Suomen Kardiologinen Seura

Finnish Cardiac Society

42nd Progress Report Meeting

April 7, 2016

Helsinki

Contents

42nd Progress Report Meeting – Programme

Fennia I **42nd Progress Report Meeting**

Chairperson Antti Hedman, Kuopio University Hospital, Heart Center

Meeting is supported by unrestricted educational grant from Boehringer Ingelheim

08.30–08.35 Opening remarks.
Antti Hedman, Cardiologist, Kuopio University Hospital, Heart Center

Young Investigators Award Competition, part I

08.35–08.50 Atrial fibrillation and ECV: Can failure of elective cardioversion or recurrence of AF after ECV be predicted?
Tapio Hellman (MD), Turku University Hospital, Cardiology

08.50–09.05 Direct oral anticoagulants in atrial fibrillation patients undergoing cardioversion. Nationwide multicentre study.
Saga Itäinen (BMed), Helsinki University Hospital, Heart and Lung Center

09.05–09.20 Follow-up of genetically confirmed adult long QT syndrome type 1 and 2 patients: clinical course and tools for mutation-specific risk stratification.
Mikael Koponen (MD), Helsinki University Central Hospital, Heart and Lung Center

09.20–09.35 Inferolateral early repolarization among non-ischemic sudden cardiac death victims.
Lauri Holmström (Student), University of Oulu, Department of Internal Medicine

09.35–09.50 Red blood cell transfusion independently increases long-term mortality even after one-year follow-up within non-coronary artery bypass grafted acute coronary syndrome patients.
Jaakko Allonen (MD), Helsinki University Central Hospital, Heart and Lung Center

09.50–10.05 Relationship between the quality of warfarin therapy and the risk of myocardial infarction in patients with atrial fibrillation. FinWAF registry with 54568 patients.
Tero Penttilä (MD), Heart Hospital, Tampere University Hospital

10.05–10.30 *Näyttely ja kahvi*

Young Investigators Award Competition, part II

10.30–10.45 Combined measurement of soluble ST2 and NT-proBNP indicates early the disease severity in patients with cardiogenic shock complicating acute coronary syndrome.
Heli Tolppanen (MD), Päijät-Häme Central Hospital, Cardiology

10.45–11.00 Risk factors for life threatening ventricular arrhythmias in giant cell myocarditis.
Kaj Ekström (MD), Helsinki University Central Hospital, Heart and Lung Center

11.00–11.15 Risk of stroke, bleeding and mortality is associated with the quality of warfarin therapy in atrial fibrillation patients. Results from the FinWAF registry.
Jussi Niiranen (MD), Helsinki University Hospital, Department of Cardiology

11.15–11.30 VEGF-B gene therapy inhibits doxorubicin induced cardiotoxicity endothelial protection.
Markus Räsänen (BMed), Wihuri Research Institute, Translational Cancer Biology

Progress in Clinical Cardiology

11.30–12.00 Emergency management in cardiology – look for the future.
Peter Verhamme, Speacialist in Cardiology, Internal Medicine, General Medicine and Hematology, Centre for Molecular and Vascular Biology, Leuven, the Netherlands

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 ylilääkäreistä 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 sanattomaksi tiukkojen kommenttien ja kysymysten edessä. Lisäksi saman abstraktin voi lähettää vaikka ESC:n kokoukseen, jonka lähetysaika päättyy samoihin aikoihin. Parhaimmillaan pääsee harjoittelemaan siellä pidettävää esitystä hyvissä 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 seuraa tutuksi uudelle kardiologipolvelle. Millään yhdistyksellä ei ole tulevaisuutta ilman nuoria.

4 Olet itsekin osallistunut kisaan, millainen kokemus se oli?

Osallistuin kisaan kahdesti 1990-luvun jälkipuoliskolla väitöskirjatyöhöni liittyneillä, sydämen vajaatoimintaa käsitelleillä 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 osallistumisessa 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 Helsingissä 6.-8.4.2016. Abstraktien lähetysaika päättyy 31.1.2016. Kilpasarjojen voittajat palkitaan Boehringer Ingelheim Finlandin lahjoittamilla 2300 euron matka-apurahoilla.

Lisätietoja kilpailusta Suomen Kardiologisen Seuran nettisivuilta
www.fincardio.fi/apurahat/progress_report_yiac/

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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	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

Atrial fibrillation and ECV: Can failure of elective cardioversion or recurrence of AF after ECV be predicted?

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Tuomas Kiviniemi, Cardiology, TYKS, Turku, Finland, Vasankari Tuija, Cardiology, TYKS, Turku, Finland, Ilpo Nuotio, Cardiology, TYKS, Turku, Finland, Juhani Airaksinen, Cardiology, TYKS, Turku, Finland

Aim

Elective electrical cardioversion (ECV) of atrial fibrillation (AF) is a standard procedure in achieving sinus rhythm. Nevertheless, data on factors predicting successful elective cardioversion or recurrence of AF after ECV are scarce.

Methods and Results

In this single center retrospective study we analyzed 1571 elective cardioversions performed for persistent atrial fibrillation in 1023 patients. Median number of cardioversions was 1 per patient (mean 1.61 per patient) with a range of 1-10. Altogether 1352 (86.1%) cardioversions were initially successful. There were no significant differences in baseline characteristics of patients with successful vs failed cardioversions. Every 90 days delay in performing the ECV decreased the success rate by 34% (95%CI 15.7 – 48.3, p 0.001). Out of the successful elective cardioversions a recurrence of atrial fibrillation within 30 days was detected in 454 cases (33.6%). The median time to recurrence was 8.0 [interquartile range (IQR) 13.0] days. Characteristics of patients with and without recurrence are listed in Table 1. Female gender (OR 1.50 95%-CI 1.16 – 1.93, p=0.002) was an independent predictor for the AF recurrence. The use of rate control medications was not associated with smaller recurrence rate of AF or higher success rate of ECV. Conversely, antiarrhythmic agents predicted a higher recurrence rate probably reflecting high baseline AF burden in this subset of patients.

Table 1.

		Recurrence (N=466)	No Recurrence (N=1105)	p
Age:	>75y	63 (13.5)	166 (15.0)	0.38
Female		149 (32.0)	279 (25.2)	<0.01
First AF episode		193 (41.9)	507 (46.4)	0.11
Prior Cardioversion		222 (49.6)	511 (48.3)	0.65
CHA_2DS_2-VASc-score	≥2	265 (56.9)	643 (58.2)	0.62
Time since AF diagnosis	<1y	197 (47.8)	495 (52.2)	0.32
Age of current AF episode[a]	>180d	32 (11.3)	94 (15.6)	0.03
Medication				
Beta blocker		328 (80.2)	758 (82.9)	0.25
Digoxin		38 (9.3)	114 (12.5)	0.09
Antiarrhythmic agent		101 (24.9)	139 (15.3)	<0.01

[a] In 686 (43.7) cases the age of current AF episode was unavailable. ECV = elective cardioversion; AF = atrial fibrillation

Conclusions

In this real world cohort of patients, sinus rhythm was restored in the majority of patients. Still, every seventh ECV failed. The delay from detection of atrial fibrillation to elective cardioversion decreased the success rate. Also at 30 days follow-up, recurrence of AF was detected in a third of the cases after elective cardioversion in spite of rate control or antiarrhythmic medications. Altogether almost half of the patients had initially unsuccessful ECV or recurring AF at 1 month follow-up. It is critical to minimize the delay between diagnosing AF and ECV. Better predictors for recurrence of AF after ECV are greatly needed.

Direct oral anticoagulants in atrial fibrillation patients undergoing cardioversion. Nationwide multicentre study

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Aim

The direct oral anticoagulants (DOAC), have been shown to be safe and effective alternatives to warfarin for stroke prevention in patients with nonvalvular AF (NVAF). There are yet limited real life data on outcomes following elective cardioversion in AF patients treated with DOACs. The aim of this study was to investigate the complications and the use of different DOACs in AF patients having cardioversion.

Methods

In this nationwide multicentre study of consecutive elective cardioversions in AF patients treated with DOACs were investigated between 1. Oct 2011 and 31. Dec 2015. Data on patient characteristics, success of cardioversion, antithrombotic treatment and acute (< 30 days) complications (stroke or systemic embolism, haemorrhage, death and AF relapse) were collected in electronic case report forms.

Results

734 patients mean (±SD) age 63 (±14) years, 76% men, treated with DOACs underwent a total of 893 elective cardioversions. 517 (57.9%) cardioversions were performed in patients receiving dabigatran, 278 (31.1%) rivaroxaban and 98 (11.0 %) apixaban, respectively. 87% of the cardioversions were successful, i.e. sinus rhythm was restored and maintained at least for five minutes. During the one-month follow-up AF recurrence rate was 28.4% (median time after cardioversion 8 days). A total of 2 strokes occurred after cardioversion (0.2%): 1 patient receiving dabigatran experienced a stroke on day 2, and 1 patient receiving rivaroxaban on day 4, respectively. Both patients had used adequate doses for 4 weeks preceding cardioversion. One of the patients was a 66-year old man with a CHA2DS2-VASc score of 3 and the other a 64-year old female with a CHA2DS2-VASc score of 2. A total of 4 (0.4%) clinically relevant, but not serious bleeding events (1 haematuria, 1 haemorrhoid bleeding, 1 nosebleed and 1 not specified) occurred in 2 patients receiving dabigatran and 2 patients receiving rivaroxaban (median time after cardioversion 16 days). No deaths were documented during the one-month follow-up.

Conclusions

This study shows that thrombotic and bleeding complications related to DOACs are uncommon (<1%) in real life patient NVAF population undergoing cardioversion.

Follow-up of genetically confirmed adult long QT syndrome type 1 and 2 patients: clinical course and tools for mutation-specific risk stratification

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Aim

Long QT syndrome (LQTS) is an inherited cardiac disorder predisposing to sudden cardiac death (SCD). Research has been scarce on its clinical course in genetically confirmed patients not receiving β-blocker therapy.

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, or non-carrier status of the family-specific LQTS mutation, and 2) the age of at least 18 years at follow-up end. A questionnaire was sent to the study subjects. Data of all deaths were obtained from Statistics Finland, and data of ICD and pacemaker implantations were acquired from Hospital discharge register (HDR). Kaplan-Meier graphs, the log-rank test and Cox regression models were applied to evaluate the contribution of risk factors to cardiac events at the age of 18-40 years.

Results

A total of 2723 subjects fulfilled the inclusion criteria. Of them 14 died during the follow-up, 1495 (55%) responded to the inquiry, and additional 12 subjects with device therapy were drawn from the HDR. The final study population (n=1521) consisted of 867 LQTS mutation carriers (617 with KCNQ1, 242 with KCNH2, and seven with ≥1 mutation), and 654 non-carrier relatives. The total follow-up time including retrospectively collected data was 18.3±6.3 years.

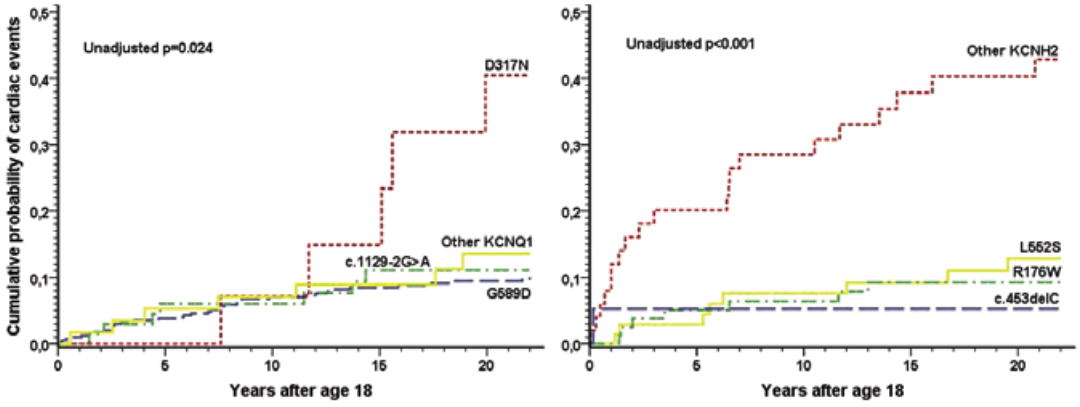

Figure. Kaplan-Meier graphs depicting cumulative probability of cardiac events in LQT1 (on the left) and LQT2 (on the right) patients by mutation before initiation of β-blocker treatment at the age of 18-40 years.

In mutation carriers, three of the seven SCDs, and 10 of the 14 aborted cardiac arrests associated with insufficient β-blocker medication. Risk factors for cardiac events before initiation of β-blocker therapy in mutation carriers included LQT2 genotype (hazard ratio [HR]=1.9, p=0.01), female gender (HR=3.1, p<0.001), a cardiac event before the age of 18 years (HR=11.1, p<0.001), and QTc ≥500 ms (vs <470 ms, HR=1.9, p=0.02). LQT1 patients carrying the KCNQ1 D317N mutation were at 3.0-3.9 -fold risk (p<0.001-0.03) compared to G589D, c.1129-2A>G and other KCNQ1 mutation carriers after adjusting for gender and QTc duration (Figure). KCNH2 c.453delC, L552S and R176W mutations associated with 76-88% lower risk (p<0.001) than other KCNH2 mutations.

Conclusions

Molecularly defined LQT1 and LQT2 patients who survive till adulthood continue being at risk of cardiac events. Specific mutations modulate the risk independently of gender and QTc duration.

Inferolateral early repolarization among non-ischemic sudden cardiac death victims

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Aim

Inferolateral early repolarization (ER) has been associated with increased risk for sudden cardiac death (SCD) in case-control studies and also in general population. Recent studies have shown that the association of ER and SCD in general population is mainly due to increased risk of SCD due to coronary disease (CAD). The association of ER and non-ischemic SCD in population based cohort has not been studied.

Methods

We have collected autopsy information from 4,032 SCD subjects since 1998 in the Fingesture study. Non-ischemic etiology was the cause of SCD in 951 subjects. We were able to collect pre-mortem ECGs from 275 subjects with non-ischemic SCD (mean age 57±12, male 75%). The control population consisted of general population cohort of 10,864 subjects (mean age 44 ± 8 years, male 52%).

Results

Hypertrophic cardiomyopathy related to hypertension (HTA) (25%), unexplained cardiomegaly (CMCMP) (23%), alcohol related dilated cardiomyopathy (ACMP) (24%) and idiopathic myocardial fibrosis (IMF) (15%) were the most common causes of SCD in the non-ischemic population with ECGs. Structurally normal heart was seen in only 1.5% (n=4). The prevalence of inferolateral ER was 20.7% (inferior 11.3%; lateral 13.1%; both 3.6%) among patients with non-ischemic SCD compared to 5.3% (inferior 3.3%; lateral 2.4%; both 0.4%) in the general population ($p< 0.001$). The ECG pattern was accompanied with horizontal/descending ST segment in 86% of inferior ER and 100% of lateral ER. The prevalence of ER was highest in HTA group (26%) and ACMP group (24%). In IMF group (20%) and CMCMP group (13%) ER prevalence was slightly lower. The highest ER prevalence was in hypertrophic obstructive cardiomyopathy group (1/1 subjects). The history of prior diagnosis of cardiac disease was not higher among subjects with ER (55%) than those without (59%, $p=0.59$).

Conclusions

The prevalence of inferolateral ER among non-ischemic SCD victims is high. Almost all ER patterns are accompanied with the malignant horizontal/descending ST segment morphology. These results suggest that inferolateral ER is not only associated with ischemic SCD but also non-ischemic SCD.

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Red blood cell transfusion independently increases long-term mortality even after one-year follow-up within non-coronary artery bypass grafted acute coronary syndrome patients

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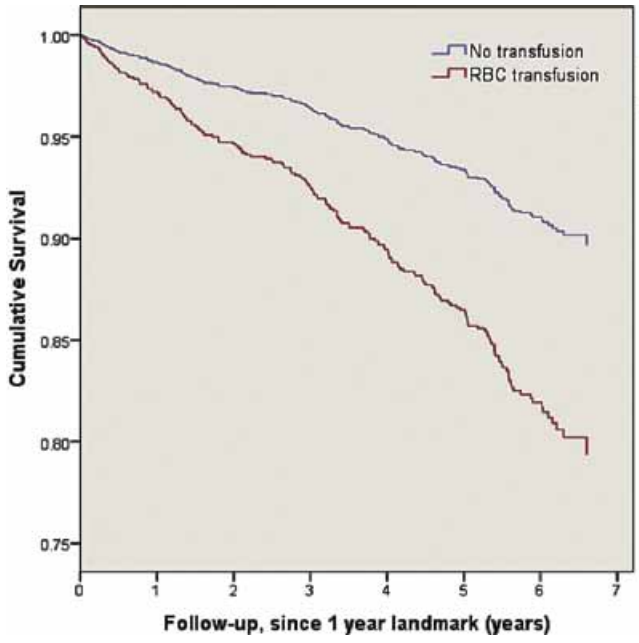
Aim

Recent registry studies have associated red blood cell (RBC) transfusion with increased in-hospital mortality among acute coronary syndrome (ACS) patients. Impact on long-term mortality after one year remains unknown. Our objective was to investigate the impact of RBC transfusion on long-term mortality within non-coronary artery bypass grafting (CABG) treated ACS patients. Furthermore, we wanted to investigate the phenomena behind the increased mortality by analyzing the causes of death.

Methods

Consecutive ACS patients (n = 2090) from a prospective COROGENE-cohort, who underwent an angiography in Helsinki University Hospital between March 2006 and March 2008, were followed for 6.8 years (interquartile range 6.3-7.3). We had complete data of 2009 patients, of which 1937 (96%) survived 30 days after discharge. Of these, 85 (4.4%) previously transfusion-naïve, non-CABG patients received at least one RBC transfusion during the hospitalization. They were compared to those 1278 (63.6%) non-CABG patients who did not receive any transfusion. Transfusion data was gathered retrospectively from HUSLAB registry and the mortality data from The Statistics Finland.



Multivariable predictors of mortality after 1-year follow-up

	Hazard ratio (95% Confidence Interval)	p Value
RBC transfusion	2.13 (1.43 – 3.15)	<0.001
3-artery disease	2.00 (1.47 – 2.72)	<0.001
Diuretics	1.78 (1.26 – 2.42)	0.001
Atrial fibrillation	1.73 (1.17 – 2.54)	0.006
GFRe < 60 ml/min	1.61 (1.15 – 2.25)	0.006
Diabetes	1.50 (1.09 – 2.07)	0.013
Age	1.06 (1.04 – 1.08)	<0.001
Percutaneous coronary intervention	0.68 (0.48 – 0.96)	0.028
Statins	0.50 (0.28 – 0.88)	0.016

Results

Unadjusted long-term mortality was significantly higher among RBC transfused patients than in non-transfused patients (51.8% vs. 15.1%; p <0.001). After a multivariate Cox proportional hazards model, RBC transfusion remained significant independent factor on overall survival (hazard ratio (HR) 1.71, confidence interval (CI) 1.17 – 2.52, p = 0.003). In a similar multivariate landmark analysis, with landmark time point set at one year, RBC transfusion turned out to be the most important factor associated with worse survival (HR 2.13, CI 1.43 – 3.15, p <0.001) (Figure1). The risen all-cause mortality of RBC transfused patients compared to non-transfused patients was explained by both cancer (14.1% vs. 2.6%, p <0.001) and cardiovascular mortality (30.6% vs. 9.5%, p <0.001). In addition, RBC transfused patients were diagnosed more frequently with a malignancy after hospitalization (17.6% vs. 9.3%, p = 0.012).

Conclusions

The strong association of RBC transfusion with increased mortality continues even after one-year follow-up among non-CABG ACS patients. To find out the causality between RBC transfusion and mortality, further randomized trials are warranted. Nevertheless, clinicians should be cautious especially when treating more fragile patients to minimize the need of transfusion. These measures could be e.g. reduced doses of antithrombotic and anticoagulant medications, radial approach in angiography or iron infusion instead of RBC transfusion. Finally, RBC transfusion seems to associate to malignancies, both their incidence and risen mortality.

Relationship between the quality of warfarin therapy and the risk of myocardial infarction in patients with atrial fibrillation. FinWAF registry with 54568 patients

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Background

Recent data indicate that atrial fibrillation (AF) has serious adverse prognostic implications among patients with myocardial infarction (MI). Vitamin K antagonist (VKA) may reduce the risk myocardial infarction in patients with atrial fibrillation (AF), but the impact of the quality of VKA therapy on the incidence of MI among patients with AF remains to be established.

Patients and Methods

We evaluated the relationship between the quality of VKA therapy (time in therapeutic range, TTR) and risk of MI in a cohort of 54568 Finnish patients using warfarin for AF (FinWAF). In the FinWAF database data from several nationwide registries are linked through the civil registration number of the patients.

Results

The number, crude rate and adjusted hazard ratio (HR) of MI among patients with AF and various TTR levels are presented in Table 1. The risk of MI was significantly higher among patients with TTR<50% than in the reference population (TTR=60-70). In contrast, patients with TTR>80 were less likely to have MI during the mean follow-up of 2.4 years (SD 1.7, range 0.0-5.0). Moreover, the risk of MI was clearly higher among those with previous MI (HR 7.0. 95% confidence limits 6.4-7.8).

Conclusions

Our data demonstrated a direct relationship between the quality of VKA therapy and the risk/incidence of MI in patients with AF. This novel finding emphasized the importance of quality control of warfarin therapy, including the risk of MI.

Table 1. Crude incidence rates per 100 patient years and adjusted hazard ratios (age, gender, hypertension, diabetes, stroke, transient ischemic attack, previous MI) of MI among patients with different TTR values.

TTR (%)	Number of MI	Rate (95% CI)	HR (95% CI)
<40	859	3.3 (3.0-3.5)	1.6 (1.4-1.9)
40-50	265	2.9 (2.6-3.3)	1.5 (1.3-1.8)
50-60	248	2.4 (2.1-2.7)	1.2 (1.0-1.5)
60-70	218	1.9 (1.7-2.2)	1 (reference)
70-80	203	1.7 (1.5, 2)	0.9 (0.8-1.1)
>80	709	1.2 (1.1-1.3)	0.7 (0.6-0.8)

Combined measurement of soluble ST2 and NT-proBNP indicates early the disease severity in patients with cardiogenic shock complicating acute coronary syndrome

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Aim

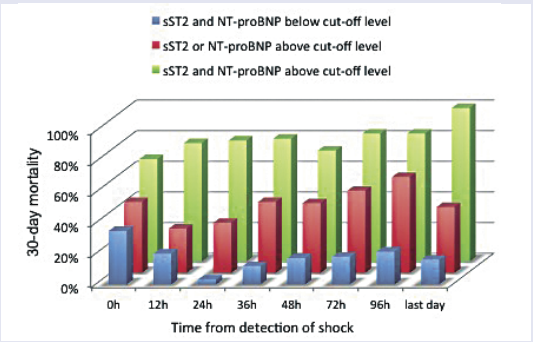
The short-term mortality in cardiogenic shock (CS) complicating acute coronary syndromes (ACS) is high, and early risk stratification is needed for rational use of advanced therapies. Soluble ST2 (sST2), a marker of adverse cardiac remodeling and fibrosis, is a strong prognosticator in various cardiovascular conditions. Furthermore, in patients with myocardial infarction and acute heart failure, the prognostic value provided by sST2 has been shown to be additive to that provided by natriuretic peptides. The aim of this study was to evaluate the added value of sST2 and NT-proBNP to clinical variables for risk stratification in patients with CS complicating ACS.

Methods

CardShock study was a prospective, observational, European multinational cohort study of CS. The main study introduced CardShock risk score, which included seven clinical variables available at baseline, and showed good discrimination for short-term mortality. In this sub-study serial plasma samples at 8 time-points from baseline to the last day of intensive cardiac care were analyzed from 145 patients with CS caused by ACS. The cut-off values for sST2 (470 ug/mL) and for NT-proBNP (4800 ng/L) were evaluated with receiver operating characteristic curves for 30-day mortality at 24 hours.

Results

Patients' mean age was 68 years, 78% were men, and all-cause 30-day mortality was 44%. The levels of both sST2 and NT-proBNP were higher in non-survivors compared to survivors at each time point measured (all p-values < 0.01). The combination of sST2 and NT-proBNP showed excellent discrimination for 30-day mortality when measured at 24 hours or later (AUC from 0.83 at 24 hours to 0.93 at last sample). Patients with both biomarkers above the cut-off level (470ug/mL for sST2 and 4800 ng/L for NT-proBNP) had markedly higher mortality compared to those with either or both biomarkers below the cut-off level when measured at any time point (figure; all p-values < 0.05). The combination of sST2 and NT-proBNP measured at 24 hours was independent of CardShock risk score result and peak value of troponin T, and gave added value to a multivariable model including those two variables (likelihood ratio 45.5 vs. 27.0, p<0.001).



Conclusions

The combined measurement of sST2 and NT-proBNP indicates the disease severity of CS complicating ACS early, accurately, and independently of clinical variables. The measurement of these biomarkers may help the risk stratification of patients with CS complicating ACS, and support clinical decision for advanced therapies.

Risk factors for life threatening ventricular arrhythmias in giant cell myocarditis

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Purpose

Not much is known on the risk factors for life-threatening arrhythmias in Giant Cell Myocarditis (GCM). Identification of patients at high risk for ventricular arrhythmias enables timely primary prevention.

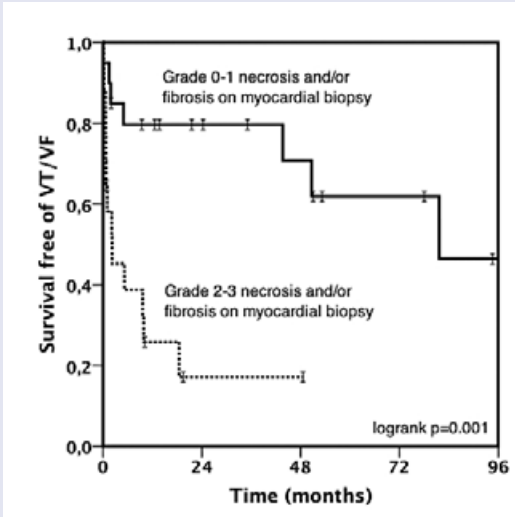
Methods

Study population consisted of 46 consecutive patients with GCM that were followed in our institution between January 1991 and May 2015. Data of the ventricular arrhythmias was retrospectively collected from ECGs, holter data, rhythm strips, and ICD data. All available myocardial biopsy material (n=44) was analyzed for the extent of myocardial necrosis and fibrosis on a semiquantitative scale from 0 to 3.

Summary of results

Of 46 patients, 31 were women and the mean age was 51±12 years. Mean LVEF at presentation was 41±15%. After a median of 2 months (range 0 - 82 months), 26 patients met the primary study endpoint defined as cardiac death (n=5) or life threatening ventricular arrhythmia (n=21), whichever occurred first. Life-threatening ventricular arrhythmia was defined as monomorphic sustained VT requiring external defibrillation or an ICD shock/antitachycardia pacing (n=15) or VF (n=6). After the primary endpoint event, there were three additional cardiac deaths and 7 patients who had VF.

As a marker of myocardial damage, the presence of moderate to severe necrosis and/or fibrosis on myocardial biopsy predicted worse cardiac survival free of life threatening arrhythmias with a HR of 5.33 (95% CI 1.84 - 15.41). Interestingly, elevated troponin T (cTnT), also a marker of myocardial damage and NT-proBNP, a marker of hemodynamic stress, predicted a different set of endpoints: cardiac death or aborted sudden cardiac death (SCD) due to VF. At the time of presentation, elevated cTnT above 85 ng/l and NT-proBNP levels per +1000 ng/l increased the likelihood of cardiac death and/or aborted SCD due to VF with a HR of 13.50 (95% CI 1.64 - 110.92) and 1.07 (95% CI 1.01 - 1.14), respectively.



Conclusion

Sustained ventricular tachyarrhythmias are common in GCM (54%). The extent of myocardial damage as evaluated by fibrosis and necrosis on myocardial biopsy and cTnT as well as hemodynamic stress, as measured by NT-proBNP, at the time of diagnosis predict cardiac mortality and life-threatening ventricular arrhythmias.

Risk of stroke, bleeding and mortality is associated with the quality of warfarin therapy in atrial fibrillation patients. Results from the FinWAF registry

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Aim

Atrial fibrillation (AF) is associated with increased risk of stroke and mortality, which can be reduced with anticoagulation therapy. In this study we evaluated the risk of stroke, bleeding events and mortality and the quality of warfarin therapy in a large cohort of AF patients.

Methods

The FinWAF study linked patient data from several nationwide registries in Finland using the civil registration number. The inclusion criteria were 1) diagnosis of AF, 2) purchase of warfarin and 3) at least one INR measurement during the study period. Patients with other indications for warfarin therapy were excluded. We analyzed a total of 54568 AF patients (31172 prevalent and 23396 new warfarin users) with data on the quality of warfarin treatment prior to the events (time in therapeutic range (TTR) during the preceding 60 days). Rates of stroke, bleeding and mortality among patients with various TTR-levels were determined.

Results

Mean age of the patients was 73.1 years (SD 10.8) and 47% of them were female. During the mean follow-up time of 3.2 ± 1.6 years (median 3.4) the mean and median TTRs were 62% and 67%, respectively. The rates of stroke, bleeding events and total mortality are shown in Table 1.

Conclusions

To our knowledge we demonstrate for the first time a direct relationship with TTR and incidence of stroke, bleeding events and mortality in an unselected nationwide cohort. The outcome was the better the higher the TTR-level. If warfarin is used to treat an AF patient, the target TTR-level should be 80 % or more.

Table 1. Incidence rates and hazard ratios (HR) of bleeding events, stroke and all-cause mortality in different TTR categories. Hazard ratios were adjusted for age, gender, congestive heart failure, hypertension, diabetes, stroke, transient ischemic attack, vascular disease and for previous hospitalization.

	TTR60 (%)	Number of	Rate / 100 patient	HR (95%CI)	P-value
Bleeding events	≤40	1890	7.5 (7.1, 7.8)	1.6 (1.5, 1.8)	<0.001
	40-50	500	5.6 (5.2, 6.1)	1.3 (1.1, 1.4)	<0.001
	50-60	518	5.1 (4.7, 5.5)	1.1 (1.0, 1.3)	0.039
	60-70	496	4.5 (4.1, 4.9)	1 (ref.)	
	70-80	495	4.3 (4.0, 4.7)	1.0 (0.9, 1.1)	0.71
	>80	1513	2.6 (2.5, 2.7)	0.6 (0.5, 0.7)	<0.001
Stroke	≤40	2330	9.3 (8.9, 9.7)	1.8 (1.7, 2.0)	<0.001
	40-50	499	5.8 (5.3, 6.3)	1.2 (1.1, 1.4)	0.004
	50-60	510	5.1 (4.7, 5.6)	1.1 (1.0, 1.2)	0.16
	60-70	506	4.7 (4.3, 5.1)	1 (ref.)	
	70-80	507	4.6 (4.2, 5.0)	1.0 (0.9, 1.1)	0.76
	>80	1765	3.1 (3.0, 3.3)	0.7 (0.6, 0.8)	<0.001
All-cause mortality	≤40	5659	20.9 (20.4, 21.4)	2.4 (2.2, 2.6)	<0.001
	40-50	1176	12.5 (11.8, 13.3)	1.4 (1.3, 1.6)	<0.001
	50-60	1098	10.2 (9.6, 10.9)	1.2 (1.1, 1.3)	<0.001
	60-70	1001	8.5 (8.0, 9.1)	1 (ref.)	
	70-80	766	6.4 (6.0, 6.9)	0.8 (0.7, 0.8)	<0.001
	>80	1899	3.1 (3.0, 3.3)	0.4 (0.4, 0.4)	<0.001

VEGF-B gene therapy inhibits doxorubicin induced cardiotoxicity endothelial protection

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Rationale

Doxorubicin, an anthracycline antibiotic, is used to treat a variety of cancers, but its utility is limited by its cumulative cardiotoxicity. As advances in cancer treatment have decreased cancer mortality, the DOX-induced cardiomyopathy has become an increasing problem, and currently there are no specific drugs available to alleviate the toxicity. We considered that vascular endothelial growth factor-B (VEGF-B), which promotes coronary arteriogenesis cardiac hypertrophy and ischemia resistance, is an interesting candidate for treating DOX-induced cardiotoxicity and congestive heart failure.

Aim

To analyse if and how VEGF-B protects the myocardium from DOX-induced toxicity and improves cardiac function during doxorubicin treatment.

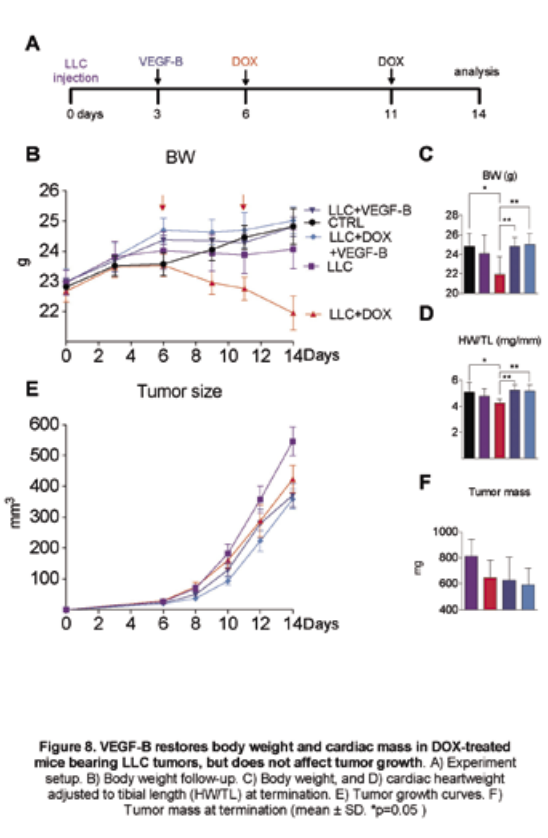

Figure 8. VEGF-B restores body weight and cardiac mass in DOX-treated mice bearing LLC tumors, but does not affect tumor growth. A) Experiment setup. B) Body weight follow-up. C) Body weight, and D) cardiac heartweight adjusted to tibial length (HW/TL) at termination. E) Tumor growth curves. F) Tumor mass at termination (mean ± SD. *p=0.05)

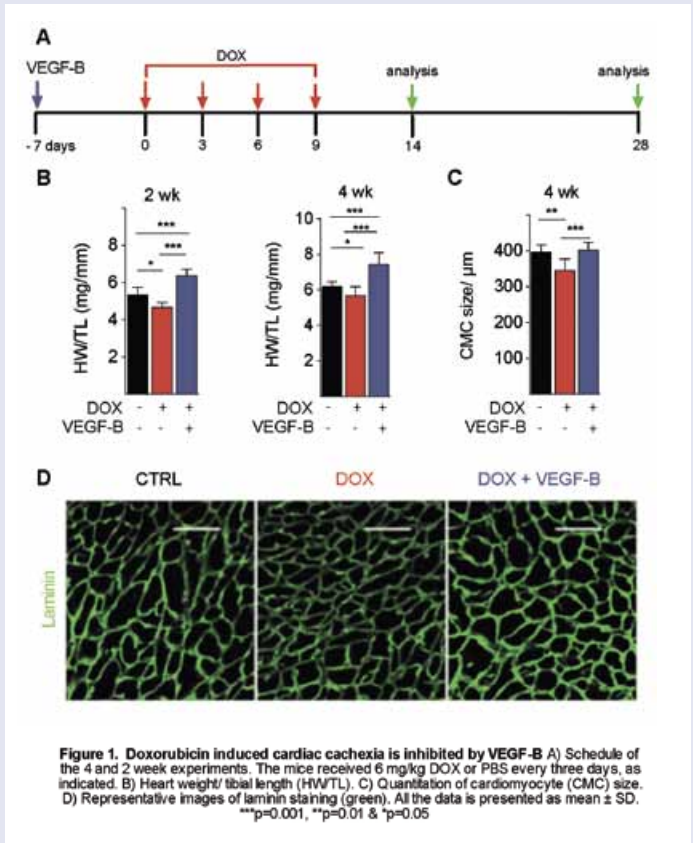

Figure 1. Doxorubicin induced cardiac cachexia is inhibited by VEGF-B A) Schedule of the 4 and 2 week experiments. The mice received 6 mg/kg DOX or PBS every three days, as indicated. B) Heart weight/ tibial length (HW/TL). C) Quantitation of cardiomyocyte (CMC) size. D) Representative images of laminin staining (green). All the data is presented as mean ± SD. ***p=0.001, **p=0.01 & *p=0.05

Methods and Results

DOX-induced cardiotoxicity was studied in normal and tumor-bearing mice transduced with adeno-associated viral vector expressing VEGF-B186 or control vector one week before the start of a 2- or 4-week DOX treatment. VEGF-B expression was verified by ELISA from serum and by immunofluorescence staining from the heart. Analysis of the heart included echocardiography, cardiac mitochondrial mass and activity, and oxygen consumption, myocardial gene expression, histology and immunohistochemistry. We also analysed the mice for food consumption, tumor growth, body weight composition and doxorubicin concentration in tissues.

To study the mechanism, we measured the apoptosis of coronary endothelial cells and cardiomyocytes in response to doxorubicin with and without pretreatment with VEGF-B.

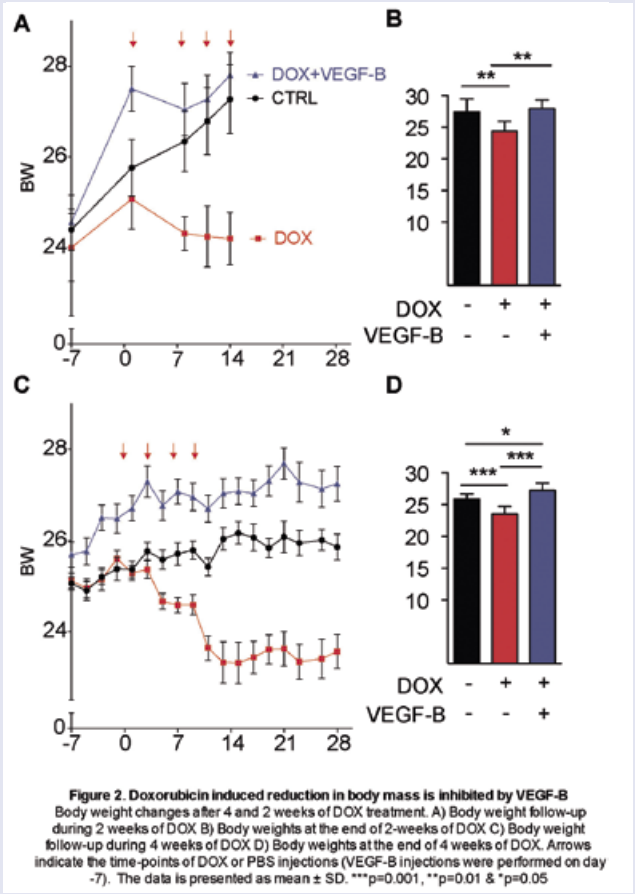

Figure 2. Doxorubicin induced reduction in body mass is inhibited by VEGF-B
Body weight changes after 4 and 2 weeks of DOX treatment. A) Body weight follow-up during 2 weeks of DOX B) Body weights at the end of 2-weeks of DOX C) Body weight follow-up during 4 weeks of DOX D) Body weights at the end of 4 weeks of DOX. Arrows indicate the time-points of DOX or PBS injections (VEGF-B injections were performed on day -7). The data is presented as mean ± SD. ***p=0.001, **p=0.01 & *p=0.05

Conclusions

VEGF-B treatment inhibited the DOX-induced decrease in cardiac mass and body weight, and increased left ventricular volume without compromising the anti-neoplastic effect of DOX. VEGF-B also inhibited capillary rarefaction and increased capillary area per cardiomyocyte, restored the DOX-induced decrease of oxygen consumption and improved mitochondrial function, inhibiting DOX-induction of DNA-damage in the cardiomyocytes. VEGF-B attenuated the apoptosis in endothelial cells, but there was no difference in apoptosis or in ROS in the cardiomyocytes. Thus VEGF-B is a safe novel therapeutic candidate for alleviating the cardiotoxic effects of DOX.

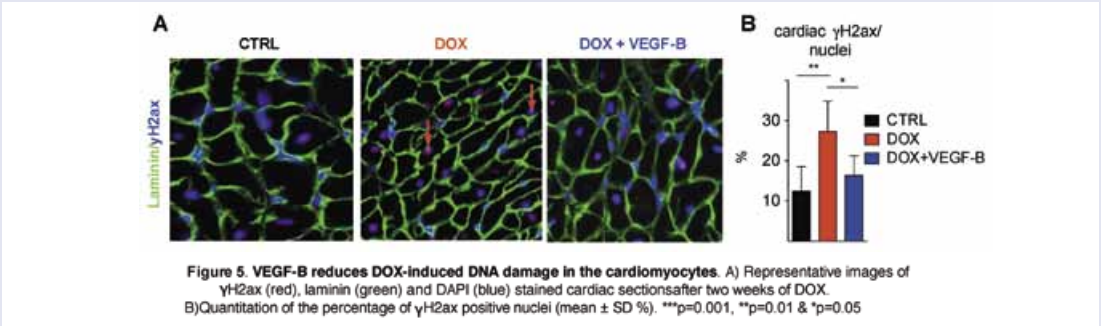

Figure 5. VEGF-B reduces DOX-induced DNA damage in the cardiomyocytes. A) Representative images of γH2ax (red), laminin (green) and DAPI (blue) stained cardiac sectionsafter two weeks of DOX. B)Quantitation of the percentage of γH2ax positive nuclei (mean ± SD %). ***p=0.001, **p=0.01 & *p=0.05