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Cardiology

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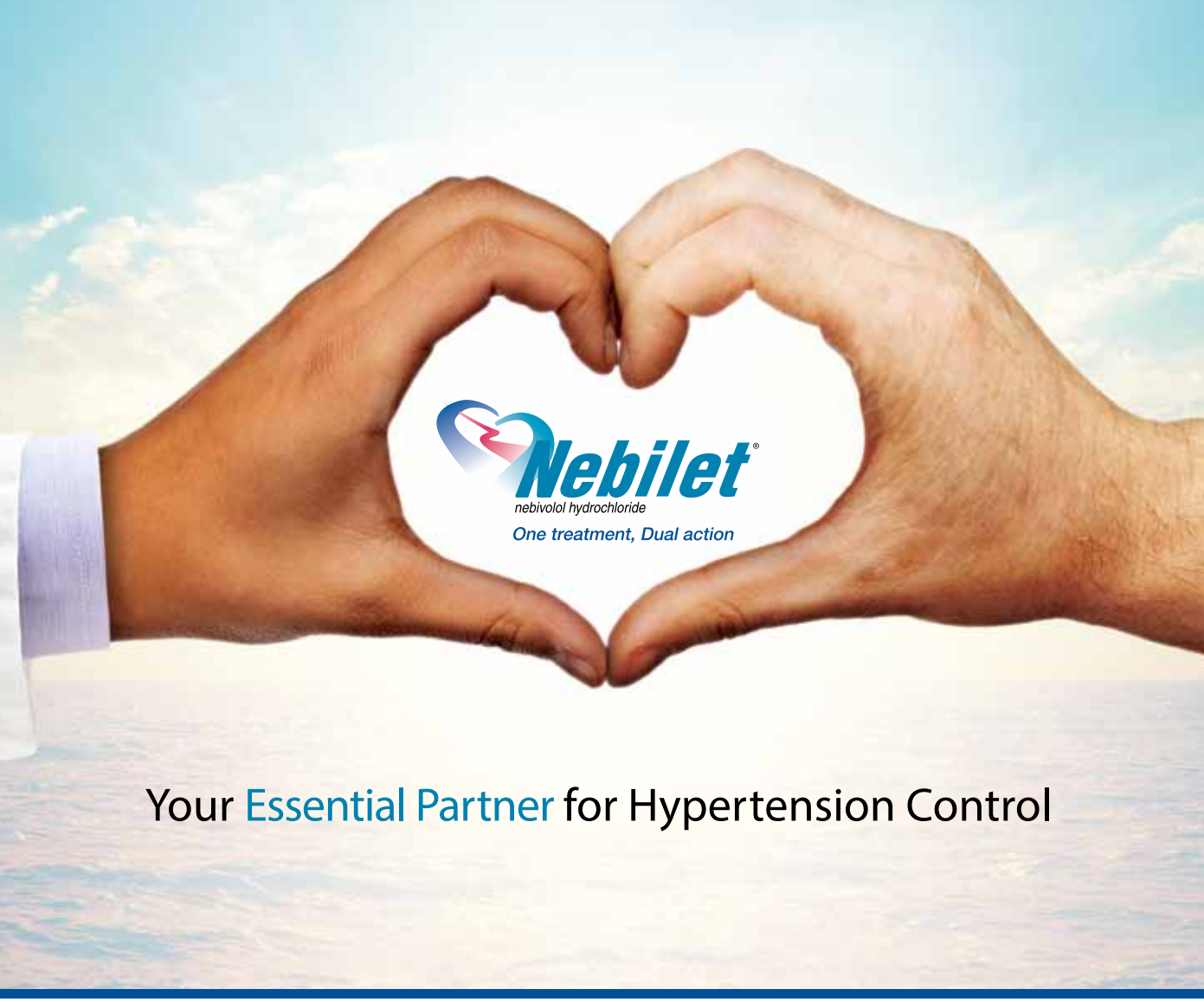

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- Hypertension remains a difficult disease to control.[1]
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- Nebilet can also be easily added to an existing antihypertensive treatment regimen, or used as monotherapy in a broad range of hypertensive and chronic heart failure patients.[8–14]

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ABBREVIATED PRESCRIBING INFORMATION:

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Indications: Hypertension. Treatment of essential hypertension. **Chronic heart failure (CHF).** Treatment of stable mild and moderate chronic heart failure in patients aged 70 or over, in addition to other therapies. **Dosage and Administration: Hypertension.** The usual dose is 1 tablet per day. The dose should be taken preferably at the same time of the day. Elderly patients and patients with a kidney disorder will usually start with ½ (half) tablet daily. **Chronic heart failure (CHF).** The initial treatment starts with ¼ (quarter) tablet per day. This may be increased after 1-2 weeks to ½ (half) tablet per day, then to 1 tablet per day and then to 2 tablets per day until the correct dose is reached. The maximum recommended dose is 2 tablets (10mg) a day. **Side effects:** Most common side effects (1-10%): headache, dizziness, tiredness, an unusual itching or tingling feeling, diarrhoea, constipation, nausea, shortness of breath, swollen hands or feet. **Precautions:** In common with other beta-blockers: anaesthesia, ischaemic heart disease, circulatory disorders, first degree heart block, diabetes, hyperthyroidism, chronic obstructive pulmonary disorders, psoriasis, allergen sensitivity. **Contraindications:** Hypersensitivity, liver impairment, pregnancy and lactation. In common with other beta-blockers: cardiogenic shock, uncontrolled heart failure, sick sinus syndrome, second and third degree heart block, history of bronchospasm, untreated phaeochromocytoma, metabolic acidosis, bradycardia, hypotension, severe peripheral circulatory disturbances.

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The Cover Shot

Bora Bora is one of the many islands of the FRENCH POLYNESIA in the middle of the PACIFIC OCEAN. The local inhabitants enjoy a peaceful and happy life. There are beautiful beaches with fine sand and corals. The sky is always blue with beautiful white clouds and a refreshing breeze. The photo was taken by an iPhone.

Sir Dr Peter Cho-yiu WONG BBS, KStJ
FACC, FRCPs, FHKAM(Med), FHKCP

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Editorial

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Specialist In Cardiology

Editor

Dr Bernard BL WONG

I would like to express my deepest thanks to the Editorial Board of the Federation of Medical Societies of Hong Kong for once again inviting me to join the family of the Hong Kong Medical Diary as the Editor of the Cardiology issue for the fifth time (2007, 2009, 2012 and 2015) in the past decade.

This is a great honour for me and my elite team of cardiologists. Over the last 2 and a half years, with the powerful drive of the free market on the computing, genetic, medical and interventional technologies, magnificent and spectacular advancements in Cardiology have been popping up relentlessly. Numerous important landmark papers, statements and guidelines have been published. Beneficial and practical "changes" to our cardiovascular preventive, medical and interventional guidelines and daily practice continue to be made every day.

In this wonderful issue, once again we have a marvelous team of practical, innovative, experienced, energetic and famous cardiologists. Over the last 2 decades, all of them, as my dearest friends, mentors and masters, have taught me a huge amount. They are Dr Charn-fai Chan, Dr William Chi-kin Chan, Dr Michael Pak-hei Chan, Dr Godwin Tai-chi Leung, Dr Yui-chi So, Dr Wai-lun Wong and Sir Dr Peter Cho-yiu Wong.

This issue will cover practical topics of interest to frontline doctors in their daily practice. From athlete's heart disease, hypertension and atrial fibrillation management to heart failure and cardiovascular intervention plus the update on the hot late-breaking trials from the ACC 18 (American College of Cardiology, Annual Scientific Congress, March 2018). Our goal is to make life easier for the practitioner, by simplifying the complex and seemingly confusing updated international statements, guidelines and trial results, rewriting and summarizing them in easy and simple notes for our dear frontline family practice and non-cardiology colleagues.

I would like to devote this separate paragraph to specially thank Sir Dr Peter Cho-yiu Wong BBS, KStj. As a Distinguished Fellow of the Hong Kong College of Cardiology and an Emeritus Fellow of the American College of Cardiology, he was so kind as to accept my invitation in writing for us a greatly inspirational article on sports and healthiness. As an eminent photographer, he has shared one of his masterpieces here as our proud cover photo for this issue.

In the midst of this global financial turmoil, terrorism activities, regional military conflicts and mounting social, economic, and political pressure in the Hong Kong society, if this Cardiology issue of the Hong Kong Medical Diary can be of any help to you and your patients in living a healthier, easier or happier life, then our humble wish is fulfilled.

I wish you and your family a happy summer.

"Concentrate your energies, your thoughts and your capital. The wise man puts all his eggs in one basket and watches the basket."

~ Andrew Carnegie (1835-1919) Scottish – American industrialist, business magnate and philanthropist, the founder of Carnegie Steel Company.

American College of Cardiology, Annual Scientific Congress (ACC 18') Late-Breaking Clinical Trials Sessions Orlando, Florida USA 9 – 12 March, 2018

Dr Bernard BL WONG

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Specialist In Cardiology

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 June 2018.

'Risk comes from not knowing what you are doing.'
~ Warren Edward Buffett (1930-), American business magnate, investor and philanthropist, Chairman and CEO of Berkshire Hathaway

There were 20 clinical trials whose latest findings was presented in the "Late-breaking Clinical Trials Sessions" in the Congress. I am going to make a comprehensive but precise and practical summary for you, my fellow colleagues. These 20 clinical trials (in the chronological order of presentation during the congress) are;

1. ODYSSEY Outcomes[1]
2. VEST[2]
3. PHARMCLO[3]
4. ARTEMIS[4]
5. TREAT[5]
6. MANAGE[6]
7. SECURE – PCI[7]
8. MOMENTUM 3[8]
9. INDIE – HFpEF[9]
10. CECCY[10]
11. Lisinopril or Carvedilol for the Prevention of Trastuzumab Induced Cardiotoxicity[11]
12. CARES[12]
13. CANTOS[13]
14. Blood Pressure Reduction in Black Barbershops[14]
15. TRIUMPH[15]
16. POISE[16]
17. STOP-PAD[17]
18. DEFENSE-PFO[18]
19. SMART- DATE[19]
20. ANNEXA-4[20]

"I wasn't lucky. I worked hard to achieve the goals I set for myself."
~ Li Ka Shing GBM, KBE, JP (1928-) Hong Kong Business magnate, investor, philanthropist. Chairman of CK Hutchison Holdings

For the ease of reading and understanding, I would like to group the above 20 studies into the followings

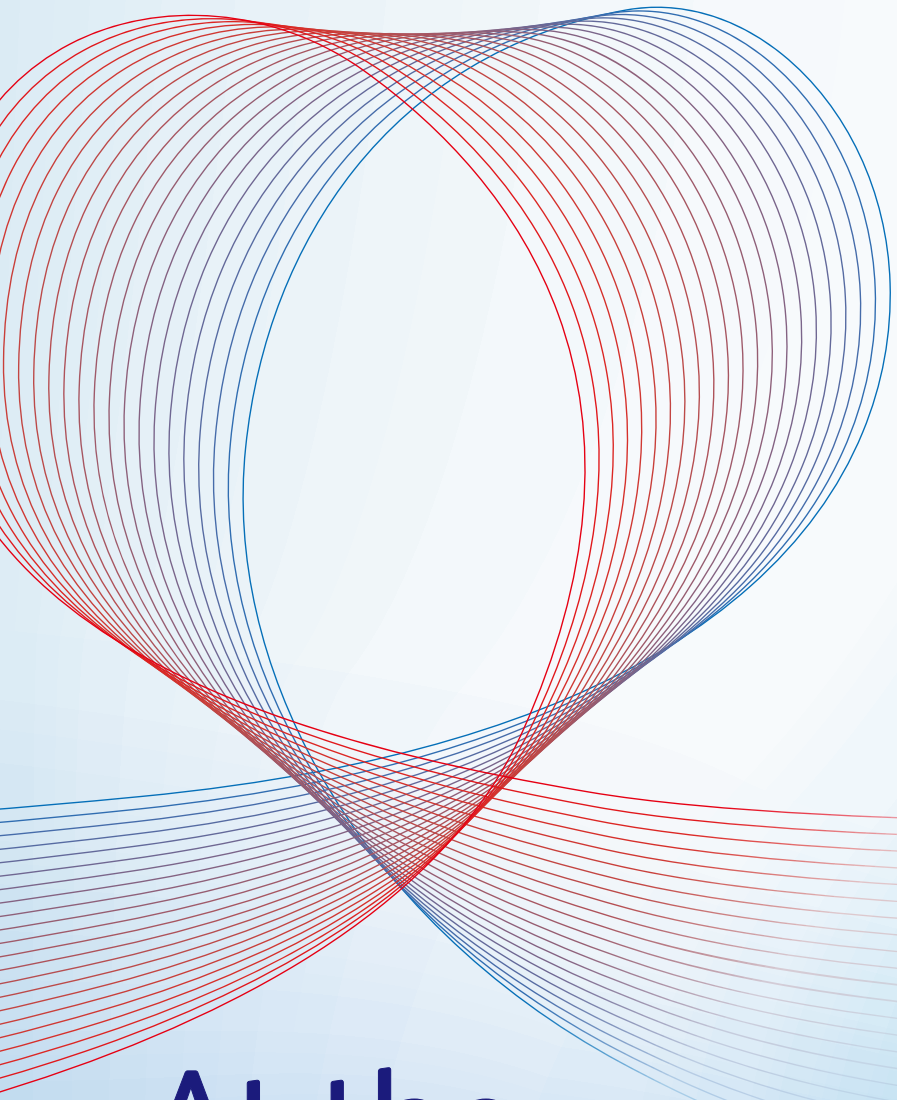
A. Lipid lowering therapy (ODYSSEY, SECURE – PCI)
B. Anti-hypertensive therapy (Blood Pressure reduction in Black Barbershops, TRUIMPH)
C. Anti-platelet therapy (PHARMCLO, ARTEMIS, TREAT, SMART-DATE)
D. Anticoagulant therapy (MANAGE, ANNEX-4)
E. Uricosuric therapy (CARES)
F. Congestive heart failure therapy (MOMENTUM 3, INDIE-HFpEF)
G. Antiarrhythmic therapy (VEST)
H. Patent foramen ovale management (DEFENSE-PFO)
I. Peripheral artery disease management (STOP-PAD)
J. Anti-inflammatory therapy and cardiology (CANTOS)
K. Chemotherapy and cardiology (CECCY, Lisinopril or Carvedilol for the Prevention of Trastuzumab Induced Cardiotoxicity)
L. Non-cardiac surgery management (POISE)

Here come the studies,

A. Lipid lowering therapy

ODYSSEY

- Cardiovascular Outcomes with Alirocumab After Acute Coronary Syndrome: Result of the ODYSSEY Outcomes Trial[1]
  - Patients:
    - 18,924 at 1,315 sites in 57 countries (including HK)
    - Acute Coronary Syndrome (ACS) within the previous 12 months
    - **LDL ≥ 70mg/dl (1.81mmol/l)**, non-HDL ≥ 100mg/dl (2.59mmol/l) or Apolipoprotein B ≥80mg/dl (0.0016mmol/L) after 2-16 weeks of intensive or maximally tolerated statin therapy (Lipitor (atorvastatin) or Crestor (rosuvastatin))
  - Treatment:
    - PCSK9 inhibitory monoclonal antibody Praluent (Alirocumab) 75mg SC (n=9,462) Q 2 weeks vs Placebo (n=9,462)
    - Up titrated to 150mg Q 2 weeks, with a **target LDL level of 25 – 50mg/dl (0.6 -1.30mmol/L)**



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PP-CVP-HKG-0003

- Follow-up duration
  - o 2.8 years (median)
  - o 2-5 years (range)
- Result
  - LDL level 53.3 mg/dl vs 101.4 mg/dl (1.38 vs 2.63 mmol/l), ↓54.7%
  - MACE – major adverse cardiac events (time to first occurrence of coronary heart disease (CHD)death or non-fatal MI or unstable angina requiring hospitalisation or ischemic CVA)
    - →9.5 vs 11.1%, ↓14.4%, P = 0.0003

Non-fatal MI	↓14%	P = 0.006
Ischemic CVA	↓27%	P= 0.01
Unstable angina	↓39%	P= 0.02
All-Cause death	↓15%	P= 0.026
CHD and CV mortality		NS
Adverse event		NS
Minor		
local -injection site adverse event	3.1 vs 2.1%	Significant

NS: non-significant

  - For a pre-specified subgroup of **baseline LDL ≥ 100mg/dl (2.59mmol/L)**, all the 4 endpoints were significantly reduced

	Praluent (N=2814)	Placebo (N=2815)	Absolute reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	0.76 (0.65 - 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	0.72 (0.53 - 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	0.69 (0.52-0.92)
All Cause death	114 (4.1)	161 (5.7)	1.7	0.71 (0.56-0.90)

- Conclusion
  - Patients with recent ACS, PCSK9 inhibitory monoclonal antibody (Praluent) alirocumab 75mg -150mg SC Q2 weeks, targeting LDL **25 – 50mg/dl (0.6 -1.30mmol/L), significantly reduced MACE, non-fatal MI, and all-caused death**
  - There was no significantly increased overall adverse event with LDL level as low as 0.39mmol/L.
  - For those patients with baseline LDL ≥ 2.59mmol/L, end-points including
    - MACE
    - CHD death
    - CV death
    - All-cause death

    were significantly reduced

SECURE - PCI

- SECURE - PCI: Loading Doses of Atorvastatin Versus Placebo in Patients with acute Coronary Syndromes and Planned Revascularization[7]
- 4,197 ACS patients, 58 Brazilian centers, planned for PCI within 7days
- Lipitor (Atorvastatin) 80mg loading followed by 80mg within 24 hours of the intended procedure vs placebo
- All patients received 40mg Lipitor (Atorvastatin) for the following 30days
- Primary end-point: MACE (Major Adverse Cardiac Event) All Cause mortality + non-fatal MI + non-fatal stroke + unplanned coronary intervention within 30 days
- Results:
  - STEMI 24.8%, NSTEMI 60.7%, unstable angina 14.5%
  - 64.5% underwent PCI in a median of 20 hours after admission
  - Primary endpoint 6.2 vs 7.1%, P= 0.27 NS
  - Primary endpoint for the PCI subgroup: 6 vs 8.5% HR 0.72 (0.54-0.96),
- Conclusion:
  - Loading dose of statin did not reduce the MACE for patients with ACS and planned PCI
  - but reduced the MACE for patients with ACS and actually received PCI

B. Anti-Hypertensive Therapy

Blood Pressure Reduction in Black Barbershops[14]

- 330 no-hispanic, black male patrons, SBP140mmHg
- 53 barbershops
- Randomisation
  - Pharmacist-led intervention: barbers encouraged meetings in the barbershops with specialty-trained clinical pharmacist → prescribed a combination drug therapy under a collaborative practice agreement with the participants' doctors to target a goal of SBP < 130/80mmHg, vs
  - Barbers gave health tips on BP management to enrolled patrons during haircuts and encouraged them to make routine doctor appointments
- Mean SBP 152.8mmHg intervention arm, 154.6mmHg comparison arm
- Mean age 54.4 vs 54.6
- Medication
  - Step I: CCB + ARB /ACEI (amlodipine + Irbesartan)
  - Step II + Thiazide diuretic (indapamide)
  - Step II + Aldosterone antagonist (eplerenone)
- Results of 6months follow-up
  - Intervention arm ↓27.0mmHg (125.8mmHg) vs Comparison arm ↓9.3mmHg (145.4mmHg)
    1. SBP 21.6mmHg more reduction CI -14.7 → -28.4, P< 0.001
  - Goal BP < 130/80, 63.6 % vs 11.7%, p<0.001
  - 95% cohort retention, few adverse events, unchanged self-rated health, improved patient satisfaction

TRIUMPH

- A Pragmatic Trial of a Low-dose Triple-Combination Blood Pressure Lowering Pill for Initial Treatment of Hypertension[15]
- Randomised, open-label trial, Sri Lanka

- 700 Hypertensive patients with
  - Initiation of medication
  - Up-titration of medication
- Randomisation to
  - "Triple pill" (telmisartan 20mg + amlodipine 2.5mg + chlorthalidone 12.5mg) continued with 1 or up to 2 tablets at / after 6 weeks vs
  - "Usual care"
- Mean age 56, 58% women, 32% DM/kidney disease, 48% untreated, mean BP 154/90mmHg
- At 6 months
  - 83% of the "Triple pill' arm still receiving medication
  - 1/3 of the usual care arm receiving ≥2 medications
  - BP target achievement (≤ 140/90mmHg, ≤130/80mmhg for patients with DM/kidney disease)
    1. 70% vs 55%, RR 1.25 (95% CI 1.09-1.39), p= 0.0007
    2. Mean BP reduction 8.7 vs 4.5mmHg
    3. No significant differences in adverse events
    4. Maximum difference was observed at 6 weeks
       a. 68% vs 44% RR 1.53 (95% CI 1.33-1.76)
- Conclusion:
  - Initial use of low-dose triple combination therapy is a safe and highly effective strategy to rapidly achieve BP control.

C. Anti-Platelet Therapy

PHARMCLO

- A Prospective, Randomised, Multicentre Study of a Pharmacogenomic Approach to the Selection of Antiplatelet Therapy in Acute Coronary Syndromes[3]
- Patient No. 888
- Assigned to P2Y12 receptor antagonist (Clopidogrel/ prasugrel/ticagrelor) selection based on both genotyping and clinical characteristics (n= 448) vs clinical characteristics alone (n=440)
- Genotyping group tested by the portable ST Q3 system for
  - ABCB1 3435
  - CYP2C19*2
  - CYP2C19*17
- Primary endpoint: CV death or 1st non-fatal MI or non-fatal CVA or major bleeding (BARC 3-5)
- Secondary End-point: Primary end-point or stent thrombosis
- Note: enrollment was stopped prematurely after 24.6% of the sample size because of the lack of in-vitro diagnosis certification for the STQ3 instrument by the Ethics Committee→ all enrolled patients were followed-up as planned
- Result:
  - Primary endpoint:- 15.9 vs 25.9% (HR 0.58) p<0.001
  - Non-fatal MI: 4.7% vs 10.7% (HR 0.42), significant
  - Bleeding endpoints more often in the genotyping vs standard care group, non-significant (4.2 vs 6.8%)
  - Stent thrombosis in 8 patients only, not enough for analysis
- Conclusion
  - This is a provocative underpowered study, showing that
    - The implementation of multiple genotyping to guide the antiplatelet therapy in ACS patients is feasible;
    - More personalised approach to the selection of antiplatelet therapy may lead to a significant improvement in clinical outcomes

ARTEMIS

- Impact of patient Copayment Reduction on P2Y12 Inhibitor Persistence and Clinical Outcomes after Myocardial Infarction: The Affordability and Real-world Antiplatelet Treatment Effectiveness after Myocardial Infarction Study (ARTEMIS) Randomized trial.[4]
- 11,001 AMI patients in 301 US Hospitals
- 100% had insurance cover
  - 64% private
  - 42% Medicare
  - 9% Medicaid
- 17% reported they previously had not filled a prescription because of the expensiveness
- Hospitals were randomised to
  - Interventional arm (131 hospitals-6, 436 patients) with vouchers to reduce the copayment, and
  - Usual care arm (136 hospitals- 4,565 patients) without vouchers
- Result
  - Co-primary end point (MI or CVA or All cause death) – no difference
  - Co-primary endpoint (adherence, defined as the continuation of the prescribed antiplatelet drug at 1 year without a gap in use of ≥ 30days) 87 vs 84% (not significant)
  - The antiplatelet choices were significantly affected on discharge

	Plavix (Clopidogrel)%	Brilinta (Ticagrelor)%	Effient (Prasugrel)%
Intervention arm	36.0	59.6	4.4
Usual care arm	54.7	32.4	12.9

P< 0.001

  - 28% of patients received the voucher but did not use them → highest rates of non-persistence and adverse clinical outcomes

	Usual care	Intervention arm	Intervention arm
		Used voucher	No voucher use
Non-persistence%	16.2	10.0	20.6

P< 0.001

- Conclusions
  - Copayment reduction by voucher significantly
    - Affect clinician choice of antiplatelet treatment, and
    - Improves persistence to treatment
  - But clinical outcomes were not significantly improved

TREAT

- A Phase III, Randomised, International, Multicenter, Open label, with Blinded Adjudication of Outcomes, Non-inferiority Clinical Trial to Explore the Safety and Efficacy of Ticagrelor Compared with Clopidogrel in Patients with Acute Coronary Syndrome with ST Elevation Treated with Thrombolysis[5]
  - Patients: STEMI ≤ 24 hours, ≥ 18 & ≤ 75 years old treated by thrombolytic therapy
    - Tenecteplase 39.6%
    - Alteplase 11.4%
    - Reteplase 16.8%
    - Streptokinase 5.7%
  - 3, 794 patients, 180 sites, 10 countries
  - Brilinta (Ticagrelor) Loading dose 180 mg then 90 mg BD vs Plavix (Clopidogrel) 300mg then 75mg QD for 12 months
  - Primary endpoint - Major bleeding (TIMI Major or PLATE Major or BARC Type 3-5)
    - o No significant difference
  - Total bleeding
    - Brilinta (Ticagrelor) vs Plavix (clopidogrel) = 5.38 vs 3.82 (p=0.02)
  - CV death + MI + Stroke – No significant differences
  - Conclusion:
    - In patients with ST elevation MI treated with fibrinolytic, Brilinta (Ticagrelor) was non-inferior to Plavix (clopidogrel) for TIMI major bleeding
    - Total bleeding was increased with ticagrelor with no benefits on clinical efficacy outcome
    - Brilinta (Ticagrelor) is a reasonable alternative for patients ≥ 18 & ≤ 75 years old with ST elevation MI and treated with fibrinolytics within 24 hours, with comparable safety to (Plavix) clopidogrel

SMART – DATE

- 6 months versus 12-months or longer dual platelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial[19]
- Prospective, multicentre, randomised, open-label
- 2,721 ACS patients, current generation drug-eluting stents (DES)
- 6 months DAPT (n= 1357) vs 12 months or longer DAPT 9mn=1355)
- Primary endpoint: all-cause death, MI, CVA at 18 months

	DAPT 6 months	DAPT ≥ 12 months	
Primary endpoint	4.6%	4.2%	P=0.51
MI	1.9%	0.8%	P=0.02
All cause death	2.4%	3.0%	P=0.35
Bleeding BARC type 2, 3, 5	2.6%	3.7%	P=0.16
Net adverse clinical events All cause death + MI+ stroke + bleeding	7.3%	7.3%	P=0.81

- Conclusions
  - In ACS patients with PCI, 6-month DAPT did not increase a risk of a composite of all-cause death, MI, CVA compared with a 12-month or longer DAPT
  - The risk of MI was increased significantly.
  - Prolonged DAPT in ACS patients without excessive bleeding risk should remain the standard of care

D. Anticoagulant therapy

MANAGE

- The Effect of Dabigatran in Patients Suffering Myocardial Injury After Noncardiac Surgery (MINS)[6]
  - 1,754 patients, 84 centres, 19 countries
  - MINS: MI / isolated troponin elevation ≤ 30 days post OT
  - Patients with MINS: ↑CV events and deaths over first 2 years post OT
  - Pradaxa 110mg BD vs Placebo, Omeprazole x placebo, 2x2 factorial design
  - Treatment period 4 months to 2 years, average 16 months
  - Endpoints:
    - Primary efficacy endpoint: vascular mortality + MI + non-haemorrhagic stroke, peripheral arterial thrombosis, amputation and symptomatic venous thromboembolism.
    - Primary safety endpoint: life-threating bleeding, major bleeding and critical organ bleeding
  - Result
    - Primary efficacy endpoint 11.1% vs 15.2%, ↓28% (p=0.012)
    - Non-haemorrhagic stroke ↓80%
    - Cardiovascular death ↓20%
    - MI ↓20%
    - Amputation↓30%
    - Venous thromboembolism ↓53%
    - Primary safety endpoint: no statistically significant differences
    - ↑ lower GI and minor bleeding with Pradaxa compared with placebo
    - Patients with MINS are at high CV risk: 1 in 7 suffered vascular complications at 16 months follow-up

- 91% of MINS were only detectable with elevation of troponin, asymptomatic
- NNT(number need to treat): - 24 patients for dabigatran to prevent 1 major CV complications

- Conclusion
  - Pradaxa (Dabigatran) significantly reduced the risk of death, MI, stroke and other vascular complications for patients with MINS (myocardial injury after non-cardiac surgery) without increased risk of major bleeding

ANNEXA - 4

- Interim Report on the ANNEXA - 4 Study: Andexanet For Reversal of Anticoagulation in Factor Xa Inhibitor – Associated Acute Major Bleeding[20]
- Andexanet is a recombinant modified FXa protein designed as a decoy molecule for FXa inhibitors, effectively sequestering and neutralising their coagulant effect
- Open-label, single -arm, prospective
- FXa taking patients with acute major bleeding, ≥18 years old, last FXa dose ≤18 hours
- Dose

On Eliquis (Apixaban) or > 7 hr from last Xarelto (rivaroxaban) dose	On Clexane(Enxoaparin), Lixiana (Endoxaban), or ≤7 hr from last Xarelto (rivaroxaban) dose
Bolus 400mg +	Bolus 800mg
480mg at 4mg/min (2 hours) infusion	960mg at 8mg/min, (2 hours) infusion

- 228 patients enrolled, mean age 77,
- 80% AF, 27% coronary artery disease, 20% venous thrombosis
- Eliquis (Apixaban) 117 patients, Xarelto (Rivaroxaban) 90 patients, Clexane (Enoxaparin) 17 patients, Lixiana (Endoxaban) 3 patients
- Intracranial bleeding 61%, GI bleeding 27%, other 11%
- Results
  - ↓median anti-fXa activity 92%
  - Good /excellent haemostasis at 12 hours 83%
  - At 30days
    - 11% thrombotic event
    - 12% mortality
- Andexanet use as a reversal agent for FXa inhibitor taking patients with acute major bleeding was associated with a rapid and pronounced decrease in anti-fXa activity and a high rate of clinically effective haemostasis, with an acceptable rate of adverse events.

E. Uricosuric Therapy

CARES

- Cardiovascular Safety of Feburic (Febuxostat) or Zyloric (Allopurinol) in Patients with gout and cardiovascular disease[12]
- Gout patients is a high CV risk population
- Feburic (Febuxostat) a potent non-purine selective inhibitor of xanthine oxidase (XO)
- Randomised, double-blind, multicentre, North American
- Feburic (Febuxostat) vs Zylorix (Allopurinol) – purine base analog XO inhibitor
- 6,190 patients with gout and baseline CV disease
- Baseline CV diseases
  - AMI 39%
  - Unstable angina (UA) hospitalization 28%
  - Stroke 14%
  - PAD 13%
- Follow-up : 6.5 years (median 32 months)
- Results and conclusion
- Primary composite endpoint: (1st occurrence of CV death, Nonfatal MI, nonfatal stroke, urgent revascularization for unstable angina (UA))
  - Feburic (Febuxostat) was non-inferior to allopurinol in patients with gout and CV disease (10.8 vs 10.4%, HR 1.03)
- All-cause mortality was greater on Feburic versus Zyloric (7.8% vs 6.4% HR 1.22 95% CI 1.01-1.47) due to imbalance in CV- deaths (4.3 vs 3.2%, HR 1.34, 95% CI 1.03-1.73), particularly sudden cardiac deaths (2.7 vs 1.8%)
- Urate lowering on Feburic was greater than Zyloric
- Similar gout flare rates between both medications
- No differences in the rates of major nonfatal cardiovascular events
- No differences for K+, lipids, glucose, Cr and BP

F. Congestive Heart failure Therapy

MOMENTUM 3

- Multicentre Study of MagLev Technology in Patient Undergoing Mechanical Circulatory Support with HeartMate 3 – Long Term Outcomes[8]
- HeartMate 3, first fully implantable heart pump LVAD (Left ventricular assist device) with magnetic levitation technology + wide blood – flow passages to reduce shear stress. It is frictionless, without mechanical bearings and produces an intrinsic pulse to reduce stasis and prevent thrombosis
- Target patients: advanced heart failure patients who are waiting for extended periods or are ineligible for heart transplantation
- 1, 028 patients NYHA IIIB or IV heart failure at 69 US centres
- HeartMate III vs HeartMate II LVAD (mechanical bearing axial continuous -flow blood pump) implantation
- Results
  - 366 patients (HeartMate 3, n=190, HeartMate 2, n=176) completed 2 years of study
  - Primary endpoint: Survival at 2 years, free from disabling stroke and reoperation 77.9 vs 56.4% (P< 0.01)
  - Freedom from re-operation to replace or remove pump: 97.2 vs 75.5%, P< 0.001

- Freedom from disabling strokes 92.8 vs 92.5% (NS)
- Free from any stroke 89.9 vs 80.8% (P=0.016)

- Conclusion:
  - HeartMate III, LVAD (Left ventricular assist device) markedly improved survival, reduced the need for repeated surgery and strokes in advanced heart failure patients at 2 years after implantation over HeartMate II
  - The disabling stroke rate is low in both arms (~ 7 % in 2 years)

INDIE – HFpEF

- Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure with Preserved Ejection Fraction[9]
- Multicentre, double-blind, 12 weeks crossover study
- Patient no. 105
- HFpEF:
  - NYHA Class II-IV,
  - EF ≥ 50%,
  - NTproBNP > 400pg/ml,
  - elevated cardiac filling pressure (cardiac catheterization),
  - peak VO_2 ≤75% predicted with respiratory exchange ratio ≥1.0 on cardiopulmonary exercise test
- each 6 weeks phase study drug nitrate /placebo via portable micronebuliser device at 46mg tds for 1 week then 80mg tds for 3 weeks
- Primary endpoint: change in peak VO_2
- Secondary endpoint: daily activity levels, functional class, quality of life (QoL), cardia filling pressures by echocardiography, NT proBNP levels
- No significant changes were detected for both Primary and secondary endpoints

G. Antiarrhythmic therapy

VEST

- VEST Prevention of Sudden Death Trial[2]
  - Wearable cardioverter-defibrillator (WCD) (a jacket with in-built ECG leads and a cardioverter -defibrillator) during the 1st 90 days of myocardial infarction (MI)
  - 2,302 patients with AMI and LVEF ≤ 35% (systolic dysfunction), 108 sites, 4 countries
  - Guideline -directed medical therapy (GDMT) + WCD (n = 1524) vs GDMT (n= 778) only
  - No reduction in the primary end-point sudden cardiac death (SCD), 1.6% vs 2.4%
  - 35%↓ in the secondary endpoint of total mortality, 3.1 vs 4.9%, P=0.04 (significant)
- Conclusion
  - Wearable cardioverter -defibrillator (WCD) is a reasonable management option for AMI patients with a low LVEF waiting for an evaluation of permanent ICD implantation in the 1st 40-90days, which may lower the total mortality (some SCDs may be miss classified as just simple mortality in the study)

H. Patent foramen ovale management

DEFENSE -PFO

- Device Closure Versus Medical Therapy for Secondary Prevention in Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale.[18]
- Multicentre, randomised, open-label
- 450 patients with
  - Cryptogenic embolic stroke
  - High risk PFO on Transoesophageal Echocardiogram (TEE)
    - Atrial septal aneurysm
    - Hypermobility
    - PFO size ≥ 2mm
- Randomized to
  - Amplatzer PFO Occluder, ST Jude Medical vs
  - Medical therapy alone
- Primary endpoint composite of stroke + vascular death, TIMI major bleeding
- Result
  - Follow-up : 2 years
  - 450 patients with Cryptogenic embolic stroke
  - 38.9% high risk TEE features
  - 120 patients were randomized
  - 100% success of device closure in the intervention arm was achieved
  - Primary endpoint: Device closure arm = 0 vs : Medical therapy arm= 6
    - P= 0.013
    - 6 Strokes + 1 TIA
  - Procedural complication
    - Atrial fibrillation (n=2)
    - Pericardial effusion (n=1)
    - Puncture site complication (n=1)
- Conclusion:
  - Device closure for cryptogenic embolic stroke patients with high morphological risk PFO (TEE) lower the rate of Primary endpoint composite of stroke + vascular death, TIMI major bleeding compared with medical therapy alone

I. Peripheral artery disease management

STOP-PAD

- A Phase II Randomised Double-Blind, Placebo Controlled Study in Patients with Critical Limb Ischaemia to Evaluate the Safety and Efficacy of hSDF-1 plasmid (JVS – 100) Post Open or Endovascular Revascularisation[17]

Improved outcomes matter

BRILINTA™ ticagrelor tablets

IN MI PATIENTS, THE LONG-TERM BENEFITS[1] OF BRILINTA™ CAN MAKE THE DIFFERENCE

Reduction in CV events[1†]

-16%
p=0.004

Reduction in MI[1]

-16%
p=0.03

Reduction in stroke[1]

-25%
p=0.03

2017 ESC Focused Update on DAPT in CAD[2]

Recommendations	Class	Level
In patients with ACS who have tolerated DAPT without a bleeding complication, **continuation of DAPT for longer than 12 months** may be considered.	IIb	A
In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, **ticagrelor 60 mg *b.i.d.* for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.**	IIb	B

* **The PEGASUS-TIMI 54 study was a randomised, double-blind, placebo-controlled trial. 21,162 patients aged ≥50 years with a history of spontaneous MI 1-3 years prior to enrollment and at least one additional atherothrombotic risk factor (age ≥65 years, DM requiring medication, a second prior spontaneous MI, multivessel CAD, or CKD) were randomised 1:1:1 to receive either BRILINTA™ 90 mg twice daily, BRILINTA™ 60 mg twice daily or placebo for a median follow-up of 33 months. All the patients took aspirin at a dose of 75 to 150 mg daily[1].**

† **CV events = CV death, MI, or stroke.**

Abbreviations: ACS = acute coronary syndrome; b.i.d. = twice daily; CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; ESC = European Society of Cardiology; MI = myocardial infarction.

Reference: 1. Bonaca MP, Bhatt DL, Cohen M et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015; 372: 1791–1800. **2.** Valgimigli M, Bueno H, Byrne RA et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2017; 0: 1–48.

AstraZeneca

AstraZeneca Hong Kong Limited
18/F Shui On Centre, 6–8 Harbour Road,
Wan Chai, Hong Kong.
Tel: 2420 7388 Fax: 2422 6788

HK-0624 20/10/2017

- JVS-100: non-viral DNA plasmid encoding human stromal cell-derived factor -1 (SDF-1) that promotes tissue repair by promoting cell survival, endogenous stem cell recruitment, and vasculogensis.
- 109 Peripheral arterial disease (PAD) patients with Chronic limb ischaemia (CLI) + ≥ 1 non-healing foot wound (Rutherford V and VI) → successful or attempted open bypass grafting or endovascular treatment of below knee arteries → demonstrated flow to ankle → post -procedure toe-brachial indexes (TNI) ≤ 0.51 → randomisation
  - Placebo
  - JVS -100 imi x 2
    1. First within 12 days of procedure
    2. Second – 3 months post- operation
- Results
  - Mean age 71.3
  - Wound size 3.99cm^2
  - No significant impacts on wound healing
  - Only ~ 25% of wound were healed despite of advanced revascularisation and rigorous follow-up care
  - ~ 25% of wound actually ↑ size after 3 months
- JVS -100, non-viral DNA plasmid encoding human stromal cell-derived factor -1 (SDF-1) has no impacts on PAD wound healing

J. Anti-inflammatory therapy and cardiology

CANTOS

- Anti-Inflammatory Therapy with Canakinumab and incident Type 2 Diabetes: A Pre-Specified Key Secondary Endpoint of the CANTOS Trial[13]
- Canakinumab, human monoclonal antibody targeting IL-1β (interleukin- beta) in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) 2017' was proved to significantly ↓ non-fatal MI, non-fatal stroke and CV death
- 10,061 patients with Hx of MI and HsCRP ≥2mg/L
- Placebo vs Canakinumab 50mg, 150mg or 300mg SC, Q 3 months
- Monitor New onset of type II diabetes by
  - HBA1C ≥ 6.5%
  - FBS ≥ 7.0mmol/L
  - Starting of antihyperglycaemic therapy
- FU 3.7 years
- Results
  - Canakinumab ↓ major CV event rates with for post MI patients with HsCRP ≥ 2mg/L for both DM, Pre-DM and normoglycaemic groups
  - Baseline levels of inflammatory markers HsCRP and IL6, predict the onset of Type II DM
  - Canakinumab ↓ HBA1C in pre-DM patients for 9-12 months and effects were attenuated with time
  - Canakinumab does not prevent the progression from Pre-DM → DM for post MI patients with HsCRP ≥ 2mg/L

K. Chemotherapy and cardiology

CECCY

- Carvedilol for Prevention of Chemotherapy – Induced Cardiotoxicity Results of the Prospective, Randomized, Double Blind, Placebo-Controlled Trial[10]
- 200 CA breast patients with normal LVEF (left ventricular ejection fraction), treated with Anthracycline- Doxorubicin chemotherapy ANT (240mg/m^2)
- Carvedilol vs placebo with the course of chemotherapy
- Result:
  - LVEF: no significant differences (primary endpoint)
  - Troponin I level: attenuated the elevation
  - Trend towards a less pronounced increase in end diastolic LV diameter
- Conclusion: carvedilol had a beneficial effect on chemotherapy – induced myocardial cardiotoxicity but without LVEF improvement

Lisinopril or Carvedilol for the Prevention of Trastuzumab Induced Cardiotoxicity[11]

- TZB
  - Trastuzumab a target therapy medication for HER2 +ve breast CA
  - Associated cardiotoxicity
    - ↓LVEF
    - Heart failure
- 468 CA breast patients treated with TZB
- Lisinopril vs carvedilol vs placebo
- Primary endpoint: change in LVEF
- Secondary endpoints
  - TZB therapy Interruptions
  - Effects in the anthracycline and non-anthrocycline cohorts
- Conclusions:
  - Lisinopril and carvedilol were not effective in the prevention of trastuzumab – induced cardiotoxicity (LVEF/interruptions)
  - Lisinopril and carvedilol were effective in preservation of LVEF (left ventricular ejection fraction) for the patients with prior exposure to anthracyclines. HR = 0.53, HR = 0.49 respectively, P< 0.05

L. Non-cardiac surgery management

POISE

- 1 year Outcomes of Perioperative Beta-blockade in Patients Undergoing Noncardiac Surgery[16]
- 8,351 undergoing noncardiac surgery patients, at risk of a perioperative cardiac event (~ 40% with coronary artery disease, 40% peripheral arterial disease, 15% Hx of stroke)
- Metoprolol CR 100mg 2-4 hours before and 6 hours after + 200mg QD up to 30 days vs placebo

- Results:
  - Mortality 9.8% vs 8.5% HR 1.16 95% CI 1.01-1.34, P=0.036
  - Stroke 2.0% vs 1.4% HR 1.52, 95% CI 1.09-2.12, P=0.014
  - MI 5.0% vs 6.2%, HR 0.78, 95% CI 0.65-0.94, P=0.008
  - Cardiac revascularisation 0.5% vs 1.1% HR 0.47, 95% CI 0.28-0.78, p= 0.004
- Conclusions:
  - The use of metoprolol CR for every 1000 noncardiac surgery patients, at 1 year
    - ↓12 MI
    - ↓ 6 cardiac revascularisation
    - ↑13 deaths
    - ↑6 strokes
  - Further research is needed to establish a way to derive the benefit of perioperative beta-blockade while mitigating the risk

"Go as far as you can see, when you get there, you'll be able to see farther."
~ John Pierpont Morgan Sr. (1837-1913) American Financier, banker and art collector, who dominated corporate finance and industrial consolidation in USA in the late 19th and early 20th centuries

After reading the above long, comprehensive and precise summary of the 20 trial results from the "Late-breaking Clinical Trials Sessions", ACC 18', I am sure that most of us are starting to forget them and they will totally be forgotten in 20 minutes time.

In the hope of making you and my life easy and happy, getting the maximum benefit for our day-in, day-out patients from the ACC 18', I am now further distilling their important findings in my humble little way as below.

In a Nutshell

1. For recent ACS patients, Praluent (alirocumab) (PCSK9 inhibitory monoclonal antibody) 75mg-150mg SC Q 2 weeks, targeting LDL 0.6-1.3mmol/L → ↓MACE + non-fatal MI+ all-cause death, with no significantly increased adverse event at LDL levels reaching 0.39mmol/L. **(ODYSSEY)**
2. Wearable cardioverter -defibrillator (WCD) in AMI patients with a low LVEF waiting for an evaluation of permanent ICD implantation in the 1st 40-90days→ ↓ the total mortality **(VEST)**
3. The implementation of multiple genotyping as a personalised approach to guide the selection of antiplatelet therapy in ACS patients → significant improvement in composite clinical outcomes : CV death + 1st non-fatal MI + non-fatal CVA + major bleeding. **(PHARMCLO)**
4. Prescription copayment reduction by voucher significantly affected clinicians' choice of antiplatelet treatment and improved persistence to treatment **(ARTEMIS)**
5. In patients with ST elevation MI treated with fibrinolytic, Brilinta (Ticagrelor) was non-inferior to Plavix (clopidogrel) for TIMI major bleeding with ↑ total bleeding and a similar clinical efficacy outcome. **(TREAT)**
6. Pradaxa (Dabigatran) significantly reduced the risk of death, MI, stroke and other vascular complications for patients with MINS (Myocardial Injury after Non-cardiac Surgery – a high CV risk group) without increased risk of major bleeding. **(MANAGE)**
7. Loading dose of statin (Lipitor (Atorvastatin) 80mg loading followed by 80mg within 24 hours) reduced MACE (All Cause mortality + non-fatal MI + non-fatal stroke + unplanned coronary intervention within 30 days) for patients with ACS and received PCI. **(SECURE)**
8. HeartMate III, a new LVAD (Left ventricular assist device) (with magnetic levitation technology + wide blood – flow frictionless, without mechanical bearings passages to reduce shear stress and produce an intrinsic pulse to reduce stasis and prevent thrombosis) markedly improved the survival, reduced repeated surgery and strokes in advanced heart failure patients at 2 years after implantation over HeartMate II. **(MOMENTUM 3)**
9. Dilatrend (Carvedilol) had a beneficial effect on Anthracycline- Doxorubicin chemotherapy – induced myocardial cardiotoxicity. **(CECCY)**
10. Zestril (Lisinopril) and Dilatrend (carvedilol) were effective in the preservation of LVEF (left ventricular ejection fraction) for patients with prior exposure to anthracyclines chemotherapy. **(Lisinopril or Carvedilol for the Prevention of Trastuzumab Induced Cardiotoxicity)**
11. For patients with gout and CV diseases, Feburic (Febuxostat) was non-inferior to Zyloric (allopurinol) in composite cardiovascular primary endpoint (1st occurrence of CV death, Nonfatal MI, nonfatal stroke, urgent revascularisation for unstable angina (UA)), despite ↑all-cause mortality due to ↑CV- deaths. **(CARES)**
12. Canakinumab (human monoclonal antibody targeting IL-1β (interleukin- beta)) ↓ major CV event rates (↓non-fatal MI, non-fatal stroke and CV death) of post MI patients with HsCRP ≥ 2mg/L for both DM, Pre-DM and normoglycaemic groups. The baseline levels of inflammatory markers HsCRP and IL6, predict the onset of Type II DM. Canakinumab ↓ HBA1C in pre-DM patients for 9-12 months and effects were attenuated with time. Canakinumab does not prevent the progression from Pre-DM → DM **(CANTOS)**
13. Antihypertensive therapy for US low education level, low household income black community in barbershops by specialty–trained pharmacists, as compared with primary care standard practices→ ↑BP reduction. **(Blood Pressure Reduction in Black Barbershops)**
14. Initial use of low-dose triple combination pill (telmisartan 20mg + amlodipine 2.5mg + chlorthalidone 12.5mg) therapy is a safe and highly effective strategy to rapidly achieve BP control. **(TRIUMPH)**

15. The use of Metoprolol CR 100mg 2-4 hours before and 6 hours after + 200mg QD up to 30 days vs placebo for noncardiac surgery patients with high CV risk → ↓ MI, ↓ cardiac revascularisation, ↑deaths and ↑ strokes at 1 year. **(POISE)**
16. Device closure (Amplatzer PFO Occluder, ST Jude Medical) for cryptogenic embolic stroke patients with high morphological risk PFO (TEE) lowers the rate of Primary composite endpoint of stroke + vascular death, TIMI major bleeding compared with medical therapy alone. **(DEFENSE -PFO)**
17. In ACS patients receiving PCI, 6-month DAPT → ↑ MI rate, but did not increase the risk of a composite endpoint of all-cause death, MI, CVA compared with a 12-month or longer DAPT **(SMART-DATE)**
18. Andexanet (recombinant modified FXa protein designed as a decoy molecule for FXa inhibitors, effectively sequestering and neutralising their coagulant effect), uses as a reversal agent for FXa inhibitor (Xarelto(rivaroxaban), Eliquis (apixaban), Lixiana(endoxaban) and Clexane (enoxaparin)) taking patients with acute major bleeding was associated with a rapid and pronounced decrease in anti-fXa activity and a high rate of clinically effective haemostasis, with an acceptable rate of adverse events. **(ANNEXA-4)**

"Don't be afraid to give up the good for the great."
~ John Davidson Rockefeller Sr. (1839-1937), American oil industry business magnate, industrialist and philanthropist, the wealthiest American of all time and the richest person in modern history

References

1. Presented by Dr. Philippe Gabriel Steg, MD, FACC, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 10, 2018, 9.00am
2. Presented by Dr. Jeffrey E. Olgin, MD, FACC, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 10, 2018, 9.30am
3. Presented by Dr. Diego Ardissino, MD, FACC, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 8.00am
4. Presented by Dr. Tracy Wang MD, FACC, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 8.15am
5. Presented by Dr. Otavio Berwanger, MD, PhD, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 8.30am
6. Presented by Dr P.J. Devereaux MD, PhD, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 8.45am
7. Presented by Dr. Otavio Berwanger, MD, PhD, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 9.00am
8. Presented by Dr. Mandeep R. Mehra, MD, FACC, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 10.45am
9. Presented by Dr. Barry Borlaung, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 11.00am
10. Presented by Dr. Monica Samuel Avila M.D., at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 11.15am
11. Presented by Dr. Maya Guglin M.D., PhD., at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 11, 2018, 11.15am
12. Presented by Dr. William B White M.D., at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 8.00am
13. Presented by Dr. Brendan Everett, M.D., at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 8.15am
14. Presented by Dr. Ronald G. Victor, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 8.30am
15. Presented by Dr. Ruth Webster, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 8.45am
16. Presented by Dr. P.J. Devereaux MD., PhD, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 9.00am
17. Presented by Dr. Mehdi Shishehbor DO., MPH, PhD., at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 10.45am
18. Presented by Dr. Jae-Kwan Song, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 11.00am
19. Presented by Dr. Hyeon-Cheoi Gwon, at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 11.15am
20. Presented by Dr. Stuart Connolly M.D., at the Late – Breaking Clinical Trials Session, American college of Cardiology Annual Scientific Session (ACC2018), Orlando, FL, March 12, 2018, 11.30am

MCHK CME Programme Self-assessment Questions

Please read the article entitled "American College of Cardiology, Annual Scientific Congress (ACC 18'), Late-Breaking Clinical Trials Sessions" by Dr Bernard BL WONG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 June 2018 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. For recent ACS patients, Praluent (alirocumab) (PCSK9 inhibitory monoclonal antibody) has no effects on MACE, non-fatal MI and all-caused death.
2. Praluent (alirocumab) (PCSK9 inhibitory monoclonal antibody) causing significantly increased adverse events at LDL level reaching 0.39mmol/L.
3. The implementation of multiple genotyping as a personalised approach to guide the selection of antiplatelet therapy in ACS patients did not improve the clinical outcomes.
4. Pradaxa (Dabigatran) significantly increased the risk of death, MI, stroke and other vascular complications for patients with MINS (Myocardial Injury after Non-cardiac Surgery – a high CV risk group) with an increased risk of major bleeding.
5. Loading dose of Lipitor (Atorvastatin) 80mg did not reduce MACE for patients with ACS and received PCI.
6. HeartMate III, a new LVAD (Left ventricular assist device) markedly improved the survival, reduced repeated surgery and strokes in advanced heart failure patients at 2 years after implantation over HeartMate II.
7. Canakinumab (human monoclonal antibody targeting IL-1β (interleukin- beta)) ↓ major CV event rates (↓non-fatal MI, non-fatal stroke and CV death) of post MI patients with HsCRP ≥ 2mg/L for both DM, Pre-DM and normoglycaemic groups.
8. Initial use of low-dose triple combination pill (telmisartan 20mg + amlodipine 2.5mg + chlorthalidone 12.5mg) therapy is a safe and highly effective strategy to rapidly achieve BP control.
9. Device closure (Amplatzer PFO Occluder, ST Jude Medical) for cryptogenic embolic stroke patients with high morphological risk PFO (TEE) lowers the rate of Primary composite endpoint of stroke + vascular death, TIMI major bleeding compared with medical therapy alone.
10. Andexanet (recombinant modified FXa protein), used as a reversal agent for FXa inhibitor-taking patients with acute major bleeding was associated with a rapid and pronounced decrease in anti-fXa activity and a high rate of clinically effective haemostasis, with an acceptable rate of adverse events.

ANSWER SHEET FOR JUNE 2018

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2018 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

American College of Cardiology, Annual Scientific Congress (ACC 18')
Late-Breaking Clinical Trials Sessions
Orlando, Florida USA 9 – 12 March, 2018

Dr Bernard BL WONG

MBBS(HK), MRCP(UK), FRCP(Edin), FRCP, RCPS(Glasg), FRCP (Irel), FHKCP(HK), FHKAM (Medicine), DGM (Irel), DCH(Lond)

Specialist In Cardiology

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to May 2018 Issue

The New 2017 ILAE classification of seizure types and the epilepsies; The evolution of concepts and terminologies; How aetiologies guide the management in Paediatric Epilepsy?

1. T 2. T 3. T 4. T 5. T 6. F 7. T 8. T 9. T 10. F

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PREDICTABLE, INTENSIVE LDL-C REDUCTIONS

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†As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).

Repatha® (Evolocumab) Abbreviated Prescribing Information
Repatha® (Evolocumab) Solution for Injection in Pre-filled Syringe/ Autoinjector 140mg
INDICATIONS: Repatha® Solution for Injection in Pre-filled Syringe/Autoinjector 140 mg is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). It is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. **DOSAGE AND ADMINISTRATION**: The recommended subcutaneous dosage of Repatha in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD is either 140 mg every 2 weeks OR 420 mg once monthly. The recommended subcutaneous dosage of Repatha in patients with HoFH is 420 mg once monthly. To administer 420 mg, give 3 Repatha injections consecutively within 30 minutes. **CONTRAINDICATIONS**: Repatha is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**: Allergic Reactions: Rash and urticaria have occurred. If signs or symptoms of serious allergic reactions occur, discontinue treatment with Repatha, treat according to the standard of care, and monitor until signs and symptoms resolve. **ADVERSE REACTIONS**: Common adverse reactions in clinical trials (>5% of patients treated with Repatha and occurring more frequently than placebo): nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of Repatha, but the long-term consequences of continuing Repatha treatment in the presence of anti-drug binding antibodies are unknown. **INTERACTIONS**: An approximately 20% decrease in the Cmax and AUC of evolocumab was observed in patients co-administered with a high-intensity statin regimen. This difference is not clinically meaningful and does not impact dosing recommendations. **PREGNANCY AND LACTATION**: Pregnancy: There are no data available on use of Repatha in pregnant women to inform a drug-associated risk. Breast-feeding: There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. **PEDIATRIC, GERIATRIC, RENAL IMPAIRMENT AND HEPATIC IMPAIRMENT**: Pediatric: The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH who are younger than 13 years old, and in pediatric patients with primary hyperlipidemia or HeFH. Geriatric: In controlled studies, 1420 patients treated with Repatha were ≥ 65 years old and 171 were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Renal Impairment: No dose adjustment is needed in patients with mild to moderate renal impairment. No data are available in patients with severe renal impairment. Hepatic Impairment: No dose adjustment is needed in patients with mild to moderate hepatic impairment (Child-Pugh A or B). No data are available in patients with severe hepatic impairment.

Abbreviated Prescribing Information Version: HKPI20150007API
Please read the full prescribing information prior to administration and full prescribing information is available upon request.

HK-00333-REP-2017-Jul

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Interventional Cardiology Update Bioresorbable Scaffold – Is It the End or the End of the Beginning?

Dr CHAN Chi-kin

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Introduction

The first metallic coronary stents came into clinical existence more than 30 years ago and were believed to have solved the issue of coronary artery disease. Since then, stent technology has undergone significant evolution with improvements in material selection, scaffold design and application of antiproliferative drugs. Yet, all permanent metallic stents have the inherent limitation of leaving a permanent metallic cage inside the vessels. This may trigger a foreign body response leading to neointimal hyperplasia with in-stent restenosis. Stent thrombosis may also occur at various time points as a consequence of incomplete or delayed endothelialisation, chronic inflammation and what not. Furthermore, the physical constraint from a metallic cage may hinder vessel physiology with loss of vasomotor reactivity[1] and may also result in permanent jailing of side branches. A metallic stent implanted at the distal segment of a coronary artery renders future revascularisation with bypass grafting difficult if not impossible.

The Dream

This has led to the enthusiasm in developing a fully absorbable scaffold, the first of which was the Igaki-Tamai stent developed in 1990's (Kyoto Medical Planning Co Ltd, Kyoto, Japan).[2] The first commercially available absorbable scaffold is the Absorb Bioresorbable Scaffold (BVS) from Abbott Vascular; Santa Clara, CA. Since its availability in 2012, the Absorb BVS has made initial success and has soon been utilised in not only simple coronary lesions but also off-labelled complex ones. However, recent trials have aroused concerns over its safety and efficacy. In 2017, Abbott Vascular decided to pull it off the market. We are now at the crossroad of losing a revolutionary stent technology.

The Facts

As of today, lactate-based polymer systems provide most of the data for bioresorbable scaffold systems. Poly-L-lactic acid (PLLA) is a thermoplastic polyester that undergoes hydrolysis into shorter lactic acid molecules, which are then converted into water and carbon dioxide via the Krebs cycle. Other lactate-based polymers such as poly-D,L-lactic acid (PDLLA) undergo a similar breakdown process but at a faster rate due to decreased crystalline structures compared with PLLA. Bioresorbable metallic scaffolds using magnesium are also being pursued and may serve as an alternative to lactate-based polymer systems. Characteristics of commonly available bioresorbable scaffolds are listed in Table 1.

Table 1: Characteristics of Commonly Available Bioresorbable Scaffolds With CE Mark

Bioresorbable Scaffolds	Absorb BVS	DESolve	ART Pure	Magmaris
Backbone	PLLA	PLLA	PDLLA	Magnesium
Drug-elution	Everolimus	Novolimus	None	Sirolimus
Strut thickness (micron)	157	120	170	150
Resorption (months)	24-48	<24	6	9-12

The most widely studied and clinically utilised bioresorbable scaffold is the Absorb BVS which consists of a PLLA scaffold coated with a layer of everolimus-eluting PDLLA. To provide adequate initial radial strength comparable to a metallic backbone, the strut thickness of the Absorb BVS is around 150 microns[3] while most contemporary metallic drug-eluting stents (DES) have strut thicknesses of 60 to 100 microns. Preclinical studies suggested that the absorption time was around 2 years. Subsequently it has been observed that the Absorb BVS can take up to 4 years to fully resorb.[4] As it resorbs, the device can create a potential nidus for very late scaffold thrombosis, necessitating prolonged dual antiplatelet therapy.

The Reality

The initial studies of the Absorb BVS focussed on patients with stable angina and simple lesion characteristics.[5] After CE mark approval, post-market registry data began to raise concern for scaffold thrombosis.[6] A subsequent meta-analysis involving over 10,000 patients demonstrated a worrying twofold increase in the rate of both myocardial infarction and definite or probable scaffold thrombosis compared with DES.[7] Then, its efficacy is challenged by the ABSORB III (A Bioresorbable Everolimus-Eluting Scaffold Versus a Metallic Everolimus-Eluting Stent III) trial that reported more target lesion failures at 12 months compared with DES.[8] More recently, the AIDA (Amsterdam Investigator-Initiated Absorb Strategy All-Comers) trial also showed an alarming almost fourfold increase in the rate of definite or probable scaffold thrombosis.[9] These are believed to have led Abbott Vascular to restrict the use of Absorb BVS in Europe to registry patients only. Later, Boston Scientific also announced that its research into its Renuvia bioresorbable scaffold system would be abandoned.

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12 Jun	Neurogenic communication disorders (II) – dysarthria and apraxia of speech	Mr. Raymond FONG Speech Therapist, Queen Mary Hospital
19 Jun	Dysphagia management in the elderly population	Mr. Joshua MAK Speech Therapist, Private Practice
26 Jun	Communication problems in patients with dementia	Ms. Rita WONG Speech therapist, The Chinese University of Hong Kong
3 Jul	Communication problems in patients with Parkinson's disease	Dr. Lorinda Chen KWAN Senior Lecturer, The Education University of Hong Kong
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23 Jul	Managing common psychiatric illness during pregnancy	Dr. CHAN Lai Wah Connie Associate Consultant, Yung Fung Shee Psychiatric Centre
30 Jul	Prediction and prevention of pre-eclampsia	Prof. POON Chiu Yee Liona Clinical Associate Professor, Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong
6 Aug	Morbidly adherent placenta - diagnosis and management	Dr. CHAN Lin Wai Daniel Consultant, Department of Obstetrics & Gynaecology, Hospital Authority Kowloon East Cluster
13 Aug	Hepatitis and pregnancy	Dr. LAW Lai Wa Specialist in Obstetrics and Gynaecology Clinical Associate Professor (Honorary) The Chinese University of Hong Kong
20 Aug	A) Use of birth ball B) Common musculoskeletal problem in pregnancy	Ms. Brigitte FUNG Senior physiotherapist, Kwong Wah Hospital

Date : 16, 23, 30 July & 6, 13, 20 August, 2018 (Every Monday)
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Several proposed mechanisms may explain the higher rates of scaffold thrombosis and target lesion failures. Thicker struts make endothelialisation more difficult[10] and the rheolytic property less favourable and therefore more thrombogenic.[11] However, thicker struts (150 micron) seem to be mandated in the 1st generation BVS to provide sufficient radial strength for the scaffold. Thicker struts have made implantation more technically demanding. The scaffolds are less deliverable as compared with contemporary DES and it is also more difficult to get the struts fully apposed to or embedded into the vessel wall to facilitate resorption. Furthermore, the Absorb BVS may have prothrombogenic characteristics. A recent preclinical study compared the acute thrombogenicity of the Absorb BVS and the Magmaris (BIOTRONIK AG; Bülach, Switzerland) resorbable magnesium scaffold, a fully bioabsorbable magnesium scaffold with sirolimus-eluting bioresorbable PLLA coating and a 150 micron strut thickness. After running for a maximum of 1 hour in a porcine arteriovenous shunt, 21% of the Absorb BVS surface was covered with platelets while only 3% of the Magmaris scaffold surface had platelet adherence.[12]

Following the emergence of trends toward increased scaffold thrombosis, the European Commission, in conjunction with the European Society of Cardiology and the European Association of Percutaneous Coronary Intervention, formed a task force to assess new stent and scaffold technologies. This led to the recommendation and adoption of a two-stage clinical evaluation, which includes initial premarket trials with pre-established invasive imaging requirements and mandatory large-scale trials before the granting of an unconditional CE mark.[13] Recently, the US Food and Drug Administration issued a letter to physicians warning them of an increased rate of major cardiac events with the Absorb BVS, leading Abbott Vascular to pull the device.[14]

The recently presented 3-year data for the ABSORB III trial and the 30-day data for the ABSORB IV (A Bioresorbable Everolimus-Eluting Scaffold Versus a Metallic Everolimus-Eluting Stent IV) trial presented at the Transcatheter Cardiovascular Therapeutics 2017 have reinforced these concerns. In the ABSORB III trial, the target lesion failure rate at 3 years was 13.4% for BVS and 10.4% in the everolimus-eluting stent group (p = 0.06).[15] Target vessel myocardial infarction (8.6 vs. 5.9% respectively, p = 0.03) and scaffold thrombosis (2.3 vs. 0.7% respectively, p = 0.01) were also significantly higher in the BVS arm. The ABSORB IV trial demonstrated that the incidence of scaffold thrombosis at 30 days was 0.6% with BVS as compared with 0.2% in the DES arm.[16] Though appropriate implantation technique (pre-dilatation, vessel sizing, and post-dilatation) may have reduced the incidences of target lesion failures and scaffold thrombosis,[17] Absorb BVS is still withdrawn from the market.

The Future

While the Absorb BVS has disappointed many, the dream of a bioresorbable scaffold has not come to an end. Remaining players in the field using PLLA include the DESolve (Elixir Medical Corporation; Milpitas, CA) and ART Pure (Arterial Remodeling Technologies SA; Paris, France). Magmaris is another new player using magnesium. The struts are absorbed after 1 year. The early and medium term clinical data on the safety and efficacy as presented at the TCT 2017 are encouraging with the scaffold thrombosis at 0% and clinically driven TLR 3.3% at 24 months.[18] However, the clinical scenarios and lesion complexity are highly controlled in clinically trial settings. It is premature to extrapolate the results of this study and try to use the new scaffold to treat the more complex-lesion subset. At this juncture, clinicians using these novel devices should not only pay attention to the implantation techniques, but it is also extremely important not to extend the clinical application beyond study-outlined patients and lesions.

The bioresorbable scaffold concept remains attractive. Despite the setbacks from the 1st generation Absorb BVS, this concept or technology has not come to its end. Advances in material science and scaffold design are continuously evolving and refining. Perhaps, this moment in coronary stenting is best described by the quote of Winston Churchill *"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."*

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Abbreviations: CKD, chronic kidney disease; ULT, urate-lowering therapy; sUA, serum uric acid.

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Abbreviated prescribing information of Feburic film-coated tablets

Version: 203 PI version: Oct 2015 **Composition:** Febuxostat **IndicationsI:** FEBURIC is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history or presence of, tophus and/or gouty arthritis). FEBURIC 120 mg is also 2 days before the beginning of cytotoxic therapy and continue for a minimum of 7 days. **Administration.** May be taken by mouth w/o regard to food. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use; Cardi** Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or monitoring as clinically appropriate. **Medicinal product allergy/hypersensitivity:** Rare reports of serious allergy/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the p Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases. Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergy/hypersensitivity reactions. Febuxostat treatment s anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time. **Acute gouty attacks** (*gout flare*) Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing s should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares. ***Xanthine deposition*** in patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatme febuxostat. Its use in patients with Lesch-Nyhan Syndrome is not recommended. ***Mercaptopurine/azathioprine*** Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitor Co-administration of febuxostat 80 mg and theophylline 400 mg single dose in healthy subjects showed absence of any pharmacokinetic interaction. Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data thereafter based on clinical judgment. **Thyroid disorders** Increased TSH values (> 5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (6.5%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyro reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience in gout patients are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild to < 1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below. The frequencies are based on studies and post-marketing experience in gout patients. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Adverse **disorders:** Uncommon: Blood thyroid stimulating hormone increased. **Eye disorders:** Rare: Blurred vision **Metabolism and nutrition disorders:** Common**: Gout flares, Uncommon: Diabetes mellitus, hypertriglyceridemia, decrease appetite, weight increase. Rare: Weight decrease, increase sp Rare: Tinnitus. **Cardiac disorders:** Uncommon: Atrial fibrillation, palpitations, ECG abnormal, left bundle branch block (see section Tumor Lysis Syndrome), sinus tachycardia (see section Tumor Lysis Syndrome). **Vascular disorders:** Uncommon: Hypertension, flushing, hot flush, haemorrh disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence gastrointestinal discomfort. Rare: Pancreatitis, mouth ulceration. Hepato-biliary disorders. Common: Liver function abnormalities**. Uncommon: Cholelithiasis. Rare: Hepatitis, jaundice*, liver injury* **Skin and sub** Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis. **Musculoskeletal** haematuria, pollakiuria, proteinuria. Rare: Tubulointerstitial nephritis*, micturition urgency. **Reproductive system and breast disorder:** Uncommon: Erectile dysfunction. **General disorders and administration site conditions:** Common: Oedema, Uncommon: Fatigue, chest pain, chest disco haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase. Rare: Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase.* Adverse reactions coming from post-marketing exp controlled studies. *Description of selected adverse reactions*: Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis). Gout flares were commonly observed soon af (FLO-01) study comparing febuxostat with allopurinol (346 patients undergoing chemotherapy for haematologic malignancies and at intermediate-to-high risk of TLS), only 22 (6.4%) patients overall experienced adverse reactions, namely 11 (6.4%) patients in each treatment group. The ma bundle branch block, sinus tachycardia. *ecular disorders: Uncommon: Haemorrhage **Full prescribing information is available upon request**.

Stroke Prevention in Atrial Fibrillation – an Update

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Background

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide.[1-3] More importantly, AF confers a five-fold higher risk of ischaemic strokes, irrespective of the type (paroxysmal, persistent and permanent) of arrhythmia.[1] Patients with AF-related ischaemic strokes have a poorer prognosis: the 1-year mortality of AF-related strokes is as high as 50% and patients with AF-related strokes have more severe residual deficits. Common risk factors for AF include advanced age, diabetes, hypertension and the presence of structural heart diseases.[4] While the prevalence of AF in Chinese is much lower than that of the Caucasian population (0.77% vs. 1.4-2%),[4-7] given the huge ageing population in China and Hong Kong, the absolute number of AF patients is much higher in our locality. The lower AF incidence and disease burden in the Chinese has been confirmed in the multi-centred ASSERT study using implanted devices in 2,580 patients from 23 countries with a mean follow up of 2.5 years.[8]

Nonetheless, in view of the increased likelihood of developing ischaemic strokes and systemic embolisation, stroke prevention remains the cornerstone of management in AF patients. A previous study in 9,727 Hong Kong Chinese patients with non-valvular AF (CHA2DS2-VASc 3.7±1.8), which constitutes one of the largest AF registries reported in Chinese, set off to determine their risk of ischaemic stroke and intracranial haemorrhage (ICH) and showed an increased risk of ischaemic stroke with increasing CHA2DS2-VASc scores.[9] Such findings are also in keeping with the clinical guideline recommendation on the use of CHA2DS2-VASc scores to determine to whom anticoagulation should be recommended for stroke prevention.[2,3] It is well known that ischaemic strokes related to AF usually result from cardio-embolism to a large cerebral artery, which therefore explains the worse clinical outcomes in terms of morbidity and mortality than strokes from other aetiologies.[10] Therefore, in managing AF patients, priority should be focused on stroke prevention except in those with CHA2DS2-VASc of 0, who are very low-risk patients.

Anticoagulation

Cardio-embolic strokes are largely preventable with appropriate use of anticoagulation. Conventionally, warfarin reduces ischaemic strokes and systemic embolisation by 64% and reduces mortality by 26% compared to placebo.[11] However, studies showed that oral anticoagulation was under-used in various geographical regions in AF patients who were at risk of developing ischaemic strokes. In a real-world registry of Chinese hospital-based cohort of 9,727 AF patients in Hong Kong, only less than 20% of patients were put on warfarin, instead many of these AF patients (40.4%) were taking aspirin for either primary or secondary prevention of ischaemic strokes. Nonetheless, given the comparable adverse effects in ICH (0.8% in warfarin vs. 0.77% in aspirin), aspirin should not be considered a safer alternative to warfarin in Chinese patients.[9] The underlying reason for such a wide misuse of aspirin is presumably due to the misperception of efficacy and safety of aspirin in the indication of ischaemic stroke prevention in AF. It has been proven that aspirin, when compared to warfarin, was neither effective nor safer in this situation.[12]

For those on oral anticoagulants, over half of the patients on warfarin did not achieve a good quality of anticoagulation, as defined by time in therapeutic range (TTR) ≥65%.[13] However, the problem of poor anticoagulation affected the Asian population as well as the Caucasian population. Even in the randomised controlled trial setting with regular frequent monitoring of INR,[14] patients from Asian countries, particularly the Chinese population, did not achieve a good TTR. This is probably multi-factorial as the dietary interaction and consumption of herbal medicines also play a role.[15]

Non-vitamin K antagonist oral anticoagulant (NOAC)

Owing to the various limitations of warfarin, NOAC becomes increasingly important in the management of ischaemic stroke prevention in AF. A meta-analysis of 4 landmark randomised control trials showed that NOAC, when compared with warfarin, could reduce strokes by 19% largely owing to the reduction in ICH.[16] Such benefit was observed to be greater among East-Asian populations than non-Asians. This is also partly contributed by the poor anticoagulation quality among Asian patients. The latest international guidelines recommend NOAC in patients with non-valvular AF who are at increased risk of ischaemic strokes, as defined by the CHA2DS2-VASc score of 1 or above.[3] With the availability of 4 NOACs (dabigatran, rivaroxaban, apixaban and edoxaban), clinicians can choose a particular NOAC and dosage for a particular patient according to the clinical characteristics, for instance, age, body weight, renal function, and prior history of gastrointestinal bleeding. (Fig. 1)

RCT with NOAC vs Warfarin in Non-valvular AF

	RELY	ROCKET	ARISTOTLE	ENGAGE-AF
Sample size	18,113	14,266	18,201	20,500
New treatment	Dabigatran 110mg BID & 150mg BID	Rivaroxaban 20mg QD 15mg QD (CrCl 30-49)	Apixaban 5mg BID 2.5mg BID (≥ 80, BW≤60kg, Serum creatinine≥1.5 mg/dL)	Edoxaban 30mg QD & 60mg QD
Design	Non-inferiority PROBE	Non-inferiority Double-blind	Non-inferiority Double-blind	Non-inferiority Double-blind
CHADS2	≥ 1	≥ 2	≥ 1	≥ 2
Primary outcome	Stroke or SSE	Stroke or SSE	Stroke or SSE	Stroke or SSE
Safety outcome	Primary: Major Bleeding	Primary: Major Bleeding	Primary: Major Bleeding	Primary: Major Bleeding
Renal Exclusion	CrCl 30ml/min	CrCl 30ml/min	CrCl 25ml/min	CrCl 30ml/min

Fig. 1

In prescribing NOAC, there are several key points to remember:[17]

1. Use of NOACs is contraindicated for AF patients with mechanical prosthetic valves or moderate to severe rheumatic mitral stenosis. However, the use of NOAC is acceptable in patients with bioprosthetic valves, mitral valve repair or transcatheter aortic valve implantation (TAVI).
2. Choice of NOAC and dosage should depend on the renal function of the patients. The calculation of renal function should be based on the Cockcroft-Gault equation. In choosing the dosage of apixaban, it should be based on the creatinine level, body weight and age. Both apixaban and rivaroxaban are Food and Drug Administration (FDA) approved for use with dialysis.
3. As NOAC is also contraindicated in patients with advanced liver disease, in particular Child-Pugh category C hepatic insufficiency, checking the liver function as baseline is recommended.
4. Prior to undergoing invasive or surgical procedures, NOAC can be withheld for 24 or 48 hours. Longer hold times may be necessary for patients taking dabigatran who have chronic kidney disease. No bridging heparin is needed for NOAC-treated patients. Full-dose NOAC can be resumed once the bleeding risk is appropriate.
5. In managing patients with coronary artery disease, for patients taking NOAC requiring single or dual antiplatelet therapy, shorter courses of antiplatelet therapy are recommended. Patients with elective PCI may benefit from dual therapy (NOAC plus clopidogrel for up to 1 year). Patients with acute coronary syndromes who undergo PCI should consider receiving triple therapy for up to 3 months, then switch to dual therapy (NOAC plus clopidogrel) until 1 year. After 1 year, all patients, as similar to other AF patients with stable coronary artery disease, should continue on NOAC monotherapy only.
6. Use of proton pump inhibitors (PPI) in patients taking NOAC is optional and recommended particularly in those taking anti-platelets or at high risk for gastrointestinal bleeding.

Non-pharmacological therapy of SPAF

Up till now, only one device – Watchman device for left atrial appendage (LAA) occlusion has been compared with warfarin in randomised control trials for its efficacy in stroke prevention and safety in terms of bleeding events.[18,19] Results showed that LAA occlusion is non-inferior to warfarin and possibly of lower bleeding rate in patients who continued follow-up.[20,21] Thus LAA occlusion can be offered to those patients who have contraindications to oral anticoagulants e.g. prior intra-cranial haemorrhage or those who are considered at high bleeding risk.

AF screening

Although oral anticoagulation therapy effectively reduces ischaemic strokes by two-thirds in patients with AF, the arrhythmia is often not diagnosed until the patient presents with an ischaemic stroke. Indeed, an ischaemic stroke is the initial presentation in up to 25% of patients with AF and at least 30-40% of patients with AF are entirely asymptomatic,[22,23] thus precluding these patients from any meaningful prophylactic therapy. Failure to identify these high-risk patients with asymptomatic AF and to provide effective primary prevention poses a substantial burden on our medical system and society to handle the long-term, devastating-and-yet-expensive complication, ischaemic stroke.

In fact, it has been increasingly recognised by clinicians that a screening programme to detect asymptomatic "silent" AF should be the integral component to combat the rising number of ischaemic stroke cases. A previous randomised controlled trial has demonstrated that both standard electrocardiogram (ECG) and pulse palpation can effectively detect AF during clinic visits.[24] Owing to various reasons, these have not been widely implemented. For instance, the routine ECG for screening is not cost-friendly to primary care physicians nor to the patients; the procedural time also lengthens the clinic stay; the latter lacks proper ECG documentation of AF. In the past decade, there has been a rapid emergence of devices targeted at AF screening, the majority of which have been validated only in selected populations or clinical settings. FDA-cleared and CE-marked AF detection technology is available: a smartphone-based heart monitor, AliveCor, incorporates dry electrodes mounted on an iPhone case and is capable of recording a lead I ECG strip. Sensitivity for AF detection can be up to 95-100% with specificity of 90-94%, giving an accuracy of around 94%.[25] In addition, the emergence of photoplethysmography (PPG), an optical method that measures changes in tissue blood volume caused by the pressure pulse, has also been shown to be possible using a smartphone without any additional peripherals.[26] Given the relatively low cost and ready availability, these devices may move the management of AF stroke prevention to a more proactive level. To evaluate the efficacy of AF screening and whether the incorporation of these mobile handheld devices in AF screening can improve the efficiency of AF detection, there were studies performed locally in a large community-based population to confirm the diagnostic accuracies of tools in AF detection, namely the Microlife home blood pressure machine and the AliveCor heart monitor.[27,28]

Conclusion

AF is an important condition that can potentially lead to substantial morbidity and mortality arising from severe ischaemic strokes through embolisation of clots formed in the left atrial appendage. Anticoagulation with NOAC for those with non-valvular AF and left atrial appendage occlusion for those with high bleeding risk provide viable options in stroke prevention. Without detection of AF, preventive strategies could not be employed and therefore, through AF screening, we can proactively diagnose and treat AF and its associated devastating complication – ischaemic stroke.

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Novel Therapeutic Agents for Heart Failure

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Introduction

Angiotensin-converting enzyme inhibitors (ACEI)/ Angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA) and beta-blockers have been shown to improve survival in patients in heart failure with reduced ejection fraction (HFrEF). However, heart failure (HF) remains a significant cardiovascular problem, with increasing incidence and prevalence rates and is still associated with significant mortality, morbidity, and health care expenditures, particularly among ageing populations. Newer pharmacological agents are needed to improve HF outcomes. A new therapeutic class of agents, angiotensin receptor neprilysin inhibitors (ARNI), has recently been shown to be superior to an ACEI in reducing the risk of death and of hospitalisation for HFrEF. Another class of drugs, sinus node inhibitors, reduces the elevated heart rate often seen in HFrEF and has also been shown to improve outcomes. A promising class of anti-diabetic drugs, sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitor), has been shown to reduce HF hospitalisation and HF death in diabetic patients with or without HF.

Angiotensin receptor neprilysin inhibitor (ARNI)

Neprilysin is an enzyme that inactivates several peptide hormones in our body. By inhibiting neprilysin, the degradation of natriuretic peptides, bradykinin and other peptides is diminished. High circulating A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) can enhance diuresis, natriuresis and myocardial relaxation and anti-remodelling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy. The first in the ARNI class is LCZ696, a molecule that combines a neprilysin inhibitor (sacubitril) and an ARB (valsartan) in a single substance.

PARADIGM-HF trial investigated the long-term effects of sacubitril/valsartan compared with an ACEI (enalapril) on morbidity and mortality in patients with ambulatory, symptomatic HFrEF[1]. In this population, sacubitril/valsartan (200 mg twice daily) was superior to ACEI (enalapril 10 mg twice daily) in reducing hospitalisations for worsening HF, cardiovascular mortality, and overall mortality. A 20% reduction in the composite endpoint of cardiovascular death or HF hospitalisation was noted, and this composite endpoint was consistent across subgroups. Sacubitril/valsartan is therefore recommended to replace ACEIs or ARB in ambulatory HFrEF patients who remain symptomatic despite optimal therapy[2,3,4]. The ACC/AHA/HFSA guideline update gives a Class I recommendation to replace an ACEI or ARB by an ARNI in selected patients with chronic symptomatic HFrEF (New York Heart Association [NYHA] class II/III) with an adequate blood pressure who are already tolerating a reasonable dose of ACEI or ARB. ARNI is also indicated in class IV HF.

Despite the superiority of sacubitril/valsartan over enalapril in the PARADIGM-HF trial, caution should be exercised when initiating this drug. The use of ARNI is associated with risk of hypotension, renal insufficiency, and the rare complication of angioedema. Symptomatic hypotension was more often present in the sacubitril/valsartan group than in the enalapril group, although there was no increase in the rate of discontinuation. The recommended starting dose is 100 mg twice-daily. The dose can be doubled after 2 to 4 weeks to the target maintenance dose of 200 mg twice-daily, as tolerated by the patient. The starting dose should be reduced to 50 mg twice-daily for patients not currently taking an ACEI or ARB or previously taking a low dose of these agents and for patients with severe renal impairment or moderate hepatic impairment. Concomitant use of ANRI with ACEI can lead to angioedema and should be avoided. This adverse effect was thought to occur because both ACE and neprilysin break down bradykinin, which directly or indirectly can cause angioedema. To minimise the risk of angioedema caused by overlapping ACE and neprilysin inhibition, ACEI should be withheld for at least 36 hours before initiating sacubitril/valsartan. An ARNI should not be administered within 36 hours of switching from or to an ACEI. Lastly, there are some concerns about its effects on the degradation of beta-amyloid peptide in the brain. Longer term observation is needed to assess whether it may accelerate amyloid deposition.

A phase II study has shown that ARNI significant reduced NT-proBNP more than ARB and reduced left atrial size in heart failure with preserved ejection fraction (HFpEF) patients[5]. A large phase III randomised study in HFpEF patients is ongoing to evaluate the role of ARNI in the treatment of HFpEF. Other clinical trials are also being carried out to study the effects of ARNI in post myocardial infarction patients and to assess if ANRI can be initiated in-hospital following hospitalisation for acute decompensation.

Sinus Node Inhibitor

Ivabradine is a relatively new therapeutic agent that

selectively inhibits the I_f current in the sinoatrial node, providing heart rate reduction. Heart rate reduction decreases energy expenditure and increases blood supply by prolonging diastole. Heart rate reduction is associated with reversal of cardiac remodelling, as shown by a reduction in left ventricular volumes and an increase in left ventricular ejection fraction. Ivabradine reduced the combined endpoint of mortality or hospitalisation for HF in patients with symptomatic HFrEF in sinus rhythm and with a heart rate ≥70 beats per minute, receiving treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose), an ACEI (or ARB) and an MRA in a randomised controlled study[6]. The European Medicines Agency (EMA) approved ivabradine for use in Europe in patients with HFrEF with LVEF ≤35% and in sinus rhythm with a resting heart rate ≥75 beats per minute, because in this group ivabradine conferred a survival benefit based on a retrospective subgroup analysis[7]. The ACC/AHA/HFSA guideline update gives a Class IIa recommendation for use of ivabradine to reduce HF hospitalisation in patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) receiving guideline-directed evaluation and management, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 beats per minute or greater at rest[3]. The guideline recommends that given the well-proven mortality benefits of beta-blockers, it should be titrated to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation. But in real life heart failure populations, suboptimal heart rate control is not uncommon and less than half of the patients can be titrated to target beta-blocker doses due to comorbidities and sides effects. Ivabradine is easier to be used and better tolerated.

Sodium-glucose co-transporter 2 inhibitor (SGLT2 inhibitor)

There is a strong connection between HF and diabetes, as 25 to 44% of patients with HF also have diabetes. Patients with diabetes also have a 2 to 5- fold increased risk of HF. A new class of anti-diabetic drugs may have additional beneficial effects in HF and may be the solution to the treatment of HF in these high-risk patients. SGLT2 inhibitor is the latest approved class of glucose-lowering agents. By blocking sodium/glucose uptake in the proximal tubules of the nephron, glycosuria is induced. The EMPA-REG OUTCOME trial studied the use of an SGLT2 inhibitor (empagliflozin) in patients with type 2 diabetes with elevated cardiovascular risks[8]. EMPA-REG OUTCOME showed a 35% reduction in hospitalisations for HF and a 38% reduction in cardiovascular death largely due to a reduction in fatal events related to worsening of HF or to sudden death in patients receiving empagliflozin. In addition, the benefit was evident very early (around 6 months) after treatment initiation. Similar results on HF have also been reported with another SGLT2 inhibitor, canagliflozin[9]. A sub-analysis of the EMPA-REG OUTCOME study showed that empagliflozin reduced the risk for HF hospitalisation and CV mortality in patients with type 2 diabetes with or without HF. In patients without HF at baseline, empagliflozin reduced HF hospitalisation and CV mortality across a spectrum of HF risk[10]. An observation study (CVD-REAL) assessed data from more than 300,000 patients across six countries with the majority of the subjects being treated with dapagliflozin. The data showed that across a broad population of patients with type 2 diabetes, treatment with SGLT2 inhibitors significantly reduced the rate of hospitalisation for HF by 39% and composite endpoint of hospitalisation for HF and death from any cause by 46% compared to other anti-diabetic medicines. This large multinational real-world study suggested that the benefits seen with empagliflozin in a randomised trial may be a class effect.

The mechanisms by which SGLT2 inhibition improves HF outcomes are not fully understood. Despite modest effects on long-term glycaemic control, highly significant reductions in heart failure hospitalisation were observed. Some mechanisms have been postulated including effects on osmotic diuresis, natriuresis contributing to blood pressure lowering and intravascular volume contraction without a compensatory increase in sympathetic nervous system activation and improved diuretic and natriuretic responses to other diuretic agents. Moreover, SGLT2 inhibitors may improve the efficiency of myocardial energetics by offering β-hydroxybutyrate ketones as a more energy efficient fuel than fatty acids for oxidation. Increases in haemoglobin and haematocrit related to SGLT2 inhibitor treatment have also been observed in some studies and may play a role. Finally, decreased vascular stiffness and improved endothelial function are observed with the use of SGLT2 inhibitors in diabetes. These multiple nonglycaemic effects render SGLT2 inhibitors as the preferred glucose-lowering drug in diabetic patients with HF or high risk of developing HF. Ongoing clinical trials are evaluating the role of SGLT2 inhibitors in the treatment of HF without diabetes.

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Athlete's Heart

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Exercise Physiology

During exercise, the O_2 demand is met by increasing pulmonary O_2 uptake (VO_2). The cardiac output (CO) is the multiplication product of stroke volume (SV) and Heart rate (HR): CO = SV x HR. CO usually increases by 5-6 times during exercise. There is an increase of sympathetic tone and withdrawal of parasympathetic tone during exercise causing an increase in the heart rate. However, during the recovery phase of exercise, the other way happens with parasympathetic tone coming in again, which causes the bradycardia.[1]

Heart rate increase accounts for the initial phase of CO of the exercise. However, the later phase increase of CO is maintained by SV increase. Intensive exercise training will not push up the maximum HR any further (inborn). Therefore, prolonged exercise training will only increase the CO solely by increasing the SV, thus creating volume overload conditions to the heart.[1]

Two different forms of exercise

Isotonic Exercise: Such as swimming, running, cycling. There is a decrease in peripheral vascular resistance during the exercise. Volume overloading condition is remarkable.

Isometric Exercise- Such as weight lifting. dumbell raising etc. These will increase the peripheral vascular resistance. Thus, the systolic BP will be increased and aggravate LV afterload. It is less volume overloading than isotonic counterpart.[1]

Individual Chambers

1. Left Ventricle (LV)
Isometric – Hypertrophy of LV; Isotonic – Hypertrophy and dilation of LV.

ECG shows LV high voltage physiologically. Echo shows an increase in end diastolic diameter (women 38-66 mm; men 43-70 mm); however, the end systolic diameter may be normal or may even decrease secondary to high catecholamine state. The hypertrophic wall thickness may be up to 13 mm for LV thickness (some Africo-Carribean race may be up to 15 mm)[2]. Although the heart is enlarged but basically, it maintains good ejection (EF) or only slightly reduced EF of 50-55%. That makes the difference from cardiomyopathy, which is associated with depressed contractile function. Most of the time, the diastolic function (using strain rate and tissue Doppler) can help to differentiate physiological (normal) vs pathological LV dilation. However, sometimes it may need a cardiac MRI or even detraining for 3 months to see any improvement in LV dimension.[1]

2. Right Ventricle (RV)
The RV is more susceptible to volume overload than the LV, manifested as dilation and hypertrophy of RV. ECG may show a positive R wave in V1 (electrical RV hypertrophy). It is more remarkable in athletes engaged in isotonic exercise. Intensive training may cause transient RV dysfunction, which is likely reversible after stopping exercise[2].

3. Aorta
Strength overloading (Isometric) will cause the aortic root to dilate with systemic hypertension. However, the root diameter seldom exceeds 4 cm with physiological training.[1]

4. Atria
Volume overloading will cause the atria to dilate up to 20% of participating athletes with LA diameters > 4cm.[1]

ECG benign findings

1. Seattle Criteria-

- Sinus Arrhythmia
- Sinus bradycardia
- Ectopic atrial rhtyhm
- Junctional rhythm
- Primary AV block
- Mobitz Type II a block
- Incomplete RBBB
- Isolated LVH high voltage
- Early Repolarization
- Convex ST segment elevation combined with T inversion of V1-V4 leads[3]

Bradycardia
The common arrhythmia is sinus bradycardia, as defined by a heart rate of less than 30 per min. Sinus pauses of more than 3 seconds are considered abnormal. Mobitz type IIa heart block (Wenkebach) are normal especially if they can be raised during exercise. Any type IIb or 3rd degree heart block are abnormal. Isolated left axis deviation (LAD) or right axis deviation (RAD) should not require further investigation without any pathological suspicion.

2. Physiological Q wave in inferior leads are common (Q wave < 3 mm and < 40 ms i.e.1 small square).[4]

3. Early repolarization is also well noted in endurance training athletes with upward ST convexity. Simple T inversion in inferior and right-sided leads are also quite common.[5]

4. Premature ectopic beats (atrial or ventricular)
They are usually quite common in athletes and are benign if they are easily suppressed by exercise without underlying pathological process.[4]

Atrial Fibrillation (AF)

AF occurs in about 3% of intensive athlete's training. The mechanism may be due to atrial dilation with re-modelling and fibrosis; sympathetic outflow during exercise or high vagal tone during resting state all can account for high AF incidences. At times, detraining is necessary to prevent any further relapse.[3]

Other important cardiac events

1. Syncope
Syncope usually occurs at the recovery phase of the exercise. The most common cause is neuro-cardiogenic syncope (vasovagal) due to a decrease in venous return, parasympathetic response, and withdrawal of high sympathetic state. It can be prevented by adequate water intake and salt intake during exercise, as well as cooling down for a longer period of time. However, syncope during exercise will never be vasovagal and it should raise the suspicion of underlying organic heart disease.[1,6]

2. Cardiac Death
Besides, the coronary artery disease makes up the most of the sudden death (upto 50 %), HOCM accounts for 25 %; Commotio Cortis 20 %; LVH 7 % etc.[6,7]

14 elements of AHA recommendations of CVS of competitive athletes' screening protocol[8,9]

History:
1. Chest discomfort related to exertion
2. Unexplained syncopy
3. Excessive and unexplained dyspnea
   fatique or palpitations associated with exercise
4. Previous history of heart murmur
5. Elevated systemic hypertension
6. Priori restriction of sports
7. Priori testing of heart

Family Hx
8. Premature sudden death of close relative < 50 years of age
9. Disability of heart disease of close relative <50 years old
10. HOCM, Dilated CMP, Channelopathies, Marfan, Genetic arrhythmia etc

P/E
11. Heart murmur
12. Radial - Femoral pulses discrepancy to exclude coarctation of aorta
13. Marfan's feature
14. BP

Conclusions

Clinicians should be careful of the benign features of the physiological changes of athletes' heart to avoid over–investigation. On the other hand, we should be on the alert to detect the ominous symptoms and signs of underlying pathology in order to avert sudden cardiac death.

God bless our athletes!

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Radiology Quiz

Dr Grace HT NG

MBChB, FRCP

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Dr Grace HT Ng

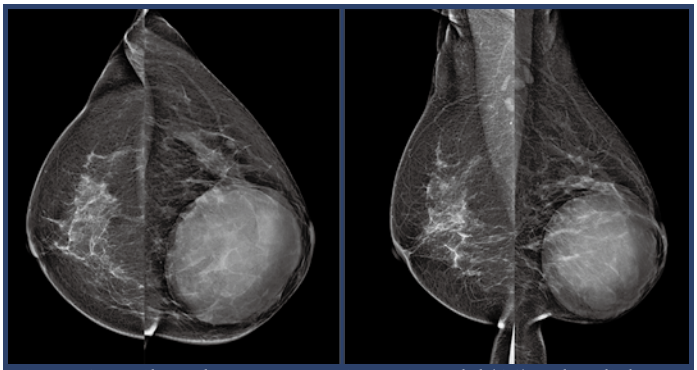

Fig. 1 A & B: Bilateral mammograms in craniocaudal (CC) and medial lateral oblique (MLO) views respectively.

A 43 year-old lady with a self-detected left breast mass for 6 months, which is non-tender but rapidly enlarging. Initial workup with mammography is as below:

Questions

1. What is the abnormality on these mammographic views?
2. What further investigations would you suggest?
3. What is your most likely diagnosis and differential diagnosis?

(See P.44 for answers)

New standard for an old problem - Hypertension

Dr Warren Wai-lun WONG

MB ChB (CUHK), FRCP (Edin), FHKCP, FHKAM (Medicine), MPH (Johns Hopkins)

Specialist in Cardiology

Dr Warren Wai-lun WONG

Introduction

The 2017 guidelines published just a few months ago is an update of the "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure" (JNC 7) in 2003 (please reference for the 2017 guidelines). The 2017 guideline provides new information about the use of ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM), defining BP thresholds to initiate antihypertensive drug treatment in order to reach treatment goals and to improve hypertension (HT) control.

Observational studies have shown associations between higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) with increased cardiovascular (CV) risk in a log-linear fashion from SBP levels <115 mmHg to >180 mmHg and from DBP levels <75 mmHg to >105 mmHg. An increase of 20 mmHg in SBP and 10 mmHg increase in DBP were associated with doubling the risk of death from stroke, heart diseases, or other vascular diseases in 30 to more than 80 year-old patients.[1,2] For an adult 45 years old without hypertension, the 40-year risk for developing hypertension is 93% for African Americans, 92% for Hispanics, 86% for Whites and 84% for Chinese adults. So it is a growing problem with any ageing population.

A growing major modifiable risk factor, locally and globally

The Centre for Health Protection in Hong Kong quoting surveys conducted by the Census and Statistics Department of the HKSAR Government found that the proportion of people with known hypertension increased from 9.3% in 2008 to 12.6% in 2014. A local cohort study in 2012 done by the School of Public Health of the University of Hong Kong revealed that only 46% among those with hypertension documented in the study were diagnosed by a doctor. It also revealed that among those ever diagnosed to have hypertension, 70% were prescribed medications, with only 42% achieving good BP control. There is obvious room for improvements in diagnosing and treating patients with hypertension in our local population.

In 2010, hypertension was the leading cause of death and disability-adjusted life-years worldwide[3,4]. In the United States, hypertension accounted for more CV deaths than any other modifiable CV risk factor and was second only to smoking as a preventable cause of death.[5] In the population-based ARIC (Atherosclerosis Risk in Communities) study, 25% of the CV events (coronary heart disease, heart failure, coronary revascularisation or stroke) were attributable to hypertension. In 2012, hypertension was the second leading cause of End Stage Renal Failure (ESRD), next to diabetes mellitus (DM), and accounted for 34% of incident ESRD cases in the US[6]. It becomes so obvious that a greater effort to diagnose and treat hypertension is needed in every health care system.

Adopting the latest hypertension guideline

Health care providers should obtain accurate BP measurements, then the BP readings should be categorised as normal, elevated, or stages 1 or 2 hypertension to prevent and treat high BP according to the 2017 guideline:

Normal BP: <120/<80 mmHg
Elevated BP: 120-129/<80 mmHg
Hypertension stage 1: 130-139 or 80-89 mmHg
Hypertension stage 2: ≥140 or ≥90 mmHg

It is important to use an average based on ≥2 readings obtained on ≥2 occasions to estimate the average BP. Home self BP monitoring is recommended to confirm the diagnosis of hypertension and for titration of HT medication. Daytime ABPM or HBPM can be used to screen for the presence of white coat hypertension. And in patients with elevated office BP (120-129/<80) but not meeting the criteria for hypertension, screening for masked hypertension with daytime ABPM or HBPM is reasonable.[7,8] Health care providers must not forget to screen for and manage other CV risk factors at the same time: over-weight, physical inactivity, smoking, unhealthy diet, psychosocial stress, diabetes, hyperlipidaemia and co-existing sleep apnoea.[9]

Secondary causes of hypertension have to be excluded for patients with the following conditions:

- new onset or uncontrolled hypertension being drug-resistant (≥3 drugs)
- abrupt onset
- young patients <30 years old
- excessive target organ damage (albuminuria, retinopathy, left ventricular hypertrophy, heart failure, coronary artery disease, chronic kidney disease, peripheral artery disease, cerebral vascular disease)
- onset of diastolic hypertension in older adults
- unprovoked or excessive hypokalaemia

Non-pharmacologic and pharmacological interventions

Non-pharmacologic interventions are an important part of any patient self-directed care plan and definitely help in achieving a treatment goal of hypertension. Each lifestyle modification can bring about 4-5 mmHg decrease in SBP and 2-4 mmHg decrease in DBP: weight reduction for overweight patients, heart healthy diet, sodium restriction with potassium diet supplementation. Low sodium / saturated fat/ total fat and increase in fruits/ vegetables/ grains may decrease SBP by up to 11 mmHg. Patients are encouraged to increase regular physical activity, preferably with a structured exercise programme. Men should limit to no more than 2 and women no more than 1 standard alcohol drink per day.[10]

The benefit of pharmacologic treatment for BP reduction is related to atherosclerotic cardiovascular disease (ASCVD) risk, with more benefits in patients with high ASCVD risk: smoker, old age, diabetes, hyperlipidaemia, chronic kidney disease or coronary heart disease. BP-lowering medications are recommended for secondary prevention of recurrent CV events in patients with clinical CVD and an average SBP ≥130 mmHg or a DBP ≥80 mmHg, or for primary prevention in adults with no history of CVD but with an estimated 10-year ASCVD risk of ≥10% and SBP ≥130 mmHg or DBP ≥80 mmHg. The prevalence of hypertension is lower in women compared with men until about the fifth decade, but becomes higher afterwards. For adults with confirmed hypertension with known CVD or 10-year ASCVD event risk of ≥10%, a BP target of <130/80 mmHg is recommended. For HT adults without increased CVD risk, a BP target of <130/80 mmHg is recommended as reasonable.[11-13]

Initial first-line therapy for stage 1 hypertension includes thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or ARBs. Two first-line drugs of different classes are recommended with stage 2 hypertension and average BP of 20/10 mmHg above the BP target. Improved adherence can be achieved with once-daily drug dosing and with combination therapy.[14-16]

Individualïzed treatment plan

CcfTreatment of hypertension is recommended for non-institutionalised ambulatory adults ≥65 years old with an average SBP ≥130 mm Hg to have a SBP treatment goal of <130 mm Hg. For patients ≥65 years old with hypertension and multiple comorbidities or limited life expectancy, a team approach to assess risk/benefit including patient preference is needed for individualising the intensity of BP lowering and choice of antihypertensive drugs. BP lowering is reasonable to prevent cognitive decline and dementia.

In low-risk patients with elevated BP or stage 1 hypertension with low ASCVD risk, BP should be repeated after 3-6 months of non-pharmacologic therapy. Stage 1 hypertension patients and high ASCVD risk (10-year ASCVD risk ≥10%) should be managed with both non-pharmacologic and drug therapy with BP repeated in 1 month. Adults with stage 2 hypertension should be treated with a combination of non-pharmacologic therapy and 2 hospitals antihypertensive drugs of different classes with repeat BP evaluation in 1 month. For adults with a very high average BP (e.g., ≥160 mmHg or DBP ≥100 mmHg), prompt evaluation and drug treatment followed by careful monitoring and upward dose adjustment is recommended. [17-19]

Summary

In summary, with the latest 2017 guideline for hypertension, health care providers should be able to refresh themselves with the following key points:

- Hypertension is a growing health problem in all ageing populations worldwide, including Hong Kong
- Hypertension is easily under diagnosed and under treated
- Hypertension is the leading cause of death and disability-adjusted life years worldwide
- Hypertension is second only to smoking as a preventable cause of death
- Proper measurement is needed for optimal patient care, home BP measurements and ambulatory BP monitoring can help in diagnosis and drug titration
- New level of diagnosis and treatment goal with SBP and DBP less than 130 and 80mmHg respectively for most patients adopted, with individualised goals for patients with multiple comorbidities
- Non-pharmacological and drug treatments are both important for achieving treatment goal, long acting and combination drugs may help to improve patient compliance
- Continue monitoring and titration of treatment are needed to achieve treatment goal, secondary causes of hypertension needed to be considered if necessary

For those interested to know more about the latest guideline for hypertension, there is much more information in the original article with further details and practical tips.

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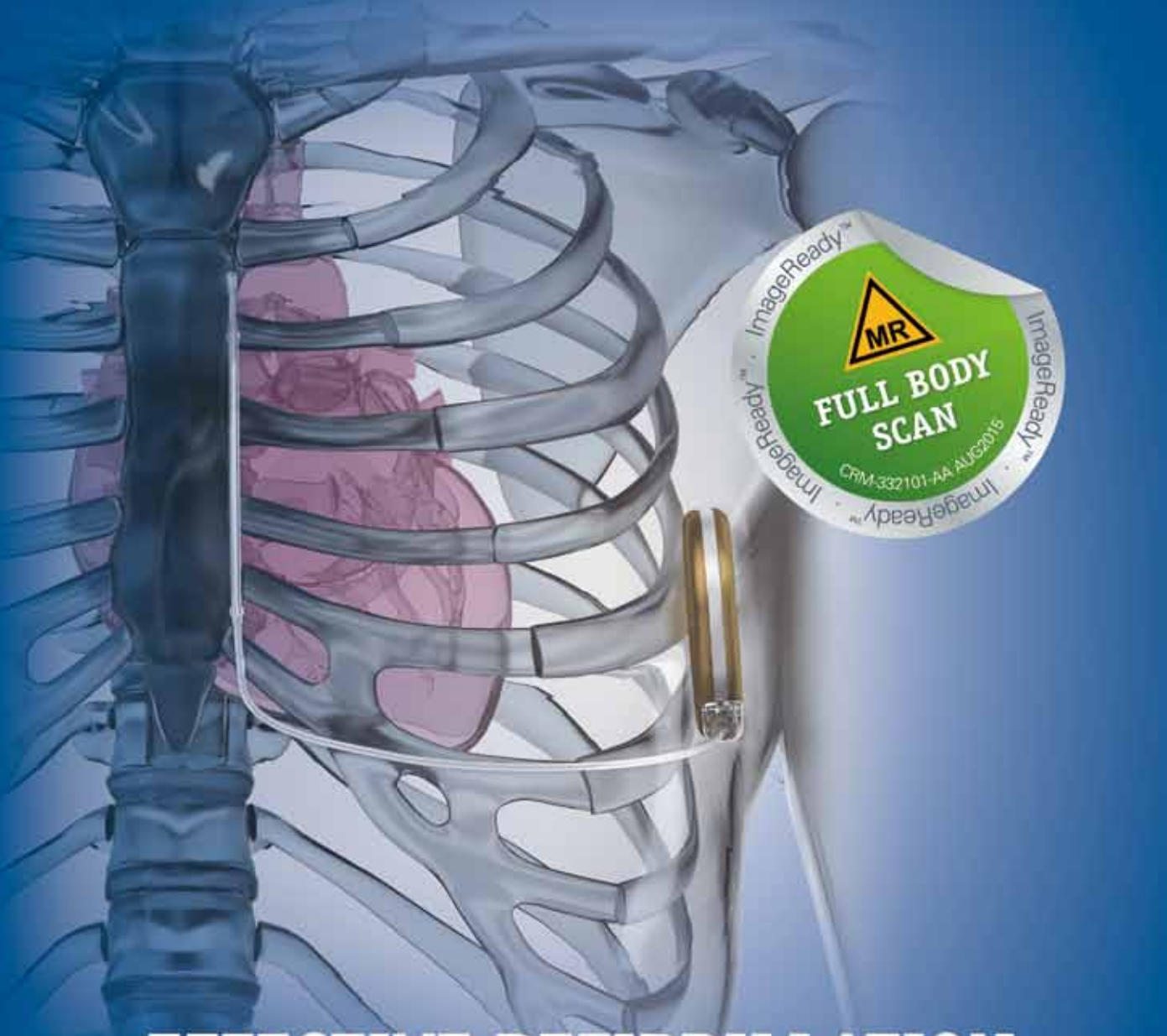

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Life-long Exercising Cardiologist

Sir Dr Peter Cho-you WONG, BBS, KStJ

FACC, FRCPs, FHKAM(Med), FHKCP

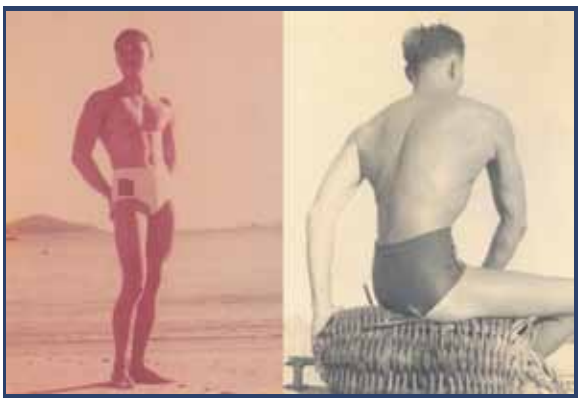
Sir Dr Peter Cho-you WONG, BBS, KStJ

I am now 86 years old.
As a child, I was really a weakling. Compared with other kids of the same age, I was much shorter and smaller. My father encouraged me to exercise more and to eat more.

Starting at the age of 7, I learned Chinese Kung Fu. One year later, I was selected to demonstrate a Double Sword pattern on stage.

After the Second World War, I attended the St Paul's Co-educational College where I began to play basketball and volleyball. The year before my medical school, I started to work out with body building in the gym nearby. The programme completely changed my body muscle shape and weight. It was so dramatic that some old schoolmates could not even recognise me.

In medical school, I joined the University Teams of basketball, volleyball and track and field concentrating on the field events. During my internship, I was trained by a famous Japanese master in Judo and I often got bruises here and there.



In 1960, I went to Boston, Massachusetts, USA for my post graduate training. Over there, I started to pick up tennis.

After another year of study in the UK, I returned home in 1967 and started and established the first Intensive Care Unit in Hong Kong and the Far East using my experience and knowledge learned in the previous two years.

One day, I noticed a big front page South China Morning Post photo of a man jumping high up to the height of two people to break a board. I was so amazed and impressed. Later I found out that this is Taekwon-Do developed and introduced by a Korean General Choi Hung Hay. The man in the photo was Master Kim Bok Man sent out to publisise the art to other countries. I followed him and was trained for about 20 years. After two years I was able to break a brick using the force of my body turning, twisting and fast accurate hit with the bare hand. So I passed the grading for first Dan Black Belt as examined by General Choi. With continued training I was gradually and finally promoted to the 5th Dan Black Belt. Knowing the secret of the technique, breaking 3 boards, piles of tiles, etc., became easy. I was often invited to give demonstrations on the TV shows, and at the City Hall and Stadiums.

During this period, I was also able to learn other Martial Arts such as Japanese Aikido, Korean Hopklido and Practical Tai Chi. They all have some resemblances and differences. However, I think the practice of breaking falls is most useful in the daily life when one is faced with an accidental fall. It will help to prevent serious injuries.

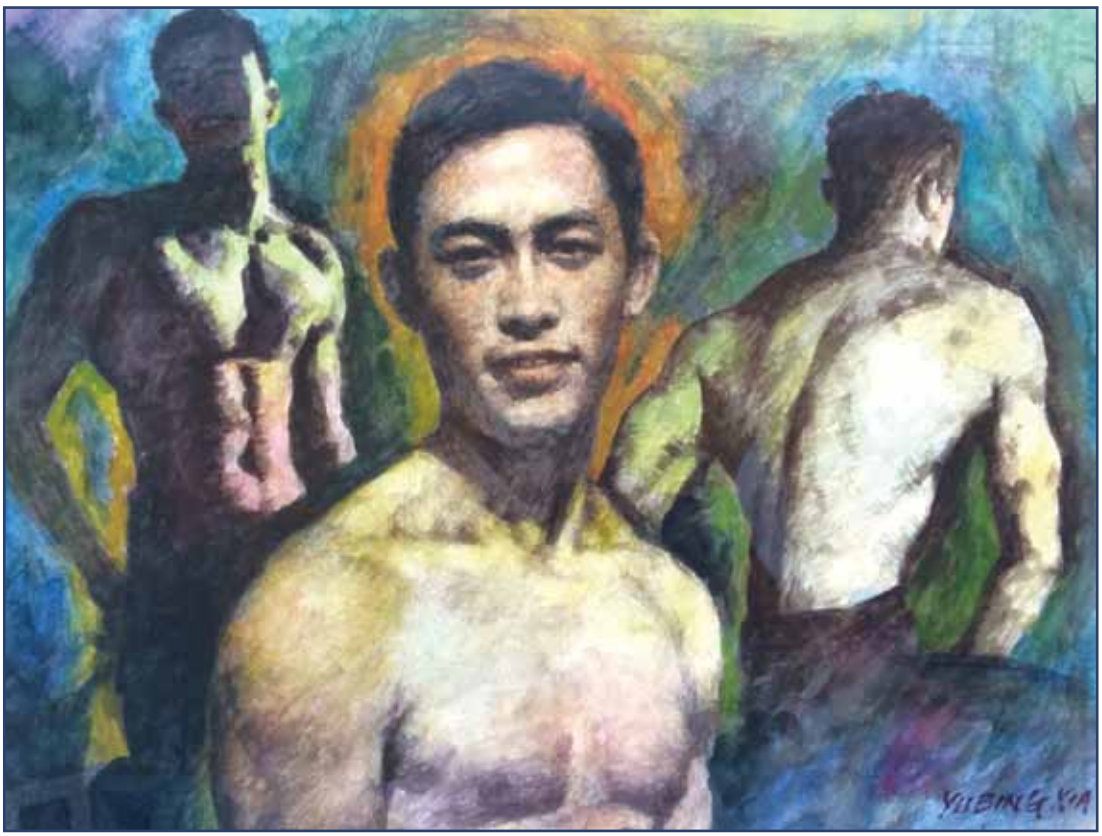
One day, as my wife and I were walking and shopping in India, 4 young men followed us closely for a long distance until there was body contact, As I was debating whether to fight back to defend ourselves or not, my wife gave a sharp and loud shout. Surprisingly, the Indians were afraid and ran away rapidly to different directions. So, all you need is just to have a fierce wife!

In 1983, when I was practising free sparring with others, we all were equipped with protective vests and helmets. I executed a side kick to the chest of my opponent. It was too strong and broke his two ribs. So I said to myself: this is too dangerous for me and I then stopped doing martial arts.

I started and established a Dragon Boat Team for doctors of the Hong Kong Medical Association in 1990 and I served as Captain since. We practised paddling training every Sunday in Sai Kung and had competed with others for races in Hong Kong. I even led the team to Japan for competition about 15 years ago.

3 years ago, I was knocked down by a motorcycle and sustained brain haemorrhage and fractures of four bones. Brain surgery was done and the Neurosurgeon advised me not to do strenuous physical activities for more than a year. I became very weak. Rehabilitation was slow. However, now I can resume playing tennis 5 mornings a week and the strength is gradually returning.

My advice is to keep exercising and keep healthy!



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2. IMS Sales YTD SEP 2017 (sales including Diovan, Co-Diovan, Exforge and Exforge HCT)

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Medical Diary of June

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4	★FMSHK Officers' Meeting ★HKMA Council Meeting 5	★HKMA Central, Western & Southern Community Network - Updates in Heart Failure Management ★HKMA Shatin Doctors Network - Diagnosis and Management of Spondyloarthritis (SpA) 6	★HKMA Hong Kong East Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors ★HKMA New Territories West Community Network - Prescription of Insulin Therapy in a Primary Clinic 7	8	★Refresher Course for Health Care Providers 2017/2018 9
★2018 Paediatric Undate No.1 10	11	★HKMA Kowloon West Community Network - Advances in Bone Densitometry and Management in Osteoporosis ★HKMA Yau Tsim Mong Community Network - Update in the Management of Idiopathic Pulmonary Fibrosis ★HKMA Tai Po Community Network - How to Tailor Lipid-lowering Treatment for Patients? 12	★Hong Kong Neurosurgical Society Monthly Academic Meeting –Paroxysmal sympathetic hyperactivity 13	★HKMA Kowloon East Community Network - Updates in Basal Insulin for Type 2 Diabetes ★HKMA – HKS&H CME Programme 2017-2018-"Update in Medical Practice" 14	15	16
17	18	★HKMA Tai Po Community Network - LUTS, Hematuria & Loin Pain – A Sharing & Update in General Practice 19	★HKMA Central, Western & Southern Community Network - Updates in Long-Term Osteoporosis Management 20	★HKMA Kowloon East Community Network - Updates in Mild Cognitive Impairment and Dementia Assessment for Busy Clinicians ★HKMA Hong Kong East Community Network - Lecture on "The Apology Ordinance and You" cum Annual Meeting ★HKMA New Territories West Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors ★FMSHK Executive Committee Meeting 21	22	23
24	25	★HKMA Kowloon West Community Network - The Diabetic Liver 26	27	28	★HKMA Yau Tsim Mong Community Network - Clinical Experience in Breakthrough Heart Failure Management 29	30

Date / Time	Function	Enquiry / Remarks
5 TUE 8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
6 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Updates in Heart Failure Management** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Dr. LAU Yuk Kong; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Shatin Doctors Network - Diagnosis and Management of Spondyloarthritis (SpA)** Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. CHAN Pak To; Venue: Diamond Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG Tel: 2527 8285 1 CME Point
7 THU 1:00 PM	**HKMA Hong Kong East Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. LAM See Yui, Joseph; Speaker: Dr. CHAN Leung Kwai, Jason; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Prescription of Insulin Therapy in a Primary Clinic** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. WU, Enoch; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, 8 Long Yat Road, Yuen Long	Mr. Ian YAU Tel: 2527 8285 1 CME Point
9 SAT 2:15 PM	**Refresher Course for Health Care Providers 2017/2018** Organiser: Hong Kong Medical Association; HK College of Family Physicians; HA-Our Lady of Maryknoll Hospital; Speaker: Dr. LAM Wing Wo; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin	Ms. Clara TSANG Tel: 2354 2440 2 CME Point
10 SUN	**2018 Paediatric Undate No.1** Organiser: Hong Kong College of Paediatricians; Chairman: Dr Simon LAM & Dr Chun-fai CHENG; Speaker(s): Dr CH KOO, Dr Ling SZETO, Dr Arthur MARK & Prof TF LEUNF; Venue:M Block, G/F, Lecture Theatre, QE	3 points, Catgory A Hong Kong College of Paediatricians Ms Lily LIU T: 2871 8752 F: 2785 1850
12 TUE 1:00 PM	**HKMA Kowloon West Community Network - Advances in Bone Densitometry and Management in Osteoporosis** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. YIP Wai Man; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chun, Mei Foo	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Yau Tsim Mong Community Network - Update in the Management of Idiopathic Pulmonary Fibrosis** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHAN Ka Wing, Joseph; Speaker: Dr. WONG Wing Ching; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:45 PM	**HKMA Tai Po Community Network - How to Tailor Lipid-lowering Treatment for Patients?** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John;Speaker: Dr. LAU Chun Leung; Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
13 WED 7:30 AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Paroxysmal sympathetic hyperactivity** Organizer : Hong Kong Neurosurgical Society; Speaker: Dr CHAN Sik Kwan, Steve; Chairman : Dr HO Lok Yan, Faith; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	1.5 points College of Surgeons of Hong Kong Dr. WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061
14 THU 1:00 PM	**HKMA Kowloon East Community Network - Updates in Basal Insulin for Type 2 Diabetes** Organiser: HKMA KLN East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. TONG Chun Yip, Peter; Venue: Lei Garden Restaurant, Shop No. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	Mr. Ian YAU Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA – HKS&H CME Programme 2017-2018 –"Update in Medical Practice"** Organiser: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. WU Wing Cheung, Stephen; Venue: Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Dept. Tel: 2527 8285 1 CME Point
19 TUE 1:00 PM	**HKMA Tai Po Community Network - LUTS, Hematuria & Loin Pain – A Sharing & Update in General Practice** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. LAM Kin Man, Justin; Venue: Chiuchow Garden Restaurant, Shop 001-003, 1/F, Uptown Plaza, No. 9, Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
20 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Updates in Long-Term Osteoporosis Management** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Dr. LEE Cheung Kei; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, HK	Mr. Ian YAU Tel: 2527 8285 1 CME Point
21 THU 1:00 PM	**HKMA Kowloon East Community Network - Updates in Mild Cognitive Impairment and Dementia Assessment for Busy Clinicians** Organiser: HKMA KLN East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Prof. Adrian WONG; Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Mr. Ian YAU Tel: 2527 8285 1 CME Point

Date / Time	Function	Enquiry / Remarks
21 THU 1:00 PM	**HKMA Hong Kong East Community Network - Lecture on "The Apology Ordinance and You" cum Annual Meeting** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. CHAN Nim Tak, Douglas; Speaker: Dr. CHIU Shing Ping, James; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - A Clinical Update in Lipid Management: PCSK9 Inhibitors** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHEUNG Kwok Wai, Alvin; Speaker: Dr. TUNGGAL Prabowo, Thomas; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Mr. Ian YAU Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
26 TUE 1:00 PM	**HKMA Kowloon West Community Network - The Diabetic Liver** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. CHAN Nor, Norman; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chun, Mei Foo	Mr. Ian YAU Tel: 2527 8285 1 CME Point
29 FRI 1:00 PM	**HKMA Yau Tsim Mong Community Network - Clinical Experience in Breakthrough Heart Failure Management** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. HO Lap Yin; Speaker: Dr. LI Siu Lung, Steven; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point

Upcoming Event

1 Sept 2018 14:00-22:00PM	**Annual Conference 2018 – Creativity for Care (創意醫療 關顧無價)** Organiser: Hong Kong College of Health Service Executives; Chairman: Dr LIU Shao-haei, President & Ms Macky TUNG, Chairlady; Speaker(s): Dr Neale FONG & Mr Bernard Charnwut CHAN GBS, JP; Venue: Cordis Hotel Hong Kong, Mongkok	Ms Rachel YAU T: 2527 8898 Email: rachel.yau@fmshk.org
29-30 Sept 2018	**The 10th Hong Kong Allergy Convention – Personalised Medicine in Allergy** Organiser: Hong Kong Institute of Allergy; Chairman: Dr Marco HO; Venue: Hong Kong Convention and Exhibition Centre	HKAC 2018 Secretariat T: 2559 9973 F: 2547 9528 CME Point: To be applied

Certificate Course for Doctors, Midwives, Nurses, Radiographers &
Other Healthcare Professionals who preferably have a basic knowledge of obstetric ultrasound

Certificate Course on

Practical Obstetric Ultrasonography

Course No. C318 | CME/CNE Course

Jointly organised by

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Hong Kong Society for Ultrasound in Medicine

Date	Topics	Speakers
7 Aug	New algorithm in prenatal diagnosis	Dr. WC LEUNG Consultant Obstetrician & Chief-of-service, Department of O&G, Kwong Wah Hospital
14 Aug	Ultrasonography of early pregnancy complications including scar pregnancy	Dr. Vincent CHEUNG Clinical Associate Professor in Obstetrics& Gynaecology The University of Hong Kong
21 Aug	Ultrasonography of placenta, liquor and membranes	Dr. TY FUNG Chief of Service, Obstetrics & Gynaecology Hong Kong Baptist Hospital
28 Aug	How to integrate three- and four-dimensional ultrasonography in obstetric sonography?	Dr. KY LEUNG Consultant and Chief-of-service, Department of O&G Queen Elizabeth Hospital
4 Sep	Nomogram, fetal growth restriction and macrosomia	Dr. Meliza KONG Consultant, Department of O&G United Christian Hospital
11 Sep	Tips in performing routine mid-trimester anomaly scan	Dr. CN LEE Consultant, Department of O&G Pamela Youde Nethersole Eastern Hospital

Date : 7, 14, 21, 28 Aug, 2018 & 4, 11 Sep, 2018 (Every Tuesday)
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Course Fee : HK$750 (6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org
Application form can be downloaded from website: http://www.fmshk.org

Answers to Radiology Quiz

Answer:

A large, well circumscribed, high density mass is noted at the lower inner quadrant of left breast on mammography, measuring 9cm in size. This is not associated with any microcalcifications or architectural distortion. No overlying skin thickening, nipple retraction or enlarged axillary lymph node is detected.

Further investigation with ultrasound was performed with selected images as shown below, where a huge heterogeneously hypoechoic mass is seen, consistent with the clinically and mammography detected lesion. Significant intralesional vascular flow is present.

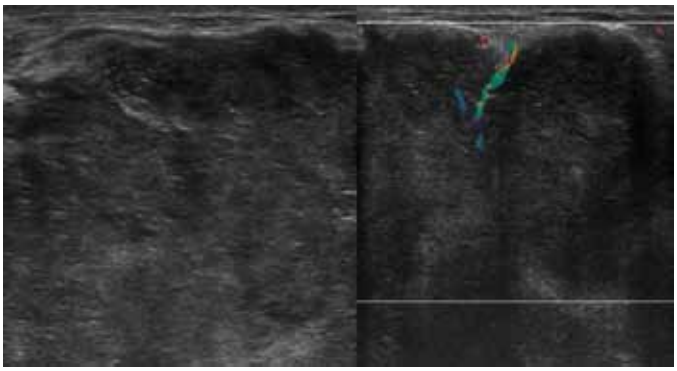

Fig. 2: Selected ultrasound images of the left breast mass.

With given history of a rapidly enlarging mass, together with the imaging findings as mentioned above, the most likely diagnosis is phyllodes tumor, with giant fibroadenoma as the major differential diagnosis.

Phyllodes tumor constitutes less than 0.3-1.5% of all breast neoplasms. In contrast to fibroadenoma, patients typically present with a painless but rapidly growing breast mass. It is a locally invasive tumor, with 5-25% of malignant degeneration. Wide surgical excision remains the treatment of choice, as they have a 15-20% recurrence rate if not completely excised.

The sonographic features of phyllodes tumor are usually non-specific and may mimic that of a fibroadenoma. Large mass with anechoic fluid-filled clefts and posterior acoustic shadow may be more suggestive of phyllodes tumor.

However most lesions are indistinguishable from fibroadenomas on both mammography and ultrasound. Therefore, core biopsy for histological correlation would be helpful, and would provide an accurate diagnosis as to whether it is benign, borderline or malignant.

References

1. Buchberger W, Strasser K, Heim K et-al. Phylloides tumor: findings on mammography, sonography, and aspiration cytology in 10 cases. AJR Am J Roentgenol. 1991;157 (4): 715-9
2. Feder JM, De paredes ES, Hogge JP et-al. Unusual breast lesions: radiologic-pathologic correlation. Radiographics. 1999;19 Spec No : S11-26
3. Wurdinger S, Herzog AB, Fischer DR et-al. Differentiation of phyllodes breast tumors from fibroadenomas on MRI. AJR Am J Roentgenol. 2005;185 (5): 1317-21
4. Dahnert. Radiology Review Manual 7th edition

Dr Grace HT NG
MBChB, FRCP
Department of Radiology, Queen Mary Hospital

As an adjunct to diet and maximally tolerated statin therapy in adult patients with **HeFH** or **clinical ASCVD**, who require additional lowering of LDL-C [1,2]

Achieves 50% LDL-C reductions[3]

The most common adverse reactions occurring in greater than or equal to 2% of Praluent-treated patients and more frequently than with placebo were nasopharyngitis, Injection site reactions and Influenza[1,2].

Achieves 61% LDL-C reductions[4]

The first PCSK9 inhibitor available in 2 starting doses that demonstrated 2 levels of LDL-C lowering[1,2,5]

ASCVD = atherosclerotic cardiovascular disease. **HeFH =** heterozygous familial hypercholesterolemia. **LDL-C =** low-density lipoprotein cholesterol. **PCSK9 =** proprotein convertase subtilisin/kexin type 9.

Praluent®
alirocumab
REDEFINING POSSIBLE

References: 1. PRALUENT 75 mg Hong Kong prescribing information. 2. PRALUENT 150 mg Hong Kong prescribing information. 3. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015;36:1186-1194. 4. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1489-1499. 5. Specialty Pharma Education Centre. Sanofi and Regeneron announce FDA approval of PRALUENT® (alirocumab) injection, the first PCSK9 inhibitor in the U.S., for the treatment of high LDL cholesterol in adult patients. Available at: http://www.specialtycme.org/2015/07/30/sanofi-and-regeneron-announce-fda-approval-of-praluent-alirocumab-injection-the-first-pcsk9-inhibitor-in-the-u-s-for-the-treatment-of-high-ldl-cholesterol-in-adult-patients/ (Accessed on 17 November 2016).

Presentation: Alirocumab solution for injection. **Indications:** Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. **Dosage:** 75 mg administered subcutaneously once every 2 weeks. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks. **Contraindications:** History of serious hypersensitivity reaction to alirocumab. **Precautions:** Hypersensitivity reactions. **Undesirable effects:** Nasopharyngitis, injection site reactions, influenza, urinary tract infection, diarrhea, bronchitis, myalgia, muscle spasms, sinusitis, cough, contusion, musculoskeletal pain, pruritus. *For other undesirable effects, please refer to the full prescribing information.* **Preparation:** 1 x 75mg/ml prefilled pen, 1 x 150mg/ml prefilled pen. **Legal Classification:** Part 1, First & Third Schedules Poison ***Full prescribing information is available upon request.*** API-HK-ALI-16.11

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THE 1ST β_3-AGONIST FOR OAB* PATIENTS
WITH PROMISING SAFETY PROFILE
PLACEBO-LIKE DRY MOUTH(1.7%) SIDE EFFECT[1]

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YOUR 1ST STEP FOR MALE LUTS+ PATIENTS
WITH PROMISING SAFETY PROFILE#
PLACEBO-LIKE DIZZINESS(1.4%) SIDE EFFECT[2]

A *FRESH* STEP IN LUTS+ MANAGEMENT

*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms
α_1-blockers are often considered the first line drug treatment of male LUTS[3]

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2013 [doi 10.1002/nau22505] **2.** Chapple C.R. et al. Eur Urol Supp. 2005; 4:33-44
3. Gravas S, et al. EAU Guidelines on the Treatment of Non-neurogenic Male LUTS. European Association of Urology. 2017.

Abbreviated prescribing information of Harnal OCAS® 0.4 mg Tablets
Version: 002 PI version: Sep 2013. **Composition:** Tamsulosin HCl **Indication:** Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). **Dosage:** 1 tab daily, can be taken independently of food. **Administration:** Swallow whole, do not chew/crunch. **Contraindications:** Hypersensitivity to tamsulosin hydrochloride or to any of the excipients. **Special warnings and special precaution for use:** As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS® 0.4 mg Tablets, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. Before therapy with Harnal OCAS® 0.4 mg Tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards. Treatment of patients with a history of orthostatic hypotension should be approached with caution. The treatment of patients with severe renal impairment (creatinine clearance of <10 ml/min) should be approached with caution, as these patients have not been studied. The treatment of patients with severe hepatic dysfunction should be approached with caution. The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administrating tamsulosin hydrochloride. **Undesirable effects:** *Common (>1%, <10%), Uncommon (>0.1%, <1%), Rare (>0.01%, <0.1%), Very rare (<0.01%). Cardiac disorder: Uncommon:* Palpitations. *Gastrointestinal disorders: Uncommon:* Constipation, diarrhoea, nausea, vomiting. *General disorders and administration site conditions: Uncommon:* Asthenia. *Nervous systems disorders: Common:* Dizziness (1.3%). *Uncommon:* Headache. *Rare: Syncope. Reproductive system and breast disorders: Common:* Ejaculation disorders. *Very rare:* Priapism. *Respiratory, thoracic and mediastinal disorders: Uncommon:* Rhinitis. *Skin and subcutaneous tissue disorders: Uncommon:* Rash, pruritus, urticaria. *Rare:* Angioedema. *Vascular disorders: Uncommon:* Orthostatic hypotension. ***Post-marketing experience:*** The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency: visual disorders (e.g. blurred vision, visual impairment), dermatitis exfoliative, erythema multiforme and epistaxis. During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported. **Full prescribing information is available upon request.**

Abbreviated prescribing information of Betmiga® prolonged-release tablets
Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with - Hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m2) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

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