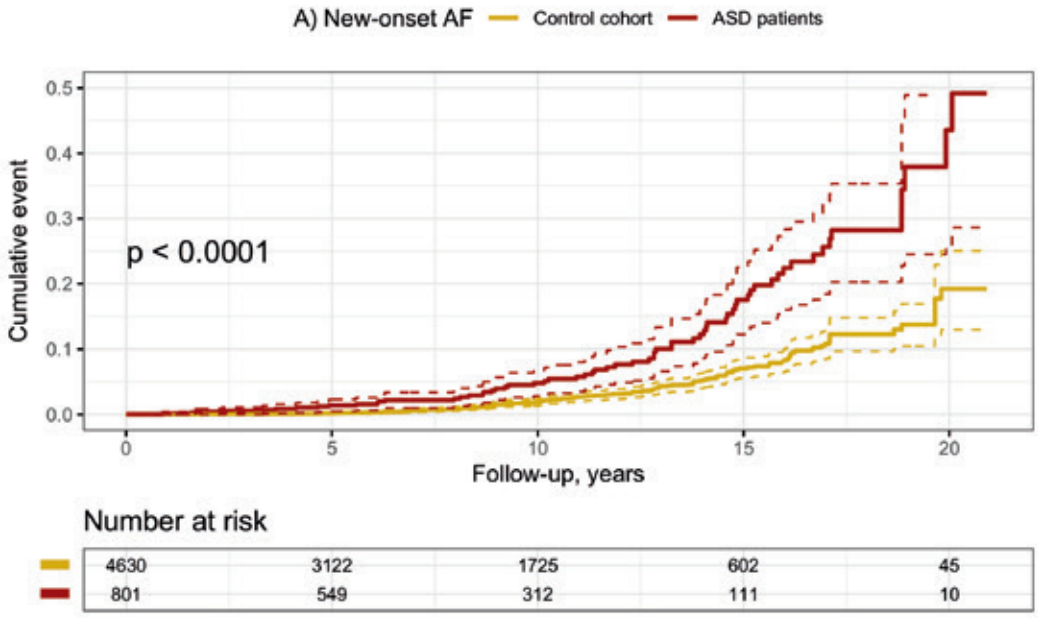
Background
Transcatheter (TC) atrial septal defect (ASD) closure has been the mainstay of therapy for secundum-type ASDs for over 20 years.

Aims
This nationwide cohort evaluated the long-term outcome of transcatheter closed atrial septal defects (ASD).

Methods
The study enrolled every transcatheter ASD closure performed in Finland from 1999 to 2019. Five age, sex, and municipality-matched controls per ASD patient were gathered from the general population. The median follow-up period was 5.9 years (range 0-20.8). We used the hospital discharge register to gather all hospital visits and diagnoses. Closure complications and echocardiographic changes were collected from the elec-tronic health records.

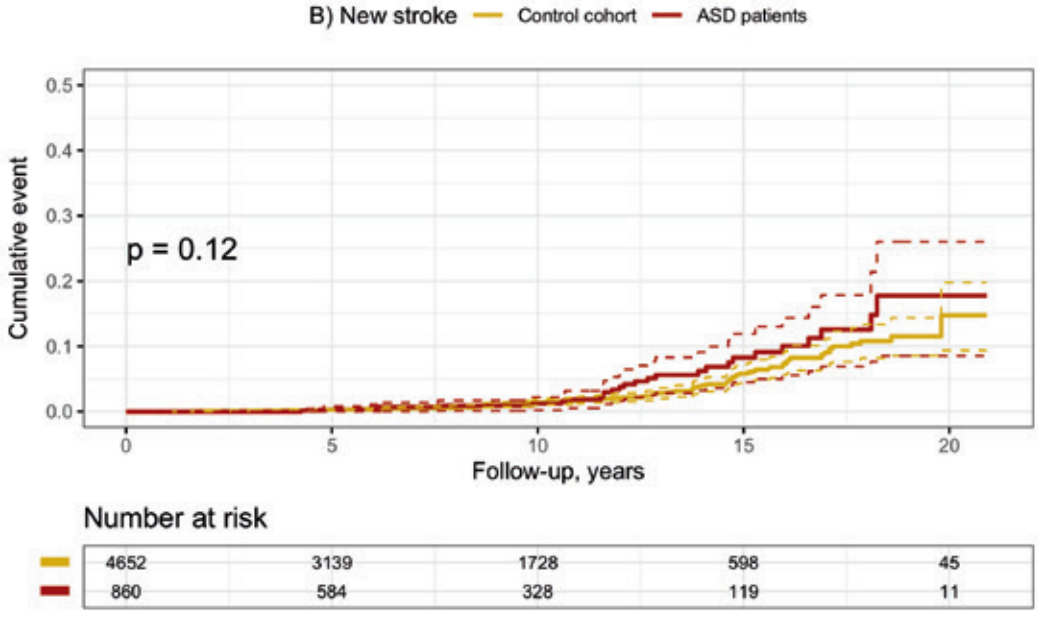
Results
Transcatheter ASD closure was performed in 1000 patients (68.5% females) during the study period. The median (range) age at the time of the procedure was 37.9 (1.8-87.5) years. ASD patients had an increased risk for new-onset atrial fibrillation (RR 2.45, 95% CI: 1.84-3.25), migraine (RR 3.61, 95% CI: 2.54-5.14), ischemic heart disease (RR 1.73, 95% CI: 1.23-2.45), ventricular fibrillation/tachycardia (RR 3.54 (95% CI: 1.48-8.43) and AV conduction disorder (RR 3.60, 95% CI: 1.94-6.70) compared to the control cohort. Stroke risk was not increased (RR 1.36, 95% CI: 0.91-2.03). Adverse events occurred in 6.3% (n = 63) of the pa-tients, including four erosions and ten device embolizations.

Conclusion
After TC closure of ASD, patients had a higher risk of new-onset atrial fibrillation and migraine. As novel findings, we found an increased risk for ischemic heart disease, AV conduction disorders, and ventricular fibrillation/tachycardia.



Number at risk

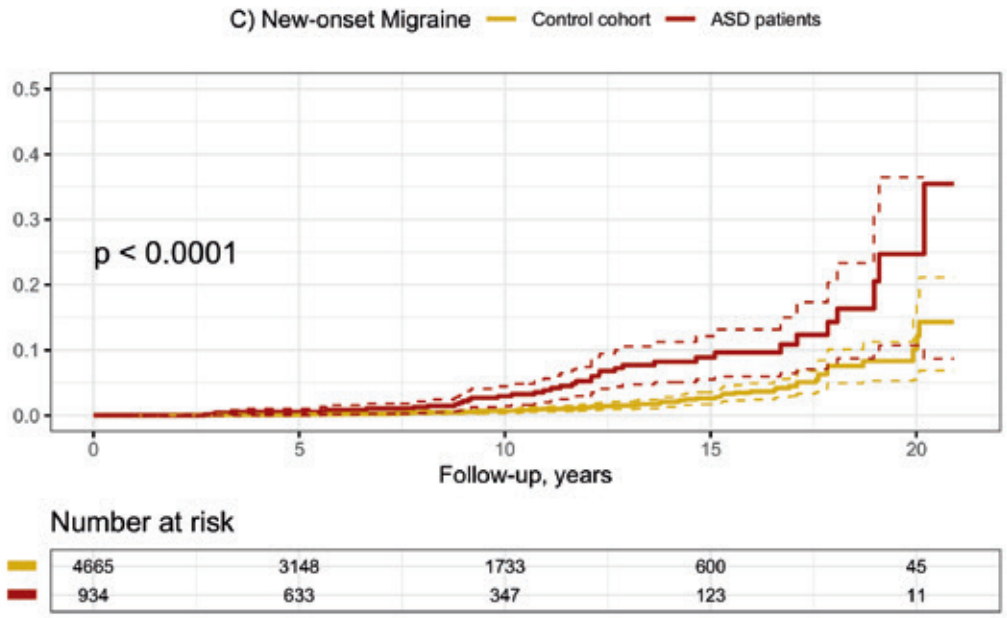
Control cohort	4630	3122	1725	602	45
ASD patients	801	549	312	111	10

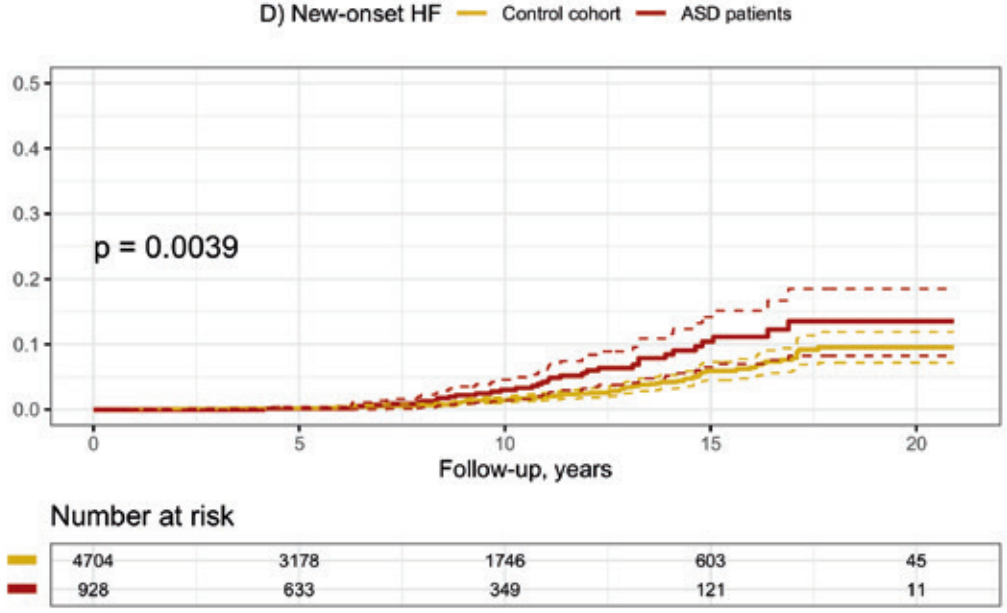


Number at risk

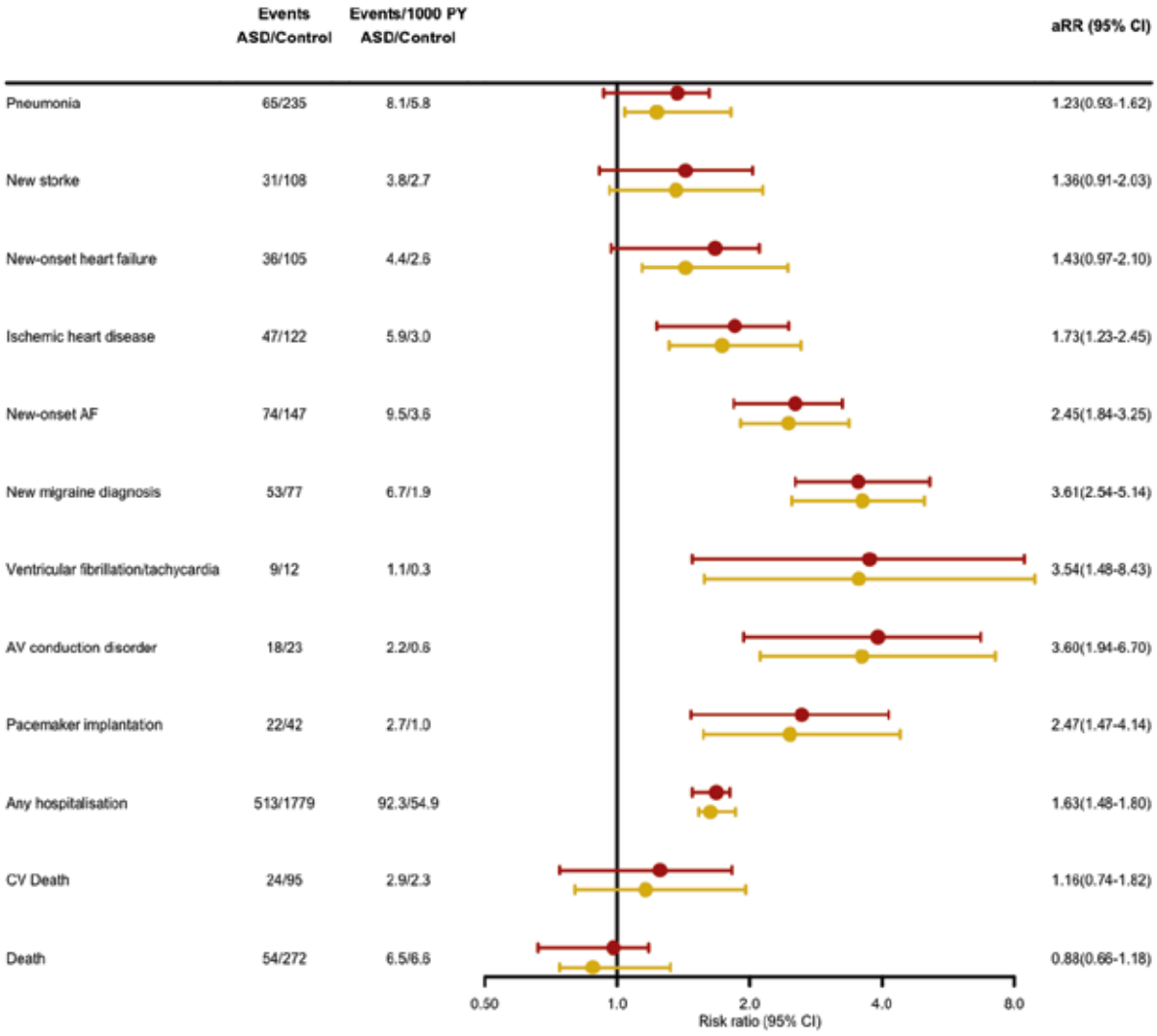
Control cohort	4652	3139	1728	598	45
ASD patients	860	584	328	119	11

Valtteri Muroke (MD)
Department of Cardiology, Helsinki University Hospital





Valtteri Muroke (MD)
Department of Cardiology, Helsinki University Hospital



Valtteri Muroke (MD)
Department of Cardiology, Helsinki University Hospital

Table 1. Descriptive characteristics: Values are presented as mean (SD), median (IQR), or percentage (number of patients). Data is based on electronic health records.

	ASD-patients N= 1000	Missing
Female (%)	68.5% (685)	0
Median age at the time of the procedure	37.9 (11.1–57.3)	0
Median BMI	23.2 (17.7–27.4)	329
Another congenital heart defect:	7.1% (71)	3
AF:		6
Chronic	10.9% (108)	
Paroxysmal	6.4% (64)	
SVT	3.0% (30)	6
History of VT/VF	0.5% (4)	0
HFrEF	1.8% (18)	3
Migraine	7.8% (77)	18
Stroke	12.4% (124)	4
TIA	3.1% (31)	4
NYHA class		
1	78.0% (750)	38
2	17.4% (167)	
3	4.6% (44)	
4	0.1% (1)	
Multi fenestrated ASD	13.5% (135)	2
Floppy septum	20.2% (90)	555
Mean Qp/Qs ratio	2.0 (0.59)	445

23

	ASD-patients N= 1000	Missing
Median native ASD size on TEE (mm)	11.6 (8.5–15)	122
Median balloon size (mm)	15.5 (12–20)	64
Brand name of the device		7
Amplatzer ASD	84.8% (842)	
Amplatzer Cribriform	1.8% (18)	
Amplatzer PFO	3.3% (33)	
Figulla	4.7% (47)	
HELEX	4.4% (44)	
STARflex	0.9% (9)	
Amplatzer ASD size:		159
<20mm	66.0% (555)	
20-30mm	31.6% (266)	
>=30mm	2.4% (20)	

AF = Atrial fibrillation, ASD = atrial septal defect, BMI = body mass index, HFrEF = Heart failure with reduced ejection fraction, NYHA = New York Heart Association, PFO = Patent foramen ovale, SVT = Supraventricular tachycardia, TIA = Transient ischemic attack, VF = Ventricular fibrillation, VT = Ventricular tachycardia.

Valtteri Muroke (MD)
Department of Cardiology, Helsinki University Hospital

Table 2. Complications during the procedure, hospital stay, and after the discharge.

	During procedure	During hospital stay	After discharge
Major bleed	1 (0.1%)		4 (0.4%)
Device embolization	2 (0.2%)	6 (0.6%)	2 (0.2%)
Device erosion		1 (0.1%)	3 (0.3%)
Catheter thrombus	11 (1.1%)		
Ruptured septum	1 (0.1%)		
Coronary occlusion	1 (0.1%)		
Access site complication	1 (0.1%)	10 (1.0%)	9 (0.9 %)
Intubation related complication	5 (0.5%)		
Pericardial effusion		3 (0.3%)	
Post op. fever		4 (0.4%)	
Allergic reaction	1 (0.1%)	1 (0.1%)	1 (0.1 %)

Wall shear stress predicts pathological and biomechanical changes in thoracic aortic aneurysm

Jaakko K. Sarin, Tampere University Hospital, Tampere, Finland, Petteri Kauhanen, Kuopio University Hos-pital, Kuopio, Finland, Jari Torniainen, University of Eastern Finland, Kuopio, Finland, Hanna Matikka, Kuo-pio University Hospital, Kuopio, Finland, Emma-Sofia Luoto, University of Eastern Finland, Kuopio, Finland, Pekka Jaakkola, Kuopio University Hospital, Kuopio, Finland, Petri Saari, Kuopio University Hospital, Kuo-pio, Finland, Timo Liimatainen, Oulu University Hospital, Oulu, Finland, Ritva Vanninen, Kuopio University Hospital, Kuopio, Finland, Seppo Ylä-Herttuala, University of Eastern Finland, Kuopio, Finland, Marja Hed-man, Kuopio University Hospital, Kuopio, Finland, Johanna P. Laakkonen, University of Eastern Finland, Kuopio, Finland

Aim

In thoracic aortic aneurysm (TAA) of the ascending aorta (AA), AA dilates progressively, and can lead to aortic rupture without any prior symptoms. Evaluation of aneurysm progression is challenging, necessitating more accurate assessment and timing of repair surgery. We investigated whether wall shear stress (WSS) induces pathological changes of the aortic wall in TAA, and thus could magnetic resonance imaging (MRI) derived WSS values be used to identify high-risk patients.

Methods

TAA patients (n=32) with tricuspid or bicuspid aortic valve were included in the study. Prior to aortic replace-ment surgery, patients' aortas were imaged with 4D flow MRI (Fig. 1A). Histopathological and biomechanical factors in the inner and outer curve of the AA, including media degeneration, elastin and cell composition, and aortic wall strength, were analyzed from resected AA samples and correlated with WSS values.

Results

WSS values were found to correlate with media degeneration (Fig. 1B), elastin content (Fig. 1C), and aortic wall strength ($r=0.540$, $p=0.017$). Outer curves of the AA had greater WSS values, were less elastic and tolerated lower strain together with thinner medial layer. Strain values correlated with MYH10+ smooth mus-cle cell (SMC) density ($r=-0.447$, $p=0.017$) indicating more synthetic, abnormal SMC type in areas with weak-er aortic wall structure. Inflammation of the aortic wall (i.e., macrophages) was observed in areas with severe media degeneration ($r=0.422$, $p=0.002$) and lower WSS values ($r=-0.484$, $p=0.017$). RNA-sequencing tech-niques are further used to understand signalopathic WSS-derived mechanisms in TAA.

Conclusions

MRI-derived WSS predicts changes in the AA wall structure in patients with TAA and might be used for iden-tification of high-risk patients.

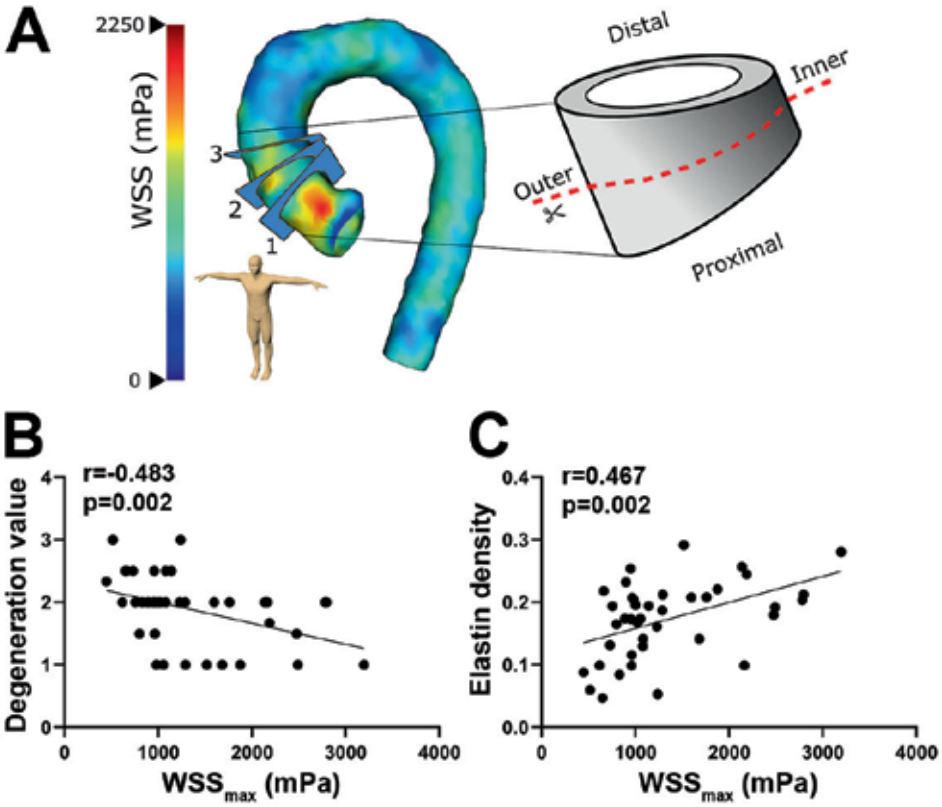


Figure 1. (**A**) 4D flow MRI was performed prior to surgery and WSS values were determined from three analysis planes. Resected sample was divided for histopathological (distal part) and biomechanical (proximal part) analyses. (**B,C**) Maximum WSS correlated with media degeneration (**B**) and elastin density (**C**) of the aortic wall in TAA depicting that lower WSS can predict more severe pathological change of the AA.

Apelin and apela for therapy of myocardial fibrosis and heart failure

Lea Rahtu-Korpela, Research unit of Biomedicine and Internal Medicine, University of Oulu, Faculty of Med-icine, Oulu, Finland, Zoltan Szabo, Research unit of Biomedicine and Internal Medicine, University of Oulu, Faculty of Medicine, Oulu, Finland, Sami Raatikainen, Research unit of Biomedicine and Internal Medicine, University of Oulu, Faculty of Medicine, Oulu, Finland, Andrey Anisimov, Research Programs Unit, Wihuri Research Institute, University of Helsinki, Helsinki, Finland, Kari Alitalo, Research Programs Unit, Wihuri Re-search Institute, University of Helsinki, Helsinki, Finland, Johanna Magga, Research unit of Biomedicine and Internal Medicine, University of Oulu, Faculty of Medicine, Oulu, Finland, Risto Kerkelä, Research unit of Biomedicine and Internal Medicine, University of Oulu, Faculty of Medicine, Oulu, Finland

The apelin/apela – apelin receptor system regulates a variety of physiological cardiovascular functions in-cluding vascular tone, cardiac contractility, angiogenesis, and energy metabolism. However, the cell type specific effects of apelin/apela in the cardiovascular system are not well understood. The aim of this study was to investigate the potential role of apelin and apela in regulating development of myocardial fibrosis and to identify the signaling mechanisms underlying the anti-fibrotic effects.

To investigate the role of apelin and apela in vivo, 2-month-old C57BL/6N male mice were injected with AAV9.LacZ, AAV9.Apelin or AAV9.Apela and subjected to thoracic aortic constriction (TAC) for 6 weeks.

Echocardiography analysis at the end of the study showed that overexpression of either apelin or apela attenuated TAC-induced left ventricular (LV) dysfunction and increase in LV mass. Analysis of cardiac tissue showed downregulation of collagen I and fibrosis related periostin mRNA expression levels and reduced accumulation of interstitial fibrosis in the left ventricles of mice overexpressing apelin or apela. Studies in human cardiac fibroblasts in vitro showed that apelin and apela attenuate TGFβ1-induced collagen expres-sion and secretion. Analyses of LV tissue and human cardiac fibroblast samples indicated that apelin and apela attenuate plateled-derived growth factor receptor (PDGFR) signaling and regulate the stress-induced activation of MAPK pathways. CRISPR-Cas9 targeting of PDGFR in fibroblasts abolished the anti-fibrotic effects of apelin and apela.

In summary, we show that apelin and apela attenuate hemodynamic pressure overload -induced LV dys-function and myocardial fibrosis and identify a key role for PDGFR signaling pathway in regulating the re-sponse. Our data suggests that activation of apelinergic signaling could offer a novel therapeutic approach to prevent the development of cardiac fibrosis and heart failure.

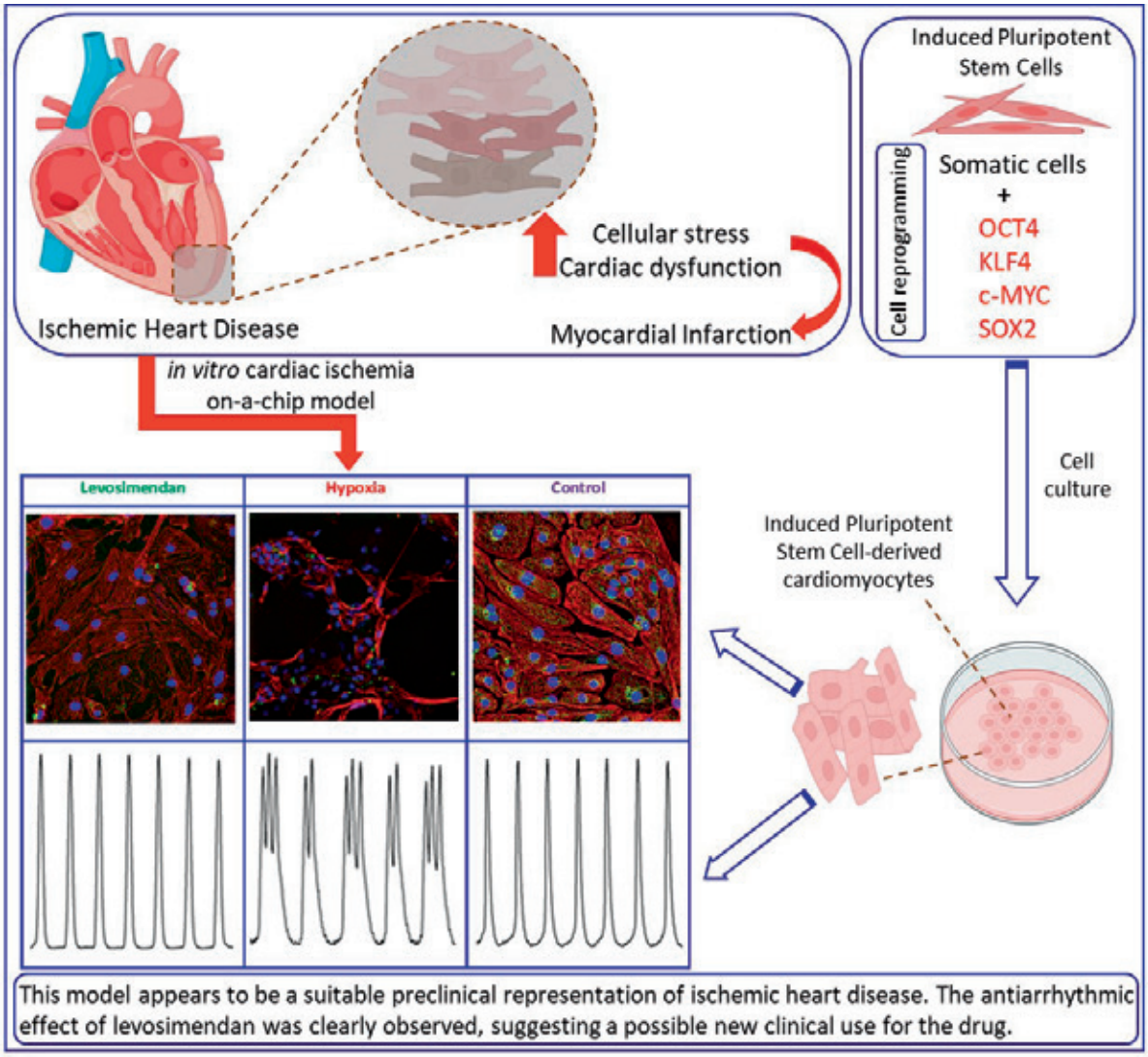
Klo 11.37–11.45 Mahmoud Gaballa (PhD Student)
Faculty of Medicine and Health Technology, Tampere University

Cardiac ischemia on-a-chip: Antiarrhythmic effect of levosimendan on ischemic human-induced pluripotent stem cell-derived cardiomyocytes

Kirsi Penttinen, Tampere University, Tampere, Finland, Joose Kreutzer, Tampere University, Tampere, Fin-land, Antti-Juhana Mäki, Tampere University, Tampere, Finland, Pasi Kallio, Tampere University, Tampere, Finland, Katriina Aalto-Setälä, Tampere University, Tampere, Finland

Ischemic heart disease (IHD) is one of the leading causes of mortality worldwide. Preserving functionality and preventing arrhythmias of the heart are key principles in the management of patients with IHD. Levosi-mendan, a unique calcium (Ca^{2+}) enhancer with inotropic activity, has been introduced into clinical usage for heart failure treatment. Human-induced pluripotent cell-derived cardiomyocytes (hiPSC-CMs) offer an opportunity to understand better the pathophysiological mechanisms of the disease as well as to serve as a platform for drug screening. Here, we developed an in vitro IHD model using hiPSC-CMs in hypoxic condi-tions and defined the effects of the subsequent hypoxic stress on CMs functionality.

Furthermore, the effect of levosimendan on hiPSC-CMs functionality was evaluated during and after hypoxic stress. The morphology, contractile, Ca^{2+} handling, and gene expression properties of hiPSC-CMs were investigated in response to hypoxia. Hypoxia resulted in significant cardiac arrhythmia and decreased Ca^{2+} transient amplitude. In addition, disorganization of the sarcomere structure was observed after hypoxia in-duction. Interestingly, levosimendan presented significant antiarrhythmic properties, as the arrhythmia was abolished or markedly reduced with levosimendan treatment either during or after the hypoxic stress. More-over, levosimendan presented significant protection from the sarcomere alterations induced by hypoxia. In conclusion, this chip model appears to be a suitable preclinical representation of IHD. With this hypoxia plat-form, detailed knowledge of the disease pathophysiology can be obtained. The antiarrhythmic effect of levosimendan was clearly observed, suggesting a possible new clinical use for the drug.


Induced Pluripotent Stem Cells
Somatic cells
+
OCT4
KLF4
c-MYC
SOX2
Cell reprogramming
Cellular stress
Cardiac dysfunction
Ischemic Heart Disease
Myocardial Infarction
in vitro cardiac ischemia on-a-chip model
Cell culture
Induced Pluripotent Stem Cell-derived cardiomyocytes
Levosimendan
Hypoxia
Control
This model appears to be a suitable preclinical representation of ischemic heart disease. The antiarrhythmic effect of levosimendan was clearly observed, suggesting a possible new clinical use for the drug.

Janne Rahola (MD)
MRC Oulu, Cardiology Research Group, University of Oulu

Prognostic significance of beat-to-beat variability of spatial heterogeneity of repolarization analyzed from 5-minute resting electrocardiogram in coronary artery disease

Antti Kiviniemi, MRC Oulu, Cardiology Research Group, University of Oulu, Oulu, Finland, Olavi Ukkola, MRC Oulu, Cardiology Research Group, University of Oulu, Oulu, Finland, Mikko Tulppo, MRC Oulu, Cardiology Research Group, University of Oulu, Oulu, Finland, Juhani Junttila, MRC Oulu, Cardiology Research Group, University of Oulu, Oulu, Finland, Heikki Huikuri , MRC Oulu, Cardiology Research Group, University of Oulu, Oulu, Finland, Tuomas Kenttä, MRC Oulu, Cardiology Research Group, University of Oulu, Oulu, Finland, Juha Perkiömäki, MRC Oulu, Cardiology Research Group, University of Oulu, Oulu, Finland

Aim

To evaluate the prognostic value of temporal variability of T-wave morphology analyzed from 5-minute rest-ing electrocardiogram (ECG) in coronary artery disease (CAD).

Methods

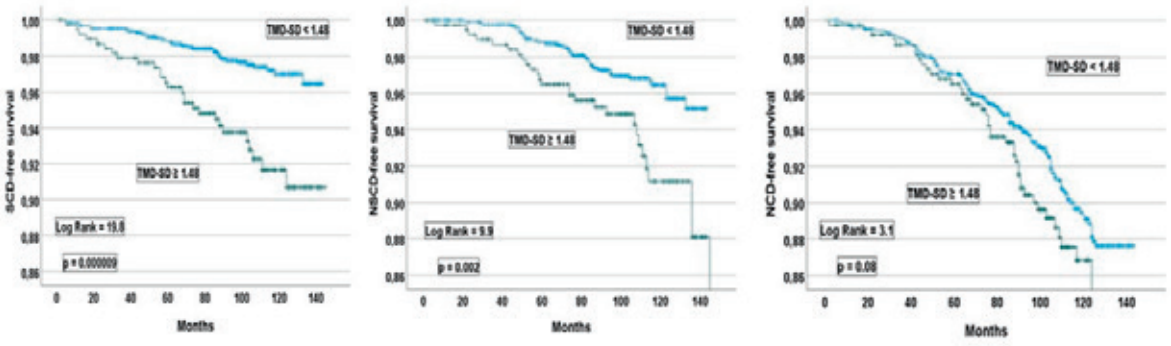
The standard deviation (SD) of T-wave morphology dispersion (TMD-SD), the SD of T-wave heterogeneity (TWH-SD), and the SD of total cosine R-to-T (TCRT-SD) were analyzed on beat-to-beat basis from a 5-minute period of resting 12-lead ECG obtained before a clinical stress test in 1,702 patients with angio-graphically verified CAD and well-preserved left ventricular function.

Results

During an average of 8.7 ± 2.2 years of follow-up, 60 (3.5 %) patients experienced sudden cardiac death (SCD) or were resuscitated from a sudden cardiac arrest (SCA), 69 (4.1 %) patients experienced non-sudden cardiac death (NSCD), and 161 (9.5 %) patients died due to non-cardiac death (NCD). TMD-SD was significantly higher in patients who experienced SCD/SCA compared with those without such an event (1.72 ± 2.00 vs. 1.12 ± 1.75, p= 0.01, respectively) and in patients who succumbed to NSCD compared with those without such an event (1.57 ± 1.74 vs. 1.12 ± 1.76, p=0.04, respectively), but did not differ signifi-cantly between patients who experienced NCD and those without such an event (1.16 ± 1.42 vs. 1.14 ± 1.79, p=0.86, respectively). After adjusting for relevant clinical risk factors in the Cox multivariate hazards model, TMD-SD retained its significant association with the risk of SCD/SCA (HR 1.110, 95 % CIs 1.008–1.222, p=0.033; HR [for TMD-SD ≥ 1.48] 2.423, 95% CIs 1.439-4.082), but not with the risk of NSCD (HR 1.065, 95 % CIs 0.951–1.193, p=0.27).

Conclusions

TMD-SD, representing temporal variability of spatial heterogeneity of electrocardiographic repolarization, is independently associated with the long-term risk of SCD/SCA in CAD patients with well-preserved left ven-tricular function.



Validation of novel electrocardiographic classification for stroke prediction in patients with atrial fibrillation undergoing cardioversion

Johanna Kääriä, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Samuli Jaakkola, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Tuija Vasankari, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Ilpo Nuotio, Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland, Juhani Airaksinen, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Tuomas Kiviniemi, Heart Center, Turku University Hospital and University of Turku, Turku, Finland

Aim

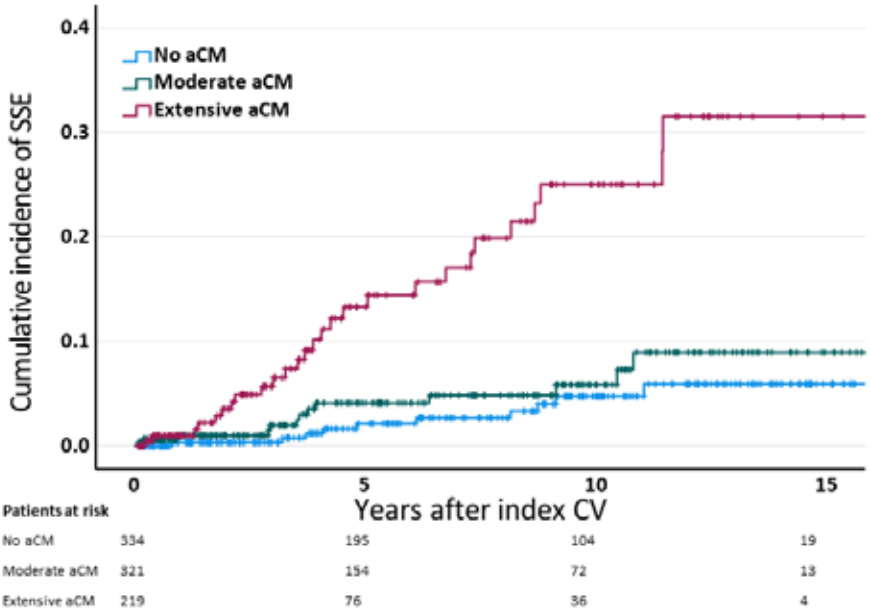
Atrial cardiomyopathy (aCM) is an electromechanical entity reflecting abnormal conduction, structure and function of the myocardium predisposing to stroke and atrial fibrillation (AF), however, its electrocardiographic (ECG) definition is poorly characterized. We systematically assessed potential ECG markers of aCM in an attempt to identify those at risk for stroke and systemic embolism (SSE) or a combination of SSE, heart failure and death (major adverse events, MAE).

Methods and Results

We manually reviewed 1591 ECGs from patients with AF undergoing an acute cardioversion from the Finnish Cardioversion study (FIN-CV). Using post-CV 30d follow-up data as the derivation cohort, we determined the predictive performance of various P-wave indices including P-wave duration, morphology, and P-terminal force (PTF) for SSE prediction. The best predictive performance was found using a combination of prolonged P-wave (≥ 180ms), deflected P-wave morphology in lead II, biphasic P-waves in all inferior leads or increased PTF (≥ 80mm*ms) as markers for extensive aCM. We validated the findings using the long-term follow-up in patients with no anticoagulation of whom 219/874 (25.1%) had extensive aCM. During the median follow-up of 4.9 years, there was 51 (5.8%) new SSE and 152 (17.4%) MAE in total. At 3 years, 9 (4.1%), 4 (1.2%) and 1 (0.3%) patients with extensive, moderate or no aCM had suffered from SSE, respectively (p=0.002). At 5 years, the rates were 16 (7.3%), 8 (2.5%) and 5 (1.5%) (p<0.001). Extensive aCM remained an independent predictor for SSE (HR 4.5, 95%CI 2.1-9.5, p<0.001) and MAE (HR 1.7, 95%CI 1.1-2.6, p=0.01) after adjusting for CHA2DS2-VASc score (Figures 1 and 2).

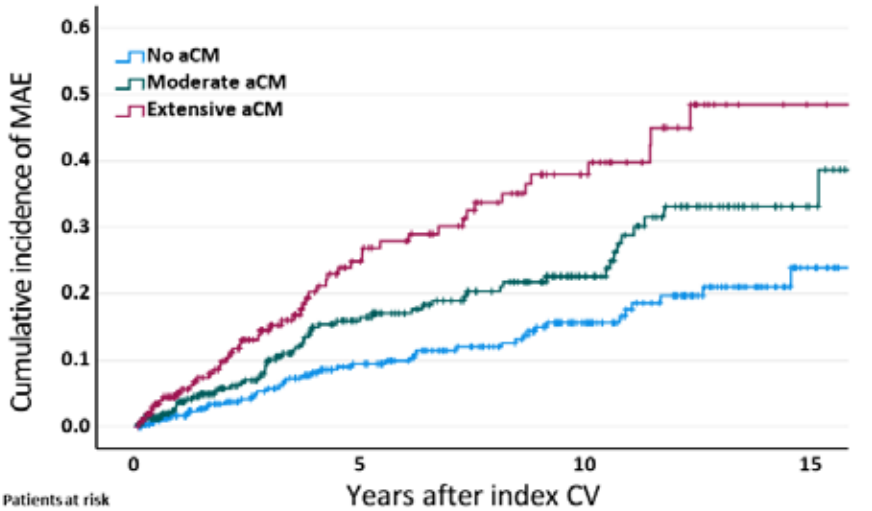
Conclusion

Novel electrocardiographic markers of extensive aCM provided additional prognostic insight on risk for stroke in atrial fibrillation patients.



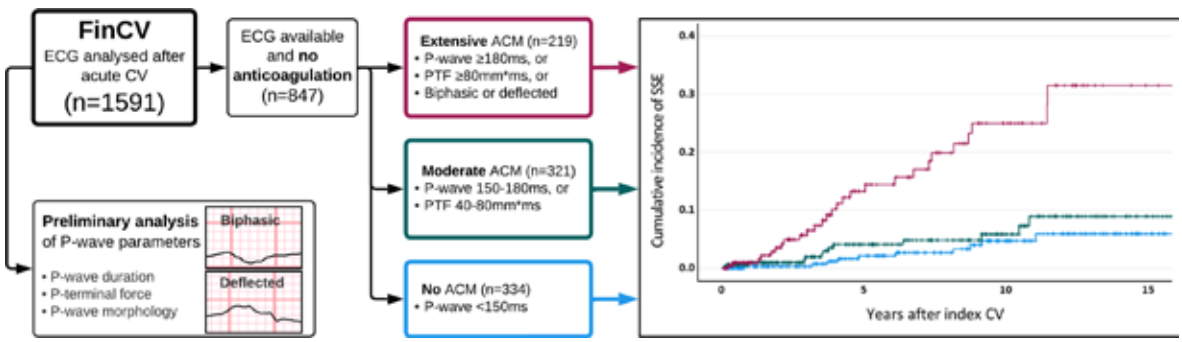
Patients at risk

No aCM	334	195	104	19
Moderate aCM	321	154	72	13
Extensive aCM	219	76	36	4



Patients at risk

No aCM	334	195	104	19
Moderate aCM	321	154	72	13
Extensive aCM	219	76	36	4



Transcatheter aortic valve implantation in nonagenarians

Jarkko Piuhola, Oulu University Hospital, Oulu, Finland, Matti Niemelä, Oulu University Hospital, Oulu, Finland, Noriaki Moriyama, Helsinki University Hospital, Helsinki, Finland, Mika Laine, Helsinki University Hospital, Helsinki, Finland

Aim

Prevalence of severe aortic stenosis is increasing due to aging population. This results in a growing number of nonagenarian candidates for transcatheter aortic valve implantation (TAVI), a patient group often underrepresented in earlier research. The aim of our study was to evaluate the safety and outcomes of TAVI in patients aged 90 years and older.

Methods

A retrospective register study was conducted with symptomatic severe aortic stenosis in 170 nonagenarians who underwent TAVI in Oulu/Helsinki University Hospital between 2009 and 2022. All data was gathered from hospital medical records. Mortality at 30 days and 1 year were defined as the primary outcomes. Secondary outcomes were 30-day incidence of stroke, permanent pacemaker (PPM) implantation, severe bleeding complication and severe vascular complication according to the Valve Academic Research Consortium II criteria. Baseline and perioperative information was assessed with focus on identifying factors affecting the outcome of the treatment.

Results

Mean age was 91 ± 1.4 years and 65.3% of the patients were female. Mortality at 30 days and 1 year was 5.9% and 12.3%, respectively. 30-day incidence of stroke was 4.1%. Severe bleeding complication occurred to 12.4% of the patients and 18.2% were identified with severe vascular complication during 30-day follow-up. The need for PPM implantation was 9.4% during the 30-day follow-up.

Prior hospital treatment for heart failure was associated with increased 1-year mortality (RR 3.2, 95% CI 1.4-7.2, P=0.008). Atrial fibrillation at baseline was associated with an increase in 30-day (RR 4.8, 95% CI 1.1-22.1, P=0.04) and 1-year (RR 3.3, 95% CI 1.2-8.6, P=0.01) mortality. BMI≤20 was found to be a predictor of increased 30-day mortality (RR 7.1, 95% CI 2.1-24.8, P=0.01).

Conclusions

Our study supports current practice that TAVI is feasible and can be performed to nonagenarians with acceptable short- and midterm outcomes. Still, further research is needed with emphasis on improving patient selection and identifying those with most to gain from the treatment.

Major complications after mechanical aortic valve replacement

Joonas Lehto, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Markus Malmberg, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Vesa Anttila, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Juhani Airaksinen, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Jarmo Gunn, Heart Center, Turku University Hospital and University of Turku, Turku, Finland, Tuomas Kiviniemi, Heart Center, Turku University Hospital and University of Turku, Turku, Finland

Aim

Because of the thrombogenicity of mechanical valves, patients entering mechanical aortic valve replacement (AVR) require permanent vitamin K antagonist (VKA) therapy. However, both strokes and major bleeding episodes are feared complications after the procedure. In the present study we sought to assess the major complications and the success of VKA treatment after mechanical AVR.

Methods

A total of 308 patients who underwent isolated mechanical AVR were included in the study. The data were retrospectively collected from electronic patient records. Follow-up data were complete for 306 patients (99.4%). The median follow-up time was 7.3 (interquartile range 4.2–10.9) years.

Results

During both the 30-day perioperative period and long-term follow-up, the risk for major bleeding was fivefold (6.2% vs. 1.3%; 20.9% vs. 4.0%) compared to major stroke. Majority of the early perioperative bleeding events (68.4%) occurred within four days after the surgery. At the time of the early perioperative major bleeding, INR was out of therapeutic range in 92.0% of the patients, most of which were under the range. In contrast, later perioperative major bleeding events primarily occurred when INR was in the therapeutic range, and only third of the events occurred when INR was over the therapeutic range. Furthermore, the mortality was relatively high, as the 5-year and 10-year survival estimates were 91.4% and 78.3%. The leading underlying causes of death during the long-term follow-up were coronary artery disease (18.5%) and aortic valve stenosis (18.5%).

Conclusion

While ischemic stroke is a well-identified adverse event after mechanical AVR, it seems that major bleeding is a more clinically relevant complication during both the perioperative period and long-term follow-up.

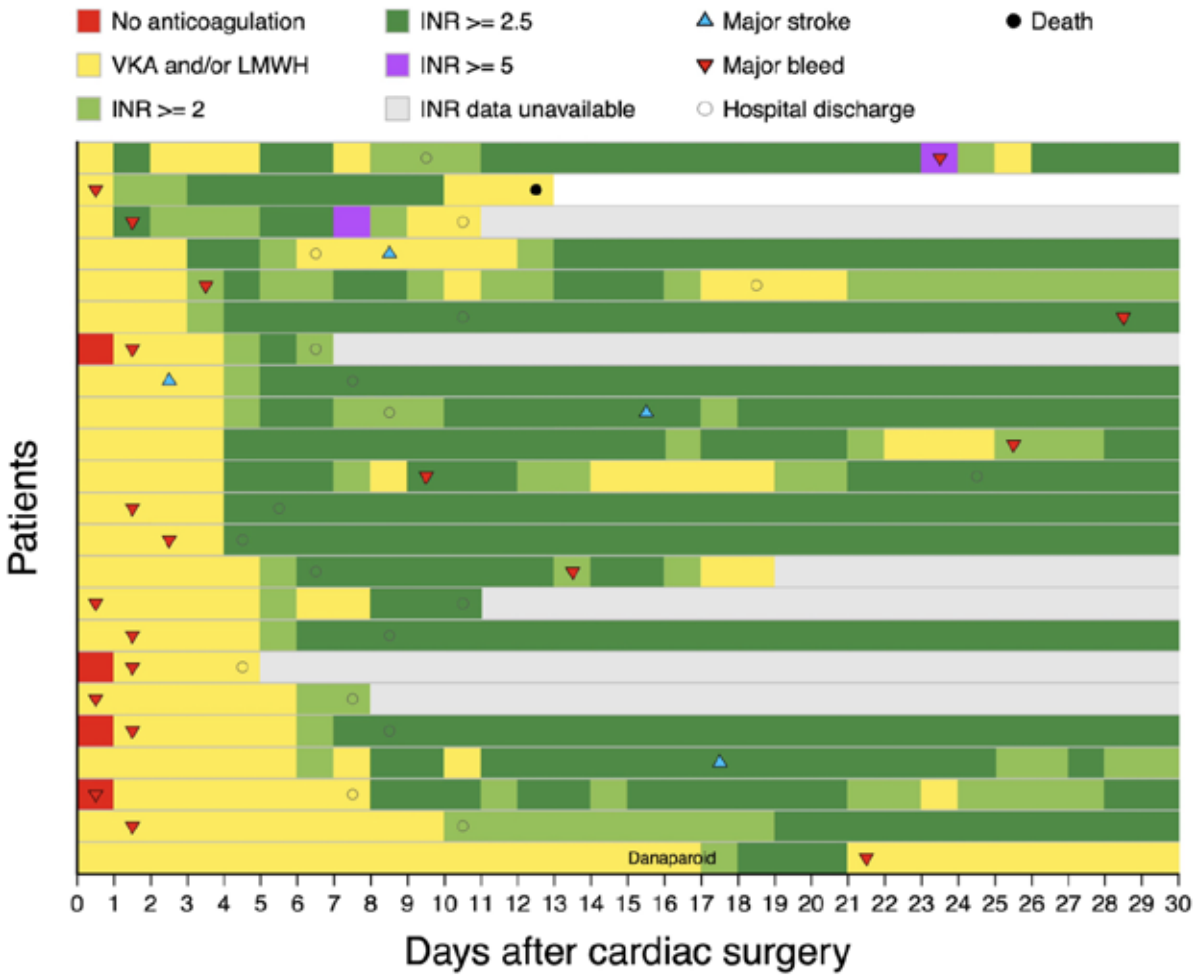


Figure 1. The perioperative anticoagulation treatment of patients experiencing major stroke or major bleeding during 30 days after mechanical isolated aortic valve replacement. *INR*, international normalized ratio; *LMWH*, low-molecular-weight heparin; *VKA*, vitamin K antagonist.

Klo 12.17–12.25

Anne Doedens (MSc)
Research unit of Biomedicine and Internal Medicine,
University of Oulu and Oulu University Hospital

Novel genetic variants associated with sudden cardiac death due to primary myocardial fibrosis

Sini Skarp, University of Oulu and Oulu University Hospital, Oulu, Finland, Lauri Holmström, University of Oulu and Oulu University Hospital, Oulu, Finland, Valerio Izzi, University of Oulu and Oulu University Hospital, Oulu, Finland, Eeva Sliz, University of Oulu, Oulu, Finland, Johannes Kettunen, University of Oulu, Oulu, Finland, Risto Kerkelä, University of Oulu and Oulu University Hospital, Oulu, Finland, Katri Pylkäs, University of Oulu, Oulu, Finland, Heikki Huikuri, University of Oulu and Oulu University Hospital, Oulu, Finland, Robert Myerburg, University of Miami, Miami, Finland, Juhani Junttila, University of Oulu and Oulu University Hospital, Oulu, Finland

Aim

Sudden cardiac death (SCD) is one of the most common modes of death in Western countries. Post-mortem investigations in SCD victims reveal that myocardial fibrosis is a common finding, as more than 90% of the SCD victims have fibrotic accumulation in the myocardium. Our aim was to identify variants in novel candidate genes associated with the presence of myocardial fibrosis in SCD victims.

Methods

Post-mortem whole exome sequencing was performed in 127 victims of SCD associated with nonischemic cardiomyopathy with primary myocardial fibrosis as the only pathological finding. We sought rare variants with minor allele frequency <0.005 estimated to be pathogenic and present in three or more cases. A computational approach was used to identify protein interactions for candidate genes in cardiomyocytes. Associations of the identified variants with cardiac disease endpoints were investigated in the Finnish national genetic study (FinnGen) dataset.

Results

We identified in total 21 missense and one nonsense variant. Heart enhanced protein interactions were identified in 16 candidate genes. Four missense variants were highly likely to be pathogenic, significantly associated with SCD associated with primary myocardial fibrosis and were also associated with cardiac diseases in the Finnish population. These variants locate in cartilage acidic protein 1 (CRATC1), calpain 1 (CAPN1), unc-45 myosin chaperone A (UNC45A) and unc-45 myosin chaperone B (UNC45B).

Conclusions

We identified novel variants and candidate genes predisposing to SCD associated with primary myocardial fibrosis. The variants identified contribute to the regulation of extracellular matrix production and cardiomyocyte function.