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Abstracts for Lectures:

L01.

Loss of Telomere-Associated Rap1 Precipitates Cardiac Aging in Mice via P53/PPARα Signaling

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Background: Telomere dysfunction has been linked to many aspects of the aging process. Increasing evidence indicates that telomere dysfunction leads to cardiac mitochondrial defects in mice. Mammalian repressor activator protein 1 (Rap1) is one of the components of shelterin complex and essential for the maintenance of telomere length and structural integrity. Our preliminary work showed that aged Rap1 knockout (Rap1-/-) mice exhibit more pronounced aging-associated phenotypes. However, the effects of Rap1 on mitochondrial function and its contribution to cardiac aging are largely unknown. Thus, the present study investigated if loss of Rap1 precipitates cardiac aging and explored the underlying mechanisms.
Methods and Results: Deletion of Rap1 aggravated aging-related cardiac structural changes and dysfunction, as evidenced by increased left ventricular (LV) posterior wall end-diastole and LV mass, reductions in ejection fraction and fractional shortening, as well as significantly impaired myocardial performance index. These changes were associated with greater cardiac senescence, cardiac hypertrophy, abnormalities in the mitochondrial ultrastructure. Mechanistically, Rap1 deficiency leads to shorter telomere, enhanced DNA damage and increased nuclear p53 level in the heart and primary cardiomyocytes when compared to age-matched counterparts (one year old). Chromatin immunoprecipitation assay revealed p53 directly bind the promote site of PPARα and repressed its expression. Indeed, Rap1 deficiency in mice exhibited impaired fatty acid metabolism [reduced CD36, CPT1α, ACADL level and palmitate-induced oxygen consumption], while in vivo PFTα (a p53 inhibitor, i.p. 1.1 mg/kg/day) treatment in Rap1-/- mice significantly alleviated cardiac aging and enhanced fatty acid metabolism by restoration of PPARα.
Conclusions With aging, Rap1 deficiency may lead to shorter telomere length, increase DNA damage and thereby activate p53, which in turn suppress the expression of PPARα, leading to impaired FAM and mitochondrial defects, compromised cardiac structural and functional changes. These findings identify a new cardiac dimension in the physiological role played by telomere-Rap1.

L02.

Mature Human Pluripotent Stem Cells Derived Cardiomyocytes to Investigate Cardiotoxicity Induced by Anti Cancer and Anti-Viral Treatment

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Human (h) pluripotent stem cell (PSC)-derived cardiomyocytes (CMs) are of significant value to cardiac disease modelling, drug and cardiotoxicity testing, but their uses are limited by the immaturity of hPSC-CMs and their inability to recapitulate some (patho)physiological attributes of adult CMs.
We recently showed that hPSC-CMs with more adult-like cardiac function can be isolated using CD36, a marker of cardiac maturation. CD36hi CMs are phenotypically and functionally more mature than CD36lo CMs and have significantly increased sensitivities to chemical (H2O2), physiological (hypoxia/reoxygenation) and cardiotoxic (doxorubicin) stimuli. Focused studies on doxorubicin-induced cardiotoxicity show that CD36hi CMs, unlike mixed and CD36lo CMs, recapitulate known clinical responses to cardioprotective drugs. This response has not been previously observed with unsorted hPSC-CMs, showing that CD36hi CMs have drug responsive traits more consistent with an adult phenotype. Additionally, we used our mature hPSC-CM platform to investigate cardiotoxicity induced by antiviral treatment and showed that remdesivir, the only FDA-approved treatment against COVID-19, could induce persistent mitochondrial and structural damage in hPSC-CMs.
In conclusion, our results demonstrate the importance of hPSC-CM maturation for the accurate prediction of adult human responses, and will greatly advance the use of hPSC-CMs for cardiac research.

L03.

Development of A Novel Strategy for Cell-Based Cardiac Repair

Kiwon Ban[1]

Since both myocardium and vasculature in the heart are excessively damaged following myocardial infarction (MI), therapeutic strategies for treating MI hearts should concurrently target both so as to achieve true cardiac repair. Here we demonstrate a concomitant method that exploits the advantages of cardiomyocytes derived from human induced pluripotent stem cells (hiPSC-CMs) and human

mesenchymal stem cell-loaded patch (hMSC-PA) to amplify cardiac repair in a rat MI model. Epicardially implanted hMSC-PA provide a complimentary microenvironment which enhances vascular regeneration through prolonged secretion of paracrine factors, but more importantly it significantly improves the retention and engraftment of intramyocardially injected hiPSC-CMs which ultimately restore the cardiac function. Notably, the majority of injected hiPSC-CMs display adult CMs like morphology suggesting that the secretomic milieu of hMSC-PA constitutes pleiotropic effects in vivo. We provide compelling evidence that this dual approach can be a promising means to enhance cardiac repair on MI hearts.

L04.

Treatment with Direct Oral Anticoagulants or Warfarin and the Risk for Incident Diabetes Among Patients with Atrial Fibrillation

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Background: Diabetes mellitus is a common comorbidity of atrial fibrillation (AF), which can complicate the management of AF. The pharmacology of oral anticoagulants (OACs) have been implicated in pathogenesis of diabetes, but the relationship between different OACs and risk of diabetes remains unexamined. This study aimed to evaluate the risk of diabetes with use of different OACs in AF patients.
Methods: Population-based retrospective cohort study using an electronic healthcare database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with AF from 2014 through 2018 and prescribed OACs were included and followed till December 31, 2019. Inverse probability of treatment weighting based on the propensity score (PS) is used to address potential bias due to nonrandomized allocation of treatment. The risks of diabetes were compared between different new OAC users using propensity score-weighted cumulative incidence differences (CID).
Results: There were 13,688 new users of OACs (warfarin: n = 3454; apixaban: n = 3335; dabigatran: n = 4210; rivaroxaban: n = 2689). The mean age was 75.0 (SD, 11.2), and 6,550 (47.9%) were women. After a median follow-up of 0.93 years (interquartile range, 0.21-1.92 years), 698 incident diabetes cases were observed. In Cox-regression analysis, dabigatran use was significantly associated with reduced risk of diabetes when compared with warfarin use [HR 0.69 (95% CI 0.56-0.86; P < 0.001)], with statistically insignificant associations observed for use of apixaban and rivaroxaban. The corresponding adjusted CIDs at 2 years after treatment with apixaban, dabigatran, and rivaroxaban users when compared with warfarin were - 2.06% (95% CI - 4.08 to 0.16%); - 3.06% (95% CI - 4.79 to - 1.15%); and - 1.8% (- 3.62 to 0.23%). In head-to-head comparisons between women DOAC users, dabigatran was also associated with a lower risk of diabetes when compared with apixaban and rivaroxaban.
Conclusions: Among adults with AF receiving OACs, the use of dabigatran had the lowest risk of diabetes when compared with warfarin use.

L05.

Association of Blood Pressure and Cardiovascular Disease in Patients With Hypertension

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Introduction: While hypertension has been a recognized risk factor for cardiovascular disease (CVD), there is currently no consensus on the optimal blood pressure level for hypertension management. This study revisits the controversy by evaluating the association between blood pressure and CVD risk in two large general population cohorts.
Methods: A total of 439,142 and 1,773,283 individuals with at least one valid blood pressure record and without CVD from the UK Biobank in 2006-2010 and from the electronic health record in Hong Kong in 2008-2017, respectively, were included. The CVD risks were compared among participants in six groups of different blood pressure levels 1: optimal (SBP <120 mmHg and DBP <80 mmHg); 2: normal (SBP 120-129 mmHg and DBP 80-84 mmHg); 3: high normal (SBP 130-139 mmHg or DBP 85-89 mmHg); 4: grade 1 hypertension (SBP 140-159 mmHg or DBP 90-99 mmHg); 5: grade 2 hypertension (SBP 160-179 mmHg or DBP 100-109 mmHg); and 6: grade 3 hypertension (SBP ≥180 mmHg or DBP ≥110 mmHg)], as defined by the ESC/ESH classification. Cox regression adjusting with subject characteristics was performed in each cohort.
Results: After 4.5 and 10.9 million person-years follow-up, 23,132 and 147,093 incident CVD events were observed across all blood pressure levels in the UK Biobank and Hong Kong cohort, respectively. Taking the optimal blood pressure group as the reference, a positive association between blood pressure levels and CVD risk was observed in both cohorts, with hazard ratios in ascending blood pressure groups being 1.07 (95% CI 1.00-1.13), 1.17 (95% CI 1.10-1.24), 1.32 (95% CI 1.25-1.39), 1.56 (95% CI 1.47-1.66), 1.91 (95% CI 1.76-2.06) in the UK Biobank, and 1.21 (95% CI 1.18-1.24), 1.25 (95% CI 1.22-1.28), 1.32 (95% CI 1.29-1.34), 1.60 (95% CI 1.56-1.65), and 2.07 (95% CI 1.96-2.18) in the Hong Kong cohort.
Conclusion: With consistent results from both cohorts, the relationship between low blood pressure levels and reduced CVD risks is well highlighted in this study, with the optimal group having the lowest risk in multiple cardiovascular outcomes. Such findings provide the grounds for reviewing the hypertension definition and optimal blood pressure control in the current guidelines.

L06.

Integrative Methodologies in Humans to Answer Relevant Questions in Cardiovascular Sciences

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Physiology is the science of life: 'How does the body work?'. The ultimate goal of any area of Physiology is to discover the fundamentals of how a given function works, thus empowering to modify outcomes as desired. Answers must be provided at multiple levels, starting from the molecule up to the integration of organ function into the overall organism. While the prevailing emphasis on molecular biology is an ineluctable consequence of technological prowess, sound integrative bases of the cardiovascular system have yet to be elucidated in a large fraction of the human population.
In this sense, comprehensive knowledge about Integrative Physiology is essential for medical students. In this seminar, we will focus on the potential use of well-established integrative methodologies in humans to answer relevant clinical questions in cardiovascular sciences. Our group has made contributions regarding the interaction of blood volume, cardiac and metabolic capacities in healthy individuals, heart failure and kidney disease patients. A myriad of questions remain to be elucidated in current and upcoming collaborative projects in Hong Kong.

L07.

Using Sirna to Lower Cholesterol

Bernard MY. Cheung [1]
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Current lipid lowering guidelines suggest a LDL-C target, 1.4 mmol/L for high cardiovascular risk persons, which is substantially lower than

previous targets. If the baseline untreated LDL-C is very high, then it is not easy to attain LDL-C target using existing drugs, which include a high-intensity statin, ezetimibe and perhaps a PCSK9 inhibitor. The scene is therefore set for newer lipid lowering drugs that are well tolerated and efficacious. Inclisiran belongs to a new generation of drug that uses RNA technology to induce prolonged and profound lowering of LDL-C. It is a small interfering RNA that inhibits translation of the protein PCSK9. It can be injected once every six months, thus ensuring good compliance. In clinical trials, it typically lowers LDL-C by 40%. Some COVID-19 vaccines use RNA technology and have shown to be safe and efficacious in millions of patients, therefore there should not be undue concerns about the safety of this new technology. Inclisiran also lowers Lp(L), which is strongly associated with cardiovascular risk. In conclusion, inclisiran represents a new generation of lipid lowering drugs that can be added to the list of drugs approved to lower LDL-C to target. The twice a year administration is patient-friendly and some patients may prefer this over daily medications or monthly injections.

L08.
Emerging Role of Regulatory T Cells in Cardiovascular Repair and Regeneration

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Accumulating evidence has demonstrated that immune cells such as macrophages play an important role in the regulation of cardiovascular repair. After injury, danger signals released by the damaged tissues trigger the initial pro-inflammatory phase essential for removing pathogens or cellular debris that is later replaced by the anti-inflammatory phase responsible for tissue healing. On the other hand, impaired immune regulation can lead to excessive scarring and fibrosis that could be detrimental for the restoration of heart function. Regulatory T-cells (Treg) have been revealed as the master regulator of the immune system that have both the immune and regenerative functions. In this talk, we will summarize their regenerative role in directing cardiovascular repair and regeneration. The latter is clearly demonstrated when Treg enhance the replication of neonatal cardiomyocytes after injury facilitating functional heart regeneration. Moreover, we will also discuss the molecular mechanism by which Treg could mediate cardiovascular repair through regulating the transcriptomic and epitranscriptomic events. Altogether, our findings may suggest some clinically relevant insights into the development of Treg therapy targeting cardiovascular repair and regeneration in the future.

L09.
Evaluation of Bi-Directional Causal Association Between Depression and Cardiovascular Diseases: A Mendelian Randomization Study

Gloria Li, Research Assistant Professor [1]
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Depression and cardiovascular disease (CVD) are associated with each other but whether their relationship is causal remains unclear. We tested genetic correlation between two depression phenotypes [(i) depression (primary analysis); (ii)broad depression (help-seeking for problems with nerves, anxiety, tension or depression; secondary analysis)] and CVD [including myocardial infarction (MI), stroke and atrial fibrillation (AF), but not coronary artery disease (CAD) as the genetic correlation was previously confirmed], followed by inferring causality between the correlated traits by Mendelian Randomization analyses using summary statistics obtained from the largest available genome-wide association studies (GWAS) or GWAS meta-analysis of depression (n=500,199), broad depression (n=322,580), CAD (n=184,305), MI (n=171,875), stroke (n=446,696) and AF (n=1,030,836). We found both depression phenotypes were genetically correlated with MI (depression: r=0.169; SE=0.029; P=9.03x10-9; broad depression: r=0.123; SE=0.032; P=1x10-4) and AF (depression: r=0.112; SE=0.025; P=7.80x10-6; broad depression: r=0.126; SE=0.027; P=3.62x10-6). Genetically doubling the odds of depression was causally associated with increased risk of CAD (OR=1.099; 95% CI: 1.031-1.170; P=0.004) and MI (OR=1.146; 95% CI: 1.070-1.228; P=1.05x10-4). Doubling the odds of broad depression also increased risk of CAD (OR=1.099; 95% CI: 1.031-1.170; P=0.004) and MI (OR=1.146; 95% CI: 1.070-1.228; P=1.05x10-4). Adjustment for blood lipid levels/smoking status abolished the causal association of depression with CAD/MI. Null causal association was observed for CVD on both depression phenotypes. A similar pattern of results was observed in the secondary analysis for broad depression. These suggest that genetic predisposition to depression may have positive causal roles on CAD/MI. Genetic susceptibility to self-awareness of mood problems may be a strong causal risk factor of CAD/MI. Blood lipid levels and smoking may potentially mediate the causal pathway. Prevention and early diagnosis of depression are important in the management of CAD/MI.

L10.
Cardiomyocyte Terminal Differentiation, Dedifferentiation, and the Centrosome

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Mammalian cardiomyocytes become terminally differentiated shortly after birth. Inducing dedifferentiation from their terminally differentiated state represents one strategy to restore proliferative potential and achieve cardiac regeneration. To date little in known as to how terminal differentiation occurs or, more so, when it begins. This is in large part due to the absence of a cellular marker which enables one to distinguish between non-terminally differentiated and terminally differentiated cardiomyocytes. The centrosome is a solitary organelle classically known as the primary microtubule organizing centre (MTOC) of the cell. Proliferative, and regenerative, cardiomyocytes of adult zebrafish and newt have a centrosome. In contrast, mammalian cardiomyocytes disassemble their centrosomes during perinatal development. In this seminar, I will present data that supports the centrosome as a bona fide cellular marker with which to distinguish terminally differentiated from non-terminally differentiated cardiomyocytes and how the centrosome enables detection of cardiomyocyte dedifferentiation from a terminally differentiated to a non-terminally differentiated state (i.e. to a state that possesses proliferative, and regenerative, potential).

L11.
Interplay Between Covid-19 and Cardiovascular Risk and Disease

Donald Singer, President [1]
[1] *Fellowship of Postgraduate Medicine*

People with cardiovascular comorbidities are more likely to be infected with SARS-CoV-2, especially those with hypertension, coronary heart disease, diabetes mellitus and obesity. They are also more likely to have worse outcomes from COVID-19, with similar associations in

reports for example from China, the USA and Italy. People with cardiovascular risk factors or established cardiovascular disease also experience a high case-fatality rate from COVID-19. For example, hypertension was reported in 40% of patients who died [odds ratio for death, 3.05 (95% CI: 1.6–5.9)] in an early report of over 40,000 confirmed COVID19 patients in China. In the same report, cardiovascular disease was associated with a 5-fold increase in risk of death from COVID-19. Reasons for the synergy between cardiovascular risk and SARS-CoV-2 will be discussed as will the impact of effective vaccination and other medical treatments on reducing severity of COVID-19 in these high-risk patients.

The involvement of policy makers is needed to complement the efforts against COVID-19 of health professionals, regulators and the pharmaceutical and biotechnology industries. These efforts will not be successful without also addressing the cardiovascular and other factors that contribute to higher risk from COVID-19. Links to the severity of COVID-19 make it all the more pressing for policy makers and public health agencies to address underlying causes and to reduce the incidence and severity of preventable cardiovascular risk.

Abstracts for Oral Presentations:

OP01:

The Role of Endothelial PPARα in Vascular Inflammation and Atherogenesis

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Objectives: Endothelial cell activation associated with dyslipidemia initiates vascular inflammation and subsequent development of atherosclerotic plaques. Peroxisome proliferator-activated receptor alpha agonists are commonly used to treat patients with dyslipidemia, and they may possess potential anti-inflammatory and anti-atherosclerotic properties. However, the mechanisms by which these agonists work against atherogenesis are largely unexplored. This study aims to investigate the role of endothelial peroxisome proliferator-activated receptor alpha in vascular inflammation and atherogenesis.

Methods: To examine the impact of endothelial peroxisome proliferator-activated receptor alpha on atherogenesis, pX601-AAV-ICAM2-sgRNA was used to knock down peroxisome proliferator-activated receptor alpha specifically in endothelial cells of apolipoprotein E-deficient mice on a western diet for 10 weeks, and the peroxisome proliferator-activated receptor alpha agonist pemafibrate was orally administered during the last 2 weeks. To investigate the beneficial effect of peroxisome proliferator-activated receptor alpha in endothelial cells, both viral vectors and pharmacological compounds were used to control the peroxisome proliferator-activated receptor alpha expression and activity in endothelial cells with and without treatment of pro-inflammatory cytokines.

Results: The peroxisome proliferator-activated receptor alpha expression and activation were suppressed in mouse aortic endothelial cells with atherosclerotic plaques and 14-day oral administration of pemafibrate reduced the western diet-induced formation of atherosclerotic plaques and these beneficial effects were abolished by endothelium specific peroxisome proliferator-activated receptor alpha knockdown. Both genetic overexpression and pharmacological activation of peroxisome proliferator-activated receptor alpha protected endothelial cells against while peroxisome proliferator-activated receptor alpha inhibition augmented interleukine-1β- or tumor necrosis factor α-induced inflammation. Furthermore, Yes-associated protein 1 phosphorylation was increased, and the expression of Yes-associated protein 1 target genes was inhibited by peroxisome proliferator-activated receptor alpha overexpression.

Conclusions: The present study reveals that endothelial peroxisome proliferator-activated receptor alpha activation is effective to inhibit vascular inflammation and atherogenesis, while inhibition of endothelial Yes-associated protein 1 activity may represent one of the potential mechanisms accounting for anti-inflammatory and atherosclerotic benefits of peroxisome proliferator-activated receptor alpha agonists, thereby providing scientific support for the use of fibrates in patients with atherosclerotic vascular diseases (Supported by HMRF 07181286 and SRFS2021-4S04).

OP02.

Temporal Trends and Patterns of Infective Endocarditis In a Chinese Population: A Population-Wide Study (2002 - 2019)

Mr. Hang Long Li [1], Ms. Yi Kei Tse [1], Mr. Si Yeung Yu [1], Ms. Lok Yee Lam [1], Ms. Kwan Yu Li [1], Mr. Ka Lam Leung [1], Ms. Nicole Wing Lam Hon [1], Mr. Pui Fai Wong [1], Ms. Shuk Yin Yu [1], Dr. Kai Hang Yiu [1]

[1] *The University of Hong Kong, Hong Kong SAR*

Objectives: The epidemiological and clinical characteristics of infective endocarditis (IE) are known to exhibit substantial geographical variability but remain poorly understood in Asians. Therefore, we aim to describe the epidemiological trends and clinical features of IE in Hong Kong, and to identify the key contributors to death in IE patients in a large Asian population.

Methods: We included all patients aged 20 or above newly diagnosed with IE between January 1, 2002, and December 31, 2019, from a well-validated territory-wide database in Hong Kong. We studied the incidence and one-year mortality of IE between 2002 and 2019 and used interrupted time series to evaluate the change in incidence after revision of antibiotic prophylaxis guidelines in 2007. Significant contributors to 1-year all-cause death were identified using the population attributable fraction (PAF). We used Poisson regression with propensity score matching to study the association of surgery with mortality over time.

Results: A total of 5,139 patients (60.4±18.2years, 37% women) were included. The overall incidence of IE was 4.4 per 100,000 persons, which did not change after the revision of antibiotic prophylaxis guideline in 2007 (relative risk of change 0.85, 95% CI 0.64 to 1.14, $P = 0.293$). Patients with IE in 2019 were older and more comorbid than those in 2002. There was a significantly increasing trend in Methicillin-resistant Staphylococcus aureus (MRSA), with an annual percentage change of 4.2% (95% CI 1.9 to 6.6, $P < 0.001$). The one-year crude mortality rate was 30% in 2002, which did not significantly change over time ($P=0.103$). Between 2002 and 2019, the rate of surgery increased and was consistently associated with a 45% risk reduction in 1-year all-cause mortality (Hazard Ratio 0.55 [0.45-0.66], $P < 0.001$). Advanced age (PAF 19%) and comorbidities (PAF 15%) were significant contributors to death, regardless of the time period.

Conclusions: We found that the incidence of IE remained stable between 2002 and 2019 in Hong Kong and was not influenced by the revision of antibiotic prophylaxis guidelines. Over time, patients with IE are increasingly older and more comorbid. Notably, the burden of MRSA endocarditis increased, together leading to a dismal prognosis. Despite rising surgery rates and associated substantial survival benefits, the mortality of IE remained high. Taken together, our findings provide important insights into the geographical disparities in epidemiological and clinical profiles of patients with IE, with several important implications for health policymakers, researchers, and clinicians.

OP03.

Trends in Cardiovascular Risk in the United States Over Two Decades, 1999 – 2018

Mr. Hang Long Li[1], Bernard MY. Cheung, Professor[1]
[1] *The University of Hong Kong, Hong Kong SAR*

Objectives: As guidelines evolve, new drugs are introduced, and the long-term trends in cardiovascular risk in the general population are of interest. We evaluated the AHA-ACC-ASCVD risk score (CVDRS) in the US in the 2 decades.
Methods: Non-pregnant participants in the National Health and Nutrition Examination Survey (NHANES) 1999-2018 aged 40-79 years were included. Temporal trends in CVDRS and its components, and the proportions of raymondparticipants at high-risk (score $\geq$20%) were characterized using linear regression, adjusted for age, sex, and ethnicity. Data analysis was performed using the R package "survey".
Results: Altogether 12744 participants (mean age 56.4 years; 55.9% male) were analyzed (Table 1). The proportion of people with diabetes and taking antihypertensives increased (both $p<0.001$), while total cholesterol (TC) level decreased ($p<0.001$). Other components, including high-density lipoprotein cholesterol and the proportion of smokers, remained static.
From 1999 to 2018, the mean CVDRS significantly increased from 11.4$\pm$0.7% to 12.5$\pm$0.5% ($p=0.014$), and the proportion of high-risk participants increased from 18.6% to 20.0% ($p<0.001$).
Conclusions: Cardiovascular risk in the US population increased slightly in the past 20 years. Despite the increased treatment rate of hypertension and the decrease in TC, the prevalence of diabetes doubled. More effort should be directed at preventing diabetes through weight control and regular physical activity.

OP04.

Immediate Risk for Cardiovascular Events in Hip Fracture Patients: A Population-Based Cohort Study

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Objectives: Emerging evidence showed that bone metabolism and cardiovascular diseases are closely related. We previously observed a potential immediate risk of cardiovascular mortality after hip fracture. However, whether there is an immediate risk of cardiovascular events after hip fracture is unclear. The aim of this study was to evaluate the risk for major adverse cardiovascular events between patients having experienced falls with and without hip fracture.
Methods: This retrospective population-based cohort study used data from a centralized electronic health record database managed by Hong Kong Hospital Authority. Patients having experienced falls with and without hip fracture were matched by propensity score at a 1:1 ratio. Adjusted associations between hip fracture and risk of major adverse cardiovascular events were evaluated using competing risk regression after accounting for competing risk of death.
Results: Competing risk regression showed that hip fracture was associated with increased one-year risk of major adverse cardiovascular events (hazard ratio, 1.27; 95% Confidence Interval, 1.21 to 1.33; $p<0.001$), with a 1-year cumulative incidence difference of 2.40% (1.94% to 2.87%). The hazard ratio was the highest in the first 90-day after hip fracture (hazard ratio of 1.32), and such an estimate was continuously reduced in 180-day, 270-day, and 1-year after hip fracture.
Conclusions: Hip fracture was associated with increased immediate risk of major adverse cardiovascular events. This study suggested that a prompt evaluation of major adverse cardiovascular events among older adults aged 65 years and older who are diagnosed with hip fracture irrespectively of cardiovascular risk factors may be important, as early management may reduce subsequent risk of major adverse cardiovascular events.

OP05.

Instant Fabrication of Angiogenic Patch for Effective Vascular Regeneration

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Objectives: To investigate a novel protein patch that can deliver effectively a cocktail of angiogenic factors for vascular regeneration
Methods: Firstly, the concentrations of chosen angiogenic factors, including vascular endothelial growth factor, basic fibroblast growth factor, epidermal growth factor, insulin-like growth factor-1 were optimized by migration and tube formation assay on endothelial cells. Then, a combination of 4 factors at optimal concentrations was compared the angiogenic effects with single and other combinations by migration, tube formation, and proliferation assay. The cytoprotective effects of the combination on endothelial cells were also examined. Parallely, droplet technique was employed to produce a patch from sodium alginate and ε-poly-l-lysine. The patch was evaluated release kinetics of both small protein (Vascular endothelial growth factor) by Enzyme-linked immunosorbent assay for 24 hours and large protein (Bovine serum albumin) by Pierce bicinchoninic acid protein assay for 72 hours. The released growth factors from the patch were tested their function by migration assay. Adaptation of the patch in vivo by encapsulating and releasing DiI in mouse legs was measured by Spectrum In Vivo Imaging System. Therapeutic effects of the patch are testing on hindlimb mouse models.
Result: The combination of angiogenic factors with 50ng/mL Vascular endothelial growth factor, 20ng/mL basic fibroblast growth factor, 10ng/mL epidermal growth factor, and 10ng/mL insulin-like growth factor-1 showed the strongest angiogenic effects in vitro compared to single factor and other combinations. It recruited the most migrated endothelial cells, maintained the most tube-like structures, and highly promoted cell proliferation. The combination of angiogenic factors significantly protected endothelial cells from ichemic injury induced by H2O2 and inflammation injury induced by lipopolysaccharide. Simultaneously, the patch demonstrated stable release kinetics with both VEGF and BSA for 72 hours. The combination of angiogenic factors encapsulated and secreted by the patch maintained good function through migration effect. Patch encapsulating DiI slowly released DiI to the muscle of the mice. DiI signal was detected and increased from day 3 to day 15 after transplantation. Angiogenic factor patch fully protected the ischemic hindlimbs from limb loss compared to the control group.
Conclusion: Our patch strategy successfully deliver proteins to the target tissue. The angiogenic patch indicated a novel approach for vascular regeneration in cardiovascular disease treatment.

OP06.

Prognostic Value of a Novel Index: Computational Pressure-Flow Dynamics Derived Fractional Flow Reserve in Patients With Deferred Lesions

Ms. Kwan Yu Li [1], Ms. Lok Yee Lam [1], Mr. Ka Lam Calvin Leung [1], Ms. Mei Zhen Wu [2], Ms. Qing Wen Ren [2], Ms. Shuk Yin Yu [1], Mr. Pui Fai Wong [1], Ms. Yun Di Feng [3], Dr Yun Long Huo [3], Dr Kai Hang Yiu [1]

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Objectives: Computational pressure-flow dynamics derived fractional flow reserve (caFFR) is a novel technique to determine the fractional flow reserve (FFR) without the use pressure wire or induction of hyperaemia in conventional FFR. Previous studies have validated that caFFR has high diagnostic accuracy in determining the functional significance of coronary lesions, compared to FFR. The aim of the study is to evaluate its clinical implications in stable coronary artery disease (CAD) with deferred lesions.

Methods: The study included a total of 340 patients (mean age 67.5 ± 10.7, 63.2% male) with 476 lesions in whom revascularization was deferred. Clinical events were compared according to lesion location and caFFR categories: caFFR ≤0.65 (n=46), caFFR= 0.66-0.8 (n=34), caFFR= 0.81-0.9 (n=174), caFFR=0.91-1.0 (n=222) in lesion basis. The primary endpoint was 3-year major adverse cardiac events (MACE), defined as a composite of death, myocardial infarction, or any unplanned revascularization.

Results: The mean caFFR was 0.84 ± 0.13 in 476 lesions. A total of 39 composite events occurred, including 23 death, 2 myocardial infarction and 14 unplanned revascularization.

caFFR is an independent predictor for MACE (per 0.01 decrease; adjusted hazard ratio [HR], 1.03; 95% confidence interval [CI], 1.01-1.04; P<0.01) and death (per 0.01 decrease; adjusted HR, 1.03; 95% CI, 1.01-1.04; P<0.01). Following multivariable adjustment, the risk of MACE was the highest in lesions with caFFR ≤0.65 (adjusted HR, 4.29; 95% CI, 2.18-8.45; P<0.01) using caFFR=0.91-1.0 as reference, followed by caFFR=0.66-0.8 (adjusted HR, 3.57; 95%CI, 1.70-7.47; P<0.01). The risk of MACE was similar in lesions with caFFR> 0.8.

In proximal lesions, caFFR remained an independent predictor for MACE (per 0.01 decrease; adjusted HR, 1.04; 95% CI, 1.03-1.06; P<0.01). Such relationship was nonetheless not observed in distal lesions.

Conclusions: In stable CAD patients, haemodynamically significant lesions have lower caFFR, and higher risks of adverse outcomes. This non-wire-based index, caFFR showed high clinical applicability in quantifying myocardial ischemia, and improving risk prognostication in deferred lesions.

Abstracts for Poster Presentations:

PP01.

PKD1 and PKD2 Associated Cardiomyopathies in 3D Engineered Cardiac Tissue Model

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Objective: Autosomal dominant polycystic kidney disease (ADPKD) is a well-known genetic disease. It is caused by mutations in either polycystin-1(PKD1) or polycystin-2(PKD2). Cardiovascular complications caused by this disease result in many deaths. However, it is still unclear of how PKD1 and PKD2 mutations could lead to cardiac disorders. We aim to elucidate the mechanisms of PKD1 and PKD2 involvement in cardiac disorders.

Methods: Human embryonic stem cells(hESC) were used to differentiate cardiomyocytes (hESC-CM). HESC-CMs were knocked-down by Ad-PKD1& Ad-PKD2. 3D human ventricular cardiac tissues strip (3D-hvCTS) was used to assess PKD1 & PKD2-associated functional abnormalities in electrophysiological, Ca2+ handling and contractile properties.1

Results: On day 7, PKD1 & PKD2¬ knockdown hvCTS displayed lower developed forces during both spontaneous contraction and electric pacing-induced contraction at all pacing frequencies. Moreover, after PKD1 & PKD2 knockdown, passive tension and total tension both decreased. No difference was observed in the following parameters between normal and PKD1/2 knockdown samples, including rise time 90, rise time 50, rise time 25, rise slope, max rise slope, AUC rise 90, decay time 90, decay time 50, decay time 25 and AUC decay 90, decay slope, max decay slope, beat rate variability and developed force variability.

Conclusions: This study provides insight into the effects of PKD1 & PKD2 knockdown on the contractility of hvCTS derived from hESC-CMs. The decrease in developed force produced by PKD1 & PKD2 knockdown hvCTS recapitulate the cardiomyopathies in ADPKD patients in an in vitro model.

PP02.

Role of TRPC5 in Endothelium-Dependent Contraction in Hypertensive Model of Mice

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The augmented endothelium-dependent contraction (EDC) can stimulate the production of contractile prostanoids, which contribute to endothelial dysfunction and hypertension. Furthermore, it is well known that EDC plays a more prominent role in hypertension. The EDC is Ca2+-dependent. However, the molecular identity of endothelial Ca2+ channels that regulate EDC is not well studies. In a previous study, we reported that endothelial cell transient receptor potential channel C5 (TRPC5), a Ca2+ -permeable channel, contributes to the EDC response by stimulating cyclooxygenase 2 (COX-2) activity in the carotid arteries of healthy mice. In the present study, I explored the molecular identities of Ca2+-permeable channels that stimulate EDC in hypertensive model. Mouse model of hypertension was established by subcutaneous infusion of angiotensin II and Nω-nitro-l-arginine (L-NNA). Systolic, diastolic and mean blood pressures were recorded by tail-cuff method. ACH-induced EDC was detected by wire myograph in the presence of NG-nitro-L-arginine methyl ester (L-NAME). [Ca2+]i was measured by a Ca2+-sensitive fluorescence dye. Results showed that ACH-induced EDC in carotid arteries was reduced by TRPC5, TRPV4 and Orai1 inhibitor in a dose-dependent way. ACH resulted in the contraction which could be abolished by a selective TP receptor antagonist. Besides, the increased EDC under hypertension condition was also reversed by these inhibitors. The findings suggest important roles of several endothelial Ca2+-permeable channels, TRPC5, TRPV4 and Orai1, in EDC under hypertension. In future, it will be worthwhile to explore the possibility of developing TRPC5/TRPV4/Orai1-based therapeutic options against EDC and hypertension.

PP03.

Association Between SGLT2 Inhibitors vs DPP-4 Inhibitors and Risk of Pneumonia Among Patients With Type 2 Diabetes

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Objectives: Sodium-glucose co-transporter 2 inhibitors (SGLT2is), the latest class of glucose-lowering agents, have been gaining popularity in recent years for their cardio-protective properties in addition to glucose-lowering. Interestingly, SGLT2is were also shown to reduce the risk of pneumonia in recent clinical trials. However, the real-world effectiveness of SGLT2is on the risk of pneumonia is largely unknown. The aim of the present study was to investigate the associations between SGLT2is use and the risk of pneumonia and pneumonia mortality compared to dipeptidyl peptidase-4 inhibitors (DPP4is) using an electronic medical database in Hong Kong.
Methods: The present study was a retrospective cohort study. The "prevalent new-user" design was adopted to account for the previous exposure to the study drugs being compared. Propensity score (PS) matching (1:4) was used to balance the baseline characteristics of the two groups. Electronic health data of type 2 diabetes patients using SGLT2is and DPP4is between 2015 and 2018 was collected from the Clinical Data Analysis and Reporting System (CDARS). Primary outcomes were pneumonia incidence and mortality.
Results: The PS-matched cohort consisted of 6,664 users of SGLT2is and 26,656 users of DPP4is, with a mean follow-up of 3.8 years. Poisson regression showed that SGLT2is use was associated with lower risk of pneumonia compared to DPP4is with an absolute rate difference of 3.78 per 1000 person-years (95% confidence interval: 2.21-5.34). The corresponding rate ratio was 0.75 (95% confidence interval: 0.66-0.85). Similar reduction in risk of pneumonia death was observed using competing risk regression (hazard ratio: 0.60; 95% CI: 0.44-0.81).
Conclusions: Compared to DPP4is, SGLT2is use was associated with a reduced risk of pneumonia and pneumonia mortality in a real-world setting.

PP04.

Hydrochlorothiazide-Associated Hypokalemia: The United States National Health and Nutrition Examination Survey 1999-2018

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Objectives: Hydrochlorothiazide is the most commonly used thiazide diuretic for hypertension in the United States. Yet, hypokalemia is a common adverse effect. A comprehensive update of the prevalence of hypokalemia among users is warranted. We aim to evaluate the prevalence and factors associated with hypokalemia among hydrochlorothiazide users.
Methods: Adults aged $\geq$ 20 years in the 1999-2018 National Health and Nutrition Examination Survey were included. Participants were categorized according to the use of hydrochlorothiazide and other antihypertensive agents simultaneously. Using multivariable logistic regression, we evaluated the factors associated with hypokalemia (serum potassium $<$ 3.5 mmol/L), including demographics and pattern of prescription (monotherapy vs fixed-dose combination therapy [single pill containing hydrochlorothiazide and $\geq$ 1 other antihypertensive agent] vs polytherapy [$>$ 1 antihypertensive pill]).
Results: A total of 4,314 hydrochlorothiazide users were identified. Hypokalemia was present in 12.6% of the hydrochlorothiazide users, equivalent to approximately two million adults. Those who were women [odds ratio (OR), 2.05; 95% confidence interval (CI), 1.54-2.72] and non-Hispanic black (OR, 1.54; 95%CI, 1.23-1.92) had a higher risk for having hypokalemia. Younger and patients taking monotherapy were more likely to develop hypokalemia. Compared to those aged 20-44 years, those aged $\geq$80 years had a lower prevalence of hypokalemia (OR, 0.38; 95%CI, 0.22-0.66). Compared to those taking hydrochlorothiazide monotherapy, patients with fixed-dose combination therapy (OR, 0.33; 95% CI, 0.22-0.49) had a significantly lower risk of hypokalemia. Among those taking potassium supplements simultaneously, 27.2% and 18.0% of patients treated with monotherapy and polytherapy had hypokalemia.
Conclusions: The prevalence of hypokalemia among hydrochlorothiazide users was alarmingly high. Women, ethnic minorities, and participants taking monotherapy were more likely to have hypokalemia. Among those taking potassium supplements, up to 27% had hypokalemia. Regular monitoring of potassium and novel strategies to reduce hypokalemia among hydrochlorothiazide users is urgently warranted.

PP05.

Systemic Arterial Hypertension and Chronic Obstructive Pulmonary Disease: Dangerous Liaisons? Results from the United States National Health and Nutrition Examination Survey 1999-2018

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Objectives: Systemic arterial hypertension (SAH) is one of the common comorbidities among patients with chronic obstructive pulmonary disease (COPD). This study aimed to investigate the association between SAH and COPD.
Methods: 46,804 eligible non-pregnant participants aged $\geq$ 20 years examined in Mobile Examination Center (MEC) of the National Health and Nutrition Examination Survey (NHANES) 1999-2018 were included in this study. Participants who had invalid data on covariates, SAH, and COPD were excluded. The association between SAH and COPD was studied using logistic regression, with adjustment for demographics, body mass index (BMI), smoking, asthma, and diabetes status.
Results: Among the participants, 46.1% (95% CI, 45.3-46.9) had SAH and 6.8% (95% CI, 6.4-7.2) had self-reported COPD. COPD was associated with SAH [OR=1.71, 95% CI (1.56-1.88), P$<$0.01], which remained significant [OR=1.16, 95% CI (1.03-1.31), P$<$0.01] after adjusting for demographics, BMI, smoking, diabetes and asthma status. The association was found in women and adults aged less than 60 years in all models (All P$<$0.01). Furthermore, there was a significant association between SAH and COPD in current heavy smokers [1.27, 95% CI (1.01-1.61); P$<$0.01].
Conclusions: In this 20-year nationwide survey, COPD was associated with SAH. The association was more robust among women and adults aged less than 60 years. The association was more significant among heavy smokers. Our study demonstrates a need for hypertension screening and blood control among COPD patients, especially heavy smokers.

PP06.

AMPK/miRNA-181B Axis Protects Against Diabetic Endothelial Dysfunction

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Objectives: Endothelial dysfunction is often the antecedent event of diabetic vascular complications, such as diabetic retinopathy and diabetic atherosclerosis. Previously, we reported that AMPK inactivation underlay endothelial dysfunction of diabetic mice. MicroRNA-181b (miRNA-181b) was shown to improve vascular function and suppress NF-κB activity in endothelial cells. However, it remains unclear about the upstream mediator of miRNA-181b, and whether the activation of such signaling axis could protect against diabetic vascular dysfunction. Therefore, the present study aimed to uncover the upstream mediator of miRNA-181b, and the presence of any physiological means for activating such signaling axis.
Methods: A diabetic mouse model was induced by high-fat diet feeding, followed by streptozotocin (STZ) injection (6 mg/ml). Aortic endothelial function of diabetic mice were evaluated by wire myography. ROS levels in different arteries were measured by both dihydroethidium (DHE) staining and lucigenin-enhanced chemiluminescence. Conventional biochemical assays, like Western blotting and RT-PCR, were performed to study the signaling axis. Diabetic mice were subjected to chronic running exercise on a rodent treadmill for 8 consecutive weeks (45 min/day). In vitro simulation of blood flow was performed by iBidi flow system to study the effect of shear stress on miRNA level.
Results: In the renal arteries of type 2 diabetic patients and aortae of diabetic mice, miRNA-181b levels were remarkably downregulated. Co-incubation of miR-181b mimics enhanced aortic vascular function, and inhibited ROS over-production in different arteries from diabetic mice. Furthermore, AMPK activation could boost miRNA-181b level in endothelial cells. Chronic exercise training increased miRNA-181b level by AMPK activation. Importantly, in vitro simulation of exercise-induced blood flow increment was shown to ignite the AMPK/miRNA-181b axis.
Conclusions: Our findings suggested that AMPK/miRNA-181b axis could protect against diabetic endothelial dysfunction. (The current study was supported by RGC-SRFS, RGC-CRF and RGC-RIF.)

PP07.

Metformin is Associated With Lower Risks of Incident Cancers Compared to Sulphonylurea Use: A Population-Based Study With Competing Risk Analyses

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Objective: To investigate the effects of sulphonylurea compared to metformin on the adverse outcomes of new-onset cancers and mortality risk among type-2 diabetes patients.
Methods: This is a retrospective population-based cohort study with 273876 type-2 diabetes patients followed from 1 January 2000 to 31 December 2019. Metformin or sulphonylurea users were matched using a propensity score at 1:2 ratio to generate the control cohort. The primary outcome was cancer events. Secondary outcomes were cancer, cardiovascular, and all-cause mortality. Univariate Cox regression models identified the associations of sulphonylurea and metformin with adverse cancer and mortality outcomes. Competing risks were considered with cause-specific hazard models and subdistribution hazard models. Sensitivity analysis using different matching methods of treatment weighting was conducted.
Results: A total of 36487 sulphonylurea and 71306 metformin users were included in the matched cohort. Univariate Cox regression showed that sulphonylurea users had higher risks of overall cancer onset (hazard ratio [HR]: 2.26, 95% confidence interval [CI]: 2.18-2.34, P<0.0001), including pancreatic (HR: 4.03 [3.37, 4.82], P value<0.0001), colorectal (HR: 2.12 [1.97, 2.27], P value<0.0001), genitourinary (HR: 1.73 [1.57, 1.90], P value<0.0001), breast (HR: 1.36 [1.22, 1.51], P value<0.0001) and lung cancer (HR: 3.37 [3.11, 3.65], P value<0.0001). Sulphonylurea users also had higher risks of cancer (HR: 2.38, 95% CI: 1.87-3.03;P<0.0001) and all-cause mortality (HR: 1.92, 95% CI: 1.78 -2.08;P<0.0001). Similar results were observed in the competing risk and the sensitivity analysis.
Conclusion: Metformin demonstrated significantly risk reduction and mortality risks on cancer among type-2 diabetes patients compared to sulphonylurea.

PP08.

Restored Autophagic Flux Improves Endothelial Function in Diabetes via Decreasing Mitochondrial Ros-Mediated Enos Monomerization

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Objectives: Endothelial nitric oxide synthase (eNOS) monomerization and uncoupling are crucial mediators of vascular dysfunction in diabetes. Transcription factor EB (TFEB), a master regulator of autophagy and lysosomal biogenesis, limits inflammation. Growing evidence indicates that autophagic dysregulation is involved in diabetic endothelial dysfunction, however, whether autophagy regulates eNOS activity through controlling eNOS monomerization/dimerization remains elusive. The present study therefore aims to investigate whether and how impaired autophagic flux reduces eNOS activity and endothelial function through suppressed eNOS dimerization. Meanwhile, we determine whether restoration of autophagic flux through TFEB induction, mTOR inhibition and calorie restriction can rescue the impaired endothelial function in diabetic mice through restoring eNOS dimerization.
Methods: The aortas of diabetic db/db mice and non-diabetic db/m+ mice were used in ex vivo organ culture, functional study on wire myograph and mitochondrial ROS (mtROS) production. Western blotting was used to determine the level of protein of target gene. Adenovirus was used to overexpress TFEB both in vivo and in vitro.
Results: Autophagic flux is impaired in the endothelium of db/db mice and in human endothelial cells exposed to advanced glycation end products or oxidized low-density lipoprotein. Pharmacological inhibition of autophagic flux by chloroquine or bafilomycin A1 were sufficient to induce eNOS monomerization and lowered NO bioavailability through increasing mtROS. By contrast, restoration of autophagic flux by TFEB overexpression reduced endothelial oxidative stress, enhanced eNOS dimerization, and improved endothelium-dependent relaxations (EDR) in diabetic mouse aortas. Meanwhile, inhibition of mammalian target of rapamycin kinase (mTOR) by rapamycin increased TFEB nuclear localization, decreased mtROS accumulation, facilitated eNOS dimerization, and improved endothelial function in db/db mice. Furthermore, calorie restriction also increased aortic TFEB expression, improved autophagic flux, and restored EDR in diabetic mice.
Conclusion: The present study uncovers a causal relationship between impaired autophagic flux-induced mtROS accumulation and eNOS dimer dissociation in diabetic endothelial dysfunction. Induction of TFEB-driven autophagic flux by inhibiting mTOR or through diet intervention are effective to treat diabetic vasculopathy.
Keywords: Autophagy, TFEB, eNOS, endothelial dysfunction, diabetes
(Supported by RGC-CRF C4024-16W and RGC-SRFS2021-4S04)

PP09.

The Anti-Inflammatory and Anti-Atherosclerotic Effects of CBL0137

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Objectives: Our previous studies showed that endothelium-specific knockdown of YAP can delay the formation of atherosclerotic plaques, indicating YAP serving as a new target for anti-atherosclerotic treatment. After screening a large number of drugs, we found that CBL0137, a non-genotoxic anti-cancer drug, can significantly inhibit the activity of YAP in endothelial cells. However, whether CBL0137 has anti-inflammatory and anti-atherosclerotic effects is still unknown. The present study investigates how CBL0137 regulates YAP to exert its anti-inflammatory effects in vitro and in vivo. Also, we will explore whether CBL0137 reduces formation of atherosclerotic plaques in ApoE knockout mice.

Methods: Cell viability of HUVEC was determined by CCK8 assay. Real-time PCR was used to detected YAP's target gene and inflammation marker at mRNA level. The phosphorylation of YAP was detected by western blotting. The anti-inflammatory effect of CBL0137 would be accessed by THP-1 monocytes attachment. ApoE knockout mice were randomly divided into two groups (control group and CBL0137 group) after partial carotid artery ligation. CBL0137 was administered by intraperitoneal injection at 1 mg/kg/d. After 3 weeks, the mice will be sacrificed. By comparing the percentage of plaque area in the left common carotid artery to evaluate whether CBL0137 is anti-atherosclerotic.

Results: CCK8 results showed that 1uM CBL0137 treatment for 24h did not affect the activity of HUVEC. Dual luciferase reporter assay showed that CBL0137 inhibited YAP (8×GTIIC-luc reporter gene) activity. Real-time PCR results showed that CBL0137 significantly suppressed the expression of YAP target genes (ANKRD1, CTGF, CYR61) in both time- and concentration-dependent manner. CBL0137 reduced the phosphorylation of YAP Y357 in HUVEC at 30 mins. CBL0137 can inhibit IL-1β-induced inflammation in HUVEC. IL-1β (10 ng/ml) was applied to induce endothelial inflammation and HUVECs were treated with CBL0137. Both mRNA and protein levels of inflammation markers (MCP-1, VCAM-1) were decreased after CBL0137 treatment. Monocyte attachment results showed that CBL0137 (1 μM) inhibited IL-1β-induced monocyte infiltration. In the partial carotid artery ligation model, the plaque area decreased from 70.9% to 50.4% after CBL0137 treatment for 3 weeks.

Conclusions: The present study provides new evidence that CBL0137 has anti-inflammatory and anti-atherosclerotic effects by regulating YAP phosphorylation. The specific mechanisms are being investigated (supported by RGC - C4024-16W, 14164817 and SRFS2021-4S04).

PP10.

Hippo Pathway Mediates the Beneficial Effect of Metformin Against Diabetic Endothelial Dysfunction and Insulin Resistance

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Objectives: Metformin is the first-line anti-diabetic drug. The pleiotropic beneficial effects of metformin have been reported; however, the underlying mechanisms are incompletely known. Previous reports showed that metformin reduced insulin resistance through activating AMPK, while metformin has been recently described to suppress the Hippo pathway effector YPA/TAZ through activation of AMPK. Our previous study revealed YAP/TAZ activation promotes vascular inflammation during atherogenesis. Therefore, we hypothesize that metformin improves insulin sensitivity through AMPK-mediated suppression of YAP/TAZ activity in vascular endothelial cells.

Methods: To investigate the role of YAP/TAZ in endothelial function regulation under diabetic conditions, we measured endothelium-dependent relaxations in mouse arteries on myographs. The insulin-induced vascular relaxation was used to determine insulin sensitivity in mouse arteries. High glucose was used to mimic hyperglycemia-induced insulin resistance in diabetic patients. AMPK inhibitor compound C was used to indicate the involvement of AMPK in metformin-induced improvement of insulin sensitivity and YAP phosphorylation. The phosphorylation of YAP, AMPK, and eNOS was measured using Western blot.

Results: Chronic treatment of metformin improved endothelium-dependent relaxations in the aortas from diabetic mice and diet-induced obese mice. The vaso-protective effect was reversed by AMPK inhibitor. High glucose exposure impaired insulin-induced vascular relaxations which can be reversed by metformin. Metformin reversed high fat diet-induced suppression of AMPK phosphorylation in mouse aortas. YAP overexpression impaired endothelium-dependent relaxations and this effect was reversed by metformin. Metformin increased YAP phosphorylation, reversed high glucose-induced YAP dephosphorylation, and elevated the expression of YAP target gene CTGF in human umbilical vein endothelial cells (HUVECs). Moreover, JNK phosphorylation is increased in high glucose-treated HUVECs, which was reversed by metformin. Metformin also increased insulin-induced eNOS phosphorylation in high glucose-treated HUVECs.

Conclusions: The present study reveals that metformin ameliorates diabetes and obesity-associated endothelial dysfunction and improves insulin sensitivity at least in part via suppressing YAP-JNK-inflammation pathway. Metformin suppresses YAP activity through AMPK-mediated YAP phosphorylation. These new findings indicate a significant role of YAP signaling in the regulation of vascular homeostasis and YAP can serve as a useful target for therapeutic intervention for restoration of endothelial function and insulin sensitivity in obesity and diabetes (supported by RGC - C4024-16W, 14164817, SRFS2021-4S04, and HMRF 05161746).

PP11.

Prognostic Value of Pre-Operative Left Atrial Strain on Composite Endpoint in Patients Received Aortic Valve Replacement for Severe Aortic Stenosis: A Prospective Cohort Study

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Objective: Severe aortic stenosis (AS) is the most common primary valvular heart disease, treatable only by aortic valve replacement (AVR). Current literatures have shown that severe AS may precede atrial dysfunction which predicts adverse outcomes. However, predictive value of pre-operative left atrial (LA) function on post-AVR clinical outcomes is uncertain. The study aims to evaluate the prognostic value of pre-operative LA strain on post AVR all-cause mortality and heart failure.

Methods: Patients aged 18 years old or above with severe AS were recruited and assessed using speckle-tracking echocardiography pre-operatively. Severe AS was defined according to 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart

Disease. Peak Atrial Longitudinal Strain (PALS) was measured as a surrogate of LA function. Patients with underlying pre-operative atrial fibrillation, other moderate to severe valvular heart diseases and cancers were excluded. High PALS was defined as PALS higher than 15.94%. Patients were followed up until death or end of the study. The primary endpoint is a composite endpoint of all-cause mortality and heart failure during hospitalization. The association of LA function with composite endpoint of all-cause mortality and heart failure was evaluated by Cox Proportional Hazards analysis.

Results: A total of 128 patients (mean age 65.3.9±9.4 years, 56.3% male) were analyzed. Patients were followed up for a mean period of 3.9 ± 2.4years. A total of 65 of 128 patients (50.8%) belonged to low PALS group. During the study period, 23 patients developed events on the composite endpoint. Among those with composite endpoint, low PALS group accounted for 18 (78.3%) patients and high PALS group accounted for 5 (21.7%) patients. Higher PALS was independently associated with lower risk of composite endpoint of all-cause mortality and heart failure (HR, 0.33; 95% CI 0.117-0.916, p=0.03) after adjustment for EuroSCORE II.

Conclusion: Higher PALS, a surrogate of LA function, is associated with a lower risk of composite endpoints of mortality and heart failure in patients with severe AS undergoing AVR, independent of EuroSCORE II. Evaluation of LA function by assessing speckle tracking derived PALS may aid in prognostication for patients undergoing AVR.

PP12.

Maple Tree Leaf (Acer Tatarium subsp. Ginnala) Extracts Confer Cardioprotection Against Myocardial Ischemia/Reperfusion (I/R) Injury Through Significant Antioxidative Potency

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Objectives: Recent studies suggested Ginnalin A extracted from maple tree leaf (Acer tataricum subsp. Ginnala) exhibited strong antioxidative and therapeutic activities in various systems, we therefore investigated whether maple tree leaf extracts can protect cardiomyocytes and heart tissues against myocardial ischemia/reperfusion (IR) injury via antioxidative efficacy.

Methods: Maple tree leaf (Acer tataricum subsp. Ginnala) from Korea were harvested and extracts were prepared using five organic solvents and their cardioprotective potentials were investigated in vitro and in vivo using cardiac muscle cells and a rat myocardial IR injury model, respectively. By 30min co-treatment or 1hr pre-treatment of extracts with H2O2 in H9C2 myoblasts and neonatal rat cardiomyocytes (NRCM), CCK-8 assay was employed to evaluate cell viability against oxidative damage, which was further validated via LIVE/Dead assay and lactate dehydrogenase (LDH) assay. In this cellular injury model, DCFDA assay was also performed using microplate reader and flowcytometry to determine and quantify the total cellular reactive oxygen species (ROS) level, which mediated most of muscle damage during reperfusion. To examine in vivo effect, 10min intramyocardial administration of extracts before reperfusion was performed in rat myocardial I/R model. 24hr after perfusion, hearts were collected and sectioned then Evan's blue- and 2,3,5-triphenyltetrazolium chloride (TTC) staining was applied to assess viable myocardium area and infarct size.

Results: Maple tree leaf extracts were prepared and fractioned successively via ethanol, hexane (HX), dichloromethane (DCM) and ethyl acetate (EA). After screening a series of concentration, DCM-fractioned and EA-fractioned extracts at the concentration around 46.8μg/ml and 128.7μg/ml, respectively, significantly improved survival of H9C2 myoblast and NRCMs against H2O2 in both 30min co-treatment and 1hr pre-treatment cell injury model: CCK-8 assay showed enhanced cell viability to 73.31±5.45% in DCM-treated and 69.09±4.36% in EA-treated NRCMs compared with 32.91±2.27% in H2O2-treated controls; Live/Dead assay stained and quantified much more live cells and LDH assay suggested less cellular damage after extracts treatment. Furthermore, extracts markedly decreased cellular ROS intensity evaluated in microplate reader system (982±47 in DCM-treated and 933±35 in EA-treated cells compared with 2292±40 in H2O2-treated controls). This result was further evidenced via flowcytometry, which indicated less DCF+ cells after treatment. For in vivo myocardial I/R injury model, extracts-administrated rat hearts exhibited significantly larger viable myocardium and smaller infarct size.

Conclusions: Collectively, our in vitro and in vivo results suggested maple tree leaf (Acer tataricum subsp. Ginnala) extracts possess significant antioxidative potency and therapeutic effects against myocardial I/R injury.

PP13.

Overexpression of SIRT1 in Endothelial Cells Prevented PER2 Mutation-Induced Diastolic Dysfunction in Heart

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Objectives: The circadian clock and rhythmicity regulate cardiovascular function and energy homeostasis. PER2 (period 2) is a key circadian regulator. SIRT1 (sirtuin 1) is a longevity regulator. Cross-regulation between PER2 and SIRT1 plays an important role in modulating circadian rhythmicity. The present study investigated the cardiac function of mice with a PER2 mutation (PER2MUT) and/or human SIRT1 overexpressed selectively in endothelial cells (eSIRT1).

Methods: Male wild type (WT), PER2MUT, eSIRT1, or litters of PER2MUT/eSIRT1 cross-breeders at the age of 34-weeks were used for the present study. Cardiac function was evaluated by the Doppler Flow Velocity system (Indus Instruments, Texas, USA).

Results: PER2MUT exhibited increased E-A peak velocity ratio (2.49 ± 0.90) when compared to WT (1.35 ± 0.07), eSIRT1 (1.76 ± 0.06) and PER2MUT/eSIRT1 (2.03 ± 0.39) mice. PER2MUT also showed increased Isovolumic Contraction Time (34.75 ±4.25 millisecond) when compared to WT (14.5 ± 5.72 millisecond), eSIRT1 (13.85 ± 3.07 millisecond) and PER2MUT/eSIRT1 (21.17 ± 6.05 millisecond) mice. Isovolumic Relaxation Time was 26.25 ± 5.13, 25.3± 1.91, 30.94 ± 9.06 and 29.92 ± 20.61 millisecond, whereas E-linear Deceleration Time was 48.57± 19.95, 35.95 ± 3.0, 16.6 ± 7.15 and 27.45 ± 1.82 millisecond, in WT, eSIRT1, PER2MUT and PER2MUT/eSIRT1 respectively.

Conclusion: Deletion in the Per-Arnt-Sim domain of the Per2 gene resulted in diastolic dysfunction in PER2MUT mice, which was attenuated by overexpression of SIRT1 in endothelial cells. The project was supported by the grants from Seeding Funds for Basic Research of the University of Hong Kong, the General Research Funds (17124718) and Collaborative Research Funds (C7037-17W) of Research Grant Council, the Areas of Excellence Scheme (AoE/M-707/18) of University Grants Committee.
Keywords: PER2, Mitral Inflow, Diastolic Dysfunction, Endothelial SIRT1

PP14.

Clinical Significance of a Novel Angiographic-Based Index in Non-Culprit Vessels Among Patients Presenting With Acute Coronary Syndrome and Concomitant Multivessel Disease

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Objectives: Computational pressure-flow dynamics derived fractional flow reserve is a novel angiographic-based index used to assess the severity of myocardial ischemia in patients with coronary artery stenoses, without the need of hyperemic stimulus and pressure wire insertion. In patients with acute coronary syndrome, multivessel disease is often present, and the ischemia status of non-culprit vessels may affect outcomes. In this study, we aimed to evaluate the clinical value of the angiographic-based index in non-culprit vessels among acute coronary syndrome patients with multivessel disease.
Methods: Patients presented with acute coronary syndrome and at least two vessels with ≥50% diameter stenosis were included. The culprit vessel was identified, and analyses of the angiographic-based index of the non-culprit vessels were performed for every patient. Based on the threshold of 0.8 adopted from fractional flow reserve studies, patients were stratified into ischemic group if the angiographic-based index was ≤0.8 in any non-culprit vessel, and into non-ischemic group if none of the non-culprit vessels had the angiographic-based index ≤0.8. The primary endpoint was major adverse cardiovascular events, defined as a composite of all-cause mortality, non-fatal myocardial infarction, and any subsequent revascularization.
Results: Our study included a total of 293 patients (mean age 65.3±13.2, male 77.5%), with 113 (38.6%) presented with ST-elevation myocardial infraction, 119 (40.6%) presented with non-ST-elevation myocardial infarction, and 41 (14.0%) presented with unstable angina. Patients in the ischemic group (n=176) had more obstructive lesions in overall compared to those in the non-ischemic group (n=117) (3.8±1.5 vs. 3.2±1.1, p<0.001). The ischemic group patients had a higher rate of primary endpoint at 3 years compared to non-ischemic group patients (28.4% vs. 15.4%; adjusted hazard ratio, 1.92; 95% confidence interval, 1.10-3.36; p=0.023).
Conclusions: In acute coronary syndrome patients with concomitant multivessel disease, myocardial ischemia in non-culprit vessels as assessed by the novel angiographic-based index was associated with adverse clinical outcomes at 3 years.

PP15.

Multiple Biomarker Strategy for Improved Outcome Prediction in Double Valve Surgery

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Objectives: Risk stratification in double valve surgery remains suboptimal due to a narrow focus on symptoms and left ventricular performance. Our study aims to evaluate the prognostic implications of a biomarker-based risk score in double valve surgery.
Methods: A total of 130 patients (age 64±8 years, 49% female) presenting for concomitant aortic and mitral valve surgery underwent echocardiography and measurements of N-terminal pro-B-type natriuretic peptide, high-sensitivity cardiac troponin-T, growth differentiation factor-15, and galectin-3. An integer-based biomarker score, with one point for each abnormal parameter, was developed based on biomarker-specific thresholds defined by penalized splines and maximally selected rank statistics. The rates of adverse outcomes (composite of heart failure [HF] hospitalization and all-cause mortality) were compared across biomarker score groups using Cox proportional hazards analysis. The Fine-Gray model was used to account for competing risks, with death considered a competing event for HF hospitalization. The incremental value of the biomarkers to EuroSCORE II and STS Score was evaluated using Harrell's C-statistic.
Results: Over a median follow-up of 3.9 years, 35 adverse events (22 HF hospitalizations and 13 deaths) occurred. Elevated concentrations of each biomarker were independently associated with long-term adverse events after adjustment for demographics, comorbidities, and echocardiographic characteristics (p<0.05 for each).
According to the biomarker score, 70 (54%), 40 (31%), and 20 (15%) patients were classified as low (0), intermediate (1-2), and high (3-4) risk, respectively. Patients with higher biomarker scores were older, had greater comorbidity burden, worse eGFR, and higher EuroSCORE II and STS score (Ptrend <0.05). The risk of death (Hazard Ratio [HR], 3.27, 95% CI 1.72-6.21), HF hospitalization (Subdistribution HR [sHR] 2.92, 95% CI 1.70-5.02), and adverse outcomes (HR 3.56, 95% CI 2.27-5.59) increased in a graded fashion across biomarker score groups, with scores of 3-4 incurring the highest event risk. The biomarker score (sHR 2.61, 95% Confidence Interval [CI] 1.50-4.53, p<0.01), but not EuroSCORE II (sHR 1.05, 95% CI 1.00-1.10, p=0.06) nor STS score (sHR 1.06, 95% CI 0.94-1.20, p=0.35), was independently predictive of HF hospitalization.
The addition of the biomarker score to EuroSCORE II and STS score improved outcome prediction (C-statistic 0.78 vs 0.71, and 0.72 vs 0.61 respectively; likelihood ratio test p<0.001). Results were consistent across combinations of valvular lesions.
Conclusions: In patients undergoing double valve surgery, a novel biomarker-testing strategy comprising NT-proBNP, hs-cTnT, GDF-15, and galectin-3 may improve risk assessment beyond conventional risk-scoring systems.

PP16.

Incidence, Clinical Correlates and Associated Outcomes of Dementia in Heart Failure: A Population-Based Cohort Study

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Background: Dementia, in the setting of heart failure (HF), portends poorer outcomes and poses great challenges in its clinical management.
Purpose: We investigated the incidence, types, clinical correlates, and the prognostic impact of dementia in a population-based cohort of patients with HF. Further, we examined the interactions of age and sex, and education status with dementia incidence.
Methods: The previously validated Hong Kong Clinical Data Analysis Reporting System (CDARS), a territory-wide database was interrogated to identify patients with HF (N= 202,121) from 1995 to 2018. Associations of clinical correlates with incident dementia and its risk with all-cause mortality were assessed using competing risk/multivariable Cox regression models where appropriate.
Results: Among a total cohort aged ≥18 years with HF (mean age: 75.3±13.0 years, 51.3% women), new-onset dementia occurred in 22,145 (11.0%) over a median follow-up of 5.5 years. Alzheimer's disease occurred in 27.0%; vascular dementia (18.1%) and unspecified dementia (in 55.1%). Age-standardized rate of dementia incidence in women was 1297 (95%CI, 1276-1318) (vs. 744, 95%CI, 723-765) per 10000 population in men. Other independent predictors of dementia include Increasing age (HR 1.08), Female sex (HR 1.19), Nil/< primary (vs tertiary) education (HR 1.29), Parkinson's disease (HR 1.73), head injury (HR 1.37), peripheral vascular disease (HR 1.31), stroke (HR 1.29), depression (HR 1.18), alcohol intake (HR1.17), anaemia (HR 1.14), hypertension (HR 1.08), among other common comorbidities in HF (Figure 1A).
Notably, a significant interaction (p<0.001) between age and sex on dementia incidence was observed, such that women in all age groups were observed to have higher sHR compared to men (Figure 1B). After

accounting for competing risk, dementia was not associated with adjusted hazard of all-cause mortality.
Conclusions: Female sex, lower socioeconomic status, increasing age and common comorbidities were associated with higher hazards of incident dementia.

PP17.

Aspirin Prescription in Cancer Patients: A Population-Based Observational Study From Nhanes 1999-2014

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Objectives: Aspirin has been associated with reduction in incidence and mortality of cancers. The prevalence of aspirin usage in cancer patients in the general population is not well known. Therefore, we investigated aspirin prescription in the U.S. population.
Methods: We analyzed data on 43,672 participants aged $\geq$ 20 years who had valid data on cancer diagnosis status and prescription information in NHANES 1999–2014.
Result: Among participants aged 20-39 years, 0.1% of participants took aspirin and all of them were non-cancer participants. The total percentage increased with age, rising to 0.7% and 2.3% in participants aged 40-59 years and above 60 years, respectively. The prevalence of cancer increased with age from 2.1% in participants aged 20-39 years to 7.6% in participants aged 40-59 years and further to 22.5% in participants aged above 60 years.1.6% of cancer patients took aspirin, which was significantly higher than 0.8% for non-cancer participants (OR=2.17, 95%CI=1.60-2.95, P<0.001). The difference was consistently found in both men (OR=2.55, 95%CI=1.83-3.56, P<0.001) and women (OR=1.89, 95%CI=1.20-2.99, P=0.006).
Conclusions: Prevalence of both aspirin prescription and cancer were found to be related to age increase. Aspirin is used in cancer patients more than in non-cancer participants. Clinicians should keep in mind the balance of aspirin's benefits and risks in different populations with sex, age and individual assessment taken into consideration.

PP18.

Echocardiographic Assessment of Pregnant Women With Tetralogy Of Fallot in Assessment of Outcome

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Objectives: Late complications of intracardiac repair of Tetralogy of Fallot in adulthood include: impaired exercise performance, heart failure, arrhythmia, and sudden cardiac death. Pregnancy may worsen these complications. This study aims to depict the outcomes of pregnancy among women with repaired TOF.
Methods: 105 pregnant episodes were identified among a cohort of 240 adult female patients with TOF from an electronic medical record system between 1990 to 2021. Echocardiographic studies from patients who had received imaging within 1 year prior to and following delivery were included. A paired sample t-test was carried out to compare echocardiographic parameters between pre-delivery and post-delivery periods. For patients with a baseline of severe PR, linear regression was utilized to highlight significant changes in echocardiographic parameters.
Results: Among all pregnancies (n=105), 65 successful pregnancies, 16 spontaneous-miscarriages, 21 termination of pregnancies and 3 ectopic pregnancies were identified. The mean maternal age was 28.9 ($\pm$6.7) years with deliveries at 37.86 (30-41) gestational weeks and a mean birth weight of 3.004 (1.705-4.050) kg. Most patients had natural spontaneous deliveries (31.8%), followed by emergency lower section cesarean section (LSCS) (29.5%), assisted delivery methods (18.2%), elective LSCS (13.6%), and indicated LSCS (6.8%). Cardiovascular events were found in 19 pregnancies with 4 patients experiencing gestational hypertension, 4 patients with pre-eclampsia toxemia, 7 patients with heart failure symptoms and 4 patients with arrhythmias (atrial tachycardia, ventricular tachycardia and ectopic beats). Other complications involved 4 patients with gestational diabetes mellitus, 3 patients with impaired glucose tolerance, 2 patients with anemia, 3 patients with maternal thyroid disease and 1 patients with proteinuria. Among the 65 successful deliveries, 7 patients received pulmonary valve replacement before to their deliveries, 11 patients received pulmonary valve replacements after their deliveries. Echocardiographic studies displayed significant changes in left ventricular ejection fraction (LVEF) (Pre-delivery = 60.69 $\pm$8.73; post-delivery = 59.39 $\pm$9.36) (P = 0.007), left ventricular end diastolic volume (LVEDV) (Pre-delivery: 89.71mL $\pm$18.22mL; Post-delivery: 80.96mL $\pm$12.32mL; P = 0.007), left end systolic volume (LVESV) (Pre-delivery: 35.43 $\pm$12.36; Post-delivery: 32.70 $\pm$ 8.83; P = 3.7x10-5) and right ventricular index of myocardial performance score (Pre-delivery: 0.34 $\pm$0.12; Post-delivery: 0.33 $\pm$0.12; P = 0.007). Significantly worse right ventricular global longitudinal strain (RV GLS) (P = 0.029) was detected in Patients with severe PR.2 patients developed severe PR after delivery.
Conclusion: Adult female patients with TOF can have pregnancies with acceptable mortality and morbidity, however intrapartum and postpartum echocardiographic monitoring is advised.

PP19.

Long-Term Prognostic Implications of Percutaneous Coronary Intervention in Acute Coronary Syndrome Patients With Non-Ischemic Intermediate Lesions Based on Computational Angiography Fractional Flow Reserve

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Objectives: A substantial proportion of patients with acute coronary syndrome (ACS) may have intermediate lesion(s) that are non-ischemic during emergency coronary angiography. The long-term prognosis of such patients, compared to stable ischemic heart disease (SIHD), is uncertain. The role of PCI in such ACS patients remains underexplored. Computational pressure-flow dynamics derived fractional flow reserve (caFFR) has been developed to assess myocardial ischemia without invasive pressure wire and hyperemic stimulus. Our aim is first to assess the prognostic differences between ACS and SIHD with non-ischemia intermediate lesions. Second, we ascertain whether PCI in these ACS patients provides survival benefit.

Methods: We studied 974 patients (mean age 65.1 years; male 61.9%) with absence of myocardial ischemia, defined as caFFR≥0.80 in all vessels. Patients were stratified into those with ACS (n=280) and those with SIHD (n=694). Among the ACS cohort, patients were divided into those with PCI (n=205) and with medical therapy (MT) (n=75). The SIHD cohort, all treated with MT, was considered as the referent group. The primary endpoint was major adverse cardiovascular events (MACE) at 3 years, defined as a composite of all-cause mortality, myocardial infarction (MI), and any revascularization.
Results: During a follow-up of 35.8 months, 136 MACE occurred, including 97 all-cause mortality, 19 MI, and 32 revascularization. Compared to SIHD, ACS was independently associated with MACE even in the absence of myocardial ischemia (adjusted HR=4.834; 95% CI=3.044-7.676; P<0.001). The 3-year incidence rate of MACE was the highest in ACS patients with MT, followed by ACS patients with PCI; SIHD patients had the lowest incidence rates (34.7% vs 23.4% vs 8.6%, P<0.001). Similar findings were observed for hospitalization for all-cause death (29.3% vs 16.6% vs 5.6%, P<0.001) at 3 years.
Conclusion: In patients with intermediate lesion(s) without myocardial ischemia, those presented with ACS had a higher risk of MACE at 3 years compared to SIHD. In patients with ACS, our finding suggests that PCI should be advocated to intermediate lesions even without myocardial ischemia.

PP20.

Waist Circumference was Associated With Hypertension in Chinese Population

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Objectives: Recent evidence demonstrated an association between waist circumference (WC) and hypertension. However, it remains unclear whether such an association exists among Chinese population. In this study, we investigated the relationship between WC and hypertension in Chinese population.
Methods: We included 2,265 participants (age≥18) from Shenzhen-Hong Kong United Network on Cardiovascular Disease (982 men and 1283 women; mean age ±SD 43.8±12.0). They had records on WC, hypertension and other confounding factors. Difference in WC between hypertensive and normotensive subjects was evaluated using Chi-square test. Multiple logistic regression was used to study the association between WC and hypertension.
Results: 30.7% of participants have hypertension. WC of hypertensive and normotensive were 86.5±9.4cm and was 80.4±9.9 cm respectively (p<0.001). In overall population, there was a significant association between WC and hypertension before adjustment (OR=1.063, 95% CI=1.053-1.074, p<0.001). The association remained significant after adjustment for age, smoking, alcohol consumption, physical activity, hypercholesterolemia and sex (OR=1.020, 95%CI=1.004-1.036, p=0.015). In sex-specific analysis, association between WC and hypertension was observed in both men and women (men: OR=1.035, 95%CI=1.020-1.050, p<0.001; women: OR=1.088, 95%CI=1.071-1.104, p<0.001) and it remained statistically significant only in women after adjustment for smoking, alcohol consumption, physical activity and hypercholesterolemia (OR=1.049, 95%CI=1.026-1.072, p<0.001), but not in men. No association was observed in both men and women after further adjustment for age (men: OR=1.015, 95%CI=0.99-1.038, p=0.174; women: OR=1.020, 95%CI=0.997-1.044, p=0.093).
Conclusions: Waist circumference was associated with hypertension in our study. Waist circumference could be considered as a predictor for the incidence of hypertension among Chinese population.

A01.

The Effect of Chronic Consumption of Sucralose on Oxidative Stress and Endothelial Function in High Fat Diet-Induced Obese Mice

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Objectives: Metabolic disorders, such as diabetes mellitus and obesity, represents a global health challenge. Endothelial dysfunction is one of the earliest pathological events that triggers vascular oxidative stress, inflammation and dysfunction, leading to the development of cardiovascular and metabolic diseases. To reduce the negative impact of high sugar content in food and beverage on metabolic health, artificial sweeteners have been widely consumed as food additives and generally considered beneficial to health owing to their low caloric content. The present study aims to evaluate the impact of chronic treatment with sucralose on endothelial function in diet-induced obese mice.
Methods: Male C57BL/6J mice were fed with a 60 kcal% fat diet to induce obesity and hyperglycemia. Some mice were treated orally with sucralose (10 and 30 mg/kg/day, Sigma), dissolved in phosphate buffered saline for 8 weeks. Serum levels of glucose and lipids were measured. Acetylcholine (ACh)-induced endothelium-dependent relaxations of mouse mesenteric arteries were recorded on multi-channel myograph and en face accumulation of reactive oxygen species (ROS) was measured in en face endothelial cells of mouse aortas using dihydroethidium (DHE) staining.
Results: ACh-induced endothelium-dependent relaxations in mesenteric arteries were impaired in diet-induced obese mice and this impairment was attenuated or reversed by sucralose treatment. Likewise, sucralose also rescued the impaired relaxation in response to insulin in the same preparations. Chronic consumption of sucralose was effective to normalize elevated endothelial ROS in obese mice. However, 8-week sucralose treatment did not affect fasting blood glucose level or body weight.
Conclusion: The present study shows that chronic sucralose treatment results in beneficial vascular effects to lower endothelial ROS production and to improve endothelial function in arteries of diet-induced obese mice. The ongoing experiments will study the cellular mechanisms underlying the vaso-protective effect of sucralose (The present study was supported by HMRF 06173956 and RGC - SRFS2021-4S04).

A02.

Antibody Treatment Targeting Different Lipocalin-2 Variants for Cardiovascular and Chronic Kidney Diseases

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Objectives: Lipocalin-2 is a kind of pro-inflammatory adipokines that is related to obesity-related cardiorenal syndrome (CRS). It has been

suggested that lipocalin-2 and its disparate variants, C87A and R81E, play a pathogenic role in the progression of the disease. This study aims to evaluate the potential of different lipocalin-2 variants as biomarkers and drug targets for cardiovascular (CVD) diseases and chronic kidney disease (CKD).

Methods: Neutralization antibodies targeting separately lipocalin-2 variants were administered to C57/BL6 mice during a six-week treatment with aldosterone and high salt after uninephrectomy (ANS). The parameters of blood pressure, heart rate and body composition and tissues weight were monitored for comparation. The heart and kidney tissue samples were collected at the endpoint of study to perform immunoassay and PSR staining. Twenty-four hours urine and serum also immunoassay the concentration of the three lipocalin-2 variants.

Results: The blood pressure of control group significantly increased by ANS while no significant changes were observed in the three groups of antibody therapy. In WT mice without anti-lipocalin-2 treatment, PSR staining showed that the kidney had typical glomerular and tubular damages induced by ANS as well as heart turned to cardiac fibrosis. Combined with enzyme-linked immunosorbent assay results indicated that treatment with antibody against C87A significantly attenuated diastolic dysfunction and cardiac injuries, whereas treatment with antibody against R81E elicited more potent protective effects on renal injuries induced by ANS.

Conclusion: Targeting the pathological forms of lipocalin-2 represents a promising strategy for alleviating the progression of cardiorenal syndrome.