



# Program & Abstracts

April 27<sup>th</sup>, 2017

**Research Institute – MUHC**  
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**Our sincere thanks to our judges for their expertise in scoring the  
abstracts submitted!**

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## **CME Accredited Event**

This event is approved for up to 5.0 credits by the Office for Continuing Health Professional Education (CHPE). The Office for CHPE, Faculty of Medicine, McGill University is fully accredited by the Committee on Accreditation of Canadian Medical Education (CACME).

This event is an Accredited Group Learning Activity as defined by the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada.

Through an agreement between the Royal College of Physicians and Surgeons of Canada and the American Medical Association, physicians may convert Royal College MOC credits to AMA PRA Category 1 Credits™. Information on the process to convert Royal College MOC credit to AMA credit can be found at [www.ama-assn.org/go/internationalcme](http://www.ama-assn.org/go/internationalcme).

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## **Acknowledgement of Institutional Sponsors**

We acknowledge and greatly appreciate the support and involvement of our institutional sponsors as an integral part of the McGill Cardiovascular Research Day.



## Schedule

Thursday, April 27<sup>th</sup>, 2017

8:00 – 8:15	<b>Registration</b>	ES1 Atrium
8:15 – 8:30	<b>Opening Remarks</b> <i>Dr. Ernesto Schiffrin</i>	ES1 Auditorium
8:30 – 9:30	<b>Oral Presentations</b> Session A Chairs <i>Chairs : Dr. Nadia Giannetti &amp; Dr. Igal Sebag</i>	ES1 Auditorium
9:30 – 10:00	<b>Break</b>	ES1 Atrium
10:00 – 11:00	<b>Oral Presentations</b> Session B <i>Chairs : Dr. Negareh Mousavi &amp; Dr. Jonathan Afilalo</i>	ES1 Auditorium
11:00 – 12:00	<b>Poster Presentations</b>	ES1 Atrium
12:00 – 1:00	<b>2016 Artur &amp; Louis Lucian Award Lecture</b>  <i>From bedside to bench and back, my career in academic medicine</i>  <b>BRIAN KOBILKA, MD</b> <b>2012 Nobel Prize in Chemistry laureate</b> Professor of Molecular and Cellular Physiology, and Hélène Irwin Fagan Chair in Cardiology at Stanford University School of Medicine	ES1 Auditorium
1:00 – 2:00	<b>Lunch</b>	ES1 Atrium
2:00 – 3:00	<b>Poster Presentations</b>	ES1 Atrium
3:00 – 3:15	<b>Highlights of the research programs</b> <i>Dr. Ariane Marelli – Research Institute – MUHC</i> <i>Dr. Jonathan Afilalo – Jewish General Hospital</i>	ES1 Auditorium
3:15 – 4:30	<b>Oral Presentations</b> Session C <i>Chair : Dr. Ariane Marelli</i>	ES1 Auditorium
4:30 – 5:30	<b>Cocktails</b>	ES1 Atrium
5:30 – 6:00	<b>Awards / Closing remarks</b>	ES1 Atrium

## **Oral Presentations (Abstracts on pages 10-23)**

- 8:30 – 8:45      Basic Science #14: Antoine Caillon: **Gamma delta t cells mediate angiotensin ii-induced hypertension and vascular injury**
- 8:45 – 9:00      Clinical or Population Health #25: Melissa Bendayan: **Patient-Level Predictors of Bleeding in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement**
- 9:00 – 9:15      Clinical or Population Health #35: Mehdi Afshar: **Risks of Incident Cardiovascular disease with High Lipoprotein(a) with and without High LDL-C - The Framingham Heart Study**
- 9:15 – 9:30      Basic Science #22: Anouar Hafiane: **ATP Binding Cassette A1 (ABCA1) Mediates Microparticle Formation during High-Density Lipoprotein (HDL) Biogenesis**
- 9:30 – 10:00      Coffee Break
- 10:00 – 10:15      Basic Science #15: Ku-Geng Huo: **In vivo miR-431 inhibition protects against vascular damage and hypertension**
- 10:15 – 10:30      Clinical or Population Health #26: Fei Wang: **Heart failure Hospitalization in Adults with Congenital Heart Diseases: what predicts it and how does it affect mortality?**
- 10:30 – 10:45      Clinical or Population Health #40: Sarah Cohen: **Exposure to Low-Dose Ionizing Radiation from Cardiac Procedures and Risk of Malignancy in Adults with Congenital Heart Disease**
- 10:45 – 11:00      Clinical or Population Health #61: Hao Yu Chen: **Genome-wide Association Study and Replication in up to 157,107 Individuals Identifies a Novel Genetic Locus for Aortic Stenosis**

## **Poster Presentations (Abstracts on pages 24-78)**

- 11:00 – 12:00      Poster presentations



## **2016 Artur & Louis Lucian Award Lecture**



### **Brian Kobilka, MD**

#### **2012 Nobel Prize in Chemistry laureate**

Professor of Molecular and Cellular  
Physiology  
Hélène Irwin Fagan Chair in Cardiology  
Stanford University School of Medicine

Brian Kobilka, MD is Professor of Molecular and Cellular Physiology, and Hélène Irwin Fagan Chair in Cardiology at Stanford University School of Medicine. He received a Bachelor of Science Degrees in Biology and Chemistry from the University of Minnesota, Duluth in 1977. He graduated from Yale University School of Medicine in 1981, and completed residency training in Internal Medicine at the Barnes Hospital, Washington University School of Medicine, St. Louis, Missouri in 1984. From 1984-1989 he was a postdoctoral fellow in the laboratory of Robert Lefkowitz at Duke University. In 1990 he joined the faculty of Medicine and Molecular and Cellular Physiology at Stanford University. Research in the Kobilka lab focuses on the structure and mechanism of action of G protein coupled receptors (GPCRs), which constitute the largest family of receptors for hormones and neurotransmitters in the human genome. GPCRs are the largest group of targets for new therapeutics for a very broad spectrum of diseases. In 2012, Kobilka was awarded the Nobel Prize in Chemistry for his work on GPCRs. He is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences.



## **Poster Presentations (Abstracts on pages 24-78)**

2:00 – 3:00      Poster presentations

## **Highlights of the research programs**

3:00 – 3:15      **Dr. Ariane Marelli** – Research Institute – MUHC

**Dr. Jonathan Afilalo** – Jewish General Hospital

## **Oral Presentations (Abstracts on pages 10-23)**

3:15 – 3:30      Basic Science #16: Tom Reid: **The Shunt Pathway: Biochemical and molecular evidence of a novel mechanism for cholesterol homeostasis in hepatocytes**

3:30 – 3:45      Clinical or Population Health #29: Ahmed Al Turki: **Predicting Electrocardiographic and Echocardiographic Response to Cardiac Resynchronization Therapy: the Use of Strict Left Bundle Branch Block Criteria**

3:45 – 4:00      Clinical or Population Health #34: Kim Phan: **Arterial stiffness is a better early predictor for pre-eclampsia than angiogenic biomarkers and uterine artery Doppler ultrasound**

4:00 – 4:15      Basic science #43: George Makhoul: **Human Amniotic Stromal Cells Encapsulated in a Chitosan/Hyaluronic Acid Based Platform Proliferate and Increase Cardiac Function in a Rat Myocardial Infarction Model**

4:15 – 4:30      Clinical or Population Health #59: Lior Bibas: **Sarcopenia and Mortality after Cardiac Transplantation**

## **Cocktails**

4:30 – 5:30      Cocktails

## **Awards & Closing Remarks**

5:30 – 6:00      Awards & Closing Remarks

# **Oral presentations abstracts**

## # 14 - Basic Science

### **Gamma delta t cells mediate angiotensin ii-induced hypertension and vascular injury**

*Antoine Caillon PhD1 Muhammad Oneeb Rehman Mian PhD1; Julio C. Fraulob-Aquino PhD1; Ku-Geng Huo1; Tlili Barhoumi PhD1; Sofiane Ouerd MSc1, Peter R. Sinnaeve MD, PhD, FSEC3; Pierre Paradis PhD1 and Ernesto L. Schiffrin MD, PhD, FRSC, FRCPC, FACP, FAHA1,2 1Lady Davis Institute for Medical Research, and 2Department of Medicine, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montréal, Québec, Canada; 3UZ Leuven Gasthuisberg, University of Leuven, Leuven, Belgium.*

**Background:** Innate antigen-presenting cells and adaptive immune T cells have been implicated in the development of hypertension. However, the T-lymphocyte subsets involved in the pathophysiology of hypertension remain unclear. There is a small subset of “innate-like” T cells expressing the  $\gamma\delta$  T cell receptor (TCR) rather than the  $\alpha\beta$  TCR that could play a role in the initiation of the immune response in hypertension. It is unknown whether gamma delta T cells contribute to the development of hypertension. We aimed to determine whether angiotensin (Ang) II caused kinetic changes in gamma delta T cells, whether deficiency in  $\gamma\delta$  T cells blunted Ang II-induced hypertension, vascular injury and T-cell activation, and whether  $\gamma\delta$  T cells are associated with human hypertension.

**Methods:** Male C57BL/6 wild-type (WT) and Tcr $\delta$ <sup>-/-</sup> mice, which are devoid of  $\gamma\delta$  T cells, or WT mice injected IP with control isotype IgG or  $\gamma\delta$  T cell-depleting antibodies, were infused or not with Ang II (490 ng/kg/min, SC) for 3, 7 or 14 days. T cell profiling was determined by flow cytometry, systolic blood pressure (SBP) by telemetry and mesentery artery endothelial function by pressurized myography. TCR  $\delta$  constant region gene expression levels and clinical data of a whole blood gene expression microarray study including normotensive and hypertensive subjects were used to demonstrate an association between  $\gamma\delta$  T cells and SBP.

**Results:** Seven- and 14-day Ang II infusion increased  $\gamma\delta$  T cell numbers and activation in the spleen of WT mice ( $P < 0.05$ ). Fourteen days of Ang II infusion increased SBP ( $P < 0.01$ ) and decreased mesenteric artery endothelial function ( $P < 0.01$ ) in WT mice, both of which were abrogated in Tcr $\delta$ <sup>-/-</sup> mice ( $P < 0.01$ ). Anti-TCR  $\gamma\delta$  antibody-induced  $\gamma\delta$  T cell depletion blunted Ang II-induced SBP rise and endothelial dysfunction ( $P < 0.05$ ), compared to isotype antibody-treated Ang II-infused mice. Ang II-induced T cell activation in the spleen and perivascular adipose tissue was blunted in Tcr $\delta$ <sup>-/-</sup> mice ( $P < 0.01$ ). In humans, the association between SBP and  $\gamma\delta$  T cells was demonstrated by a multiple linear regression model integrating whole blood TCR  $\delta$  constant region gene expression levels, and age and sex ( $R^2 = 0.12$ ,  $P < 1 \times 10^{-6}$ ).

**Conclusion:**  $\gamma\delta$  T cells mediate Ang II-induced SBP elevation, vascular injury and T-cell activation in mice.  $\gamma\delta$  T cells might contribute to development of hypertension in humans.

**Keywords**

Hypertension, T cell, Immune cell

## # 15 - Basic Science

### **In vivo miR-431 inhibition protects against vascular damage and hypertension**

*Ku-Geng Huo<sup>1</sup>, Julio C. Fraulob-Aquino<sup>1</sup>, Tlili Barhoumi<sup>1</sup>, Chantal Richer<sup>3</sup>, Suellen C. Coelho<sup>1</sup>, Sofiane Ouerd<sup>1</sup>, Antoine Caillon<sup>1</sup>, Mathieu Lajoie<sup>3</sup>, Daniel Sinnett<sup>3,4</sup>, Pierre Paradis<sup>1</sup>, Ernesto L. Schiffrin<sup>1,2</sup> <sup>1</sup>Vascular and Hypertension Research Unit, Lady Davis Institute for Medical Research, <sup>2</sup>Department of Medicine, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, <sup>3</sup>Division of Hematology-Oncology, Research Center, CHU Ste-Justine, <sup>4</sup>Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montréal, Canada*

**Background:** Vascular injury is an early manifestation and a cause of end-organ damage in hypertension. microRNAs (miRNAs) play an important role in cardiovascular disease, but their implication in vascular injury remains unclear. In this study, we used RNA sequencing and systems biology to identify miRNAs and its targets that mediate global gene expression changes in the course of vascular injury in angiotensin (Ang) II-induced hypertension.

**Methods and results:** Ten-week-old male C57BL/6 mice were infused or not with Ang II for 14 days. Blood pressure (BP) was measured by telemetry and small mesenteric artery (MA) function and mechanic by myography. Total RNA was extracted from the MA for small and total RNA sequencing. Differentially expressed (DE) miRNAs (23 up and 12 down) and mRNAs (550 up and 256 down) were identified. Interactions between DE-miRNAs and inversely expressed DE-mRNAs and between DE-transcription factors (TF) and DE-genes were analyzed and presented in molecular networks. Seventeen upregulated miRNAs are located in a conserved miRNA cluster of the Dlk1-Dio3 region, 9 of which had expression levels correlated with BP ( $P < 0.05$ ). Among those 9, the first-ranked DE-miRNA miR-431 ( $q < 0.0005$ ) that is 100% conserved in humans, and a conserved putative DE-mRNA target, a BP-correlated TF ETS homologous factor (Ehf) that regulates numerous ECM genes including alpha-1 type I collagen (Col1a1) and another Dlk1-Dio3 miRNA miR-382, were selected for functional studies. In vitro gain- and loss-of-function experiments in human aortic smooth muscle cells validated that miR-431 targeted Ehf, which in terms upregulated Col1a1 and miR-382 ( $P < 0.05$ ). This was also validated in vivo in MA of Ang II-infused mice injected IV with miR-431 inhibitor ( $P < 0.05$ ). Interestingly, in vivo miR-431 inhibition in Ang II-infused mice delayed BP elevation and reduced endothelial dysfunction and vascular stiffening ( $P < 0.05$ ).

**Conclusion and perspectives:** miR-431 and its target Ehf may act as master regulators in the pathophysiology of vascular damage in hypertension. miR-431 inhibition has the potential to serve as a novel therapeutic approach for treatment of vascular damage and hypertension.

**Keywords**

miRNA, Hypertension, Vascular damage

## # 16 - Basic Science

### **The Shunt Pathway: Biochemical and molecular evidence of a novel mechanism for cholesterol homeostasis in hepatocytes**

*Tom Reid - Research Institute of the McGill University Health Centre   Dr. Robert Scott Kiss - Research Institute of the McGill University Health Centre   Dr. Allan Sniderman - Research Institute of the McGill University Health Centre*

The traditional model for intracellular cholesterol homeostasis dictates that low density lipoprotein (LDL) particles are taken up into cells via the LDL receptor (LDLR), wherein the cholesterol from the particle interacts with a rapidly equilibrating regulatory pool in the endoplasmic reticulum. This results in decreased expression of the LDLR and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the rate-limiting step of endogenous cholesterol synthesis, resulting in decreased de novo synthesis of cholesterol due to inhibition of the sterol response element-binding protein 2 (SREBP-2). While this model was elucidated in fibroblast cells, the liver is the organ most responsible for both LDL clearance and cholesterol homeostasis, thus implicating the hepatocyte as a more relevant model for the study of cholesterol metabolism. Using radiolabeling assays and immunofluorescence, this study corroborates the “shunt pathway” model for cholesterol homeostasis that describes an LDL pathway in which LDL-derived cholesterol does not appreciably interact with the regulatory pool at the ER, but is rather preferentially esterified by acyl-CoA:cholesterol acyltransferase 2 (ACAT2) and re-secreted in VLDL particles. Using 3 different hepatocyte models (IHH, HepG2 and mouse primary hepatocytes), we observe preferential esterification of LDL derived cholesterol as well as increased ACAT activity upon LDL loading, as measured by addition and incorporation of radiolabeled substrates and into cholesteryl-ester (CE). Additionally, increased de novo synthesis of cholesterol upon LDL loading was also observed. Furthermore, immunofluorescence assays confirmed both the preferential colocalization of LDL particles with ACAT2, as well as the nuclear accumulation of SREBP-2 upon LDL loading. The implications of this study follow those of the first shunt pathway study, in that the conventional model for cholesterol homeostasis cannot sufficiently be applied to the liver. Moreover, therapeutic targeting of proteins involved in the shunt pathway may prove crucial for treatment of cardiovascular disease caused by atherosclerosis.

Keywords

Shunt, Liver, Hepatocyte, ldl, Chylomicron, Cholesterol, ACAT2

## # 22 - Basic Science

### **ATP Binding Cassette A1 (ABCA1) Mediates Microparticle Formation during High-Density Lipoprotein (HDL) Biogenesis**

*Anouar Hafiane and Jacques Genest Cardiovascular Laboratory, Cardiology Division, McGill University Health Centre/Royal Victoria Hospital, Montréal, Québec H3A 1A1, Canada*

**Background and aims:** Micro-particles (MP) are secreted by various cells. Their biological roles in health and in disease remain unknown. Here we describe formation of MP in the process of ABCA1-dependent cholesterol efflux in different cell types.

**In Vitro Methods and results:** The ATP-binding cassette transporter, subfamily A, member 1 (ABCA1) is the rate-limiting step in the biogenesis of high-density lipoproteins (HDL). Using FPLC and nanoparticle tracking analysis from media cell-based systems with overexpression and selective inactivation of ABCA1, pharmacological blockade and modulation of membrane cholesterol content, we characterized MP release from various cell lines. We studied MP release in BHK cells stably expressing ABCA1 under mifepristone control, human THP-1 macrophages and HepG2 cells without, or with incubation with human apoA-I. We have found that ABCA1 without apoA-I or with apoA-I contribute to the formation of MP. Importantly, BHK-mock cells not expressing ABCA1 show no MP release. Analysis of MP released from human THP-1 cells isolated by FPLC followed by ultracentrifugation and equilibrium sucrose gradient density (2-0.5M) indicate that ABCA1 mediates the production of MPs containing cholesterol with highly heterogeneous size distribution (50-250nm) corresponding to sucrose density range ( $1.10 < d < 1.19 \text{ g/mL}$ ). This was also confirmed in primary human monocyte-derived macrophages (MDMs) under same experimental conditions. Adding apoA-I markedly increases MP from cells in a parallel process to HDL biogenesis. Indeed, we found that MPs contributes approximately 30% of ABCA1- and apoA-I mediated cholesterol efflux. Inhibition of ABCA1 with probucol or decreasing plasma membrane cholesterol with methyl- $\beta$  cyclodextrin (CDX) markedly reduced MP release and nascent HDL formation. MPs do not contain apoA-I, but contain flotillin-2 a marker of plasma membrane and CD63, an exosome markers.

**Conclusion:** In conclusion, we report that MPs are lipoprotein-sized structures created by the ABCA1 transporter, contribute to cellular efflux in a parallel fashion to apoA-I. In addition, MP releases from cells consist, in part, of exosomes and depend on the same pathway used for HDL biogenesis.

**Keywords**

HDL, Apolipoprotein apoA-I, Cholesterol efflux, ABCA1, Microparticles, Flotillin-2, CD63



## # 25 - Clinical or Population Health

### **Patient-Level Predictors of Bleeding in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement**

*Melissa Bendayan - Department of Experimental Medicine, McGill University, Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital Sandra Lauck - St. Paul's Hospital Dae Hyun Kim - Beth Israel Deaconess Medical Center Thierry Lefèvre - Hôpital Jacques Cartier Nicolo Piazza - McGill University Health Centre Kevin Lachapelle - McGill University Health Centre Giuseppe Martucci - McGill University Health Centre Andre Lamy - Hamilton General Hospital Marino Labinaz - Ottawa Heart Institute Mark Peterson - St. Michael's Hospital Rakesh Arora - St. Boniface Hospital Nicolas Noiseux - Centre hospitalier de l'Université de Montréal Andrew Rassi - Massachusetts General Hospital Philippe Gagnéux - Hôpital du Sacré-Coeur Brian Lindman - Washington University School of Medicine Anita Asgar - Institut de Cardiologie de Montréal Caroline Kim - Beth Israel Deaconess Medical Center Amanda Trnkus - Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital Jose Morais - Department of Cardiology, Jewish General Hospital Yves Langlois - Department of Cardiology, Jewish General Hospital Lawrence Rudski - Department of Cardiology, Jewish General Hospital Jeffrey Popma - Beth Israel Deaconess Medical Center John Webb - St. Paul's Hospital Louis Perrault - Institut de Cardiologie de Montréal Jonathan Afilalo - Department of Cardiology, Jewish General Hospital*

**Background:** Bleeding complications are harbingers of mortality and major morbidity in patients undergoing surgical (SAVR) or transcatheter (TAVR) aortic valve replacement. Prediction of bleeding risk is crucial to tailor the procedural approach and implement preventative strategies. Despite the high prevalence of frailty in this population, little is known about the effect of frailty on bleeding risk. Thus, we sought to define patient-level predictors of major bleeding complications in older adults undergoing TAVR or SAVR.

**Methods:** We performed a post hoc analysis of the Frailty-AVR cohort study that prospectively enrolled older adults aged 70 years or older undergoing TAVR or SAVR at 14 institutions in Canada, the United States, and France. Before the procedure, we administered a short physical performance battery and frailty questionnaire, and ascertained comorbid conditions and laboratory data from the electronic health record. For the purposes of this analysis, the primary endpoint was major or life-threatening bleeding during the index hospitalization defined according to the VARC-2 criteria.

**Results:** The cohort consisted of 929 patients with a mean age of 81.4 years, of which 116 patients had a major bleed (55/576 [9.5%] in the TAVR group, 61/353 [17.3%] in the SAVR group). Patients with major bleeds were more likely to have gastrointestinal diseases, a recent myocardial infarction, lower baseline platelet counts, lower baseline serum albumin, and a higher number of diseased coronary vessels requiring bypass grafts (for those undergoing concomitant revascularization with SAVR). Frailty, defined by either Fried's scale or Rockwood's clinical frailty scale, was not predictive of bleeds. In a multivariable logistic regression model, the number of diseased coronary vessels (OR 1.31, 95% CI 1.02 to 1.69), GI disease (OR 1.83, 95% CI 1.03 to 3.27) and serum albumin (OR 0.50, 95% CI 0.30 to 0.84) were independent predictors of major bleeds. Compared to patients without a major bleed, those with a major bleed required more red cell transfusions (6.5 vs. 0.9 units,  $P < 0.001$ ) and had higher 1-year mortality (27% vs. 11%,  $P < 0.001$ ).

**Conclusion:** Low serum albumin, gastrointestinal disease, and advanced coronary artery disease requiring multi-vessel revascularization are patient-level risk factors for major bleeding complication in older adults undergoing TAVR or SAVR. Future research should aim to delineate the responsible mechanisms and develop targeted preventative strategies.

**Keywords**

Aortic valves, Surgery, Prognosis, Bleeding

## **# 26 - Clinical or Population Health**

### **Heart failure Hospitalization in Adults with Congenital Heart Diseases: what predicts it and how does it affect mortality?**

*Fei Wang, MSc; Aihua Liu, PhD; Sarah Cohen, MD; Liming Guo, MSc; Judith Therrien, MD; Ariane Marelli, MD, MPH; McGill Adult Unit for Congenital Heart Disease Excellence (MAUDE Unit)*

**Background:** Adults with congenital heart disease (ACHD) are not cured and residual disease predispose them to congestive heart failure (CHF). This study aimed to calculate the cumulative probability of CHF, identify predictors of one-year risk of CHF and assess the impact of CHF on mortality.

**Method:** The cumulative risk cohort was derived from the Quebec CHD database and consisted of 27975 patients aged 18-65 between 1995 and 2010. We calculated the cumulative probability of CHF hospitalization using the Practical Incidence Estimator macro to adjust for the competing risk of death. To assess the impact of CHF hospitalization on mortality, we first used propensity score matching to select random controls for each CHF hospitalized patient. We then compared the mortality rates between the CHF patients and their matched controls. We applied nested case control study and conducted binary logistic regression analyses to identify the predictors of one-year risk of CHF hospitalization. We further used the regression model to construct a clinically useful risk scoring system (RAAID-CHF) for CHF hospitalization to identify patients in the need of accelerated referral to specialized ACHD centres.

**Results:** The lifetime cumulative risk of CHF hospitalization by age 65 was 33.2%. CHF hospitalization was associated with a 5 fold increase in mortality risk (Hazard Ratio=5.4, 95% CI: 3.5, 8.3). Age, sex, CHD severity, CHF hospitalization history and comorbidities including arrhythmia, pulmonary hypertension, and coronary heart disease in the previous 12 months were significant predictors of one-year CHF hospitalization. The RAAID-CHF had excellent predictive performance for CHF hospitalization (C-statistics=0.92).

**Conclusion:** The cumulative risk of CHF hospitalization in ACHD is significantly higher than that in the general population. CHF hospitalization is strongly associated with an increased risk of death in ACHD population. We developed and validated a convenient clinical risk score for predicting the risk of CHF hospitalization in 1 year. It could be readily applied at clinics for identifying high-risk patients of CHF hospitalization who are most likely to benefit from highly specialized services in reducing hospitalization risk.

**Keywords**

Congenital heart disease, Heart failure, Mortality, Risk

## **# 29 - Clinical or Population Health**

### **Predicting Electrocardiographic and Echocardiographic Response to Cardiac Resynchronization Therapy: the Use of Strict Left Bundle Branch Block Criteria**

*Ahmed Al Turki, McGill University Health Center; Alexios Hadjis, McGill University Health Center; Riccardo Proietti, Swansea University; Vidal Essebag, McGill University Health Center*

**Background:** Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in heart failure with reduced ejection fraction (HFrEF). CRT efficacy is greater in patients with left bundle branch block (LBBB). This study aimed to determine if strict LBBB criteria predicts an improved CRT response.

**Methods:** HFrEF patients who received a de novo CRT device at a single tertiary center were included. Patients were divided into 3 groups based on QRS morphology. Strict LBBB was defined as mid QRS notching or slurring in two of the following leads (I, aVL, V1, V2, V5, V6), QRS > 140ms in men and >130ms in women in addition to conventional criteria, defined as QS or rS in V1 and a monophasic R with no q waves in I, V6; for conventional LBBB, the QRS had to be >120ms. Group 1 consisted of patients with strict LBBB. Group 2 had conventional LBBB and group 3 had non-LBBB morphology. The primary endpoint was change in QRS duration after CRT. The secondary endpoints were change in EF and the correlation between change in QRS duration and change in EF.

**Results:** In 204 patients, mean age was 73.1 years, 74% were men and 51% had ischemic cardiomyopathy. In addition, 74% were hypertensive, 38% had diabetes mellitus and 13% had a previous stroke. 51% of patients were in group 1, 27% were in group 2 and 22% were in group 3. The mean change in QRS was  $-20.7 \pm 12.6$ ,  $+5.2 \pm 17.0$  and  $+18.5 \pm 28.4$  in groups 1, 2 and 3 respectively. Strict LBBB predicted a significant improvement in QRS compared to conventional LBBB ( $p < 0.0001$ ) and non-LBBB morphology, ( $p < 0.0001$ ); there was no significant difference between groups 2 and 3 ( $p = 0.46$ ). Regarding EF, the mean change was  $+19.4 \pm 11.3$ ,  $+6.9 \pm 15.3$  and  $+0.5 \pm 11.7$  in groups 1, 2 and 3 respectively. Strict LBBB also predicted a significant improvement in EF compared to conventional LBBB ( $p < 0.0001$ ) and non-LBBB morphology ( $p < 0.0001$ ); there was no significant difference between groups 2 and 3 ( $p = 0.18$ ). There was a statistically significant, moderate negative correlation between change in QRS duration and change in EF (correlation coefficient =  $-0.48$ ,  $p < 0.0001$ ).

**Conclusions:** Strict LBBB predicted an improved QRS and EF response compared to conventional LBBB and non-LBBB morphology in patients with HFrEF who received CRT.

**Keywords**

Cardiac resynchronization therapy, Left bundle branch block, Heart failure with reduced ejection fraction, QRS duration

## **# 34 - Clinical or Population Health**

### **Arterial stiffness is a better early predictor for pre-eclampsia than angiogenic biomarkers and uterine artery Doppler ultrasound**

*Kim Phan, Yessica-Haydee Gomez, Jessica Gorgui, Amira El-Messidi, Robert Gagnon, Stella Daskalopoulou*

**Background:** Pre-eclampsia is an important cause of maternal and fetal morbidity and mortality, and is associated with increased risk for long-term cardiovascular events. Currently, there is no early predictive tool for pre-eclampsia in clinical use.

**Methods:** In this prospective longitudinal study, women with high-risk singleton pregnancies were recruited and arterial stiffness was measured using applanation tonometry (SphygmoCor, AtCor) and compared between women who developed pre-eclampsia and those with a normotensive pregnancy. Arterial stiffness and hemodynamics were assessed, in the 1st trimester, every 4 weeks thereafter, and at 6 weeks postpartum. Angiogenic biomarkers were measured (Quantikine, R&D Systems) at each trimester and at six weeks postpartum, and a bilateral uterine artery Doppler was performed in the 2nd trimester.

**Results:** Of the 155 women recruited, 13 developed pre-eclampsia. Analyses adjusted for both maternal age and body mass index showed women who developed pre-eclampsia had decreased wave reflection start time and increased carotid-femoral pulse wave velocity in the 1st trimester, throughout pregnancy, and at 6 weeks post-partum with a carotid-femoral pulse wave velocity:carotid-radial pulse wave velocity mismatch seen in the 1st and 3rd trimester (all p-values < 0.05). Arterial stiffness (AUC-ROC: 0.80) was a better predictor than angiogenic biomarkers (AUC-ROC: 0.60; p = 0.04) or uterine artery Doppler (AUC-ROC: 0.53 p < 0.001) and improved detection of pre-eclampsia when combined with all other predictors, including clinical characteristics (arterial stiffness sensitivity: 79.8% vs other predictor combinations sensitivity: 69.2%).

**Conclusions:** Arterial stiffness and wave reflection was greater in the 1st trimester, throughout pregnancy, and does not resolve 6 weeks after pregnancy in women who develop pre-eclampsia. A greater central to peripheral arterial stiffness mismatch was also observed in the 1st and 3rd trimester. Arterial stiffness indices had superior predictive value for pre-eclampsia over angiogenic biomarkers and uterine artery Doppler alone and improved detection rates when combined with all other predictors including clinical characteristics.

**Keywords**

Arterial stiffness, Pre-eclampsia, Prediction

## # 35 - Clinical or Population Health

### **Risks of Incident Cardiovascular disease with High Lipoprotein(a) with and without High LDL-C - The Framingham Heart Study**

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**Background:** Elevated lipoprotein(a) (Lp[a]) affects 20% of the population and is a causal factor for cardiovascular (CV) disease. Whether Lp(a) confers greater risk when LDL-C is elevated is not well-established. We sought to evaluate the CV risks associated with elevated Lp(a) in the presence of high LDL-C.

**Methods:** We used prospective data from the Framingham Heart Study (FHS) examination cycle 5 (1991-1995). This cohort includes 2680 participants (median age = 54 years, 46% males) with complete follow-up at 15 years (n = 392 incident CV events). Lp(a) was measured at baseline using ELISA with a monoclonal antibody against apo(a), independent of the apo(a) isoform size. LDL-C was calculated using the Friedwald equation using standard methods. High Lp(a) was defined as > 100nM (~80th percentile) based on known epidemiological cut-offs for increased risk of CVD and high LDL-C was defined as ~3.37 mmol/L.

**Results:** When combined in the same model and after adjustment for other known risk factors, high Lp(a) and high LDL-C were significant predictors of CVD (High LDL-C: HR 1.34; 95% CI 1.09-1.64, p=0.006; High Lp(a): HR 1.31; 95% CI 1.03-1.66, p=0.026). Across the 4 groups of high/low Lp(a) and high/low LDL-C, the absolute risks at 15 years were 22.6% (high Lp(a)/high LDL-C), 17.3% (low Lp(a)/high LDL-C), 12.7% (high Lp(a)/low LDL-C) and 11.5% (low Lp(a)/low LDL-C). After adjustment for other risk factors, hazard ratios for high Lp(a)/high LDL-C were 1.83 (95% CI 1.34-2.47, p=0.0001) as compared to low Lp(a)/low LDL-C; 1.57 (95% CI 1.03-2.49, p=0.04) as compared to low Lp(a)/high LDL-C and 1.44 (95% CI 1.05-1.97, p=0.02) as compared to low Lp(a)/low LDL-C. Results were unchanged after further adjustment for lipid treatment.

**Conclusion:** Presence of both high Lp(a) and high LDL-C is associated with a high absolute risk of incident cardiovascular disease. Our results suggest that individuals with both high Lp(a) and high LDL-C represent a high risk group that may benefit from statin therapy. Lp(a) measurement in individuals with high LDL-C who do not meet criteria for statins may be warranted.

**Keywords**

Lipoprotein(a), Cardiovascular disease, Dyslipidemia, Framingham

## # 40 - Clinical or Population Health

### **Exposure to Low-Dose Ionizing Radiation from Cardiac Procedures and Risk of Malignancy in Adults with Congenital Heart Disease**

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**Background:** Adults with congenital heart disease (ACHD) are exposed to increasing number of low-dose ionizing radiation (LDIR) from cardiac procedures. The prevalence of cancer in this population is higher compared to the general population. Our objective was to determine if there is an association between LDIR-exposure from cardiac procedures and cancer incidence in ACHD patients.

**Method:** A cumulative risk cohort was derived from the Quebec CHD database and consisted of 24,833 ACHD aged 18-65 between 1995-2009. We conducted time-to-event analyses to calculate the cumulative risk of cancer and to assess if high LDIR-exposure ( $\geq 6$  procedures) was associated with an increased risk of cancer than low LDIR-exposure ( $\leq 1$  procedure). Propensity score and inverse probability weighting were used to adjust for potential confounders such as comorbidities. Further we performed a nested case-control study to investigate if LDIR-exposure from cardiac procedures was predictive of cancer using a multivariable logistic regression model. Each case was matched on sex, CHD severity, age and calendar time with 4 randomly selected controls. A lag time of one year between LDIR exposures and cancer diagnosis was applied to all analyses.

**Results:** In over 250,791 person-years of follow-up, 602 cancer cases were observed (median age: 55.4 years). The cumulative risk of cancer by age 64 was 15.3% (95% CI, 14.2-16.5). Breast cancer (34.5%) was the most frequent site in women and genitourinary (30.8%) among men. The cumulative cancer-free survival probability was significantly lower in the high LDIR-exposure group than the low LDIR-exposure group. High LDIR-exposure was associated with a 2.6-fold increase risk of cancer (hazard ratio=2.61, 95% CI: 2.30-2.96) comparing to low LDIR-exposure. In the nested case-control study, cancer cases had more LDIR-related cardiac procedures than controls (1,410 versus 921 per 1000 ACHD patients,  $p < 0.0001$ ). Cumulative LDIR exposure was independently associated with cancer (odds ratios (OR)=1.07 per procedure, 95% CI: 1.03-1.10). Similar results were obtained from all sensitivity analyses including 1/using dose estimates for LDIR-exposure (OR=1.08 per 10 milliSieverts, 95% CI: 1.03-1.12); 2/excluding smoking-related cancer cases (OR=1.06 per procedure, 95% CI: 1.01-1.11); and 3/applying a three-year time-lag (OR=1.06 per procedure, 95% CI: 1.02-1.11).

**Conclusions:** This is the first population-based study to document an association between LDIR-related cardiac procedures and cancer risk in ACHD population. This finding provides support to policy recommendations for radiation surveillance in CHD patients where no regulation currently exists

**Keywords**

Cancer incidence, Adults with congenital heart disease, Exposure to Low-Dose Ionizing Radiation



## **# 43 - Basic Science**

### **Human Amniotic Stromal Cells Encapsulated in a Chitosan/Hyaluronic Acid Based Platform Proliferate and Increase Cardiac Function in a Rat Myocardial Infarction Model**

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**Background:** Myocardial ischemia can lead to an irreversible injury and an eventual cardiac failure. Stem cells stand as one of the leading experimental therapies. Nonetheless, stem cell based cardiac repair suffers from the absence of an ideal cell type and low cellular engraftment rates. Here, we investigated the cardio-protective potential of a novel composite inserting human amniotic stromal cells (hASCs) in a chitosan/hyaluronic acid (C/HA) based platform to increase cellular retention rates and combat heart degeneration.

**Method:** A re-designed C/HA scaffold mixed with hASCs in culture was synthesized. Its structural characteristics were determined. To examine its cellular preservation, Alamar blue was performed on hASCs encapsulated in the C/HA. The cardiac impact of hASCs + C/HA composite was then assessed in an induced myocardial infarction model. Female Lewis rats (n=40) divided into 4 groups were injected with either 3x10<sup>5</sup> hASCs, C/HA, 3x10<sup>5</sup> hASCs + C/HA, or control. Cardiac function was assessed with echocardiography and histological analysis was conducted postmortem.

**Results:** Mechanical characterization of the C/HA platform indicated in a temperature sweep assay a swift elastic conversion at 40°C. At 37°C, the sol-gel transition time of C/HA occurred rapidly. Alamar blue assay presented an active and proliferating hASCs after 8 days in C/HA. In vivo, on week 5, the groups injected with C/HA and hASCs + C/HA had significantly higher ejection fraction, fractional shortening, and left ventricular end systolic diameter. Interestingly, the hASCs in the hASCs + C/HA group were abundantly detected 6 weeks after myocardial injection. Immunofluorescence labeling of these encapsulated cells showed a co-expression of cardiac proteins such as connexin 43, myosin heavy chain, and troponin T. Labeling additionally revealed the co-expression of the Ki67 proliferative marker in the injected hASCs. Moreover, the hASCs + C/HA composite triggered a significant and massive neovascularization of CD31+ cells at the infarction site.

**Conclusion:** Despite low injected quantities at baseline, our findings showed that the hASCs encapsulated in C/HA were abundantly retained at the infarction site and increased cardiac functional parameters. Moreover, the C/HA platform provided an active milieu for the hASCs to proliferate, co-express cardiac proteins, and induce new vessel formation. Thus, this novel composite of hASCs encapsulated in a C/HA biological platform is a conceivable candidate that could restore cardiac function and reduce remodeling.

**Keywords**

Heart failure, Amniotic stromal cells, Chitosan, Hyaluronic acid

## # 59 - Clinical or Population Health

### **Sarcopenia and Mortality after Cardiac Transplantation**

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**Background:** Psoas muscle area (PMA) is a validated indicator of frailty and sarcopenia that can be easily measured on abdominal computed tomography (CT) scans. There has yet to be a study examining the prognostic impact of sarcopenia in patients undergoing cardiac transplantation.

**Methods:** In this retrospective study, pre- and post-operative CT scans were retrieved for adult patients transplanted between 2000-2015 and followed at the Heart Transplant Clinic of the McGill University Health Centre. PMA was measured on axial images at the level of the L4 vertebrae using the CoreSlicer software. Outcomes of interest were ascertained by chart review and included long-term mortality and in-hospital major adverse postoperative events (MAPE; defined as mortality, prolonged intubation, stroke, dialysis, mediastinitis, or reoperation).

**Results:** Out of 166 patients transplanted, 82 patients had at least one abdominal CT scan over an average follow-up of 3 years. The median PMA was 24.7 cm<sup>2</sup> (IQR 20.9, 30.0) in men, 16.6 cm<sup>2</sup> (IQR 14.9, 19.1) in women, and decreased by 8-11% from the first to the last available CT scan. Patients with smaller PMA, defined as less than the sex-stratified median, had a four-fold increase in MAPE (OR 4.28; 95% CI 1.18, 15.46) and a trend towards a three-fold increase in long-term mortality (HR 3.12; 95% CI 0.96, 10.20). Adjusting for age, sex, BMI, and cardiomyopathy etiology, every 1 cm<sup>2</sup> increase in PMA was found to be significantly associated with a 17% reduction in MAPE (OR 0.83; 95% CI 0.72, 0.96) and a 9% reduction in long-term mortality (HR 0.91; 95%CI 0.83-0.99).

**Conclusion:** Sarcopenia as defined by PMA is associated with a higher risk of mortality and major morbidity after cardiac transplantation. Further studies are needed to define the longitudinal progression of sarcopenia in this population and test the value of muscle-building interventions such as exercise and protein supplementation to improve short- and long-term outcomes.

**Keywords**

Cardiac transplantation, Sarcopenia, Heart Failure, Frailty

## # 61 - Clinical or Population Health

### **Genome-wide Association Study and Replication in up to 157,107 Individuals Identifies a Novel Genetic Locus for Aortic Stenosis**

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**Introduction:** Aortic stenosis (AS) is the most prevalent valvular disease in the western world, affecting more than one million individuals in North America. At present, only the LPA locus is known to confer genetic risk. The identification of additional genetic loci could inform future drug development for AS, a disease for which there is no effective medical therapy.

**Methods:** We conducted a genome-wide association study (GWAS) for AS in the Genetic Epidemiology on Adult Health and Aging (GERA) cohort (44,703 individuals; 3,469 AS cases) across 15.3 million genetic variants, adjusted for age and sex. A locus which demonstrated suggestive evidence of association with AS in GERA ( $p < 1 \times 10^{-6}$ ) was examined in both the UK Biobank (111,560 individuals; 535 AS cases) and a Swedish, matched case-control cohort (844 individuals; 219 AS cases), followed by meta-analysis. Further validation was performed in the CHARGE Consortium using aortic valve calcium (AVC) (6,942 individuals; 2,245 with AVC), a subclinical phenotype which often precedes AS. The contribution of significant genetic variants to gene expression was examined using data from the Gene-Tissue Expression project. Instrumental variable analysis (IVA) was performed using the Genetic ToolBox to assess whether the locus identified was causally associated with AVC and AS.

**Results:** In the GERA cohort, we identified a locus demonstrating strong evidence of association with AS (odds ratio [OR] per allele 1.15; 95% confidence interval [CI] 1.09-1.20;  $p = 9.70 \times 10^{-7}$ ). Replication of the association of this locus with AS was achieved in both the UK Biobank (OR per allele 1.24; 95% CI 1.01-1.53;  $p = 0.04$ ) and the Swedish, matched cohort (OR per allele 1.53; 95% CI 1.09-2.15;  $p = 0.01$ ). Meta-analysis of the region strengthened the association identified in the discovery cohort (OR per allele 1.14; 95% CI 1.08-1.19;  $p = 5.00 \times 10^{-7}$ ). The lead variant in the discovery cohort was also significantly associated with AVC in the CHARGE Consortium (OR per allele 1.10; 95% CI 1.01-1.20;  $p = 0.03$ ), and strongly associated with mRNA expression in the locus ( $p \leq 3.50 \times 10^{-5}$ ). IVA revealed the association of the locus with AS and AVC to be causally mediated through a well-established metabolic pathway ( $p = 7.80 \times 10^{-9}$  and  $p = 1.90 \times 10^{-3}$ , respectively).

**Conclusions:** We identified a second genetic locus that is associated with clinical AS. Our discovery implicates a key metabolic pathway in AS development and progression, which may represent a novel therapeutic target for AS.

**Keywords**

Genetics, Aortic stenosis, Metabolism, Genome-wide association study, Electronic health records

# **Poster presentations abstracts**

## **# 1 - Basic Science**

### **The CCR7+ PDGFRa+ Cell Population Is Increased In Regressing Atherosclerotic Plaques**

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**Introduction:** Atherosclerosis is characterized by the accumulation of lipids, cells and fibers in the arterial wall. Atherosclerotic plaques form in regions of low blood flow, whereas vessels exposed to high shear stress remain lesion-free. We created a surgical mouse model, arteriovenous fistula (AVF), which increases blood flow in the brachiocephalic artery (BCA) specifically, without altering serum lipid levels.

**Methods & Results:** LDLR KO mice were placed on a high-fat diet (HFD). Control mice were sacrificed at week 12. Sham and AVF surgery was performed at week 12 and mice were kept on a HFD for a further 1-4 weeks. We found that high blood flow is beneficial and leads to a significant ~50% regression of BCA plaque size in AVF mice compared with Controls, by week 4. We performed flow cytometry to characterize the different cell populations within Sham and AVF plaques. At day 7 after surgery, there was no difference in macrophage (F4/80+) or dendritic cell (CD11c+) content between Sham and AVF. However, we found a significant, 4-fold increase in the total number of CD45-/CCR7+/PDGFRa+ cells in the BCA plaques of AVF mice vs Shams (p<0.01). No such change was observed in the aortic sinus plaques of AVF or Shams. CCR7 was previously found to be overexpressed in regressing plaques upon an abrupt lowering of plasma lipids, but in CD45+ cells. In our model, plasma lipids remained high and CCR7+ cells instead expressed PDGFRa, a perivascular and multi-lineage differentiation marker. This cell population also expressed mesenchymal stem cell markers (CD90, CD44, CD34) and CD68.

**Conclusion:** Our data point to an unexpected increase in the CD45-/CCR7+/PDGFRa+ cell population in the early plaque regression process. They suggest that mesenchymal-type cells may promote regression in plaques exposed to high blood flow.

**Keywords**

Atherosclerosis, Regression, Plaque, Pdgfra, CCR7, Mesenchymal, High blood flow

## **# 2 - Clinical or Population Health**

### **Depression as a Predictor of Mortality in Older Adults Undergoing Transcatheter or Surgical Aortic Valve Replacement**

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**Background:** The importance of depression as a risk factor for morbidity and mortality has been recently investigated in patients with CAD. The objective of this study was to investigate the association between depression and mortality in older adults being considered for surgical (SAVR) or transcatheter (TAVR) aortic valve replacement.

**Methods:** This was a post-hoc analysis of the FRAILITY-AVR prospective cohort study including 14 centers in 3 countries. Older adults  $\geq 70$  years undergoing TAVR or SAVR with or without revascularization were enrolled. The pre-procedural depression assessment included the 15-item Geriatric Depression Scale Short Form (GDS-SF) with a score  $>5$  being suggestive of depression. The pre-procedural physical frailty assessment included a short physical performance battery (SPPB), and cognitive impairment was assessed with the mini-mental status exam (MMSE). The outcomes were all-cause mortality at 1-month and 12-months. Logistic regression was used to model 1- and 12-month mortality against a variety of clinical and procedural predictor variables. Finally, the changes in GDS-SF scores at 6 months was used to estimate 12-month mortality in a multivariable logistic regression model.

**Results:** Among 10,010 older adults with a mean age of  $81.4 \pm 6.4$  years, depression was only pre-operatively diagnosed in 8% of patients. However, once screened, the prevalence of depression was 32% ( $N=323$ ) in the cohort. After adjusting for clinical and geriatric risk factors, depression was found to predict mortality at 1-month (OR 2.09, 95% CI: 1.14 to 3.77) with an attenuated response at 12-months (OR 1.06, 95% CI 0.92 to 1.22). However, worsening GDS-SF scores at 6 months predicted 12-month mortality (OR 2.88, 95% CI 1.16 to 7.84). Some postulated mechanisms linking depression to adverse cardiac events and mortality include platelet abnormalities, endothelial dysfunction, and inflammation.

**Conclusion:** Depression was found to be a predictor of 1-month mortality with worsening depression scores predictive of 12-month mortality in older adults undergoing TAVR or SAVR.

**Keywords**

Depression, Surgical Aortic Valve Replacement, Transcatheter Aortic Valve Replacement, Frailty



## # 3 - Clinical or Population Health

### **Interaction Between Frailty and Access Site in Older Adults Undergoing Transcatheter Aortic Valve Replacement**

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**Background:** Frailty can predict outcomes and guide therapy in older adults being considered for transcatheter (TAVR). Non-femoral TAVR procedures are more invasive and impart a greater risk of morbidity and mortality compared to trans-femoral TAVR procedures. We sought to explore if frail older adults may be less capable of tolerating the operative stress associated with non-femoral transcatheter aortic valve replacement (TAVR) and face a higher relative risk of 30-day and 12-month mortality as compared to their non-frail counterparts.

**Methods:** This study was a post hoc analysis of the FRAILTY-AVR prospective multicenter cohort that consisted of older adults undergoing TAVR from 2012-2015. Interaction tables and multivariable logistic regression models were used to investigate the relationship between physical frailty and access site on our endpoints of 30-day and 12-month all-cause mortality. Frailty was assessed using the short physical performance battery (SPPB). Effect modification was calculated on the additive and multiplicative scales.

**Results:** The cohort consisted of 638 patients with a mean age of  $84 \pm 6$  years, of which 492 (77%) had femoral access and 146 (23%) had non-femoral access. In frail patients with low SPPB scores  $\leq 5$  (42%), non-femoral access was associated with increased 30-day mortality (OR 3.69, 95% CI 1.37 to 10.00); whereas in non-frail patients with SPPB scores  $>5$  (58%), non-femoral access had no effect (OR 0.94, 95% CI 0.21 to 3.49). There was evidence of effect modification between frailty and TAVR access site on the additive scale (RERI = 2.56) and a trend on the multiplicative scale (adjusted OR 2.42, 95% CI 0.55 to 11.95). Results were slightly attenuated for 12-month mortality.

**Conclusions:** The risk of mortality is nearly 3-fold higher when physically frail older adults undergo a TAVR procedure via a non-femoral access route, while more robust older adults tolerate the procedure irrespective of access route.

**Keywords**

Frailty, Transcatheter aortic valve replacement, Peripheral arterial disease, Access

## **# 4 - Clinical or Population Health**

### **Predictive Impact of Operative Time on Mortality and Major Morbidity in Frail Patients Undergoing Coronary Artery Bypass Grafting**

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Background: Frailty has become an emerging public health concern in the cardiovascular population, considering that frailty and cardiovascular disease share an overlapping pathophysiology involving common inflammatory markers. Frailty is defined as a syndrome of diminished physiological reserve and increased vulnerability to stressors, such as cardiac surgery. The goal of this study is to determine whether increases in operative time in coronary artery bypass grafting (CABG) have a more negative predictive impact on post-operative outcomes in frail patients compared to non-frail patients. It was sought to correlate operative time with incidence of complications 30 days and 1 year post-CABG.

Study design: This study is a post-hoc analysis of a prospective multicenter cohort study, based on the Prospective Frailty-ABCs Longitudinal Frailty Registry. The exposure – operative time – was set as cardiopulmonary bypass time (CPBT). Primary outcomes were merged into a single composite end point – MAPE (major adverse post-operative event) – which included all-cause mortality as well as major morbidity within 30 days. Mortality 12 months post-op was included as a secondary endpoint. Logistic regression models were used to study the interaction between CPBT and outcomes. Models were adjusted for the Society of Thoracic Surgeons (STS) predicted risk of mortality. Statistical analyses were performed using the STATA software package.

Results: Data were analyzed from 403 and 337 patients at 30 days and 1-year follow-up respectively. It was found that 31.7% of frail patients, in contrast to 17.9% of non-frail, ended up with a MAPE after 30 days. Outcomes were also worse for frail patients after 1 year. CPBT was found to be a negative predictor of MAPE in both frail and non-frail patients (OR=1.02 for each additional minute,  $p<0.05$ ). The rate of increase of those outcomes with CPBT was not higher in frail versus non-frail patients 30 days post-CABG. However, after 1 year, there was a 4% difference in mortality between frail and non-frail for CPBT=25mins, in contrast to 10% difference at CPBT=200mins.

Conclusions: Duration of surgery is correlated with higher incidence of complications both 30 days and 1 year post-CABG. Frailty itself is associated with higher rates of poor outcomes post-CABG. The predicted risk of MAPE does not increase faster with increasing CPBT in frail patients versus non-frail patients within 30 days post-CABG, but there is a potential differential increase rate in mortality within 1 year.

Keywords

Frailty, Coronary artery disease, Cardiopulmonary bypass time, Coronary artery bypass grafting

## # 5 - Basic Science

### **Mechanobiology of intracranial aneurysms: A novel in vitro model**

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An intracranial aneurysm (IA) is a serious health concern as its spontaneous rupture is associated with catastrophic outcomes and fatality. Despite recent advances, our understanding of what causes IA is limited. On one hand, medial imaging and computational fluid dynamic analysis have shed light on the specific flow patterns occurring inside IAs without clearly identifying hemodynamic factors responsible for rupture. On the other hand, animal models have shown evidences of the implication of hemodynamics and inflammation in the process of vascular remodeling but lack from controlled flow conditions and characterization of the endothelial cell (EC) signaling. ECs, being the cells in contact with blood flow, convert mechanical stimuli to intra/intercellular biochemical signals, a process known as mechanotransduction. This normally balanced regulation can be disrupted by aberrant hemodynamics. Therefore, it is hypothesized that focal exposure to aberrant level of wall shear stress (WSS) in the vicinity of IA drives the pathological outward vascular remodeling. A geometrically realistic in vitro cell culture model based on real patient dimensions was developed. Numerical flow simulations were used to define IA typical flow patterns for the model geometries. Three geometries were designed to represent the gradual vascular remodeling occurring at the apex of a bifurcation artery. A novel sugar casting method along with 3D printing allowed the creation of phantom models with complex shapes. These models consist in a tubular-shaped negative geometry, representing the lumen of an artery, embedded in a matrix material, polydimethylsiloxane. Human aortic ECs were cultured in the models to form a monolayer before being exposed to physiologically relevant level of WSS. Preliminary results have shown evidence of successful cell culture of the ECs and their response to flow. Immunofluorescence imaging of F-actin has shown the differential adaptation of ECs in the regions of the models (inlet, apex, outlet). Similarly, VE-Cadherin was expressed by ECs throughout the model, showing cell-cell junctions, an hallmark of a formed cell monolayer.

Conclusion. Novel IA phantom models suitable for the characterization of ECs mechanobiology have been developed and will be used for further characterization of biomarkers involved in IA pathology.

#### Keywords

Intracranial aneurysm, Realistic in vitro model, Mechanobiology, Wall shear stress, Vascular remodeling

## **# 6 - Clinical or Population Health**

### **Risk of Stroke and Major Bleeding Associated with Anticoagulation in Patients with Atrial Fibrillation and Advanced Chronic Kidney Disease**

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Background: Chronic kidney disease (CKD) is an independent risk factor for stroke in patients with atrial fibrillation (AF). The management of oral anticoagulation (OAC) is particularly difficult in this population as warfarin is associated with a significantly increased risk of bleeding. In an attempt to balance stroke and bleeding risks, direct oral anticoagulants (DOACs) have been used despite limited data. OBJECTIVE: To evaluate the risk of stroke and major bleeding associated with use of DOACs and warfarin in AF patients with advanced CKD.

Methods: A population-based cohort was constructed of AF patients with stage IIIb to stage V CKD from the MarketScan Research Database (2005-2009). Patients with a glomerular filtration rate (GFR) of <44 ml/min within  $\pm 30$  days from AF hospitalization were included. A Cox proportional hazard model adjusting for time-dependent DOAC and warfarin use, GFR, and CHA2DS2-VASc variables was used to assess risk factors for stroke. A second Cox model adjusting for time-dependent DOAC and warfarin use, GFR, and HAS-BLED variables was used to assess risk factors for major bleeding events.

Results: Our cohort included 28,310 patients (age  $65.8 \pm 14.0$ , CHA2DS2-VASc  $1.7 \pm 1.5$ , HAS-BLED  $1.9 \pm 1.0$ , GFR  $26.0 \pm 15.5$  ml/min). Over the 4-year study period, 2117 patients were prescribed DOACs and 1798 were prescribed warfarin. Adjusted cox regression models revealed a statistically significant increase in stroke with DOAC use [HR 1.18 (95% CI: 1.54, 2.12)]. Warfarin use was also associated with increased stroke [HR 2.10 (95% CI: 1.69, 2.39)]. An increased risk of major bleeding was observed with both DOAC and warfarin use [HR 1.35 (95% CI: 1.19, 1.53) and HR 1.33 (95% CI: 1.14, 1.55), respectively] except in the stage IIIb-IV subgroup where a non-significant trend towards major bleeding was observed with DOAC use [HR 1.12 (95% CI 0.88, 1.44)].

Conclusion: OAC use with either warfarin or DOAC was associated with an increased incidence of stroke and major bleeding in patients with AF and advanced CKD. In patients with stage IIIb-IV CKD, DOAC use did not affect the incidence of major bleeding.

#### **Keywords**

Atrial Fibrillation, Chronic Kidney Disease, Anticoagulation, Direct Acting Oral Anticoagulation, Major Bleeding, Stroke

## **# 7 - Clinical or Population Health**

### **CO as the best predictor in Tetralogy Fallot patients. Is CO the root of the story?**

*Maria Ordoñez , Ariane Marelli, Luc Jutras, Therrien Judith.*

Background: Cardiac index (CI) was shown to be the best predictor to cardiac hospitalization and cardiac interventions in patients with congenital heart disease. However, it has not been studied specifically in patients with Tetralogy of Fallot (TOF). The goal of our study, was to see if CI differed in TOF patients with and without clinical deterioration.

Methods: Patients with TOF who underwent a transannular patch repair with residual severe pulmonary regurgitation (PR) were enrolled in this study. CI was measured from their first cardiac magnetic resonance imaging (MRI) study performed as an adult and clinical charts were reviewed for any clinical outcome including 1) the development of arrhythmias, syncope, sudden death, worsening NYHA class or admission for heart failure.

Results: 82 patients (52% male) were included in the study. Mean age at MRI was 20,5 years and mean follow was 5 years. Twenty two patients (27%) developed outcomes. SVT in 13 patients, VT in 6 patients, SCD in 3 patients and worsening NYHA in 18 patients. Patient with clinical outcome had a CI of X compared to Y in the no cardiac outcome ( $p=0,06$ ) . The lower the CI, the more the outcomes. There was also a non significant inverse relationship between the CI and the burden of outcome.

Conclusions: CI in patients with TOF repair and residual severe PR may predict clinical outcome. Pediatric patients will be included in our next analysis to increase our numbers.

Keywords

Tetralogy of Fallot, Cardiac index, Long term outcomes

## **# 8 - Clinical or Population Health**

### **Efficacy and Safety of Smoking Cessation Interventions in Patients With Cardiovascular Disease: A Network Meta-Analysis of Randomized Controlled Trials**

*Karine Suissa, Jordan Lariviere, Mark J. Eisenberg, Maria Eberg, Genevieve C. Gore, Roland Grad, Lawrence Joseph, Pauline Reynier, Kristian B. Filion.*

**Background:** Although the efficacy and safety of smoking cessation interventions are well established, their efficacy and safety in patients with cardiovascular disease (CVD) remain unclear. The objective of this study was to evaluate the efficacy and safety of pharmacological and behavioral smoking cessation interventions in CVD patients via a meta-analysis of randomized controlled trials.

**Methods:** EMBASE, PsycINFO, MEDLINE, PubMed, and the Cochrane Tobacco Addiction Specialized Register were searched for randomized controlled trials evaluating the efficacy of smoking cessation pharmacotherapies and behavioral therapies in CVD patients. Outcomes of interest were smoking abstinence at 6 and 12 months, defined using the most rigorous criteria reported. Data were pooled across studies for direct comparisons using random-effects models. Network meta-analysis using a graph-theoretical approach was used to generate the indirect comparisons.

**Results:** Seven pharmacotherapy randomized controlled trials (n=2809) and 17 behavioral intervention randomized controlled trials (n=4666) met our inclusion criteria. Our network meta-analysis revealed that varenicline (relative risk [RR]: 2.64; 95% confidence interval [CI], 1.34-5.21) and bupropion (RR: 1.42; 95% CI, 1.01-2.01) were associated with greater abstinence than placebo. The evidence about nicotine replacement therapies was inconclusive (RR: 1.22; 95% CI, 0.72-2.06). Telephone therapy (RR: 1.47; 95% CI: 1.15-1.88) and individual counseling (RR: 1.64, 95% CI: 1.17-2.28) were both more efficacious than usual care, whereas in-hospital behavioral interventions were not (RR: 1.05; 95% CI, 0.78-1.43).

**Conclusions:** Our meta-analysis suggests varenicline and bupropion, as well as individual and telephone counseling, are efficacious for smoking cessation in CVD patients.

#### **Keywords**

Behavior therapy, Bupropion, Cardiovascular disease, Meta-analysis, Smoking, Tobacco use cessation products, Varenicline



## # 9 - Basic Science

### **Role of the inflammasome in angiotensin II-induced hypertension and vascular injury**

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**Background:** Innate immune cells (monocyte/macrophages) and adaptive immune cells (T lymphocytes) play an important role in the development of vascular lesions in hypertension. Innate immune cells play a role in the initiation and subsequent direction of the adaptive immune response, mechanisms that could also occur in hypertension and vascular injury. In hypertension, this cross-talk might be initiated in innate immune cells via activation of caspase-1 by the NLRP3 inflammasome, and followed by release of pro-inflammatory cytokines such as interleukin (IL)-1b, which will activate adaptive immune cells. However, it is unclear whether NLRP3 plays a role in vascular injury in hypertension. We hypothesized that Nlrp3 knockout would prevent angiotensin (Ang) II-induced hypertension and vascular injury.

**Methods:** NLRP3 knockout (Nlrp3<sup>-/-</sup>) and wild-type (WT) mice were infused with Ang II (490 ng/kg/min, SC) for 14 days. Systolic blood pressure (SBP) was measured by telemetry, and small mesenteric artery (MA) endothelial function and vascular remodeling by pressurized myography. Spleen monocyte profile was assessed by flow cytometry.

**Results:** After 14 days of treatment, Ang II increased SBP by 43 mm Hg in WT mice, which was unaffected by Nlrp3 knockout. Endothelium-dependent acetylcholine relaxation was decreased by ~40% in the mesenteric arteries of Ang II-infused WT mice compared to control. This effect was abrogated in Nlrp3<sup>-/-</sup> mice ( $P < 0.05$ ). MA media-to-lumen ratio was increased 1.5-fold in Ang II-infused WT mice compared to control ( $P < 0.05$ ), effect which was not blunted in Nlrp3<sup>-/-</sup> mice. Nlrp3<sup>-/-</sup> mice have a reduced number of activated myeloid cells (CD11b<sup>+</sup>, Ly-6C<sup>+</sup>) in the spleen, compared to wild-type mice.

**Conclusion:** These results suggest that the NLRP3 inflammasome plays a predominant role in the induction of Ang II-induced endothelial dysfunction. IL-1b-producing innate immune cells could be key cells involved in the communication between the innate and adaptive immune responses during the development of arterial hypertension.

**Keywords**

Hypertension, NLRP3 inflammasome, Vascular injury, Immune response

## # 10 - Basic Science

### **Induction of human endothelin-1 overexpression for 3 months causes blood pressure rise and small artery endothelial dysfunction and stiffening**

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**Background:** Mechanisms of blood pressure (BP) regulation by endothelin (ET)-1 produced by endothelial cells are complex and remain unclear. We have previously shown that tamoxifen-inducible endothelium-restricted human ET-1 overexpression (ieET-1) mice exhibited BP rise after 3 weeks of induction in an ET type A receptor (ETAR) -dependent manner, in absence of vascular injury. It is unknown if long-term exposure to ET-1 overexpression results in sustained BP elevation and vascular injury.

**Methods:** Nine to 12-week old male ieET-1 and control ieCre mice expressing a tamoxifen-inducible Cre recombinase in the endothelium were treated with tamoxifen (1 mg/kg/day, s.c.) for 5 days and studied 3 months later. ieET-1 mice were treated or not with ETAR blocker, atrasentan (10 mg/kg/day, PO) in the last 2 weeks of the study. BP by telemetry, mesenteric artery (MA) endothelial function and vascular remodeling determined by myography, reactive oxygen species (ROS) generation using dihydroethidium staining, and immune cell infiltration by immunofluorescence in MA or perivascular fat (PVAT) were determined at the end of the study.

**Results:** Systolic BP increased 27 mmHg in ieET-1 compared with ieCre ( $P < 0.001$ ) and was reduced by 9 mmHg by atrasentan treatment ( $P < 0.01$ ). Endothelium-dependent relaxation responses to acetylcholine decreased by 50% in ieET-1, which was not corrected by atrasentan compared to ieCre ( $P < 0.01$ ). Small artery stiffness increased in ieET-1, and was normalized by atrasentan compared to ieCre ( $P < 0.05$ ). ROS generation was enhanced 1.4-fold in PVAT of ieET-1 and was normalized by atrasentan compared to ieCre ( $P < 0.05$ ). Monocyte/macrophage infiltration was 1.6-fold higher in MA PVAT of ieET-1 and was normalized by atrasentan compared to ieCre ( $P < 0.05$ ).

**Conclusions:** Long-term exposure to endothelial ET-1 overexpression caused sustained BP elevation, endothelial dysfunction, vascular stiffening, oxidative stress and monocyte/macrophage infiltration.

**Keywords**

Endothelin-1, hypertension, vascular injury, oxidative stress, inflammation

## # 11 - Clinical or Population Health

### **Treatment-induced diastolic hypotension attenuates benefits from blood pressure control**

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**Background:** The Systolic Blood Pressure Intervention Trial (SPRINT) concluded that intensive systolic blood pressure (SBP) lowering to  $\leq 120$  mmHg, as compared with standard treatment targets of  $\leq 140$  mmHg, was associated with lower rates of fatal and non-fatal cardiovascular events. As excessive lowering of DBP may cause harm, we reanalyzed SPRINT data focusing on treatment induced diastolic hypotension, and the primary composite outcome, or death.

**Methods:** Diastolic hypotension was defined as  $\leq 55$  mmHg as SPRINT automated BP estimates yield values at least 5-10 mmHg below standard office measurements. We excluded patients without follow-up visits, with missing data on the primary outcome, or with incomplete data for aspirin and statin use. We further restricted our analysis to specifically address treatment-induced diastolic hypotension. We performed a multivariable cox-proportional hazards analysis to evaluate the effects of diastolic hypotension on the composite primary outcome (myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes), or all cause death. To avoid misclassification of exposure,  $DBP \leq 55$  mmHg was modelled as a time-dependent covariate.

**Results:** On multivariable analysis, among 7977 patients (4009 intervention and 3968 control), treatment of hypertension leading to a  $DBP \leq 55$  mmHg was associated with an increased risk for the primary outcome or death (HR 1.68; 1.25-2.27,  $p=0.001$ ). This was true both for participants randomized to intensive (HR 1.55; 1.05-2.28,  $p=0.028$ ) and standard treatment (HR 2.21; 1.39-3.52,  $p=0.001$ ), with no statistically significant interaction ( $p=0.098$ ) between diastolic hypotension and treatment strategy allocation.

**Discussion:** In reanalyzing SPRINT, we confirmed that treatment induced diastolic hypotension is associated with an increased risk of combined cardiovascular morbidity and mortality. Despite similar hazard ratios between intensive and standard-treatment groups, the rate of diastolic hypotension was more than three times higher with intensive therapy. Although the randomized design of SPRINT suggests that the association between treatment strategy and low DBP is causal, it is not clear that low DBP has a direct causal effect on adverse outcomes or if it is merely a marker of overall frailty or poor health. Nonetheless, targeting a SBP of  $\leq 120$  mmHg is now being incorporated into practice guidelines, possibly without adequate consideration of the unintended consequences of excessive DBP lowering.

**Conclusion:** A post-hoc analysis of SPRINT trial data suggests that treatment-induced diastolic hypotension may lead to harm, potentially counteracting benefits associated with intensive SBP lowering. Regardless of SBP target, it may be advisable to maintain an adequate DBP in order to maximize cardiovascular outcomes.

**Keywords**

Data parasites, Hypertension, High value Healthcare, Overtreatment

## **# 12 - Clinical or Population Health**

### **Frailty is Associated with Baseline Functional Limitation and 1-Year Mortality in Older Adults Undergoing Transcatheter Aortic Valve Replacement**

*Mina Girgis, MD; Jonathan Afilalo, MD, MSc. McGill University, Montreal, Canada*

**Background:** New York Heart Association (NYHA) class is a critical measure of functional status and prognosis in patients with severe aortic stenosis (AS) being considered for transcatheter aortic valve replacement (TAVR). These patients are affected by multiple comorbid conditions such that the drivers of NYHA class are multi-dimensional and incompletely understood. We evaluated the correlates of baseline NYHA class in this population, and determined which of these NYHA correlates were predictive of subsequent mortality after TAVR.

**Methods:** The Frailty-AVR cohort study prospectively enrolled older adults with severe AS undergoing TAVR between 2012-2015 at 14 centers in 3 countries. NYHA class was ascertained at baseline along with comorbid conditions and echocardiographic parameters. Physical frailty was quantified with the short physical performance battery (SPPB) that is scored 0-12 based on 5-meter gait speed, timed chair rises, and balance. The primary outcome was all-cause mortality after 1 year of follow up post-TAVR.

**Results:** Among 621 patients, with an average age of 84±6 years and 46% females, 70% had a baseline NYHA class of 3 or 4. Multivariable logistic regression showed that NYHA class was associated with: frailty, obesity, lung disease, aortic valve area, and left ventricular ejection fraction. The following were not significantly associated with baseline NYHA class: age, sex, mean aortic gradient, peripheral arterial disease, coronary artery disease, and atrial fibrillation. Of the NYHA correlates, frailty was most predictive of 1-year mortality with an odds ratio (OR) for SPPB ≤5 of 4.17 (95% CI 2.16, 8.04) and for SPPB 6-8 of 2.79 (95% CI 1.39, 5.57). Oxygen-dependent lung disease was also predictive of 1-year mortality (OR 3.11; 95% CI 1.10, 8.79) whereas obesity had a protective effect (OR 0.54; 95% CI 0.30, 0.95).

**Conclusion:** Physical frailty is strongly associated with NYHA limitation and predictive of mid-term mortality in older adults with severe AS undergoing TAVR. Other factors associated with NYHA limitation are chronic lung disease, AS severity, and left ventricular dysfunction. Obesity is associated with NYHA limitation but, paradoxically, predictive against mid-term mortality.

**Keywords**

NYHA, Frailty, TAVR, Aortic stenosis, SPPB

## **# 13 - Clinical or Population Health**

### **Variability in High-Sensitivity Cardiac Troponin T in Patients with Stable Coronary Artery Disease**

*James Brophy MD PhD, Peter Bogaty MD, Gilles Dagenais MD Divisions of Cardiology, McGill University & Laval University*

**Background:** Increase of high-sensitivity cardiac troponin (hs-cTn) T above the upper 99th percentile is the diagnostic cutoff for acute myocardial infarction without knowing its variability in stable patients with different coronary artery disease (CAD) history. We assessed hs-cTnT variability in such patients.

**Methods:** We prospectively studied 4 groups of 25 stable subjects (aged 64, 83% men): 1) recurrent acute coronary syndrome (ACS) with last event > 3 months; 2) a single myocardial infarction (MI)  $\geq$  7 years and no other CAD; 3) CAD without any previous ACS; 4) no angiographic evidence of CAD. Hs-cTnT was obtained 3 times during one day; 5 consecutive days; 4 consecutive weeks; 4 consecutive months; and every 3 months over the year. Variability and contributing factors were assessed using multivariate analyses and hierarchy models. Each patient therefore had a possible 15 measurements which were taken exclusively during clinical quiescence. All hs-cTnT measurements were performed simultaneously on an automated platform modular analytics E170 using a highly sensitive immunoassay (Troponin T hs Roche Diagnostics). All data exploratory analyses and mixed linear modeling was performed in R.

**Results:** In 1491 hs-cTnT samples from the 100 participants, 103 (6.9%) were above the conventional acute MI threshold of 14 ng/L. Among the 75 stable CAD patients 9.1% of the 1116 hs-cTnT measurements were > 14 ng/l while only 0.5% of the 375 hs-cTnT measurements in the 25 stable patients were > 14 ng/l was 0.5 %. In the recurrent group, 66 of the 370 samples (17.8%) were above 14 ng/l. Other independent factors associated with increased hs-cTnT measurements were diabetes ( $p < 0.001$ ) and worsening renal function ( $p < 0.001$ ). The 99% for normal hs-troponin values in the no CAD group was 14 ng/l but was 39 ng/l for the combined CAD groups.

**Conclusions:** In patients with stable CAD the 99th percentile for hs-cTnT level was almost three fold higher than what has been reported (and observed in this study) for normal controls. CAD patients with a past history of recurrent events, diabetes and impaired renal function are particularly likely to have elevated hs-cTnT levels even when clinically stable. These findings suggest the need to consider the past CAD history, diabetes status and renal function when interpreting hs-cTnT measurements.

**Keywords**

High-Sensitivity Cardiac Troponin T, Stable coronary artery disease, Variability

## # 17 - Clinical or Population Health

### **Echocardiographic mid-ventricular linear dimensions are more accurate than traditional basal-level linear dimensions: An MRI validation study**

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**Background:** Echocardiographic assessment of left ventricular (LV) size begins with the simple measurement of linear dimensions that approximate its volume based on the ellipsoid model. One of the fundamental limitations is that linear dimensions are - based on antiquated conventions - measured at the basal level of the LV that does not represent the true diameter of the ellipsoid. **Objective** The objective of this study was to determine the optimal level to measure the LV cavity diameter and wall thickness which would provide the most accurate estimate of LV end-diastolic and end-systolic volumes (LVEDV, LVESV), LV mass (LVM), and LV ejection fraction (LVEF).

**Methods and Results:** To determine the optimal level to measure linear dimensions, a derivation cohort of 75 patients having undergone a clinically-indicated cardiac MRI at the Jewish General Hospital was assembled. Patients had ischemic heart disease (N=25), nonischemic cardiomyopathy (N=25), or no structural heart disease (N=25). The 3-chamber view was analyzed using a custom MATLAB program to measure the LV cavity diameter and wall thickness at 15 equidistant levels from base to apex. The volumetric estimates derived from each of these levels was compared against the method of discs from the short-axis stack (reference standard). The optimal level was found to be the mid LV at the inflection point of the septum, having a stronger correlation with the method of discs than the basal LV for LVEF (R 0.83 vs. 0.78), LVEDV (R 0.86 vs. 0.84), and LVM (R 0.83 vs. 0.80). A validation cohort of 100 patients having undergone a clinically-indicated echocardiogram before cardiac surgery was extracted from the POSSE study. The mid LV cavity diameter yielded a stronger correlation with the method of discs than the basal LV cavity diameter for LVEF (R 0.96 vs. 0.80) and LVESV (R 0.90 vs. 0.86).

**Conclusion:** Measurement of LV dimensions at the optimal mid-ventricular level provides a more accurate estimate of LV size and function as compared to the traditionally recommended basal level. In particular, calculation of LVEF based on measurements at the mid-ventricular level appears to be more robust and less vulnerable to sigmoid septum variants or regional wall motion anomalies.

**Keywords**

Linear Dimensions, Echocardiography, Ejection Fraction, Teicholtz

## # 18 - Basic Science

### **Endothelin-1 exaggerates type-1 diabetes-accelerated atherosclerosis through nadph oxidases 1 and 4**

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**Objective:** NADPH oxidase (NOX) 1 but not NOX4-dependent oxidative stress plays a role in diabetic vascular disease, including atherosclerosis. Endothelin (ET)-1 has been implicated in diabetes-induced vascular complications. We showed that crossing mice overexpressing ET-1 selectively in endothelium (eET-1) with apolipoprotein E knockout (ApoE<sup>-/-</sup>) mice exaggerated high-fat diet-induced atherosclerosis in part by increasing oxidative stress. We hypothesized that ET-1 overexpression in the endothelium would exaggerate diabetes-accelerated atherosclerosis through a mechanism involving NOX1 but not NOX4.

**Method:** Six-week-old male ApoE<sup>-/-</sup> mice, eET-1/ApoE<sup>-/-</sup> and eET-1/ApoE<sup>-/-</sup> mice deficient in Nox1 (eET-1/ApoE<sup>-/-</sup>/Nox1<sup>-/-</sup>) or Nox4 (eET-1/ApoE<sup>-/-</sup>/Nox4<sup>-/-</sup>) were rendered diabetic with 55 mg/kg/day streptozotocin (STZ) IP injections for 5 days and studied 14 weeks later. Endothelial function and vascular remodeling were assessed in mesenteric arteries (MA) using pressurized myography. Aortic atherosclerotic lesions were quantified using Oil Red O staining. Plasma cholesterol, HDL and triglycerides were measured.

**Results:** Diabetic ApoE<sup>-/-</sup> mice presented an impaired endothelium-dependent vasodilatory response to acetylcholine, which was not observed in diabetic eET-1/ApoE<sup>-/-</sup>, eET-1/ApoE<sup>-/-</sup>/Nox1<sup>-/-</sup> or eET-1/ApoE<sup>-/-</sup>/Nox4<sup>-/-</sup> mice (E<sub>max</sub>: 20±6 vs 99±1, 98±1 and 100±0%). ET-1 overexpression caused a 1.8-fold increase in MA media/lumen of diabetic ApoE<sup>-/-</sup> mice (5.3±0.3 vs 2.9±0.2%), which was further increased 1.2-fold by Nox4 (6.4±0.3%) but not Nox1 knockout (5.5±0.3%). ET-1 overexpression exaggerated >2-fold the atherosclerotic lesion area in the aortic sinus in diabetic ApoE<sup>-/-</sup> mice (plaque area [x10<sup>5</sup> μm<sup>2</sup>]: 5.3±0.5 vs 2.9±0.6), which was reduced ~40% by Nox1 and Nox4 knockout (plaque area [x10<sup>5</sup> μm<sup>2</sup>]: 3.3±0.6 and 3.6±0.6). Plasma triglycerides were unaffected by ET-1 overexpression but reduced by Nox1 (2.2±0.4 vs 3.4±0.3 mmol/L) and Nox4 knockout (1.8±0.4 mmol/L). Plasma HDL and cholesterol were similar between groups.

**Conclusions:** Increased levels of ET-1 exaggerate diabetes-accelerated atherosclerosis through NOX1 and NOX4, despite paradoxically improving endothelium-dependent relaxation in small arteries.

**Keywords**

Diabetes, Endothelin-1, NADPH oxidase isoforms, Atherosclerosis, Vascular injury

## # 19 - Clinical or Population Health

### **Optimal Timing of Complete Revascularization in Acute Coronary Syndrome: A Systematic Review and Meta-Analysis**

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**Background:** Previous studies have suggested that complete revascularization is superior to culprit-only revascularization for the treatment of enzyme-positive acute coronary syndrome (ACS). However, the optimal timing of a complete revascularization strategy remains unclear. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing single-stage complete revascularization to multi-stage percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) or non-STEMI patients with multi-vessel disease.

**Methods:** We systematically searched the Cochrane Central Register of Controlled Trials, EMBASE, PubMed, and Medline for RCTs comparing single-stage complete revascularization to multi-stage revascularization in enzyme-positive ACS patients. The primary outcome was the incidence of major adverse cardiovascular events (MACE) at longest follow-up. Data were pooled using DerSimonian and Laird random-effects models.

**Results:** Four RCTs (n=838) were included in our meta-analysis. The risk of unplanned repeat revascularization at longest follow-up was significantly lower in patients randomized to single-stage compared to multi-stage revascularization (risk ratio [RR]: 0.68; 95% CI: 0.47, 0.99). Results also suggest a trend towards lower risks of MACE for patients randomized to single-stage revascularization at 6 months (RR: 0.67; 95% CI: 0.40, 1.11) and at longest follow-up (RR: 0.79; 95% CI: 0.52, 1.20). Risks of all-cause and cardiovascular mortality and recurrent MI at longest follow-up were also lower with single-stage revascularization, but 95% CIs were wide and included the null.

**Conclusion:** Single-stage complete revascularization is safe and may have a protective effect against MACE in the long-term, which appears to be driven by a lower risk of unplanned repeat revascularization.

**Keywords**

Percutaneous coronary intervention, Complete revascularization, Staged revascularization, Acute coronary syndrome, Meta-analysis



## # 20 - Clinical or Population Health

### **Using transesophageal echo strain imaging to measure the mechanical state of ascending aortic aneurysms**

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**Background:** Aneurysms of the ascending aorta (AA), at large diameters, require invasive prophylactic surgery to guard against the deadly risk of aortic wall rupture or dissection. Current clinical guidelines recommend resection of AA aneurysms at diameters  $\geq 5.5$ cm; however,  $\sim 40\%$  of all AA dissections occur below this threshold. Here, we propose that using pre-operative transesophageal echocardiography (TEE) strain imaging with parallel blood pressure measurements can reveal the mechanical state of the aortic wall, thereby highlighting its potential use in surgical decision-making.

**Methods:** Echocardiography-A total of 18 patients undergoing aortic resection were recruited with consent to participate in this study. At the time of surgery, before the patient was put on cardiopulmonary bypass, TEE imaging (GE Vivid 7) of the aortic short-axis and invasive radial blood pressure traces were taken for 3 cardiac cycles. Using EchoPac™ and post-processing in Matlab™, circumferential stretch profiles were generated from the echo profile and combined with the blood pressure traces. From this data, two novel in vivo stiffness moduli were developed. Ex vivo biomechanics-for each patient, a specimen of the resected aortic ring was clipped for orientation and stored in saline. Four 1.5x1.5cm<sup>2</sup> testing squares were isolated at even intervals around the aortic circumference. Each square underwent equibiaxial tensile testing at 37°C to generate stress-stretch profiles for each patient. Two parameters were calculated from these profiles: aortic stiffness and energy loss. Samples of the aortic wall were processed for histological staining using Movat's pentachrome.

**Results:** In vivo aortic diameter is only weakly predictive of ex vivo aortic biomechanics. The novel stiffness moduli derived from TEE imaging demonstrate strong, positive significant covariance with ex vivo tensile biomechanical indices, including stiffness and energy loss. Similarly, these TEE-derived indices are predictive of the histopathological expression of aortic collagens and elastin, the balance of which define the passive biomechanical behavior of the aortic wall.

**Conclusion:** TEE-derived stiffness moduli co-vary with aortic wall biomechanics and histopathology. This analysis demonstrates that added benefit using dynamic imaging over an accounted-for change in blood pressure, which we believe may provide added precision to better stratify patient populations by mechanical dysfunction, than by simply using diameter alone.

**Keywords**

Aorta, Biomechanics, Echocardiography, Aneurysms

## # 21 - Basic Science

### **Mapping of chromosome 2 differentially expressed aortic genes linked to vascular inflammation using congenic rats**

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**Background:** Rat chromosome (RNO) 2 introgression from normotensive Brown Norway (BN) rats into hypertensive Dahl salt sensitive (SS) background (consomic SB2) reduced vascular inflammation. We hypothesized that the BN-RNO2 contains genes that reduce vascular inflammation, which could be identified using microRNA (miRNA) and total RNA expression profiling in aorta of congenic rats containing different portions of BN-RNO2 on the SS background.

**Methods:** Twelve-to-13-week-old male SS rats and congenic rats containing the distal portion of BN-RNO2 (SB2a), the middle segment (SB2b) and the proximal segment (SB2e) on the SS background, fed a normal-salt diet, were studied. Systolic blood pressure (SBP) was measured by telemetry. Total RNA was extracted from aorta and used to construct libraries for small and total RNA sequencing using Illumina HiSeq-2500. The bioinformatics pipeline included: FastQC for quality control, STAR for genome (*Rattus norvegicus*, release-86) alignment, mirdeep2 for miRNA annotation and counting, Htseq-count for mRNA and long non-coding RNA annotation and counting; R for differential expression analysis.

**Results:** SBP was lower in SB2a and SB2b but not SB2e compared to SS (125±3, 127±6, 138±4 vs 146±2 mm Hg,  $P<0.05$ ). Differentially expressed miRNAs and genes (mRNA and non-coding RNA) were identified in SB2a vs SS (miRNAs: 3 up and 2 down, genes: 1 up and 3 down), SB2b vs SS (miRNAs: 2 up and 3 down, genes: 67 up and 112 down) and SB2e vs SS (miRNAs: 29 up and 25 down, genes: 12 up and 35 down), with FDR<0.05. Differentially expressed genes encoded within different BN-RNO2 congenic portions were identified in SB2a vs SS (2 down), SB2b vs SS (14 up and 18 down) and SB2e vs SS (1 down).

**Conclusions:** Differentially expressed BN-RNO2 encoded genes were identified in aorta of congenic SB2a, SB2b and SB2e rats. Whether these genes play a role in inflammation or vascular injury remains to be determined.

**Keywords**

Congenic rats, Chromosome 2, RNA sequencing, Blood pressure, microRNA

## **# 23 - Basic Science**

### **A Novel Dual-Angle Blade, Coreless Ventricular Assist Device**

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**Background:** Heart failure is a serious cardiovascular disease and the main cause of death in the world. The gold standard of treatment of end stage heart failure is transplantation. Given the severe universal shortage of suitable organ donors, long term mechanical heart support serves as an alternative to heart transplantation. To this end, there is an ongoing quest to improve the technology that will compete favorably with heart transplantation. Despite technological advancement, current pump designs present important limitations. Conventional pumps are designed to operate optimally at one speed, usually in a patient's resting state, and generate high shear stress due to narrow clearance gaps between the rotor and the pump casing at high speeds, which damages blood cells.

**Methods:** Using engineering design methodology and computer simulations, a research team in McGill has set an objective of overcoming these challenges faced by current pump designs. Novel coreless pump designs were developed and compared to conventional designs by employing CFD simulations.

**Results:** A "Dual-Angle Blade" rotor was initially created to provide optimal flows in multiple operation points for a conventional rotor. This unprecedented rotor design consists of two sets of blades with two different angles, each corresponding to an optimal operating speed, on a single hub. Simulation has shown a reduction of 20% in overall wall shear stress in comparison to conventional rotor with single angle blades. By integrating this advantage to the coreless concept, a "Coreless Pump" was developed to allow blood to flow through its non-obstructed center and provide multiple operating regime. Latest design refinements feature magnetic bearing set-up that can house coreless rotor with various configurations, such as multiple blade-angles and variable vane thickness and height. Simulation results have shown an additional improvement upon the previous design iteration.

**Conclusion:** We have demonstrated that these novel coreless pump designs reduce the overall blood cell shear stress by minimizing the blood deflections within the pump casing and creating optimal flow at multiple operating regimes

**Keywords**

Ventricular Assist Device, Heart Failure, Coreless Pump

## # 24 - Basic Science

### **Identification of a novel plasma membrane micro-domain interacting with apolipoprotein A-I**

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**Aims:** The biogenesis of high-density lipoprotein (HDL) particles by cholesterol-laden foam cells in atherosclerotic lesions is crucial for the removal of excess cholesterol from the lesions. Impairment in the HDL biogenic process contributes to the progression of atherosclerosis. The aim of this study is to identify novel cellular factors regulating HDL biogenesis.

**Methods and results:** HDL biogenesis is a process of apolipoprotein (apo)-mediated solubilization of specific plasma membrane (PM) micro-domains generated in cholesterol accumulated cells. We established a new method to isolate PM micro-domains interacting with the major HDL protein constituent, apoA-I: apoA-I-cell interactions occurred at 4°C were linked using a membrane-impermeable cross-linker, separated from subcellular organelles using a discontinuous sucrose gradient centrifugation, and purified by performing anti-apoA-I immunoprecipitation. Lipidomic and proteomic analyses of the PM micro-domain revealed that apoA-I binds to a cholesterol-rich PM micro-domain associated with 96 proteins. Interestingly, two PM proteins, caveolin and ABCA1 were excluded from the domain, indicating that the apoA-I-associated PM micro-domains purified under our experimental conditions are different from previously proposed PM domains required for HDL biogenesis as ABCA1-created PM domains and caveolin-containing PM domains have been known to contribute to HDL biogenesis.

**Conclusions:** We established a new method to isolate PM micro-domains interacting with apoA-I. Using this method, we found the presence of a novel apoA-I binding PM micro-domain, suggesting that apoA-I function in HDL biogenesis may be regulated by multiple PM factors.

**Keywords**

Atherosclerosis, Cholesterol, High-density lipoprotein, Plasma membrane micro-domains

## **# 27 - Clinical or Population Health**

### **Experience with Lomitapide for the treatment of Homozygous familial hypercholesterolemia/ The Quebec Experience with Lomitapide**

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**Background:** HoFH is defined as severe hypercholesterolemia (LDL-C >13.0 mmol/L) and the presence of bi-allelic mutations in the low-density lipoprotein receptor (LDLR) gene. In Quebec, there are 29 known HoFH subjects, followed at McGill, Quebec City and Saguenay. Patients with a null mutation of the LDLR gene require LDL apheresis every two weeks. Presently, this technique is only available in Québec City. The MTP inhibitor “Lomitapide” prevents the hepatic formation of apo B lipoproteins and decreases LDL-C by approximately 50% by an LDL-R independent mechanism. Here, we report the first experience using Lomitapide in five patients with HoFH already on LDL apheresis.

**Method:** This is a retrospective review of five patients with HoFH. The patients were followed at 3 lipidology centers in Quebec; McGill University Health Center, Centre hospitalier de l'Université Laval, and Université de Montréal Hospital in Chicoutimi. All patients were treated with extracorporeal LDL apheresis every week in Qubec city. They received Lomitapide as an adjunctive treatment to their conventional therapy. Lomitapide was started at 10 - 20 mg daily and the dose was reduced if not tolerated. LDL-C was measured pre and post apheresis and the average was calculated.

**Results:** Among the 5 patients, 3 were initially complaint on Lomitapide and their LDL-C levels were significantly reduced (44% in two and 52% in one). Significant transaminases elevation in the first patient normalized after reducing the dose from 20 mg to 5 mg daily in association with low fat diet. Gastrointestinal symptoms improved after reducing the dose from 10 mg daily to 5 mg weekly in the second patient. The third patient had to stop treatment despite good therapeutic response because of gastrointestinal side effects. The other two patients were non-complaint on Lomitapide from the beginning and had minimal reduction in their LDL-C (14% and 5%), both eventually discontinued treatment mainly because of the intolerable gastrointestinal symptoms.

**Conclusion:** Our experience of using Lomitapide in HoFH patients was successful in lowering LDL-C levels by 40-50%. However, the majority of the patients discontinued the treatment because of the gastrointestinal side effects. Hepatic steatosis needs to be considered with Lomitapide treatment.

**Keywords**

Homozygous familial hypercholesterolemia, Lomitapide, Hepatic steatosis

## **# 28 - Clinical or Population Health**

### **Right ventricular STEMI as a cause of death in idiopathic pulmonary arterial hypertension**

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**Introduction:** The cause of death in advanced idiopathic pulmonary arterial hypertension (IPAH) is commonly cardiogenic shock or arrhythmia. We describe a 33 year old female with advanced IPAH on IV epoprostenol and oxygen, who had a normal coronary angiogram 12 months prior to admission. She presented with two days of stuttering angina that became constant. Initial ECG showed new ST Elevation in leads 1, aVL, V2-V6. Rapid CT pulmonary angiogram excluded pulmonary embolism. Urgent cardiac catheterization showed discrete obstruction of the first and second acute marginal branches supplying most of her right ventricle (RV). Angioplasty and stenting was performed, with partial reperfusion. Echocardiography showed a severely dilated and hypokinetic right ventricle with no evidence of right to left shunt. She subsequently died of refractory cardiogenic shock before heart-lung transplant could be performed. Right ventricular ischemia is a major cause of chest pain in IPAH, and may cause myocardial necrosis with high troponins. However, a witnessed right ventricular STEMI, particularly in a young female, has not been described. She developed coronary lesions within a 12 month period, and one explanation might be that her massive right ventricular dilatation resulted in compression of her acute marginals between the RV myocardium and chest wall, with endothelial trauma and thrombus formation. In addition, the dilated right ventricle overlaid the whole anterior chest wall explaining the ECG findings on presentation.

**Conclusion:** Acute myocardial infarction should be suspected in patients with severe IPAH and ongoing chest discomfort, even without common cardiovascular risk factors. The dilated right ventricle occupies much of the precordium, making ECG localization unreliable. Severe right ventricle dilation might cause coronary compression leading to vascular injury and thrombus formation.

#### **Keywords**

Right ventricular ST-elevation myocardial infarction, Pulmonary hypertension, Cardiogenic shock

## # 30 - Clinical or Population Health

### **Risk Stratification of WPW Syndrome: A Deadly Low-Risk Pathway**

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**Background:** A 43-year-old man with no medical history presented after out-of-hospital cardiac arrest. The initial rhythm was ventricular fibrillation (VF). The patient was defibrillated into pre-excited atrial fibrillation (AF), then subsequently underwent direct current cardioversion. The electrocardiogram demonstrated sinus rhythm with pre-excitation and no ischemic changes.

**Method:** The patient underwent electrophysiological study (EPS) which revealed an accessory pathway (AP) effective refractory period (ERP) of 280ms on and off isoproterenol. With decremental pacing from the atrium the accessory pathway had 1:1 atrio-ventricular (AV) conduction at 230ms. AF could not be induced despite burst pacing on and off isoproterenol. With isoproterenol infusion and atrial burst pacing there was 1:1 AV conduction at 200ms, reinforcing the high-risk properties of this pathway. The pathway was successfully ablated.

**Results:** The incidence of VF in patients with ventricular pre-excitation is approximately 1.5%. There are currently three proposed strategies for EPS risk stratification of a patient with asymptomatic pre-excitation: 1) measurement of the shortest R-R interval (SPERRI) during spontaneous or induced AF; 2) measuring the accessory pathway ERP with atrial programmed extra-stimulation at different cycle lengths; 3) using decremental pacing to define the shortest cycle length in which 1:1 AV conduction through the AP is maintained. The SPERRI during AF is considered the best indicator of a high-risk pathway because it reproduces the clinical situation that would lead one to develop VF. The accessory pathway ERP is strongly correlated with the shortest pre-excited R-R interval (SPERRI) and also with the mean R-R interval during AF. Isoproterenol can be used in an attempt to unmask a high-risk pathway, but data are limited regarding its ability to predict VF. Our patient did not demonstrate a high-risk pathway ERP with 2 different cycle lengths or with isoproterenol. However, 1:1 AV conduction over the AP with decremental pacing at 230ms demonstrated high risk properties. The high-risk nature of this pathway was based on extrapolation of SPERRI data.

**Conclusion:** The presentation of this patient with VF demonstrated the high-risk nature of the AP. However, had this patient presented for routine EPS with current guideline-based risk stratification, which does not include decremental pacing as tool for risk stratification, the pathway could have been considered low risk. The challenge presented by this case is the potential for misclassifying high-risk pathways using the current methods of risk stratification.

**Keywords**

Wolff-Parkinson White Syndrome, Cardiac arrest, Electrophysiology study, Risk stratification

## **# 31 - Clinical or Population Health**

### **Early Left Ventricular Ejection Fraction as a Predictor of Survival After Cardiac Arrest**

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**Background:** Cardiopulmonary resuscitation and early defibrillation have been shown to improve outcomes of cardiac arrest. The significance of the post-arrest echocardiogram, specifically the left ventricular ejection fraction (LVEF) is unknown .

**Methods:** We performed a retrospective cohort study of patients who suffered from cardiac arrest between January 1, 2009 and December 31, 2013. We included all patients who achieved return of spontaneous circulation (ROSC), and were admitted to the Intensive Care Unit (ICU) or Coronary Care Unit (CCU) of a tertiary care academic center. Patients who underwent echocardiography within 24 hours of cardiac arrest were included for analysis. The primary outcome was survival.

**Results:** We identified 151 patients who achieved ROSC of which 97 underwent post-arrest echocardiogram within 24 hours. 70.8 % were males and the mean age was 67.8 years (SD 15.9). The mean LVEF at 24 hours was 35.7 (SD: 17.8). LVEF > 40% was not a predictor of survival at 30 days or hospital discharge. The only significant predictors on multivariate analyses were age, presence of shockable rhythm and time to ROSC.

**Conclusion:** Although echocardiograms are frequently ordered, LVEF greater than 40% in patients who are resuscitated after a cardiac arrest is not a predictor of survival.

**Keywords**

Cardiac arrest, Echocardiography, Left ventricular function



## # 32 - Clinical or Population Health

### **Impact of HOPE-3 on Statin Eligibility for the Primary Prevention of Cardiovascular Disease**

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**Background:** The ACC/AHA guidelines suggest initiation of statin therapy for primary prevention in patients who have an LDL-C between 70 and 189 mg/dL and an estimated 10-year ASCVD risk  $\geq 7.5\%$ . Risk calculators are primarily driven by age resulting in the inclusion of many older adults with otherwise few ASCVD risk factors. We demonstrated that an individualized-benefit approach using an absolute risk reduction (ARR) of  $\geq 2.3\%$  identified a substantial number of Americans with a 10-year ASCVD risk  $< 7.5\%$  who would derive at least as much benefit from statin therapy as those eligible for treatment per the guidelines. The publication of the HOPE-3 trial demonstrated benefit of rosuvastatin for primary prevention of ASCVD in a large, multiethnic population. We sought to evaluate whether HOPE-3 improved the evidence-base to support the 2013 guidelines.

**Methods:** Survey data from the National Health and Nutrition Examination Survey (NHANES) was used to create a sample of 2,134 patients representing 71.8 million Americans without ASCVD or other lipid-eligible conditions. Each individual was defined as meeting any of the following 3 criteria: (1) a 10-year risk of  $\geq 7.5\%$  by pooled cohorts equation (PCE) as per the 2013 ACC/AHA guidelines; 2) an expected ARR  $\geq 2.3\%$  based on PCE risk and individualized relative risk reductions; and 3) eligibility to any one of the primary prevention RCTs based on trial inclusion criteria.

**Results:** With the addition of HOPE-3, an additional 7.1 million would meet eligibility for a RCT for a total of 31.8 million individuals. The proportion of individuals with trial evidence among those deemed eligible by the risk criterion in the 2013 guidelines increased from 52.7% to 84.0%. The number of individuals with ARR  $\geq 2.3\%$  with eligibility to at least 1 statin trial increased from 55.3% to 80.1%. Of the 7.1 million HOPE-3 eligible individuals, 5.7 million (80.3%) would obtain an expected ARR  $\geq 2.3\%$ . The majority of HOPE-3 eligibles (66.2%, n = 4.7 million) also met eligibility for statins based on 2013 guidelines.

**Conclusion:** The addition of HOPE-3 markedly improves the randomized trial evidence-base for the 2013 ACC/AHA guidelines. The RCT evidence is also strengthened among individuals with an ARR  $\geq 2.3\%$ . Our results demonstrate the importance of directly considering individualized benefit, specifically when using HOPE-3 eligibility criteria, to initiate statins for a given individual.

**Keywords**

Prevention, Lipids, Statin

## # 33 - Clinical or Population Health

### **Hybrid Coronary Revascularization Versus Coronary Artery Bypass Grafting for Multivessel Coronary Artery Disease: A Systematic Review and Meta-Analysis**

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**Background:** Hybrid coronary revascularization (HCR) has emerged as a potential alternative to coronary artery bypass grafting (CABG) for multivessel coronary artery disease. However, its efficacy and safety versus CABG remain unclear. We therefore conducted a systematic review and meta-analysis to compare these interventions.

**Methods:** We systematically searched PubMed, MEDLINE (via Ovid), EMBASE (via Ovid), Cochrane Library of Clinical Trials, and the Web of Science for studies comparing HCR to CABG in patients with multivessel coronary artery disease. The primary outcome was major adverse cardiovascular and cerebrovascular events (MACCE) and its components (myocardial infarction, stroke, mortality, and target vessel revascularization) at  $\geq 1$  year. Secondary outcomes included MACCE at  $\leq 30$  days, its components, and postoperative safety outcomes: renal failure, blood transfusion, new-onset atrial fibrillation, and infection. Meta-analysis was performed using DerSimonian and Laird random-effects models.

**Results:** One randomized controlled trial and eight cohort studies were included in our systematic review. When data were pooled across studies, HCR appeared to reduce the risk of MACCE at  $\geq 1$  year (odds ratio [OR]: 0.71; 95% confidence interval [CI]: 0.31, 1.62) compared with CABG. However, the 95% CI was wide. Available evidence also suggests that HCR may improve the components of MACCE at  $\geq 1$  year except for target vessel revascularization (OR: 2.69; 95% CI: 0.89, 8.12), and reduce postoperative complications, but most CIs were wide. The difference between HCR and CABG was inconclusive for MACCE at  $\leq 30$  days.

**Conclusion:** Although CIs were wide, the data suggest that HCR confers benefits for long-term MACCE and all its components except target vessel revascularization. However, with the available evidence regarding all the outcomes mostly derived from observational studies, our study highlights the need for a large, definitive, well-designed randomized controlled trial to compare the efficacy and safety of these interventions.

**Keywords**

Hybrid Coronary Revascularization, Coronary Artery Bypass Grafting, Multivessel Coronary Artery Disease, Systematic review, Meta-analysis

## # 36 - Basic Science

### **Cytoprotective and Proliferative Impact of YAP1 to Cardiac Myocytes Under Oxidative Stress and Hypertrophy**

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**Background:** Although adult cardiomyocytes are considered post-mitotic, more recent evidence suggests that the heart displays some regenerative capabilities. In this regard, recent work has investigated the Hippo-signaling pathway, a mechanism implicated in cardiac myocytes proliferation and cardiac regeneration after a myocardial infarction (MI). Yes-associated protein 1 (YAP1) is the effector protein in the Hippo-signaling pathway, binding to transcription factors in the nucleus to activate genes involved in cellular proliferation and survival. However, the exact mechanisms by which YAP1 protects the heart post-MI is currently unknown. Here, we propose that YAP1 plays a critical role in cardiac myocytes regeneration during oxidative stress and hypertrophy that occur after a MI.

**Method:** The AC-16 human left ventricular cardiomyocytes are used in this study. To mimic the post-infarct effects, H<sub>2</sub>O<sub>2</sub> and doxorubicin were applied at different concentrations and timelines to induce oxidative stress and hypertrophy, respectively. To overexpress YAP1, the AC-16 cells are infected with a lentiviral plasmid that upregulates or silences YAP1. Subsequently, cells are exposed to 24 hours of H<sub>2</sub>O<sub>2</sub> and doxorubicin. Cellular viability and cytoprotection are assessed via Alamar blue staining, TUNEL, and MTT assays. Western blotting is used to analyze protein expression, while PCR was used to assess gene activation. Data is represented as mean ± SEM using one-way ANOVA and student t-test statistical analysis.

**Results:** Immunofluorescence staining indicated a significant hypertrophy in AC-16 cells treated with 0.5 µM doxorubicin after 24 hours of exposure and minimal loss in cell viability. Alamar blue proliferation assay and flow cytometry analysis determined that 200 µM of H<sub>2</sub>O<sub>2</sub> is a viable concentration for subsequent experiments. Immunostaining indicated that the YAP1 antibody is readily found within the nucleus of AC-16 cells, while phosphorylated YAP1 is found throughout the cytoplasm.

**Conclusion:** Preliminary results suggest that H<sub>2</sub>O<sub>2</sub> and doxorubicin induce damage and hypertrophy in AC-16 cells, respectively. Our next step focuses on infecting the AC-16 cells with YAP1 and exposing these cells to oxidative stress and hypertrophy. Future experiments will analyze protein and genomic expression of cardiac markers after YAP1 infection.

**Keywords**

Hippo, YAP, Oxidative Stress, Hypertrophy, Cardiomyocyte, Regeneration

## **# 37 - Clinical or Population Health**

### **The burden of breast cancer in adult women with congenital heart disease**

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**Background:** Breast cancer is the most common cancer among women in Quebec. Screening plays an important role in reducing its burden. Breast cancer incidence in adult women with congenital heart disease (ACHD) has not been studied. Moreover, breast is a high sensitive tissue and we recently documented an association between LDIR-related cardiac procedures and all-cancer incidence in ACHD population. We aimed 1) to compare the incidence rates of breast cancer in ACHD women to general population, 2) to determine if LDIR exposure from cardiac procedures is associated with breast cancer incidence in ACHD women, 3) to assess if ACHD women have comparable cancer screening rates to non-ACHD women.

**Methods:** The Quebec CHD database was used to calculate the incidence rate of breast cancer among ACHD women. The standardized incidence ratio (SIR) was calculated as the ratio of the number of observed ACHD cancer cases in Quebec to the number of expected cancer cases given the provincial cancer incidence rates in 2006. To investigate if LDIR exposure from cardiac procedures is predictive of breast cancer risk we performed a nested case-control study. Each case aged 18-65 between 1995 and 2009 was matched on CHD severity, age and birth year with 10 randomly selected controls. A lag time of one year between LDIR exposures and cancer diagnosis was applied to all analyses. Multiple logistic regression was used to assess the association between LDIR exposure and breast cancer risk. Finally, we compared the yearly breast cancer screening participation rate to the Quebec general population from 1989 to 2009 among women aged 50 to 69.

**Results:** The calculated SIR was 1.19 indicating an increased risk of breast cancer among women with CHD than general population. Cumulative LDIR exposure from cardiac procedures was not associated with cancer (odds ratios =0.96 for one procedure increment, 95% CI: 0.85-1.08). Similar results were obtained using dose estimates for LDIR exposure. Compared to general women population ACHD women patients had lower yearly rates of mammogram from 1989 (16.4% versus 22.1%) to 2009 (59.8% versus 67.9%).

**Conclusion:** ACHD women had increased breast cancer risk than general population. LDIR exposure from cardiac procedures was not associated with breast cancer risk. Primary care physicians and cardiologists should collaborate to ensure appropriate cancer screening for ACHD women among whom attention to cancer screening may be overlooked.

**Keywords**

Breast cancer, Cardiac procedure, Low dose ionizing radiation, Cancer screening

## # 38 - Clinical or Population Health

### Safety and effectiveness of Sacubitril/Valsartan in real life practice

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**Introduction:** The most recent medical addition to heart failure management, in those with reduced left ventricular ejection fraction, has been the use of Sacubitril/Valsartan.

**Methods:** Several clinical parameters were investigated, including some that were not studied in PARADIGM. Our goal was to perform a single center, retrospective, descriptive study, evaluating our patients' clinical outcomes, on Sacubitril/Valsartan.

**Results: Demographics** From December 2015-December 2016: Sacubitril/Valsartan was initiated in 140 patients. More than half of the patients (51%) suffered from ischemic cardiomyopathy; 21% were females. The mean age and left ventricular ejection fraction were 62 and 25%, respectively. The majority were NYHA 2 and 28% were NYHA 3.

**Diuresis** Following initiation of Sacubitril/Valsartan, 16% were able to have doses of diuretics decreased, 12% had to have diuretics dosage increased, 58% had unchanged doses of diuretics (6% were not on diuretics before initiation of Sacubitril/Valsartan).

**Blood pressure** Sacubitril/Valsartan was initiated in 19 patients with systolic blood pressures of less than or equal to 100mmHg. The lowest measured blood pressure at initiation was 84/53. The medication was well tolerated in 79% of these patients and 52% were able to have up-titration of Sacubitril/Valsartan

**Left ventricular Ejection Fraction** Of 31 patients who obtained repeat left ventricular ejection fraction (LVEF) measurement, 13 (42%) had improved LVEF.

**Cardiac Transplantation** On our transplantation and Ventricular assist device (VAD) list, 17 patients were on Sacubitril/Valsartan. 4 of these patients were deactivated from the transplant list, once on Sacubitril/Valsartan due to improving clinical status. 3 of these patients reached maximal dose Sacubitril/ Valsartan, while 1 patient reached medium dose.

**Conclusion:** In this single-center retrospective cohort study, we showed that Sacubitril/Valsartan was well tolerated even in patients with baseline hypotension. We observed decreases of diuretics requirement and improvement in LVEF in several patients. Moreover, there was no further need for cardiac transplantation and/or LVAD in some patients. Overall, our data suggested that Sacubitril/Valsartan had good safety and effectiveness in "real-life" practice.

**Keywords**

Heart failure, Blood pressure, Renal failure

## # 39 - Clinical or Population Health

### Update on the Familial Hypercholesterolemia Canada (FH Canada) Registry

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Familial hypercholesterolemia (FH) is the most frequent genetic lipoprotein disorder associated with premature CAD. The prevalence of FH in the general population has been recently revised to 1 in 250, so in Canada, the burden of disease is now estimated to be approximately 140,000 patients, with less than 5% of patients diagnosed so far. Objective: The goal of this initiative was to create a registry of subjects with FH across Canada designed to identify subjects with FH and to improve health and healthcare delivery. Rare diseases of lipoprotein metabolism are also included (SMASH initiative).

Methods and results: The registry was initiated in 2014 and regroups more than 150 basic researchers, clinicians specializing in lipidology, endocrinology, pediatric endocrinology, obesity and cardiology, clinic coordinators and industry partners. Over the 19 academic centers involved, 8 have been or are in the process of being approved by their institutional ethic committee. The registry is also being extended to various communities radiating from these academic centers ("hub and spoke" model). In Quebec, 9 sites will be approved by ethics following the MSSS multicentric process, with the MUHC site as the central evaluating site. The database (iCAPTURE platform, James Hogg Research Centre at St-Paul's Hospital, UBC, Vancouver) is using a uniform set of criteria and data entry, which includes clinical, biochemical and demographic information. Specimens (plasma/serum and DNA) are collected for local biobanking. Approximately 2900 patients have been entered in the database so far. The FH Canada registry has a strong knowledge translation component. A website has been set-up ([www.fhcanada.net](http://www.fhcanada.net)) to educate and inform patients and health care professionals. The registry members worked together to implement evidence-based clinical practice guidelines for the adult and pediatric FH population. The FH registry network is also working on the creation of educational resources and web-based applications to simplify FH diagnosis and treatment (new Canadian FH definition, new FH calculator ([www.circl.ubc.ca](http://www.circl.ubc.ca)), new algorithm for imputed baseline LDL-C and for molecular diagnosis in Quebec), which will help to increase awareness of FH among health care professionals, their patients and family members.

Conclusion: Through the creation of a Canada-wide network of academic clinics, integrating lipid specialists, endocrinologists and cardiologists, the FH Canada registry will lead to significant benefits for FH patients, clinicians and researchers, biopharmaceutical industry and government.

#### Keywords

Familial hypercholesterolemia, Registry, Low-density lipoprotein, Cholesterol, Lipid disorders

## # 41 - Clinical or Population Health

### **Methodological Considerations for Physical Activity Measurement using Accelerometers: The Impact of Wear Location on the Relationship between Step Counts and Arterial Health in Free-Living Adults**

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**Background:** Wrist accelerometer placement is convenient but less accurate than waist placement in terms of estimating physical activity (PA). Nevertheless, wrist placement is increasingly adopted in research studies. No previous studies have compared PA measurements from wrist and waist locations in terms of associations with health outcomes. Therefore, we aimed to evaluate the impact of wrist and waist accelerometer placement on the association between PA and a responsive arterial health indicator, carotid-femoral pulse wave velocity (cfPWV).

**Methods:** We previously demonstrated an inverse association between waist-worn pedometer-assessed step counts (Yamax SW-200, 7 days) and cfPWV (-0.20 m/s, 95% CI -0.28, -0.12 per 1,000 step/day increment) in 366 free-living adults. A subgroup of 46 participants concurrently wore accelerometers (Actigraph GT3X+) at the wrist; however, placement was at the waist for remaining participants. Herein, we compared PA measures between waist and wrist accelerometer placement in participants matched for sex, age, and pedometer-assessed steps (N=46 per group). We evaluated associations with cfPWV (applanation tonometry, Sphygmocor) in linear regression models.

**Results:** Participants were on average 61 (SD 12) years old with a BMI of 31 (SD 4) kg/m<sup>2</sup>. Compared to the waist, wrist group participants had higher accelerometer-assessed step counts (mean difference 3980 steps/day; 95% CI 2517, 5443), energy expenditure (967 kcal/day, 95% CI 755, 1179), and moderate-to-vigorous-PA (138 mins; 95% CI 114, 162). The association between pedometer-assessed step counts and cfPWV was similar in both groups. Accelerometer-assessed step counts at the waist signaled an association with cfPWV (-0.28 m/s, 95%CI -0.58, 0.01) but no association was apparent with step counts assessed at the wrist (0.02 m/s, 95% CI -0.24, 0.27).

**Conclusion:** We have demonstrated large differences in PA measures between the wrist and waist accelerometer locations. Furthermore, misclassification of PA levels specifically due to the wrist location eliminated any sign of a relationship between step counts and cfPWV. These findings add a new element to the evidence base supporting waist as the preferred accelerometer wear location in research.

**Keywords**

Accelerometer, Pedometer, Wrist, Arterial health, Physical activity, Carotid-femoral pulse wave velocity, Step counts

## # 42 - Clinical or Population Health

### **Development and quality assessment of a novel clinical reporting concept for advanced cardiac imaging adapted to primary and secondary care.**

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**Objectives:** Important concerns about overuse of invasive diagnostic imaging methods, exposure to radiation, and subsequent implications for patient safety in Canada were recently expressed. In this context, a novel imaging technique involving oxygenation-sensitive (OS) cardiac magnetic resonance (OS-CMR) is currently being applied in clinical research, allowing a non-invasive, radiation-free and comprehensive assessment of the coronary vascular response. Although this imaging technique offers a fast, safe and simple cardiovascular examination, the lack of a dedicated clinical report design limits its application in clinical settings. Thus, the purpose of this study is to develop and test a clinical report for OS-CMR that can be adapted to primary and secondary care and to assess its quality.

**Methods:** In a collaboration between academia (McGill University Health Centre) and industry (Circle Cardiovascular Imaging Inc., Calgary), a clinical reporting and dissemination system is being developed and tested in patients with coronary artery disease with an indication for testing their myocardial oxygenation response. With a reporting system that contains adaptable features deemed appropriate for the intended primary or secondary health care setting, twenty family physicians and 10 cardiologists associated with the McGill University Health Center will be asked to assess the quality of the clinical report system using standard principles for defining report quality.

**Results/Anticipated results:** Current progress shows that the clinical report will provide meaningful diagnosis, etiology, prognosis and treatment planning based on prior evidence and examination for myocardial oxygenation. The report will also offer precise information on cardiac structure, concise clinical impressions, and will be designed with respect to the current guidelines for reporting CMR examinations. Work to improve the automaticity and the customizability of the clinical report is ongoing. Physicians' utility assessment is anticipated to provide insights about quality principles, such as the structure, clarity, comparability and balance of the clinical report.

**Conclusion:** The development of a clinical report for OS-CMR may contribute to advancements of innovative diagnostic imaging modalities adaptable to primary and secondary care. The implementation of an improved reporting system and easily customizable clinical reports may ultimately have a positive impact on patient safety, clinical decision-making, cost and outcomes. Novel features of the reporting system and further results will be presented.

**Keywords**

Clinical Report, Primary care, Secondary care, Cardiovascular Magnetic Resonance



## # 44 - Clinical or Population Health

### **Early versus late onset hypertensive disorders in pregnancy and the risk of incident hypertension and cardiovascular disease**

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**Background:** Previous studies suggest that women with early onset preeclampsia have an increased risk of subsequent cardiovascular disease (CVD). However, it is unclear whether the timing of onset of any hypertensive disorder in pregnancy (HDP) is associated with CVD risk.

**Methods:** We identified a population-based cohort of 146,748 women, aged 15-45 years, with a first recorded pregnancy in the Clinical Practice Research Datalink. HDP were defined using physician diagnoses, prescriptions, or blood pressure measurements between 18 weeks gestation and 6 weeks postpartum. Exposure was defined based on the first pregnancy (ignoring subsequent ones) and further divided into early- (<34 weeks gestation) and late-onset HDP (≥34 weeks of gestation). The primary outcome was time to incident CVD (physician diagnoses), and the secondary outcome was incident hypertension (diagnoses or new use of anti-hypertensive medications). We used Cox proportional hazards models to estimate the associations of interest.

**Results:** Women with early onset HDP were more likely to be obese and to have a history of diabetes compared with women with no HDP or late onset HDP, with no other important differences between groups. Compared with women with no HDP, those with early HDP had a higher risk of developing incident CVD (HR 2.6, 95% CI 1.5, 4.3) and hypertension (HR 4.3, 95% CI 3.6, 5.0). The HR for early- vs late-onset HDP were 1.29 (95% CI 0.73, 2.27) for CVD and 0.88 (95% CI 0.74, 1.05) for hypertension.

**Conclusions:** HDP in the first pregnancy was associated with an increased risk of subsequent CVD or hypertension, irrespective of time of diagnosis. Women with early onset HDP may be at a higher risk of CVD and a lower risk of hypertension than those with late onset HDP, but confidence intervals were wide.

**Keywords**

Hypertensive disorders in pregnancy, Cardiovascular disease, Hypertension, Pregnancy

## # 45 - Clinical or Population Health

### **The “READYorNot” e-Health Intervention---READiness in Youth for traNsition Out of pediaTric care**

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**Background:** Lifespan conditions are increasing in prevalence as children survive to adulthood with chronic diseases such as cancer, juvenile onset diabetes, congenital heart disease (CHD) and brain-based disabilities (BBD); including cerebral palsy, autism, and epilepsy. Transition from pediatric to adult care is a resource-intensive and complex process that needs to engage health systems, patients, families, and intersectoral pediatric and adult care providers. Despite guideline recommendations that transition of care should be anchored to structured processes, few programs exist. There is thus a growing need for health interventions that bridge care between pediatric and adult providers.

**Method:** A multidisciplinary collaboration—combining thought leadership in clinical psychology, translational medicine, CHD and BBD, as well as patient insights—was initiated to design, develop, and clinically validate the READYorNot e-Health intervention to educate and empower young adolescents and their families as they undergo transition from pediatric to adult care. The READYorNot intervention combines key elements of existing technologies including the TAVIERX virtual nurse (360MedLink), the MyTransition App (McMaster) and the MyHealth Passport App (SickKids) into a single resource. In addition, modules to enhance education and medical information management will be delivered using a virtual transition coach. A training curriculum targeting social skills to enable self-management in preparation for adult health care systems for the patient will be delivered in the form of an App with a built-in gaming platform. A text-messaging platform aimed at enhancing patient and family/clinic and provider interactions will facilitate reminders and access with the patient-centered care community.

**Results:** The READYorNot prototype is currently under development and will undergo multiple iterations of usability testing. Focus group interviews will identify technology deficiencies and unmet patient needs. Participatory design sessions and formative usability testing will engage users in technology design, user interface optimization, and feature integration. To ensure that the optimized READYorNot intervention effectively meets end-user requirements, summative usability testing using the first version of the READYorNot intervention will be conducted for quality assurance and measures of user experience.

**Conclusions:** The READYorNot intervention is expected to improve quality of care and patient and family experiences during transition with a potential for reduction in cost that is expected to be translatable across pediatric and adult health care systems. Our findings are also expected to inform guidelines and policy recommendations for a growing number of patients with childhood conditions requiring life-long care.

#### **Keywords**

Transition of care, Congenital heart disease, Brain-based disabilities, e-Health intervention, Technology development, Virtual nurse, Patient-centered design

## # 46 - Basic Science

### **Expression of Circulating MicroRNAs in Women Hospitalized with Acute Coronary Syndrome and a Prior History of Preeclampsia**

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**Background:** Women who have had preeclampsia (PE) have an increased risk for premature ischemic heart disease. The molecular determinants underlying this risk have not been clearly defined, but potentially involve sustained vascular damage and/or dysfunction. This may be reflected by alterations in the levels of specific circulating microRNAs (miRNA). Our aim was to identify miRNAs that circulate at different levels in women diagnosed with acute coronary syndrome (ACS), with and without a prior history of PE.

**Methods:** We conducted a two-step derivation and validation experiment of women with premature (age < 55 yrs) ACS (defined according to standard criteria), divided into three groups based on a prior history of gestational hypertension, PE, or normotensive pregnancy, ascertained by detailed self-report. For the derivation step, 12 participants per group were matched on age, chronic hypertension, dyslipidemia, and smoking status. Total RNA was extracted from citrate plasma of each participant, and the relative levels of 372 miRNAs were measured by high-density PCR array. Previously annotated miRNAs with significant fold change and mean circulating level were compared between groups in the entire cohort using never-thawed EDTA plasma. Statistical analyses were descriptive, using t-tests on log transformed biomarker data. We performed logistic regression adjusting for hypertension, modeling each miRNA as a dichotomous variable with the cutoff at the median level. Measurements and analyses were performed blinded to exposure status.

**Results:** The circulating levels of 16 miRNAs were significantly ( $p < 0.05$ ) altered in the PE versus normotensive pregnancy groups. Priority candidates assessed in the validation step were miRNAs linked to angiogenesis (miR-126-3p), inflammation (miR-146a-5p), and cholesterol metabolism (miR-122-5p). Each of these was significantly downregulated among women with prior PE ( $p = 0.021$ ,  $0.017$ , and  $0.013$  respectively), even after adjustment for chronic hypertension.

**Conclusions:** Circulating levels of miR-126-3p, miR-146a-5p and miR-122-5p were significantly downregulated in women with prior PE compared to women with prior normotensive pregnancy at the time of ACS. These findings suggest that these pathways, activated at time of PE, may contribute to premature ischemic heart disease in these women.

**Keywords**

Preeclampsia, microRNA, Acute coronary syndrome

## # 47 - Clinical or Population Health

### **Anticoagulation in Hemodialysis Patients with Atrial Fibrillation: the Effect of Intense Monitoring on Time in Therapeutic Range**

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**Background:** Warfarin is a mainstay therapy in reducing stroke risk in atrial fibrillation. Time in Therapeutic Range (TTR), a measure for anticoagulation intensity and stability, correlates well with bleeding and thromboembolic complications. There is conflicting evidence of benefit versus harm for anticoagulation in hemodialysis patients. This may be explained by suboptimal TTR. Our objective is to compare nephrologist-led management of warfarin therapy, in terms of TTR and frequency of INR testing, to that led by specialized anticoagulation clinic.

**Methods:** This is a retrospective cohort study of chronic hemodialysis patients between January 2015 and November 2016 in two institutions. We identified patients with atrial fibrillation, and receiving warfarin for thromboembolic prophylaxis. A maximum of 1-year of non-hospitalized INR data was used to calculate TTR based on Rosendaal method and Fraction in Range. The mean TTRs, proportion of patients achieving TTR  $\geq 60\%$ , and frequency of INR testing were compared between both institutions, using logistic regression model.

**Results:** In Institution A, 57 out of 341 hemodialysis patients (16.7%) had a history of atrial fibrillation, of whom 21 (36.8%) were on warfarin. In Institution B, 54 out of 300 hemodialysis patients (18%) had a history of atrial fibrillation, and 30 (55.5%) were on warfarin. The mean TTR was 61.8% (SD 14.5) in Institution A, and 60.5% (SD 15.8) in Institution B (p-value 0.95). However, the proportion of patients achieving TTR  $\geq 60\%$  was 65% versus 43.3% (Adjusted OR 2.22, CI 0.65 - 7.63) and mean frequency of INR testing was every 6 days versus every 13.9 days in Institutions A and B respectively.

**Conclusions:** There was no statistical difference of mean TTR between nephrologist-led management of warfarin to that of clinic-led management. However, the former achieved a trend of higher proportion of patients with optimal TTR associated with more frequent monitoring.

**Keywords**

Atrial fibrillation, Hemodialysis, Warfarin, Time in therapeutic range

## **# 48 - Clinical or Population Health**

### **Patterns of long-term use of non-vitamin K antagonist oral anticoagulants for non-valvular atrial fibrillation: Quebec observational study**

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**Background:** Patients with non-valvular atrial fibrillation (NVAF) using non-vitamin K antagonist oral anticoagulants (NOACs) show an increased treatment persistence compared with patients using vitamin K antagonists (VKAs) during the first year. This study evaluated long-term persistence in NOAC and VKA users.

**Methods:** This population-based cohort study used the computerized databases of the Canadian Province of Quebec's health insurance. Patients with a first NVAF diagnosis and newly treated with oral anticoagulants from January 2011 until December 2014 were included. Using a Cox proportional hazards model adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of discontinuation (end of persistence) for NOACs relative to VKAs were estimated. Thromboembolic risk was assessed with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (congestive heart failure, arterial hypertension, age  $\geq 75$  [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65-74, sex category: female).

**Results:** Of the 62,867 newly diagnosed NVAF patients, 17,685 initiated VKAs and 14,746 NOACs. Among the 17,685 VKA initiators, 4,761 switched to NOACs during follow-up. After 3 years, treatment persistence was 54% with NOACs and 25% with VKAs. The HR of treatment discontinuation of NOACs relative to VKAs was 0.45 (95% CI 0.44-0.47). Factors mostly accounting for this difference were age  $\geq 80$  years (HR 0.47, 95% CI 0.40-0.55), high thromboembolic risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 8$ : HR 0.58, 95% CI 0.41-0.82), and prior ischemic stroke (HR 0.86, 95% CI 0.80-0.92).

**Conclusion:** Patients on NOACs showed a higher treatment persistence than patients on VKAs after 3 years. Older age and high thromboembolic risk were the factors with the strongest association.

**Keywords**

NOAC, Direct oral anticoagulants, Treatment persistence

## **# 49 - Clinical or Population Health**

### **Incremental prognostic value of echocardiography to predict mortality in octogenarians in a tertiary care heart failure clinic**

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**Background:** The echocardiogram contributes valuable prognostic information in patients with chronic heart failure, however, only left ventricular ejection fraction is included in existing risk scores. We sought to determine the incremental value of echocardiographic variables to the Seattle Heart Failure Model (SHFM). In particular, we focused on octogenarians who are under-represented in heart failure imaging studies.

**Methods and results:** We conducted a retrospectively cohort study of 142 patients aged 80 years and above attending a specialized heart failure clinic at a single center from 2010-2013. We reviewed the electronic heart records to collect clinical data and calculate the SHFM-based mean life expectancy using validated equations. We retrieved digital echocardiograms to measure a comprehensive panel of variables encompassing left and right ventricular size, systolic and diastolic function. The primary outcome was all-cause mortality over a mean follow-up of  $3.2 \pm 1.9$  years. The mean age of the population was  $85 \pm 3.9$  years, 63% were male and 54% had ischemic cardiomyopathy. In our multivariable Cox regression model adjusted for SHFM, systolic pulmonary arterial pressure (SPAP) was found to be an independent and additive predictor of mortality with a HR of 1.79 (95% CI 0.95-3.28) for SPAP 40-49 mmHg and 2.11 (95% CI 1.21-3.7) for SPAP  $\geq 50$  mmHg. Patients with higher SPAP were more likely to have chronic obstructive pulmonary disease, right ventricular dysfunction, and higher daily doses of furosemide. After adding the echocardiographic variables to the SHFM, the C-statistic improved from 0.716 to 0.761 indicating a meaningful gain in model discrimination.

**Conclusion:** Pulmonary hypertension as measured by echocardiography is predictive of mortality in octogenarians with chronic heart failure, and adds incremental prognostic value to the SHFM.

**Keywords**

Chronic heart failure, Echocardiography, Octogenarians, Mortality prediction

## **# 50 - Clinical or Population Health**

### **Sex Differences in the Adipokine, Lipid, and Immune Profiles of Men and Women with Severe Carotid Atherosclerosis**

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**Introduction:** Sex differences in plaque morphology and composition exist; men develop more unstable plaques than women. Yet, stroke kills more women than men. Despite these differences, no sex-specific guidelines for carotid disease management exist. Thus, circulating markers that reflect sex-specific features in the plaque should be explored for better prediction of stroke risk. Herein we investigated differences in the adipokine, lipid, and immune profiles of men and women with severe carotid atherosclerosis.

**Methods:** Consecutive subjects with  $\geq 50\%$  carotid stenosis scheduled for a carotid endarterectomy (CEA) were recruited from McGill-affiliated hospitals. Pre-operative plasma adipokine levels (adiponectin, leptin, chemerin, and resistin) were measured using ELISA. Using sera samples, lipid profiling was performed, and the levels of various cytokines, chemokines, angiogenesis, and vascular injury markers were measured (Human Biomarker 40-Plex Kit). Sex-hormone analyses are ongoing. Stability of carotid plaque specimens was assessed by two gold standard histological classifications.

**Results:** In our growing database ( $n=342$ ) there were twice as many men who underwent a CEA compared to women (68 vs. 32%). Men had more unstable plaques than women ( $P<0.001$ ), exhibiting greater plaque hemorrhage ( $P=0.014$ ), less fibrous tissue ( $P<0.001$ ), larger lipid core size ( $P<0.001$ ), greater number of foam cells ( $P=0.020$ ) and inflammatory cells ( $P<0.001$ ), and greater cap infiltration ( $P<0.001$ ). Despite having less vulnerable plaques, women had more severe (80-99%) plaque stenosis than men (75.8 vs. 69.1%). Interestingly, men and women shared a similar percentage of ruptured plaques ( $P>0.05$ ). However, more men suffered a stroke than women (41.1 vs. 32.5%), while more women suffered a transient ischemic attack (48.8 vs. 41.1%). A greater percentage of men had a history of coronary artery disease (44.1 vs. 33.0%,  $P=0.060$ ), despite no other differences in demographics, medical history, medication use, and lifestyle habits. Total and globular adiponectin, an anti-inflammatory adipokine, and leptin levels were significantly higher in women than men. Increasing adiponectin levels were correlated with increased total cholesterol, high-density lipoprotein cholesterol, and ApoA1 levels ( $P<0.01$ ), which were also higher in women than men ( $P<0.001$ ). In contrast, men had significantly higher levels of pro-inflammatory cytokines and chemokines, IL-6 ( $P=0.039$ ), TNF- $\alpha$  ( $P=0.005$ ), MIP1- $\alpha$  ( $P=0.009$ ), and sVCAM-1 ( $P=0.031$ ), and a greater percentage of monocyte to white blood cell counts.

**Conclusion:** Women exhibit more favourable adipokine, lipid, and immune profiles compared to men, which may explain the lower instability grade in their carotid atherosclerotic plaques.

**Keywords**

Sex differences, Plaque instability, Adipokines, Lipids, Immune profile

## # 51 - Basic Science

### **Electrochemical corrosion study of Nanostructured Bioresorbable Medical Stent Implants fabricated by Plasma-Based Physical Vapor Deposition**

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Iron (Fe) based alloys are attractive materials for bioresorbable applications. However, their degradation rate is too slow, possibly leading to complications. In an attempt to increase the degradation rate of Fe while improving its mechanical properties we propose the fabrication of iron/stainless steel (Fe-SS) nanostructured stents through Plasma-Based Physical Vapor Deposition (PVD). It is hypothesized that the intermixed grains of Fe-SS will lead to higher bioresorption rates through a galvanic effect. This work presents an electrochemical corrosion study showing that the mixture of Fe-SS leads to higher degradation rates compared to bare Fe and SS samples. The Fe-SS intermixed particulate material was produced through an industrial PVD deposition system (IonBond PVD-350) with a continuous current arc discharge (50 A) under controlled vacuum ( $1 \times 10^{-2}$  Torr) and bias conditions (-150 V). The morphology of the samples was observed with a transmission electron microscope (TF20 200 kV TEM) showing the presence of particles from 2 to 50 nm. Immersion experiments were performed in Hank's solution with an initial pH of 7.4 and a temperature of 37 °C for a time period of 1 h. The corrosion behaviour of plasma-prepared Fe-SS (ratio of 1:1), Fe, SS and non-treated SS (control) samples was investigated by open circuit potential (OCP), potentiodynamic polarization (PP) and electrochemical impedance spectroscopy (EIS) using a potentiostat/galvanostat (Autolab PGSTAT30). PP measurements were performed in the potential range from -300 mV to 400 mV with respect to OCP at a scan rate of 1 mV/s. EIS measurements were performed at OCP potential with AC amplitude of 10 mV over a frequency range from 10 mHz to 100 kHz. All measurements were done by duplicates. OCP results show a more negative corrosion potential and thus higher corrosion susceptibility for the Fe-SS samples. The higher corrosion susceptibility of Fe-SS samples could be confirmed by PP and EIS measurements, showing a decreasing corrosion resistance in the order SS>Fe>Fe-SS.

**Conclusion.** Electrochemical tests showed faster degradation rates on coatings where Fe and SS are combined, compared to Fe, SS and plasma-deposited SS coatings. A tuned ratio of Fe and SS can form a galvanic couple allowing for an 'optimal' degradation rate and thus paving the path for bioresorbable stents with tailored dissolution rates. Future work involves testing different ratios of Fe-SS mixture with their corresponding mechanical and cytotoxicity tests.

**Keywords**

Medical Stent Implants, Bioresorbable stents, Electrochemical corrosion, Plasma-Based Physical Vapor Deposition, Iron based stents



## # 52 - Basic Science

### **Comparison study of the quantitative and semi-quantitative analysis of pathological features of carotid atherosclerotic plaque instability**

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**Background:** Atherosclerosis and its thrombotic complications are a major cause of morbidity and mortality worldwide. Plaque instability and rupture is an important causative factor of these complications. To estimate plaque instability level, Lovett et al has proposed a histological classification that ranges from definitely stable to definitely unstable plaques based on semi-quantitative assessment of 10 plaque pathological features. Although this method represents the gold-standard for assessing plaque stability, semi-quantitative analysis can be subject to variability, and therefore not always sufficiently reliable as quantitative data. Thus, herein, we aimed to develop a method to quantitatively measure plaque pathological features and validate it with established semi-quantitative results.

**Methods:** Carotid surgical specimens were obtained from patients who underwent carotid endarterectomy (CEA). The atherosclerotic specimens were processed and embedded in paraffin. Sections were taken from the site of maximum stenosis, and stained with hematoxylin & eosin, smooth muscle cell actin, CD68 (for macrophages), and CD3 (for lymphocytes). Plaque features and stability were assessed by two vascular pathologists following Lovett's semi-quantitative classification. Whole plaque specimen sections were scanned digitally. Pathological characteristics listed in the semi-quantitative classification were quantitatively measured using ImagePro Primer software. The quantitative image analysis results were analyzed and compared with the semi-quantitative pathological scores.

**Results:** The quantitative results of major pathologic features are significantly different between stable and unstable plaques and they are in accordance with the semi-quantitative analysis, performed by the pathologists. The quantitative results show that fibrous tissue occupies a major part of stable plaques (35-45%), while the lipid core occupies a large part of unstable plaques (40-47%). Furthermore, inflammatory cell infiltration is much greater in unstable plaques ( $P < 0.01$ ). On the other hand, plaque calcification, neovascularization, and hemorrhage have no obvious differences between stable and unstable plaques.

**Conclusions:** Our results demonstrate that quantitative image analysis can provide new insight into plaque morphology and composition: 1) the amount of fibrosis, necrotic core, fibrous cap, and inflammatory cell infiltration are major decisive factors of plaque instability; 2) Calcification, neovascularization, and hemorrhage are not closely related with plaque instability. Furthermore, quantitative image analysis of plaque features is a promising method for accurate classification of plaque instability. This new quantitative method needs to be externally validated in a larger subset of CEA plaques in order to be used in future clinical practice for plaque instability classification.

**Keywords**

Atherosclerosis, Pathology, Plaque instability, Quantitative study

## **# 53 - Clinical or Population Health**

### **Risk of Cardiovascular Events among Patients Receiving Androgen Deprivation Therapy for Prostate Cancer**

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**Introduction:** Prostate Cancer (PC) is the most common cancer and the 3rd leading cause of death from cancer among Canadian men. Androgen Deprivation Therapy (ADT) is the first-line treatment for PC. The relationship between ADT and cardiovascular disease remains controversial. This population-based study aims to investigate the relationship between ADT and cardiovascular events.

**Methods:** The administrative, computerized health insurance databases of Québec constitute the primary data source. We are conducting a retrospective cohort study within a provincial linked database of patients with prostate cancer (ICD-9 and 10 codes: 185 and C61) between 2000 and 2011. Patients are stratified according to ADT use. The primary outcome is Myocardial Infarction (MI) or death due to MI. Cox proportional hazard models analyses will be performed.

**Results:** We have identified 7288 patients with prostate cancer within this database. These patients will be stratified based on ADT use. Each patient will be individually tracked for the study duration period to identify those who had subsequently received a diagnosis of MI or had died due to MI. We will then estimate the incidence rate of MI or death due to MI per 100 person-years over a mean time to event/censoring for the study group (ADT) as compared to the comparison cohort. In a Cox proportional hazard model, we will be adjusting for age (continuous and categories), gender, prior history of stroke/TIA, diabetes, dyslipidemia, atrial fibrillation, chronic kidney disease (CKD), heart failure (CHF) and hypertension (HTN), to identify whether ADT use was associated with an increase in the subsequent development of MI or death due to MI. These results will be presented in the research day.

**Conclusion:** In this large observational study, we aim to identify the association of ADT therapy with a possible increase in MI or death due to MI in a population of patients with prostate cancer. \*\* The results will be ready for presentation on April 27th. \*\*

**Keywords**

Prostate cancer, Myocardial infarction, Androgen deprivation therapy, Cardiovascular event

## # 54 - Clinical or Population Health

### **Statin Use and Risk of Vascular Events among Cancer Patients after Radiotherapy to the Thorax, Head and Neck**

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**Aims:** Radiation-induced atherosclerosis (RIA) independently increases the risk for cardiovascular and cerebrovascular events. In the general population, Statins are associated with a reduction in vascular events. There are no studies exploring whether Statins diminish vascular complications in cancer patients post radiotherapy (RT) to the thorax, head and neck. Thus, this study examines whether Statins are protective after radiotherapy (RT).

**Methods and results:** We conducted a retrospective cohort study within a provincial linked database of 6843 elderly cardiac patients with thorax and head or neck cancer having undergone RT between 2000 and 2011. Two thousands and twelve patients were identified as non-Statin users and 4741 as Statin users. The primary outcome of interest was the composite of cerebrovascular (stroke, transient ischemic attack (TIA), death due to stroke) or cardiovascular events (myocardial infarction (MI) or death due to MI). Time-dependent Cox proportional hazard analyses were performed. The crude event rate was 20.1% for non-users and 11.9% for Statin-users (Hazard Ratio (HR) of 0.59 (95% CI 0.52-0.67,  $p < 0.0001$ )), over a mean time to event/censoring of  $493 \pm 677$  days for non-users and  $601 \pm 724$  days for the Statin-users. After adjusting for age (continuous and categorical), gender, prior history of stroke/TIA or MI, diabetes, dyslipidemia, atrial fibrillation, chronic kidney disease (CKD), heart failure (CHF) and hypertension (HTN), Statin use at the time of the RT on a time-dependent analysis was associated with a 29% relative risk reduction in the subsequent stroke, MI and death due to MI or stroke (HR= 0.71 95% CI 0.62-0.82,  $p < 0.0001$ ).

**Conclusion:** In this large observational study, Statin use post radiation therapy was associated with a 29% reduction in cardiovascular and cerebrovascular events.

**Keywords**

Statin, Radiotherapy, Cancer, Myocardial infarction, Stroke

## # 55 - Basic Science

### **Lipoprotein (a) induces human aortic valve interstitial cell calcification**

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**Objective:** The purpose of this study was to determine the effects of Lipoprotein (a) on human aortic valve interstitial cell (HAVICs) calcification. **BACKGROUND:** Aortic valve calcification afflicts a significant percentage of our elderly population and younger subjects with familial hypercholesterolemia. Recent genetic studies demonstrated an association between aortic valve calcification and lipoprotein (a).

**Methods:** We examined the effects of Lipoprotein (a) on proliferation, apoptosis and mineralization of HAVICs, and the mechanism involved. We also determined the expression of LPA gene in diseased human aortic valves and HAVICs. Immunohistochemistry with antiserum to Lipoprotein (a) and E06 antibody was used to determine the cellular localization of Lipoprotein (a) and oxidized phospholipids in diseased aortic valves.

**Results:** Lipoprotein (a) significantly increased alkaline phosphatase activity, release of phosphate, calcium deposition, hydroxyapatite, cell apoptosis, matrix vesicle formation, phosphorylation of signal transduction proteins such as MAPK38, MSK2, MKK3/6 and GSK3 $\beta$ , increased expression of chondro-osteogenic mediators and decreased SOX9 and matrix gla protein ( $P<0.001$ ). Inhibition of MAPK38 and GSK3 $\beta$  significantly reduced Lipoprotein (a)-induced calcification of HAVICs ( $P<0.001$ ). RT-PCR and western blot revealed the presence of LPA mRNA and protein in calcified aortic valves and HAVICs. There was abundant presence of Lipoprotein (a) and E06 immunoreactivity in diseased human aortic valves. Immunostaining for Lp(a) and E06 correlated with the presence of lipids and calcification ( $P<0.05$ ).

**Keywords**

Stenosis, Oxidized phospholipids, Real-Time-PCR, Raman spectroscopy

## # 56 - Clinical or Population Health

### **Sex differences in the circulating and carotid atherosclerotic plaque expression of resistin, chemerin, and chemerin's receptor in association with plaque instability**

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**Background:** Stroke remains a leading cause of death annually, killing more women than men. Despite established sex-differences in plaque composition, there is a lack of sex-specific guidelines for carotid endarterectomy (CEA). The degree of carotid stenosis, which is used as the sole indication for CEA candidacy, is limited in its assessment of plaque stability. Thus, identifying potential sex-specific markers or mechanisms involved in plaque instability is crucial. Herein, we investigated sex differences in the relationship between carotid plaque instability and the expression of proinflammatory adipokines resistin, chemerin, and its receptor, ChemR23.

**Method:** Clinical information and blood samples were collected preoperatively from subjects undergoing CEA at McGill-affiliated hospitals. Circulating chemerin and resistin were measured using ELISA. Plaque instability was assessed by vascular pathologists according to two gold standard histological classifications. Resistin, chemerin and ChemR23 were stained on plaques by immunohistochemistry. Digital quantification of the level of resistin, chemerin, and ChemR23 staining was performed using Image-Pro Premier. The percentage of positively stained macrophages/foam cells and their intensity of staining for resistin, chemerin, and ChemR23 was determined using semi-quantitative scales. mRNA expression was assessed by RT-qPCR.

**Results:** Circulating resistin was reduced in subjects (n=94) with unstable vs. stable plaques and correlated with stroke in men only (P=0.015). Plaque resistin expression in terms of percent area stained (P=0.026), total area stained (P=0.050), intensity of staining on macrophages/foam cells (P=0.002), and the percentage of macrophages/foam cells stained (P<0.001) was greater in unstable plaques. However, these associations remained significant in men only (P<0.05). Similarly, greater plaque instability was associated with increased percent area of chemerin staining (P=0.040), and more intense chemerin (P<0.001) and ChemR23 (P=0.013) staining on macrophages/foam cells, strictly in men. In contrast, the mRNA expression of resistin was significantly decreased in unstable plaques only in women (P=0.037). Increased resistin staining was associated with more unstable plaque features (highly present in men's plaques), including greater plaque haemorrhage (P=0.022), lipid core size (P<0.001), plaque inflammation (P=0.007), cap infiltration (P=0.006), and foam cell presence (P<0.05).

**Conclusion:** We are the first to identify a direct relationship between carotid plaque instability and plaque expression of resistin, chemerin, and ChemR23, specifically in men. Whether a sex-dependant mechanism regulated by resistin and chemerin is implicated in the progression of atherosclerotic plaque instability remains to be examined in our future studies.

**Keywords**

Stroke, Adipokine, Sex differences, Plaque instability, Resistin, Chemerin, Chemerin receptor

## **# 57 - Clinical or Population Health**

### **Extracellular Volume Imaging by Magnetic Resonance Imaging Post Mediastinal Radiotherapy in Survivors of Hodgkin's Lymphoma**

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**Background:** Radiotherapy (RT) for Hodgkin's lymphoma often involves incidental exposure of the cardiovascular system to ionizing radiation causing myocardial fibrosis. Novel quantitative imaging of extracellular volume fraction (ECV) may be able to detect subtle abnormalities such as diffuse fibrosis not visible on delayed hyper-enhancement imaging. **OBJECTIVE:** We aimed to determine whether the myocardial extracellular volume (ECV), measured using T1 measurements obtained during cardiac magnetic resonance (CMR) imaging were increased in patients treated with mediastinal radiation therapy for Hodgkin's lymphoma.

**Methods:** This was a prospective pilot study. Cardiac magnetic resonance imaging was performed in 10 patients treated with radiotherapy with T1 mapping before and after injection of gadolinium contrast. **RESULTS:** The radiation-treated cohort consisted of 5 males and 5 females with a mean age of  $38 \pm 10$  years, presenting at a median of 173 months after radiotherapy with a mean left ventricular ejection fraction of  $62 \pm 7\%$ . The indexed LV mass was  $60 \pm 7$  g/m<sup>2</sup>, native T1 for myocardium was  $1245 \pm 66$  msec, and the ECV was  $(0.25 \pm 0.01)$ . As compared to the values in healthy volunteers who were not part of this cohort, these values were not significantly different.

**Conclusion:** In this small pilot study, radiotherapy was not associated with an increase in ECV values as compared to healthy individuals. It is possible that novel radiation techniques such as image-guided radiation therapy and 4-dimensional image planning have reduced radiation exposure to the heart. Further research and larger-scale studies are still needed to validate these findings and to evaluate the effect of these advanced RT techniques on the cardiovascular system.

#### **Keywords**

Hodgkin's Lymphoma, Magnetic Resonance Imaging, Extracellular Volume Imaging, Mediastinal Radiotherapy, Cardiac

## # 58 - Basic Science

### **Bisphenol and phthalate escape from medical devices used in cardiac surgery and impact on mice after a myocardial infarction.**

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The extent and consequences of patient exposure to bisphenols and phthalates escaping from the medical devices used in coronary bypass grafting surgery (CABG) is unknown. Most medical devices including perfusion pumps, catheters and IVs have plastic parts. Flexible medical tubing can contain phthalates; hard polycarbonate plastics are polymers of bisphenol monomers. Yet, no one has identified comprehensively which and how much of these chemicals escape into patients or considered whether increased exposure contributes to poor wound healing. Here, we hypothesized that substantial amounts of bisphenols and phthalates escape from medical devices and that mice exposed to bisphenols and phthalates after an MI will recover poorly. First, we sought to identify and quantify the metabolites of 6 bisphenols and 10 phthalates present in patient urine before and 12 hours after cardiac surgery. Secondly, we exposed mice to vehicle and patient-reflective mixtures after surgery to create an infarct and examined the impact on recovery. Men, n=9, had similar urine levels of 6 bisphenols and 10 phthalates as men in the Canadian Health Measures Survey before surgery suggesting no difference in initial exposure. An average fold-increase in BPA (12.6), BBzP (4000), DEHP (1400), DIDP (86), DnBP (77) and DMP (2.0) was detected after cardiac surgery. No correlation could be found between individual exposures and the time spent on the cardiopulmonary pump or with the total number of transfusions. Thus, the main source of the leaching has yet to be identified. Male C57bl/6n mice were orally treated during the first 3 days of recovery post-MI with the human equivalent doses of BPA in the drinking water and injected with a mix of the phthalates detected in patients. When compared with control, all treated mice had greater cardiac dilation and reduced cardiac function. Also, exposed mice had increased infiltration of MerTK+ macrophages, Ly6chigh and Ly6c low monocytes and neutrophils. The increased infiltration correlates with increased monocyte chemoattractant chemokine CCL2 in the infarct homogenates. We conclude 1) that there is substantial leaching of multiple phthalates and BPA from medical devices within 12 hours of surgery and 2) mice which were exposed during recovery from a cardiac surgery were unable to heal normally.

Keywords

Medical devices, Myocardial infarction, Bisphenols and phthalates, Inflammation

## # 60 - Clinical or Population Health

### **Rare Genetic Variants are Significantly Associated with Aortic Stenosis**

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**Background:** Aortic stenosis causes calcification and narrowing of the aortic valve, and affects roughly 12.4% of the elderly population. Previous genome-wide association studies have shown that the lipoprotein(a) (LPA) gene is associated with aortic stenosis. Genome-wide association is a valuable tool, but it overlooks the contribution of rare variants to disease phenotypes. In this work, we assess the contribution of rare variants to aortic stenosis both in previously identified candidate genes and on a genome wide basis to better understand disease pathways and gain insight into the biology of this disease.

**Methods:** Using genome-wide genotyping data from a large cohort living in the United States (N = 44703, 50.6% female) 16,074,082 SNPs were imputed using the 1,000 Genomes (1kG) reference panel. Chromosome 6, which contains the LPA gene, was re-imputed to a denser reference panel (Haplotype Reference Consortium (HRC)) to capture additional rare variants. We then compared the results of gene burden tests on both the HRC and 1kG imputed sets for the LPA locus to highlight the importance of considering very rare variants when assessing genetic risk. We have considered the differences in genetic risk contribution conferred by amino acid changes versus other rare variants. We will apply gene burden testing genome wide to assess if rare variants in other genes contribute to aortic stenosis risk.

**Results:** The results of the Sequence Kernel Association Test (SKAT) in the software package rvtests on the HRC imputed LPA gene show a significant contribution of rare variants ( $p < .03$ ), however the same test on the 1kG imputed set does not show a significant contribution ( $p > .19$ ). Another gene that almost achieved genome-wide significance in prior analyses using common variants showed a significant contribution of rare variants in the 1kG imputed set ( $p < .0005$ ). Genome-wide rare variant analysis is currently underway.

**Conclusion:** We have demonstrated the importance of very rare variants in the genetic architecture of aortic stenosis and identified a higher burden of such variants in a novel locus.

**Keywords**

Aortic stenosis, Genetic epidemiology, Rare variant analysis, Gene burden testing



## # 62 - Clinical or Population Health

### Dietary Calcium Intake and Vascular Health: How are they related?

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**Introduction:** Calcium intake, recommended for osteoporosis prevention has been reported to be associated with cardiovascular (CV) outcomes. We examined the association of dietary calcium intake (dCa) with surrogate CV markers, including carotid intima-media thickness (cIMT), arterial stiffness and hemodynamics in healthy postmenopausal women.

**Methods:** Healthy postmenopausal women without any CV risk factors, participating in a randomized controlled trial studying the effect of calcium supplementation vs. dietary calcium on vascular health, were recruited. Cross-sectional analyses of baseline data of the participants are presented. Peripheral systolic and diastolic blood pressures (pSBP, pDBP) were measured by BpTRU device. cIMT of both common-carotid arteries was measured by B-mode ultrasonography (Philips-iU22). Arterial stiffness (carotid-to-femoral pulse wave velocity [cfPWV] and carotid-to-radial pulse wave velocity), central SBP and DBP (cSBP, cDBP), mean arterial pressure (MAP), and hemodynamic parameters (pulse pressure, augmentation pressure, augmentation index corrected for 75 bpm) were obtained non-invasively by applanation tonometry (SphygmoCor). Usual dCa intake of the previous month was estimated using a validated food frequency questionnaire. Measurements were compared across groups of <600, 600-1000 and >1000 mg/day of dCa by one-way analysis of variance (ANOVA) and covariance (ANCOVA).

**Results:** Ninety-seven postmenopausal women have participated in the study so far. Analysis of 88 participants (mean age 60.5±6.4 years; body mass index 25.6±3.9 kg/m<sup>2</sup>; and mean dCa 882±357 mg/day) were performed. A significant inverse association between history of smoking and calcium intake was noted. The average intake of vitD from diet was significantly higher in >1000 mg/d dietary calcium intake group in comparison to <600 mg/d and 600-1000 mg/d intake groups. In unadjusted as well as adjusted analysis, no association of dietary calcium intake and vascular parameters including cIMT and cfPWV was noted.

**Conclusion:** The preliminary results suggest that dietary calcium intake is not associated with vascular parameters in healthy postmenopausal women. Our ongoing study including a larger sample-size will allow for better evaluation of the effect of calcium intake on vascular health.

**Keywords**

Dietary calcium intake, Dietary vitamin D intake, Arterial stiffness, Carotid intima-media thickness, Peripheral blood pressure, Central blood pressure, Cardiovascular outcomes

## # 63 - Clinical or Population Health

### **A Preliminary Analysis of Statin Therapy in Rheumatoid Arthritis: Improved Arterial Stiffness In Women But Not In Men**

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**Objectives:** Patients with rheumatoid arthritis are at increased risk for cardiovascular disease. Statin therapy has demonstrated anti-inflammatory and immunomodulatory effects, thereby reducing cardiovascular risk. Arterial stiffness is a composite indicator of cardiovascular health and a predictor of cardiovascular risk. We assessed the effect of statin therapy on arterial stiffness and hemodynamics in subjects with rheumatoid arthritis.

**Methods:** A prospective cohort study including adults with rheumatoid arthritis and an indication for statin therapy (cases) or not (controls) is being conducted. Peripheral systolic and diastolic blood pressures were measured as recommended by Hypertension Canada (BpTRU, Coquitlam, Canada). Arterial stiffness (carotid-to-femoral pulse wave velocity [cfPWV] and carotid-to-radial PWV), central systolic and diastolic blood pressures, mean arterial pressure, and augmentation index corrected for 75 bpm were obtained non-invasively (SphygmoCor, AtCor, Australia). All measurements were performed prior to statin initiation and at 6-month post-treatment or upon reaching lipid level target (which ever came last). Independent t-tests evaluated differences in changes between groups. Carotid intima-media thickness (cIMT) measurements were also performed.

**Results:** To date, 14 subjects (mean age 61.4±9.5 years, 9 females), have completed the study. All cases achieved recommended lipid level targets. Beyond lipid levels, there were no statistical differences in patient characteristics at baseline or at 6-months between cases and controls. In sex-specific analyses, statin therapy was associated with a significant decrease in cfPWV in women taking statin therapy compared to women of the control group (-0.71±0.18 m/s vs +0.96±1.13 m/s, respectively; p<0.05), which was not observed in men. No other associations were observed.

**Conclusion:** Our preliminary results suggest that in women with rheumatoid arthritis, statin therapy may reduce cfPWV, a predictive marker of cardiovascular disease and events, which was not observed in men. Whether sex differences in the effect of statin on arterial stiffness are sustained with a larger sample size of rheumatoid arthritis patients will be addressed in our ongoing study.

**Keywords**

Rheumatoid arthritis, Statin therapy, Vascular health, Arterial stiffness, Carotid intima-media thickness, Pulse wave velocity

## # 64 - Clinical or Population Health

### **Shared Genetic Etiology of Aortic Stenosis and Coronary Artery Disease revealed by GWAS Data**

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**Background:** Aortic stenosis (AS) and coronary artery disease (CAD) share a number of risk factors, including Body Mass Index (BMI), hypertension, lipoprotein(a) levels, high blood pressure, diabetes, and low density lipoprotein cholesterol (LDL-C) levels. Recent genome-wide association studies (GWAS) have shed light on the genetic etiology of these diseases as well as a plethora of others. This accumulation of GWAS data has allowed for the development of methods that compare the genetic etiology of diseases. One approach, Linkage Disequilibrium (LD) Regression Scores, compares the total SNP heritability of any pair of diseases. Another method, Cross-Phenotype Analysis of GWAS (CPAG), examines the overlap of specific highly significant SNPs for multiple diseases or risk factors.

**Methods:** We analyzed > 16 million SNPs from a genome-wide association study (GWAS) for AS and CAD in a European-ancestry cohort from the United States (n = 44,703). We calculated LD regression scores for both diseases against a wide variety of publicly available GWAS results (219 traits total) to assess overlapping heritability. Additionally, we used CPAG to compare each disease to an online catalogue of highly significant GWAS results. We then compared the results for both diseases.

**Results:** LD regression tests demonstrated that the genetic etiology of AS is significantly shared with BMI (and other similar anthropomorphic traits), LDL-C, and mono-unsaturated fatty acids. The LD tests found that BMI was most significantly correlated with AS (P-value of 0.0005 for genetic correlation). Both total cholesterol and LDL were significant at P=0.0074 and P=0.0081 respectively. In addition we find that AS and mono-unsaturated fatty acids are also significant at P=0.021. The CPAG for AS SNPs, using a p-value cut point of 1e-6, demonstrated that multiple known risk factors for AS have overlapping SNPs. These include Lp(a) levels, LDL-C, and mono-unsaturated fatty acids (palmitoleic acid and oleic acid). CPAG results at p-value 1e-6 also show that CAD has a similar constellation of risk factors, but with important distinctions.

**Conclusions:** This is the first large-scale confirmation that AS and CAD have a shared genetic etiology – in general as well as with specific genes. The shared heritability and SNP overlap with specific risk factors demonstrates that these risk factors are causal and not just a correlation. An increased understanding will also come from the risk factors and traits that are not shared between AS and CAD.

**Keywords**

Genetics, SNPs, GWAS, Causality, Risk factors

## # 65 - Clinical or Population Health

### **Dilated Cardiomyopathy Patients with Titin Mutations can Recover Left Ventricular Function with Medical Therapy**

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**Background:** There is a growing evidence of left ventricle (LV) recovery in patients with dilated cardiomyopathy (DCM) including DCM caused by some genetic mutations. Titin (TTN) truncating mutations (TTNtv) are identified in ~27% of DCM patients, accounting for the largest share of genetic etiology. DCM patients with TTNtv have shown LV recovery with left ventricle assist devices (LVAD) including successful explantation of the LVAD, and transplant free survival. Patients with TTNtv associated postpartum cardiomyopathy (PPC) have also shown recovery similar to non-TTNtv PPC. However, little is known about LV recovery in TTN associated DCM with medical therapy alone. We hypothesize that patients with DCM due to a TTNtv mutation can have complete recovery of left ventricle function on medical therapy.

**Method:** We performed a prospective evaluation of patients with non-ischemic DCM who presented with heart failure and established a cohort to evaluate the role of genetic mutations. Patients were followed from time of enrolment till discharge from our clinics and long-term outcomes were also evaluated. A total of 141 patients diagnosed with non-ischemic DCM were evaluated and Next Generation Sequencing was performed to identify TTNtv mutations. The Exome Aggregation Consortium (ExAC) data was used as a “control” population to allow for the identification of novel mutations.

**Results:** The mean age of diagnosis was 53.6 years and 67.4% were male and 31 (22.0%) experienced LV recovery (defined as LVEF > 50%). Ethnicity was mixed: 37 (26.2%) were French Canadian, 72 (51.1%) were other European and 9 (6.4%) were African American. A family history of DCM was reported in 31 (22.0%) of the patients. TTNtv variants were found in 26 patients (20%). Among these 26 patients, 8 (30.8%) had a cardiac transplant and 14 (53.8%) patients had persistent LV dysfunction. However, LV recovery, occurred in 4 (15.4%) patients. In comparison, in patients without a TTNtv mutation, 16 (15.4%) were transplanted, 63 (60.6%) had persistent LV dysfunction, and 25 (24.0%) recovered. These clinical outcomes were not significantly different between the two groups.

**Conclusion:** Patients with TTNtv mutations associated with cardiomyopathy can have complete recovery of their LV function with medical therapy alone. The clinical outcome in these patients can be as favourable as for other DCM patients.

**Keywords**

Exome-sequencing, Genetics, LVEF

## # 66 - Clinical or Population Health

### **Protein Intake in Cardiac Surgery: The PRINCE Pilot Study**

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**Background:** Frailty, a multifactorial syndrome characterized by low muscle mass and strength, is a risk factor for mortality and functional decline after cardiac surgery. A systematic review conducted by our group previously found that nutritional interventions, more specifically protein supplementation, could be used to improve frailty in community-dwelling older adults. Before testing the effectiveness of protein supplementation in cardiac surgery patients, the pre- and post-operative protein intake and deficits must be elucidated.

**Methods:** PRINCE was a prospective pilot study of patients undergoing cardiac surgery at the Jewish General Hospital in 2016-2017. A trained nutritionist directly observed patient's food intake on post-operative days 2-4 to quantify calorie and protein consumption in-hospital, and administered a food frequency questionnaire to determine their usual food intake at home before and 2 months after surgical hospitalization. In addition, research personnel administered questionnaires and physical performance tests to determine the patient's level of frailty, clinical comorbidities, and outcomes. The primary outcome was achieving the recommended daily amount (RDA) of protein, defined as 2 grams per kilogram of body weight (g/kg) during the in-hospital post-operative period and 1.2 g/kg before and after hospitalization.

**Results:** We enrolled 23 patients with a mean age of 72 +/- 13, 62.5% males and 34.8% females. Before surgery, the mean protein consumption was 1.3 g/kg, representing 105.7% of the RDA. During post-operative days 2-4, the mean protein consumption was 0.7 g/kg, representing 53.8% of the RDA and a mean daily deficit of 86 g below RDA. The main barriers for food intake were: low appetite (95.27%), food dislikes 82.6% and nausea 21.7%. Two months after surgery, the mean protein consumption was 1.3 g/kg, representing 109% of the RDA.

**Conclusions:** Patients undergoing cardiac surgery do not meet their recommended protein targets during the critical post-operative period when they are at risk for muscle loss and deconditioning. Further research is underway to supplement the protein deficits identified in this study and thereby reduce hospital length of stay and functional decline.

**Keywords**

Frailty, Protein, Cardiac surgery

## # 67 - Clinical or Population Health

### **Longer-Term Angina-Related Quality of Life Benefits after Percutaneous Coronary Intervention of Chronic Total Occlusions**

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**Background:** Data on the impact of coronary chronic total occlusion (CTO) percutaneous coronary intervention (PCI) on quality of life (QOL) are limited to a few domains of the Seattle Angina Questionnaire (SAQ) or to limited samples. We aimed to evaluate the relationship between CTO PCI and QOL within the full spectrum of the SAQ and assess the impact of a non-fatal major adverse cardiac event (MACE) during follow-up (myocardial infarction, target vessel revascularization or occlusion or recurrent angina) on QOL.

**Methods:** SAQ was administered at baseline and 12 months after CTO PCI. The primary endpoint was the change in SAQ scores. The secondary endpoints were the determination of the impact of a MACE on QOL, and the univariate relationship between post-CABG status, dissection-reentry techniques and CTO complexity (by the J-CTO score) on QOL.

**Results.** A total of 178 patients answered the baseline SAQ and 120 answered both questionnaires. SAQ responders were more likely to be male, stable and had more successful PCI than non-responders at baseline. We observed highly statistically significant improvement ( $p < 0.0001$ ) in physical limitation (mean difference (MD) +27; 95%CI +23 to +32), angina stability (MD +16; 95%CI +10 to +21), angina frequency (MD +27; 95%CI +22 to +32), treatment satisfaction (MD +10; 95%CI +6 to +13), and QOL domains (MD +28; 95%CI +24 to +32). Patients who presented a MACE had significantly worse SAQ scores at one year. Post-CABG patients, dissection-reentry techniques, and high complexity (J-CTO $\geq$ 3) were associated with similar benefits for the vast majority of domains compared to patients with no prior CABG, intra-plaque crossing techniques and simpler CTOs, respectively. In multivariable analysis, procedure success was associated with benefits in physical limitation, angina frequency and QOL domain scores.

**Conclusions:** There is significant improvement in patient's QOL 1 year after CTO PCI compared to pre-procedural state. Patients with higher complexity derive similar benefits as those with less complex CTOs. The presence of clinical event at 1-year follow-up was associated with worse QOL.

**Keywords**

Quality of life, Percutaneous coronary intervention, Chronic total occlusion, Angioplasty

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