University of Western Ontario
Department of Medicine

# RESEARCH DAY

Thursday, May 30, 2013
Best Western Lamplighter Inn
591 Wellington Road South
London, Ontario  N6C 4R3

This program has no commercial support.

## CME INFORMATION

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of The Royal College of Physicians and Surgeons of Canada and approved by Continuing Professional Development, Schulich School of Medicine & Dentistry, Western University (6.75 hours). Each participant should claim only those hours of credit that he/she actually spent participating in the educational program.

Learning Objectives:

- To describe new research findings of relevance to Internal Medicine and related subspecialties.
- To appreciate clinical research conducted by the trainees in the Department of Medicine.
- To appreciate basic research conducted by trainees in the Department of Medicine.

# Department of Medicine Research Day 2013

Thursday May 30, 2013
Best Western Lamplighter Inn
591 Wellington Road South

| Schedule of Events | | |
|---|---|---|
| Start | End | |
| 8:00 | 8:30 | **Breakfast and Poster Setup** *(Crystal Ballroom South)* |
| 8:30 | 8:40 | **Welcome & Opening Remarks** *(Crystal Ballroom North)* |
| 8:40 | 9:20 | Serotoninergic antidepressants and brain hemorrhage **Dr. Dan Hackam** *(Crystal Ballroom North)* |
| 9:20 | 10:00 | The Academic Health Sciences Centre: Still the academic playground of choice **Dr. David Hill** *(Crystal Ballroom North)* |
| 10:00 | 11:00 | **BREAK** **Poster Presentation and Judging** *(Crystal Ballroom South)* |
| 11:00 | 11:45 | ICES@Western **Keynote Speaker: Dr. Amit Garg** *(Crystal Ballroom North)* |
| 11:45 | 13:45 | **LUNCH** **Poster Presentation and Judging** *(Crystal Ballroom South)* |
| **Afternoon Session – Highlight Research by Department of Medicine Trainees** | | |
| 14:00 | 15:00 | **Trainee Oral Presentations** *(Crystal Ballroom North)* |
| 15:00 | 15:15 | **REFRESHMENT BREAK** *(Atrium)* |
| 15:15 | 16:15 | **Trainee Oral Presentations** *(Crystal Ballroom North)* |
| 16:30 | 16:45 | **Presentation of Awards & Final Remarks** *(Crystal Ballroom North)* |

*Please ensure that you fill out the evaluation form provided in your Research Day package before you leave for the day and drop it in the box at the Registration Desk on your way out.*

# Poster Presentations

| Poster # | Presenter | Program | Abstract Title |
|---|---|---|---|
| 1 | Saleh Alghofaili | PGY-2 | A single nucleotide polymorphism at the 9p21.3 cardiovascular risk locus is associated with a very high risk of coronary artery disease in patients with a positive family history |
| 2 | Alyse Goldberg | PGY-3 | Ciprofloxacin and rifampin have opposite effects on levothyroxine absorption |
| 3 | Emily Brennan | PGY-2 | Tolerability and efficacy of differing lipid-lowering management strategies in patients with a history of statin-related myopathy |
| 4 | Majed Malak | PGY-2 | Ultrasound guidance for vascular access in patients undergoing coronary angiography via the transradial approach: A prospective clinical study. |
| 5 | Hatem Salim | PGY-2 | Effect of Education and Performance Feedback on Reducing Inappropriate Urinary Catheter Use in Medicine In-patients |
| 6 | Bourke TIllmann | PGY-3 | Listening to the warning: Does delay in activation of critical care outreach teams impact patient care? |
| 7 | Paul Barnfield | PGY-2 | Characterization of a stable gene set in Ovarian Cancer |
| 8 | Mahmoud Bokhari | PGY-2 | QT Intervals in Ventricular Paced Rhythms |
| 9 | Amna Ahmed | PGY-2 | Prognostic Significance of elevated Troponin T in acutely hospitalized CTU patients without a primary cardiac diagnosis. |
| 10 | Justin Chan | MSc Student | Hair Cortisol over Testosterone Ratio Predicts Hospitalization in Patients with Systolic Heart Failure |
| 11 | Sali M.K. Farhan | MSc Student | Exome sequencing identifies NFS1 deficiency in a novel Fe-S cluster disease, infantile mitochondrial complex II/III deficiency |
| 12 | Jameel Abdulrehman | PGY-2 | Impact of Thrombophilia Screening on Venous Thromboembolism Management Practices |
| 13 | Chrysi Bogiatzi | MSc Student | Secular Trends in Ischemic Stroke Subtypes |
| 14 | Rebecca Jarvis | PGY-2 | Development of a multiple-choice question examination to assess interpretation of the clinical examination |

| Poster # | Presenter | Program | Abstract Title |
|---|---|---|---|
| 15 | Ahraaz Wyne | PGY-3 | Inadequate Pain Control in End Stage Renal Disease (ESRD) |
| 16 | Dong Zheng | PhD Student | Cardiac-specific over-expression of calpain-2 attenuates doxorubicin-induced cardiotoxicity |
| 17 | Alexander Pavlosky | MSc Student | RIPK3 regulates microvascular endothelial cell necroptosis and cardiac allograft rejection |
| 18 | Anam Islam | MSc Student | Dynapenia is associated with gait variability in community-dwelling older adults |
| 19 | Alaa Monjed | PGY-6 | Utility of N-of-1 trials in the Assessment and Management of Patients with Statin-related Myopathy |
| 20 | Jenny Shu | PGY-1 | Treatment on Healing and Prevention of Digital Ulcers in Systemic Sclerosis (SSc): Results from a Meta-Analysis |
| 21 | Brandon Banaschewski | MSc Student | Pulmonary surfactant as a carrier for cathelicidins in the proposed treatment of bacterial pneumonia |
| 22 | Cartherine Barrett | PGY-2 | Effectiveness and Safety of Outpatient Alpha and Beta Blockade Titration Protocol in Pheochromocytoma |
| 23 | Bainian Chen | Post-Doctoral Fellow | High palmitate diet without obesity decreases cardiac function in mice which is restored by over-expression of calpastatin |
| 24 | Ronen Gurfinkel | PGY-5 | Use of an N-of-1 trial to assess levothyroxine intolerance in a patient with hypothyroidism |
| 25 | Ali Kara | PGY-2 | A situative education and patient care tool developed through Incorporation of Lean Theory into Distributed Medical Education design |
| 26 | Tao Sun | Post-Doctoral Fellow | Accumulation of calpain-1 in mitochondria mediates mitochondrial ROS generation and contributes to cardiac TNF-α expression during endotoxemia |
| 27 | Jennifer Watt | PGY-2 | Correlation Between FRAX Score and Likelihood of Adherence with Current Osteoporosis Treatment Guidelines Among Rheumatologists Caring for Patients with Rheumatoid Arthritis (RA) |
| 28 | Neel Malhotra | PGY-2 | Incidence of Venous Thromboembolism in Gastrointestinal Bleeding |

| Poster # | Presenter | Program | Abstract Title |
|---|---|---|---|
| 29 | Maud Racapé | Post-Doctoral Fellow | Anti-Homocitrullinated Protein/Peptide Antibodies are specific for RA and can recognize citrullinated proteins/peptides |
| 30 | Yunbo Yang | Post-Doctoral Fellow | IL-37 prevents renal ischemia-reperfusion injury by attenuating IL-18-induced pro-inflammatory cytokine expression in tubular epithelial cells |
| 31 | Andrew Appleton | PGY-3 | Understanding Determinants of Resident Adoption of Medical Education Tools<br>Available on Personal Digital Assistants |
| 32 | Jade Coyne | PGY-2 | Necrotizing Pneumonia: An observational trial to identify risk factors associated with mortality. |
| 33 | Arthur Lau | PhD Student | RIPK3 mediated necroptosis promotes donor kidney inflammatory injury and reduces allograft survival |
| 34 | Aze Wilson | PGY-5 | Transient elastography for monitoring of liver fibrosis in methotrexate-treated patients with inflammatory disorders: a systematic review |
| 35 | Rania Ahmed | Clinical Fellow | Web DR  Patient Portal: Patient Perceived Usefulness. |
| 36 | Rashad Ali | PGY-3 | Diagnosing Primary Antibody Deficiency: Availability of essential diagnostic tests in Canada |
| 37 | Nimrit Dhillon | PGY-3 | Application of ADAPTE framework in developing Canadian Systemic Lupus Erythematosus guidelines: A review of SLE literature |
| 38 | Qingming Ding | Post-Doctoral Fellow | Aldosterone-mediated GPER activation stimulates proliferation of renal cancer cells |
| 39 | Rui Ni | PhD Student | Targeted over-expression of calpain-1 in mitochondria induces reactive oxygen species generation and apoptosis in cardiomyocytes |
| 40 | Stephanie Siu | PGY-3 | Lower socioeconomic status is associated with more advanced thyroid cancer stage at presentation: a study in two Canadian centres |
| 41 | Zaodi Gu | PGY-2 | The Adverse Effects of Dabigatran on the Gastrointestinal System |

| Poster # | Presenter | Program | Abstract Title |
|---|---|---|---|
| 42 | Aasim Hasany | PGY-2 | Case Report of Oscillatory Positive Expiratory Pressure Treatment in Chronic Obstructive Pulmonary Disease |
| 43 | David Sanford | PGY-4 | Patient Preferences for Stopping Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia |
| 44 | Dan Segal | PGY-2 | Low dose naltrexone for induction of remission in Crohn's disease. |
| 45 | Dou-Anne Siew | PGY-2 | Desmopressin responsiveness at a capped dose of 15 ug in von Willebrand disease and mild hemophilia A |
| 46 | Ye Su | Post-Doctoral Fellow | CD4+ but not CD8+ memory T cells evade Granzyme B attack by DN-Treg via expression of Spi6 |
| 47 | Susan Muir | Post-Doctoral Fellow | Parathyroid Hormone But Not Vitamin D Is Associated With Gait Impairment in Older Adults |
| 48 | Leslie Skeith | PGY-3 | The equipoise of perioperative anticoagulation management: a Canadian cross-sectional survey |
| 49 | James Jeong | PGY-3 | The use of anti-platelet agents in the prevention of large vessel vasculitis-associated ischemic complications: a meta-analysis. |
| 50 | Selay Lam | PGY-5 | Less is More in the Geriatric Population? Safety and Efficacy of R-mini-CHOP chemotherapy for Treatment of Diffuse Large B Cell Lymphoma in the Very Elderly: A Prospective Quality Assurance Study |
| 51 | Stephanie Siu | PGY-3 | Effect of disease modifying drugs on bone mineral density in patients with rheumatoid arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis: A meta-analysis. |
| 52 | Amna Ahmed | PGY-2 | Prognostic Significance of Elevated Troponin in Non-cardiac Medicine Inpatients: A Systematic Review and Meta-analysis |
| 53 | Usha Manian | PGY-2 | Global Predictors of Response to Cardiac Resynchronization Therapy from Pre-Implantation Cardiovascular Magnetic Resonance Imaging |
| 54 | Saleh Alghofaili | PGY-2 | Malignant pleural mesothelioma presenting with recurrent hydropneumothorax and an abdominal mass. |

| Poster # | Presenter | Program | Abstract Title |
|---|---|---|---|
| 55 | Fahad Almehmadi | PGY-3 | A Series of Unfortunate Events "ST Elevation Myocardial Infarction Secondary To Coronary Paradoxical Emboli In The Setting Of Massive Pulmonary Embolism And Essential Thrombocytosis" |
| 56 | Leslie Skeith | PGY-3 | A Case Report of Kidney and Pancreatic Extramedullary Relapse in Adult Acute Lymphoblastic Leukemia |
| 57 | Brian Feagan | Faculty | Observer Agreement and Construct Validity in Central Endoscopic Assessment of Disease Activity in Ulcerative Colitis |
| 58 | Brian Feagan | Faculty | Responsiveness of Central Endoscopic Assessment of Disease Activity Using the Modified Mayo Clinic Score in Ulcerative Colitis |
| 59 | Seyed M. Hosseini-Moghaddam | Faculty | The Effect of Current Induction Regimens on Post-Transplant Cytomegalovirus Infection in CMV Seropositive Liver Transplant Patients |

# Oral Presentations

| Time | Presenter | Status | Abstract Title |
|---|---|---|---|
| 2:00pm | Waleed Chehadi | PGY-5 | Impact of a Critical Care Response Team on Night Time Discharges from an Intensive Care Unit. |
| 2:15pm | Amy Burke | MSc Student | Reversal of obesity, insulin resistance and dyslipidemia by the flavonoids, nobiletin and naringenin, in a mouse model of the metabolic syndrome. |
| 2:30pm | Jacqueline Malette | PGY-2 | Are We Asking Residents To Do Too Much? Web-Based Evaluation by Residents in Postgraduate Medicine. |
| 2:45pm | Selay Lam | PGY-5 | Enumeration of Bone Microparticles in Plasma of Multiple Myeloma Patients. |
| **3:00pm** | **Refreshment Break** | | |
| 3:15pm | Andrew Lim | MD Student | Predicting The C282Y Homozygote Genotype From Serum Ferritin And Transferrin Saturation In Your Patient. |
| 3:30pm | Amanda Brahm | PGY-2 | Rare LMF1 Mutations in Patients with Hypertriglyceridemia. |
| 3:45pm | Fahad Almehmadi | PGY-3 | Mid-wall Striae Pattern on Late Gadolinium Enhancement Imaging Predicts Future Cardiovascular Events in Patients with Systolic Dysfunction. |
| 4:00pm | Joseph Dube | MSc Student | The private, common LDLR G116S variant has a large effect on plasma LDL cholesterol in circumpolar populations. |
| 4:15pm | Grace Yang | PGY-2 | Association of Socioeconomic Status with Disease Outcome in Patients with Early Rheumatoid Arthritis. |

# Abstract Index

## Impact of Thrombophilia Screening on Venous Thromboembolism Management Practices

**Jameel Abdulrehman**, Jay E. Taylor, Shobha Sharma, Michael J. Kovacs, and Alejandro Lazo-Langner.

BACKGROUND
In patients with idiopathic venous thromboembolism (VTE), thrombophilia screening (TS) is usually done to help guide long term management. We aimed to study the current impact of TS on VTE management practices, particularly since the advent of the REVERSE study (Rodger et al., CMAJ 2008), which stratifies recurrence risk based on clinical and laboratory risk factors excluding thrombophilia (TPh).
METHODS
We conducted a single-center, retrospective cohort study of all patients with objectively confirmed idiopathic VTEs from January 1st, 1996 to December 31st 2011. The primary outcome was the decision of maintaining anticoagulation (AC) beyond the initial planned period based on TS. Secondary outcomes included decision of maintaining AC based on REVERSE criteria or other reasons, and incidence of recurrent VTE.
RESULTS
We included 1033 out of 3333 eligible patients. Mean age was 55.59 years, the mean length of follow up was 55.5 months, and 48.11% were female. Results for TPh testing and primary and secondary outcomes are shown in Tables 1 and 2. Compared to patients without TPh and after adjusting for AC continuation beyond 6 months, the presence of non-major TPh resulted in a modest increase in VTE recurrence risk (OR 1.71, P<0.01) whereas the presence of major TPh did not (OR 0.55, P=0.27). Continuation of AC beyond the initial planned period resulted in 75% reduction in VTE recurrence risk (OR 0.25, P<0.001).
CONCLUSIONS
The impact of TPh on VTE recurrence is small and the proportion of patients in whom TS results in long term AC is low.

## Prognostic Significance of elevated Troponin T in acutely hospitalized CTU patients without a primary cardiac diagnosis.

**Amna Ahmed**, Marko Mrkobrada.

Background:
Troponin can be elevated in the absence of acute coronary syndrome. We investigated prevalence of Troponin T testing in hospitalized CTU patients that did not have a primary cardiac diagnosis and the relationship of Troponin elevation with adverse outcomes including mortality and readmissions.
Methods:
A retrospective chart review of medicine inpatients, without a primary cardiac diagnosis, was conducted at two hospitals. Patient population was selected over a two week period when both fourth generation troponin T (TnT) and high-sensitivity troponin T (hsTnT) were being measured. Prevalence of troponin testing within 36 hours of admission was studied. Patient charts were followed for adverse outcomes.
Results:
242 patients were enrolled and 130 (54%) had troponin measured within 36 hours of admission. Of the 130 patients, 84 (65%) had elevated hsTnT and 37 (28%) had elevated TnT. The in-hospital mortality for elevated hsTnT group was 8 (9.5%) and 4 (10.8%) for elevated TnT group. The long-term mortality at 6 months for the elevated hsTnT was 19 (23%) with an OR of 4.19 (95% CI 1.17 – 15.03) and 10 (27%) for elevated TnT, with OR of 2.47 (95% CI 0.96 – 6.36). For 30 day hospital readmissions, the OR for elevated hsTnT was 2.40 (95% CI 0.83 – 6.92) and 3.24 (95% 0.99 – 6.32) for elevated TnT.
Conclusions:
Troponin T is measured in more than 50% of CTU patients at the time of admission. Elevated troponin levels are associated with increased adverse outcomes including mortality and hospital readmissions.

## Prognostic Significance of Elevated Troponin in Non-cardiac Medicine Inpatients: A Systematic Review and Meta-analysis

**Amna Ahmed**, Marko Mrkobrada.

Background:
Cardiac biomarkers can be elevated in the absence of acute coronary syndrome. Troponin elevations have been measured in non-cardiac inpatients such as those with acute pulmonary embolism, exacerbation of chronic obstructive lung disease (COPD), or sepsis. The prognostic significance of detectable and elevated troponin levels in various non-surgical patients admitted to the hospital without a primary cardiac diagnosis is not known.
Methods:
Literature search was done using two different databases. Two independent investigators assessed studies and reviewed full text studies for final inclusion. Studies with non-surgical patients admitted without a primary cardiac diagnosis were included. Included studies compared adverse outcomes in patients with normal versus elevated troponin levels.
Results:
Twenty five studies, enrolling 7255 patients had 1092 deaths for short-term mortality (in-hospital and  30 days). There were 766 (23%) death in the elevated troponin group and 326 (8.3%) in the normal troponin group, with an OR of 3.88, and 95% CI of 2.90 to 5.19. Eight studies with a total of 4801 patients looked at long-term mortality ( 6 months). There were a total of 1400 deaths, with 1013 (51%) in the elevated troponin group and 387 (14%) in the normal troponin group. The OR for long-term mortality was 4.83, with 95% CI 2.02 to 11.54.
Conclusions:
Increased troponin level in various non-cardiac medical patients is a marker of worse prognosis and is associated with increased short and long-term mortality

## Web DR Patient Portal: Patient Perceived Usefulness.

**Rania Ahmed**, Selam Mequanint, Irene Hramiak, Stewart Harris, Tamara Spaic.

The rapid increase in incidence of diabetes mellitus (DM) and complexity of diabetes care call for innovative disease self-management solutions. Patient-web-portals (PWP), secure website that allow patients to view and maintain limit part of their health records, and communicate with their care providers, are shown to increase satisfaction with care, improve disease management, and clinical outcomes such as glycated hemoglobin levels. However, the cost of implementing PWP is substantive, long-term adherence is limited, and their use may be associated with unexpected increase in utilization of clinical services. The objective of this study is to explore patient preferences in content of PWP and explore if there is a difference by diabetes type. A total of 165 participants at St Joseph's Health Care, London diabetes clinics were surveyed. Of these, 91(55.2%) were male, 131(79.4%) were ≥45 years of age, 37% had T1DM and 117(70.9%) had DM for ≥10 years. The top 4 features ranked as important are access to reliable DM information (79%), access to answers to frequently asked diabetes related questions (75%), access to selected summary of DM records (72%), and ability to update personal information (67%). Participants with T1DM are 3.3 times more likely (95% CI 1.44-13.4) to have access to the Internet at home than individuals with T2DM. They are also more likely (OR 1.64, 95% CI 1.4-7.0 ) to identify glucose self-monitoring features as the most important. Diabetes PWP may preferentially be used by T1DM patients who may benefit more from this promising new technology than T2DM patients.

## A single nucleotide polymorphism at the 9p21.3 cardiovascular risk locus is associated with a very high risk of coronary artery disease in patients with a positive family history

**Dr.Saleh Alghofaili**, Dr. R. Hegele.

Background: The 9p21.3 cardiovascular risk genotype has been replicated in several large clinical studies. The exact contribution of single nucleotide polymorphisms (SNPs) occurring at this locus to the risk of developing coronary artery disease (CAD) in patients with a positive family history of CAD has not been definitively established. We therefore examined the association of the rs1333049 SNP with family history in patients with CAD.
Methods: One hundred and sixty patients <65 years old were genotyped for the rs1333049 SNP. Genotype and allele frequency were analyzed with respect to family history of CAD.
Results: There was an increased frequency of high-risk rs1333049 genotypes and alleles in patients with a positive family history of CAD. Patients heterozygous for the risk allele (G>C) with a positive family history had an OR of 4.26 (95% CIs 1.90-9.51; p=0.0002) for incident disease.
Conclusions: Patients with a high-risk genotypes and a positive family history are at very high risk of developing CAD. Genotyping may have a valuable role in further stratifying patients with a positive family history into very high risk groups who may benefit from more aggressive preventative management.

## Malignant pleural mesothelioma presenting with recurrent hydropneumothorax and an abdominal mass.

**Dr. Saleh Alghofaili**, Dr.C. Mackenzie, Dr.J. Lewis, Dr.C. Licskai.

An 80-year-old retired mechanic presented with recurrent left hydropneumothorax and a superficial mass in the left flank. A CT scan demonstrated a large mass in the left loin, extending from the 10th rib to the iliac crest. Histopathologic examination, which required the use of confirmatory electron microscopy, resulted in a diagnosis of epithelioid malignant mesothelioma. Although malignancy, in particular mesothelioma, is only a rare cause of recurrent spontaneous pneumothorax, this underlying pathology needs to be considered especially in older patients with histories relevant to occupational exposure to asbestos.

## Diagnosing Primary Antibody Deficiency: Availability of essential diagnostic tests in Canada

**Rasha Ali**, Kyla Hidebrand.

Background:
CVID is one of the most common primary immunodeficiencies, characterized by lack of immunoglobulin production and antibody failure. Treatment consists of lifelong immunoglobulin replacement. Diagnosis requires demonstration of the lack of antibody production
Objective:
-determine the degree of accessibility to basic immunology testing across Canada for the assessment of antibody deficiency
-determine if patients have been initiated on lifelong replacement without confirmatory specific antibody titre testing
Methods:
An online of all specialists with membership in the Canadian Society of Allergy and Clinical Immunology. Out of 56 responses received, 22 were incomplete and nine practiced exclusively Allergy. The 25 remaining complete responses are summarized here. The availability of pre and post pneumococcal vaccine antibody titre testing was used as a surrogate marker for the ability to order specific antibody titres to other vaccines.
Results:
Eleven out of 25 respondents (44%) are able to obtain antibody titres to pneumococcal vaccine locally, including only half of the 14 respondents from academic centres. Over 70% of those practicing in either combined (6/9 respondents) or exclusively community (2/2 respondents) settings could not order it locally. One quarter of respondents (6/25) had initiated immunoglobulin replacement without a full diagnostic assessment
Conclusion:

Basic immunology testing for the investigation of antibody deficiency is not readily accessible to many Immunologists in Canada even in academic centres. Access is more limited in community centres where a significant proportion of patients are referred to tertiary centres, likely resulting in higher costs to the healthcare system

## A Series of Unfortunate Events "ST Elevation Myocardial Infarction Secondary To Coronary Paradoxical Emboli In The Setting Of Massive Pulmonary Embolism And Essential Thrombocytosis"

**Almehmadi FS**, Mehdar AM , Teefy P.

Essential thrombocytosis (ET) is a myeloproliferative disorder characterized by pathological clonal proliferation of megakaryocytes with persistently elevated platelets count. 1. We describe the first case in literature of ST-segment Elevation myocardial infarction (STEMI ) secondary to a Right Coronary Artery (RCA) paradoxical embolus (PDE) through a Patent Foramen Ovale (PFO)in a patient with essential thrombocytosis .

A 67 female with history of ET presented with shortness of breath . She was found to have elevated JVP , S1Q3T3 pattern on first ECG, a normal platelets count and an elevated D-dimer . V/Q scan showed a high probability for Pulmonary Embolism , it also showed unusual evidence of right to left shunt . Patient treated with Deltaparin.

She developed new chest pain with ST-elevation in inferior leads. An RCA thrombus was successfully aspirated with no further catheter intervention . She subsequently found to have a massive bilateral PE on CT scan requiring Thrombolysis due to hemodynamic instability . A Trans-Esophageal Echo showed a patent PFO with significant immediate right to left shunt . After her discharge ,she was treated medically with antiplatelets, anticoagulants and Hydroxyurea with no planned PFO closure . Patient has done well for almost 3 years since this event .

This case describes the first case of PDE to a coronary artery in the setting of ET. This case emphasized on the poor utility of platelets count in predicting thrombotic events. It also described a potentially effective treatment strategy in treating paradoxical coronary emboli with normal coronaries .

## Mid-wall Striae Pattern on Late Gadolinium Enhancement Imaging Predicts Future Cardiovascular Events in Patients with Systolic Dysfunction

**Fahad Almehmadi, MBBS**, Immaculate Nevis, Mahmoud Bokhari, Mohammad Zahrani, John Stirrat, Raymond Yee, James A. White.

Background: Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is increasingly performed for evaluation of systolic dysfunction. Patterns of hyper-enhancement (HE) are frequently identified and reported. This study aimed to evaluate the prognostic significance of HE patterns among a referral population with systolic dysfunction.

Methods: 318 consecutive patients with cardiomyopathy referred for LGE-CMR and an LVEF<55% were followed for the primary composite endpoint of; cardiac death, heart failure admission or appropriate ICD therapy. LGE images were blindly scored for the presence and pattern of HE and categorized as follows; subendocardial, mid-wall striae, mid-wall patchy, RV insertion site, sub-epicardial, and diffuse. Total HE volume was quantified using a signal threshold of ≥5SD above reference mean myocardial signal.

Results: Mean age was 62.0±12.9 and mean LVEF was 32.6±11.9%. Any HE was reported in 243 (76%) with HE patterns reported as follows; ischemic: 146 (46%), mid-wall striae 57 (18%), mid-wall patchy 35 (11%), RV insertion site: 51 (16%) sub-epicardial 34 (11%), and diffuse 9 (3%). At a median of 778 days 61 patients (19.1%) suffered a primary outcome. Among all baseline characteristics LVESV, LVEF, RVEF,

Total HE volume and mid-wall striae were significantly associated with the primary outcome ($p<0.05$). Multivariate analysis showed mid-wall striae to be the strongest independent predictor of the primary outcome with a HR of 2.6 (95%CI 1.5–4.7, p=0.001).
Conclusions: Mid-wall striae pattern HE is the strongest independent predictor of cardiovascular events in patients referred for CMR evaluation of systolic dysfunction.

## Understanding Determinants of Resident Adoption of Medical Education Tools Available on Personal Digital Assistants

**Andrew Appleton**, Elaine Zibrowski, Shanil Narayan.

Background: Usage of personal digital assistants (PDA) for education is ubiquitous among residents. We sought to better understand how residents choose and utilize medical apps on PDA.
Methods: A mixed methods approach was undertaken involving a questionnaire and focus group interviews of internal medicine residents at Western. The questionnaire was informed by determinants of Information Technology adoption identified in other settings. Prevalence and determinants of residents' usage of 'gold standard' apps (Dyanmed and UpToDate) versus other user-selected apps was estimated. Emerging themes from focus groups were explored to further elucidate determinants of use.
Results: Residents are in the early majority of adopting technology. 58% used medical apps >1x/day and 83% >= 1x/wk. Gold standard and user-selected apps were rated highly for ease-of-use and usefulness by current users. The opinions of peers and superiors were not strong determinants of use. Barriers of cost and accessibility were associated with residents not using, nor intending to use, gold standard apps. Residents predominantly use PDA to find very specific information, often related to pharmacology and differentials. Residents are focused on time as a major factor in determining which apps are used.
Conclusions: Time pressure in residency impacts the choice of medical apps used on PDA. Residents satisfy the need for expedient access to targeted information by favouring user interfaces that are the easiest and fastest to navigate. This is instructive in highlighting the value of intelligent user interface design, and deliberate selection of the information provided, to maximally facilitate knowledge translation via PDA technology.

## Pulmonary surfactant as a carrier for cathelicidins in the proposed treatment of bacterial pneumonia

**Brandon Banaschewski**, Eleonora Keating, Edwin Veldhuizen, Cory Yamashita, Ruud Veldhuizen.

Treatment of bacterial pneumonia is complicated by two main factors – the difficulty in delivering adequate levels of antibiotics to the sites of infection, and the increasing prevalence of antibiotic resistance. To overcome these complications, we have proposed to fortify pulmonary surfactant, a substance that reduces surface tension and spreads throughout the lung, with cathelicidins, an antimicrobial peptide capable of treating bacterial infections with a reduced risk bacterial resistance developing.
The administration of surfactant, fortified with cathelicidins, will improve outcomes in bacterial pneumonia.
The first objective in this hypothesis was to investigate the functions of a cathelicidin/pulmonary surfactant mixture in vitro.
Bovine lipid-extracted surfactant (BLES) and chicken cathelicidin CATH-2 were the models used in these objectives. BLES was suspended to 10 mg/ml of phospholipid in saline, and CATH-2 was added in varying concentrations. Surface tension reduction capabilities of the compounds were measured using a Langmuir balance. The structure of BLES/CATH-2 was observed using atomic force microscopy (AFM)

at surface tensions of 42mN/m. Bactericidal activity of CATH-2 in surfactant was measured through the killing curves of two distinct bacterial cell lines.
There was no significant difference in the ability of BLES to reduce surface tension in the presence of CATH-2. AFM images showed a change in microdomain size when CATH-2 was present. CATH-2 remained bactericidal in the presence of BLES.
These experiments demonstrate that the mixture of BLES/CATH-2 does not affect the surface activity of BLES, while maintaining CATH-2's bactericidal capabilities.

## Characterization of a stable gene set in Ovarian Cancer

**Paul C. Barnfield**, Anqi Jiang, Coby Viner, Stephanie N. Dorman, Ben C. Shirley, Mark D. Vincent, Joan H.M. Knoll and Peter K. Rogan.

Recently, several large-scale genomic analyses have identified molecular abnormalities influencing pathophysiology and clinical outcomes in high-grade serous ovarian cancers (HGS-OvCa). However, tumor heterogeneity and cancer genome instability complicates prognostication and therapeutic intervention. Thus, identifying a set of essential and stable genes required for tumour survival may yield novel therapeutic targets and important insight into the biology of cancer. To this end, we have previously characterized a breast cancer gene set, stable with respect to gene expression and copy number variation. We have now employed somatic mutation, copy number variation, and gene expression data from The Cancer Genome Atlas Research Network, to define a stable gene set in HGS-OvCa. Moreover, all reported single nucleotide polymorphisms were analyzed using the Shannon Pipeline for Human Splicing. Several hundred mutations predicted to decrease natural splice site activity, or create cryptic splicing sites were identified and genes harboring these mutations were excluded from the stable gene set. Importantly, many of these mutations had been previously classified as silent.
In total, 5299 genes met our stability criteria–having no mutations, aberrant RNA expression or copy number variation. This gene set was enriched for essential pathways in cellular metabolism, DNA packaging, protein assembly and signal transduction. Comparison between HGS-OvCa and breast cancer stable gene sets, revealed 1189 conserved genes. Notably, this gene set was enriched most significantly for signaling pathways including Erb1, VEGF, PI3K/mTOR, and TGFβ.
The stable gene set likely represents essential cellular machinery for cancer cell survival. Its further characterization may yield novel therapeutic targets.

## Effectiveness and Safety of Outpatient Alpha and Beta Blockade Titration Protocol in Pheochromocytoma

**Catherine Barrett**, Daryl Gray, Christopher Harle, Stephen Pautler and Stan Van Uum.

BACKGROUND: Pheochromocytomas are rare catecholamine secreting tumors. Surgery is the mainstay of treatment but carries a significant risk of triggering a hypertensive crisis or cardiac arrhythmia. Pre-operative blockade is recommended but regimens vary and have not been evaluated for the outpatient setting.
OBJECTIVES: To evaluate the safety and efficacy of an outpatient titration protocol using phenoxybenzamine and propranolol for the pre-operative preparation of patients with pheochromocytoma.
PATIENTS AND METHODS: We identified all patients with a pheochromocytoma who received pre-treatment according to our protocol from 2004 to 2012. Patients were started on phenoxybenzamine and propranolol 10-14 days prior to their scheduled surgery date and were titrated to a target dose of 30mg TID and 40mg QID respectively. Patients measured orthostatic blood pressure and heart rate using an automated home blood pressure device and body weight daily. We monitored the effects on mean arterial pressure (MAP), heart rate, weight

and side effects, and analyzed peroperative hemodynamics.
RESULTS: We included 13 patients (7M6F), aged 45±16 years, 11 pheochromocytoma and 2 paraganlioma. The final daily doses of phenoxybenzamine and propranolol were 88±14 and 165±42mg. Supine MAP was 99±12 versus 92±13mmHg (P=0.12 paired student T-test), standing MAP was 99±12 versus 82±12mmHg (P=0.01) and weight was 81± 18 and 82±19kg (P=0.03) for baseline and end of titration parameters. Intra-operatively, 9 patients experienced hypertension (SBP>160mmHg) and 5 patients experienced hypotension (MAP<60mmHg).
CONCLUSIONS: In this small retrospective study, outpatient pre-treatment with phenoxybenzamine and propranolol is safe when closely monitored and doses individually adjusted.

## Secular Trends in Ischemic Stroke Subtypes

**Chrysi Bogiatzi M.D.**, Daniel G. Hackam M.D., A. Ian McLeod Ph.D., J David Spence M.D..

Background: With the aging of the population, and with increasing prevalence of therapy for hypertension and hyperlipidemia, it might be expected that stroke subtypes would be changing over time. Limited information exists on the distribution of ischemic stroke subtypes in Canada.
Methods: Patients referred to Urgent TIA Clinic, in London, from 2002 to 2012 were included. Secular trends were analyzed using Poisson regression analysis. Ischemic stroke subtype classification was validated.
Results: 3445 consecutive patients with mean age+SD of 64.76+14.9 were included; 51% were women, 81% had hypertension; 18% had diabetes; 9% had atrial fibrillation; 14% had open patent foramen ovale; 20% were current smokers. Cardioembolic strokes increased significantly from 21% in 2002 to 56% in 2012, whereas all other ischemic stroke subtypes decreased (p<0.01). Additional analysis showed a decrease in blood pressure, LDL and pack years of smoking, and an increase in medications used to treat hyperlipidemia (p<0.05).
Conclusions: The decrease in atherosclerotic risk factors resulted in fewer strokes caused by large artery atherosclerosis and small vessel disease. Cardioembolic strokes have increased significantly as a proportion of first-ever ischemic strokes. This has important implications for more intensive investigation and treatment to reduce the risk of recurrent embolic stroke.

## QT Intervals in Ventricular Paced Rhythms

**Mahmoud Bokhari**, Krahn AD, Almehmadi, F, Massel D, Gula LJ, Yee R, Manlucu J, Klein GJ, Skanes AC, Leong-Sit P.

Introduction:
The normal range of QT during Right Ventricular Paced (RVP) rhythm has not been reported in the literature. We aimed to assess the QT interval in RVP rhythm.
Methods:
Consecutive patients from a single centre ICD and Pacemaker Clinic were prospectively enrolled. Patients with a device implantation < 3 months, pacemaker-dependent, or ventricular-pacing at presentation were excluded. A 12-lead ECG was performed during a non-ventricular paced rhythm (nonP) and repeated while in RVP rhythm. Two independent investigators performed all ECG measurements using electronic software.
We considered the sub-group with QRS less than 120msec, QTc shorter than 450 msec for males and 470 msec for females, who are not on any drugs that might affect the QT as a standard normal group. We used the simulation method for 10000 times to establish a normal QT in paced rhythm.
Results:
176 patients were enrolled (mean age 70, 118 (67%) male, 86 (49%) with a pacemaker). The mean ejection fraction was 47% (SD 17%) and the mean QRS 121(SD 28.5). The baseline

(NonP) mean QTc of 443 msec (SD 37 msec). RVP increased the QTc mean by 74 msec (95% CI 74.3-84.8). 36 males and 29 females, total 65 (37%) met the standard normal sub-group criteria. In the standard sub-group, RVP QTc mean was 494 msec (95%CI 439-547) in males, and 524 msec (95% CI 473- 575).
Conclusion:
547 msec for males and 575 msec for females can be considered as an upper limit of normal QTc in RVP Rhythm.

## Rare LMF1 Mutations in Patients with Hypertriglyceridemia

**Amanda Brahm**, Matthew R. Ban, Christopher T. Johansen, Adam McIntyre, Jian Wang, Robert Hegele.

Purpose: Severe hypertriglyceridemia in the form of hyperchylomicronemia can lead to significant clinical complications. Originally thought to be due exclusively to mutations in the LPL gene, recent work suggests mutations in other genes, such as lipase maturation factor 1 (LMF1) may also be involved. The purpose of this study is to analyze the data from hypertriglyceridemia patients identified as having a mutation in LMF1 and evaluate the potential of these mutations for clinical significance.
Methods: 493 patients with hypertriglyceridemia were tested for LMF1 gene mutations. Mutations identified were analyzed by PolyPhen and SIFT to predict the likelihood that they would affect LMF1 functioning. The frequency of the mutations in the hypertriglyceridemia population was compared to a control population of 8932 subjects collected from general population gene banks and odds ratios comparing the two populations were calculated.
Results: Ten patients with seven separate mutations in LMF1 were identified. Mutations included R451W, M238T, D491N, A469T, M122V, R101T, and E531D. Four of the mutations were identified as damaging by SIFT and probably or possibly damaging by PolyPhen (R451W, M238T, D491N and A469T). Odds ratio was significant for R451W (164.23, P-value 0.0006), and M238T, D491N, M122V and R101T (54.41, P-value 0.014) and for the overall frequency of LMF1 mutations in the hypertriglyceridemic population compared to the control population (2.35, P=0.0117).
Conclusions: This study shows evidence for a significant association between LMF1 mutations and the hypertriglyceridemia phenotype and suggests a possible causal link. Further investigations are warranted to further explore this relationship.

## Tolerability and efficacy of differing lipid-lowering management strategies in patients with a history of statin-related myopathy

**Emily T Brennan**, Tisha R Joy.

Context: Statin-related myopathy occurs in at least 10% of patients prescribed statins. Management strategies include: statin switching, rechallenge, alternate dosing schedules, or use of non-statins. There is limited data on the tolerability and efficacy of these strategies regarding achievement of low-density lipoprotein cholesterol (LDL-C) goals.
Objectives: In patients with statin-related myopathy, we evaluated the above strategies with regards to tolerability and achievement of LDL-C targets (2009 CCS Dyslipidemia Guidelines)
Methods: Retrospective analysis of patients with statin-related myopathy referred to our tertiary lipid clinic (2007-2012) and with at least 1 follow-up visit and/or blood work result.
Results: 116 individuals were included for analysis (age 64.1±11.6 years, 48% male, 87% high cardiovascular risk). After median follow-up of 15.5 months (range 1.5-60 months), 77% tolerated statin therapy, with 51% tolerating high dose therapy. Tolerability for statin switching, rechallenge, and alternate dosing strategies was 68%, 74%, and 57% respectively. In those who switched statins, 34% and 60% tolerated the 3rd and 4th statins trialed respectively. LDL-C targets were achieved in 52% of those tolerating statin switch or rechallenge and 44% of those tolerating alternate dosing strategies. Compared

to patients on only non-statins, patients on statins had lower LDL-C values (2.19±0.88 vs. 3.34±1.22, p<0.001) and more often achieved their LDL-C target (53% vs. 14%, p=0.001).
Conclusions: The above statin-based strategies are highly tolerable and effective in patients with statin-related myopathy. These patients should aim to remain on statin therapy if possible, since statin therapy is associated with better achievement of their LDL-C targets.

## Reversal of obesity, insulin resistance and dyslipidemia by the flavonoids, nobiletin and naringenin, in a mouse model of the metabolic syndrome

**Amy C. Burke**, Brian G. Sutherland, Cynthia G. Sawyez, Dawn E. Telford, Joseph Umoh, Maria Drangova, and Murray W. Huff.

Previous studies demonstrated that addition of the flavonoids naringenin or nobiletin to a high-fat diet prevented the development of most metabolic disorders linked to the metabolic syndrome. In the present study, we assessed the ability of nobiletin and naringenin to reverse pre-established obesity, insulin resistance and dyslipidemia. Ldlr-/- mice were fed chow or a high fat, cholesterol-containing diet (HFHC) for 12 weeks. Subsequently, the HFHC-fed mice were assigned to 1 of 4 diets for an additional 12 weeks: (1) continuation of the HFHC diet or transfer to (2) chow, (3) HFHC + 3% naringenin, or (4) HFHC + 0.3% nobiletin. Following rapid weight gain during the 12-week HFHC induction phase, intervention with naringenin or nobiletin stimulated weight loss, while maintaining caloric intake. Micro-CT imaging revealed flavonoid intervention reversed adipose tissue accumulation, achieving a 40-60% reduction in both subcutaneous and visceral adipose tissue depots. At 12 weeks, the HFHC diet increased fasting plasma insulin 6-fold. Subsequent intervention with both flavonoids decreased insulin by 50% and normalized impaired insulin tolerance. The modest increase in blood glucose and significant deterioration of glucose tolerance in HFHC-fed mice were completely reversed by the flavonoids. The HFHC diet stimulated an increase in plasma cholesterol (10-fold) and plasma TG (6-fold). Intervention with naringenin decreased both lipids by 35% and nobiletin decreased both lipids by 50%. These studies demonstrate that intervention by the addition of naringenin or nobiletin to a HFHC diet markedly reverses obesity, dyslipidemia and insulin resistance in mice with pre-existing metabolic dysregulation.

## Hair Cortisol over Testosterone Ratio Predicts Hospitalization in Patients with Systolic Heart Failure

**Justin Chan and David Pereg**, Evan Russell, Tatiana Berlin, Morris Mosseri, Jamie Seabrook, Gideon Koren, Stan Van Uum.

Background: Congestive heart failure (CHF) is associated with alterations in metabolism, favouring catabolism over anabolism. Hormonal profiles of patients with heart failure have been assessed using serum and saliva as matrices, which are only point measurements and do not provide long-term information. Scalp hair is a novel matrix that allows for measurement of hormones over a period of several months. We measured cortisol and testosterone in the hair of patients with CHF to determine any associations between testosterone and the cortisol over testosterone (C/T) ratio with CHF prognosis.

Patients and Methods: Hormone levels were measured using an immunoassay in the proximal 2 cm of hair (representing two months of systemic hormone exposure). We determined the association between testosterone and the C/T ratio in hair and the New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), NT-proBNP, exercise capacity, body mass index (BMI), and one year CHF-related hospitalization.

Results: The C/T ratio correlated with BMI better than hair testosterone alone. High hair cortisol over testosterone ratio predicted one year heart failure-related hospitalizations (OR 1.036, p=0.04). We did not find association between

hair testosterone levels or C/T ratio with NYHA class, LVEF, NT-proBNP, or exercise capacity.
Conclusions: Hair C/T ratio is superior to hair testosterone alone in its association with BMI. Given the association between hair C/T and hospitalization, future studies may analyze if this ratio may predict CHF-related hospitalization and mortality.

## Impact of a Critical Care Response Team on Night Time Discharges from an Intensive Care Unit

**Chehadi W,** Kao R.

Increasingly, discharges from intensive care units are occurring after normal working hours, the effect of which has been previously shown to be associated with increased mortality. Despite this clear risk to patients, night discharges continue to occur, often rationalized as being safe since we now have Critical Care Response teams (CCRTs) unlike the previously published studies. We sought to investigate whether this relationship still exists in the era of CCRT's.
Methods: Charts were reviewed for all patients transferred out of an ICU consecutively between January 2011 and March 2011. Baseline data, ICU discharge time, 30 day mortality and CCRT interventions were collected and grouped as occurring during the day or night (21:00-6:59).
Results: There were 151 total discharges with 36% occurring at night. Mortality was significantly higher for night time discharges at 7.27% vs. 1.4% (P =0.039). Rate of readmission to the ICU were not statistically significant. Night time discharges required more assessments for respiratory failure, secretions, low urinary output and end of life discussions and required more interventions for oxygen and fluid administration and mechanical ventilation.
Conclusions: Night time discharges still pose significant risk to patients despite the presence of CCRT's with an absolute risk increase in mortality of 5.87%. Furthermore, patients transferred at night required more assessments and interventions. Every attempt should be made to avoid night discharges and a coordinated 'surge plan' should be developed and implemented to avoid the need for night discharges in the first place.

## High palmitate diet without obesity decreases cardiac function in mice which is restored by over-expression of calpastatin

**Bainian Chen**, Dong Zheng, Rui Ni, Tianqing Peng.

Studies have revealed that dietary fatty acids oversupply may account for cardiac lipotoxicity, leading to the lipid metabolic abnormalities in hearts. Palmitate, the most dominant fat in Western fast food, induces apoptosis and contractile dysfunction in cardiomyocytes. The present study aimed to investigate the effect of palmitate diet on cardiac hypertrophy and function in mice, and to evaluate whether over-expression of calpastatin could restore the myocardial function. Adult wild-type and calpastatin transgenic mice were fed with high palmitate diet (HPD, 21% total fat of which 47% is palmitate) for 6 and 12 weeks. A customized diet containing medium chain triglycerides was used as a high fat control diet (CTD, 21% of total fat). There was no change of body weight among the normal, CTD and HPD groups after 6 and 12-week diet period. HPD increased the blood cholesterol level compared with CTD and normal diet fed mice. Both HPD and CTD induced an increase in cardiomyocyte size, indicative of cardiomyocyte hypertrophy. Echocardiography demonstrated systolic and diastolic dysfunction in HPD but not CTD fed mice compared with normal diet fed mice. HPD but not CTD increased calpain activities in the heart. Over-expression of calpastatin decreased cardiac dysfunction in HPD fed mice; however, it did not have any effect on cardiomyocyte size in HPD and CTD fed mice. In summary, this study shows that high palmitate diet induces cardiac hypertrophy and myocardial dysfunction in mice without causing obesity. Calpain activation may play a role in palmitate-induced cardiac dysfunction but not cardiac hypertrophy.

## Necrotizing Pneumonia: An observational trial to identify risk factors associated with mortality.

**Jade Coyne M.D.**, Karen Bosma M.D., Philip Jones M.D., Dalilah Fortin M.D.

Purpose:
Necrotizing pneumonia is a rare but severe complication of community-acquired pneumonia with high risk of respiratory failure, sepsis and death. We conducted a retrospective observational study to evaluate factors associated with improved survival in critically ill patients with necrotizing pneumonia.
Methods:
Patients admitted to an intensive care unit at London Health Sciences Centre, between July 2005 to July 2010, were screened for inclusion if they had an admitting diagnosis of pneumonia, or had undergone bronchoscopy or computed tomography (CT) scan of the thorax (N=590). We identified 38 cases of necrotizing pneumonia for chart review.
Results:
All patients received antibiotics, 35 (92%) received ventilation, 28 (74%) required vasopressors, 29 (76%) underwent bronchoscopy, 24 (63%) had ≥1 chest tubes inserted, 10 (26%) went to the operating room for open thoracotomy for debridement of devitalized tissue, and 2 (5%) had ultrasound-guided abscess drainage. Death occurred in 17 (45%) cases.
Multivariable logistic regression analysis, using mortality as the dependent variable demonstrated an odds ratio (OR) of 0.06 (CI 0.003-1.02, P=0.052) for thoracic surgery consultation. APACHE II score demonstrated an OR of 1.12 (CI 1.00– 1.26, P=0.050). Vasopressor use demonstrated an OR of 12.90 (CI 0.67 – 246.93, P=0.090).
Conclusions:
Thoracic surgery consultation was associated with decreased odds of mortality. High APACHE II score and vasopressor use were associated with increased odds of mortality.
Clinical Implications:
A high APACHE II score and shock may herald a more sinister outcome. Obtaining a thoracic surgery consult may improve patient monitoring and clinical outcomes.

## Application of ADAPTE framework in developing Canadian Systemic Lupus Erythematosus guidelines: A review of SLE literature

**Nimrit Dhillon**, Janet Pope.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with a remitting and relapsing course, and variable clinical presentation. While gains have been made in the diagnosis and management of SLE, there remains a lack of unifying Canadian SLE guidelines or recommendations. The purpose of this study was to begin the establishment of such Canadian guidelines using the ADAPTE framework.
A search of previously published SLE guidelines (1980 to 2012) was completed by searching through databases including PUBMED, EMBASE, CINAHL and national guideline clearinghouse, and via bibliographic hand search. Databases were searched with the terms ('SLE' or 'lupus' or 'systemic lupus erythematosus') AND ('guildelines' or 'recommendations'). Articles were initially screen by title and abstract content. Initial screening revealed 108 articles meeting these criteria.
Those meeting initial screening approval were then fully evaluated. Articles were excluded if the major population of interest was not SLE patients or if recommendations were not specifically applicable to the SLE population (13), were written in non-English language (18), were systematic or narrative reviews (16), and if recommendations were made by a single expert (5). Guidelines and recommendations not relevant to clinical diagnosis or management were also excluded (7). Sixteen articles have thus far been included and thirty-three articles remain to be screened.

The next phase of the study is to review all preliminarily included guidelines for quality, and those of poor methodological quality will be excluded. Remaining guidelines and recommendations will be pooled, and SLE experts will be surveyed in order to identify guideline gaps.

## Aldosterone-mediated GPER activation stimulates proliferation of renal cancer cells

**Qingming Ding**, Robert Gros, Jozef Chorazyczewski and Ross D. Feldman.

Renal cell cancer is the most common type of kidney cancer in adults. A number of risk factors have been identified for this disease; among them are obesity and hypertension. Although increases in aldosterone (Aldo) circulating concentrations have been shown in both hypertension and obesity, whether the link exists between these established risk factors and the development of renal cancer and whether this relationship could be causally related to higher aldosterone level remain unexplored. We hypothesized that the link between renal cell cancer and aldosterone might occur via its actions on GPER- a GPCR widely expressed in variety of tissues including renal cancer cells. GPER has been shown to regulate the growth of cancer cells. Further, we have shown that GPER is potently activated by aldosterone. However the impact of aldosterone-mediated GPER activation on renal cell cancer cell growth and spread are unknown.Therefore we sought to determine the importance of aldosterone-mediated GPER activation in the regulation of renal cancer cell growth. To do this, we assessed the effects of aldosterone and of the GPER agonist G1 in regulating EdU in renal cancer cells (RENCA). Both aldosterone and G1 mediated a dose-dependent stimulation of EdU incorporation in RENCA cells with a maximal effects at concentration of 10nM and 10μM respectively. Moreover, either downregulation of GPER expression via shGPER gene transfer or pre-treatment with GPER antagonist G15 blocked both aldosterone and G1-mediated stimulatory effects. These findings suggest an essential role of GPER in regulating the aldosterone-mediated stimulation of proliferation.

## The private, common LDLR G116S variant has a large effect on plasma LDL cholesterol in circumpolar populations.

**Joseph B. Dube**, Jian Wang, Matthew R. Ban, Kue Young, Eric Dewailly, Peter Bjerregaard, Bert Boyer, and Robert A. Hegele.

Introduction: Common DNA polymorphisms in LDLR modestly affect plasma low-density lipoprotein (LDL) cholesterol (C) levels, while rare loss-of-function mutations in LDLR cause familial hypercholesterolemia (FH). To date, FH has not been reported in North American indigenous populations. We thus sequenced the LDLR gene in Inuit with elevated LDL-C to identify new genetic variants. Methods: Using Sanger sequencing of LDLR protein coding regions, we discovered two nonsynonymous variants in LDL-C >95th percentile for age and sex: 1) a glycine-to-serine substitution at amino acid 116 (G116S), and 2) an arginine-to-tryptophan substitution at amino acid 730 (R730W). We genotyped these two variants in Inuit from four regions: Greenland (n=1191); Nunavik, Quebec (n=450); Nunavut (n=214); Inuvik, Northwest Territories (n=281); and Alaska (n=1222). We tested for association between each variant and plasma lipids using multivariate linear regression. Results: Variant frequencies for G116S and R730W were 13%, 9%, 2%, 5% and 10% and 11%, 13%, 17%, 13%, and 16% in Greenland, Nunavik, Nunavut, Inuvik, and Alaska respectively. We found that LDLR G116S genotype was strongly associated with LDL-C in each region, and in a combined analysis of all Inuit (β=0.60 mmol/L, SE=0.045, P=4.6x10E-40). We also detected an association between R730W genotype and LDL-C through combined analysis (β=-0.08 mmol/L, SE=0.042, P=0.047). Conclusions: We report a common DNA variant in LDLR, G116S, which uniquely has a large effect on plasma LDL-C

levels, although not as large as FH-causing mutations. Follow-up experiments include cell-based in vitro assays of the effects of both variants on LDLR expression and function.

## Exome sequencing identifies NFS1 deficiency in a novel Fe-S cluster disease, infantile mitochondrial complex II/III deficiency

**Sali M.K. Farhan**, Jian Wang, John F. Robinson, Piya Lahiry, Victoria M. Siu, Chitra Prasad, Jonathan B. Kronick, David A. Ramsay, C. Anthony Rupar, and Robert A. Hegele.

Iron-sulfur (Fe-S) proteins are a class of highly conserved and ubiquitous prosthetic groups with unique chemical properties that allow them to assist in various key biochemical pathways. Eukaryotic Fe-S proteins are present in the mitochondria, cytosol, endoplasmic reticulum and nucleus. Fe-S proteins form Fe-S clusters, which can transfer electrons, stabilize proteins or execute regulatory functions. Herein, we describe Infantile mitochondrial complex II/III deficiency, a novel autosomal recessive mitochondrial disease characterized by lactic acidemia, hypotonia, respiratory chain complex II and III deficiency, multisystem organ failure and abnormal mitochondria. We applied autozygosity mapping to identify a homozygous region on chromosome 20 containing 453 genes. Next, through exome sequencing we generated a list of variants within the autozygous region. We applied a filtering strategy using in silico analyses, population studies and functional tests to determine mutation pathogenicity, which allowed us to converge on NFS1 p.Arg72Gln as the likely causative mutation. We thus describe the first disease in man likely caused by deficiency in NFS1, a cysteine desulfurase localized to the cytosol and mitochondria that is implicated in respiratory chain function and iron maintenance by forming Fe-S clusters. Our results demonstrate the importance of Fe-S cluster biogenesis and proper assembly in human physiology.

## Observer Agreement and Construct Validity in Central Endoscopic Assessment of Disease Activity in Ulcerative Colitis

Pola S; **Feagan BG**; Fahmy M; Vandervoort MK; D'Haens GR; McDonald JW; Panaccione R; Rutgeerts PG; Travis S; Van Assche GA; Vermeire S; Loftus EV; Zou GY; Nelson S; Sandborn W; Levesque B.

Introduction: The validity and operating properties of endoscopic indices (EIs) for UC remains unknown. Scoring of EIs by a common central reader is believed to enhance the quality of RCTs, however variability of EIs across multiple readers has not been studied.
Aim: To evaluate the inter- and intra-observer agreement of central readers across the UC EIs.
Methods: Seven experts reviewed 50 sigmoidoscopic video recordings of patients with UC. Disease activity was assessed on 3 occasions using the Modified Baron Score (MBS), Modified Mayo Clinic Score (MMCS), and the UC Endoscopic Index of Severity (UCEIS). A 100mm Visual Analog Scale (VAS) global rating of severity was also completed. A 2-way random effects ANOVA model estimated the inter- and intra-observer agreement. A mixed model assessed the construct validity of descriptors by measuring correlation with VAS.
Results: The pooled data for intra-observer agreement was 0.89 (0.85-0.92) for UCDAI, 0.88 (0.84-0.92) for MBS, 0.89 (0.85-0.93) for UCEIS, and 0.91 (0.88-0.94) for VAS. The corresponding values for inter-observer agreement were 0.79 (0.72-0.85), 0.78 (0.71-0.85), 0.83 (0.77-0.88), and 0.78 (0.70-0.85). The pooled data for intra-observer agreement was 0.79 (0.73-0.84) for vascular pattern, 0.78 (0.73-0.83) for bleeding, and 0.86 (0.82-0.90) for erosions. The corresponding values for inter-observer agreement were 0.68 (0.61-0.76), 0.64 (0.56-0.72), and 0.77 (0.70-0.83).
Conclusion: Central reading of EIs for UC by experts had excellent intra- and inter- observer agreement. These findings imply that central reading is highly reliable for the assessment of UC endoscopic severity. UCEIS descriptors

substantially correlate with global endoscopic severity ratings.

## Responsiveness of Central Endoscopic Assessment of Disease Activity Using the Modified Mayo Clinic Score in Ulcerative Colitis

Levesque BG, Pola S; King D; D'Haens GR; McDonald JW; Zou G; Sandborn W; **Feagan BG.**

Introduction: The Modified Mayo Clinic Score (MMCS) is commonly used to assess disease activity in ulcerative colitis (UC). MMCS scoring is inconsistent between investigators and its validity has never been fully investigated. Scoring by a common central expert reviewer reduces the variability in disease activity scoring. It is crucial that indices are responsive to changes in disease activity to be considered effective and valid for use in clinical trials.
Aim: To evaluate the responsiveness of the MMCS endoscopic sub-score to changes in UC disease activity following therapeutic intervention.
Methods: An expert central reviewer scored videos from a placebo-controlled randomized trial of Asacol™ (800mg mesalamine formulation) in patients with mildly-moderately active UC.
Patient Eligibility:
- A MMCS endoscopy sub-score ≥ 2 points.
- A total MMCS score of 4-10 points.

Two-sample t-tests calculated the significance of disease activity changes from week 0 to week 6 and 10 weeks.
Results: At week 6 the median change is endoscopic sub-score from baseline was -0.25 (95% CI 0.08-0.42) for the placebo group and -0.54 (95% CI 0.37-0.71) in the Asacol group (p=0.017). The corresponding values at week 10 were -0.14 (95% CI 0.06-0.34) and -0.66 (95% CI 0.49-0.83), p<0.001.
Conclusion: The endoscopic sub-score of the MMCS is a responsive index to a treatment of known efficacy in UC disease activity following therapeutic intervention. Additional study is merited to evaluate the responsiveness of other endoscopic indices, and their accuracy for detecting change.

## Ciprofloxacin and rifampin have opposite effects on levothyroxine absorption

**Alyse Goldberg**, Rommel G. Tirona, Linda J. Asher, Richard B. Kim, Stan H.M. Van Uum.

Background: Levothyroxine (T4) absorption varies between individuals, and can be affected by various concomitantly administered drugs. Case reports have indicated that treatment with ciprofloxacin or rifampin can interact with T4 treatment in hypothyroid patients.
Purpose: We hypothesize that T4 transporting proteins expressed in the gut are the mechanistic site for inhibition of thyroid hormone absorption by concomitantly administered drugs. Thus, the goal of this study was to formally determine the acute effect of co-administration of ciprofloxacin on T4 absorption and compare that with a well-known OATP inhibitor (rifampin) to better elucidate the potential relevance of intestinal transporters to T4 absorption.
Methods: The effects of that two antibiotics on T4 absorption were prospectively assessed in double blind-randomized, crossover fashion. Eight healthy volunteers received 1000 microgram T4 combined with placebo, ciprofloxacin 750 mg or rifampin 600 mg as single doses. We measured total plasma T4 concentrations over a 6 hour period after dosing using liquid chromatography-tandem mass spectrometry (LC-MS/MS). For each study arm, T4 areas under the plasma concentration-time curve (AUC) were compared.
Results: Co-administration of ciprofloxacin significantly decreased the T4 AUC by 39% (p=0.035), while, surprisingly, rifampin significantly increased T4 AUC by 25% (p=0.003).
Conclusion: Intestinal absorption of T4 is differentially affected by acute co-administration of ciprofloxacin or rifampin. Mechanistic studies focused on intestinal, and possibly hepatic

thyroid hormone transporters are required to explain the observed drug interactions with T4.

## The Adverse Effects of Dabigatran on the Gastrointestinal System

**Zaodi Gu**, Nilesh Chande.

Dabigatran is a one of the newer anticoagulants that have been approved for clinical use. It is a direct thrombin inhibitor. Compared to warfarin, it has the advantage of not requiring clinical monitoring. However, there are no antidotes. Several trials have been done on dabigatran, and there is some emerging data to suggest that it may cause more upper GI bleed and dyspepsia. We conducted a systematic review of all the trials published on dabigatran to further investigate this. A total of 11 trials from 2004 to 2013 were reviewed. They included the use of dabigatran for four different indications: atrial fibrillation, post myocardial anticoagulation, VTE treatment and DVT prophylaxis post orthopedic surgeries. 10 trials were included in the systematic review. Except for the use of dagibatran for DVT prophylaxis post orthopedic surgery (4 of 10 trials) where the dose and length of administration are different, there seems to be a trend towards more upper gastrointestinal bleeding for dabigatran than warfarin (3 of 6 trials). Dabigatran also results in almost twice as much gastrointestinal adverse effects such as dyspepsia (4 of 6 trials). A possible explanation for this is dabigatran requires a lower pH for absorption.

## Use of an N-of-1 trial to assess levothyroxine intolerance in a patient with hypothyroidism

**Ronen Gurfinkel**, Justin Leushner, Terri L. Paul, Jeffrey L. Mahon.

Background: Levothyroxine (l-thyroxine) is a well-tolerated treatment for hypothyroidism. A 29-year-old man previously treated with l-thyroxine 150 mcg/d for primary hypothyroidism developed headaches and lethargy that were ascribed to the drug. An N-of-1 trial was done to determine whether the symptoms could be objectively linked to l-thyroxine therapy.
Methods: L-thyroxine 25 mcg and placebo were compounded in identical capsules, and each given in 10 day periods in pairs, with the order within pairs being randomly determined. In total, 6 exposures (3 active and 3 placebo) were performed with washout periods of at least 7 days. The physician and patient were masked to treatments. The patient recorded daily occurrence of headaches and lethargy and, if present, symptom intensity using a 7-point (0 = no symptoms; 7 = severe symptoms) Likert scale.
Results: Visual inspection of symptom score plots showed strong associations between headache and lethargy within 3 days of starting l-thyroxine. Early discontinuation occurred during each l-thyroxine period because of symptoms (mean duration of treatment 7.3 days), whereas the entire 10 days of treatment were completed during all placebo periods. The mean symptom score for headaches on l-thyroxine across all 3 periods was 2.85 vs. 0 while on placebo ($p = 0.003$). For lethargy, the corresponding values were 2.96 vs. 0 ($p = 0.009$).
Conclusion: This N-of-1 trial provided objective evidence that headache and lethargy were due to l-thyroxine in this patient. This highlights how N-of-1 trials can guide decisions about l-thyroxine therapy in individual patients.

## Case Report of Oscillatory Positive Expiratory Pressure Treatment in Chronic Obstructive Pulmonary Disease

**Aasim Hasany**, Sarah Svenningsen, Brian N Jobse, Nikhil Kanhere, Miranda Kirby, Jason Suggett, Grace Parraga, and David G McCormack.

Rationale: There are few studies of airway clearance techniques in Chronic Obstructive Pulmonary Disease (COPD). Here we evaluated a prototype hand-held oscillatory

positive expiratory pressure (oPEP) device (Aerobika™, Trudell Medical International) in two ex-smokers with COPD. Both patients were part of a larger study of seventeen subjects enrolled in a randomized cross-over study of the safety and efficacy of oPEP use in COPD.
Methods: Two ex-smokers with COPD were randomized to self-administered oPEP therapy and evaluated on three occasions during a 4 week treatment period using hyperpolarized 3He MRI, pulmonary function tests (PFT), six-minute walk test (6MWT), the St. Georges Respiratory Questionnaire (SGRQ), and a sputum clearance diary.
Results: Subject 1, was a self-reported responder (Female, age=73, GOLD stage III) who also showed improved FVC%pred, TLC%pred, FRC%pred, RV%pred, dyspnea score and SGRQ overall score. There was also a small decrease in 3He MRI ventilation defect percent. This self-reported responder remained on therapy for an extended longitudinal evaluation and after an additional 3 months she continued to show improved symptoms, mucous clearance and imaging. Subject 2 was a self-reported non-responder (Female, age=69, GOLD stage II) and she had worse RV, TLC, FVC and no improvement in 3He MRI measurements after 4-weeks of oPEP therapy.
Conclusions: In this pilot, proof-of-concept study, self-administered oPEP therapy in ex-smokers with COPD variably affected lung volumes, functional imaging measures, and symptoms. These are preliminary results of a larger study investigating oPEP therapy in COPD.

## The Effect of Current Induction Regimens on Post-Transplant Cytomegalovirus Infection in CMV Seropositive Liver Transplant Patients

**Seyed M. Hosseini-Moghaddam**, Chian Yong Low, Coleman Rotstein, Eberhard L. Renner, Shahid Husain.

Introduction: We evaluated the relative risks of different immunoprophylaxis regimens in CMV seropositive LTRs at one year.
Methods: In a historical cohort design, we studied 343 CMV seropositive (R+) and 83 seronegative (D-/R-) consecutive LTRs from 2004 to 2007. Immunoprophylaxis regimens used included steroid-only, steroids plus rabbit antithymocyte globulin (rATG) and steroids plus basiliximab. CMV prophylaxis (ganciclovir or valganciclovir) was used in selected patients with rATG induction at the discretion of the treating physicians. Logistic regression analysis, Cox proportional-hazards regression model and log-rank test were performed for multivariate analysis as appropriate.
Results: CMV infection rates were 15.7% (54/343) in CMV R+ LTRs and 2.4% (2/83) in CMV R- LTRs. Among CMV R+ LTRs who received rATG, the use of at least 6 weeks of CMV prophylaxis reduced the rate of CMV infection from 24.4% (19/78) to 11.7% (9/77). In multivariate analysis, CMV R+ versus D-/R- (OR=13.1, 95%CI: 1.8-97.2), rATG >3mg/kg versus steroid-only induction (OR=1.6, 95%CI: 1.1-2.3) and CMV prophylaxis <6 weeks versus ≥6 weeks (OR=2.7, 95%CI: 1.2-6.4) were independently associated with CMV infection. At least 6 weeks CMV prophylaxis significantly decreased the risk of CMV infection (OR=1.9, 95%CI: 1.1-3.9; p=0.03).
Conclusion: The use of rATG induction regimen enhances the risk of CMV infection in CMV R+ LTRs, specifically in the CMV D-/R+ group. Prophylaxis with valganciclovir for at least 6 weeks in this group reduces the risk of CMV infection.

## Dynapenia is associated with gait variability in community-dwelling older adults

**Anam Islam**, Manuel Montero-Odasso.

Loss of muscle mass, sarcopenia, in older adults is an important marker of frailty due to the association with mobility decline, falls, fractures, and mortality. However, dynapenia, the loss of muscle strength, has been shown to manifest earlier than sarcopenia and is more consistently associated with disability and mortality. It is

unknown whether dynapenia is associated with early gait disturbances, specifically gait variability. Gait variability is a measure of gait regulation, and high gait variability is an early marker of mobility decline and a predictor of falls. Our aim was to determine if dynapenia in community older adults is associated with poorer gait performance, specifically high gait variability. In 184 community-dwelling older adults (age ≥75) muscle weakness was assessed by measuring the average grip strength in the dominant hand using a handheld dynamometer. Gait variables were assessed under "usual" and "fast" pace conditions using an electronic walkway. Relative risk analysis evaluated the association of muscle weakness to each of the gait parameters. Older male adults in the lowest quartile of grip strength (<20.67 kg) had slower gait velocity [Mean %CoV (SD)= 82.93 (34.51)] [RR (95%CI)= 1.53(0.58,4.06)], and increased stride time variability [Mean %CoV (SD)= 5.81(1.94)] [RR (95%CI)= 1.71(0.82, 3.57)], then those in the highest quartile of grip strength (≥32.33 kg). Results were similar in female participants. Our findings have interesting clinical implications because muscle strength assessments can be used in the clinic as an early screening tool to detect those with high gait instability, risk of falls, and mobility decline.

## Development of a multiple-choice question examination to assess interpretation of the clinical examination

**Rebecca Jarvis,** Kathryn Myers, Elaine Zibrowski.

Background:
Interpreting findings from the clinical examination is a critical skill for residents. While bedside case review presents the opportunity for residents to review these skills with faculty, time constraints often intervene.
Methods:
The Evidence-based Examination MCQ (EEMCQ), a 50-question case-based examination, was designed to assess Internal Medicine (IM) resident interpretation of the clinical examination. Items were developed using standard references in evidence-based examination. After pilot-testing and revisions, the EEMCQ was administered to 75 IM residents, followed by a satisfaction survey. Using SPSS software, resident exam performance was explored using one-way analysis of variance, item-to-total correlations, and internal consistency reliability which was estimated by Cronbach alpha.
Results:
The overall mean score on the 50-item examination was 26.85 (SD 5.7; min 12; max 40). Internal consistency was moderate for items with item-to-total correlation above 0.2 ($\alpha = 0.64$). A main effect of postgraduate year on exam performance was not detected. Residents reported that the EEMCQ was of appropriate difficulty and content. Moreover, they perceived that the examination was clinically relevant and would be likely to stimulate their future learning.
Conclusion:
Resident feedback suggests that the EEMCQ provided an opportunity for formative feedback about their ability to interpret the clinical examination. Low overall scores, in combination with the lack of impact by PGY on exam performance, suggests that interpretation of the clinical examination presents a challenge throughout residency. Next steps include exploring the performance of PGY-4 residents on the EEMCQ upon their completion of certification examinations.

## The use of anti-platelet agents in the prevention of large vessel vasculitis-associated ischemic complications: a meta-analysis.

**James Jeong**, Lillian Barra.

Objective. To determine the effectiveness of antiplatelet therapy at reducing ischemic events in patients with large vessel vasculitis.
Methods. We performed a random effects meta-analysis of studies examining antiplatelet and/or anticoagulant therapy (AP/AC) and ischemic events in large vessel vasculitis (LVV). Severe

ischemic events were defined as stroke, ischemic ocular manifestations and claudication symptoms. Any ischemic event included jaw claudication in addition to the above manifestations.
Results. Seven studies met inclusion criteria. The primary study outcome was the risk of severe ischemic events in patients treated with AP/AC versus no treatment expressed as an odds ratio (OR). The risk of any ischemic event was a secondary outcome. When accounting for baseline atherosclerotic risk factors, AP/AC was protective for severe ischemic events: OR 0.20 (95% CI 0.12-0.32); as well as for any ischemic events: OR 0.33 (95% CI 0.13-0.81). Subgroup analyses established a priori were also performed comparing i) AP and AC therapy alone ii) ischemic events reported at baseline and follow-up. AP alone had a protective effect on ischemic events when compared to no treatment when controlling for cardiovascular risk factors (OR 0.21, 95% CI 0.09-0.50). On follow-up alone, a protective effect with an OR 0.18 (95% CI 0.04-0.83) in the AP/AC group was observed versus controls.
Conclusion: Antiplatelet therapy significantly decreases ischemic events in patients with LVV. However, in most cases, the treatment was initiated prior to the diagnosis of vasculitis. Available studies do not address whether initiating anti-platelet therapy at the time of GCA diagnosis is beneficial.

## A situative education and patient care tool developed through Incorporation of Lean Theory into Distributed Medical Education design

**Ali Alnoor Kara**, Shanil Vinode Narayan.

Introduction:
Medical education has changed over recent years, emphasizing CanMEDS and competency-based medical education. Implementation threatens to overwhelm with process design concerns. Lean Theory is applied as a successful strategy for process management in the manufacturing and health care sectors. Lean Theory can help to inform Education Design.
Method:
We created a web-based medical education application (app), GenMedicine, using Lean Theory to direct development. Design elements identified by Lean include a focus on delivering high-yield resources to trainees, sequencing educational and patient-care activities derived from a clinical encounter, and providing a user-friendly interface to facilitate flow and use. Trainees can document their progress in real-time, and use is monitored allowing for iterative improvement.
Summary of Innovation:
We collaborate with PatientKeeper, a hospital EMR provider, to link patient data with our diagnosis-specific resources. When trainees encounter a diagnosis, a situative information network is automatically created. Resources mapped to the CanMEDS framework for this particular patient encounter can be accessed by the user. Trainees can access educational information and resources, and document their review of this information in real time. Moving resources directly to the trainee takes advantage of adult-learning theory and the concept of "information stickiness" that comes with situativity.
Conclusion:
GenMedicine is a web-based app which can provide educational and point-of-care resources particular to a current clinical encounter, with an e-Portfolio feature to allow real-time documentation. It is a tool for educators to distribute medical education and facilitates knowledge translation by capitalizing on Lean Theory.

## Less is More in the Geriatric Population? Safety and Efficacy of R-mini-CHOP chemotherapy for Treatment of Diffuse Large B Cell Lymphoma in the Very Elderly: A Prospective Quality Assurance Study

**Selay Lam**, Gwynivere Davies, Leonard Minuk, Joy Mangel.

Background: Elderly patients are known to have worse outcomes than younger patients with DLBCL, partly due to comorbidities and poor performance status that decrease tolerability to treatment. A recent phase II study demonstrated that elderly patients with DLBCL treated with an attenuated dose of R-CHOP called "R-mini-CHOP" had excellent tolerability and good efficacy. This prompted a change in treatment policy of very elderly patients (age > 80) with DLBCL at the LRCP.
Objective: This quality assurance study was undertaken in order to monitor and ensure the safety and efficacy of this practice change.
Methods: Data was collected prospectively on 17 elderly patients with DLBCL treated on R-mini-CHOP since November 2011. A retrospective chart review was also performed on 16 patients > 80 who were treated with full dose R-CHOP at our centre in the preceding years as a historical control group for our prospective cohort.
Results: All 17 patients in prospective group had advanced disease vs. only 6/16 patients in the retrospective group (p=0.00004). Overall response rate thus far is 10/12 (83%) with 7 CRs (58.3%) and 3 PRs (25%) with attenuated dose chemotherapy. This compares favorably to the retrospective group who had an ORR of 13/16 (81%, p=0.30), 7 CRs (43.8%) and 6 PR's (37.5%).
Conclusions: Despite the more aggressive disease in our R-mini-CHOP patients compared to the historical controls treated with R-CHOP, similar response rates are being achieved, with fewer adverse effects and better tolerability.

## Enumeration of Bone Microparticles in Plasma of Multiple Myeloma Patients

**Selay Lam**, Colleen Biggs, Laura Meraw, Andre St. Amant, Len Luyt, Hon Leong, Leonard Minuk.

Objective: To develop a non-invasive test to measure bone resorption in multiple myeloma patients.
Methods: A novel blood test was developed to enumerate bone microparticles in the blood due to myeloma-induced osteolytic activity. This test utilizes a bone specific probe,
which is a bisphosphonate conjugated with a fluorophore (Alendronate-Cy5) to bind to bone. Nanoscale flow cytometry is used to enumerate microparticle. Alendronate-Cy5/FITC-positive
events exhibiting a diameter between 110-880 nm were classified as bone microparticles. Bone microparticles were enumerated in: 1) healthy volunteers, 2) patients with monoclonal gammopathy of undetermined significance (MGUS) and 3) patients with newly diagnosed MM.
Results: Plasma samples were obtained from 21 healthy volunteers, 12 MGUS patients, and 22 patients with MM. Alendronate-Cy5/FITC dual-positive bone microparticle events were 3648±1034/µL, 4836±1423/ µL, and 6230±1913/µL respectively. Compared to healthy volunteers, only MM patients exhibited higher bone microparticle levels. A greater portion of healthy volunteer plasmas exhibited zero bone microparticle than the MM patients (9/21 vs. 4/22).
Conclusion: In a pilot study, we demonstrated the feasibility of this assay and observed high counts of bone microparticles in MM patient plasmas while lower levels were found in
normal volunteer plasmas and in patients with MGUS. This assay is a promising non-invasive measure of osteolytic bone disease and for following response to anti-myeloma/bone directed
therapy.

## RIPK3 mediated necroptosis promotes donor kidney inflammatory injury and reduces allograft survival

**Arthur Lau**, Shuang Wang, Jifu Jiang, Aaron Haig, Alexander Pavlosky, Zhu-Xu Zhang, Anthony M. Jevnikar.

Kidney transplant injury occurs with ischemia and alloimmunity. Members of the receptor interacting protein kinase family (RIPK1,3) are key regulators of 'necroptosis', a newly

recognized, regulated form of necrosis. Necroptosis and apoptosis death appear to be counterbalanced as caspase-8 inhibition can divert death from apoptosis to necrosis. Inhibition of necroptosis in donor organs to limit injury has not been studied in transplant models. In this study, necroptosis was triggered in caspase inhibited tubular cells (TEC) exposed to TNFa in vitro, while RIPK1 inhibition with Nec-1 or use of RIPK3-/- TEC, prevented necroptosis. In vivo, shRNA silencing of caspase-8 in donor B6 mouse kidneys increased necroptosis, enhanced HMGB1 release, reduced renal function and accelerated rejection when transplanted into BALB/c recipients. Using ethidium homodimer (EHD) perfusion to assess necrosis in vivo, necrosis was abrogated in RIPK3-/- kidneys post-ischemia. Following transplantation, recipients receiving RIPK3-/- kidneys had longer survival (p=0.002) and improved renal function, (p=0.03) when compared to controls. In summary, we show for the first time that RIPK3 mediated necroptosis in donor kidneys can promote inflammatory injury, and has a major impact on renal IRI and transplant survival. We suggest inhibition of necroptosis in donor organs may similarly provide a major clinical benefit.

## PREDICTING THE C282Y HOMOZYGOTE GENOTYPE FROM SERUM FERRITIN AND TRANSFERRIN SATURATION IN YOUR PATIENT.

**Andrew Lim**, M Speechley PhD. Dept of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario; PC Adams MD. Division of Gastroenterology, University Hospital, London, Ontario.

Background:
Serum ferritin and transferrin saturation have been used as a clinical guide to informally lead physicians to a diagnosis of Hemochromatosis. One etiology of Hemochromatosis is from C282Y mutations of the HFE gene on both alleles. In this study, a large population based sample of caucasians was used to create an equation to predict the C282Y homozygote genotype using serum ferritin and transferrin saturation levels. In addition, a smartphone application was developed to provide physicians with easy access to predicting C282Y homozygosity.
Methods:
The HEIRS study screened over 100,000 participants for the C282Y mutation of the HFE gene. Analysis of the dataset (n=44,808) was done using a Bernoulli regression with logit link in the form where the binary response variable was C282Y homozygotes, and explanatory variables were serum ferritin, and transferrin saturations. The numerical solution of the Bernoulli regression generated a C282Y homozygote probability equation for all serum ferritins, and transferrin saturations. A new Android application was developed using the Java computer language to allow for immediate C282Y homozygote probabilities to be estimated.
Results:
An example of the analysis is a caucasian man with a transferrin saturation of 85% and a ferritin of 700 μg/L has a 32.2% [95% Confidence Interval 8.33-70.9%] probability of being a C282Y homozygote.
Conclusions:
A large population based sample of 44,808 participants has led to the development of a new computer/smartphone based tool to predict the probability of C282Y homozygosity on your smartphone.

## Ultrasound guidance for vascular access in patients undergoing coronary angiography via the transradial approach: A prospective clinical study.

**Malak M**, Preston SD, Camuglia AC, Sharma A, Lavi S.

Background:
Transradial access (TRA) for invasive coronary assessment and percutaneous coronary intervention (PCI) has evolved as an alternative default strategy for vascular access to the femoral approach. successful cannulation of the radial artery, both in a timely fashion, and with

minimal needle passes so as to reduce the rate of arterial spasm still a challenge. We sought to assess the value of using ultrasound (US) to improve these parameters.
Methodology:
prospective, single centre study of consecutive patients presenting for invasive coronary angiography (or PCI) via the transradial approach. The first phase of the study enrolled consecutive patients underwent TRA without the assistance of ultrasound (US) followed by consecutive patients who underwent TRA using US guidance. Primary outcome measures were time between commencing needle attempts for arterial access and sheath insertion, number of needle passes through the skin to achieve arterial access and number of artery punctures to secure access with wire and sheath.
Results:
200 consecutive patients were enrolled. 95 consecutive patients underwent TRA without US guidance followed by 105 patients with US assistance. There were no statistically significant differences in any of the primary outcome measures.
Conclusions:
Use of US guidance to assist in TRA did not significantly reduce time to vascular access or the number of access attempts required. Our study does not support the routine use of US to assist in obtaining vascular access for TRA cases. The use of US to assist in obtaining TRA should therefore be reserved for selected cases only.

## Are We Asking Residents To Do Too Much? Web-Based Evaluation by Residents in Postgraduate Medicine

**Jacqueline Malette**, Elaine Zibrowski, Jeff Crukley, Kathryn Myers.

Background/Purpose: In most postgraduate programs, 'pencil-and-paper' assessments have been replaced by web-based online evaluation. Despite their use, we know little about how these have affected residents in their role as assessors.
Methodology: We performed a three-year retrospective audit of web-based evaluations completed by a cohort of 30 internal medicine residents who began training in 2009. For each academic year, evaluation requests were aggregated by resident and content analyzed in terms of the type of form, number of items, and whether the trainee submitted the form back to the program by the administrative deadline. To gain insight into residents' experiences as assessors, this data was triangulated with group interviews.
Results: 8,672 evaluation requests were sent. The most common probed residents' assessments of academic sessions (49.1%), faculty teaching (33.4%), and rotation/services (13.8%). At the end of their training, residents had completed an average of 258.1 evaluations (SD 135.7; min-max, 5-553). While an association was not detected between the overall prevalence of requests and PGY (chi-squared=0.74; p=.69), residents left increasing numbers of evaluations outstanding as they progressed thorough their training (chi-squared=29.72; p<.0001). Thirty percent had outstanding evaluations [mean(SD)=56(70.3); min-max, 1-282]. The majority were for academic sessions (83.8%). When asked about how they have approached their evaluation tasks, residents reported being 'bombarded' and 'annoyed' by the volume of requests.
Conclusions/Discussion: Although this method of evaluation administration is efficient, our data suggest that the volume of evaluation requests sent to residents creates a burden that results in diminishing completion rates.

## Incidence of Venous Thromboembolism in Gastrointestinal Bleeding

**Neel Malhotra**, Nilesh Chande.

Background: Patients with acute gastrointestinal (GI) bleeding represent a challenging population to manage with respect to the safety of anticoagulant therapy for prophylaxis against venous thromboembolism. Methods: Inclusion criteria included those admitted with a primary diagnosis of a GI bleed along with any

endoscopic confirmed source (over a two year period). The primary end point was the development of venous thromboembolism (deep venous thrombosis or pulmonary embolism) within one year after presentation. Results: Data for 504 patients admitted with GI bleeding was eligible for review. The total number of VTE events was 20 (3.97%). 397 patients were not given VTE prophylaxis during their hospitalization. Of those that were, 36 patients were given prophylactic dalteparin or heparin for the full duration of their stay. 113 patients had at least one other risk factor for VTE including recent or subsequent surgery, past thrombotic events or malignancy, however only 24 of these patients received VTE prophylaxis. The incidence of thrombosis in those with other risk factors for VTE was significantly higher than those without (9.7% vs. 2.3% p=0.001). Overall, there was no significant difference in thrombotic events in those receiving pharmacologic prophylaxis from those who did not (1.19% vs. 2.78% p=0.4). Conclusion: Although there was not a statistically significant benefit to the use of prophylaxis in those with a GI bleed, there was likely some underlying benefit. Overall, VTE prophylaxis should be considered for all patients admitted with an active bleed particularly if they have other factors predisposing them to thrombosis.

## Global Predictors of Response to Cardiac Resynchronization Therapy from Pre-Implantation Cardiovascular Magnetic Resonance Imaging

**Usha Manian**, Raymond Yee, Immaculate Nevis, David McCarty, John Stirrat, Jorge Wong, David Scholl, Lorne Gula, Peter Leong-Sit, Maria Drangova and James A. White.

Background: Cardiac resynchronization therapy (CRT) is an established treatment for symptomatic heart failure. However, up to 40% of eligible patients do not respond. The predictive utility of global measures for ventricular remodeling and scar burden remains unclear.

Methods and Results: Ninety patients receiving CRT underwent pre-implant cardiovascular MRI followed by echocardiography at 3 and 6 months. Blinded measurement of Left Ventricular (LV) and Right Ventricular (RV) dimensions, volumes and mass were obtained as markers of global remodeling, measured using semi-automated analysis of short axis cine datasets. Total LV scar was determined from Late Gadolinium Enhancement (LGE) images using manual tracing of endocardial and epicardial borders and a signal threshold ≥5SD above reference myocardium. Response to CRT was defined as a reduction in LV end-systolic volume (ESV) ≥15% at 6 months. The mean age was 65.8 ± 9.1 years with a mean LV Ejection fraction (EF) of 25.4 ± 7.3%. Overall, 62 patients (69%) met response criteria. Among all baseline variables only ischemic etiology, GFR, presence of RBBB, and total LV scar burden were significantly associated with CRT response ($p<0.05$). Total LV scar remained independently associated with response following multivariate logistic regression adjusting for ischemic etiology ($p=0.019$). ROC analysis identified total LV scar to yield an AUC of 0.7 for prediction of CRT response.
Conclusions: Baseline LV and RV chamber remodeling did not predict CRT response in this study. However, total LV scar was inversely associated with this outcome, and remained independently predictive following adjustment for cardiomyopathy etiology.

## Utility of N-of-1 trials in the Assessment and Management of Patients with Statin-related Myopathy

**Alaa Monjed**, Jeffrey L Mahon, Charlotte Mcdonald, Robert Hegele, Tisha Joy.

Statin-related myopathy occurs in 10-20% of individuals prescribed statins, sometimes resulting in premature statin withdrawal.
Aim: To assess potential of N-of-1 trials for evaluating reproducibility of myalgias from statins in patients with a history of statin-related myopathy.

Methods: 10 patients who previously developed myalgias within 3 weeks of statin initiation were enrolled. The statin previously associated with myalgias formed the active arm; matching placebos were compounded into identical capsules. Each active and placebo drug was given in 3-week periods in pairs, separated by a 3-week washout. The order within pairs was randomly determined. A complete N-of-1 trial was 3 active and 3 placebo treatment periods and lasted 33 weeks.
Outcomes and Analysis: Main outcome was myalgias documented by Visual Analogue Scale; secondary outcomes were Pain Severity Score and Pain Interference Score. Point estimate and 95% confidence intervals were determined on the difference in mean symptom scores within treatment pairs. An N-of-1 trial was considered positive if the point estimate was statistically higher during statin therapy in completed pairs, based on a p value < 0.05 using paired t tests.
Results: Of 10 patients enrolled, 2 withdrew prior to starting; 7 completed 3 pairs; 1 finished 2 pairs. In all 8 N-of-1 trials, no statistically significant differences in VAS, PIS, and PSS between statin and placebo periods were demonstrated. After discussion of the results, 5 of 7 patients resumed and remain on statin therapy.
Conclusions: In these patients, N-of-1 trials provided objective data that statins did not cause their prior myalgias.

## Parathyroid Hormone But Not Vitamin D Is Associated With Gait Impairment in Older Adults

**Susan W Muir**, Karen Gopaul, Richard Crilly, Manuel Montero Odasso.

Background: Vitamin D deficiency is associated with disability including poor physical performance, weakness, falls and fractures. Elevated parathyroid hormone (PTH) is also associated with increased falls risk. While vitamin D supplementation can improve balance function, its effect on gait is contradictory. The effect of PTH on gait has not been published. The aim was to evaluate the association of vitamin D and PTH levels on spatiotemporal measures of gait.
Methods: Cross-sectional study of 66 community-dwelling older adults (mean age = 80.4±7.3, 57.6% female). Gait (usual pace) was evaluated with the GaitRITE® mat. A force platform (Bertec®) was used for the Modified Clinical Test for Sensory Integration in Balance (MCTSIB) to measure centre of pressure motion. Multivariable linear regression evaluated the relationship between serum vitamin D levels and PTH on gait and balance.
Results: The distribution of vitamin D levels were: 0% deficient (<30nmol/L); 15.2% insufficient (30-50nmol/L); 16.7% normal (51-75nmol/L); and 68.2% supernormal (>75nmol/L). Elevated levels of PTH (>5.00pmol/L) were found in 25.8%. Vitamin D was not associated with gait performance (p>0.05). Increasing PTH levels were independently associated with poor gait performance. Neither vitamin D nor PTH levels were associated with centre of pressure displacement (total sway area, mediolateral or posterolateral maximal excursion) in any of the MTSIB test conditions.
Conclusions: Increasing PTH was independently associated with poor gait performance. Lack of an effect with vitamin D could be that few people were below therapeutic levels. Our findings suggest that PTH may have a neuromuscular action independent of Vitamin D.

## Targeted over-expression of calpain-1 in mitochondria induces reactive oxygen species generation and apoptosis in cardiomyocytes

**Rui Ni**, Dong Zheng,Tianqing Peng.

Introduction: Calpains have been implicated in a wide variety of cardiovascular diseases. We have demonstrated a critical role of calpain in diabetic cardiomyopathy. Our recent study has shown that diabetes induces calpain-1 accumulation in mitochondria of the heart, which correlated with mitochondrial reactive oxygen species (ROS) generation. Importantly,

inhibition of calpain reduced mitochondrial ROS generation in diabetic hearts. These previous studies suggest that calpain-1 accumulation in mitochondria may mediate ROS generation, contributing to diabetic cardiomyopathy. Thus, this study investigated whether calpain-1 accumulation in mitochondria is sufficient to induce ROS generation and apoptosis in cardiomyocytes.
Methods and Results: A recombinant expressing plasmid pCMV/Myc/Mito-capn1 was made to selectively over-express calpain-1 in mitochondria. 48 hours after transfection in rat myoblast H9c2 cells, western result confirmed selective over-expression of calpain-1 in mitochondria but not cytosols. Over-expression of mitochondrial calpain-1 increased superoxide production in H9c2 cells as determined by DHE staining. To confirm mitochondrial superoxide generation, we assessed single mitochondrial 'superoxide flashes' in living H9c2 cells by fluorescent confocal microscope. Consistently, superoxide flashes were significantly increased in pCMV/Myc/Mito-capn1 compared with control plasmid transfected H9c2 cells. The mitochondrial superoxide generation nicely correlated with increases in caspase-3 activity and DNA fragmentation in H9c2 cells. Both mitochondrial superoxide production and apoptosis were inhibited by mitochondrial targeted antioxidants SS31 and mito-TEMPO.
Conclusions: Given the important significance of mitochondrial ROS generation in apoptosis and hypertrophy in the heart, mitochondrial ROS generation may represent a novel mechanism by which calpain contributes to diabetic cardiomyopathy.

## RIPK3 regulates microvascular endothelial cell necroptosis and cardiac allograft rejection

**Alexander Pavlosky**, Xuyan Huang, Arthur Lau, Ziqin Yin, Aaron Haig, Dameng Lian, Anthony M. Jevnikar, Zhu-Xu Zhang.

Despite recent advances in immunosuppression, over 50% of patients who have undergone allogeneic cardiac transplantation still suffer from graft loss after 11 years. Cell death in donor grafts results in tissue damage, and ultimately graft rejection, and can occur as an active molecular process through apoptotic, autophagic, and newly identified Receptor Interacting Protein 1 and 3 kinase (RIPK1/3) mediated necroptotic pathways. These variations in cell death may be important for graft survival as necroptosis can lead to the release of chemotactic and activating danger molecules which can activate host immune cells. This pathway has yet to be studied in transplantation.
In this study, necroptosis was induced in murine cardiac microvascular endothelial cell (MVEC) under anti-apoptotic conditions following TNFα treatment. Necroptotic cell death and release of the danger molecule high mobility group box 1 (HMGB1) were inhibited by the RIPK1/3 inhibiting molecule necrostatin-1 and by genetic deletion of RIPK3. In addition, tissue necrosis, release of HMGB1, and graft cell infiltrate were attenuated in RIP3 null heart allografts following transplantation. Finally, a brief sirolimus treatment markedly prolonged RIPK3 null cardiac allograft survival in Balb/c recipients as compared to wildtype C57BL/6 donor grafts. These data suggest that RIPK1/3 contributes to inflammatory injury in cardiac allografts through necroptotic death and the release of danger molecules. The ability of immunosuppression to provide rejection protection or permit tolerance is influenced by the level of cell death and inflammation. We therefore suggest that targeting RIPK mediated necroptosis may be an important therapeutic strategy in organ transplantation.

## Anti-Homocitrullinated Protein/Peptide Antibodies are specific for RA and can recognize citrullinated proteins/peptides

**Maud Racapé**, Mathias Scinocca, David A. Bell, Radha Joseph, Lillian Barra, Ewa Cairns.

Background
Rheumatoid Arthritis (RA) is a chronic autoimmune disease leading to joint destruction. Antibodies to citrullinated proteins/peptides (ACPA) (e.g. citrullinated fibrinogen) are highly specific for RA and are arthritogenic. Citrullination is a posttranslational modification converting the amino acid arginine into citrulline. It has been shown that carbamylation converts lysine into homocitrulline, chemically and structurally similar to citrulline. We have recently showed that RA patients have antibodies (AHCPA) that target homocitrullinated protein (fibrinogen) and that these AHCPA are also specific for RA. Currently the role of AHCPA in RA is unknown.
Hypothesis
AHCPA occur frequently with ACPA, are functionally related to ACPA and may be involved in the pathogenicity of RA in the same way as ACPA.
Objectives
1) To confirm AHCPA specificity for RA and 2) to determine whether AHCPA are functionally related to ACPA by examining AHCPA reactivity with homocitrullinated as well as citrullinated peptides.
Methods
JED peptides containing identical number of citrullinated or homocitrullinated sites were employed. Sera from RA, systemic lupus erythematosus and psoriatic arthritis patients were screened for AHCPA using ELISA. AHCPA reactivity with CitrullinatedJED was examined using inhibition assays and affinity chromatography.
Results
AHCPA were detected only in RA sera and were present in 61/84 (73%) RA patients of whom 57/61 (93%) had ACPA. AHCPA were captured by CitrullinatedJED on affinity column. AHCPA were inhibited by HomocitrullinatedJED and CitrullinatedJED.
Conclusion
AHCPA are specific for RA and their expression correlate with ACPA expression. Most AHCPA recognize CitrullinatedJED suggesting that they are functionally related to ACPA.

## Effect of Education and Performance Feedback on Reducing Inappropriate Urinary Catheter Use in Medicine In-patients

**Hatem Salim**, Dr. Saira Zafar.

Background: Urinary catheters may lead to infectious and noninfectious complications and are associated with increase in healthcare costs, length of stay, morbidity and mortality. Urinary catheters are frequently used when not indicated, or, if indicated, remain in the patient longer than necessary. Studies reveal that interventions promoting timely removal of urinary catheters and use only when indicated have been associated with a reduction in catheter-associated UTI.
Objective: To evaluate the effect of education and performance feedback to team members on CTU in reducing the rate and duration of inappropriately indicated urinary catheterization
Methods: Literature review was performed to determine appropriate indications for urinary catheterization. The rate and duration of appropriate urinary catheterization in medicine in-patients during a baseline period of active surveillance without education and feedback were compared to the rate and duration after implementing education and feedback.
Results: The proportion of catheterized patients on admission with appropriate indications increased from 57 % at baseline to 74% after intervention.
The mean duration of total catheterization decreased from 4.7 days at baseline to 3.6 days after intervention (mean difference -1.1 days).
The mean duration of inappropriate urinary catheter days decreased from 3.4 days at baseline to 2.4 days after intervention (mean difference -1.0 day)
Conclusion: A simple intervention such as implementing education and performance feedback regarding appropriate urinary catheterization was associated with a reduction of unnecessary urinary catheter use. Eefforts should be undertaken to sustain the reduction, such as automatic stop orders or computerized documentation with clear indications for insertion.

## Patient Preferences for Stopping Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia

**David Sanford**, Rachel Kyle BSc, Alejandro Lazo-Langner MD MSc, Anargyros Xenocostas MD, Ian Chin-Yee MD, Kang Howson-Jan MD, and Cyrus Hsia MD.

We explored patient reactions, preferences and risk acceptability of stopping Tyrosine Kinase Inhibitor (TKI) treatment through an interview-assisted survey of patients with Chronic Myeloid Leukemia (CML) at a single tertiary care centre. We included patients with confirmed CML currently being treated with a TKI. A survey was conducted through structured interviews using Visual Analog Scales and 5-point Likert scales. Fifty-six of sixty-three CML patients approached completed the survey. Participant responses suggest that stopping TKI use is appealing to many patients if there is a chance of long-term stable disease and a high probability of response upon restarting a TKI. Participants were more likely to stop their TKI with decreasing risk of relapse. With the current estimated rate of relapse of 60% after discontinuing TKI therapy, the majority of individuals chose to continue their TKIs. However at lower relapse rates reported with 2nd generation TKIs participants are more undecided about stopping.

## Low dose naltrexone for induction of remission in Crohn's disease.

**Dan Segal**, John K MacDonald, Nilesh Chande.

Crohn's disease is a transmural, relapsing inflammatory condition afflicting the gastrointestinal system. The burden of Crohn's disease is growing worldwide and more treatment options are required. Naltrexone, a long-acting opioid antagonist, is known to affect secretion and motility in the gut. Animal studies have found that naltrexone may also have anti-inflammatory effects in a Crohn's disease model. In an open label study low dose naltrexone induced remission in Crohn's. This Cochrane review aims to assess the efficacy and safety of low dose naltrexone (LDN) for the induction of remission in Crohn's disease. Secondary outcomes include clinical response, endoscopic response, improvement in quality of life, and adverse events. A literature search identified two trials that met pre-defined inclusion criteria. There was a statistically significant difference in the proportion of patients (LDN 89% vs. placebo 38%) who achieved a clinical response of at least 70 points on the CDAI scale (RR 2.37; 95% CI 1.23 to 4.56; P =.01; 1 study; 34 patients). There was no significant difference in the proportion of patients (LDN 33% vs. placebo 6.2%) who achieved endoscopic remission defined by a CDEIS score less than 6 (RR 5.33; 95% .72 to 39.69; P=.1; 1 study; 34 patients). The remainder of the results will be presented at research day.

## Treatment on Healing and Prevention of Digital Ulcers in Systemic Sclerosis (SSc): Results from a Meta-Analysis

**Jenny Shu**, Theresa Tingey, Joseph Smuczek, Janet Pope.

Objective(s): To assess the efficacy of therapies in healing and preventing digital ulcers (DU) in systemic sclerosis (SSc).
Method(s): MEDLINE and EMBASE databases and ACR/EULAR abstracts were searched. Randomized controlled trials (RCTs) with outcomes investigating healing or prevention of DU in SSc and comparing a pharmacological therapy with placebo or an active agent were included. The pooled risk ratios (RR) using the fixed-effects model was calculated and heterogeneity was tested using the I2 statistic.
Result(s): Sixty studies were found; 19 were not randomized, 10 did not give DU quantitative data or no comparison of a different drug, leaving 31 RCTs with 1989 patients. Quality was

3/5 or less for 11 trials. DU were not the primary outcome in many RCTs. Phosphodiesterase type 5 (PDE5) inhibitors were significant for DU healing (RR 3.28 [95% CI 1.32,8.13]; p=0.01). Two large bosentan trials were significant for mean number of new DU (standard mean difference [SMD] -0.34 [-0.57, -0.11]; p=0.004). Prostacyclins were not statistically different from placebo, but IV iloprost prevented new DUs (SMD-0.77 [-1.46, -0.08]; p=0.03). Single trials for atorvastatin and vitamin E were positive in the prevention and healing of DU respectively. There were many negative trials: antiplatelet therapy, heparin, dimethyl sulfoxide (DMSO), ketanserin, prazosin, prostaglandin E1 (PGE1), cyclofenil, quinapril, oral N-acetylcysteine (NAC) and topical nitroglycerin formulation.
Conclusion: Small sample sizes, few comparative trials, and heterogeneity limits the conclusions. The results suggest a role for PDE5 inhibitors in the healing of DU; bosentan, IV iloprost and atorvastatin may prevent new DU.

## Desmopressin responsiveness at a capped dose of 15 ug in von Willebrand disease and mild hemophilia A

**Siew Dou-Anne**, Mangel Joy, Laudenbach Lori, Schembri Sheila, Jardine Lawrence, Minuk Leonard.

Introduction: Desmopressin (DDAVP) is a synthetic analogue of vasopressin used in the treatment of patients with type 1 von Willebrand disease (vWD) and mild hemophilia A (HA). A patient's responsiveness to subcutaneous or intravenous DDAVP based on a 0.3ug/kg dose to a maximum of 20 ug (a recommendation present on the Canadian monograph of desmopressin) determines future therapeutic efficacy of the drug.
Aim: To determine whether a lower maximum dose of 15ug subcutaneous DDAVP is able to achieve the same level of DDAVP responsiveness as previously reported findings, and whether this lower dose could be used for adult patients >50kg.
Methods: Retrospective review of patient data from 1995-2011 in adults and children with vWD and HA. Levels of Factor VIII coagulant, von Willebrand factor ristocetin cofactor activity and von Willebrand factor antigen were measured before and one hour after administration of DDAVP in both children and adults with vWD. FVIII:C was measured pre and post-DDAVP in patients with HA.
Results: Overall biologic response rates of 94.9% (in vWD) and 81.3% (in HA) were observed in our adult patients after a DDAVP challenge using a 15ug maximum dose of DDAVP. These results are similar to previously published reports on DDAVP responsiveness using the 0.3ug/kg dosing.
Conclusion: The smaller 15ug DDAVP dose appears to be a reasonable alternative to 20ug in patients >50kg with vWD and mild HA.

## Lower socioeconomic status is associated with more advanced thyroid cancer stage at presentation: a study in two Canadian centres

**Stephanie Siu**, Ted McDonald, Murali Rajaraman, Jason Franklin, Terri Paul, Irina Rachinsky, Deric Morrison, Syed Ali Imran, Steven Burrell, Robert Hart, Albert Driedger, Mahmoud Badreddine, John Yoo, Martin Corsten, Stan Van Uum.

Introduction: Some studies have shown higher incidence of thyroid cancer in patients with insurance coverage and higher socioeconomic status (SES) and more advanced thyroid cancer stage in patients with lower SES, suggesting SES-related health disparity in thyroid cancer. However, it is not known if the same is evident under a universal health care system like Canada.
Methods: We used data from the Canadian Thyroid Cancer Consortium, a large thyroid cancer registry that collects data from two major thyroid cancer referral centers (London, Halifax). We included patients who presented with thyroid cancer between 1998 and 2011. We determined age at presentation, sex, and thyroid cancer

status using the AJCC staging criteria. Individual's postal codes were used to retrieve data from the Canadian Census to approximate household income. Logistic regression was used to determine odds ratios of presenting with advanced stage thyroid cancer as they relate to income, age, and sex.
Results: We included 1701 patients, 1334 cases from London and 367 from Halifax. Thyroid cancer was diagnosed more frequently in the higher SES groups (p<0.001). Compared to patients in the top income quintile, patients in the lowest and second lowest income quintiles had significantly higher odds of having more advanced stage thyroid cancer at presentation (OR 1.58, p=0.002; 1.37, p=0.024 respectively).
Conclusion: Our study suggests that health disparity in thyroid cancer is present in Canada. While thyroid cancers were diagnosed more frequently in patients of higher SES, patients in the lower SES groups had more advanced stage thyroid cancer at presentation.

## Effect of disease modifying drugs on bone mineral density in patients with rheumatoid arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis: A meta-analysis.

**Stephanie Siu**, Janet Pope.

Background: Inflammatory arthritis is a minor risk factor for osteoporosis and it may be that treating systemic inflammation can improve bone mineral density (BMD). The aim of this study was to examine if DMARDs, steroids, and biologics for rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis (PSO), and ankylosing spondylitis (AS) affect BMD.
Methods: Medline, Embase, and Cochrane were searched from 1960 to present using English randomised controlled trials in adults. Review articles were excluded. Studies were grouped based on disease, treatment type, and site of BMD measurement (wrist, lumbar spine (LS), hip).
Results: 180 studies were identified; 19 were eligible (17 RA, 0 PsA, 0 PSO, 2 AS). For RA, significantly less wrist bone loss was seen with biologics (SMD=0.23SD, 95% CI 0.06-0.40, P=0.009, I2=0%) and similarly in one study that examined corticosteroids. Biologics had no significant effect on LS and hip BMD. Corticosteroids had more bone loss compared to placebo on LS (SMD=-0.37SD, 95% CI -0.61 to -0.12, P=0.003, I2=53%) but no difference for hip. For AS, significant BMD increase was seen with biologics in both LS (SMD=0.98SD, 95% CI 0.73-1.23, P<0.001, I2=16%) and hip (SMD=0.38SD, 95% CI 0.13-0.62, P=0.003, I2=0%). There was insufficient data to meta-analyze other diseases.
Conclusion: Based on our RA analysis, biologics and steroids yielded less wrist bone loss (where synovitis is often present) but had no effect on hip. Corticosteroids affected more bone loss in LS whereas biologics had no effect on LS. For AS, biologics yielded increase in both LS and hip BMD.

## The equipoise of perioperative anticoagulation management: a Canadian cross-sectional survey

**Leslie Skeith**, Alejandro Lazo-Langner, Michael J. Kovacs.

INTRODUCTION: While perioperative anticoagulation guidelines exist, there is little evidence to support an optimal management strategy in patients with venous thromboembolism (VTE) on warfarin or rivaroxaban. We sought out to assess general practices among Canadian specialists who manage perioperative anticoagulation. METHODS: In January 2013, we completed a cross-sectional Canadian survey among hematologists and general internists. The survey assessed perioperative warfarin and rivaroxaban management using six hypothetical patient scenarios. The data was collected online using SurveyMonkey® and entered into a database for analysis. 95% confidence intervals for proportions were calculated using the Wilson's score methods. RESULTS: Of the 480 surveys that were distributed, 76 individuals responded (16%). There were 52 general internists (68.42%), 19 hematologists (26.31%), and 5

respondents who classified themselves as 'other' (identified as: 1 thrombosis physician, 2 cardiologists with a thrombosis interest and 2 anticoagulation clinic pharmacists). There was wide variation in responses across all questions. For example, when a 70-year old patient with recurrent DVT/PE underwent a laparoscopic cholecystectomy, 20% of respondents gave no LMWH, 40% used prophylactic-dose LMWH, and 40% used therapeutic-dose LMWH. The highest response percentage for any question of warfarin management was less than 50%, further highlighting the variability in management. CONCLUSION: There is large practice variation in perioperative anticoagulation management among Canadian general internists and hematologists. The variability in responses highlights the lack of consensus for an optimal anticoagulation strategy for commonly encountered perioperative scenarios and underlines the urgent need for studies in this area.

## A Case Report of Kidney and Pancreatic Extramedullary Relapse in Adult Acute Lymphoblastic Leukemia

**Leslie Skeith**, Alejandro Lazo-Langner, Joy Mangel.

Extramedullary relapse of acute lymphoblastic leukemia (ALL) is rare, and has been primarily reported in pediatric patients or hematopoietic stem cell transplant recipients. We report a case of a 62-year old woman who presented with relapsed ALL involving her kidneys, pancreas and bone marrow 2 years after completing chemotherapy with a standard ALL protocol. She initially presented to hospital with a one month history of fatigue and worsening abdominal pain associated with nausea, vomiting and early satiety. Her examination was non-contributory except for a mildly tender abdomen. Investigations showed a normal total leukocyte count and differential, and a normal platelet count, however, she had developed a new normocytic anemia (hemoglobin 85 g/L, previously 146 g/L) and had an elevated creatinine of 193 umol/L (CrCl 30.4 mL/min), up from her baseline of 51 umol/L. Imaging of the patient's abdomen with ultrasound and computed tomography (CT) revealed an enlarged hypoechoic pancreas and bilateral renal enlargement. The kidneys had a diffuse nodular appearance with T2 hyperintensity seen on magnetic resonance imaging, with an exophytic circumscribed homogeneous left renal mass (5.4 x 4.6 cm). A biopsy of the kidney was performed, and the pathology was consistent with B-cell ALL. She initially responded to FLAG (fludarabine, cytarabine, G-CSF) chemotherapy, but unfortunately her disease progressed despite treatment. To the best of our knowledge, this is the first reported case of extramedullary relapse of B-cell ALL to the kidneys and pancreas occurring in an adult patient who had not previously undergone a hematopoietic stem cell transplant.

## CD4+ but not CD8+ memory T cells evade Granzyme B attack by DN-Treg via expression of Spi6

**Ye Su**, Xuyan Huang, Dameng Lian, Zhu-xu Zhang.

Memory T (Tm) cells pose a major barrier to the long term transplant survival. The competency of Tregs in controlling Tm cells remains poorly-defined. Previously we established that double-negative (DN)-Treg cells suppress T-cell and prolong allograft survival. Here we demonstrate that DN Tregs, which highly express FasL, Granzyme B (GzmB) and Perforin (PFN), suppress CD4+ / CD8+ effector T (Teff) and CD8+ memory T (Tm) cells but not CD4+ Tm cells, whereas the suppression on CD8+ Tm is abrogated by PFN deficiency in DN-Tregs. Consistently, in a BALB/c to B6 skin allograft transplantation, adoptive transfer of DN Treg suppressed the rejection mediated by CD4+ / CD8+ Teff and CD8+ Tm cells (76.0±4.9, 87.5± 5.0, and 63.0±4.7 days respectively) but not CD4+ Tm cells (25.3±1.4 days). Both effector memory (Tem) and central memory (Tcm) compartments were significantly suppressed by DN-Treg in vivo, in CD8+ but not CD4+, Tm cells. CD4+ Tm highly expresses GzmB inhibitor

Serine Protease Inhibitor-6 (Spi6). Spi6 deficiency renders CD4+ Tm cells susceptible to DN-Treg in vitro. DN-Treg efficaciously inhibited the skin allograft rejection mediated by Spi6-/- CD4+ Tm (75.5±7.9 days). Resistances to DN-Treg suppression in vivo in both CD4+ Tem and Tcm were abrogated by Spi6 deficiency. In conclusion, CD4+ and CD8+ Tm cells were differentially respond to DN-Tregs' suppression. The GzmB resistance conferred by Spi6 in CD4+ Tm cells might hint a physiological significance of Tm persistence, and correlated strategies could be effective in limiting their expansion.

## Accumulation of calpain-1 in mitochondria mediates mitochondrial ROS generation and contributes to cardiac TNF-α expression during endotoxemia

**Tao Sun**, Rui Ni, Futian Tang, Dong Zheng, Tianqing Peng.

Background: We have demonstrated that calpain-1 and mitochondrial reactive oxygen species (ROS) significantly contribute to lipopolysaccharide (LPS) induced TNF-α expression in cardiomyocytes. This study investigated whether calpain-1 plays a role in mitochondrial ROS generation in regulating LPS-induced TNF-α expression.
Methods: Sepsis was induced by LPS (4 mg/kg, i.p.) in mice. ROS generation, calpain protein and activity, ATP synthase activity and its α subunit protein were measured in isolated mitochondria. The mitochondrial localization of calpain-1 and its interaction with ATP Synthase-α were examined.
Results: Western blot analysis and immunofluorescent confocal microscopy revealed increases of calpain-1 protein and activities in mitochondria of LPS-injected compared with sham mouse hearts. The up-regulation of calpain-1 correlated with an increase in mitochondrial ROS generation and decreases in ATP synthase activity and its α subunit protein in LPS-injected mouse hearts. These effects of LPS were significantly attenuated by calpastatin over-expression and capn4 knockout. Furthermore, the direct interaction between calpain-1 and ATP synthase-α was observed by co-immunoprecipitation and immunofluorescent confoal microscopy. In cultured adult cardiomyocytes, inhibition of ATP synthase activity abrogated the inhibitory effects of calpain inhibition on ROS production induced by LPS. In H9c2 myoblasts, selective over-expression of calpain-1 in mitochondria was sufficient to induce ROS production and TNF-α expression, which were prevented by mitochondrial-targeted anti-oxidant SS31.
Conclusions: Increased calpain-1 in mitochondria contributes to ATP synthase dysfunction, mitochondrial ROS generation and TNF-α expression induced by LPS. Thus, disruption of ATP synthase/mitochondrial ROS generation may represent a novel mechanism by which calpain-1 mediates cardiac TNF-α expression in sepsis.

## Listening to the warning: Does delay in activation of critical care outreach teams impact patient care?

**Bourke Tillmann**, Michelle Klingel, Shelley McLeod, Scott Anderson, Wael Haddara, Neal Parry.

Introduction: The Modified Early Warning System (MEWS) consists of criteria to identify when Critical Care Outreach Teams (CCOT) should be activated for hospital inpatients. The objective was to determine if delay in CCOT activation had an impact on patient morbidity and mortality.
Methods: This was a retrospective review of new CCOT activations over a 4-year study period (2007-2011). CCOT delay was defined as the time from which MEWS criteria was met to the time CCOT was activated.
Results: There were 3,133 unique activations during the study period. 2,160 (68.9%) were <1 hour of the patient meeting MEWS criteria and 973 (31.1%) were >1 hour. Patients with a delay >1 hour were more likely to be admitted to ICU

compared to patients with a delay <1 hour (47.5% vs 41.5%; Δ 6.0%, 95% CI: 2.2 , 9.8) and higher mortality was seen in patients with a delay > 1 hour (34.8% vs. 29.4%; Δ 5.4%, 95% CI: 1.8, 9.0). After adjusting for delay, surgery patients were as likely to be transferred to ICU (OR 0.96, 95% CI: 0.83, 1.10) but more likely to be ventilated (OR 1.38, 95% CI: 1.10, 1.73). Surgical patients however were half as likely to suffer in-hospital mortality (OR 0.52, 95% CI: 0.44, 0.60).
Conclusions: A delay in CCOT activation > 1 hour was associated with increased in-hospital mortality and ICU admissions. After CCOT activation, surgical patients appear to do better than medical patients. Quality improvement initiatives to decrease CCOT delay should be explored.

## Correlation Between FRAX Score and Likelihood of Adherence with Current Osteoporosis Treatment Guidelines Among Rheumatologists Caring for Patients with Rheumatoid Arthritis (RA)

**Jennifer Watt**, Janet Pope, Andy Thompson, Nicole Le Riche.

Objectives: To assess whether the Fracture Risk Assessment Tool (FRAX) score in patients with RA correlates with likelihood of osteoporosis (OP) prescription including drug treatment, calcium and vitamin D.
Methods: Charts of serial RA outpatients (age>40 with a calculable BMI) were reviewed to determine the 10-year risk of major osteoporotic fracture with the FRAX. Use of calcium, vitamin D, OP treatment, and a patient's BMD results were recorded. Odds ratios (OR) were calculated to determine if a higher FRAX score increased the likelihood of OP prescribing.
Results: 10-year risk of fracture was high in 92 (12.5%), moderate in 216 (29.3%), and low in 429 (58.2%). No patients had a FRAX score calculated in their records. Compared to those at low risk, patients identified as high risk were more likely to receive OP treatment (OR 16.31, 95% CI 9.45-28.13, p<0.0001); calcium (OR 3.89, 95% CI 2.43-6.25, p<0.0001); vitamin D (OR 3.46, 95% CI 2.12-5.64, p<0.0001); and have a BMD performed (OR 10.22, 95% CI 5.50-18.96, p<0.0001). Among 137 patients currently taking prednisone, 44.5% were prescribed a bisphosphonate. BMD tests were performed in 415 (56.3%), but only 228 were recorded on the specialists' charts.
Conclusions: Higher risk patients are more likely to have a BMD and receive treatment, as indicated by the clear dose response seen along the 10-year fracture risk from low to medium to high-risk groups. Although rheumatologists didn't calculate the FRAX score, they recognize important clinical risk factors for OP and prescribe appropriately.

## Transient elastography for monitoring of liver fibrosis in methotrexate-treated patients with inflammatory disorders: a systematic review

Pari Basharat, **Aze Wilson**, Mark Levstik, Lillian Barra.

Introduction:
Methotrexate (MTX) is used for the treatment of inflammatory disorders but can cause liver enzyme abnormalities. Liver enzyme elevations are neither specific nor sensitive for detecting liver fibrosis. Liver biopsy is an imperfect gold standard with its own limitations. Fibroscan is a non-invasive technique used to evaluate liver fibrosis. The objective of this study was to review the literature to characterize the utility of Fibroscan for detection of liver fibrosis compared to biopsy in a methotrexate-taking population.
Methods:
A systematic literature search was carried out of all English publications. The search was limited to studies involving subjects greater than 18 years of age, meeting criteria for the diagnosis of Crohn's Disease (CD), Rheumatoid Arthritis (RA), psoriasis (Ps) or psoriatic arthritis (PsA). Studies where liver biopsy was not performed were excluded.
Results:
Among 18 references identified, three publications met the criteria. The selected

studies were prospective, cross-sectional studies (n=21-518). The cutoffs for significant or severe fibrosis based on Fibroscan score (FSS) differed amongst the studies (7kPA-8.7kPa). FSS did not reflect biopsy findings in a large portion of patients (40%-69%). The accuracy of Fibroscan for the detection of no or mild fibrosis (F<2) ranged from 0%-88%. The accuracy of Fibroscan for the detection of significant fibrosis or cirrhosis (F2-4) ranged from 0%-30%.
Conclusions:
There is insufficient evidence to support the use of Fibroscan for detecting liver fibrosis in a MTX-taking population with inflammatory disorders.

## Inadequate Pain Control in End Stage Renal Disease (ESRD)

**Ahraaz Wyne**, Shuyang Li, Jessica Sontrop, Sharon Baker, William Clark, Rita Suri.

INTRODUCTION: Patients with ESRD report high burden of uncontrolled pain and reasons for this are poorly understood.
METHODS: To determine factors associated with inadequate pain control in ESRD, we compared patients whose pain was adequately controlled with analgesics (Gp A) to those who had ongoing pain despite analgesic use (Gp B), in a cross-sectional observational study, across 4 dialysis units at London Health Sciences Center (LHSC).
RESULTS: 189 patients were surveyed. Mean age was 63.7yrs, 55% were male, 54% had diabetes, and median duration on dialysis was 2.6 yrs. Among patients that were receiving analgesics (N=123), 29 (24%) reported adequate pain control (Gp A), and 94 (76%) had ongoing pain (Gp B). There were no significant differences between groups in their demographics, comorbidities, psychiatric symptoms or medication use (data in table). Median daily equivalent dose of morphine was similar (Gp A=3mg/d, Gp B=5mg/d, p=0.4). Most patients in Gp B felt their physicians were aware of their pain (88%) and working to control it (76%). However, patients in Gp B were more likely to reject additional analgesics if offered, compared to patients in Gp A (69% vs. 33%, p=0.04), citing fears of: too many medications (38%), side effects (15%), and addiction (10%).
CONCLUSION: Inadequate pain control in ESRD patients is highly prevalent and not associated with comorbidity, medication use or physician inattention, but rather, patients` unwillingness to accept more analgesics. There is a need to explore non-analgesic, non-pharmacologic treatments to optimize pain control in this population.

## IL-37 prevents renal ischemia-reperfusion injury by attenuating IL-18-induced pro-inflammatory cytokine expression in tubular epithelial cells

**Yunbo Yang**, Zhu-Xu Zhang, Dameng Lian, Aaron Haig, Rabindra Bhattacharjee, Ziqing Yin, Xuyan Huang, Shengwu Ma, Anthony M Jevnikar.

IL-37 is a new member of IL-1 family, which suppresses immune response and inflammation. Cytokines and chemokines produced by renal tubular epithelial cells( TECs) are critical factors in inflammatory processes of renal ischemia-reperfusion injury (IRI). To date, the role of IL-37 in IRI is unknown. In this study, we observed that pretreatment with IL-37 has significantly attenuated hypoxia-induced mRNA expression of TNFα, IL6 and IL1β in both murine NG 1.1 TECs and primary TECs. Since IL-37 shares the receptor with IL-18 and IL-18BP, we have tested if renal TECs express these receptors. Interestingly, we observed basal level expression of IL-18Rα, IL-18Rβ and IL-18BP in TECs. Treatement with IL-37 significantly down-regulated the expression of TNFα, IL-6 and IL-1β in both murine NG 1.1and human PT-2 TECs. Upon silencing IL37 mRNA, upregulation of TNFα, IL-6 and IL-1β was also observed in PT-2 cells. In contrast, overexpression of IL-37 in PT-2 TECs significantly downregulated the expression of TNFα, IL-6 and IL-1β. Consistently in vivo expression of IL-37 in mice inhibited the expression of TNFα, IFNγ, IL-6 and IL-1β in kidney after renal IRI. In addition, transgenic expression of IL-37 in kidney resulted in reduced

serum creatinine levels, renal tubular necrosis and interstitial infiltrates in kidney after IRI. In conclusion, IL-37 was shown to suppress renal inflammatory response and immune infiltration in kidney, thus protected kidney from tubular damage and promoted kidney function after renal IRI. Augmenting kidney IL-37 levels represents a novel strategy which has potential therapeutic implication in IRI during transplantation.

## Association of Socioeconomic Status with Disease Outcome in Patients with Early Rheumatoid Arthritis

**Grace Yang**, Janet Pope.

Objective. Assess the impact of socioeconomic status (SES) on outcomes in patients with early inflammatory arthritis using data from the Canadian Early Arthritis Cohort (CATCH) study.
Methods. 2023 patients were recruited to a prospective cohort study, and allocated to low- or high-SES groups based on education and income. Outcomes at baseline and 12 months analyzed against SES include the Disease Activity Score (DAS28), pain, patient global assessment scale, the Health Assessment Questionnaire Disability Index (HAQ), and the SF12-v2 Health Survey.
Results. The low-education group presented with higher DAS28 (p=0.045) at baseline that becomes non-significant at 12 months. Low education was also associated with lower physical component score on SF12-v2 at baseline (p=0.018) and at 12 months (p=0.024). Patients from the low-income group presented with higher HAQ (p=0.017), pain (p=0.035), patient global assessment score (p=0.004), and the simplified disease activity index (SDAI) (p=0.022). A change from high-income to low-income group is associated with an odds ratio (OR) of 1.220 (95% CI 1.013-1.470) for an above-median HAQ, 1.284 (95% CI 1.067-1.546) for an above-median patient global assessment score, and 1.240 (95% CI 1.018-1.509) for an above-median SDAI at baseline. The predictive value of low income for above-median HAQ remains at 12 months, OR 1.304 (95% CI 1.018-1.669). Low-income effects on pain, patient global assessment score, and SDAI become non-significant at 12 months.
Conclusion. Low SES is associated with higher disease activity, poorer physical function, more pain, higher patient global assessment, and higher HAQ. Physical function and HAQ remain worse at one-year follow-up.

## Cardiac-specific over-expression of calpain-2 attenuates doxorubicin-induced cardiotoxicity

**Dong Zheng**, Rui Ni, Yangpeng Wang, Tianqing Peng.

Background: Doxorubicin, a highly effective chemotherapeutic agent, can cause cumulative dose-dependent cardiotoxicity, which may present as cardiomyopathy. We have recently shown that inhibition of calpain increases apoptosis in cardiomyocytes and aggravates myocardial dysfunction and mortality in mice with calpastatin over-expression. This suggests that endogenous calpain may provide cardioprotection in doxorubicin-induced toxicity. However, it remains to be determined which isoform of calpains protects cardiomyocytes against doxorubicin-toxicity and what the underlying mechanisms are unknown. Thus, this study investigated the role of calpain-2 in doxorubicin-induced cardiotoxicity. Methods: A novel line of transgenic mice with cardiac-specific over-expression of calpain-2 was generated (Tg-tTA/capn2). Cardiotoxicity was induced in Tg-tTA/capn2 mice and their wild-type littermates. Five days and 2 months after doxorubicin injection, myocardial function was assessed by Echocardiography. Cardiac apoptosis and hypertrophy were determined. The mRNA and protein levels of AKT1 were analyzed by real-time RT-PCR and western blot, respectively. Results: Western blot analysis confirmed cardiac-specific over-expression of calpain-2 in the heart but not other organs. In both acute (5 days) and chronic (2 months) mouse models of cardiotoxicity, doxorubicin injection induced cardiac apoptosis and hypertrophy, and decreased myocardial function

in wild-type mice. These effects of doxorubicin were inhibited by calpain-2 over-expression in Tg-tTA/capn2 mice. Over-expression of calpain-2 also up-regulated the mRNA and protein levels of AKT1 in Tg-tTA/capn2 mice compared with their wild-type littermates. Conclusions: Calpain-2 provides cardiac protection in doxorubicin-induced cardiotoxicity. The role of calpain-2 may be associated with up-regulation of AKT1 expression. Thus, calpain-2 may represent a novel therapy to reduce doxorubicin-induced cardiotoxicity.