

Suomen Kardiologinen Seura

Finnish Cardiac Society



***41<sup>st</sup> Progress Report  
Meeting***

March 25, 2015

Turku



Boehringer Ingelheim on tukenut Suomen Kardiologisen Seuran järjestämää nuorten tutkijoiden Progress Report -kilpailua yli 40 vuoden ajan.

Tämä perinne jatkuu myös vuonna 2015. Progress Report Meeting järjestetään Suomen Kardiologisen Seuran 4. Kevätkokouksen yhteydessä Turussa 25.3.2015.

Progress in Clinical Cardiology -osuudessa esiintyy Kööpenhaminan yliopiston kardiologian apulaisprofessori **Ulrik Dixen** aiheenaan ”Stroke prevention in modern clinical practice – how do the Danes do it?”

#### **41st Progress Report Meeting**

Chairperson **Antti Hedman**,  
Kuopio University Hospital, Heart Center  
Meeting is supported by unrestricted educational grant from Boehringer Ingelheim.

- 13.30**            **Opening remarks**  
Antti Hedman, Cardiologist,  
Kuopio University Hospital,  
Heart Center
- 13.35 - 15.05** **Young Investigators**  
**Award Competition, part I**  
Topics 1 to 6
- 15.05 - 15.30** **Exhibition and coffee**
- 15.30 - 16.30** **Young Investigators**  
**Award Competition, part II**  
Topics 7 to 10

#### **Progress in Clinical Cardiology**

- 16.30 - 17.00** **“Stroke prevention in modern clinical practice – how do the Danes do it?”**  
Ulrik Dixen, Associate Professor,  
University of Copenhagen,  
Department of Cardiology,  
Hvidovre Hospital, Copenhagen
- 17.00 - 17.05** **Closing remarks**



# Progress Report -kilpailu tulee, miksi nuoren tutkijan kannattaa osallistua?

Vastaajana kardiologi, Suomen Kardiologisen Seuran puheenjohtaja **Mikko Pietilä**.



## 1 Miksi Suomen Kardiologisen Seuran Progress Report -kilpailuperinne on tärkeä?

Kilpailu on nuorelle tutkijalle paraatipaikka esitellä omia tutkimustuloksia suomalaiselle kardiologikunnalle. Tilaisuus on kannustava, mutta toisaalta siinä on riittävästi painetta antamaan esimakua siitä, millaista on esittää tuloksia ulkomaisilla areenoilla. Kilpailu mittaa paitsi tutkimuksen tasoa myös esiintymistaitoa. On erittäin tärkeää osata tuoda tutkimustuloksia esille sujuvassa muodossa.

Kilpailu on myös eräänlainen ponnahduslauta suuremmille areenoille. Aika moni nykyisistä professoreista ja ylläkäreistä on sijoittunut hyvin näissä kilpailuissa.

## 2 Miksi nuoren tutkijan kannattaa osallistua kisaan?

Kilpailu on hyvä tilaisuus saada itsensä suomalaisen kardiologikunnan tietoisuuteen ja kouliintua esiintymistaidoissa. Omasta kokemuksestani tiedän, että esimerkiksi amerikkalaiskokouksissa vastaanotto saattaa olla kylmää ja aggressiivistakin. Kun on harjoitellut esiintymistä, ei jää sanottomaksi tiukkojen kommenttien ja kysymysten edessä. Lisäksi saman abstraktin voi lähettää vaikka ESC:n kokoukseen, jonka lähetyisaika päättyy samoihin aikoihin. Parhaimmillaan pääsee harjoittelemaan siellä pidettävää esitystä hyvisä ajoin!

Kisa on myös tilaisuus saada palautetta oman tutkimusryhmän ulkopuolelta meritoituneilta suomalaistutkijoilta. Tämä voi avata uusia näkemyksiä omaan tutkimusalueeseen.

## 3 Mikä rooli Progress Report -kilpailulla on Suomen Kardiologisen Seuran toiminnassa?

Seuran jäsenyys ei ole osallistumisen edellytys. Seuran tärkeimpiä tehtäviä on viedä suomalaista tutkimusta eteenpäin, ja kilpailu palvelee tätä tarkoitusta. Kilpailu on toisaalta yksi tapa tehdä seuraan tutuksi uudelle kardiologipolvelle. Millään yhdistyksellä ei ole tulevaisuutta ilman nuoria.

## 4 Olet itsekkin osallistunut kisaan, millainen kokemus se oli?

Osallistuin kisaan kahdesti 1990-luvun jälkipuoliskolla väitöskirjatyöhöni liittyneillä, sydämen vajaatoimintaa käsittelevillä tutkimuksilla. Kun ensimmäisellä kerralla esittelin työni tuloksia, se oli kohtuullisen jännittävä tilanne. Toisella kerralla sitä suhtautui jo vapautuneemmin. Itselläni osallistuminen lievitti myös turhaa jännitystä siitä, osaanko esittää tuloksiani kansainvälisillä areenoilla.

Vaikken sijoittunut kahden parhaan joukkoon, kokemus oli silti hyvä. Jo esikarsinnasta esiintymään pääseminen tuntui saavutukselta. Erityisen positiivista osallistumisesta oli, että moni kollega oli silloin kilpailemassa. Se lujitti meidän samanikäisten wannabe-kardiologien yhteishenkeä.

**Suomen Kardiologisen Seuran nuorten tutkijoiden Progress Report -kilpailu järjestetään seuran kevätkokouksen yhteydessä Turussa 25.-27.3.2015. Abstraktien lähetyisaika päättyy 31.1.2015. Kilpasarjojen voittajat palkitaan Boehringer Ingelheim Finlandin lahjoittamalla 2300 euron matka-apurahoilla.**

Lisätietoja kilpailusta Suomen Kardiologisen Seuran nettisivuilta [www.fincardio.fi/apurahat/progress\\_report\\_yiac/](http://www.fincardio.fi/apurahat/progress_report_yiac/)

# Contents

History of the Progress Report Meetings.....	120
<b>Young Investigators Award Competition abstracts</b>	
Abstracts in the order of presentation	
41 <sup>st</sup> Progress Report Meeting - Young Investigators Award Competition .....	121
Competition is supported by unrestricted educational grant from Boehringer Ingelheim.	
<b>13.35–13.50</b> Prognostic value of combined coronary computed tomography angiography and positron emission tomography perfusion imaging in patients with suspected coronary artery disease. Teemu Maaniitty (BM), University of Turku, Turku PET Centre.....	121
<b>13.50–14.05</b> Strokes after cardioversion of atrial fibrillation. Antti Palomäki (MD), Turku University Hospital, Heart Center .....	122
<b>14.05–14.20</b> Female sex, age and time delay to cardioversion as risk factors in the cardioversion of acute atrial fibrillation. The FinCV Study. Aissa Bah (BM), Kuopio University Hospital and UEF, Heart Center .....	123
<b>14.20–14.35</b> Increasing BMS and DES endothelialization with local adenoviral VEGF-A gene therapy in naïve pig coronary arteries. Jarkko Hytönen (MD), University of Eastern Finland, Molecular Medicine .....	124
<b>14.35–14.50</b> How common is coronary microvascular dysfunction in patients with suspected coronary artery disease? Iida Stenström (Bachelor of Medicine), University of Turku, Turku University Hospital, Turku PET Centre .....	125
<b>14.50–15.05</b> Cancer risk after heart transplantation highly elevated in comparison to general population. Salla Jäämaa (erikoistuva lääkäri), HYKS, Sydänkeskus.....	126

- 15.30–15.45** Cardiorespiratory fitness modifies the association between leisure-time physical activity and the risk of sudden cardiac death among middle-aged men.  
Magnus Hagnäs (Dr), Lapland Central Hospital,  
Department of Internal Medicine..... **127**
- 15.45–16.00** Gadolinium late enhancement and septal thinning predict adverse events in cardiac sarcoidosis.  
Kaj Ekström (Doctor), Helsinki University Central Hospital,  
Department of Cardiology and Päijät-Häme Central Hospital,  
Department of Cardiology ..... **128**
- 16.00–16.15** Endothelial Bmx tyrosine kinase activity is essential for myocardial hypertrophy and remodeling.  
Markus Räsänen (BMed, PhD Student), University of Helsinki,  
TCB / Wihuri Research Institute ..... **129**
- 16.15–16.30** Follow-up of 316 molecularly defined pediatric long QT syndrome patients – clinical course and fulfillment of  $\beta$ -blocker treatment.  
Mikael Koponen (MD), Helsinki University Central Hospital,  
Heart and Lung Center ..... **131**

# 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 practical 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 has been received to either category, the organizers reserve the right to combine the categories.

Year	1 <sup>st</sup> Prize	2 <sup>nd</sup> 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, 3 <sup>rd</sup> 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 Juntila	Markus Leskinen
2004	Jere Paavola	Tuomas Rissanen
2005	Mikko Mäyränpää	Satu Helske
2006	Olli Tenhunen	Johan Lassus
<b>Year</b>	<b>Basic Science category</b>	<b>Clinical Research category</b>
2007	Satu Helske	Ville Kytö
2008	Mirella Hietaniemi	Minna Kylmä
2009	Johanna Lähteenvuo o.s. Markkanen	Annukka Marjamaa
2010	1 <sup>st</sup> Prize Jani Tikkanen 2 <sup>nd</sup> Prize Riina Kandolin	
2011	Markku Lähteenvuo	Aapo Aro
2012	1 <sup>st</sup> Prize Kirsi Kujala 2 <sup>nd</sup> Prize Maija Bry	
2013	Suvi Syväranta	Toni Grönberg
2014	1 <sup>st</sup> Prize Leena Kaikkonen 2 <sup>nd</sup> Prize Heli Tolppanen	

## Prognostic value of combined coronary computed tomography angiography and positron emission tomography perfusion imaging in patients with suspected coronary artery disease

**Teemu Maaniitty**, Turku PET Centre, University of Turku, Turku, Finland

**Iida Stenström**, University of Turku, Turku, Finland

**Antti Saraste**, Turku University Hospital, Turku, Finland

**Valtteri Uusitalo**, University of Turku, Turku, Finland

**Heikki Ukkonen**, Turku University Hospital, Turku, Finland

**Sami Kajander**, University of Turku, Turku, Finland

**Maija Mäki**, University of Turku, Turku, Finland

**Jeroen Bax**, Leiden University Medical Center, Leiden, Netherlands

**Juhani Knuuti**, University of Turku, Turku, Finland

### Aim

Hybrid imaging using coronary computed tomography angiography (CTA) and positron emission tomography (PET) perfusion imaging accurately detects functionally significant coronary artery disease (CAD), but its optimal clinical use remains unknown. We studied the prognostic significance of strategy utilizing sequential CTA for exclusion of CAD followed by PET perfusion imaging for evaluating functional significance of any suspected obstructive lesions with a hybrid PET-CT device in symptomatic patients with suspected intermediate probability of CAD.

### Methods

We identified a cohort of 864 consecutive patients undergone hybrid PET-CT for the detection of suspected CAD. All patients had CTA and based on CTA findings, haemodynamic significance of any suspected stenoses was evaluated by PET perfusion imaging using  $^{15}\text{O}$ -H $_2\text{O}$  during adenosine-induced stress. Major adverse cardiac events (MACE) including death, myocardial infarction (MI) and unstable angina pectoris (UAP), were collected from the national and local healthcare statistics.

### Results

After exclusion of 97 patients undergone early (< 6 months) revascularization, 767 patients with age of  $61 \pm 10$  years (41% males) were followed-up for a median time of 3.5 years. During the follow-up 13 deaths, 5 MIs and 4 UAPs occurred. In 462 patients, obstructive CAD was excluded based on CTA alone and the remaining patients with suspected stenoses ( $n=305$ , 39.8%) underwent PET perfusion imaging. In patients with normal or non-obstructive CTA annual incidence of MACE was only 0.42%, whereas in patients with suspected stenosis based on CTA it was 1.28% ( $p=0.015$  vs. no stenosis). In patients with suspected obstructive lesion based on CTA, patients with normal PET perfusion had significantly lower event rate than patients with reduced perfusion (0.41% vs. 2.77%,  $p=0.001$ ).

### Conclusions

In patients with suspected obstructive CAD PET perfusion imaging after CT angiography is able to accurately identify those patients with high risk of future MACE. Sequential use of CTA and PET perfusion imaging appears powerful and safe strategy for targeting therapeutic procedures in high risk individuals.

## Strokes after cardioversion of atrial fibrillation

**Antti Palomäki**, Heart Center, Turku University Hospital, Turku, Finland

**Pirjo Mustonen**, Keski-Suomi Central Hospital, Jyväskylä, Finland

**Juha Hartikainen**, Kuopio University Hospital, Kuopio, Finland

**Ilpo Nuotio**, Turku University Hospital, Turku, Finland

**Tuomas Kiviniemi**, Turku University Hospital, Turku, Finland

**Antti Ylitalo**, Lapland Central Hospital, Rovaniemi, Finland

**Päivi Hartikainen**, Kuopio University Hospital, Kuopio, Finland

**Heidi Lehtola**, Keski-Suomi Central Hospital, Jyväskylä, Finland

**Riho Luute**, Kuopio University Hospital, Kuopio, Finland

**Juhani Airaksinen**, Turku University Hospital, Turku, Finland

### Aim

Patients with atrial fibrillation (AF) have an increased risk of stroke, but little is known how many of the strokes are preceded by a cardioversion of AF. We aimed to determine the proportion of post-cardioversion strokes in patients with AF and to characterize these cardioversions.

### Methods

In this retrospective study we analyzed data from 2970 patients with previously diagnosed AF who suffered a total of 3252 ischemic strokes during 2003-2012. The type of AF was paroxysmal or persistent in 1215 events, chronic in 1745 events and undefined in 292 events. All cardioversions during the 30 days preceding the stroke were identified.

### Results

Seventy-seven patients had a cardioversion performed during the 30 days preceding the stroke, accounting for 2.4 % of all strokes and 6.3 % of strokes of patients with paroxysmal or persistent AF. Of the cardioversions 61/77 (79 %) were acute, and 10/61 (16 %) of the patients with acute cardioversion had been using oral anticoagulation (OAC) prior to cardioversion (Table). The median delay from acute and elective cardioversion to stroke was 2 days and 3 days, respectively ( $p=0.096$ ). The median delay from cardioversion to stroke was longer in patients with OAC prior to cardioversion than in patients without OAC (median 3 vs 2 days,  $p=0.007$ ).

### Conclusion

A majority of post-cardioversion strokes occur after acute cardioversion and to patients not using OAC. Most strokes occur 2-3 days after the cardioversion.

Table 1. Data of 77 cardioversions (CV) leading to ischemic stroke

	Acute cardioversion n (%)	Elective cardioversion n (%)
N (% of all CV)	61 (79)	16 (21)
Warfarin prior to CV	10 (16)	16 (100)
WIR at the time of CV, median [range]	2.1 [1.2-4.0]	2.4 [2.0-3.2] *
WIR < 2	4 (40)	0
WIR 2.0-2.5	3 (30)	7 (58)
WIR > 2.5	3 (30)	5 (42)
Warfarin at the time of stroke	18 (30)	16 (100)
WIR at the time of stroke, median [range]	1.8 [0.9-3.0]	2.3 [1.3-5.4]
CHA <sub>2</sub> DS <sub>2</sub> -VASc, median [IQR]	3.0 [2.0-4.0]	3.5 [2.0-4.0]
0	6 (30)	0 (0)
1	6 (30)	1 (6)
≥ 2	49 (80)	15 (94)
Days from CV to stroke, median [IQR]	2 [1.0-3.3]	3 [2.0-5.0]
0-2 days	43 (71)	7 (44)
3-5 days	6 (30)	7 (44)
> 6 days	12 (20)	2 (13)

\* Data unavailable for 4 patients



## Female sex, age and time delay to cardioversion as risk factors in the cardioversion of acute atrial fibrillation. The FinCV Study

**Aissa Bah**, Heart Center, Kuopio University Hospital and UEF, Kuopio, Finland

**Ilpo Nuotio**, Department of Acute Internal Medicine, Turku University Hospital, Turku, Finland

**Toni Grönberg**, Heart Center, Turku University Hospital, Turku, Finland

**Antti Ylitalo**, Department of Internal Medicine, Lapland Central Hospital and University of Oulu, Oulu, Finland

**Marko Nikkinen**, Heart Center, Kuopio University Hospital, Kuopio, Finland

**Kiia Ruuhijärvi**, Heart Center, Turku University Hospital, Turku, Finland

**Juhani K.E. Airaksinen**, Heart Center, Turku University Hospital, Turku, Finland

**Juha E.K. Hartikainen**, Heart Center, Kuopio University Hospital and UEF, Kuopio, Finland

### Aim

Female gender is a risk factor for thromboembolic complications (TEC) in atrial fibrillation (AF). It is also associated with an increased risk for complications such as bradycardia and TEC after cardioversion of acute AF. The aim of this study was to compare clinical presentation, comorbidities and complications during a 30 day follow-up in women and men with electrical cardioversion of acute AF (< 48 hours) performed without anticoagulation.

### Methods

A total of 4715 scheduled electrical cardioversions without periprocedural or postprocedural anticoagulation were performed in 2313 patients with AF lasting < 48 hours. The outcomes were failure of cardioversion, bradyarrhythmic complications, AF recurrence and TEC after cardioversion (30-day follow-up) and their combination, the net harm, was calculated. Finally, the interaction of age, sex and delay to cardioversion on the risk of TEC was assessed.

### Results

Women with acute AF were older, had more comorbidities and higher heart rate ( $117 \pm 23$  bpm vs.  $108 \pm 25$  bpm,  $p < 0.001$ ). The failure of electrical cardioversion was higher (6.7 % vs. 4.0 %,  $p < 0.001$ ) and bradyarrhythmic complications were more common in women (1.9 % vs. 0.4 %,  $p < 0.001$ ). AF tended to reoccur more often in women in the 30-day follow-up (13.7 % vs. 11.7 %,  $p = 0.05$ ). Female sex also associated with an increased risk of TEC (OR 2.12, CI 1.09-4.11,  $p = 0.03$ ). The net harm was higher in women (21.9 % vs. 16.0 %,  $p < 0.001$ ). Older age ( $p = 0.001$ ), time delay from the onset of AF to cardioversion ( $p = 0.001$ ) and vascular disease ( $p = 0.03$ ) were the other significant predictors of TEC. The risk of TEC increased from 0.3 % in men < 65 years and cardioversion delay < 12 hours to 2.7 % ( $p = 0.004$ ) in women > 75 years and delay > 12 hours.

### Conclusion

Older women are at high risk for complications and failure of cardioversion of acute AF. This should be taken into account when considering the treatment strategy of this increasing patient population.

## Increasing BMS and DES endothelialization with local adenoviral VEGF-A gene therapy in naïve pig coronary arteries

**Jarkko Hytönen**, Molecular Medicine, University of Eastern Finland, Kuopio, Finland

**Paavo Halonen**, University of Eastern Finland, Kuopio, Finland

**Santeri Tarvainen**, University of Eastern Finland, Kuopio, Finland

**Jouni Taavitsainen**, University of Eastern Finland, Kuopio, Finland

**Arto Koistinen**, University of Eastern Finland, Kuopio, Finland

**Johanna Laakkonen**, University of Eastern Finland, Kuopio, Finland

**Juha Hartikainen**, Heart Center, Kuopio University Hospital, Kuopio, Finland

**Seppo Ylä-Herttuala**, University of Eastern Finland, Kuopio, Finland

### Aim

We aimed to increase stent endothelialization with gene therapy known to promote endothelial healing and homeostasis. In addition, we evaluated OCT and angioscopy imaging as tools for detecting endothelium and thrombus formation with comparison to robust ex-vivo analyses including scanning electron microscopy (SEM), multi-photon microscopy and immunohistology.

### Methods

24 stents, BMS and DES, were implanted into naïve porcine coronary arteries and received either AdVEGF or control AdLacZ gene transfers with a porous drug delivery catheter. Stents were imaged in-vivo with angiography, OCT and angioscopy immediately after stenting and one week and two weeks after stenting and gene therapy. At d14 the stents were collected for histology, multi-photon microscopy and scanning electron microscopy for assessment of endothelialization. Strut coverage was analyzed from SEM images and graded 0 (no coverage) to 3 (fully covered). Angioscopy pullbacks were analyzed for thrombus in the stented artery and graded similarly 0 (no thrombus present) to 3 (lumen occluded by thrombus).

### Results

Initial SEM analyses from stented arteries two weeks after intervention showed increased strut coverage with BMS after VEGF-A gene therapy compared to control LacZ ( $2.8 \pm 0.4$  vs.  $1.8 \pm 0.4$ , respectively,  $p=0.0031$ ). Gene therapy did not change strut coverage in DES with stent coverage of  $1.6 \pm 0.5$  and  $1.8 \pm 0.4$ ,  $p=NS$ , AdLacZ and AdVEGF respectively. Angioscopic thrombus formation was low in all groups with a trend towards less thrombi on BMS groups ( $0.2 \pm 0.4$  and  $0.3 \pm 0.5$  in AdLacZ and AdVEGF) compared to DES ( $0.8 \pm 0.8$  and  $0.8 \pm 0.7$  in AdLacZ and AdVEGF).

### Conclusions

Our early findings indicate that AdVEGF treatment at the time of stenting increased coverage of BMS but did not improve healing of DES two weeks after stenting. Most likely the strong cytotoxic drugs in DES hamper stent healing even with local supraphysiological growth factor concentrations. Angioscopy may be useful in assessment of arterial healing after treatment with a coronary stent. Data analysis from OCT imaging as well as multi-photon microscopy and immunohistology is under review.

## How common is coronary microvascular dysfunction in patients with suspected coronary artery disease?

**Iida Stenström**, Turku PET Centre, University of Turku, Turku University Hospital, Turku, Finland

**Teemu Maaniitty**, Turku PET Centre, University of Turku, Turku University Hospital, Turku, Finland

**Antti Saraste**, Heart Center, Turku University Hospital, Turku, Finland

**Essi Pikkarainen**, Heart Center, Turku University Hospital, Turku, Finland

**Valtteri Uusitalo**, Turku PET Centre, University of Turku, Turku University Hospital, Turku, Finland

**Heikki Ukkonen**, Heart Center, Turku University Hospital, Turku, Finland

**Sami Kajander**, Turku PET Centre, University of Turku, Turku University Hospital, Turku, Finland

**Maija Mäki**, Turku PET Centre, University of Turku, Turku University Hospital, Turku, Finland

**Jeroen Bax**, Department of Cardiology, Leiden University Medical Center, Leiden, Netherlands

**Juhani Knuuti**, Turku PET Centre, University of Turku, Turku University Hospital, Turku, Finland

### Aim

Coronary microvascular dysfunction (CMD) is defined as impaired myocardial perfusion in the absence of epicardial artery obstruction. This may cause chest pain, ECG abnormalities and stress perfusion results mimicking epicardial coronary artery disease (CAD). We evaluated CMD in symptomatic patients with intermediate probability of CAD with comprehensive anatomical and functional imaging tests.

### Methods

We recruited prospectively 189 patients with intermediate pre-test probability of CAD. All patients underwent computed tomography coronary angiography (CTCA), quantitative positron emission tomography (PET) perfusion imaging with  $^{15}\text{O}$ -water during adenosine stress using a hybrid scanner, invasive coronary angiography (ICA) and fractional flow reserve (FFR) when feasible. CMD was defined as abnormal myocardial perfusion (stress MBF  $\leq 2.4\text{mL/g/min}$ ) and absence of haemodynamically significant CAD ( $<50\%$  stenosis or FFR  $>0.8$ ).

### Results

Significant obstructive CAD was found in 39%, non-obstructive in 39%, whereas 22% had no coronary atherosclerosis. Stress myocardial perfusion abnormalities were present in 72 patients (38%). These were explained by matching epicardial stenosis in 55, whereas 17 patients (9.0%) had CMD. Of these, 2 had globally reduced stress perfusion without any coronary atherosclerosis. Five patients had globally reduced stress perfusion in the absence of haemodynamically significant CAD, but non-obstructive atherosclerosis on CTCA. Ten patients, who had significant obstructive CAD, had additional perfusion abnormalities in regions unmatched with the obstructive lesions. Of CMD patients 23% were female, 41% had diabetes or prediabetes, 70% dyslipidemia, 47% hypertension, 63% family history of CAD and 19% were currently smoking. Type of chest pain was atypical in 53% of the patients.

### Conclusions

In a patient population with intermediate probability of CAD, some features of CMD can be identified in 9% of the patients who have numerous risk factors. However, CMD without any coronary atherosclerosis is rare (1%). Co-existence of CMD with non-obstructive CAD (3%) and obstructive CAD (5%) is more common. Quantitation of myocardial perfusion combined with anatomical imaging provides comprehensive way to identify CMD.

## Cancer risk after heart transplantation highly elevated in comparison to general population

**Salla Jäämaa**, Sydänkeskus, HYKS, Helsinki, Finland

**Birgitta Salmela**, HYKS, Helsinki, Finland

**Eero Pukkala**, Suomen Syöpärekisteri, Helsinki, Finland

**Karl Lemström**, HYKS, Helsinki, Finland

**Jyri Lommi**, HYKS, Helsinki, Finland

### Aim

Malignancies are the leading cause of death for adult heart transplant recipients beyond five years after transplantation. The aim of this study was to assess the cancer risk of heart transplant (HTx) recipients in Finland.

### Methods

We studied cancer incidence of Finnish adult HTx recipient cohort of years 1985-2011 by linking the cohort with the national Finnish Cancer Registry's data until the end of year 2012. HTx cohort included 424 patients producing 3763.6 person years. Median age at HTx was 51 years (range 15-68 years, interquartile ratio 17) and median survival after HTx 7.4 years (range 0-25.2, IQR 13.1). Most common etiologies for HTx were dilated cardiomyopathy (50%) and coronary artery disease (33%). Cancer-specific standardized incidence ratios (SIR) were defined as ratios of observed and expected numbers of cases, the latter ones calculated from the cancer incidence in the Finnish population stratified by age, sex and calendar time.

### Results

155 cancers (SIR for overall cancer 5.1; 95% confidence interval 4.3-5.9) and 70 basalomas (SIR 10.8, 95% CI 8.4-13.6) were detected in 106 HTx recipients during the follow-up period. Median time from transplantation to first cancer was 10.1 years (range 0 – 22.9 years; 95% CI 9.1-11.3). Relative risk was most elevated for squamous cell skin cancer (48 observed; SIR 57.4; 95% CI 42.4-72.2), Non-Hodgkin lymphoma (31; SIR 25.9; 17.6-36.7), oral and pharyngeal cancer (11; SIR 14.9; 7.5-26.7), of which especially for lip cancer (5; SIR 36.1; 11.7-84.3) and cancer of tongue (4; SIR 32.6; 8.9-83.4). Risk for renal cancer (11; SIR 10.1; 5.0-18.0) and respiratory organs' cancer (15; SIR 3.6; 2.0-6.0) was also markedly elevated. Risk for all malignancies, except for Non-Hodgkin lymphoma which risk was highest between the second and the fifth year after HTx, kept growing as the time passed after HTx, risk being highest beyond 10 years from the transplantation.

### Conclusions

HTx recipients' cancer risk of is highly elevated compared to the general Finnish population's cancer risk and it grows still at 10 years and beyond from the transplantation. Our results demonstrate the high importance of life-long, frequent cancer surveillance after HTx in order to detect the possible malignancies at early stage and thus improve the long term survival of these patients.

## Cardiorespiratory fitness modifies the association between leisure-time physical activity and the risk of sudden cardiac death among middle-aged men

**Magnus Hagnäs**, Department of Internal Medicine, Lapland Central Hospital, Oulu, Finland

**Timo Lakka**, Department of Physiology, University of Eastern Finland, Kuopio, Finland

**Sudhir Kurl**, Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

**Timo Mäkikallio**, Internal Medicine, Oulu University Hospital, Oulu, Finland

**Kai Savonen**, Clinical Physiology and Nuclear Medicine, University of Eastern Finland, Kuopio, Finland

**Rainer Rauramaa**, Clinical Physiology and Nuclear Medicine, University of Eastern Finland, Kuopio, Finland

**Jari Laukkanen**, Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

### Aim

We investigated whether cardiorespiratory fitness (CRF) modifies the association between leisure-time physical activity (LTPA) and the risk of sudden cardiac death (SCD) among middle-aged men.

### Methods

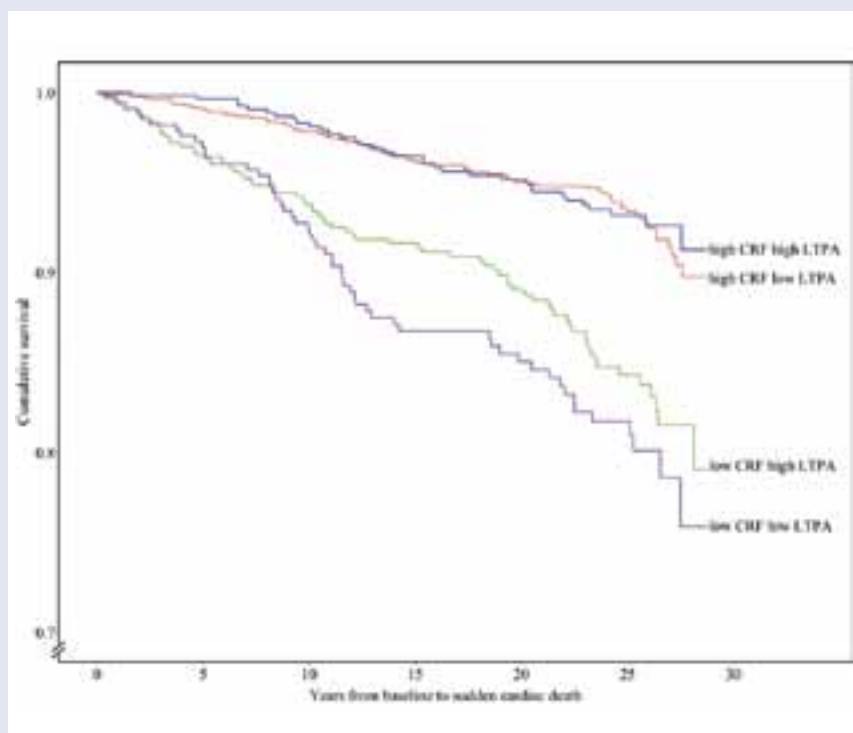
The participants were a population sample of 2656 Finnish men aged 42-60 years at baseline. The energy expenditure of LTPA was assessed with a questionnaire using kilocalories per day (kcal/d). CRF was measured directly using respiratory gas analysis during maximal exercise test and was expressed in metabolic equivalents (METs). The participants were divided into the following 4 groups according to the lowest tertiles of CRF (7.9 METs) and LTPA (191 kcal/d) as cut-offs: high CRF and LTPA, high CRF and low LTPA, low CRF and high LTPA and low CRF and LTPA. The risk of SCD was analysed using Cox regression models adjusted for age, smoking, alcohol consumption, body mass index, systolic blood pressure, low density lipoprotein cholesterol, C-reactive protein, prevalent type 2 diabetes and prevalent coronary heart disease.

### Results

During the mean follow-up time of 21 years 242 SCDs occurred. Men with low CRF and LTPA had a 1.8 (95% confidence interval 1.3-2.6,  $p=0.001$ ) times higher risk of SCD than men with high CRF and LTPA. Men with high CRF and low LTPA or men with low CRF and high LTPA did not differ statistically significantly in the risk of SCD from men with high CRF and LTPA. Figure 1 shows the cumulative survival from SCD in the 4 groups. CRF was independently related to the risk of SCD. One MET increase in CRF was associated with a 16% (95% confidence interval 10% - 22%,  $P<0.001$ ) decrease in the risk of SCD after adjustment for other risk factors.

### Conclusion

Our study shows that men with low CRF and low LTPA have increased risk of SCD. The amount of LTPA did not modify the risk of SCD among men with high CRF.



### Gadolinium late enhancement and septal thinning predict adverse events in cardiac sarcoidosis

**Kaj Ekström**, Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland and Päijät-Häme Central Hospital, Department of Cardiology, Lahti, Finland

**Jukka Lehtonen**, Helsinki University Central Hospital, Helsinki, Finland

**Helena Hänninen**, Helsinki University Central Hospital, Helsinki, Finland

**Markku Kupari**, Helsinki University Central Hospital, Helsinki, Finland

#### Aim

The diagnostic value of cardiac magnetic resonance imaging (CMR) in cardiac sarcoidosis (CS) is well known. The purpose of this study was to investigate the prognostic value of CMR in CS.

#### Methods

We retrospectively reviewed the CMR studies and follow-up data of the 60 CS patients who underwent CMR in our institution from February 2004 to July 2014. Criteria used for CS diagnosis included imaging finding consistent with CS combined with histological verification of CS (myocardial biopsy, n=31; mediastinal lymph node, n=19; other extra-cardiac tissue, n=9; autopsy, n=1). The late gadolinium enhancement (LGE) mass was calculated by the full width half-maximum threshold method and the amount of LGE was expressed as a percentage of the total left ventricular (LV) mass. Thickness of the basal septum (defined as the thinnest point of American Heart Association segments 2 and 3) was measured.

#### Results

There were 21 males and 39 females with a mean age of 46 years (range 18–66). The mean left ventricular ejection fraction (LVEF) by CMR was 43% (range 12–69). Major adverse cardiovascular events (MACE) included death (n=4), cardiac transplantation (n=2), ventricular fibrillation (n=8) or ventricular tachycardia requiring ICD therapy (shocks or ATP) or external defibrillation (n=17), whichever occurred first. The median follow-up from the CMR study to end of follow-up or first MACE was 14 months. All patients exhibited LGE with a median of 17% (range 2–52) of LV mass. The extent of LGE was a strong predictor of MACE (HR 1.054; 95%CI 1.018–1.091; p=0.003 by Cox regression). The thickness of basal septum was <4 mm in 6/55 patients. These patients had significantly worse MACE-free survival (5/6 MACE, median MACE-free survival 2 months vs. 18/49 MACE; median MACE-free survival 60 months; logrank p=0.008). LVEF did not predict MACE in these patients.

#### Conclusion

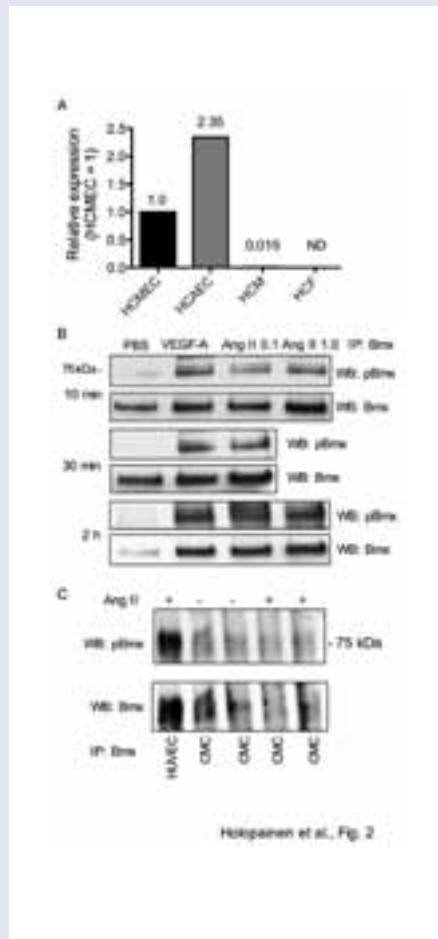
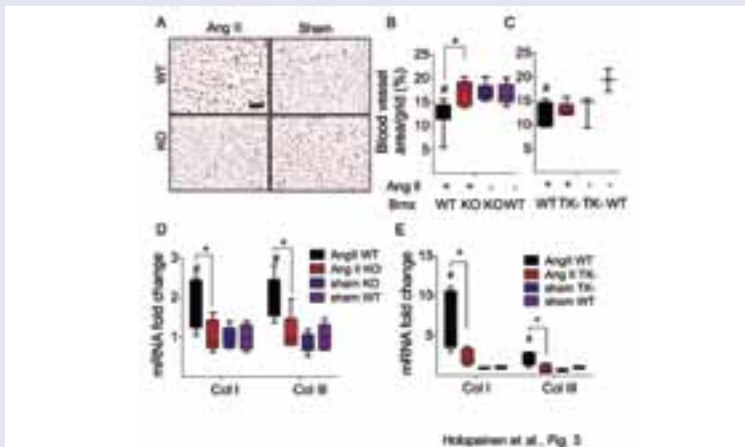
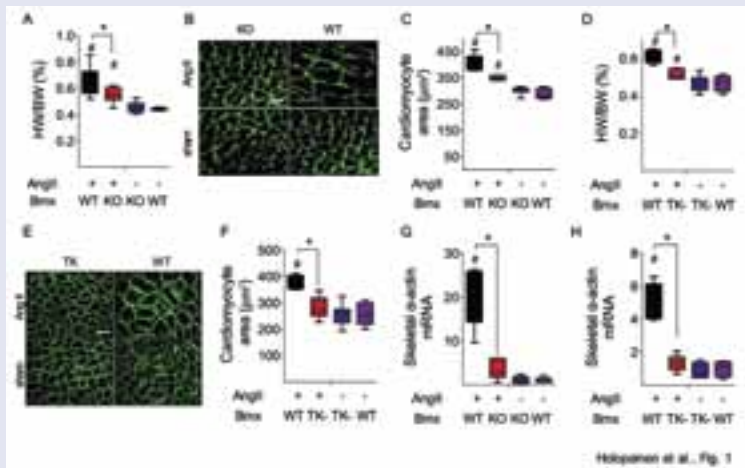
CMR with quantitative LGE analysis helps to assess prognosis in CS. Both overall LGE extent and abnormal LV septal thinning predict an increased risk of MACE.

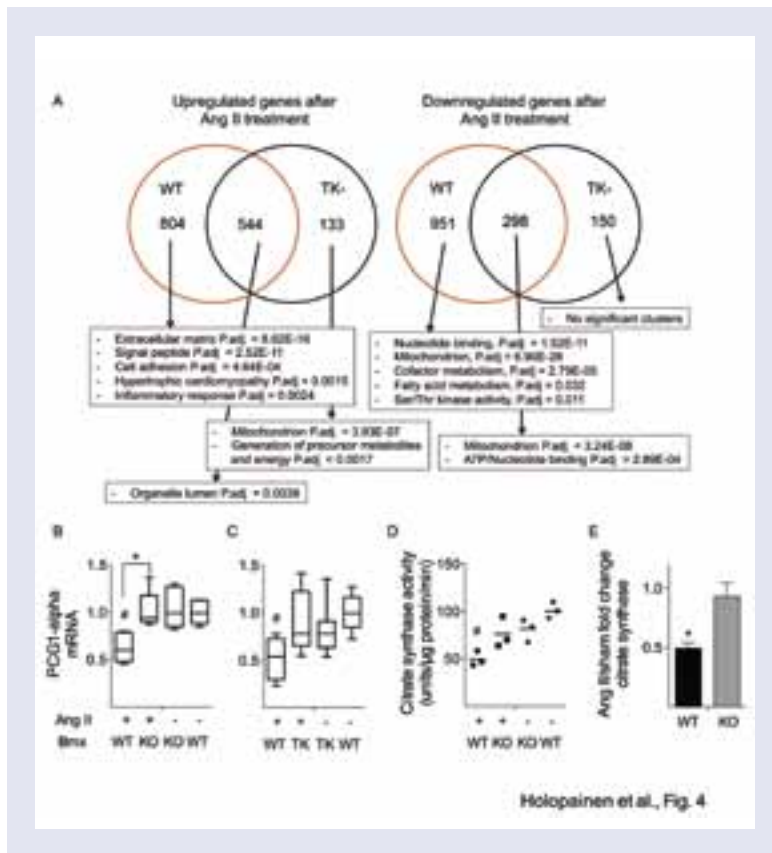
## Endothelial Bmx tyrosine kinase activity is essential for myocardial hypertrophy and remodeling

**Markus Räsänen**, TCB/ Wihuri Research Institute, University of Helsinki, Helsinki, Finland  
**Tanja Holopainen**, TCB/ Wihuri Research Institute, University of Helsinki, Helsinki, Finland  
**Wei Zheng**, University of Helsinki, Helsinki, Finland  
**Tomi Tuomainen**, University of Eastern Finland, Kuopio, Finland  
**Denis Tvogorov**, University of Helsinki, Helsinki, Finland  
**Andrey Anisimov**, University of Helsinki, Helsinki, Finland  
**Juha J Hulmi**, University of Jyväskylä, Jyväskylä, Finland  
**Leif C Andersson**, University of Helsinki, Helsinki, Finland  
**Bruno Cenni**, Novartis, Basel, Switzerland  
**Pasi Tavi**, University of Eastern Finland, Kuopio, Finland  
**Eero Mervaala**, University of Helsinki, Helsinki, Finland  
**Riikka Kivelä**, University of Helsinki, Helsinki, Finland  
**Kari Alitalo**, University of Helsinki, Helsinki, Finland

### Aim

The Bmx non-receptor tyrosine kinase is highly expressed in arterial endothelium, and Bmx-deficient mice are healthy and fertile. Bmx has been shown to participate in the pathogenesis of cardiac hypertrophy; however, little is known about the mechanisms how this endothelial tyrosine kinase would regulate cardiomyocyte growth.

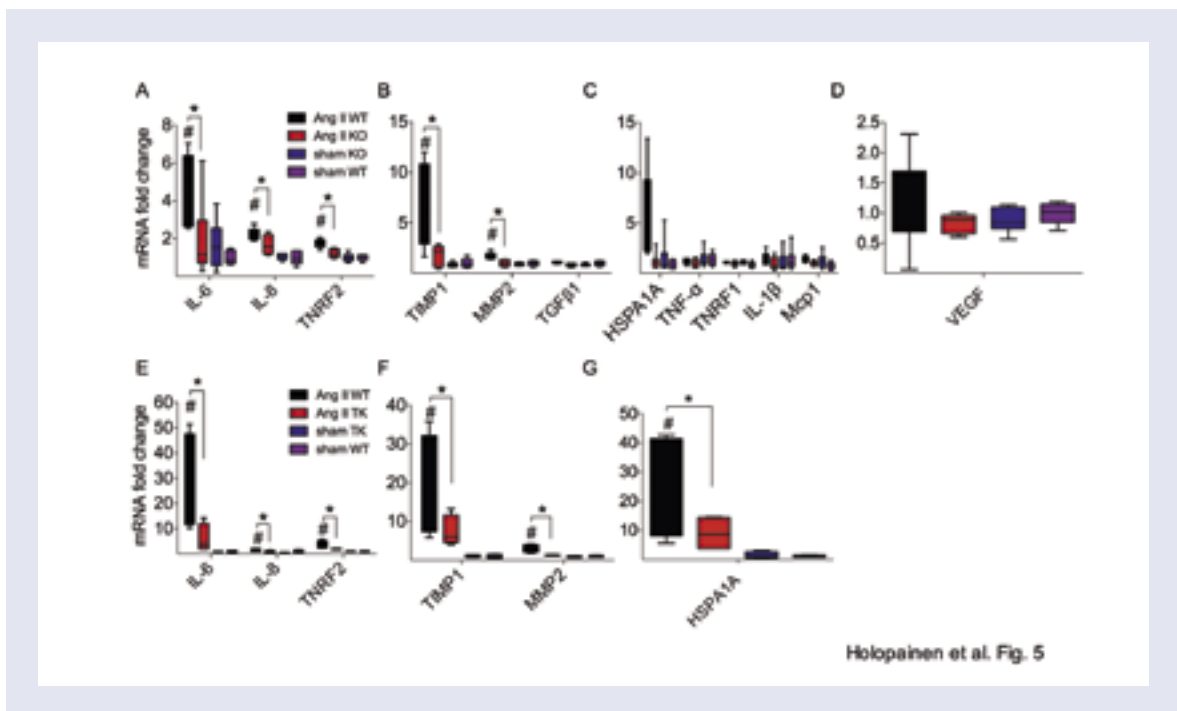




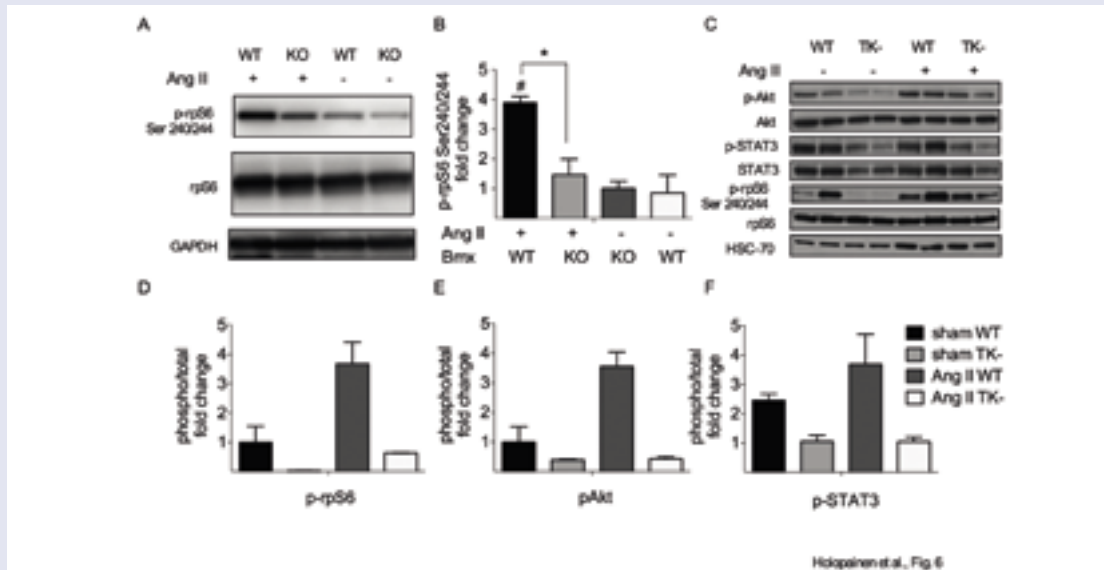
The aims of this study were to determine the molecular mechanisms mediated by Bmx in cardiac hypertrophy, and specifically, if the Bmx tyrosine kinase activity is necessary for pathological cardiac remodeling.

### Methods

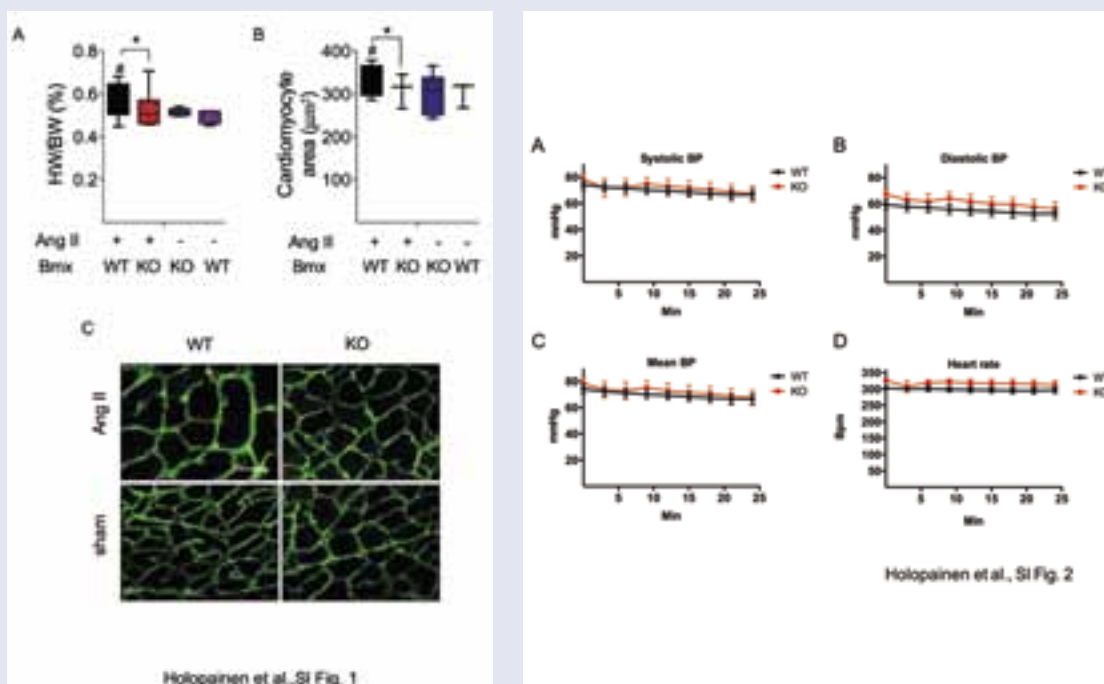
We studied the role of Bmx in angiotensin II (Ang II)-induced cardiac hypertrophy and remodeling using two different mouse lines: mice constitutively lacking the Bmx protein and mice with a specific loss of Bmx tyrosine kinase activity. The Ang II-induced cardiac hypertrophy was significantly reduced in mice deficient of Bmx and in mice with inactivated Bmx tyrosine kinase compared to wild-type mice.







Holopainen et al., Fig 6



Holopainen et al., SI Fig. 1

Holopainen et al., SI Fig. 2

## Results

Genome-wide transcriptome profiling showed that Bmx inactivation suppressed myocardial expression of genes related to the Ang II-induced inflammatory and extracellular matrix responses, whereas expression of RNAs encoding mitochondrial proteins were more abundant in Bmx-inactivated hearts after Ang II. Importantly, the activation of the mTORC1 signaling pathway by Ang II treatment was decreased in the Bmx-deficient hearts.

## Conclusions

Our results demonstrate that inactivation of the Bmx kinase activity inhibits Ang II-induced cardiac hypertrophy and remodeling by attenuating the growth and inflammatory signaling from endothelial cells to cardiomyocytes. Furthermore, these results suggest that inhibition of endothelial Bmx kinase activity could be a strategy to attenuate the development of pathological cardiac remodeling.

## Follow-up of 316 molecularly defined pediatric long QT syndrome patients - clinical course and fulfillment of $\beta$ -blocker treatment

**Mikael Koponen**, Heart and Lung Center,

Helsinki University Central Hospital, Helsinki, Finland

**Annikka Marjamaa**, Helsinki University Central Hospital, Helsinki, Finland

**Anita Hiippala**, Helsinki University Central Hospital, Helsinki, Finland

**Juha-Matti Happonen**, Helsinki University Central Hospital, Helsinki, Finland

**Kimmo Kontula**, Helsinki University Central Hospital, Helsinki, Finland

**Heikki Swan**, Helsinki University Central Hospital, Helsinki, Finland

### Aim

Inherited long QT syndrome (LQTS) is associated with risk of sudden death. We assessed the clinical course and fulfillment of  $\beta$ -blocker treatment in genotyped pediatric long QT syndrome type 1 and (LQT1) and type 2 (LQT2) patients.

### Methods

The study population was drawn from the Finnish Inherited Cardiac Disorder Research Registry comprising 4000 molecularly tested subjects. The inclusion criteria were 1) genetically confirmed KCNQ1 or KCNH2 mutation, and 2) age <16 years at enrollment. In 2011-2012 a questionnaire was sent to the study subjects or their parents. Data of all deaths were obtained from Statistics Finland. Kaplan-Meier graphs, the log-rank test and time-dependent Cox regression model were used to evaluate the contribution of risk factors to cardiac event.

### Results

A total of 457 subjects fulfilled the inclusion criteria. Three of them died during the follow-up, and 313 (69%) responded to the inquiry. The final study population (n=316) consisted of 224 KCNQ1 and 85 KCNH2 mutation carriers, and 7 carriers with more than one mutation. The total follow-up time including the retrospectively collected data from birth was 12.0 $\pm$ 5.5 years.

No arrhythmic deaths occurred during the follow-up. LQT1 Finnish founder (FF) mutation carriers had fewer cardiac events by the age of 18 years than other LQT1 patients (cumulative probability [CP]= 11% vs 26%, p=0.008, and hazard ratio [HR]=0.38, p=0.04, Figure 1).

Similar trend was observed in LQT2 FF and non-FF patients (CP= 4% vs 43%, p=0.002, and HR=0.17, p=0.02). QTc interval  $\geq$ 500 ms increased the risk of cardiac events compared to QTc <470 ms (HR=3.92, p=0.002) and QTc 470-499 ms (HR=2.76, p=0.03). Treatment with  $\beta$ -blocker medication was associated with reduced risk of first cardiac event (HR=0.27, p=0.005). Non-compliant LQT2 patients were more often symptomatic than compliant LQT2 patients (18% vs 0%, p=0.03). Side effects were encountered in 23% of  $\beta$ -blocker users, and side effects did not affect compliance.

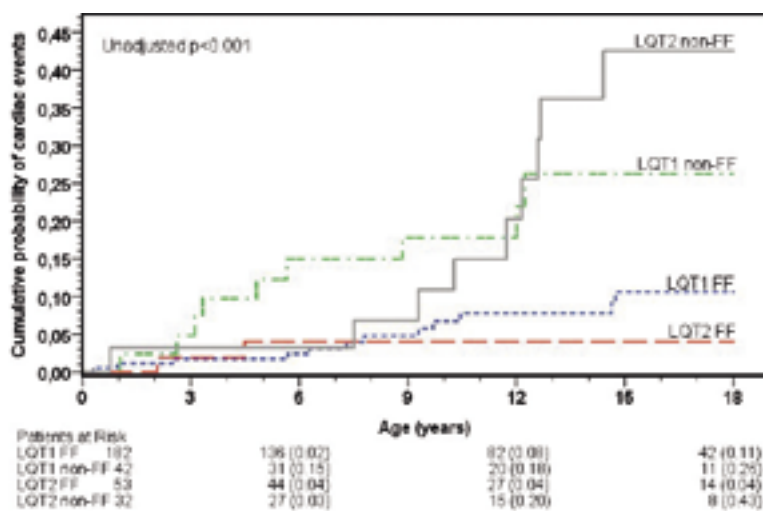


Figure 1. Kaplan-Meier graph of cumulative probability of cardiac events in LQT1 and LQT2 FF and non-FF patients. FF = Finnish founder, LQT1 = long QT syndrome type 1, LQT2 = long QT syndrome type 2

### Conclusions

Severe cardiac events are uncommon in molecularly defined and appropriately treated pediatric LQTS mutation carriers.  $\beta$ -blocker medication reduces the risk of cardiac events, and is generally well tolerated in this age group of LQTS patients.