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Cardiology

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- ↓ 26% HF mortality[1]
- ↓ 17% CV mortality[1]
- ▶ Improves ejection fraction[2]
- ▶ Reverses cardiac remodeling[2]

on top of ACEI & β -blocker

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1. Swedberg K, Komajda M, Böhm M, et al. *Lancet*. 2010;376(9744):875-885.
2. Tardif JC. et al. *Eur Heart J*.2011, doi:10.1093/eurheartj/ehr311

Contents

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The Cover Shot

Buddha's Heart

The path to inner harmony and peace is to embrace the purity of your heart.

The photo is taken at 內蒙賀蘭山廣宗寺 .

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Editorial

Dr. Bernard BL WONG

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Editor

Dr. Bernard BL WONG

Thank you very much to the editorial board, the Federation of Medical Societies of Hong Kong and I am more than happy to re-join the Hong Kong Medical Diary again and again as a cardiology issue editor since February 2007 and January 2009. This is really a great honour to me and my elite team of cardiologists & neurologist. In the past 3 years, because of the drive from the powerful invisible hand of the free market and the magnificent advancements in medical and interventional technologies, numerous important landmark papers have been published. A lot of real "changes" in our cardiovascular preventive, medical and interventional guidelines and daily practices have been going on and on.

In this issue, I am very happy that we have a marvelous team of practical, innovative, experienced, energetic and famous cardiologists and neurologist. Throughout the past decades, all of them, as my dearest friends and teachers, I really learned a lot from them. They are Dr. Chen Wai Hong, Dr. Lee Pui Yin Clement, Dr. Leung Tat Chi Godwin, Dr. So Yui chi Bobby, Dr. Tsang Kin Lun, Alan, Dr. Wong Wai Lun Warren and Dr. Yip Shing Biu Alex.

We are going to cover very practical topics from the disease relationship between the heart and brain to wide complex arrhythmia, from medicine to angioplasty intervention and from systolic heart failure to novel oral anticoagulant management. Our aim is to make lives easier, to simplify the confusing and difficult international updated statements and guidelines, to write them down in easy and simple points for all our dearest family practice and non-cardiology specialty colleagues.

In the middle of this "Global financial chaos", and a year of "Change", if this cardiology issue of the Hong Kong Medical Diary can in some day and some way help you and your patients to live healthier, easier and happier, then our little simple wish would be fulfilled.

Wish you and your family a wealthy, healthy and happy Summer!

"Try as you will, you cannot annihilate that eternal relic of the human heart, love."
Victor Hugo 1802-1885

For the pharmacologic treatment of recent-onset atrial fibrillation (AF)

IT'S TIME FOR RAPID CARDIOVERSION

NEW BRINAVESS® (vernakalant) for infusion

BRINAVESS is indicated for rapid conversion of recent-onset AF to sinus rhythm (SR) in adults

- For non-surgery patients: AF ≤7 days duration
- For post–cardiac surgery patients: AF ≤3 days duration

The first pharmacologic innovation in over a decade for the treatment of recent-onset AF[1]

- Rapid time to cardioversion
- Low recurrence rate at 24 hours
- Significantly more effective cardioversion than amiodarone IV ($P<0.0001$)

Selected Safety Information for Brinavess:

CONTRAINDICATIONS

- Hypersensitivity to vernakalant hydrochloride or to any of the excipients (see Inactive Ingredients).
- Patients with severe aortic stenosis, patients with systolic blood pressure <100 mm Hg, and patients with heart failure class NYHA III and NYHA IV)
- Patients with prolonged QT at baseline (uncorrected > 440 msec), or severe bradycardia, sinus node dysfunction or second degree and third degree heart block in the absence of a pacemaker.
- Use of intravenous rhythm control anti-arrhythmics (class I and class III) within 4 hours prior to BRINAVESS administration.
- Acute coronary syndrome (including myocardial infarction) within the last 30 days.

Precaution: During infusion of BRINAVESS, if a patient develops clinically meaningful bradycardia, has an unexpected drop in blood pressure, becomes hypotensive, or develops ECG changes (such as a clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischemia or infarction and ventricular arrhythmia), the administration of BRINAVESS should be discontinued and these patients should receive appropriate medical management. If these events occur during the first infusion of BRINAVESS, patients should not receive the second dose of BRINAVESS.

In clinical studies, the most commonly reported adverse reactions (>5%) seen in the first 24 hours after receiving BRINAVESS were dysgeusia (taste disturbance) (20.1%), sneezing (14.6%), and paraesthesia (9.7%). These events occurred around the time of infusion, were transient and were rarely treatment limiting.

Before initiating therapy, please consult the full prescribing information.

AVRO: A multicenter, randomized, double-blind, active-controlled, double-dummy study in patients with symptomatic AF of 3 hours to 48 hours' duration (BRINAVESS n=116, amiodarone IV n=116). The primary end point was the proportion of patients who achieved SR at 90 minutes after initiating therapy, limiting the conclusions to the effects in this time window. Amiodarone IV was given over 2 hours (ie, 1-hour loading dose of 5 mg/kg, followed by 1-hour maintenance infusion of 50 mg).

MSD

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Atrial Fibrillarion – A Guide to Clinical Practice

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Dr. Bernard BL WONG

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 2012.

We shall draw from the heart of suffering itself the means of inspiration and survival.
Winston Churchill 1874-1965

What is Atrial Fibrillation?

Definition

Atrial fibrillation (AF) a supraventricular arrhythmia with the following ECG features (Figure 1):

- Low amplitude baseline fibrillatory wave (f waves)
- Irregularly irregular ventricular rhythm
- With no medical control, the ventricular rate is typically 100-160 beats/min

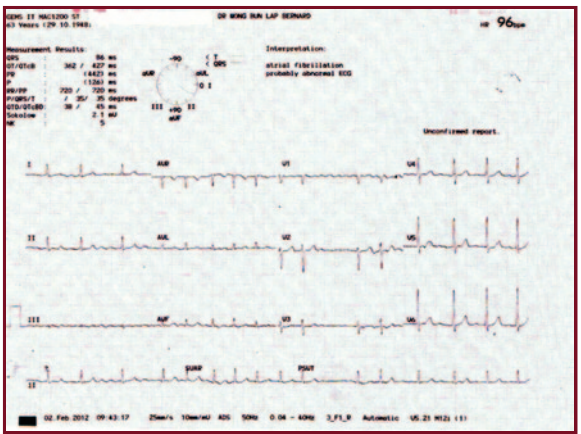


Figure 1. A 63 years old retired office lady with permanent atrial fibrillation, tachycardia cardiomyopathy under rate control by beta-blocker and digoxin

Classification of AF (Table 1)

Table 1.	
Paroxysmal AF	**AF terminates spontaneously < 7days**
Persistent AF	AF persist continuously > 7 days
Long Standing AF	AF persist continuously > 1 year
Permanent AF	Long standing AF refractory to cardioversion , accepted by doctor and patient

Lone AF:

- Patient < 60years old
- No hypertension
- No structural heart disease
- Enjoys very low risk of thromboembolic complications e.g. Stroke

Why is Atrial Fibrillation important in our daily clinical practice?

Atrial Fibrillation is a common disease

- The most common sustained cardiac arrhythmia[1,2]
- 1-2% of the general population[1]
- Over 6 million Europeans suffering[1]
- Prevalence will ↑ 2X in the next 50 years with the ageing population[1]
- Incidence of AF[2]
  - Before 40 years old → 0.1%/year
  - Age > 80 → female 1.5%/year , male 2% /year
- Life-time risk for development of AF after 40 Years old[2]
  - Male 26%
  - Female 23%
- From the above data, we can easily estimate that we have ~ 70,000 → 140, 000 AF population in Hong Kong and we have approximately a 1 out of 4 chance suffering from AF sooner or later after 40 years old

Atrial Fibrillation is a dreadful disease[3,4,5]

- The most common arrhythmic cause for hospital admission, constitutes 33% of all arrhythmia – related admissions.
- All cause mortality 2x ↑
- Risk of stroke: 5x ↑
- 20% total stroke is AF related
- The AF embolic strokes are more severe in the degree of disability, mortality and rate of recurrence
  - 30-day mortality 25%
  - 1 year mortality 50%

What are the causes of atrial fibrillation? (Table 2)

Table 2.	
Hypertension*	Left ventricular hypertrophy* Left atrial dilatation*
Ischaemic heart disease*	Acute coronary syndrome* Chronic stable ischaemic heart disease*
Valvular heart disease*	Mitral stenosis*
Cardiomyopathy	Hypertrophic cardiomyopathy (HCM)* Dilated cardiomyopathy (DCM) Restrictive cardiomyopathy e.g. Amyloidosis
Pericarditis	Acute or chronic
Pulmonary hypertension	
Systemic causes	Hyperthyroidism*
Neoplasm	Cardiac tumours Tumours secondary to pericardium
Acute causes	Excessive alcohol intake* Open heart, thoracic surgery, acute coronary syndrome*, pericarditis, myocarditis, pulmonary embolism

* common causes

When you fish for love, bait with your heart, not your brain.
Mark Twain 1835-1910

What are the clinical features of Atrial Fibrillation?

The clinical course of AF

Silent paroxysmal AF → perisistent AF → Long standing persistent AF → Permanent AF

The clinical presentations also vary from asymptomatic to severe symptoms and disabling symptoms. The treatment is also changing throughout the course.(Figure 2) [1]

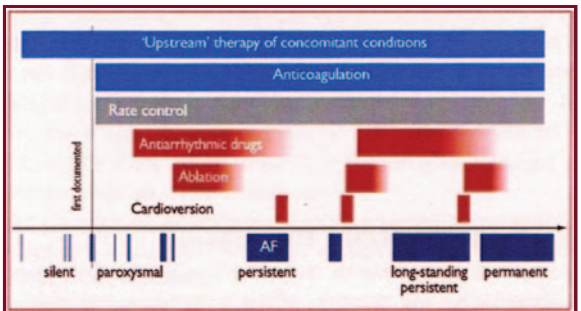


Figure 2. Natural clinical course of AF

Clinical course (Deep Blue)
Treatment modality

- Light Blue: proven improvement in hard outcomes e.g. Stroke , heart failure
- Red: for symptom management at this juncture, but there is accumulating evidence that outcome improvement may be possible in the future.
- Grey: symptom management, may improve clinical outcome.

Asymptomatic patients

25% AF patients are asymptomatic, for them, AF is a real silent killer!

For patients have one or more of the following characteristics, they are more likely to be asymptomatic:

- Persistent AF in
- sedentary,
- elderly patients

Symptomatic patients

For the other 75% symptomatic patients, they are suffering from :

Common symptoms

- Palpitations
  - common in paroxysmal AF
- Heart failure
  - Fatique
    - Exercise intolerance
  - Dyspnoea
    - exertional,
    - paroxysmal nocturnal
- Polyuria
  - Particularly after AF attack → atrial stress ↑ → atrial natriuretic hormone release
- Syncope
  - During the termination of AF attack in sick sinus syndrome (SSS) patient → a delay in the resumption of sinus rhythm → Sinus pause → syncope
- Stroke
  - Major severe stroke
  - Minor stroke /Transient ischaemic attack
  - Multiple infarct state
    - Vascular dementia
    - Vascular parkisonism

Common signs

- Irregularly irregular pulse
- Apical & radial pulse deficit
  - Variation in beat to beat left ventricular output → not every pulse is palpable in the radial artery → Apical pulse rate > radial pulse rate
  - For AF patient, auscultation of apex beat is a more accurate heart rate measurement
- Irregularly irregular jugular venous pulsations
- Variable intensity of heart sound
- Lower limb oedema

I know in my heart that man is good. That what is right will always eventually triumph. And there's purpose and worth to each and every life.
Ronald Reagan (1911-2004)

How to diagnosis and investigate Atrial Fibrillation?

History

- When was the first onset?
- Is it paroxysmal /persistent?
- What are the triggers e.g. coffee, tea, emotion, exertion, alcohol?
- When is the common palpitation time? e.g. day/ night.
- What is the severity, with reference to the EHRA Score? (Table 3)

Table 3. European Heart Rhythm Association (EHRA) Score [1]	
EHRA Class	
I	Asymptomatic
II	Mild symptoms, normal daily activity not affected
III	Severe symptoms, normal daily activity affected
IV	Disabling symptoms, normal daily activity discontinued

- Smoker/Drinker?

Physical examination
- What is the current rhythm?
- Any heart failure symptoms? e.g. JVP, oedema, lung base crepitations
- Any signs of valvular problems ? e.g. mitral stenosis

CXR
- Any pulmonary disease?

ECG
- What is the current rhythm?
- Any evidence of structural and ischaemic heart disease?

Blood
- Fasting lipid profile,
- Fasting blood sugar, HBA1C
- Thyroid function test
- Base line complete blood picture, coagulation profile, liver and renal function tests

Urine
- Protein
- Microalbuminuria (MAU)

Echocardiogram
Transthoracic Echocardiogram (TTE)
- What is the left atrial size?
- What is the left ventricular size and function?
- Any left ventricular hypertrophy?
- Any evidence of structural, valvular & ischaemic heart disease?

Trans-oesophageal Echocardiogram (TEE)
- In case of recent onset AF > 48 Hours or uncertain period,→
- to detect for left atrial appendage thrombus→
- If no thrombus detected → full anticoagulation by heparin/low molecular weight heparin →
- Electrical /pharmacological cardioversion

Treadmill Stress ECG examination
- Any evidence of ischaemic heart disease?
- Is the AF stress induced?

Holter
- For the evaluation for
  - daily occurring paroxysmal AF attacks
  - The length of ventricular pause in patients with paroxysmal AF attacks and sick sinus syndrome
  - The range of ventricular rate for persistent, prolonged and permanent AF

Event recorder
- For the evaluation of paroxysmal AFs which only have 1 attack in weeks

CT coronary angiogram
- For the delineation of the site and extent of coronary artery disease

MRI scan
- Perfusion scan
  - To delineate the thickness and extent of myocardial ischaemia
- Structure scan
  - To delineate and confirm structural heart disease

Nuclear myocardial perfusion Scan
- To delineate the severity & extent of myocardial ischaemia and viability

Love is of all passions the strongest, for it attacks simultaneously the head, the heart and the senses.
Lao Tzu ~ 640BC, Zhou dynasty

How to manage Atrial Fibrillation?

Acute Atrial Fibrillation – Rate & rhythm management
Acute management
The first question to answer → Is the patient stable or not?

- Haemodynamically unstable patients
  - Tachycardia
    - electrical cardioversion
    - Biphasic defibrillators have better efficacy than monophasic defibrillators
    - 150 → 200J then followed by 360J
    - ~ 95% success rate in recent onset AF
    - Associated with 1-2% thromboembolic risk
    - Ibutilide, amiodarone, sotalol, flecainide and propafenone pre-treatment increase the success rate

    or
    - IVI Verapamil (Isoptin) (0.0375-0.15mg/Kg over 2 min), metoprolol(Betaloc) (2.5-5mg bolus over 2 mins, up to 3 doses) or esmolol (50-200ug/Kg/min) for rate control (Target ventricular rate: 80-100bpm)
  - Bradycardia
    - Temporary pacing
    - Atropine 0.5-2mg IVI
- Haemodynamically stable patients

- If the patient is stable→ the second question to answer → Which way are we going for? rate or rhythm control pathway ?
  - **Rhythm control** – try to cardiovert (Electrical, Medical, Ablation) and keep patient in sinus rhythm as much as possible
  - **Rate control** – Try to control the resting ventricular rate at a target of ~ < 110bpm or lower < 80bpm (medication and or AV nodal ablation + pacemaker implantation) until asymptomatic, without an attempt for cardioversion to sinus rhythm (AFFIRM , RACE II study 2010')[7,8]
- **AFFIRM study 2002'** [7]
  - 4060 patients
  - Rhythm vs rate control
  - Mean age 70
  - AF for 6 hours to 6 months
  - Follow-up for 5 years
  - No significant difference in total mortality, stroke, quality of life
  - Rhythm control arm resulted in significantly more
    - Hospitalisation (80 vs 73%)
    - Adverse drug effects e.g. torsades de pointes (0.8 vs 0.2%)
- With the analysis of AFFIRM and other trials namely PIAF 2000', RACE 2002', STAF 2003', HOT CAFÉ 2004 & AF-CHF 2008, the following table can help us in determining which is the best way for our individual patients. (Table 4)

Table 4. The choices of Rate control vs Rhythm control

Suggested Candidate for Rate Control	Suggested candidate for Rhythm control
≥65 Yrs old	<65 years
Asymptomatic (EHRA I)	Symptomatic(EHRA II-IV)
History of failed cardioversion (Medical / Electrical)	No history of cardioversion (Medical /Electrical)
Long standing AF (Persistent AF > 1 Year)	Persistent AF < 1 year
Left atrial diameter > 5.0cm	Normal left atrial diameter
Sedentary life-style	Active life-style

- Rhythm control – try to cardiovert and keep patient in sinus rhythm as much as possible
  - Onset < 48 hours
    - No structural Heart Disease (No ischaemic heart disease & left ventricular dysfunction)
      - flecainide
      - propafenone
      - ibutilide
    - With Structural Heart Disease (Ischaemic Heart disease &/or Left ventricular dysfunction)
      - Amiodarone (Table 5)
    - A new hope!
      - →Vernakalant (Brinavess) (to be marketed in HK Summer 2012) (See below)
  - Onset > 48 Hours (or exact onset time cannot be sure)
    - Po Anticoagulation 3 weeks (Target INR 2.0-3.0) → Electrical/medical cardioversion or
    - Trans-oesophageal Echocardiography (TEE) → left atrial thrombus excluded → Heparin / Low Molecular Weight Heparin (LMWH) anti-coagulation → Electrical/medical cardioversion, then
    - Keep PO anticoagulation for 4 more weeks (Target INR 2.0-3.0)
  - Long term anti-arrhythmic medication for the prevention of AF recurrence
    - please refer to the next section "Long term management of atrial fibrillation"
  - Long term systemic embolisation & stroke prophylaxis
    - please refer to the next section "Long term management of atrial fibrillation"

- Vernakalant – A new anti-arrhythmic drug (will be on-market in Summer 2012)
  - Mechanism
    - Prolong atrial refractoriness
    - Rate –dependly slow impulse conduction

Table 5. Drugs Recommended for Medical cardioversion

Drug	Dose IVI	Dose PO	Efficacy for short AF duration (< 24 hours)	Conversion time (Mean)	Side Effects
Flecainide	2mg/Kg IV over 10mins	200-300mg PO	~ 62-92%	IV< 1 hour	Not suitable for Structural heart disease. Prolong QRS & QT interval. May convert AF → A. Flutter → 1:1 AV conduction → Ventricular rate↑.
Ibutilide	1mg IV over 10 mins Then after waiting for 10 mins 1mg IV over 10 mins		~ 50%	~ 30mins	Prolong QT interval → torsades de pointes. Bradycardia.
Propafenone	2mg /Kg IV over 10min	450-600mg PO	~ 41-91%	IV 30min → 2Hrs PO 2-6 hrs	Not suitable for Structural heart disease. Prolong QRS interval. May convert AF → A. Flutter → 1:1 AV conduction → Ventricular rate↑.
Amiodarone	5mg /Kg Over 1 hour Then 50mg /hour IV infusion		~ 80-90%	IV 4-6 Hours	Phlebitis BP↓ Bradycardia Long term use may cause retropertoneal fibrosis, pulmonary fibrosis & thyroid disorder

- By blocking Ito, IKur, IKr, IK-Ach & late Ina ion channels

- **Indication**
  - Non-cardiac- surgical patients – AF ≤7days
  - Post –cardiac surgical patients- AF ≤3days

- **Usage**
  - 3mg/Kg IV over 10mins
  - Observe for 15mins, if still in AF
  - 3mg/Kg IV over 10mins (Second and final dose)
  - Can be followed by electrical cardioversion if needed
- **Efficacy – much better than Amiodarone!**
  - IN AVRO Study(Active – controlled, multi-centre, superiority study of Vernakalant injection versus amiodarone in subjects with Recent Onset Atrial Fibrillation)[6]
    - Conversion from AF→ Sinus Rhythm
      - Vernakalant 51.7% vs Amiodarone 5.2%
    - Mean time for conversion in responders = 11 minutes

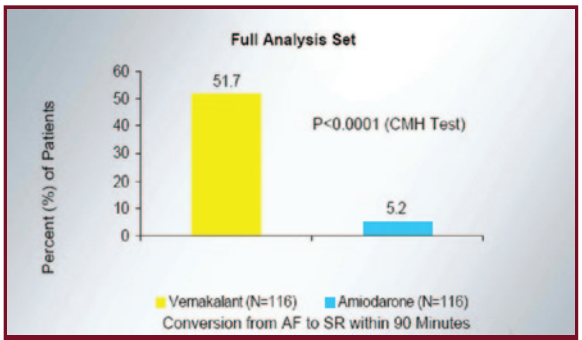


Figure 3. Primary Endpoint AVRO Study

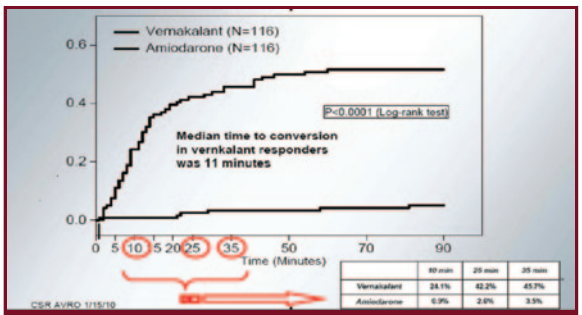


Figure 4. Secondary Endpoint AVRO Study

- Contraindications
  - Systolic BP < 100mmHg
  - Severe aortic stenosis
  - Severe heart failure (NYHA III & IV)
  - Acute coronary syndrome (ACS) < 30 days
  - QT prolongation
- Precautions
  - Ensure adequate hydration
  - Cardiac rhythm and haemodynamic monitoring indicated
- **Rate control** – Try to control the ventricular rate at a target of ~ < 110bpm or lower < 80bpm until asymptomatic, without an attempt for cardioversion to sinus rhythm (Table 6)

Table 6. drug for rate control

Beta-blockers	IVI	PO	Note
Metoprolol	Metoprolol tartrate (Betoloc)2.5-5mg IVI over 2 min, up to 3 doses	Metoprolol Succinate (Betaloc Zok) 100-200mg QD	Good for patients with heart failure, ischaemic heart disease
Bisoprolol (Concor)	-	2.5-10mg QD	As above
Esmolol	50-200ug/Kg/min	-	As above
Carvedilol (Dilatrend)	-	3.125-25mg BD	As above
Calcium Channel Blocker (Non-dihydropyridine)	**IVI**	**PO**	-
Verapamil	0.0375-0.15mg/Kg	40mg BD ->360mg (ER) QD	-ve ionotropic, not for patients with heart failure
Diltiazem	-	60mg tds -> 360mg (ER) QD	As above
Digitalis glycosides	**IVI**	**PO**	-
Digoxin	0.5-1mg	0.0625-0.5mg QD	Good for resting heart rate control, but not during exercise. Improve hospitalisation rate in patients with heart failure.(16) May increase in mortality in patients without heart failure(17)

- What is the exact optimal heart rate for patients in AF? Are there any good data available?
  - AFFIRM study 2002'[7]
    - At rest 60-75bpm
    - Mild to moderate exertion (brisk walking) 90-115bpm
    - Strenuous exercise 120-160bpm
    - Monitor by treadmill exercise stress test and 24 hour Holter
  - Rate Control Efficacy in permanent atrial fibrillation (RACE II study 2010')[8]
    - 614 patients
    - Lenient rate control resting heart rate < 110bpm vs Strict rate control, resting < 80bpm, with an adequate increase in heart rate upon exertion
    - No significant difference in cardiovascular death, heart failure hospitalisation, stroke, systemic embolism, bleeding and life-threatening arrhythmic events
    - No significant difference in symptoms, and quality of life
    - More hospital admissions in the strict control group
  - So with the analysis of the above 2 studies, my conclusion is
    - **Try to control the resting ventricular rate at a target of < 110bpm**
    - **or lower to < 80bpm until asymptomatic**

I think there is only one quality worse than hardness of heart and that is softness of head.
Theodore Roosevelt 1858-1919

Long term Management of Atrial Fibrillation

Rate control vs Rhythm control (medical and interventional)

- **Rhythm Control (once the patient is in Sinus rhythm now, what next?)**
  1. Since there is no survival benefits for rhythm control over rate control, and the anti-arrhythmic medications are not side-effect free the following principles must be observed:
     - Decisions must be made with patients' agreement
     - Treatment must be targeted at symptom control
     - Safety considerations are more important than efficacy considerations
     - If symptomatic AF recurs within 6 months of cardioversion, rhythm control can be considered
     - If one drug is not working, we can try another one
     - Be realistic, you can continue the same medication if it can delay or limit the AF recurrence to 1 episode per season, or better still, up to one year
     - If patient remains symptomatic, AF ablation is a choice (see below)
  2. Medications
     - The most effective medication - most drugs with ~ 50-60% efficacy in AF recurrence reduction except the following 2 drugs
       - Amiodarone (Class III) - ↓60-70 % more AF recurrence than sotalol[9]
       - Dronedarone (Class III) less side –effects and a bit less effective than amiodarone(36.5 vs 24.3% AF recurrence in 6 months, DIONYSOS Trial 2009')
     - The choice for an otherwise normal heart (without heart failure and Ischaemic heart disease
       - Flecainide (Class IC)
       - Propafenone (Class IC)
       - Sotalol (Class III)
       - Dronedarone (Class III)
     - The choice for patients with heart failure &/ or ischaemic heart disease
       - Amiodarone (Class III)
     - Dronedarone (Multaq) – our newest weapon in the market (since 2011')
       - Class III
       - Dose 400mg BD
       - No more iodine side-chain→ no increase in thyroid and pulmonary side effects (better than amiodarone)
       - Efficacy just a bit weaker than amiodarone[9]
       - 26% reduction in CV hospitalisation
       - 29% reduction in CV mortality
       - 34% reduction in stroke[11] (ATHENA 2009')
       - Increase mortality in patients with heart failure - same problem with Class IC agent (ANDROMEDA 2008')[12]
       - In patients with high risk permanent AF (Permanent AF > 6 months & and risk factors for major cardiovascular events) →↑combined end point of stroke, myocardial infarction, systemic embolism or death. (PALLAS 2011')[13] Figure 5

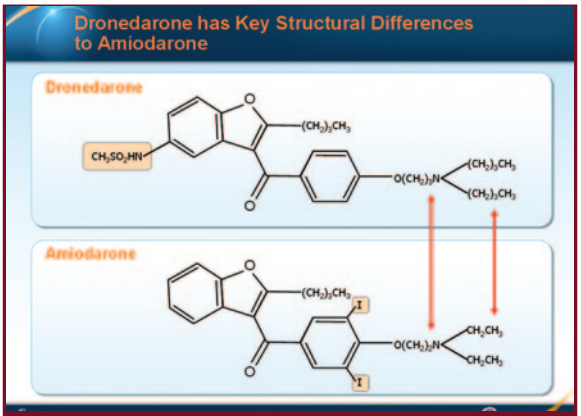


Figure 5.

3. Catheter Ablation (Figure 6)

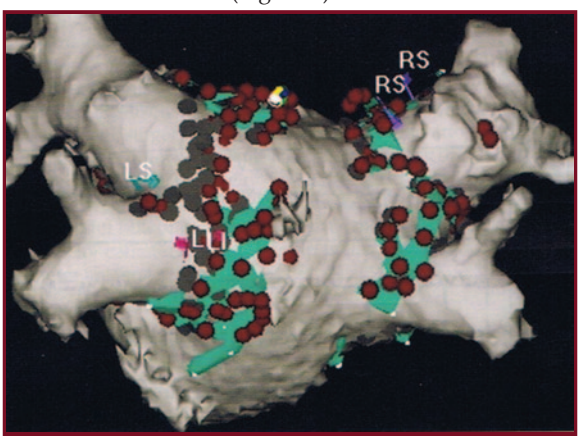


Figure 6. Combined electroanatomical map with CT scan during catheter ablation of left atrium. The red and green tags are the energy delivered ablation site. RS: Right superior pulmonary vein, LS= Left superior pulmonary vein, LI: Left inferior pulmonary vein.

1. A Catheter based technique
2. Indication :
   - Symptomatic paroxysmal AF that is uncontrolled with anti-arrhythmic agent (ACC/ AHA- class I 2001', ESC Class IIa 2010') [1,14]
3. How to choose the best candidates:
   - Symptomatic paroxysmal AF that is uncontrolled with at least one anti-arrhythmic agent tried
   - Quality of life affected by AF
   - Normal or near normal left atrial size
   - Persistent/long standing AF for not more than 4 years
   - Younger patients
4. Navigation in the left atrium by electromagnetic 3-D navigation system and or combining the images from MRI or CT scan (Figure 6)
5. Target:
   - Electrical isolation of pulmonary vein (the most important site in triggering and maintaining Paroxysmal AF)
   - Extended ablation (to reduce the AF recurrence rate)
     - Linear ablation of left atrial roof
     - Mitral isthmus
     - Cavotricuspid isthmus..etc
6. The delivery of ablation energy

- Traditional : point by point delivery of Radiofrequency energy
- New techniques:
  - Simultaneous delivery of energy to multiple points by the same catheter
  - Cryoballoon, laser balloon, high-intensity focused ultrasound balloon → Pulmonary vein circumferential ablation

7. End point:
   - Pre-ablation cardioversion and the completion of planned ablation sites
   - Step by step ablation until cardioversion achieved
8. Adverse effects
   - Tamponade 1.2%
   - Pulmonary vein stenosis 1.3%
   - Cerebral thromboembolism 0.94%
   - Atrioesophageal fistula < 0.1% (fatal complication)
   - Mortality 0.1%[18]
9. What is the prognosis:
   - Similar to previous studies, with highly selected candidates in major ablation centres, a recent meta-analysis : Ablation vs medical therapy : 77% vs 52% 1 year succes rate in keeping patients in sinus rhythm.
   - No significant mortality benefit nor systemic thromboembolism improvement over medical therapy was proved.

- **Rate Control**
  - Details on management and monitoring similar & please refer to the previous session on Acute Management, Rate control
  - For medications, please refer to Table 6
  - Radiofrequency Atrio-ventricular node (AVN) Ablation + pacemaker implantation
    - AVN ablation → blocked all the AF signals from reaching the ventricles → regular ventricular pacemaker rhythm as programmed
    - For patients with symptomatic AF and not good ablation candidates
      - Permanent AF with rapid ventricular rate despite of medication +/- tachycardia cardiomyopathy
        - Improved left ventricular systolic function
        - Improved quality of life & functional capacity
    - Life- long pacemaker dependency
    - No Atrio-ventricular synchrony can be achieved as in rhythm control pathway
    - Relatively simple procedure, very high success rate > 98%

Are you bored with life? Then throw yourself into some work you believe in all with all your heart, live for it, die for it, and you will find happiness that you had thought could never be yours.

Dale Carnegie 1888-1955

Stroke – systemic embolisation prevention – Anticoagulation

- Point to note:
  1. The embolisation risk (stroke risk) is similar for all types of AF, including Paroxysmal, persistent, long-standing and permanent AF.
  2. The old anticoagulant, Warfarin is still a must for all patients with mechanical heart valves
  3. For AF patients with Warfarin (without a mechanical heart valve), the optimal INR range is 2.0-3.0
  4. Some authorities suggest a lower range of INR in the elderly, 1.8-2.5, but there are no large trial evidence base data available for support.
  5. For INR 1.5-2.0 → cohort data showing that stroke rate is 2 fold more than the suggested range of 2.0-3.0 and therefore, is not recommended.
  6. As the new anticoagulants available on the market (Dibigatran, Rivaroxaban, Apixaban), with a better bleeding profile and similar or better stroke prevention efficacy, the indication of oral anticoagulant will be much wider and deeper than the current guidelines (ESC 2010'[1], ACCF, AHA, HRS 2011'[19] in the near future.
  7. In my clinical practice, Warfarin is near totally replaced by Dabigatran (Pradaxa) and Rivaroxaban (Xarelto) except for the small numbers of patients with mechanical heart valves.
  8. For more details of the old & new anticoagulants, please kindly refer to the superb, cutting-edge article by my colleague, Dr. Chen Wai Hong, in this same issue.
- For the prescription of stroke prevention, there is a simple 3 steps rule to follow
  1. The assessment of annual stroke risk by the CHA2DS2 VAS score [20]
     - CHA_2DS_2 VAS score table

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥75	2
Diabetes Mellitus	1
Stroke/TIA/Thrombo-embolism	2
Vascular disease (prior myocardial infarction, Peripheral arterial disease, aortic plaque,)	1
Age 65-74	1
Female sex	1
Maximum Score	9

- Adjusted stroke risk according to the CHA2DS2 VAS score

CHA2DS2 VAS score	Adjusted stroke rate (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

2. The prescription of antiplatelet or anticoagulant as stated by the ESC 2010' guideline (to me, this is the most user friendly guideline)

CHA2DS2 VAS score	Recommended therapy
≥ 2	Oral anticoagulant *1
1	Oral anticoagulant or aspirin 75-325mg QD (Preferred : OAC rather than aspirin)*2
0	Either aspirin 75-325mg QD or no treatment (preferred no treatment)*3

*1 Warfarin, Dabigatran (Pradaxa) or Rivaroxaban (Xarelto)
*2 In elderly, the bleeding rate of aspirin is similar to Warfarin, oral anticoagulant preferred[22]
*3 In elderly, the bleeding rate of aspirin is similar to Warfarin , with efficacy unknown in this group, so no treatment was preferred.

3. Discuss with patient and family members for the chance and monitoring of bleeding with the most updated data available including the HAS-BLED bleeding risk score

Letter	Clinical characteristic	Points awarded
H	Hypertension (SBP > 160mmHg)	1
A	Abnormal renal (Cr ≥ 200umol/L) and liver function (Bilirubin > 2X upper limit normal & ALT/AST/ALP > 3x upper limit of normal) (1 point each)	1 → 2
S	Stroke	1
B	Bleeding (bleeding diathesis, anemia)	1
L	Labile INR (poor time in therapeutic range < 60%)	1
E	Elderly > 65 years	1
D	Drugs or Alcohol (1 point each) (concomittent NSAID, Aspirin usage or Alcohol abuse)	1→ 2
	Maximum	9 points

Score	Risk	Bleeding risk per year %
0	Low risk	1.02
1	Low risk	1.13
2	Low risk	1.88
3	High risk	3.74
4	High risk	8.70
5	High risk	12.50
6	High risk	12.50
7	High risk	12.50
8	High risk	12.50
9	High risk	12.50

- A score of ≥ 3 indicated "high bleeding risk", careful monitoring for bleeding needed.[21]

- Warfarin
  - Approved for human use in the year 1954
  - Target INR 2.0-3.0 (narrow therapeutic range)
  - Need to monitor INR every 4-8 weeks
  - Interact with a lot of food, health food, herbs and medications (Figure 7)
  - Stroke reduction ~ 67% [23]
  - Mortality reduction ~ 26% [23]
  - Bleeding rate not negligible (refer to HAS-BLED Score above)
  - Not a user friendly drug → Usage rate remain low for AF patient (≤50%)

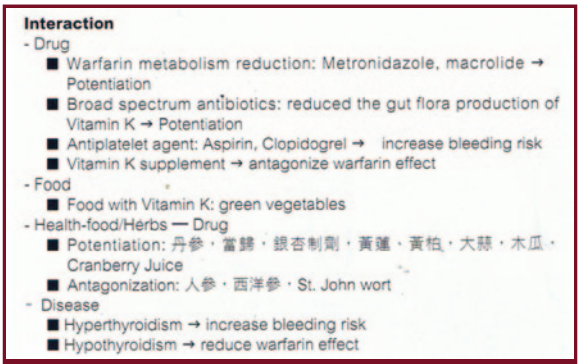
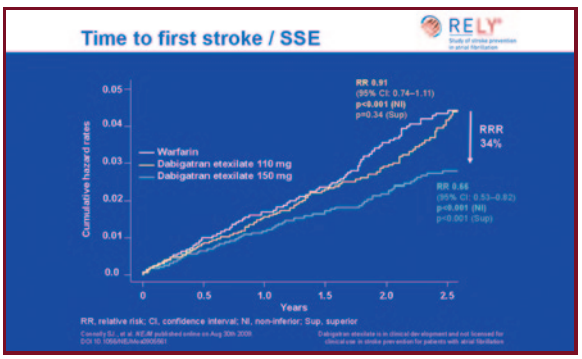
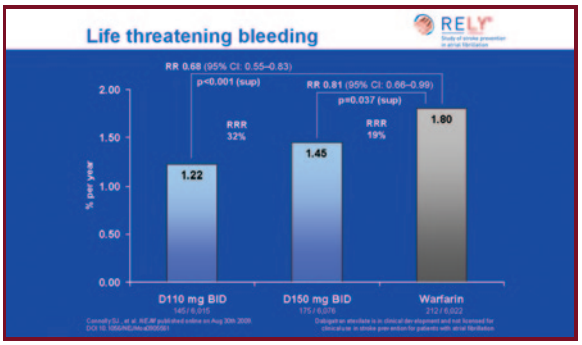


Figure 7. Warfarin interaction

- Dabigatran (Pradaxa)(RELY 2009')[24]
  - A new direct thrombin inhibitor
  - On market since 2010'
  - Low drug- drug, drug –food, drug-herbs interaction
  - No need to titrate
  - No need to monitor by blood taking
  - RELY Trial 2009
    - 18,113 AF patients
    - Warfarin vs Dabigatran 110mg BD & 150mg BD
    - Median follow-up period = 2 years
    - Only clinical side-effect is mild dyspepsia (11.3-11.8%), can be easily overcome by antacids/Proton pump inhibitor
    - Much more user friendly than Warfarin
    - The efficacy & side effect of Pradaxa is better than Warfarin in various dosages

Dabigatran	110mg BD	150mg BD
Stroke prevention	Similar to Warfarin	Better than Warfarin
Severe bleeding risk	Better than Warfarin	Similar to Warfarin





- Rivaroxaban (Xarelto) (ROCKET –AF 2011')
  - Oral Factor Xa inhibitor
  - On market since 2012'
  - Low drug- drug, drug –food, drug-herbs interaction
  - No need to titrate
  - No need to monitor by blood taking
  - Much more user friendly than wWarfarin
  - ROCKET –AF 2011'
    - 14, 264AF patients
    - Warfarin vs rivaroxaban 20mg QD
    - Median follow-up period 590days
    - Stroke prevention –non-inferior to Warfarin
    - Less intracranial hemorrhage than Warfarin (0.5% vs 0.7%, P=0.02)

Apixaban

- Oral Factor Xa inhibitor
- Not yet on market
- Low drug- drug, drug –food, drug-herbs interaction
- No need to titrate
- No need to monitor by blood taking
- Much more user friendly than Warfarin
- ARISTOTLE trial 2011' [26]
  - 18,201 AF patients with CHAD2 score 2
  - Warfarin vs Apixaban 5mg QD
  - Mean follow 1.8 years
  - Warfarin INR 2-3
  - Small but significant stroke and systemic embolism reduction(1.27% vs 1.60% per year)
  - Significant reductions in major bleeding (2.13% vs 3.09% per year)
  - Significant reductions in intracranial hemorrhage (0.33 %vs 0.80% per year)

A loving heart is the truest wisdom.
Charles Dickens 1812-1870

In a Nutshell

1. AF is one the most common arrhythmia (1-2%) of the general population.
2. It is a very dreadful disease, with a 5 times increase in stroke risk.
3. It is very easy to diagnose in most cases, simply by careful history taking, palpitation of radial pulse and followed by a simple 12 leads ECG.
4. If the presenting patient is hemodynamically unstable, various management techniques including electrical cardioversion and /or IV medical rate control or cardioversion have a very high successful rate.
5. If the presenting patient is stable, we should decide on whether our management is going for rhythm control or rate control based on the patient's characteristic and investigation data.
6. No matter which pathway we are going for, with the innovative, cutting-edge recent medical and interventional advancement, the symptoms and morbidity can be very much improved
7. For all types of AF, the annual stroke risk must be assessed by the CHA2DS2 VAS score and anticoagulant or aspirin must be prescribed as stated on the guidelines
8. The bleeding risk of oral anticoagulant must also be assessed by the HAS-BLED score and discuss with the patient and family in detail.
9. Compared with Warfarin, the new novel oral anticoagulants are more user friendly, with a better bleeding profile and similar or better stroke prevention efficacy.
10. AF, a long termed illness, good education and communication built on a solid trust between doctors and patients is the only road to success.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Atrial Fibrillarion – A Guide to Clinical Practice" 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 2012. 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. **Persistent AF is a AF persistent for more than 7 days.**
2. **AF prevalence is 1-2% of general population.**
3. **AF increase the all cause mortality by 2 times over normal population.**
4. **Hypertension and ischemic heart disease is the most common aetiology for AF.**
5. **25% of AF patients are asymptomatic**
6. **If the presenting AF patient is in a state of collapse and shock, IV medical cardioversion is the treatment of choice.**
7. **For a 75 years old patient with persistent AF > 1 year and having an enlarged heart, rhythm control is the best choice for him.**
8. **For acute rhythm control, Vernakalant is lower in potency when compare with amiodarone.**
9. **For a paroxysmal AF patient in sinus rhythm, Dronedarone (Multaq) is a more effective drug then amiodarone in keeping the patient in sinus rhythm.**
10. **Apixaban, the new noval oral anticoagulant, have a higher bleeding complication rate and lower stroke protection efficacy compared with Warfarin.**

ANSWER SHEET FOR JUNE 2012

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2012 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Atrial Fibrillarion – A Guide to Clinical Practice

Dr. Bernard BL WONG
MBBS(HK), MRCP(UK), FHKCP(HK), FHKAM(Medicine), DME(Ireland), DCH(London)

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

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

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Contact Tel No.:_____

Answers to May 2012 Issue

Psychological Characteristics of Patients with Dentofacial Deformities and Considerations for Corrective Surgery

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

DR TERENCE CHOW'S

MIND-BODY MEDICINE for DOCTORS

"The natural healing force within each one of us is the greatest force in getting well." - Hippocrates

身心醫學課程【 貳 】： 以說服力拉近醫患距離 【講者：鄒重堪醫生】

Mind-Body Medicine for Doctors by Dr Terence Chow is a 4-segment practical course designed for medical practitioners of all specialties and other healthcare workers interested in harnessing the power of the mind to positively influence physical and emotional health.

Segment Two : How to Win Friends & Influence Patients (Persuasion, Compliance & Hypnotic Language Patterns)

Following the success of the first segment "Basic Hypnosis in Clinical Practice" held in May 2012, Dr Chow will show you, in this second segment of the course, how you can be more persuasive than you think you are so that your patients, and people in general, will move in the direction you want them to go. You will learn what hypnotic language patterns are, how to shift resistance, get compliance and focus people on your agenda.

Date : 15 July 2012

Time : 10:00am – 5:00pm

Venue : Happy Valley Clubhouse, Hong Kong Jockey Club
25 Shan Kwong Road, Happy Valley, Hong Kong

Fees : HK$3,800

Enquiries : info@tyhealthcare.com

***** *Please mail the following registration slip with the remittance to us on or before 1 July 2012* *****

>>>----------<<<

TY Healthcare Corporation Ltd
B/F, 473 Hennessy Road
Causeway Bay, Hong Kong
Attn: Course Manager (Mind-Body Medicine)

Date: _____

Dear Sir,

I wish to register with Segment Two of "Mind-Body Medicine for Doctors" to be held on 15 July 2012. Enclosed please find a cheque of HK$3,800 payable to "TY Healthcare Corporation Ltd".

Name		Signature	
Email		Phone	

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- STEMI / NSTEMI / UA[1]
- On invasive or non invasive treatment[1]

International Guidelines recommended[2,3]

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*Result from Plato study – BRILINTA™ reduced CV deaths vs clopidogrel without increasing overall major or fatal bleeding but have an increase in non-CABG major & minor bleeding.
ACS= acute coronary syndrome †OAP= oral antiplatelet

More information is available upon request

Presentation: Ticagrelor 90mg film-coated tablet. Indication: Co-administered with aspirin, for prevention of atherothrombotic events in adult patients with ACS (UA, NSTEMI or STEMI); including patients managed medically and those who are managed with PCI or CABG. Dosage: 180mg single loading dose with 90mg twice daily for maintenance up to 12 months. Co-administrated with 75-150mg aspirin daily. Contraindications: Hypersensitivity to any ingredients of this product; Active pathological bleeding; History of intracranial haemorrhage; Moderate to severe hepatic impairment; Co-administration with strong CYP3A4 inhibitors e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir; Children <18 years; Pregancy and lactation. Precautions: Patients with a propensity to bleed; Patients with concomitant administration of medicinal products that may increase the risk of bleeding within 24 hours of dosing; Concomitant use of medicinal products known to alter haemostasis e.g. antifibrinolytic therapy and/or recombinant factor VIIa; Patients at risk for bradycardic events; Concomitant use of medicinal products known to induce bradycardia; History of asthma and/or COPD; Patients ≥75 years; Moderate/severe renal impairment; Concomitant treatment with an ARB; History of hyperuricaemia or gouty arthritis; Patients with uric acid nephropathy; High maintenance dose aspirin (>300mg); Co-administration with strong CYP3A4 inducers e.g. rifampicin, dexamethasone, phenytoin, carbamazepine and phenobarbital; Coadministration with CYP3A4 substrates with narrow therapeutic indices i.e. cisapride and ergot alkaloids; Patients on renal dialysis; Concomitant use of simvastatin or lovastatin ≥40mg; SSRIs e.g. paroxetine, sertraline and citalopram. Interactions: Strong and moderate CYP3A4 inhibitors e.g. diltiazem, amprenavir, aprepitant, erythromycin and fluconazole; CYP3A inducers; Medicinal products metabolised by CYP3A4; CYP3A4 substrates with narrow therapeutic indices. Undesirable effects: Dyspnoea, epistaxis, gastrointestinal haemorrhage, subcutaneous or dermal bleeding, bruising and procedural site haemorrhage. Full local prescribing information is available upon request. API.HK.BRI.1210

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Old ACS, New Drugs and Strategies

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Introduction

In 1772, Heberden had the clinical description of angina, but it took almost a century for pathologists to understand the underlying pathophsyiology. In 1879, pathologist Ludvig Hektoen concluded that myocardial infarction was caused by coronary thrombosis secondary to its sclerotic changes. In the late 1930s, people noticed there were patients with severe chest pain and biochemical evidence of myocardial injury, thus discovering the importance of unstable angina and non–ST-segment elevation myocardial infarction (NSTEMI). Patient suffering from these diseases are threefold more than those with ST-segment elevation myocardial infarction (STEMI). Among various treatments available for these patients, the use of aspirin and a platelet P2Y12-receptor antagonist continues to be a main component for medically treated patients, as well as for those patients receiving percutanous coronary intervention.[1]

Unlikely the same old aspirin which has been here for more than 100 years, there are different platelet P2Y12-receptor antagonists that one may use in different clinical scenarios in order to achieve the best benefit to risk ratio for individual patients. The following is a brief review of the efficacy and safety profile of three available P2Y12-receptor antagonists.

Platelet P2Y12-receptor antagonists

Clopidogrel (Plavix) is a thienopyridine. It was first marketed in 1998, being issued a black box warning from the Food and Drug Administration (FDA) in 2010 because an estimated 2-14% of the US patients having low levels of the CYP2C19 liver enzyme that needed to activate Clopidogrel may not get the desired drug effect (non-responder).

Prasugrel (Effient) is another member of the thienopyridine class, approved for use in Europe and the USA in 2009. Prasugrel activation does not involve oxidation by the enzyme CYP2C19.

Ticagrelor (Brilinta) is also a platelet aggregation inhibitor. The drug was approved for use in the European Union in 2010 and was approved by the US FDA in 2011. In contrast, Ticagrelor has a binding site different from ADP, making the blockage reversible, the first of its class. It needs no hepatic activation, and genetic variation regarding the enzyme CYP2C19 does not affect its efficacy.

CURRENT-OASIS 7

In the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS (CURRENT-OASIS) 7 trial, it studied over 25,000 patients with Acute Coronary Syndrome (ACS) planned for early invasive management, and the primary outcome was a composite of Cardiovascular (CV) death, Myocardial Infarction (MI), or stroke at 30 days. The study showed no significant difference between standard and double-dose Clopidogrel for the composite of CV death, MI, or stroke. Despite a significant decrease in stent thrombosis, there was no overall benefit on CV death, MI, or stroke.[2]

TRITON-TIMI 38 Trial

Prasugrel, also a thienopyridine, is in the same chemical class as Clopidogrel. It is an irreversible inhibitor of the P2Y12 receptor. In this study, over 13,000 patients with ACS planned for Percutaneous Coronary Intervention(PCI) were randomised to Prasugrel vs Clopidogrel. There was a 19% relative risk reduction in the rate of CV death, MI, or stroke over 15 months, but it does not reduce CV death alone. It primarily reduces MI. In terms of the timing of benefits, it benefits both the early and late stages in the study. For stent thrombosis, Prasegrul reduced it by half for definite or probable stent thrombosis. In diabetics, a higher 4.8% absolute difference was found, translating into treating about 21 patients with Prasugrel vs Clopidogrel to prevent a CV death, MI, or stroke over the course of 15 months. STEMI is another high risk group and at 30 days there was not only a reduction in the composite of CV death, MI, or stroke, but also significant reduction in CV death at 30 days alone, as well as a reduction in MI or stent thrombosis.

However, non-CABG TIMI major bleeding increased from 1.8 up to 2.4%. Intracranial haemorrhage (ICH) did not increased in the group as a whole. But for patients who had a history of prior stroke or transient ischaemic attack (TIA), the rate was about 2.3%, unacceptably high vs none of those treated with Clopidogrel. This has also led to its black box warning of not using the drug if there is history of prior TIA or stroke. Further analysis also revealed increased bleeding risk in elders aged 75 or older and among those with low body weight of < 60 kg.[3]

PLATO

Ticagrelor is another third-generation ADP receptor blocker. It is not a thienopyridine, not a pro-drug. It is in fact an active compound and has a very fast onset of action. It is a reversible inhibitor. In the study, over 18,000 patients presenting within 24 hours of the onset

of ACS were studied, showing a 21% reduction in CV death and similar risk reduction for all-cause mortality. There is again more non-surgical or non-CABG–related bleeding. Prior ICH is a contraindication to both Prasugrel and Ticagrelor, no matter whether it is initial ICH or secondary to an ischaemic event.

In addition, more patients had sinus pauses found during monitoring, and more patients reported the sensation of dyspnoea, increased from 7.8% to 13.8%, in excess of about 5% which had led to the concern of reducing drug compliance. But what clinical significance of these findings represents would remain uncertain until more clinical experience about the drug is available.[4]

Duration of dual antiplatelet therapy (DAPT)

Another question is how long should patients be on DAPT to get the best outcome. Meanwhile most guidelines would agree on an 12 month duration for patients with drug eluting stent (DES) placement. Prolonging Dual Antiplatelet Treatment after Grading Stent-induced Intimal Hyperplasia (PRODIGY) trial is a study of about 2013 patients trying to look at this issue, comparing 6 months of aspirin and Clopidogrel vs 24 months DAPT, and there was no difference in efficacy with that extended duration in reducing the composite of death due to any cause, MI, or stroke, but there was a consistently greater risk of haemorrhage in the 24-month Clopidogrel group according to all pre-specified bleeding definitions. So in the future, with more evidence and newer stents, the duration of antiplatelet can be shortened to further reduce the risk of bleeding which seems related to the duration of exposure. [5]

What the European and US guidelines say

According to the ESC 2011 guideline for ACS, a P2Y12 inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications, such as excessive risk of bleeding, and anticoagulants are recommended for all patients in addition to antiplatelet therapy.

Ticagrelor according to the PLATO regimen (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate to high risk of ischaemic events (e.g. increased troponin level), regardless of the initial treatment strategy, including patients previously on Clopidogrel, which should be discontinued when Ticagrelor is started. This is an IB recommendation based on the evidence that Ticagrelor is superior to Clopidogrel in PLATO concerning the reduction in mortality.

Recommendation for Prasugrel is more restrictive in the guideline due to the TRITON study. Prasugrel (60 mg loading dose, 10 mg daily) is recommended for P2Y12 inhibitor–naive patients, especially in diabetic patients undergoing PCI, unless there is a high risk of life-threatening bleeding or other contraindications.

Clopidogrel (300-mg loading dose, 75 mg daily) is recommended for patients who cannot take Ticagrelor or Prasugrel due to contraindications or relative contraindications. [6]

On the other hand, PCI guidelines from the ACCF, AHA, and Society for Cardiovascular Angiography and Interventions (SCAI) suggest a loading dose of P2Y12 inhibitor for patients undergoing PCI with stenting (600-mg Clopidogrel as loading).

Prasugrel also gets an IB recommendation but is contraindicated in patients with prior cerebrovascular events due to higher risk of bleeding. It is also not recommended in patients over 75 years old. A lower maintenance dose should be considered in patients less than 60 kg, as suggested by the FDA.

Ticagrelor also gets an IB recommendation. So in this guideline you cannot get a clear preference for which P2Y12 inhibitor to use. In terms of duration of P2Y12 inhibition after stenting, it recommends at least 12 months, with any one of the 3 available P2Y12 inhibitors. [7]

Platelet reactivity test

In the current guideline update for NSTEMI, it is the first time mentioning that a platelet function test can be done if it would affect clinical management. Clopidogrel resistance can be sub-clinical. The TRITON study showed that up to 30% of patients have inadequate response to Clopidogrel, and even doubling the dose does not bring all to the therapeutic range in GRAVITAS.

In GRAVITAS, patients with high on-treatment platelet reactivity after PCI with DES were studied, the use of high-dose Clopidogrel did not reduce the incidence of deaths from CV causes, nonfatal MI, or stent thrombosis when compared with standard-dose Clopidogrel. [8]

P2Y12 inhibition testing seems more appropriate when physicians are concerned about whether there is adequate platelet inhibition in high-risk patients, e.g. DM patients, patients with diffuse disease, multiple stents, history of stent thrombosis or poor drug compliance. And if patients are markedly under-inhibited, switching to more potent agents seems reasonable. ESC guidelines state that increasing the maintenance dose of Clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases (IIB). Genotyping and/or platelet function testing may be considered in selected cases when Clopidogrel is used. In some PCI centres, there is a point-of-care test for patients' genotypes to guide the use of anti-platelet before starting the procedure. However, there has been no study so far demonstrating that a certain point-of-care test is 100% specific and sensitive or can be correlated with the clinical outcomes.

Co-commitent aspirin doseage

To achieve the best benefit to risk ratio for ASC patients, it seems not only which P2Y12 inhibitor to use that matters, but also the co-commitent dosage of aspirin. The prescribing label for Ticagrelor calls for low-dose aspirin

as 4 curves for cumulative incidence of CV death, MI, or stroke split not only by the allocation to Ticagrelor or Clopidogrel, but also by their chronic aspirin doseage, high versus low. And best efficacy was revealed by the curve of Ticagrelor and low-dose aspirin, having lowest event rates, which mandates the need to treat patients on Ticagrelor with low-dose aspirin. [9]

Anti-platelet for Coronary Artery Bypass Graft patients

According to the 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft (CABG) Surgery, preoperative antiplatelet therapy should include:

Aspirin (100 mg to 325 mg daily) should be given to CABG patients preoperatively. For elective CABG patients, Clopidogrel and Ticagrelor should be discontinued for at least 5 days before surgery and Prasugrel for at least 7 days to limit blood transfusions. For urgent CABG patients, Clopidogrel and Ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications. For urgent CABG, it may be reasonable to perform surgery less than 5 days after Clopidogrel or Ticagrelor has been discontinued and less than 7 days after Prasugrel has been discontinued.

For postoperative antiplatelet therapy, if aspirin (100 mg to 325 mg daily) had not been initiated preoperatively, it should be initiated within 6 hours postoperatively and then continued indefinitely to reduce saphenous vein graft closure and adverse cardiovascular events. For patients undergoing CABG, Clopidogrel 75 mg daily is a reasonable alternative for patients not tolerating or allergic to aspirin.[10]

Proton-pump inhibitors and DAPT

Concerns have been raised about the potential for Proton Pump Inhibitors (PPI) to blunt the efficacy of Clopidogrel. So far the evidence did not show much harm. A randomised trial, the Clopidogrel and the Optimisation of Gastrointestinal Events Trial (COGENT), did not find any excess in CV events but showed a two-thirds reduction in Gastrointestinal (GI) ulcer or bleeding. So it seems the use of PPI can help to reduce GI bleeding in high risk patients without affecting the protection against CV events. [11]

Conclusion

Owing to the increasing burden of ACS patients, the use of DAPT will be more common. With the availability of new drugs, clinical experience and new evidence from trials, the outcome of patients can be improved by maximizing the benefit to risk ratio through individualized treatment plans: a combination of the right dose of aspirin, the appropriate P2Y12 inhibitor, the optimal duration of treatment, the correct use of platelet reactivity test, the continued monitoring of compliance and side effects and the proper reference to guidelines. The one-size-fits-all treatment would not be able to offer the best clinical outcome for every patient. The new drugs and new trials would serve as new weapons and new strategies for doctors and patients to flight this battle against ACS.

P.S. As of today, the daily costs for the drugs in a typical local pharmacy are as follows for your reference: HK$ 20 for Plavix 75mg, HK$ 22 for Effient 10mg, HK$ 34 for Brilanta 90mg BD. And a VerifyNow P2Y12 test cost around HK$ 400-850 among most local laboratories.

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The Forthcoming Major Advance in Intervention Cardiology - Bioabsorbable Vascular Scaffold

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With the proven efficacy in reducing angiographic restenosis and recurrent ischaemia necessitating repeat revascularisation, drug-eluting stents (DES) are extensively used in nowadays percutaneous coronary intervention (PCI). Despite the use of metallic coronary stents for more than two decades, cardiologists are frequently asked by patients about the longevity of these scaffolds. Also, patients might query the need to remove these small implants after certain period of time. It is understandable that patients just do not want to leave foreign bodies permanently inside their own bodies. In the foreseeable future, a drug-eluting bioabsorbable vascular scaffold (BVS) might be the answer to, if not all, some of these patients.

Background

There were significant revolutionary advances in the field of interventional cardiology in the past two decades. Metallic coronary stent was designed to support the coronary artery to prevent significant recoil which might occur within the first four months after balloon angioplasty. It also served as a mechanical skeleton to prevent acute occlusion of the artery due to dissection and, hence, it made the PCI procedure much safer to perform as reflected from the dramatic decrease in the incidence of emergency CABG surgery after PCI. However, it brought on another problem - restenosis secondary to neointimal hyperplasia (NIH). NIH resulted in approximately 30% clinical restenosis requiring repeated intervention at nine months after PCI. Restenosis might be particularly problematic in high risk populations, such as diabetic mellitus and diffuse coronary disease. DES was specifically designed to deal with the problem of restenosis. It consisted of a metallic stent platform and a polymer layer on the surface of the stent to hold a specific anti-proliferative drug. The drug would be released from the polymer in a time-dependent fashion. The drug would then prevent the uncontrolled proliferation of the smooth muscle cells and, hence, might reduce the occurrence of restenosis. DES was shown to reduce in-stent restenosis from 35% to <10% at nine months when compared with bare metal stents (BMS)[1,2].

These impressive DES results have unfortunately been tampered by the occurrence of late stent thrombosis (LST), an infrequent (0.6%/year) but potentially deadly complication[3,4]. The cause of LST was believed secondary to delayed healing and to a hypersensitivity reaction. The problem occurred only after the drug was fully released from the stent and, hence, it was thought to be a polymer-induced foreign body reaction. This has raised the awareness about the importance of the biocompatibility of permanent polymer implants and their potential role in contributing to LST. Therefore, recent focus has been on developing a biocompatible polymer and incorporating it in DES so as to minimise restenosis while improving long-term outcome by reducing risks for long-term inflammation and LST. This article will focus on a fully biodegradable stent.

Bioabsorbable Vascular Scaffold (BVS)

The fully absorbable BVS (Abbott Vascular, Santa Clara, CA, USA) is made of semicrystalline polymer called Poly-L-lactic acid (PLLA) (Figure 1). The coating consists of poly D, L-lactide (PDLLA) which has a lower crystallinity than the BVS backbone. The coating contains and controls the release of the anti-proliferative drug, everolimus, which has been extensively used in clinical practice in the Xience V / Prime platform (Abbott Vascular). Both PLLA and PDLLA are fully bioabsorbable as they will be hydrolysed and degraded into lactic acid, which is further metabolised via the Krebs cycle. The final products are carbon dioxide (CO2) and water (H2O). In a porcine coronary artery model, the stent mass would progressively decrease with time. 30% stent mass would be lost at 12 months and up to 60% by 18 months post implantation.

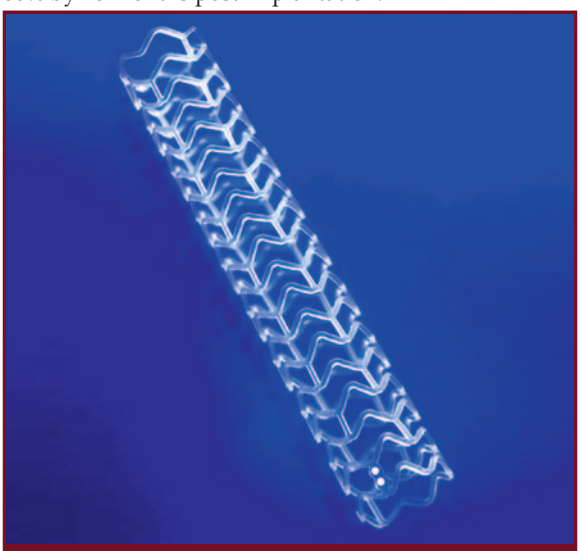

Figure 1. Bioabsorbable Vascular Scaffold (Abbott Vascular, Santa Clara, CA, USA)

Indeed, the first clinical experience with bioabsorbable

polylactide stent was reported 10 years ago[5]. The 6-month follow-up did not show any safety issue, but the restenosis rate was comparable with a BMS. Recently, 10-year long term outcome in this group of patients was reported and it showed the stent was safe out to 10 yeas with similar MACE rates as BMS6.

ABSORB trial

The ABSORB trial (A Clinical Evaluation of the Bioabsorbable Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) was a single-arm, prospective, open-label first-in-man study with safety and imaging endpoints[7]. 30 low-risk patients with simple but significant coronary artery stenosis received at least a BVS. Upon 6 month follow-up, the extent of NIH was comparable to that observed with a metallic everolimus-eluting stent. But, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) clearly documented a loss in scaffold area that resulted in higher restenosis rate if compared with a historical control[8]. Hence, it was believed the BVS was being absorbed too quickly to provide adequate scaffold to the stented artery.

However, at 2-year follow-up, IVUS and OCT demonstrated full resorption of the polymeric structs, with return of vasomotion in the scaffolded area (which would be lost in segment with a metallic stent). This reappearance of normal vasomotion suggested the presence of functionally active endothelium at the site of stent implantation.

Furthermore, IVUS and OCT showed late luminal enlargement, thinning of the vessel wall and absence of constrictive or expansive remodelling. The volumetric reduction in structs induced by bioresorption might explain this late increase in the size of the lumen. Otherwise, everolimus could exert a specific effect on the plaque to induce a reduction in plaque size between six months and 24-month follow-up.

At 2-year, in this small study, there was only one non-Q wave myocardial infarction and, hence, the rate of major adverse cardiac events (MACE) was 3.4%.

BVS revision 1.1

During the ABSORB trial, the mechanical properties of the polymeric stent were assessed. It was observed that there was more acute recoil in the BVS when compared with the Xience V stent. This suggested the mechanical properties to support the vessel wall were weaker in the BVS. Also, there was also more late recoil in the BVS in six month and this accounted for approximately two-thirds of the luminal area reduction (restenosis).

Hence, the BVS design was revised (revision 1.1). The BVS revision 1.1 used the same polymers in both the scaffold and coating as the original 1.0 design. The design change allowed more uniform struct distribution and provided greater uniform vessel wall support and drug transfer. The radial support was higher and persisted longer whereas retaining the same complete reabsorption time at two years.

ABSORB Cohort B trial

The ABSORB Cohort B trial was a multi-centre single-arm trial assessing the safety and performance of the ABSORB BVS revision 1.1 in the treatment of native coronary artery lesions[9]. In total, 101 patients were enrolled in the ABSORB Cohort B trial. It showed the degree of NIH was similar to a historical series of metallic everolimus-eluting stents. Meanwhile, there were signs of resorption as evidenced on IVUS and OCT. In addition, it confirmed the absence of late or very late recoil with this BVS revision 1.1. Similar to the first Cohort study, vasomotion was documented in the stented segment. The MACE rate at 1 year was 7.1% and was comparable to that observed in a historical series of metallic everolimus-eluting stents.

Conclusion

Metallic DES is one of the major breakthroughs in intervention cardiology as evidenced by its rapid utilisation in daily clinical practice. However, the occurrence of stent thrombosis remains a clinical concern. Furthermore, permanent metallic stenting may preclude surgical revascularisation, result in jailed side branches, eliminate reactive vasomotion and impair the non-invasive imaging of coronary arteries with multi-slice computed tomography (MSCT) and magnetic resonance (MRI). Bioabsorbable polymer DES may provide short-term vessel scaffolding combined with drug delivery capability but avoid the long-term limitations of metallic stents. However, it is still too early to suggest that BVS will replace metallic stents. Before making the recommendation, we still have to wait for the result of a large scale randomised-controlled trial comparing the BVS with the metallic stent eluting the same drug.

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CHD

22% additional RRR

of major CV events in patients with CHD (p<0.001)[4]

Highest Risk

ACS

16% RRR

of major CV events in patients with ACS (p=0.005)[5]

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Update on Pharmacological Therapies for Systolic Heart Failure

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Heart failure (HF) is complex clinical syndrome associated with significant morbidity and mortality. Recently published clinical trials have provided new information to the existing standard pharmacological therapies for chronic systolic heart failure. On the other hand, some new drugs have been shown to exacerbate HF and should be used with caution in patients with HF.

Standard Therapies (Angiotensin-converting enzyme Inhibitors, Beta-blockers)

Treatment with ACEI and beta-blockers improves ventricular function and patients' well-being, reduces hospital admission for worsening HF, and increases survival. Blockade of the renin–angiotensin–aldosterone system is the cornerstone of successful therapy for systolic ventricular dysfunction. All patients with systolic left ventricular dysfunction, whether symptomatic or asymptomatic, should be commenced on angiotensin-converting enzyme Inhibitors (ACEI) with every effort made to up-titrate to the dose shown to be of benefit in major trials[1,2]. Beta-blockers inhibit the adverse effects of chronic activation of the sympathetic nervous system acting on the myocardium. Three beta-blockers — carvedilol (beta-1, beta-2 and alpha-1 antagonist)[3], bisoprolol (beta-1 selective antagonist)[4] and metoprolol extended release (beta-1 selective antagonist)[5] — prolong survival in stable patients with current or prior symptoms of HF. This survival benefits include both reductions in sudden death, as well as death due to progressive pump failure. More recently, nebivolol (a selective beta-1 receptor antagonist with vasodilating properties) has been shown to be safe and effective in elderly patients with either relatively preserved or impaired ejection fraction[6-8] and may be an appropriate treatment in elderly patients. Chronic diuretic therapy has not been shown to improve survival and should be reserved for symptom control only. Diuretics should be used, if necessary, to achieve euvolaemia in fluid-overloaded patients. When clinical euvolaemia is achieved, the diuretic dose should be decreased to the lowest achievable dose. The dose should be regularly reassessed and adjusted according to volume status. Patients should also be monitored for hypokalaemia during treatment with a loop diuretic. The cardiac glycoside, digoxin, inhibits sodium–potassium ATPase. The only placebo-controlled trial of digoxin yielded a neutral outcome regarding mortality[9]. However, there was a reduction in hospitalisations, and patients with more severe symptoms appeared to obtain symptomatic benefits from the introduction of digoxin if they are already on optimal dose of ACEI and beta-blocker.

Aldosterone antagonists

Aldosterone receptor antagonists have been shown to provide benefits by reducing all-cause mortality and symptoms in patients with advanced HF[10] and should be used in patients with severe symptoms. Recently, a study of the selective aldosterone antagonist eplerenone (without antiandrogenic effects) in patients with systolic HF and mild (New York Heart Association [NYHA] Class II) symptoms has been shown to reduce cardiovascular mortality and hospitalisation for heart failure[11]. Aldosterone blockade should therefore be considered in patients with systolic HF who still have mild (NYHA Class II) symptoms despite receiving standard therapies. Monitoring for hyperkalaemia and renal dysfunction should be performed regularly.

Angiotensin II receptor blockers

Angiotensin II receptor blockers (ARB) can be used as an alternative for patients who do not tolerate ACEI due to cough or angioedema and they should also be considered for reducing morbidity and mortality in patients with systolic HF who remain symptomatic despite receiving ACEI.[12-13] Valsartan and Candesartan are the drugs of choice in treating HF patients. A recent study demonstrated that a higher dose of an ARB is superior to a lower dose in reducing death or admission for heart failure for patients with systolic CHF who do not tolerate ACEI.[14] These findings suggest that maximising the renin–angiotensin system blockade provides additional clinical benefits in such patients. However, ARB should not be given to patients who are treated with both ACEI and aldosterone antagonist.

Direct sinus node inhibitors

Ivabradine is a direct sinus node inhibitor which selectively inhibits the I_f ion current in the sinoatrial node. Blocking this channel reduces cardiac pacemaker activity and slows the heart rate. A study of ivabradine versus placebo has recently demonstrated improvements in terms of the primary composite end point of cardiovascular mortality and hospitalisation for HF in patients with symptomatic systolic HF, sinus rhythm

(heart rate ≥ 70 beats per min) and recent hospitalisation for HF[15]. This benefit was largely due to a reduction in hospitalisations, and was additional to patients already being on the highest tolerated dose of background beta-blocker (although only 26% were being treated with the target dose). It is therefore recommended that direct sinus node inhibition with ivabradine be considered for HF patients with impaired systolic function and a recent hospitalisation for HF who are in sinus rhythm, where their heart rate remains ≥ 70 beats per min despite efforts to maximise dosage of background beta-blocker.

Drugs to be used with caution in HF

Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced left ventricular ejection fraction (LVEF) should be avoided or withdrawn whenever possible. Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) have negative inotropic effects and can lead to worsening HF and have been associated with an increased risk of cardiovascular events. Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors can cause sodium retention and peripheral vasoconstriction and can attenuate the efficacy and enhance the toxicity of diuretics and ACE inhibitors. Thiazolidinediones (pioglitazone, rosiglitazone) can cause fluid retention and worsening of HF and are contraindicated in patients with HF.

Antiarrhythmic agents (except amiodarone) can exert important cardiodepressant and proarrhythmic effects and should be avoided in patients with HF. Dronedarone is a new antiarrhythmic agent used for treating paroxysmal atrial fibrillation. It is associated with increased mortality in patients with NYHA Class IV HF, or in those with NYHA Class II–III CHF with a recent decompensation requiring hospitalisation[16], and is contraindicated in such patients.

Some new anti-cancer drugs such as trastuzumab[17] and tyrosine kinase inhibitors such as sunitinib[18] are associated with the development of reduced LVEF and HF. Trastuzumab is contraindicated in patients with symptomatic HF or reduced LVEF (< 45%). Tyrosine kinase inhibitors should be used with caution in patients with a history of symptomatic HF or cardiac disease. Baseline and periodic evaluation of LVEF should be considered in patients treated with these agents.

On the other hand, metformin was previously considered unsafe in patients with HF. Recent analyses of patients with heart failure have shown that it is safe except in cases of concomitant renal impairment.[19]

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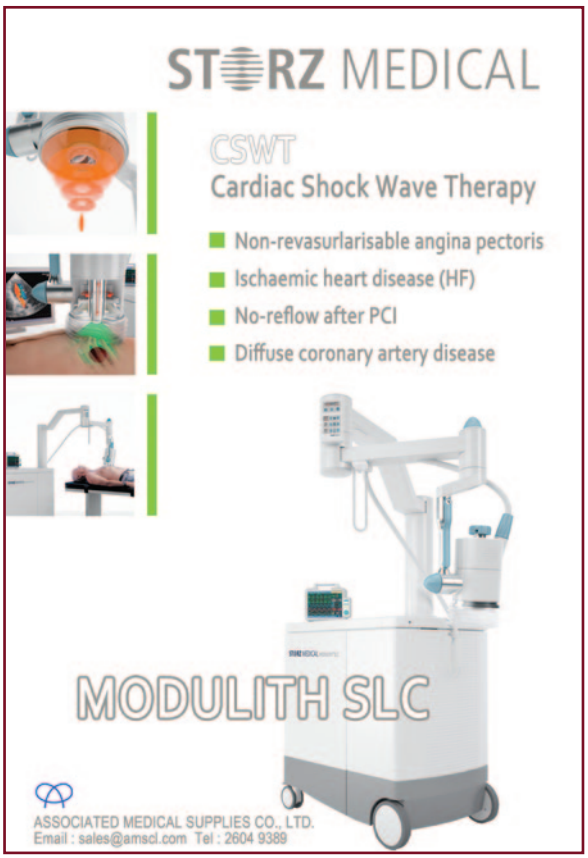

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+ Stroke or systemic embolism: dabigatran 150 mg BID (*n*=6076, no. of events=134) vs. warfarin (*n*=6022, no. of events=202).

‡ Intracranial bleeding includes adjudicated hemorrhagic stroke, subarachnoid, and/or subdural bleeding.

§ Intracranial bleeding: dabigatran 150 mg BID (no. of events=38) vs. warfarin (no. of events=90).

As with all anticoagulants, PRADAXA® should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with PRADAXA®. Should severe bleeding occur, treatment with PRADAXA® must be discontinued and the source of bleeding investigated promptly.

Patients at an increased risk of bleeding should be closely monitored clinically. A coagulation test, such as aPTT may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

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Novel Oral Anticoagulants in Atrial Fibrillation

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Introduction

Thrombosis mediates the final occlusive events of cardiovascular diseases. Thrombus formation is a complex process involving the interaction of predominantly platelets and coagulation factors. Platelets are the major player in thrombosis of the arterial circulation except cardiogenic thromboembolism in atrial fibrillation (AF), which together with venous thromboembolism are contributed principally from activation of coagulant factors. In the recent two decades we have witnessed substantial advances in antithrombotic therapy targeting platelets and coagulant factors, respectively. This article is intended to review the latest development and application of oral anticoagulants in atrial fibrillation.

Mechanisms and General Pharmacology of Novel Oral Anticoagulants

Until recently, the only oral anticoagulants available were vitamin K antagonists (VKAs), such as warfarin, which are cumbersome to use because of multiple food and drug interactions and the requirement of frequent laboratory tests for dosage adjustment, and increase bleeding risks compared with controlled therapy.[1]

The new oral anticoagulants differ from VKAs in one important aspect in blocking a single coagulant factor, instead of inhibiting multiple steps due to reduced synthesis of vitamin K-dependent coagulant factors (Fig. 1). The direct thrombin inhibitors (DTI) bind to both free and fibrin-bound thrombin and inhibit the following thrombin activities: 1) conversion of fibrinogen to fibrin, 2) activation of factors V, VIII, and IX, and 3) platelet activation. Dabigatran etexilate is currently the first DTI that is in clinical use. Upstream inhibition of the coagulation factors is also an effective means of blocking thrombin activities by reducing thrombin generation. Two factor Xa inhibitors, rivaroxabin and apixaban, have completed phase III clinical studies in different arenas of cardiovascular diseases.

Dabigatran etexilate

Some of the key pharmacological properties of dabigatran etexilate and oral factor Xa inhibitors are summarised in table 1. Dabigatran etexilate is an oral prodrug that has a 6.5% oral bioavailability and is rapidly hydrolyzsed by a serum esterase to dabigatran, which binds directly and reversibly to thrombin. Plasma levels peak at 2 to 3 hours after oral administration and the serum half-life is 12 to 17 hours. As 80% of the given dose is eliminated by the kidneys, dose reduction is required for patients with creatinine clearance (CrCl) <30ml/min. P-glycoprotein (P-gp) inhibitors, e.g verapamil and amiodarone, increase while P-gp inducers, e.g. rifampicin, cabamazepine, and phenytoin, decrease plasma concentrations. However, no dosage adjustment is recommended for use of verapamil and amiodarone in AF patients while concomitant us of rifampicin should be avoided.

No antidote or specific reversal agent for dabigatran exists at the current time. In cases of overdose, oral administration of activated charcoal to adsorb the drug from the stomach and haemodialysis to remove the drug from the blood are measures that may be effective. Although administration of coagulation factors has not been shown to reverse prolongation of laboratory coagulation abnormalities in human volunteers caused by dabigatran,[2] animal studies have demonstrated a beneficial effect of prothrombin complex concentrate (PCC) on dabigatran-induced bleeding. Therefore, PCC or recombinant factor VII may still be attempted when there is uncontrolled bleeding.

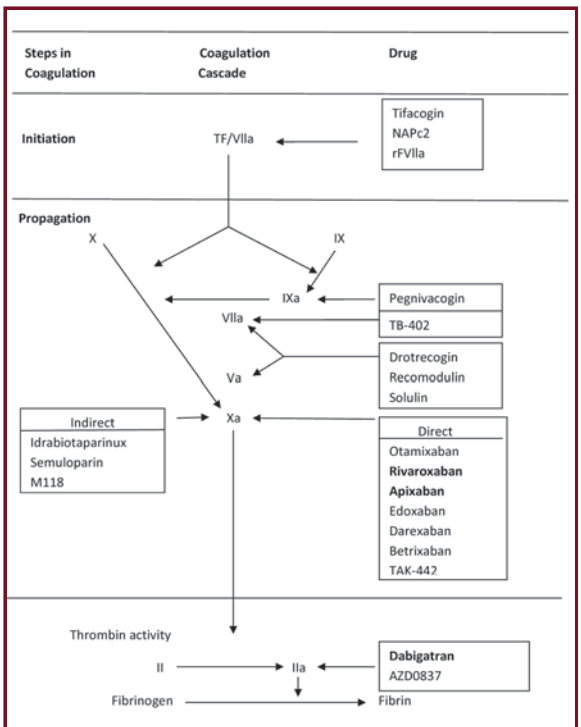

Figure 1. Coagulation Cascade and Targets of Novel Anticoagulants

Table 1. Pharmacological Properties of Oral Direct Thrombin Inhibitor and Oral Factor Xa inhibitors

	Dabigatran	Rivaroxaban	Apixaban
Target	Factor IIa	Factor Xa	Factor Xa
Oral bioavailability, %	6.5	80-100	50
Half-life, hours	12-17	5-13	8-15
Renal elimination, %	85	66	27

Rivaroxaban

Rivaroxaban is a direct and reversible oral inhibitor of factor Xa. It has an oral bioavailability of 80-100%, lower in the fasting state and higher with food. Plasma levels peak at 2 to 4 hours after oral administration and the serum half-life is 5 to 13 hours. About two-thirds of the drugs are eliminated by kidneys, half of which are inactive metabolites and the rest are unchanged. Patients with a CrCl <15 ml/min are not recommended to take the drug. Rivaroxaban undergoes hepatic metabolism via CYP3A4 -dependent and –independent mechanisms and is a substrate of P-gp. Co-administration of strong inhibitors of CYP3A4 and P-gp, e.g. azole-antimycotics (ketoconazole, itraconazole) and HIV protease inhibitors, is not recommended. Caution should be exercised in patients receiving strong inducers of CYP3A4 and P-gp, e.g. rifampicin, phenytoin, and carbamazepine.

No antidote or specific reversal agent for rivaroxaban exists at the current time. In cases of overdose, oral administration of activated charcoal may adsorb the drug from the stomach. As rivaroxaban is highly protein-bound, haemodialysis is not likely to remove the drug from the blood. Administration of PCC has been shown to correct prolongation of prothrombin time caused by rivaroxaban.[2]

Apixaban

Apixaban is another oral factor Xa inhibitor bearing a number of similarities with rivaroxaban. It exhibits direct, highly selective and reversible binding to factor Xa. It has an oral bioavailability of 50%, peak plasma levels at 3 to 4 hours, and a half-life of 8 to 15 hours. About one quarter of the administered dose is excreted unchanged in the urine and it is not recommended for patients with a CrCl <15 ml/min. Apixaban is metabolised in the liver via CYP3A4-dependent and -independent mechanisms. Co-administration of strong inhibitors of CYP3A4 and P-gp is not recommended and the drug should be used cautiously in patients receiving strong inducers of CYP3A4 and P-gp. In cases of overdose, similar considerations as for rivaroxaban apply.

Novel Oral Anticoagulants in Atrial Fibrillation

Dabigatran etexilate

The RE-LY (Randomised Evaluation of Long-Term Anticoagulant Therapy) was a prospective, randomised, open-label clinical phase III trial comparing 2 blinded doses of dabigatran etexilate (110 mg bid or 150 mg bid) with open-label, adjusted-dose warfarin targeting an international normalised ration (INR) of 2.0 to 3.0.[3] A total of 18,113 patients with nonvalvular AF and at least 1 risk factor for stroke were recruited. The mean $CHADS_2$ (C: congestive heart failure, H: hypertension, A: age ≥75 years, D: diabetes, each factor scoring 1; S: prior stroke/systemic embolism scoring 2) score was 2.1; 31.9% of the patients had 0 to 1, 35.6% of the patients had 2, and 32.5% of the patients had 3 to 6. The mean and median times in therapeutic range (TTR) for the warfarin-treated patients were 64% and 67%, respectively.

The efficacy outcome of stroke or systemic embolism was reduced from 1.69% per year in the warfarin group to 1.53% per year in the dabigatran 110 mg group (relative risk [RR] 0.91; 95% confidence interval [CI] 0.74 to 1.11; p<0.001 for noninferiority) and 1.11% per year in the dabigatran 150 mg group (RR 0.66; 95% CI 0.53 to 0.82; p<0.001 for superiority) (Fig. 2). The safety outcome of major bleeding was 3.36% per year in the warfarin group and was not different statistically from 3.11% per year in the dabigatran 150 mg group (p=0.31), but was reduced to 2.71% per year in the dabigatran 110 mg group (p=0.003) (Fig. 3). Gastrointestinal bleeding was, however, increased from 1.02% per year in the warfarin group to 1.51% per year in the dabigatran 150 mg group ((RR 1.50; 95% CI 1.19 to 1.89; p<0.001). The rate of haemorrhagic stroke was reduced from 0.38% per year in the warfarin group to 0.12% per year in the dabigatran 110 mg group (p<0.001) and 0.10% in the dabigatran 150 mg group (p<0.001) (Fig. 4). The rate of myocardial infarction (MI) was higher in the dabigatran 150 mg group than in the warfarin group; 0.74% per year vs 0.53% per year (p=0.048). A more comprehensive analysis of myocardial ischaemic events including revascularisation, unstable angina, cardiac death as well as MI revealed a nonsignificant increase in MI but not other myocardial ischaemic events.[4] Annual mortality rates were not different statistically comparing the warfarin group with the dabigatran 110 mg group (4.13% vs 3.75%; p=0.13) and the dabigatran 150 mg group (3.64%, p=0.051). The conclusions of RE-LY were that in patients with nonvalvular AF and increased risk of stroke, dabigatran at a dose of 110 mg bid achieved rates of stroke or systemic embolism similar to that of warfarin but with a lower rate of major haemorrhage. Dabigatran at a dose of 150 mg bid was associated with a lower rate of stroke or systemic embolism but similar rates of major and extracranial haemorrhage. Results of the RE-LY trial led to the approval of both doses of dabigatran etexilate for stroke prevention in AF in many countries worldwide. Unexpectedly, the U.S. Food and Drug Administration approved the 150 mg bid regimen and 75 mg bid for patients with severe renal insufficiency, both the patient group and the dosage not tested in the trial. Availability of the 110 mg regimen enables physicians to administer anticoagulation to AF patients for stroke prevention while minimising their bleeding risk especially in high-risk patients and this is commonly practised in Asian countries.[5]

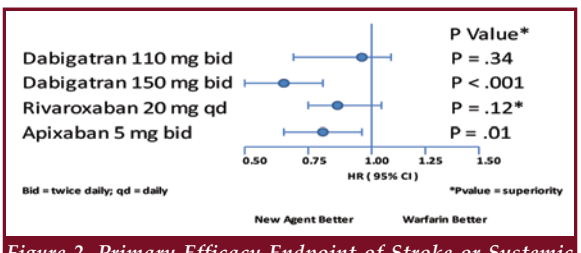

Figure 2. Primary Efficacy Endpoint of Stroke or Systemic Embolism in RE-LY, ROCKET-AF, and ARISTOTLE

Rivaroxaban

Rivaroxaban was tested against warfarin in the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation),[6] which enrolled 14,264 patients with nonvalvular AF and a $CHADS_2$ score ≥2. In this double-blind trial, patients were randomly allocated to adjusted-dose warfarin with a target INR of 2.0 to 3.0 versus rivaroxaban 20 mg qd or 15 mg qd in patients with a CrCl 30 to 49 ml/min. Patients included in this trial were at higher risk of stroke than similar trials of AF; 87% had a $CHADS_2$ score ≥3 and 55% had a history of stroke, transient ischaemic attack, or systemic embolism. The mean and median TTR for the warfarin-treated patients were 55% and 58%, respectively, and these were lower than in comparable AF trials.

In the intention-to-treat analysis, the primary efficacy endpoints of stroke (ischaemic or haemorrhagic) and systemic embolism was 2.1% per year in the rivaroxaban group and 2.4% per year in the warfarin group (hazard ration [HR] in the rivaroxaban group, 0.88; 95% CI 0.74 to 1.03; p<0.001 for noninferiority; p=0.12 for superiority) (Fig. 2). The rates of major bleeding were similar in both groups; 3.6% per year in the rivaroxaban group and 3.45% in the warfarin group (p=0.58) (Fig. 3). Major bleeding from gastrointestinal tract was more common (3.2% vs 2.2%; p<0.001). Rates of intracranial haemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0.5% vs 0.7% per year; HR 0.67, 95% CI 0.47 to 0.93; p=0.02) (Fig. 4). Annual rates of MI (0.9% vs 1.1%; p=0.12) and mortality (4.5% vs 4.9%; p=0.15) were similar in the two groups. The ROCKET-AF investigators concluded that in patients with nonvalvular AF at increased risk of stroke, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. No differences in major bleeding were identified but intracranial bleeding was less frequent with rivaroxaban. Based on the ROCKET-AF results, rivaroxaban has been approved in the US and Europe for stroke prevention in AF.

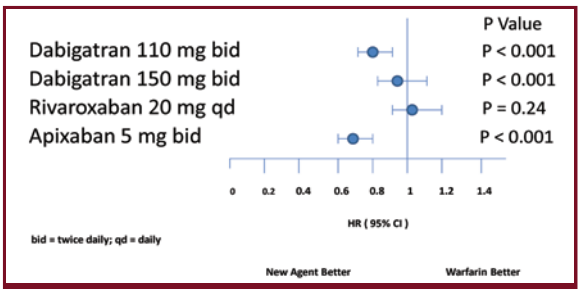

Figure 3. Primary Safety Endpoint of Major Bleeding in RE-LY, ROCKET-AF, and ARISTOTLE

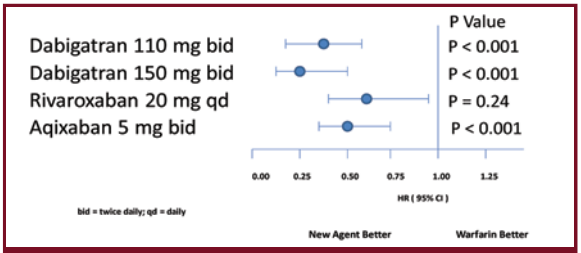

Figure 4. Hemorrhagic stroke in RE-LY, ROCKET-AF, and ARISTOTLE

Apixaban

The pivotal ARISTOTLE (Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation) was a randomised double-blind trial comparing apixaban 5 mg bid with dose-adjusted warfarin targeting an INR of 2.0 to 3.0 in 18,201 patients with atrial fibrillation and ≥1 additional risk factor for stroke.[7] The dose was reduced to 2.5 mb bid when ≥2 of the followings were present: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 μmol/l. The mean $CHADS_2$ score was 2.1 and the distribution of the $CHADS_2$ scores were: 34.0% of the patients had 0 to 1, 35.8% of the patients had 2, and 30.2% of the patients had 3 to 6. The mean and median TTR for the warfarin-treated patients were 62.2% and 66.0%, respectively. Patients with a CrCl <25 ml/min were excluded.

The results of ARISTOTLE were positive in each of the major outcomes of stroke, bleeding, and mortality. The rate of the primary outcome (ischaemic or haemorrhagic stroke or systemic embolism) was reduced from 1.60% per year in the warfarin group to 1.27% per year in the apixaban group (HR 0.79; 95% CI 0.66 to 0.95; p<0.001 for noninferiority; p=0.01 for superiority) (Fig. 2). The rate of major bleeding was reduced from 3.09% per year in the warfarin group to 2.13% per year in the apixaban group (HR 0.69; 95% CI 0.60 to 0.80; p<0.001) (Fig. 3). Total mortality was significantly lower in the apixaban group (3.52% per year), as compared with 3.94% per year in the warfarin group (HR 0.89; 95% CI 0.80 to 0.99; p=0.047). The rate of haemorrhagic stroke was reduced from 0.47% per year in the warfarin group to 0.24% per year in the apixaban group (HR 0.51; 95% CI 0.35 to 0.75; p<0.001) (Fig. 4). No significant differences in gastrointestinal bleeding and MI were found between the two groups. It was concluded from ARISTOTLE that in patients with nonvalvular AF at increased risk of stroke, apixaban was superior to warfarin in preventing stroke or systemic embolism and was associated with less major and nonmajor bleeding as well as lower mortality than warfarin.

Incorporation of New Oral Anticoagulants in Clinical Practice

Now that dabigatran and rivaroxaban are in the market and apixaban will be approved soon, we have a number of choices of oral anticoagulants for thromboembolism prevention in AF. Based on the currently available trial results, apixaban is associated with improved outcomes in stroke, mortality, and bleeding compared with warfarin. As we may never have head-to-head trials of these agents, we have to rely on cross-trial comparisons while remembering the pitfalls. The risks of the populations are different; high-risk in ROCKET-AF and moderate-risk in RE-LY and ARISTOTLE. The open-label design of RE-LY, as opposed to the double-blind ROCKET-AF and ARISTOTLE, may be advantageous for dabigatran. The lower mean level of TTR in ROCKET-AF may reflect the differences in the standards of care of participating countries. Another difference that may have put rixaroxaban at a disadvantage is that the primary endpoint was set at a point after rixaroxaban was stopped, with many events occurring when patients were crossed over back into warfarin.

The next question is who should receive the new ones instead of warfarin. The three new drugs are associated with superior or similar stroke rates to warfarin but all have shown reduced intracranial haemorrhage. Regarding major bleeding, dabigatran 150 mg and rivaroxaban are similar to warfarin while dabigatran 110 mg and apixaban have less major bleeding than warfarin. Together with the advantages of no clear interactions with food, few drug interactions, and no need for frequent laboratory monitoring and dose adjustments, they should be preferred to warfarin for AF patients. This is especially true for new patients and those who have unstable INRs on warfarin despite reasonable compliance to drug and food. Even for patients who are stable on warfarin, a lessened risk of intracranial haemorrhage is a clear advantage. However, certain issues exist concerning these new oral anticoagulants. Cost will be a barrier to their use in some patient populations but at a societal level dabigatran etexilate has been shown to be cost-effective as a first line treatment for stroke prevention in AF patients in a UK model.[8] More information is needed about dosing in patients with renal failure, management of patients with bleeding or who need urgent reversal of anticoagulation, clinically available assays for accurate determination of anticoagulation status (e.g. ecarin clotting time for dabigatran; anti-Xa assay for rivaroxaban and apixaban) in selected populations or situations.

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Wide Complex Arrhythmia

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Definition

PVC/PVE (Paroxysmal Ventricular complex/ectopic) - single ventricular ectopic(complex) emanating from the ventricles.
Couplet - 2 VE in sequence; **Triplets -** 3 VE in sequence
Ventricular bigemni - sinus rhythm alternating with ventricular ectopic
Nonsustained VT (ventricular tachycardia) - 3 or more beats of VE (ventricular ectopics) terminated within 30 seconds; at a rate of greater than 100 bpm
Monomorphic - single QRS morphology
Polymorphic - changing QRS morphology at cycle lengths between 180 and 600 ms
Sustained VT - VT greater than 30 seconds and/or requiring termination due to haemodynamic instability in <30 seconds
Ventricular Flutter- a type of ventricular tachycardia resulting in a zig –zag pattern without clearly formed QRS complex.
Torsade de Pointes- a special case of VT with wide QRS complex changing around the axis (so called twisting around the axis)
Ventricular Fibrillation- a totally disorganised appearance on the ECG with no discernible ventricular complexes.
Mechanisms:-
Automacity:- It is a focus of cells that depolarises faster than the SA node. It will spread out the wavefront and be conducted throughout the whole heart. Example is catecholamine polymorphic ventricular tachycardia (CPVT)
Re-entry:- Accounts for 75 % of ventricular arrhythmia. It is caused by 2 distinct pathways that exist between anatomical/functional block areas. The block usually happens to have a myocardial scar e.g. ischaemia.
Triggered activity:- It is caused by triggers that provoke depolarisation in (EAD) phase 3 or (DAD) phase 4. The triggers are usually premature beats. Therefore,the premature beats can easily induce torsades de pointes and digoxin toxins. RVOT VT is a typical example of the trigger activity mechanism.
In normal heart - PVC (Premature ventricular complex) occurs in a range of 0.5 % among 20 yrs old to 2.2 % in those over 50 yrs old. Mortality risk is minimal in a normal heart subject with PVC only during resting period. However, monomorphic NSVT(non sustained ventricular tachycardia), polymorphic VT (ventricular tachycardia) even in normal heart are indicators of risk. Many nonsustained VT are due to abnormalities of molecular level or due to electrolyte imbalance or adverse drug effects. However, some studies showed that PVC and NSVT during exercise and recovery phase correlated with increased risk.

In diseased heart - Most studies cited a frequency cutoff of 10 PVCs per hours and occurrence of repetitive forms VE as increased risk. Since risk of sudden death is already quite high because of the underlying heart disease. Suppression of VE/NSVT is no longer considered a therapeutic target for the prevention of sudden cardiac death. For post MI patients, ventricular arrhythmias occurred during the 24-48 hours do not imply continuing risk over time - so called primary VT/VF. However, for non- ischaemic diseased heart, there is no such primary VT/VF. Ventricular arrhythmias already carry poor prognosis.

The incidence of ventricular sudden cardiac deaths is low around 0.1-0.2 %.The risk of sudden cardiac death is highest in the first 6-18 months after MI or heart failure events.

Clinical presentations of ventricular arrhythmias :-

1. Asymptomatic finding of VE/NSVT with or without ECG abnormalities
2. Symptoms:- palpitations; dyspnoea; syncope; chest pain
3. VT that is haemodynamically stable.
4. VT that is haemodynamically unstable
5. Cardiac arrest

Causes of wide complex tachycardia(WCT):-

1. Ventricular tachycardia (VT) :- 80 % of all occurrences of WCT.
2. SVT with bundle branch block
3. Preexcited tachycardia i.e. AVRT with antidromic conduction.
4. Ventricular paced rhythm.

Investigation

Resting ECG - All patients who are evaluated for ventricular arrhythmias.; Look out for congenital abnormalities such as (long QT;short QT; Brugada syndrome, etc). Identify those with electrolytes disturbance, underlying structural heart disease with bundle branch block; Q wave, ventricular hypertrophy, AV block etc. QRS duration and repolarisation abnormalities are both independent predictors of sudden cardiac events too. Studies showed that a risk ratio of CVS death of 2.4 in the presence of an ischaemic ECG and 4.4 for abnormal T wave axis. An QTc >440 msec predicted CVS death with relative risk 2.1.
Exercise ECG - Class 1 indication (highly recommended) – those patients who have an intermediate or greater probability of coronary heart disease. Also, it was

recommended for patients with known or suspected exercise induced ventricular arrhythmias such as catecholamine VT to achieve a diagnosis.

Ambulatory ECG recorder - Holter is needed to detect arrhythmias, QT interval changes, T wave alternans, ST changes etc. It is useful when the arrhythmia appeared at least once daily.

Event recorder is used for sporadic cases with symptoms such as palpitations; dizziness; syncope that are caused by transient arrhythmia.

Implantable recorders - extremely useful in diagnosing serious tachyarrhythmias and bradyarrhythmias in patients with life -threatening symptoms such as syncope.

Echo - To identify the structural abnormalities of heart. LV systolic function and regional wall motion can be assessed. Stress echo may also be needed who are suspected to have ischaemia causing ventricular arrhythmia.

Electrophysiological Testing (EP testing) - We use 8 ventricular stimuli at cycle lengths of 400 ms and 600 ms at RV apex then deliver 1-3 extra ventricular stimuli. EP testing is recommended for patients with ischaemic heart history who had symptoms of ventricular tachyarrhythmias such as palpitations, presyncope, or syncope. It is also useful to differentiate wide complex tachycardia. For patients with asymptomatic NSVT and EF <40 %, inducibility was around 20-40 %. However, for non- ischaemic aetiology, EP testing is of very low value in predicting cardiovascular events.

To differentiate NCT vs WCT

Clinical features		SVT with BBB		VT
History of MI		Less likely		More likely
Canon waves		absent		Present
Carotid massage		Terminates		Not able to terminate
ECG features				
QRS duration		<140 millseconds (ms)3.5 small square		>140 milliseconds
QRS Frontal plane		Normal		Right Superior

RBBB morphology		SVT with BBB		VT
QRS in V1		Triphasic		Mono or biphasic
QRS in V6		R/S ratio >1		R/S <1
LBBB morphology				
QRS in V1		Narrow r,sharp descent		Notching,R to S >60 ms (1.5 small sq.)
QRS in V6		RS		QR,QS
LBBB RAD		Less likely		Likely to be VT
RBBB normal axis		Likely		Less likely

Other features		SVT with BBB		VT
Concordance		Less likely		common
Q wave during WCT		Less likely		common
AV dissociation,fusion,capture. No.V>A		Unlikely		common
RS pattern in V leads		RS < 100 ms		RS > 100 ms
QRS narrower during tachycardia than SR		Unlikely		Likely

Differentiation

		SVT with BBB		VT
Contralateral BBB during WCT		Unlikely		Likely
Change in axis from SR		<40 degree		> 40 degree
QRS similar during SR and WCT		suggestive		Uncommon

Therapy

Drug treatment- For simple VE or NSVT, we can treat the underlying pathology. If the heart is structurally normal, we can just reassure the patient or give blocker or Ca blocker to relieve symptoms. We should try to avoid anti –arrhythmic drugs for ectopic beats treatment.

For sustained monomorphic VT with a normal structure heart such as RVOT VT, we can try radiofrequency ablation or drug treatment. If wide complex tachycardia happened to have structurally heart disease, it usually means ICD implantation.

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18 Jul	Utility Measures in QOL Research	Dr. Elegance LAM Post-doctoral Fellow Department of Family Medicine and Primary Care, HKU Council member, Hong Kong Society for Quality of Life
25 Jul	QOL Assessment in Chinese Medicine	Dr. Wendy WONG Post-doctoral Fellow Department of Family Medicine and Primary Care, HKU Secretary, Hong Kong Society for Quality of Life
1 Aug	Psychometric Evaluation of QOL Measures	Dr. Daniel Y.T. FONG Associate Professor, School of Nursing, HKU Council member, Hong Kong Society for Quality of Life
8 Aug	Interpretation of QOL Data	

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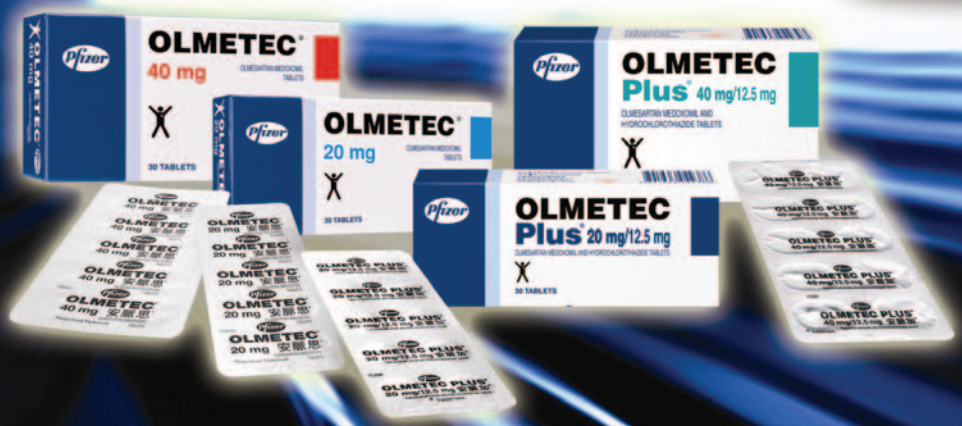

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Heart and Brain

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The heart-brain connection

No single organ in our body is isolated and advances in medicine tell us the relationship of previously described "distant" organs. Heart and brain are anatomically and functionally different by conventional medical textbook teaching. However, in many cultures throughout history, the heart has been considered the source of emotions, passion and wisdom. Also, people used to feel that they experienced the feeling or sensation of love and other emotional states in the area of the heart. Interestingly, recent studies have explored physiological mechanisms by which the heart communicates with the brain, thereby influencing information processing, perceptions, emotions and health. These studies provided the scientific basis to explain how and why the heart affects mental clarity, creativity and emotional balance. There was a proposed concept of 'heart brain'. The heart has a complete intrinsic nervous system that is sufficiently sophisticated to qualify as a 'little brain' in its own right[1]. The heart's brain is an intricate network of several types of neurons, neurotransmitters, proteins and support cells similar to those found in the brain proper. Its elaborate circuitry enables it to act independently of the cranial brain – to learn, remember, and even feel and sense. The heart's nervous system contains around 40,000 neurons, called sensory neurites. Information from the heart – including feeling sensations – is sent to the brain through several afferents. These afferent nerve pathways enter the brain at the area of the medulla, and cascade up into the higher centres of the brain, where they may influence perception, decision-making and other cognitive processes.

Physiologically, the heart's magnetic component is about 500 times stronger than the brain's magnetic field and can be detected several feet away from the body. It was proposed that this heart field acts as a carrier wave for information that provides a global synchronising signal for the entire body[2]. There is now evidence that a subtle yet influential electromagnetic or 'energetic' communication system operates just below our conscious awareness[3]. Energetic interactions possibly contribute to the 'magnetic' attractions or repulsions that occur between individuals, and also affect social relationships. It was also found that one person's brain waves could synchronise with another person's heart[4].

Heart as a hormonal organ

Atrial natriuretic peptide is well known and is used to assess heart failure[5]. The heart also contains a cell type known as 'intrinsic cardiac adrenergic' cells. These cells release noradrenaline and dopamine neurotransmitters, once thought to be produced only by neurons in the CNS. The heart also secretes oxytocin[6], commonly referred to as the 'love' or bonding hormone. In addition to its functions in childbirth and lactation, it is also involved in cognition, tolerance, adaptation, complex sexual and maternal behaviours, learning social cues and the establishment of enduring pair bonds. Concentrations of oxytocin in the heart were found to be as high as those found in the brain.

Two-way dialogue between brain and heart

Strong emotion and mental stress are now recognised as playing a significant role in severe and fatal ventricular arrhythmias. The mechanisms, although incompletely understood, include central processing at the cortical and brain stem level, the autonomic nerves and the electrophysiology of the myocardium. Each of these is usually studied separately by investigators from different disciplines. However, many are regulatory processes which incorporate interactive feedforward and feedback mechanisms. The heart is in a constant two-way dialogue with the brain — our emotions change the signals the brain sends to the heart and the heart responds in complex ways. However, we now know that the heart sends more information to the brain than the brain sends to the heart. And the brain responds to the heart in many important ways. As we experience feelings like anger, frustration, anxiety and insecurity, our heart rhythm patterns become more erratic[7]. These erratic patterns are sent to the emotional centres in the brain, which it recognises as negative or stressful feelings. These signals create the actual feelings we experience in the heart area and the body[8]. The erratic heart rhythms also block our ability to think clearly. Many studies have found that the risk of developing heart disease is significantly increased for people who often experience stressful emotions such as irritation, anger or frustration[9]. These emotions create a chain reaction in the body — stress hormone levels increase, blood vessels constrict, blood pressure rises, and the immune system is weakened. If we consistently experience these emotions, it can put a strain on the heart and other organs, and eventually lead to serious health problems[10]. When we experience heart-felt emotions like love, care, appreciation and compassion, the heart produces a very different rhythm. In this case it is a smooth pattern that looks like gentle rolling hills. Harmonious heart rhythms, which reflect

positive emotions, are considered to be indicators of cardiovascular efficiency and nervous system balance. This lets the brain know that the heart feels good and often creates a gentle warm feeling in the area of the heart. Learning to shift out of stressful emotional reactions to these heartfelt emotions can have profound positive effects on the cardiovascular system and on our overall health[11]. It is easy to see how our heart and emotions are linked and how we can shift our heart into a more efficient state by monitoring its rhythms.

It is well known that myocardial infarction affects the limbic system, a region of the brain that is responsible for mood, which explains as much as 15-30% of depression frequently observed after heart attacks. In rat models, apoptosis of the limbic system was enhanced right after myocardial infarction[12]. It is also associated with the release of factors that provoke the inflammation of tissues, including the brain, and specifically the regions that control sleep, notably the paradoxical sleep phase[13]. The particular function of that phase is to activate regions in the brain that are responsible for integrating our emotions. If that is affected, the risk of depression also increases. Poor-quality sleep is a known risk factor for cardiovascular disease. Since it can affect remission after an infarction, the risk of complications and recurrent infarction rises and a vicious circle may be set in motion.

In terms of disease categories, the heart brain connections can be in many dimensions, at least in 3 categories. Neurocardiac syndromes (like in Freiedreich disease which affects both the brain and heart), heart's effects on the brain (e.g. cardiac embolic stroke, which is well covered by other authors in this issue), and the brain's effects on the heart.

Some of the cardiac effects from major acute neurological disorders are well known. For example, in subarachnoid haemorrhage, ECG abnormalities in terms of T wave inversions and ST changes are often encountered. These changes can be reproduced by overstimulation of the heart by autonomic system, especially the sympathetic arm. There is powerful evidence to suggest that overactivity of the sympathetic limb of the autonomic nervous system is the common phenomenon that links the major cardiac pathologies seen in neurological catastrophes. These profound effects on the heart may contribute in a major way to the mortality rates of many primarily neurological conditions such as subarachnoid haemorrhage, cerebral infarction, status epilepticus, and head trauma. These phenomena may also be important in the pathogenesis of sudden unexpected deaths (SUD) in adults, sudden infant death, sudden death during asthma attacks, cocaine- and amphetamine-related deaths, and sudden death during the alcohol withdrawal syndrome, all of which may be linked by stress and catecholamine toxicity. Investigations aimed at alteration of the natural history of these events with catecholamine receptor blockade, calcium-channel blockers, free-radical scavengers, and antioxidants are in progress in many centres around the world.

A healthy brain needs a healthy heart

Observational studies, which follow people as they get older without directly intervening in their treatment, have uncovered some suggestive trends. One study has shown that people who have good control of their blood pressure from age 65 to 80 are less likely to develop dementia[14]. After age 85, controlling blood pressure does not have much effect on dementia risk. That doesn't mean anyone older than 85 should stop taking blood pressure medication. Lowering high blood pressure still prevents congestive heart failure and promotes kidney health.

As for physical activity, there was evidence in favour of its benefits for the brain. One study proved regular 20-minutes exercises daily could reduce the risk of vascular dementia but not Alzheimer's disease[15]. This was the first time that anyone had proved in a randomised controlled trial that exercise could improve mental functioning in people with some cognitive problems.

No one understands on a biochemical level why physical activity might help the brain. The best explanation so far is that exercising the heart somehow stimulates growth factors to produce new nerve cells in the brain[16]. The new cell growth is associated with a marked improvement in learning and memory. The new nerves also show qualitative differences from their older counterparts. The younger cells are better at establishing new connections with other cells. The effect is somewhat temporary. After a couple of months, the new cells start acting like the older cells, although they do not die off.

Exercise can greatly control risk factors for cardiovascular diseases. Take a common clinical example: an elderly gentleman suffers from embolic stroke and is noted to have atrial fibrillation. Anti-coagulation is indicated but his brain imaging shows severe leukoaraiosis which is due to previous untreated hypertension. The leukoaraiosis is known to increase the bleeding risk of anti-coagulation[17]. This puts us into a dilemma though we ultimately would still prescribe anti-coagulant while knowing the increased bleeding risk. Had the gentleman been more health-conscious in his preceding 20 years and had the risk factors controlled, the situation would then be less difficult; or the stroke might have been avoided.

Conclusion

"It is not the brains that matter most, but that which guides them --- the character, the heart, generous qualities, progressive ideas." (Fyodor Dostoyevsky (1821-1881), Russian novelist.

"The brain gives the heart its sight. The heart gives the brain its vision." (Rob Kall, a blog site director)

Neurocardiology or cardio-neurology is a hybrid field. The strokologist will teach the cardiologist about the brain and the neurologist will learn how the heart is affecting the brain. For these reasons, there is a very strong connection in the stroke field between the heart and brain.

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End-of-Life Care Workshops
Department of Medicine & Therapeutics
Faculty of Medicine
The Chinese University of Hong Kong

Date:
6th September 2012 to 4th October 2012, every Thursday evening (7:00 p.m. – 9:00 p.m.)

Venue:
Lecture Theatre, 2/F Clinical Sciences Building, Prince of Wales Hospital, Shatin, N.T.

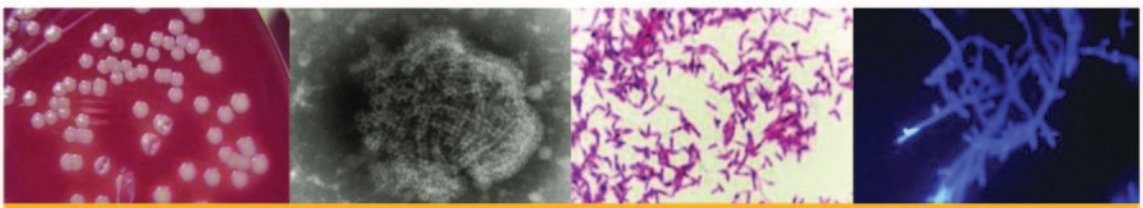
Target participants:
Doctors, nurses, allied health professionals, social workers and all health care professional interested in end-of-life care

Maximum number of Participants: 150

Course Fees: $1,200 (by crossed cheque)
Content:

Date	Topic	Speaker
6 Sept 12	01. Introduction: Principles and philosophy of palliative and end of life care	Dr Raymond Lo
	02. What is a good death? Patients' perspectives: dignity, autonomy, their expectations of health care professionals	Prof Jean Woo
13 Sept 12	03. Breaking bad news: a Chinese perspective	Dr CY Tse
	04. Ethical issues: decision-making, advance directives, assisted death	Dr CY Tse
20 Sept 12	05. Principles of pain control and use of opioids	Dr M Sham
	06. Symptom control in advanced cancer patients	Dr M Sham
27 Sept 12	07. End-of-life care in non-cancer setting	Dr Raymond Lo
	08. End-of-life for older patients	Prof T Kwok
4 Oct 12	09. Professionals' reflections in facing death and dying	Dr Vincent Tse
	10. Grief, bereavement, psychosocial and spiritual issues	Dr Doris Tse

Registration/enquiries: ****Accreditation in progress**
Contact : Ms Edith Chan
Tel : 9168 7005
Fax : 2604 8091
Email : b127716@mailserv.cuhk.edu.hk
Address : Room 124021, 10/F., c/o Dept. of Medicine & Therapeutics, Clinical Sciences Building, Prince of Wales Hospital, Shatin, NT
Website : http://www.mect.cuhk.edu.hk/taughtpostgraduate.html (Deadline: 17 Aug'12)



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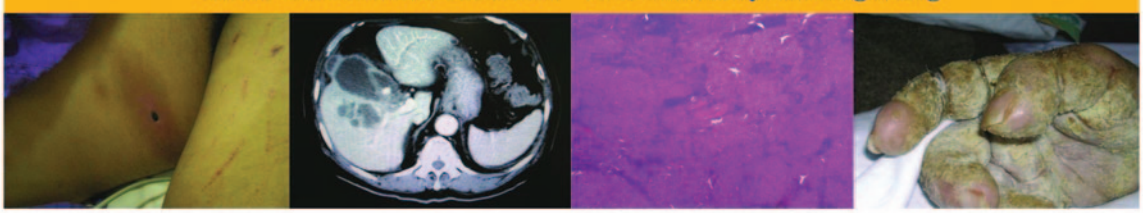

On Collecting Strings

Dr. Alex SB YIP

Dr. Alex SB YIP

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Specialist in Cardiology, Private Practice

This article aims to give a brief introduction to the collection of antique string instruments.

Wealthy amateurs and businessmen have been collecting antique string instruments for well over a century. From the investment perspective, this hobby may be perceived as a hedge against inflation. In the past two decades, many Asian string players have appeared on the scene. Therefore, the demand for old instruments far outstrips the supply. Unfortunately, this has put the top tier instruments beyond the reach of the vast majority of professional musicians. The trend in the past 50 years has seen many professional musicians relying on trusts and foundations to loan them valuable instruments. One such prominent collection in South East Asia is the Chi Mee Foundation in Taiwan. This collection has representation from all the major makers from the old and modern Italian schools.

Yip-Violin Golden Period Stradivarius; bow Dominique Peccatte

Some knowledge of the history of violin making adds to one's appreciation of these fine instruments. Violin-making is thought to have started in Italy. Distinguished makers such as Gasparo da Salo appeared as early as the end of the 16th century. Highest accolade violins were made by 17th century Cremona makers like Maggini, Amati and his most famous pupil Antonio Stradivari. The Guarneri family, in particular Guarneri del Jesu had a reputation that rivals Stradivarius. In the 18th century, numerous excellent makers emerged, including Carlo Bergonzi, Guadagnini, the Gagliano family, Ruggierie, Testore, Tecchler and Storioni. The above named makers are commonly referred to as the Old Italian Masters. Outstanding 19th century makers are Pressenda, Ceruti and Rocca. Modern Italian violins are fine instruments which have the potential to mature and improve with age. Examples include Leandro Bisiach, Fagnola, Degani, Antoniazzi, and Oddone

Great violins can produce variegated characters of sound when played by different players, whereas ordinary instruments typically produce a uniformly bland sound. Some old Italian instruments typically have a complex silvery sound with excellent projection right down to the last row of a concert hall. This is highly desirable in a romantic concerto performance, but less so for chamber music, where a group of instruments should blend in harmony. So, ideally, each musician should have 2 different instruments, one for power, and the other for sweetness. For trained ears it is usually not difficult to distinguish between old masters' instruments and modern ones. A handful of contemporary makers have put in a lot of effort to create violins which can produce more mature sounds. A Stradivarius violin is thought to owe its unique sound quality to the special treatment of its wood and varnish, in addition to superb workmanship.

French makers from the end of the 17th century have also created some nice and more affordable instruments. Violins made by Lupot, Vuilliame, Gand, Benadrel, and Silvestre have become increasingly sought out by musicians and collectors.

I have compiled a checklist to hopefully help new collectors of antique string instruments avoid paying too much tuition fee.

1. Correct attribution. Familiarise yourself with the typical appearance of instruments and their labels. It helps when an instrument is accompanied by one or more certificate(s) of authenticity issued by respected authorities.
2. Condition of the instrument. Old instruments, especially those more than 150 years old, almost invariably have some repairs. A condition report from your dealer will give details regarding the position and extent of cracks and repairs, and whether all parts including the varnish are original.
3. Naturally, prestigious makers command higher prices and have greater investment potential. However, some instruments made by less well known or unknown makers may have surprisingly good sound quality and playability. There is a market for these instruments among amateur musicians, as well as professionals in need of a second instrument.

4. Tone quality is subjective to the preference of individual players. Some musicians prefer bright powerful instruments, whilst others are happier with warm mellow sounds. However, projection of an instrument is a universal requirement. Some instruments which sound loud adjacent to a player's ear have surprisingly inadequate projection in a large room or hall.
5. To uncover the full potential of an instrument, it should be properly set up by a luthier. An added advantage of this manoeuvre is that a luthier will take a player's style, ability and preferences into account to optimise the set up.
6. A string instrument should be played frequently to maintain and develop its sound quality. It makes little sense to buy a valuable instrument to lock up in a safe.
7. Aside from the sound enhancing aspect of outstanding French bows by makers like Peccatte, Tourte, Sartory, Lamy and Fetique, they are a good investment. In general, the value of your bow should roughly correspond up to 40 % of the value of your instrument.
8. Finally, strings and rosins do make a difference. I find it most interesting to explore the different combinations to alter the sound produced by an instrument. An inquisitive player can use his own imagination to create his favourite effect.

In conclusion, I recommend potential collectors to research specialist shops in Hong Kong for useful advice before purchasing quality instruments.

Yip Family Trio - violin Eugenio Degani 1897; cello Aegidius Klotz c.1790

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10 Oct	Investigations and management of Multidrug-resistant TB (MDR-TB) and Extensively drug-resistant TB (XDR-TB)	Dr. Wing-sze LAW 羅頴思醫生 Senior Medical Officer, TB & Chest Department of Health
17 Oct	Cardio-pulmonary exercise testings – clinical practice and research application	Dr. Wai-kei LAM 林偉奇醫生 Associate Consultant, Department of Medicine North District Hospital

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Reference:
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Exforge® Film-coated tablets

Presentation: Exforge: Amlodipine (as amlodipine besylate) and valsartan 5 mg/80 mg, 5 mg/160 mg and10 mg/160 mg **Indications/Posology:** Treatment of essential hypertension in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy. Recommended dose is one film-coated tablet per day (5 mg amlodipine and 80 mg valsartan, or 5 mg amlodipine and 160 mg valsartan, or 10 mg amlodipine and 160 mg valsartan). **Contraindications:** •Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients. •Severe hepatic impairment, biliary cirrhosis or cholestasis. ⊠Severe renal impairment (GFR <30 ml/min/1.73 m2) and patients undergoing dialysis. •Second and third trimesters of pregnancy. **Precautions/Warnings:** •Risk of hypotension in sodium- and/or volume-depleted patients. •Beta-blocker withdrawal should be gradual •Severe renal impairment (creatinine cleareance < 10 mL/min) and dialysis. •No data available in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney or after recent kidney transplantation. •Hyperkalaemia •Primary hyperaldosteronism •Heart failure •Caution in patients with mild to moderate hepatic impairment or biliary obstructive disorders. •As with all other vasodilators, special caution in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy •Avoid use in women planning to become pregnant and while breast-feeding. Not recommended in patients below 18 years of age. **Interactions:** •Caution and monitoring of serum potassium levels when used concomitantly with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium level. **Adverse reactions:** •The most common: Nasopharyngitis, influenza, headache, oedema, putting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia, hot flush •Uncommon: vertigo, tachycardia, palpitations, orthostatic hypotension, cough, pharyngolaryngeal pain, diarrhoea, nausea, abdominal pain, constipation, dry mouth, rash, erythema, joint swelling, back pain, arthralgia, dizziness, somnolence, dizziness postural, paraesthesia •Rare: Hypersensitivity, hypotension, muscle spasm, sensation of heaviness, hyperhidrosis, exanthema, pruritus, pollakisuria, polyuria, visual disturbance, syncope, tinnitus, erectile dysfunction, anxiety. Adverse drug reactions previously reported with one of the individual components (amlodipine or valsartan) **Amlodipine:** •Common: Vomiting. •Uncommon: Gastritis, gingival hyperplasia, gynaecomastia, leucopenia, myalgia, pancreatitis, hepatitis, thrombocytopenia, vasculitis, alopecia, altered bowel habits, dyspnoea, rhinitis, hyperglycaemia, importance, increased urinary frequency, malaise, mood changes •Rare: Arrhythmia, myocardial infarction. Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Arrhythmia (including ventricular tachycardia and atrial fibrillation) have also been reported. These adverse events may not be distinguishable from the natural history of the underlying disease •Very Rare: Cholestatic janundice, AST and ALT increase, purpura, rash and pruritus. Exceptional cases of extrapyramidal syndrome have been reported. •In a long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. **Valsartan:** •Not known: Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness. **Packs and prices:** Country specific. **Note:** Before prescribing, please read full prescribing information.

Diovan® Film-coated tablets

Important note: Before prescribing, consult full prescribing information. **Presentation:** Valsartan: film-coated tablets of 40 mg, 80 mg, 160 mg and 320 mg. **Indications:** Hypertension (HTN), heart failure (NYHA class II-IV), post-myocardial infarction and, reduce cardiovascular mortality. **Dosage •Adult Hypertension:** Recommended dose is 80 mg or 160 mg once daily when used as monotherapy who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Diovan may be used over a dose range of 80mg to 320mg daily, administered once a day. Diovan may be administered with other antihypertensive agents. **•Heart Failure:** Starting dose is 40 mg twice daily. Uptitration to 80 and 160 mg twice daily as tolerated by patient. The maximum daily dose administered in clinical trials is 320 mg in divided dose. **•Treatment of postmyocardial infarction:** Starting dose is 20 mg twice daily. Patients may be uptitrated within 7 days to 40mg twice daily, with subsequent titrations to a target maintenance dose of 160mg twice daily, as tolerated by patient. Diovan may be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin, beta-blockers, and statins. **Contraindications:** •None. **Precautions/Warnings/Interactions:** •Risk of hypotension in volume- and/or salt-depleted patients. •Caution is advised when administering valsartan to patients with renal artery stenosis, severe renal impairment (creatinine clearance < 10 mL/min), biliary cirrhosis or obstruction. •Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction. •Use with caution in patients with impaired hepatic function. •In patients with severe heart failure, treatment with Diovan may cause impairment of renal function. •Drugs that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. •Concomitant treatment with potassium-sparing diuretics or potassium supplements may increase serum potassium levels, and in heart failure patients, increases in serum creatinine. •Women planning to become pregnant and while breast-feeding should be discontinued. **Adverse reactions: Hypertension:** Most common adverse reactions are headache, dizziness, viral infection, fatigue and abdominal pain **Heart Failure:** Most common adverse reactions are dizziness, hypotension, diarrhea, arthralgia, back pain, fatigue and hyperkalemia Post-Myocardial Infarction: Most common adverse reactions which caused patients to discontinue therapy are hypotension, cough and increased blood creatinine Tell your doctor if you get any side effect that bothers you or that does not go away. These are not all the possible side effects of DIOVAN. For a complete list, ask your doctor or pharmacist. **Packs and prices:** Country specific.

Co-Diovan® Film-coated tablets

Presentation: Coated tablets containing 80 mg valsartan (an angiotensin II receptor antagonist) and 12.5 mg hydrochlorothiazide (a thiazide diuretic), or 160 mg valsartan and 12.5 mg hydrochlorothiazide or 160 mg valsartan and 25 mg hydrochlorothiazide, or 320 mg valsartan and 12.5 mg hydrochlorothiazide, or 320 mg valsartan and 25 mg hydrochlorothiazide. **Indications:** Hypertension. **Dosage:** One tablet of Co-Diovan 80/12.5 mg or 160/12.5 mg or 160/25 mg or 320 mg/12.5 mg or 320 mg/25 mg daily. **Contraindications:** •Known hypersensitivity to the components of this product or to sulfonamides• pregnancy • severe hepatic impairment, biliary cirrhosis and cholestasis •anuria, severe renal impairment (creatinine clearance < 30 mL/min) • refractory hypokalemia • hyponatremia • hypercalcemia • Symptomatic hyperuricemia. **Precautions/Warnings:** •Risk of hypotension in sodium- and/or volume-depleted patients. •Caution is advised when administering Co-Diovan to patients with renal artery stenosis, renal and liver disease or systemic lupus erythematosus. •Disturbance of serum electrolyte balance, glucose tolerance and serum levels of cholesterol, tryglicerides and uric acid. •Caution in driving or operating machinery. • Avoid use in women planning to become pregnant and while breast-feeding. **Interactions** •Concomitant treatment with potassium-sparing diuretics or potassium supplements may increase potassium levels. •Caution if combined with other antihypertensives, lithium (serum lithium monitoring), curare derivatives, NSAIDs, Digoxin, antidiabetic agents, allopurinol, amantadine, cytotoxic drugs, anticholergenic agents, cholestyramine, vitamin D, calcium salts and cyclosporine. **Adverse reactions:** headache, dizziness, fatigue. For the hydrochlorothiazide component, other reported adverse reactions include hypokalemia, hyperuricemia and other electrolyte imbalance, orthostatic hypotension and lipids increased. Rare: jaundice, arrhythmias, blood disorders. Very rare: vasculitis, pancreatitis, pneumonitis, pulmonary edema. Post-marketing experience revealed very rare cases of hypersensitivity (e.g. angioneurotic oedema), renal impairment, myalgia and thrombocytopenia. Laboratory findings: Neutropenia, elevations in blood creatinine and blood urea. **Packs and prices:** Country specific. **Note:** Before prescribing, please read full prescribing information.

Exforge HCT® Film-coated tablets

Important note: Before prescribing, consult full prescribing information. **Presentation:** Film coated tablets containing 5 mg amlodipine as amlodipine besylate, 160 mg valsartan and 12.5 mg hydrochlorothiazide, or 10 mg amlodipine as amlodipine besylate, 160 mg valsartan and 12.5 mg hydrochlorothiazide or 5 mg amlodipine as amlodipine besylate, 160 mg valsartan and 25 mg hydrochlorothiazide or 10 mg amlodipine as amlodipine besylate, 160 mg valsartan and 25 mg hydrochlorothiazide or 10 mg amlodipine as amlodipine besylate, 320 mg valsartan and 25 mg hydrochlorothiazide. **Indications:** Treatment of hypertension. Indicated in patients whose blood pressure is not adequately controlled on dual therapy or as replacement therapy in patients already receiving amlodipine, valsartan and hydrochlorothiazide at the same dose levels from separate tablets. **Dosage:** One tablet of Exforge HCT 5/160/12.5 mg or 10/160/12.5 mg or 5/160/25 mg or 10/160/25 mg or 10/320/25 mg daily **Contraindications:** •hypersensitivity to any of the active substances or excipients •pregnancy and lactation •severe hepatic impairment, biliary cirrhosis or cholestasis •severe renal impairment (creatinine clearance < 30 mL/min) •anuria •refractory hypokalemia •hyponatremia •hypercalcemia •symptomatic hyperuricemia. **Warnings/Precautions:** •Avoid use in women planning to become pregnant and while breast-feeding •Risk of hypotension in sodium- and/or volume-depleted patients. •Caution is advised when administering Exforge HCT to patients with renal impairment or systemic lupus erythematosus. •No data available in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney or after recent kidney transplantation •Disturbance of serum electrolyte balance (monitoring recommended), glucose tolerance and serum levels of cholesterol, tryglicerides and uric acid. •Not recommended in patients below 18 years of age. •Beta-blocker withdrawal should be gradual •Caution in patients with hepatic impairment or biliary obstructive disorders. •As with all other vasodilators, special caution in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy. **Pregnancy:** Contraindicated **Breast-feeding:** Not recommended **Driving and using machines:** Caution when driving or using machinery **Interactions:** •Monitoring when used concomitantly with lithium •Caution when used concomitantly with drugs that may increase potassium levels. •Caution if combined with other antihypertensives, curare derivatives, NSAIDs, corticosteroids, ACTH, amphotericin, carbenoxolone, Penicillin G, salicylic acid derivatives, Digoxin, antidiabetic agents, allopurinol, amantadine, diazoxide, cytotoxic drugs, anticholergenic agents, methyldopa, cholestyramine, vitamin D, calcium salts, carbamazepine and ciclosporin. **Adverse reactions: Common:** Hypokalaemia, Dizziness, headache, Hypotension, Dyspepsia, Pollakiuria, Fatigue, oedema. **Uncommon:** Loss of appetite, hypercalcaemia, hyperlipidaemia, hyperuricaemia, weight gain, hyponatraemia, Insomnia, sleep disorders, Adnormal coordination, postural dizziness, exertional dizziness, dysgeusia, lethargy, paraesthesia, peripheral neuropathy, neuropathy, syncope, drowsiness, Visual disturbances, Vertigo, Tachycardia, Orthostatic hypotension, phlebitis, Cough, thrombophlebitis, dyspnoea, throat irritation, Abdominal discomfort, upper abdominal pain, dry mouth, halitosis, diarrhoea, nausea, vomiting, Hyperhidrosis, pruritus, Back pain, joint swelling, muscle spasm, muscle weakness, myalgia, pain in the extremitites, Elevation of serum creatinine, acute renal failure, Erectile dysfunction, Abasia, abnormal gait, asthenia, discomfort, malaise, non - cardiac chest pain, Elevated levels of blood urea nitrogen (BUN) and blood uric acid. **Additional Information on the individual active substances: Amlodipine - Common:** Palpitations, Hot flushes. **Uncommon:** Weight loss, Mood swings, Tremor, hypoaesthesia, Tinnitus, Rhinitis, Altered bowel habits, Alopecia, exanthema, purpura, rash, skin depigmentation, photosensitivity reactions, Arthralgia, Disturbances of micturition, nocturia, Gynaecomastia, Pain. **Very rare:** Leukopenia, thrombocytopenia, Hypersensitivity, Hyperglycaemia, Arrhythmia(including bradycardia, ventricular tachycardia and atrial fibrillation), myocardial infarction, Vasculitis, Gastritis, gingival hyperplasia, pancreatitis, Elevated liver emzymes(including elevated serum bilirubin), hepatitis, intrehepatic cholestasis, jaundice, urticaria, Angioedema, erythema multiforme. **Valsartan - Common:** Viral infections, Postural dizziness. **Uncommon:** Upper respiratory tract infection, pharyngitis, sinusitis, Neutropenia, Hyperkalaemia, Reduced libido, Heart failure. **Rare:** Light-headedness. **Very rare:** Thrombocytopenia, reduced levels of haemoglobin and haematocrit, Hypersensitivity, Arrhythmias, Vasculitis, Elevated liver enzymes(including elevated serum bilirubin), Angioedema, rash, exanthema, Arthralgia, Renal impairment, Fetal complications. **Hydrochlorothiazide - Common:** Elevated blood lipids. **Uncommon:** Hypomagnesaemia, Reduced appetite, Rash, urticaria. **Rare:** Thrombocytopenia, in isolated cases with purpura, Hyperglycaemia, glycosuria, deterioration of diabetic metabolic status, Depression, Light-headedness, Arrhythmias, Constipation, Intrahepatic cholestasis, jaundice, Photosensitivity reactions. **Very rare:** Leucopenia, agranulocytosis, bone-marrow depression, haemolytic anaemia, Hypersensitivity, Hypochloraemic alkalosis, Pancreatitis, Pneumonitis, pulmonary oedema, Lupus-erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, necrotizing vasculitis and toxic epidermal necrolysis. **Packs and prices:** Country specific. **Legal classification:** Country specific.

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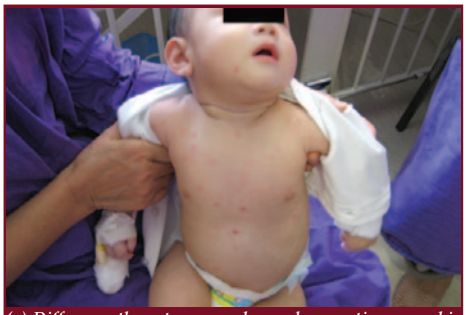
Dermatological Quiz

Dr. Lai-yin CHONG

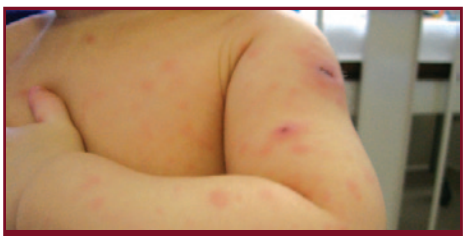
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)

Private Dermatologist

Dr. Lai-yin CHONG



(a) Diffuse erythematous maculopapular eruptions over his trunk and limbs



(b) Close-up of the skin eruptions

This 6-month-old baby developed widespread erythematous maculopapular eruptions over his trunk and limbs for one week (Fig. 3a & 3b). Some of the papules had an umbilicated centre which then dried up with a crust. There were associated low-grade fever and occasional cough. On examination, he had generalised lymphadenopathy and hepatosplenomegaly. Laboratory investigations showed a highly elevated ESR and elevated hepatic transaminases. Chest XR showed diffuse mottling in both lung fields.

Question:

1. What is your provisional diagnosis?
2. What are your differential diagnoses?
3. What investigations would you do to confirm the diagnosis?

(See P. 45 for answers)

Rental Fees of Meeting Room and Facilities at The Federation of Medical Societies of Hong Kong

(Effective from October 2009)

Venue or Meeting Facilities	Member Society (Hourly Rate HK$)			Non-Member Society (Hourly Rate HK$)		
	Peak Hour	Non-Peak Hour	All day Sats, Suns & Public Holidays	Peak Hour	Non-Peak Hour	All day Sats, Suns & Public Holidays
Multifunction Room I *(Max 15 persons)*	150.00	105.00	225.00	250.00	175.00	375.00
Council Chamber *(Max 20 persons)*	240.00	168.00	360.00	400.00	280.00	600.00
Lecture Hall *(Max 100 persons)*	300.00	210.00	450.00	500.00	350.00	750.00
Non-Peak Hour: 9:30am - 5:30pm Peak Hour: 5:30pm - 10:30pm						
LCD Projector	500.00 per session					
Microphone System	50.00 per hour, minimum 2 hours					

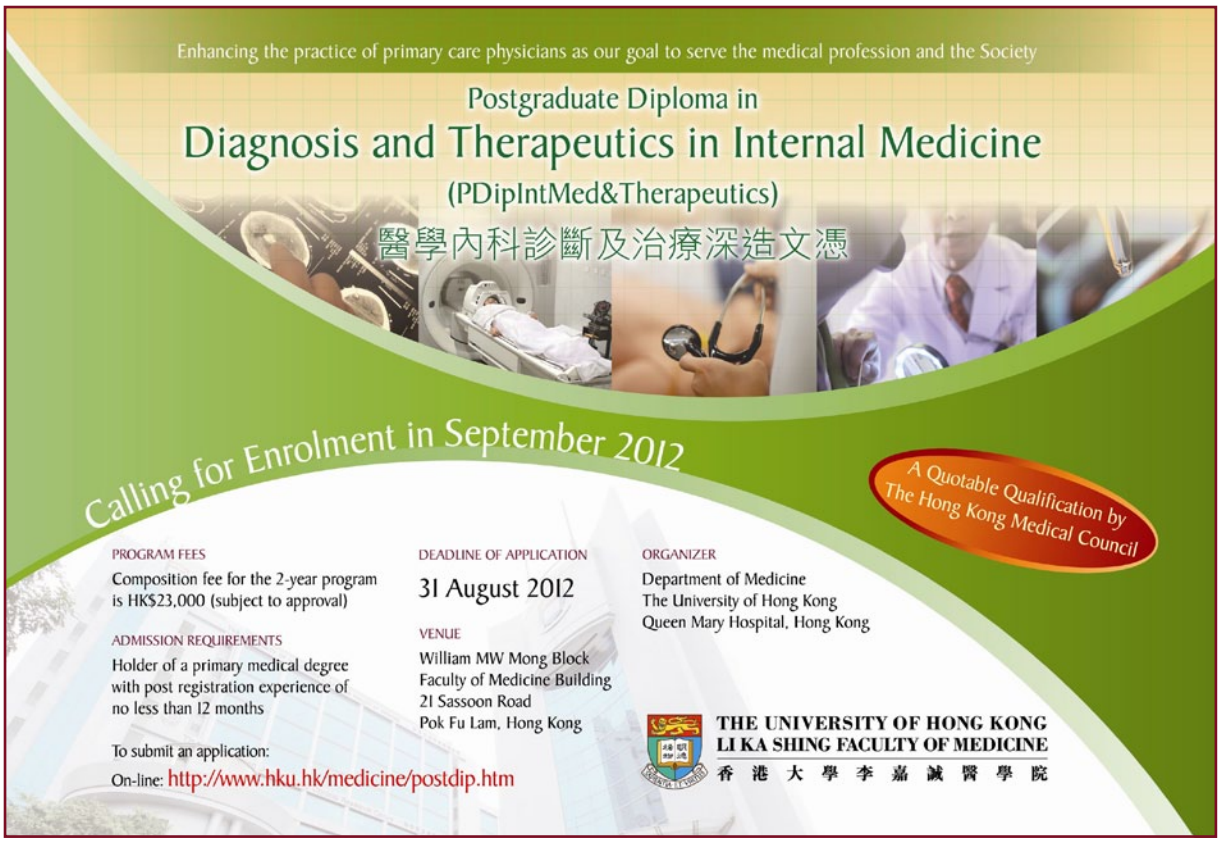
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					* Joint Surgical Symposium - Recent Advances in Paediatric Surgery and Urology 1	* HKMA CME – 1) Recent Advances in Medical Imaging; 2) Recent Advances in Cardiothoracic Surgery * MPS Workshop – Mastering Difficult Interactions with Patients 2
* Joint Professional Basketball Tournament 2012 * HKMA Table-Tennis Tournament 2012 (Day 2) * MPS Workshop – Mastering Adverse Outcomes * FMSHK Officers' Meeting 3	* Sharing from BAUS Preparation Course 4	* HKMA Council Meeting 5	6	* Recent Advance in Osteoporosis Management 7	8	* Refresher Course for Health Care Providers 2011/2012 9
* HKMA Ten-pin Bowling Tournament 2012 10	11	* HKMA Kln West Community Network - Newer Trends in Management of Acute Diarrhea in Children 12	* Hong Kong Neurosurgical Society Monthly Academic Meeting –Craniopharyngioma * HKMA CW&S Community Network – Tentative 13	* HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2012 – The ABC of molecular pathology testing * Gender Neutral HPV Vaccination: The Real World Impact 14	15	* FMSHK Annual Scientific Meeting 2012 - Brain Health * HKMA CME – Health Personnel 2012 16
* FMSHK Annual Scientific Meeting 2012 - Brain Health * Joint Professional Basketball Tournament 2012 * HKMA Table-Tennis Tournament 2012 17	18	19	20	* The Invisible Man is Now Visible - Gender Neutral HPV Vaccination * HKMA Hong Kong East Community Network – 4th Annual Meeting cum CME Lecture on "Management of Stroke Hand-in-Hand, Public-Private Interface" * FMSHK Executive Committee Meeting 21	22	* HKMA Dragon Boat Team – Sun Life Stanley International Dragon Boat Championships 2012 23
* "Drug Free Community" Public Education Day 24	25	26	* HKMA CW&S Community Network – Tentative 27	* Treatment Options of Major Depressive Disorder 28	29	* YTM Community Network – Certificate Course on Bringing Better Health to Our Community (2nd Session) 30

Date / Time	Function	Enquiry / Remarks
1 FRI 8:00 am	**Joint Surgical Symposium - Recent Advances in Paediatric Surgery and Urology** Organiser: Department of Surgery, University of Hong Kong & Hong Kong Sanatorium & Hospital, Chairman: Dr. Wong Wai-Sang, Speakers: Dr. Kenneth Wong & Dr. Lawrence Lan, Venue: Hong Kong Sanatorium & Hospital	Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 1 CME point
2 SAT 12:45 pm	**HKMA CME – 1) Recent Advances in Medical Imaging; 2) Recent Advances in Cardiothoracic Surgery** Organiser: The Hong Kong Medical Association, Chairmen: Prof. Lee Shiu Hung & Dr. Choi Kin, Speakers: Dr. Fan Tsz Wo & Dr. Ma Chan Chung, Venue: Conference Rooms 1&2, 2/F, Main Building, Kowloon Hospital, 147A Argyle Street, Kowloon	Mrs. Bianca Lee Tel: 3129 6167 2 CME points
2:00 pm	**MPS Workshop – Mastering Difficult Interactions with Patients** Organiser: The Hong Kong Medical Association, Speaker: Dr. Cheng Ngai Sing, Justin, Venue: Crystal Room 2, Level B3, Holiday Inn Golden Mile Hong Kong	HKMA CME Department Tel: 2527 8452 2.5 CME points
3 SUN 2:00 pm	**Joint Professional Basketball Tournament 2012** Organiser: The Hong Kong Medical Association	Ms. Dorothy KWOK Tel: 2527 8285
2:00 pm	**HKMA Table-Tennis Tournament 2012 (Day 2)** Organiser: The Hong Kong Medical Association, Venue: Luen Wo Hui Sports Centre	Ms. Dorothy KWOK Tel: 2527 8285
2:30 pm	**MPS Workshop – Mastering Adverse Outcomes** Organiser: The Hong Kong Medical Association, Speaker: Dr. Anthony FUNG, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Department Tel: 2527 8452 2.5 CME points
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
4 MON 7:30 pm	**Sharing from BAUS Preparation Course** Organiser: Hong Kong Urological Association, Chairman: Dr. Lam Yiu Chung, Thomas, Speakers: Dr. Chui Yi & Dr. Franklin Ho, Venue: Multi-disciplinary Simulation and Skills Centre, 4/F Block F, QEH	Dr. Hing-hoi HUNG Ms. Tammy HUNG Tel: 2958 6006/ 9609 6064 1 CME point
5 TUE 8:00 pm	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association, Chairman: Dr. CHOI Kin, Venue: HKMA Head Office (5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)	Ms. Christine WONG Tel: 2527 8285
7 THU 1:00 pm	**Recent Advance in Osteoporosis Management** Organiser: HKMA New Territories West Community Network, Chairman: Dr. CHUNG Siu Kwan, Ivan, Speaker: Dr. Ho Yiu Yan, Andrew, Venue: Maxim's Palace Chinese Restaurant, Tuen Mun Town Hall, 3 Tuen Hi Road, Tuen Mun	Mr. Alan LAW Tel: 25278285 1 CME point
9 SAT 2:30 pm	**Refresher Course for Health Care Providers 2011/2012** Organiser: The Hong Kong Medical Association, Speaker: Dr. Hoi Sze LEUNG, Venue: OLMH	Ms. Clara Tsang Tel: 2354 2440 2 CME points
10 SUN 2:00 pm	**HKMA Ten-pin Bowling Tournament 2012** Organiser: The Hong Kong Medical Association, Venue: South China Athletic Association	Ms. Dorothy KWOK Tel: 2527 8285
12 TUE 1:00 pm	**HKMA Kln West Community Network - Newer Trends in Management of Acute Diarrhea in Children** Organiser: HKMA Kln West Community Network, Chairman: Dr. LEUNG Gin Pang, Speaker: Dr. CHENG Yan Wah, Vinson, Venue: Crystal Room I-III, 30/F., Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Candice TONG Tel: 2527 8285 1 CME point
13 WED 7:30 am	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Craniopharyngioma** Organiser: Hong Kong Neurosurgical Society, Chairman: Dr. HUNG Wai Man, Speaker: Dr. CHU Sai Lok, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital	Dr. Gilberto LEUNG Tel: 2255 3368 1.5 CME points
1:00 pm	**HKMA CW&S Community Network – Tentative** Organiser: HKMA CW&S Community Network, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	Mr. Alan LAW Tel: 25278285
14 THU 2:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2012 – The ABC of molecular pathology testing** Organiser: The Hong Kong Medical Association, Speaker: Dr. Ma Shiu Kwan, Edmond, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	HKMA CME Department Tel: 2527 8452 1 CME point
1:00 pm	**Gender Neutral HPV Vaccination: The Real World Impact** Organiser: HKMA-KLN East Community Network, Speaker: Dr. Lo Kuen Kong, Venue: Lei Garden Restaurant, Shop No. L5-8 on Level 5, APM Millennium City 5, 418 Kwun Tong Road, Kwun Tong	Mr. Alan LAW Tel: 25278285 1 CME point
16 SAT *(17)*	**FMSHK Annual Scientific Meeting 2012 - Brain Health** Organiser: The Federation of Medical Societies of Hong Kong & Macau Physician Association of Public Hospital, Venue: Grand Function Room, 1st Floor, Mandarin Oriental Macau Hotel, Please visit http://www.fmshk.org/fmshk.html?id=340 for details	FMSHK Secretariat Tel: 2527 8898
1:30 pm	**HKMA CME – Health Personnel 2012** Organiser: The Hong Kong Medical Association, Chairman: Dr. Chan Pui Wai, Speaker: Dr. Veronica Chan Lee, Venue: Lecture Theatre, G/F, Block F, UCH	Ms. Gary Wong Tel: 3513 4821 1.5 CME points
17 SUN 2:00 pm	**Joint Professional Basketball Tournament 2012** Organiser: The Hong Kong Medical Association, Venue: t.b.c.	Ms. Dorothy KWOK Tel: 2527 8285
2:00 pm	**HKMA Table-Tennis Tournament 2012** Organiser: The Hong Kong Medical Association	Ms. Dorothy KWOK Tel: 2527 8285
21 THU 1:00 pm	**The Invisible Man is Now Visible - Gender Neutral HPV Vaccination** Organiser: HKMA-New Territories West Community Network, Chairman: , Speaker: Dr. Kun Ka Yan, Venue: Maxim's Palace Chinese Restaurant, Tuen Mun Town Hall, 3 Tuen Hi Road, Tuen Mun	Mr. Alan LAW Tel: 25278285 1 CME point
7:00 pm	**HKMA Hong Kong East Community Network – 4th Annual Meeting cum CME Lecture on "Management of Stroke Hand-in-Hand, Public-Private Interface"** Organiser: HKMA Hong Kong East Community Network and Hong Kong East Cluster, Chairman: Dr. WONG Bun Lap, Bernard, Speaker: Dr. TSANG Kin Lun; Dr. TSOI Tak Hong; Dr. CHAN Ping Hon, Johnny, Venue: HKMA Head Office (5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)	Miss Candice TONG Tel: 2527 8285

Date / Time	Function	Enquiry / Remarks
21 THU 8:00 pm	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
23 SAT 8:00 am	**HKMA Dragon Boat Team – Sun Life Stanley International Dragon Boat Championships 2012** Organiser: The Hong Kong Medical Association, Venue: Stanley Main Beach	Ms. Dorothy KWOK Tel: 2527 8285
24 SUN	**"Drug Free Community" Public Education Day** Organiser: The Hong Kong Medical Association, Venue: Tseung Kwan O	Mr. Alan LAW Tel: 25278285
27 WED 1:00 pm	**HKMA CW&S Community Network – Tentative** Organiser: HKMA CW&S Community Network, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central	Mr. Alan LAW Tel: 25278285
28 THU 1:00 pm	**Treatment Options of Major Depressive Disorder** Organiser: HKMA Kln East Community Network, Chairman: Dr. Danny MA Ping Kwan, Speaker: Dr. WONG Chun Hin, Willy, Venue: East Ocean Seafood Restaurant, Tseung Kwan O	Mr. Alan LAW Tel: 2527 8285
30 SAT 1:00 pm	**YTM Community Network – Certificate Course on Bringing Better Health to Our Community (2nd Session)** Organiser: YTM Community Network and and Dept. of Family Medicine & General Outpatient Clinic and Dept. of Medicine, Kowloon Central Cluster, Speaker: Dr. FU Chiu Lai; Dr. Kingsley CHAN, Venue: Block M, Lecture Theatre, Queen Elizabeth Hospital,30 Gascoigne Road, Kowloon, Hong Kong	Miss Candice TONG Tel: 2527 8285

Upcoming Meeting

7-8/7/2012	**Chinese Medicine in Geriatrics, Hong Kong International Integrative Medicine Conference** Organisers: Hospital Authority & Hong Kong Association for Integration of Chinese-Western Medicine (HKAIM), Venue: Hong Kong Academy of Medicine, Enquiry: Ms Toki CHAN & Ms Justin NG Tel: (852) 28718787/ 2871 8896
13/7/2012	**Basic Histocompatibility Course** Organiser: Hong Kong Society for Histocompatibility and Immunogenetics, Venue: The University of Hong Kong, Enquiry: Mr. Tony Yau, Tel: (852) 2255 4600, Email: contactus@hkshi.org



Answer to Dermatological Quiz

Answer

1. Miliary tuberculosis with cutaneous involvement should be considered in view of the clinical context of this patient. This type of true cutaneous tuberculosis is due to endogenous infection, usually of pulmonary origin, resulting from widespread dissemination of the Mycobacterium tuberculosis through haematogenous spread. The cutaneous lesions of military tuberculosis typically present with pinhead-sized erythematous papules. Some lesions are minute vesicles which dry up with crusts and central umbilication, and then heal with scar. Patients younger than 5 years are more likely to develop life-threatening miliary and/or meningeal tuberculosis. A high index of clinical suspicion is essential to obtain an early diagnosis and early treatments should be started to improve the clinical outcomes. Although miliary tuberculosis is usually wide-spread, the contagiousness is low because it spreads via blood circulation rather than the endobronchial system.

2. The other important differential diagnoses in this patient include Langerhans cell histiocytosis, eczema herpeticum with viraemia, chickenpox, and other viral infections like cytomegalovirus infection, HIV infection, etc.

3. As it is difficult to collect sputum from a baby, gastric aspiration had been done in this baby and it showed multiple acid-fast bacilli (AFB). Skin biopsy had also been done and AFB had been demonstrated in the histology.
In miliary tuberculosis, CXR may show bilateral miliary nodules, but the tuberculin test is often negative. Lumbar puncture should be done as up to 25% of patients may have meningeal involvement.

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