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The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

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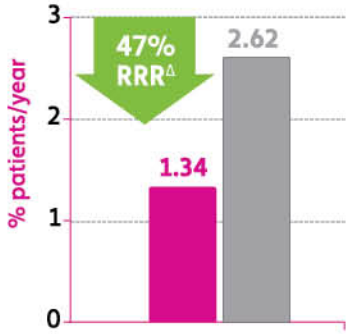
The Optimal NOAC for Asian Patients

Asian Data Matters
Because we are Asian!

Engage AF
TIMI 48

Largest and longest follow up NVAF# study with 1943 **East Asian** population[1]

Stroke / SEE
(mITT, on-treatment period^)

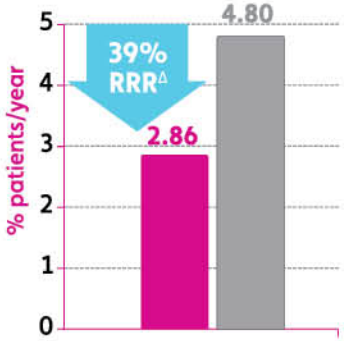


(HR 0.53; 95%CI 0.31 to 0.90; p=0.020)

PROVEN EFFICACY

Compared to well-managed^∞ warfarin Asian patients

Major Bleeding
(on-treatment period^)



(HR 0.61; 95%CI 0.41 to 0.89; p=0.011)

SUPERIOR SAFETY

Compared to well-managed^∞ warfarin Asian patients

■ LIXIANA® (n=642) ■ Warfarin (n=641)

2017 APHRS AF Consensus*

ONCE daily LIXIANA® is the **ONLY** NOAC that has proven significant reduction in **All-cause death** in Asians[2]

Nonvalvular Atrial Fibrillation / ^ Time from first dose of study drug to last dose plus 3 days / Δ Relative risk reduction / ∞ Median time in therapeutic range is 67.1% / * 2017 Consensus of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation

Ref. 1. Yamashita T et al., Circ J 2016; 80: 860-869. 2. Chiang CE et al., J. Arrhyth 33 (2017) 345-367.

LIXIANA® 60mg/30mg/15mg film-coated tablets. Each film coated tablet contains 60mg/30mg/15mg edoxaban (as tosilate). List of excipients: Mannitol (E421), Pregelatinised starch, Crospovidone, Hydroxypropylcellulose, Magnesium stearate (E470b), Hypromellose (E464), Macrogol 8000, Titanium dioxide (E171), Talc, Carnauba wax, Iron oxide yellow (E172), Iron oxide red (E172). Therapeutic Indications: Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA): 60mg LIXIANA® once daily. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults: 60mg LIXIANA® once daily following initial use of parenteral anticoagulant for at least 5 days. For NVAF and VTE 30 mg LIXIANA® once daily in patients with moderate or severe renal impairment (CrCL 15-50mL/min), body weight ≤60kg or concomitant use of P-glycoprotein (p-gp) inhibitors ciclosporin, dronedarone, erythromycin, or ketoconazole. Contraindications: Hypersensitivity to the active substance or any of the excipients; clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk; Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; Uncontrolled severe hypertension; Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; Pregnancy and breast-feeding. Undesirable effects: Common: anaemia; epistaxis; lower GI haemorrhage; upper GI haemorrhage; oral/pharyngeal haemorrhage; nausea; blood bilirubin increased; gammaglutamyltransferase increased; cutaneous soft tissue haemorrhage; rash; pruritus; macroscopic haematuria/urethral haemorrhage; vaginal haemorrhage; puncture site haemorrhage; liver function test abnormal. Uncommon: hypersensitivity; intracranial haemorrhage (ICH); conjunctival/scleral haemorrhage; intraocular haemorrhage; other haemorrhage; haemoptysis; blood alkaline phosphatase increased; transaminases increased; aspartate aminotransferase increased; urticaria; surgical site haemorrhage. Rare: anaphylactic reaction; allergic oedema; subarachnoid haemorrhage; pericardial haemorrhage; retroperitoneal haemorrhage; intramuscular haemorrhage (no compartment syndrome); intra-articular haemorrhage; subdural haemorrhage; procedural haemorrhage.

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INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drugs & Therapeutics
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

e-mail: ***editor@hkpj.org***
address: ***Room 1303, Rightful Centre, 12 Tak Hing Street, Jordan, Hong Kong.***

For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

Themed issue – a new attempt of HKPJ

I am proud to present this themed issue of Hong Kong Pharmaceutical Journal (HKPJ). This issue contains a collection of articles related to atrial fibrillation and anticoagulation.

Atrial fibrillation (AF) is a common cardiac arrhythmia and has been associated with increased risk of stroke and thromboembolism. By 2050, it is estimated that 72 million people will be diagnosed with AF and 2.9 million of them will suffer from AF-associated stroke in Asia[1]. Oral anticoagulants (including warfarin and other direct-acting oral anticoagulants (DOACs)) have been proven to be an effective strategy to reduce the risk of stroke and mortality[2] and have become a vital treatment for stroke prevention in patients with AF.

Earlier this year, the American Heart association (AHA)/American College of Cardiology (ACC)/the Heart Rhythm Society (HRS) has updated their guideline for the management of patients with AF. Similar to the 2014 guideline, the 2019 update continues to recommend anticoagulation for patients with AF. Nevertheless, the 2019 update now recommends DOACs as the preferred anticoagulants over warfarin which reflects the increased data on the safety and efficacy of DOACs (p.6).

Pages 20-28 features a collection of papers from a recent symposium organized by the Hong Kong Geriatrics Society/Brain Health Special Interest Group. This symposium discussed a multidisciplinary approach to stroke management. Professor David Siu shared his knowledge on stroke prevention in patients with AF followed by Dr. Shirley Li who reviewed the gastrointestinal bleeding risk of DOACs using Hospital Authority (HA) data. Finally, Dr. Shea Yat Fung and Mr. William Ng discussed post-stroke cognitive rehabilitation.

The article written by Ms. Vivian Ho (p. 29) featured edoxaban, the latest DOAC marketed. Although it has been registered in Hong Kong since May 2016, the inclusion of edoxaban in the 2019 AHA/ACC/HRS Guideline for the management of patients with AF worth a re-visit to this medicine.

Restoration of sinus rhythm is equally important in the management of patients with AF. Amiodarone is an effective antiarrhythmic agent for AF and yet is associated with serious extra-cardiac adverse effects with prolonged use. Mr. Nagi Wai Man provided a review on dronedarone, an alternative to amiodarone for the treatment of AF (p. 12).

Lastly, the welcome speech from the Chairlady of the Hong Kong Pharmacy Conference 2019 is included in this issue. The theme of this year was “The Time is Now” and the Conference covered topics that prepare pharmacists for the imminent opportunities. The captured welcome speech reminisces about the enlightening and inspiring experience from the Conference.

The articles in this themed issue are meant to highlight some of the current practices in the area of AF management. I hope that you enjoy this special issue. As always, your suggestions on any part of the Journal is valuable and can send the comments to me or other members of the Editorial Committee.

May PS Lam
Editor-in-Chief
12 April 2019

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1. Li Y, Lee S, Choi E, Lip G (2018). Stroke Prevention in Atrial Fibrillation: Focus on Asian Patients. *Korean Circ J*, 48(8): 665-84.
2. Alamneh E, Chalmers L, Bereznicki L (2016). Suboptimal Use of Oral Anticoagulants in Atrial Fibrillation: Has the Introduction of Direct Oral Anticoagulants Improved Prescribing Practices? *Am J Cardiovasc Drugs*, 16(3):183-200.

Prepared by Howard Chan; Chiu Tsz Ching

Association of Aspirin Use for Primary Prevention with Cardiovascular Events and Bleeding Events - A Systematic Review and Meta-Analysis

Date: January 22, 2019

The role of aspirin in primary prevention of cardiovascular diseases (CVD) remains controversial, with potential benefits limited by an increased bleeding risk. A systematic review was conducted to assess the association of aspirin use for primary prevention of CVD and bleeding.

PubMed and Embase were searched on Cochrane Library Central Register of Controlled Trails from the earliest available date through November 1, 2018. Randomized clinical trials enrolling ≥1000 participants with no known CVD and a follow-up of at least 12 months were included. Included studies compared aspirin use with no aspirin (placebo or no treatment). The primary cardiovascular outcome was a composite of cardiovascular mortality, non-fatal myocardial infarction (MI), and non-fatal stroke. The primary bleeding outcome was any major bleeding (defined by the individual studies).

A total of 13 trials randomizing 164 225 participants with 1 050 511 participant-years of follow-up were included. The median age of trial participants was 62 years (range, 53-74), 77 501 (47%) were men, 30 361 (19%) had diabetes, and the median baseline risk of the primary cardiovascular outcome was 9.2% (range, 2.6%-15.9%). Aspirin use was associated with significant reductions in the composite cardiovascular outcome compared with no aspirin (57.1 per 10 000 participant-years with aspirin and 61.4 per 10 000 participant-years with no aspirin) (hazard ratio [HR], 0.89, 95% confidence interval (CI), 0.84 –0.95]; absolute risk reduction, 0.38% [95% CI, 0.20%-0.55%]; number needed to treat [NNT], 265). Aspirin use was associated with an increased risk of major bleeding events compared with no aspirin (23.1 per 10 000 participant-years with aspirin and 16.4 per 10 000 participant-years with no aspirin) (HR, 1.43 [95% CI, 1.30-1.56]; absolute risk increase, 0.47% [95% CI, 0.34%-0.62%]; number needed to harm [NNH], 210).

The use of aspirin in individuals without cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding.

Source: www.jamanetwork.com

Cardiovascular Risk of Linagliptin Non-Inferior to Placebo in High-risk Patients with Type 2 Diabetes Mellitus

Date: January 24, 2019

Linagliptin, a dipeptidyl peptidase (DPP-4) inhibitor, has been used for glycemic management in type 2 diabetes mellitus (T2DM). Other members under DPP-4 inhibitors such as saxagliptin, were reported to pose greater cardiovascular (CV) risk in patients with T2DM. It was suggested in a recent randomized, double-blind, placebo-controlled trial held from 2011 to 2016 that the CV risk of linagliptin is non-inferior to placebo in patients with T2DM and concurrent CV and renal risks.

In Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) trial, 6991 adult patients with T2DM, HbA1C values of 6.5% to 10.0% inclusive, and high CV and renal risk were included in the study. High CV risk is defined as a history of coronary artery disease, stroke or peripheral vascular disease, microalbuminuria or macroalbuminuria; high renal risk was defined as estimated glomerular filtration rate (eGFR) lying between 45 to 75 mL/min/1.73m^2, and urinary albumin: creatinine ratio (UACR) ≥200 mg/g or equivalent, or eGFR of 15 to 45mL/min/1.73m^2 regardless of UACR. Participants were randomized in blocks in 1:1 ratio to receive either oral linagliptin 5mg or corresponding placebo once a day respectively. Primary outcome for the study was major adverse CV event (3-point MACE), including the time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, with secondary outcome defined as time to first occurrence of renal-associated functional deterioration and death.

In terms of 3-point MACE, the number of occurrence in treatment group (5.77 per 100 person-years) and did not differ significantly from that in placebo group (5.63 per 100 person-years) with the absolute incidence rate difference of 0.13 (95% CI, −0.63 to 0.90) per 100

person-years (HR, 1.02; 95% CI, 0.89-1.17; p<0.001 for non-inferiority). Subsequent superior testing was not statistically significant (p=0.74). Similar results were yielded for secondary kidney risk outcome, with the numbers for treatment and placebo group being 4.89 and 4.66 per 100 person-years respectively (absolute incidence rate difference, 0.22 [95% CI, −0.52 to 0.97] per 100 person years). Such results suggest that linagliptin may be considered as usual care for adults with T2DM and relevant risks.

Source: www.nejm.org

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation

Date: January 28, 2019

The American Heart Association (AHA), American College of Cardiology (ACC) and the Heart Rhythm Society (HRS) have co-published an update to their 2014 Guideline for the Management of Patients with Atrial Fibrillation (AF).

Female sex has been dropped as a risk factor in CHA_2DS_2-VASc scores if it is the only risk factor present, i.e. female sex does not confer a CHA_2DS_2-VASc score of 1. Female sex adds to the score only when other risk factor(s) is/are present. Oral anticoagulants are recommended for patients with AF and elevated CHA_2DS_2-VASc scores – ≥2 in men and ≥3 in women. Aspirin is no longer recommended in patients with low CHA_2DS_2-VASc scores (i.e. 1 in men and 2 in women). For those patients, oral anticoagulants may be reasonable.

This update has recommended direct-acting oral anticoagulants (DOACs) over warfarin, with edoxaban added to the list of DOACs already included in the 2014 Guidelines (dabigatran, rivaroxaban and apixaban). Apixaban is recommended as a reasonable alternative to warfarin in patients with end-stage renal disease or on dialysis alongside warfarin. Idarucizumab is recommended in this update as a FDA-approved reversal agent for dabigatran, along with andexanet alfa for reversal of rivaroxaban and apixaban.

The update has also clarified the use of anticoagulants in AF patients undergoing percutaneous coronary intervention (PCI) with stenting. If triple therapy (i.e. an oral anticoagulant + aspirin + a $P2Y_{12}$ inhibitor) is prescribed, it is reasonable to choose clopidogrel in preference to prasugrel and transit to a double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at 4–6 weeks. For double therapy, the recommended options for oral anticoagulation include dose-adjusted vitamin K antagonist, low-dose rivaroxaban (15 mg daily) and dabigatran 150 mg twice daily, whilst recommended choices for $P2Y_{12}$ inhibitors include clopidogrel and ticagrelor.

Source: www.onlinejacc.org

American Geriatric Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Date: January 29, 2019

The American Geriatric Society (AGS) has updated its Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older Adults, an explicit list of PIMs that are typically best avoided by older adults in most circumstances or under specific situations, such as in certain diseases or conditions. The Beers Criteria was last updated in 2015.

25 medications were removed from the list. Examples include ticlopidine and pentazocine due to their rare use, and chemotherapeutic agents, which were out of the scope of most primary care providers. H2 blockers were changed from avoid in all older adults to avoid in those with delirium due to its low incidence of adverse effects on most older adults and to provide an alternative for proton-pump inhibitors (PPIs).

Newly added medications include tramadol due to hyponatremia, glimepiride due to prolonged hypoglycaemia, and serotonin non-selective reuptake inhibitors (SNRIs) due to their risk of falls. Aspirin was added to be avoided in prevention for those with age ≥70 or a creatinine clearance (CrCl) of <30 mL/min. Rivaroxaban was similarly added to the list along with dabigatran to be avoided for people aged ≥75 or CrCl <30 mL/min due to GI bleeding risk. Trimethoprim-sulfamethoxazole (TMP-SMX) should be used with caution in patients with reduced kidney function due to the risk of hyperkalaemia, especially with other drugs

that may also lead to an increase in serum potassium levels. Pregabalin, gabapentin and other gabapentinoids were recommended only in low doses and received an additional recommendation to be avoided in combination with opioids due to sedation, respiratory depression, and death.

Source: www.americangeriatrics.org

First Generic Advair Diskus Approved by FDA

Date: January 30, 2019

The United States Food and Drug Administration (FDA) recently approved the first generic Advair Diskus, inhalation powder of fluticasone propionate and salmeterol, for treating asthma and chronic obstructive pulmonary disease (COPD) in patients.

Asthma is a chronic respiratory disease leading to inflammation and narrowing of airways, with typical symptoms such as wheezing, chest tightness, shortness of breath and coughing. Patients with COPD, on the other hand, experience increasing difficulty in breathing as the disease progresses; while sharing common symptoms with asthma, COPD can cause coughing with large amounts of mucus. Advair Diskus, as a combination product, controls symptoms by both direct bronchodilation and reducing airway inflammation.

Three formulations manufactured by Mylan obtained approval for generic marketing: fluticasone propionate 100mcg/salmeterol 50mcg, fluticasone propionate 250mcg/salmeterol 50mcg, and fluticasone propionate 500mcg/salmeterol 50mcg. Currently there are three combination products available in Hong Kong which share the same dosage form, with Hong Kong Registration Numbers of HK-48129, HK-48130 and HK-48128 respectively.

Fluticasone propionate and salmeterol inhalation powder is used for asthma treatment in patient aged four or above, as well as maintenance therapy for relieving airflow obstruction and exacerbations in patients with chronic obstructive pulmonary disease (COPD). Common side effects associated with the medication include irritated upper respiratory tract, dysphonia, oral candidiasis and headache. Advair Diskus is a dry powder formulation; it should be ensured that patients have rapid and deep inhalation force to allow powder deposition into the respiratory tract.

Source: www.fda.gov

Dapagliflozin as First Oral Add-on Treatment to Insulin for Type 1 Diabetes Mellitus Treatment

Date: February 1, 2019

The Human Medicines Committee (CHMP) of European Medicines Agency has recently recommended dapagliflozin, a selective sodium/glucose co-transporter 2 (SGLT2) inhibitor, as an adjunct treatment to insulin for patients with type 1 diabetes mellitus (T1DM) meeting specified conditions.

New recommendations established by CHMP extended the use of dapagliflozin for patients with T1DM whose optimal insulin therapy alone does not offer sufficient control of blood glucose levels. Such opinion is based on data retrieved from two Phase III studies involving 548 patients with T1DM, and subjects treated with dapagliflozin experienced a combined effect on weight loss, effects on blood pressure, improved and stabilized glucose levels as the main benefit of treatment.

While adjunct oral dapagliflozin enhances glycemic control therapy, diabetic ketoacidosis (DKA) becomes a major, potentially life-threatening concern as a considerable risk of developing such complication was reported in associated clinical trials. In order to minimize the risk, CHMP recommends limitation of treatment amongst obese or overweight patients with BMI ≥27kg/m^2, and to avoid use in patients with low insulin requirement. In addition, it is also essential to empower patients in self-regulating ketone levels and recognizing DKA symptoms should dapagliflozin be used as an adjunct agent.

Source: www.ema.europa.eu

JAVELIN Renal 101 trial – Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Date: February 16, 2019

Most patients with a diagnosis of renal carcinoma have clear-cell renal-cell carcinoma, which harbours genetic abnormalities that lead to excessive production of vascular endothelial growth factor (VEGF), a key driver of angiogenesis. While sunitinib, a VEGF receptor (VEGFR) inhibitor, is a standard-of-care first-line therapy for patients with advanced renal-cell carcinoma, many patients have inherent resistance to antiangiogenetic drugs or have progressive disease. The combination of an immune checkpoint inhibitor, avelumab, and a highly selective VEGFR inhibitor, axitinib, is hypothesized to provide enhanced benefit through complementary mechanisms of action.

The JAVELIN Renal 101 trial compared avelumab plus axitinib to sunitinib in patients with previously untreated advanced renal-cell carcinoma. 886 patients were enrolled and were randomly assigned in a 1:1 ratio to receive avelumab (10 kg + body weight in kg) intravenously every 2 weeks plus axitinib (5 mg) orally or sunitinib (50 mg) orally once daily for 4 weeks (6-week cycle). The two independent primary end points were progression-free survival and overall survival among patients with programmed death ligand 1 (PD-L1)–positive tumors. A key secondary end point was progression-free survival in the overall population; other end points included objective response and safety.

Among the 560 patients with PD-L1-positive tumours (63.2%), the median progression-free survival was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib (hazard ratio [HR] for disease progression or death, 0.61; 95% confidence interval [CI], 0.47–0.79, $p < 0.001$). In the overall population, the median progression-free survival was 13.8 months, as compared with 8.4 months (HR, 0.69; 95% CI 0.56–0.84, $p < 0.001$). Among the patients with PD-L1 positive tumours, the objective response rate was 55.2% with avelumab plus axitinib and 25.5% with sunitinib; at a median follow-up for overall survival of 11.6 months and 10.7 months in the two groups, 37 patients and 44 patients had died respectively. Adverse events during treatment occurred in 99.5% of patients in the avelumab-plus-axitinib group and in 99.3% of patients in the sunitinib group; these events were grade 3 or higher in 71.2% and 71.% of the patients in the respective groups.

Progression-free survival was significantly longer with avelumab plus axitinib than with sunitinib among patients who received these agents as first-line treatment for advanced renal-cell carcinoma.

Source: www.nejm.org

Drug Office: Safety Review on Finasteride on Increased Risk of Suicidal Ideation

Date: February 27, 2019

Finasteride, which is usually prescribed for androgenetic alopecia, may have linkage with increased suicidal thoughts and self-harm, announces Health Canada in a safety review.

Such review of the potential risk of suicidal ideation with finasteride use has been investigated on an ongoing basis by Health Canada since 2011; two safety reviews were completed in 2011 and 2014 respectively. Reporting rate for finasteride and suicide or self-harm events in Canada has risen by 2.5 times between 2012 and 2016, and 26 associated reports were submitted to Health Canada at the time of review. As of September 16, 2018, Adverse Drug Reaction Database of the World Health Organization revealed 368 worldwide reports of self-harm or suicidal events. While some literature and report assessment support linkage, a strong cause-and-effect relationship between the use of finasteride and suicidal ideation is yet to be established.

In overseas regions, the European Medicines Agency (EMA) added a warning in finasteride-containing products on potential suicidal ideation as well as recommended monitoring of psychiatric symptoms. Possible linkage with depression was also previously reported by the Medicines and Healthcare products Regulatory Agency (MHRA). On top of common side effects such as decreased libido and erectile dysfunction, healthcare professionals are advised to monitor changes in mental status of patients currently on finasteride.

A total of 38 pharmaceutical products registered in Hong Kong contain finasteride; by far the Department Health has not received reports on adverse drug reactions with respect to increased suicidal thoughts. Relevant safety updates will be announced by the Drug Office timely.

Source: www.drugoffice.gov.hk

The Time is Now - Hong Kong Pharmacy Conference Welcome Speech from the Chairlady

INTRODUCTION

The Hong Kong Pharmacy Conference 2019 has been successfully conducted on 9-10 March 2019 (Sat & Sun), at the Hong Kong Conventional & Exhibition Centre, Wanchai. This year the Conference Organising Committee has invited some speakers & guests of high caliber to join the occasion. In this issue, the welcome speech of the Conference Chairlady, Ms. Phoebe WL Chan has been captured.

Ms. Phoebe Chan delivering her Welcome Speech in the Opening Ceremony

THE SPEECH

The Honorable Professor Chan, Professor Kao, Professor Craig, Professor Yeoh, Professor Lam, distinguished guests, esteemed speakers, colleagues & participants, ladies & gentlemen.

I would like to start by welcoming you all to the Hong Kong Pharmacy Conference 2019, the annual important event to the pharmacy profession in Hong Kong. It is with great honour and pleasure that I am empowered by the Department of Pharmacology & Pharmacy, the University of Hong Kong to chair this momentous event. The conference theme this year is very direct, ***"The Time is Now"***. While this theme may seem simple, it has dual meaning to us all. First and foremost, it is a calling to all pharmacists from different walks of the profession. While we excel in our individual domain, we should keep an open mind and be ready to seize the vast opportunities that are open for us. Secondly, it is to show our stakeholders that the pharmacy profession has the dedication to work even closer with the SAR Government, all healthcare professionals and all citizens of HK in enhancing patient's continuity of care and improve the quality of pharmaceutical care service that our patients well deserved. Both of these callings help to distil the intention of building a healthier Hong Kong, and all good things start with a good intention.

Mahatma Gandhi said "The Future Depends on What You Do Today". Not long ago we heard strong appeals from some of the healthcare professionals in Hong Kong.

But instead of joining them in voicing our demand and substantial workload, instead of 鬧爆, pharmacists decided to hold fast onto our duties to serve as the ultimate gate-keepers to see to the safe use of medications. Pharmacists are such steadfast professionals, we are like sentinels, who when others have faltered, we keep going against all odds, all because of one word, "Love". We love our patients, we love Hong Kong, we love our jobs, But most important of all, is the love of our profession, I am certain that all of us sitting here bear the title of being a pharmacist with much pride.

Louis Pasteur (the father of the germ theory, who invented the process of pasturisation, which was named after him) said "Chances Favours the Prepared Mind"(in Chinese「機會是留給有準備的人」). Allow me to share with you what Pharmacists have also been doing meanwhile when others鬧爆. Teams of pharmacists decided to reach out and deliver influenza vaccinations to kindergarten children, from prestigious areas such as Kowloon Tong, to more "grass-root" areas such as Tin Shui Wai and Sham Shui Po. Some of us, including myself, even went on training courses to learn the hands-on skills in delivering influenza vaccines intramuscularly, and increasing our presence in the domain on travel medicines. There are also teams of pharmacists who reach out to old-aged care homes to reconcile the numerous medications used by the elderly residents, and to implement smart-ways

using automation in medication distribution. Hospital pharmacists in every single cluster in the Hospital Authority and in private institutions try to deliver ward-based pharmaceutical care even under such stressful times, to help shoulder the workload from our busy doctors and nurses. Many of them even obtained board certified specialisations in nearly all of the specialties that are made available. These are only the beginnings. Therefore, Professor Chan, honourable guests, ladies & gentlemen, I would like to seize the occasion to tell you all clear and sound, that ***"Pharmacists Are Ready!"***

Professor Chan, as a faithful friend to the pharmacy profession, it is such a pleasure to have your graceful presence. Your support means so much to me and my colleagues, in recognising our work and contributions. Our 4 esteemed theme speakers today shall set the tone in resonance with the conference theme. Professor John Kao will start by telling us why it is important to step up our game in the field of healthcare. Professor Duncan Craig from my alma mater will explain to us why the time is indeed now for pharmacists to act upon the geopolitical changes around us. Professor EK Yeoh will illustrate to us the how pharmacists should position themselves in primary care service. Last but not least, Professor CC Lam will elaborate on expanding our visibility and presence in elderly care in Hong Kong.

Lectures and workshops tomorrow shall provide more hands-on skills in preparing pharmacists who aspire to become better healthcare providers. These include the exploration of opportunities in the Greater Bay Area, the skills in crisis management by Dr. CC Luk, sharing opportunities with colleagues from the e-Health Record office, just to name a few; and on-site certification of Adult Cardiopulmonary Resuscitation (CPR) by St. John's Ambulance, first time ever in the history of the Hong Kong Pharmacy Conference.

Colleagues, ladies & gentlemen, to quote Cervantes in his book Don Quixote, "The Sky's the Limit". **And the Time is Now**.

Photo of Mr. Johnny Wong (vice-chairman), the Hon. Dr. CC Lam & Ms. Phoebe Chan (chairlady)

XANAP

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GI Bleeding	0.5%[1]	**ICH**	0.7%[1]

GI: gastrointestinal, ICH: intracranial haemorrhage, NVAF: non-valvular atrial fibrillation

Xarelto 10 mg / 15 mg / 20 mg film-coated tablets
Abbreviated Prescribing Information (Please refer to the full prescribing information before prescribing)
Composition: Active ingredient: 10 mg / 15 mg / 20 mg rivaroxaban. Excipients: Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide red (E172).Indication and Posology: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Recommended dose is 20 mg once daily (recommended maximum dose). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults: The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE. When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. A dose of 20 mg once daily should be considered in patients with high risk. Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery: The recommended dose is 10 mg once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established. For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended. For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended. Patients with NVAF who undergo percutaneous coronary intervention (PCI) with stent placement: There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with moderate renal impairment [creatinine clearance 30 – 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement. Renal impairment: No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min). In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply: For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily. For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily. When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary. Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased; therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min. Contraindications: Hypersensitivity to the active substance or any of the excipients; active clinically significant bleeding; lesion or condition if considered a significant risk for major bleeding; concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C; pregnancy and breast feeding. Warnings and Precautions: Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period. Not recommended: in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole antimycotics or HIV protease inhibitors; in patients with increased bleeding risk; in patients with severe renal impairment (creatinine clearance < 15 ml/min); in the treatment of acute pulmonary embolism, due to lack of data; in patients below 18 years of age, in patients with prosthetic heart valves, in patients concomitantly treated with dronedarone, in NVAF-PCI patients with a history of stroke/transient ischemic attack. Use with caution: please refer to the full prescribing information. Xarelto contains lactose. Undesirable effects: Common: anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, gastrointestinal tract haemorrhage, gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous and subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage, fever, renal impairment, peripheral oedema, decreased general strength and energy, increase in transaminases, post procedural haemorrhage, contusion, wound secretion. Other undesirable effects (uncommon, rare, frequency not known): please refer to the full prescribing information.

References: 1.YH Kim et al. XANAP: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Asia. Journal of Arrhythmia 2018;1-10.

XANAP is a large, prospective, observational, single-arm study enrolled 2,273 patients with non-valvular atrial fibrillation from 10 Asia Pacific countries to investigate the safety and efficacy of Xarelto for stroke prevention in routine clinical practice for 1 year. Primary outcomes were treatment-emergent major bleeding events, adverse events (AEs), serious AEs and all-cause mortality.

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Dronedarone: A Review in Atrial Fibrillation

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ABSTRACT

Amiodarone is currently the most widely used and effective antiarrhythmic agent for atrial fibrillation. Its prolonged use, however, has been associated with some serious extra-cardiac adverse effects. Dronedarone is a newer antiarrhythmic drug that does not possess the toxicity associated with amiodarone. With the addition of a methylsulfonyl group and the removal of iodine moieties, dronedarone has lower tissue accumulation and a shorter half-life than amiodarone. In clinical trials, dronedarone was shown to reduce ventricular rate and atrial fibrillation recurrence and is the first antiarrhythmic drug to show a reduction in cardiovascular mortality and hospitalization in atrial fibrillation patients. However, dronedarone is contraindicated in patients with heart failure or permanent atrial fibrillation. It was less effective in maintaining sinus rhythm than amiodarone after cardioversion, but was associated with fewer premature drug discontinuations and fewer adverse effects. The most common side effects associated with dronedarone are nausea, vomiting and diarrhea. Dronedarone has been approved in the United States, Canada, the European Union and Hong Kong. According to the European Society of Cardiology (ESC) 2016 Guidelines, dronedarone is currently suggested for long-term indication in atrial fibrillation patients with (1) No or minimal signs of structural heart disease, and (2) with coronary artery disease, significant valvular heart disease, or abnormal left ventricular hypertrophy. This paper will review the current evidence of safety and effectiveness of dronedarone in treating patients with atrial fibrillation and discuss the position of this drug in the currently available antiarrhythmic armamentarium.

Key words: *Atrial fibrillation, antiarrhythmic agent, dronedarone, amiodarone, sotalol, propafenone*

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice.[1,2] Clinical consequences associated with AF include a three-fold increase in congestive heart failure, a five-fold increase in the risk of stroke and a two-fold increase in mortality.[3] As the proportion of seniors continues to grow, the number of patients with AF in Hong Kong is expected to rise, with prevalence increasing from 0.7% in people aged 55-59 years to 18% in those older than 85 years.[4,5]

Currently, there are two strategies to restore and maintain sinus rhythm: rhythm and rate control. Clinical trials, however, have failed to demonstrate superiority of one strategy over the other.[6] Patients who present with symptoms, but do not wish to undergo catheter ablation will require antiarrhythmic drugs to relieve symptoms and manage their disease.

Existing antiarrhythmic drugs indicated for AF include all class 1C (such as propafenone and flecainide) and class III drugs (such as sotalol and amiodarone), which interact with the sodium and potassium channels of the cardiac tissue, respectively. Such therapies, however, have limitations in efficacy and safety. Class 1C drugs flecainide and propafenone pose the risk of serious side effects such as ventricular proarrhythmia, while sotalol tends to cause drug-induced prolongation of the QT interval which increases the risk of *torsades de pointes*.[7] In a meta-analyses directly comparing antiarrhythmic drugs, amiodarone showed significantly fewer withdrawals and fewer instances of proarrhythmia.[8] Additionally, a large randomized controlled trial comparing amiodarone to sotalol and propafenone found that amiodarone was nearly twice as effective as the other treatments in maintaining sinus rhythm in patients with atrial fibrillation.[9] Although amiodarone is the most potent antiarrhythmic agent, its long half-life leads to drug accumulation and end organ toxicity, such as pulmonary fibrosis, ocular deposits, hypothyroidism and liver enzyme abnormality. In fact, one study reported the incidence of amiodarone-associated hypothyroidism to be as high as 30%.[10]

DRONEDARONE

Structure and Pharmacodynamics

Dronedarone is a synthetic benzofuran derived from amiodarone, a popular antiarrhythmic. Its structure has been altered such that the toxic effects often affiliated with continuous amiodarone therapy may be decreased.

An additional methylsulfonyl group makes dronedarone more water-soluble and less thus likely to accumulate in organ tissue, while the removal of two iodine atoms prevent the accumulation of the drug in the thyroid, thus avoiding thyroid toxicity **(Figure 1)**.[11-15]

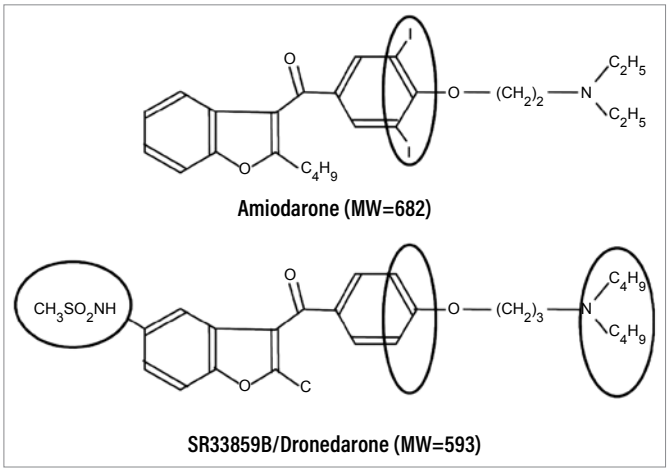

Figure 1. Chemical structures of dronedarone and amiodarone. Reprinted with permission from the Journal of Cardiovascular Pharmacology.

In terms of electrophysiology, dronedarone exhibits all four class effects of antiarrhythmic agents, as it interferes with a sodium, potassium, and calcium channels, and has anti-adrenergic properties.[15] The ability to block multiple channels reduces its likelihood of causing pro-arrhythmia.[12,13] Dronedarone also blocks alpha and beta receptors, and acts to prolong atrial and ventricular refractory periods, thus reducing the rate of sinus activity.[10,14,15,16]

Pharmacokinetics

Dronedarone has a smaller volume of distribution and shorter half-life than amiodarone.[8,17] The half-life of dronedarone is 24 – 30h and is eliminated mainly in the feces.[18]

Dronedarone is metabolized in the liver via CYP3A4 isoenzymes, and as previously mentioned, is more water-soluble and has lower tissue accumulation compared to amiodarone. It has a bioavailability of only 15%; however, when dronedarone is taken with food there is a two- to three-fold increase in serum concentration.[15] Thus, it is recommended that dronedarone be taken at a dose of 400mg twice daily (BID) with meals, which allows it to reach steady-state levels in 5-7 days.[9,14]

Increases in serum creatinine associated with dronedarone have been reported in numerous clinical studies, although these increases were noted to be mild and reversible.[19,20,21] This increase in serum creatinine is not indicative of nephrotoxicity, as it has also been shown that dronedarone disrupts the renal cation transport system.[11]

Dronedarone should not be used with antifungals, macrolide antibiotics and protease inhibitors since dronedarone and antifungals are metabolized by the 3A4 system.[22] Thus, concomitant antifungals may increase the plasma levels of dronedarone, leading to adverse events.[23] Both macrolide antibiotics and dronedarone act to prolong the QT interval, and when administered together, may cause serious adverse effects such as *torsades de points*.[24] Additionally, when dronedarone is co-administered with verapamil, diltiazem, simvastatin, metoprolol, digoxin or dabigatran, lower doses of concomitant drugs should be used.[22,25,26] As a Pgp inhibitor, dronedarone increases levels of digoxin or dabigatran by 1.1 to 2.5-fold when co-administered.[22] It is also not recommended to administer dronedarone in patients who are or may become pregnant, or are nursing, as the drug may cross the placenta, or may be excreted into breast milk.[27]

Rhythm Control (DAFNE, ERUDIS and ADONIS) (Table 1)

Table 1. Summary of clinical trials.

Trial	Subjects enrolled	Follow-up period	Main outcome	Common side effects
DAFNE	270	6 months	First AF recurrence was 60 days with 400 mg b.i.d. dronedaronevs. 5.3 days with placebo; relative risk reduction of 55% (95% CI, 28% to 72%; p = 0.001	Gastrointestinal
EURIDIS and ADONIS	612 in EURIDIS and 625 in ADONIS	12 months	First recurrence of AF/AFL was 64.1% with dronedarone vs 75.2% with placebo (p < 0.001)	Gastrointestinal ADONIS (diarrhea)
ERATO	174	4 months	Reduction of 11.7 bpm in ventricular rate at day 14 (p < 0.0001) – this effect was sustained for the duration of trial (-8.8 bpm at 4 months) (p < 0.001)	Infections Mild increase in serum creatinine levels
ANDROMEDA	627	13 months (including additional 6 months after premature discontinuation of study)	Premature termination of trial due to excess mortality related to the worsening of heart failure in dronedarone group (hazard ratio of 2.13; 85% CI 1.07 to 4.25; p = 0.003)	Worsening heart failure Increase in serum creatinine levels
ATHENA	4628	21 months	First hospitalization due to cardiovascular events or death was 31.9% in dronedarone group vs 39.4% in placebo group (hazard ratio of 0.76; 95% CI 0.69 to 0.84; p < 0.001)	Gastrointestinal (diarrhea, nausea) Increase in serum creatinine levels Rash Bradycardia

Reproduced from Patel et al with permission from the publisher.[36]

The Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) was the first double-blind, randomized, placebo-controlled trial that sought to establish the optimal dose of dronedarone (400, 600, 800 mg *b.i.d.*) for preventing AF recurrence after cardioversion in 270 patients with persistent AF for 6 months.[16]

After 6 months of follow-up, dronedarone 400 mg *b.i.d*. was shown to be the most effective in prolonging the time to first AF recurrence (60 days in the 400 mg *b.i.d*. dronedarone group vs. 5.3 days in the placebo group; relative risk reduction of 55% [95% CI, 28% to 72%], p = 0.001). Higher doses showed no significant improvement in time to AF relapse. Besides rhythm control, dronedarone also showed a dose-dependent reduction in heart rate at the time of first AF recurrence with patients receiving 400, 600, 800mg *b.i.d*. of dronedarone experiencing reductions of 13.2, 19.2, and 17.8 beats per minute (bpm) in ventricular rate, respectively, compared to the placebo group. In terms of safety, higher doses were associated with higher discontinuation rates due to adverse events (3.9% in the 400 mg *b.i.d* group, 7.6% in the 600 mg *b.i.d* group, and 22.6% in the 800 mg *b.i.d* group, all *b.i.d*.). Adverse events at higher doses were mainly gastrointestinal.

To evaluate the efficacy of dronedarone to maintain sinus rhythm over a longer period, two identical pivotal trials were conducted: The European trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS).[19] Both studies randomized a total of 1,237 patients to dronedarone 800 mg or placebo for 12 months. Patients were included if they were taking standard rate-controlling agents and had at least one episode of AF or atrial flutter (AFL) during the past 3 months but were in sinus rhythm before enrollment.

The combined results indicated that dronedarone was effective for increasing the time to first AF recurrence (median 116 days in the dronedarone group vs 53 days in the placebo group [12 months HR 0.75, 95% CI, 0.65 to 0.87, p < 0.0001]) and in reducing ventricular rate. The recurrence rate of symptomatic AF or AFL after 1 year was 64.1% for dronedarone versus 75.2% for placebo (HR 0.75; p < 0.001). Post-hoc analysis also revealed a 27% reduction in all cause hospitalization and death (22.8% vs 30.9%, p = 0.01). Despite a 2.4% increase in serum creatinine in the dronedarone group, discontinuation rates due to adverse events were low (9.5% with dronedarone and 6.1% with placebo). Dronedarone also showed an impressive safety profile, with no significantly increased rate of adverse events, with the exception of hyperthyroidism and elevation of serum creatine.

Rate Control (ERATO)

Besides rhythm control, dronedarone also possesses rate-controlling properties. In the Efficacy and Safety of Dronedarone for Control of Ventricular Rate (ERATO) trial, dronedarone was found to significantly reduce the heart rate by 11.7 bpm at rest and 24.5 bpm during exercise (p < 0.0001 for both) on day 14 in 174 permanent, symptomatic AF patients whose heart rate was uncontrolled (≥ 80 bpm) with prior rate control therapies.[20]

The rate controlling effects of dronedarone were additive to those of other rate controlling agents (beta-blockers, digitalis, or calcium channel antagonists) and the effect was sustained for the 4-month trial period. Dronedarone also had no effect on the international normalized ratio in patients taking oral anticoagulants. As expected, there was a mean increase of 41.4% in digoxin levels in those taking dronedarone; however, the proportion of patients with greater than normal digoxin levels was not significantly different between groups (4.5% with dronedarone vs. 2.8% with placebo). Safety data were comparable to that of the pooled EURIDIS and ADONIS trials, where dronedarone showed no occurrences of proarrhythmia or extracardiac adverse effects, and only slightly increased serum creatine levels.

Mortality and Morbidity (ANDROMEDA and ATHENA)

While studies of dronedarone in AF patients indicated that it has an excellent safety profile, a heart failure trial was prematurely stopped due to increased mortality. The Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) investigated the use of dronedarone in 1,000 hospitalized patients who had severe left ventricular dysfunction and had at least one New York Heart Association class III-IV episode in the month prior to enrollment.[28] The trial was stopped prematurely at 7 months after 25 (8.1%) patients in the dronedarone arm and 12 patients (3.8%) in the placebo group had died (hazard ratio [HR] 2.13, 95% CI 1.07 to 4.25, p = 0.027) **(Figure 2).** Excessive mortality rates seen in this study were attributed to worsening heart failure.

A review of the clinical pharmacology, electrophysiology, clinical trial data, and efficacy and safety of dronedarone provided by the sponsor of the trial, highlighted a possible explanation of ANDROMEDA's results, provided by a sponsor of the trial.[22] They explained that the increase in mortality in the dronedarone arm might have been due to the early withdrawal of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB). However, this explanation does not agree with the sub-group analysis conducted by the authors of the ANDROMEDA trial, in which 50 placebo patients were naïve to ACE inhibitors and ARBs, and only 3 (6%) died, compared to 7 (19%) deaths in 36 ACE inhibitors and ARB naïve patients in

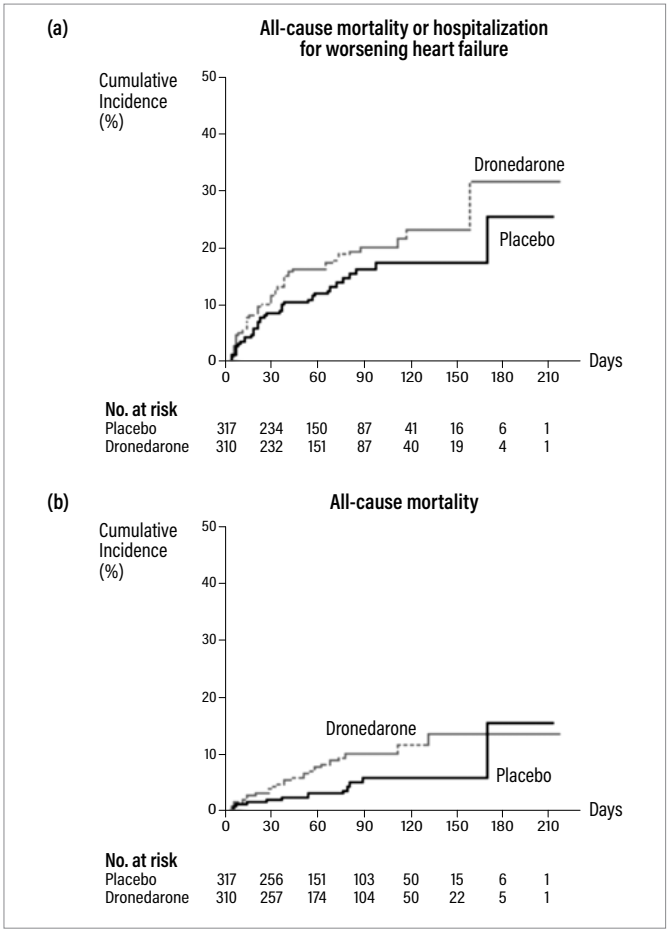

Figure 2. Upper panel: Kaplan–Meier cumulative incidence curves for all-cause mortality or hospitalization for worsening of heart failure in the ANDROMEDA trial among patients allocated to receive dronedarone or placebo. Lower panel: Kaplan–Meier incidence curves for all-cause mortality. Reproduced with permission.[24]

the dronedarone group.[28] Since dronedarone causes a reversible increase in serum creatinine that might have been mistaken for ACE inhibitor or ARB toxicity, the premature withdrawal of ACE inhibitors or ARBs in the dronedarone group may have contributed to the increase in heart failure mortality. Taking the results of this trial into consideration, dronedarone should not be administered in patients with congestive heart failure.

The results of the ANDROMEDA trial prompted the investigators to conduct the largest outcome trial, Assess the Efficacy of Dronedarone for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA), to evaluate the efficacy and safety of dronedarone in reducing the composite endpoint of hospitalization and death.

The ATHENA trial was a landmark study of 4,628 patients which evaluated the impact of adding dronedarone to standard rate controlling agents in the management of AF. Patients who had paroxysmal or persistent AF/AFL and had at least one cardiovascular risk factor were included and randomized to receive either dronedarone 800 mg or standard rate controlling agents.[21,29] Exclusion criteria were patients with class IV New York Heart Association grade, permanent AF, or unstable heart failure.

After a follow-up of 21 months, the primary outcome of hospitalization due to cardiovascular events or death occurred in 734 (31.9%) dronedarone-treated patients (HR 0.76 [95% CI, 0.69 to 0.84; p < 0.001)) compared to 917 (39.4%) placebo-treated patients. Patients in the dronedarone arm experienced a 29% reduction in cardiovascular death (HR 0.71, CI = 0.51-0.98, p < 0.05) and 26% reduction in hospitalization (HR 0.74, CI = 0.67-0.82, p < 0.05) **(Figure 3)**. These benefits (hospitalization reduction and death) did not differ between patients with or without structural health disease, those greater or younger than 65 years of age, and those with presence or absence of sinus rhythm at baseline. A post-hoc analysis of ATHENA also revealed that dronedarone reduced the number of days spent in hospital (28% reduction, p < 0.001) and that the reduction in hospitalization was due to the reduction in hospitalizations due to AF, acute coronary syndrome, heart failure and stroke.[30] These findings suggest that dronedarone offers clinical benefits beyond rhythm and rate control.

Dronedarone was well tolerated with slightly more patients in the dronedarone arm discontinuing treatment due to adverse effects than the placebo group (12.7% in the dronedarone group vs. 8.1% in the placebo group). The most commonly reported adverse effects were bradycardia, QT prolongation, nausea, diarrhea, rash and increased serum creatinine. Only one case of *torsades de pointes* was reported. No serious adverse events (thyroid dysfunction or pulmonary fibrosis) were reported during the follow-up period.

Comparative Efficacy

The Efficacy and Safety of Dronedarone vs. Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation (DIONYSOS) trial randomized 504 amiodarone-naïve patients to a treatment regimen of either dronedarone 400 mg twice daily or amiodarone 600 mg once daily for 28 days, followed by 200 mg once daily.[31] Patients were followed for a median of 7 months. Results showed that a composite of AF recurrence (including unsuccessful electrical cardioversion, no spontaneous conversion and no electrical cardioversion) or premature study discontinuation occurred more frequently in the dronedarone arm vs amiodarone at 12 months (75.1 vs. 58.8%, respectively; HR 1.59). Additionally, dronedarone was less effective in maintaining the sinus rhythm than amiodarone after cardioversion (36.5% in the dronedarone arm vs. 24.3% in the amiodarone arm), but was associated with fewer premature discontinuations of drug treatment (10.4 vs. 13.3%) and fewer adverse effects including thyroid, neurologic, skin, and ocular events (HR 0.80).

The Effects of Dronedarone on Atrial Fibrillation Burden in Subjects with Permanent Pacemakers (HESTIA) was a double-blind, multicenter, randomized, placebo-controlled clinical trial that compared the

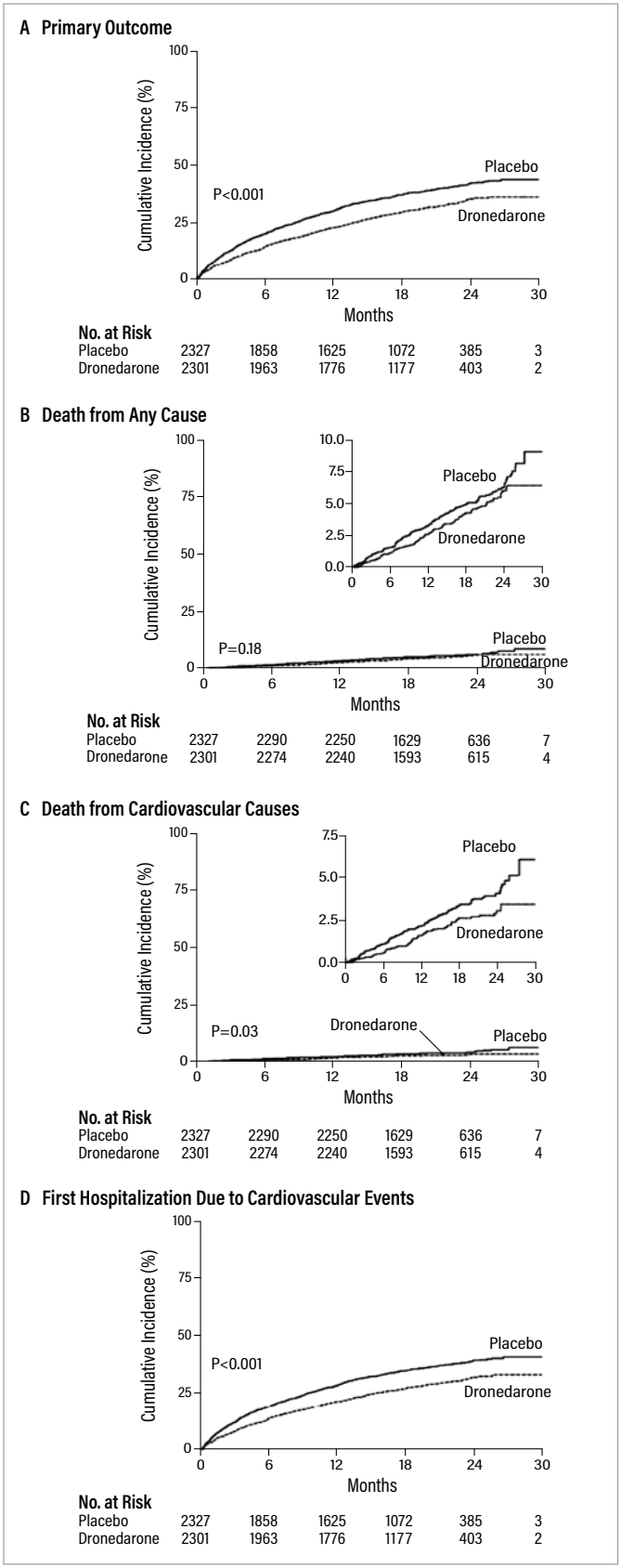

Figure 3. Kaplan–Meier cumulative incidences of the primary and secondary outcomes in the ATHENA trial. Treatment with dronedarone significantly reduced the occurrence of (A) the composite primary outcome of first hospitalization due to cardiovascular events or death from any cause (HR 0.76), (C) secondary outcomes of death from cardiovascular causes (HR 0.71), and (D) first hospitalization due to cardiovascular events (HR 0.74). (B) There was no difference in all-cause mortality (HR 0.84). Reproduced from Hohnloser et al with permission from the publisher.[25] Copyright © 2009, the Massachusetts Medical Society.

disease burden at 12 weeks in 112 AF patients with permanent pacemakers treated with dronedarone 400 mg *b.i.d*. versus placebo.[32] By the end of the study period, AF burden had decreased by 54.5% (standard error of the mean [SEM] 0.22; p = 0.0009) from baseline in the dronedarone-treated patients compared to a statistically insignificant increase of 12.8% (SEM 0.16; p = 0.450) in those treated with placebo. Treatment-emergent adverse events were slightly higher with dronedarone (65% vs 56%), but treatment discontinuation due to adverse events were comparable between groups (14% dronedarone vs. 16% placebo). Overall, the investigators concluded that the safety results observed were comparable to the known profile of dronedarone, and that dronedarone is effective in reducing disease burden in AF patients.

The Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) was a recent randomized, double-blind, placebo-controlled, multicenter, international trial investigating the effect of dronedarone 400 mg *b.i.d.* on the rate of major vascular events or cardiovascular hospitalization in patients with permanent AF.[33] The composite outcome of stroke, myocardial infarction, systemic embolism, or cardiovascular death was reported in 43 dronedarone-treated patients compared to 19 of those treated with placebo (HR 2.29; p = 0.002). Similarly, unplanned hospitalizations for cardiovascular complications or death occurred in 127 patients on dronedarone versus 67 placebo patients (HR 1.95; p < 0.001). Due to the high rate of death occurring in this trial, the authors concluded that dronedarone was in fact unsafe for use in this high-risk population and this study was terminated early for safety reasons. A major difference between this trial and ATHENA was the inclusion of permanent AF patients, a population in whom normal sinus rhythm is unlikely to be restored. Accordingly, the current Food and Drug Administration label lists dronedarone as contraindicated in permanent AF.

Freemantle et al. conducted a meta-analysis of 39 randomized controlled trials (RCTs), which included DIONYSOS, ATHENA and etc., investigating dronedarone and several other antiarrhythmic drugs, namely flecainide, propafenone, sotalol, or placebo for the treatment of AF.[34] Across all treatments analyzed, amiodarone showed the largest reduction in recurrence of AF (odds ratio [OR] 0.22), but also showed the highest rate of patients experiencing at least one serious adverse event (OR 2.41) and treatment withdrawals due to adverse events (OR 2.91). For outcomes of all-cause mortality, analysis of 18 RCTs (n = 10,032) showed no increase in mortality with the use of dronedarone compared to placebo (OR 0.85). Both amiodarone and sotalol were associated with an increased risk of death **(Figure 4)**. Analysis of 4 RCTs (n = 7,034) reporting on stroke outcomes showed that dronedarone was associated with decreased risk of stroke compared to placebo (OR 0.69; p = 0.015), while no significant reduction of stroke was present with use of amiodarone or sotalol compared to placebo. However, there were no significant differences in the risk of stroke between each of the antiarrhythmic drugs. For serious adverse events,

analysis of 20 RCTs (n = 9,734) revealed no significant difference for any antiarrhythmic drug compared to placebo, and no significant differences in serious adverse events between antiarrhythmic drugs. However, dronedarone showed the lowest rate of proarrhythmic events among all drugs compared to placebo (OR 1.45).

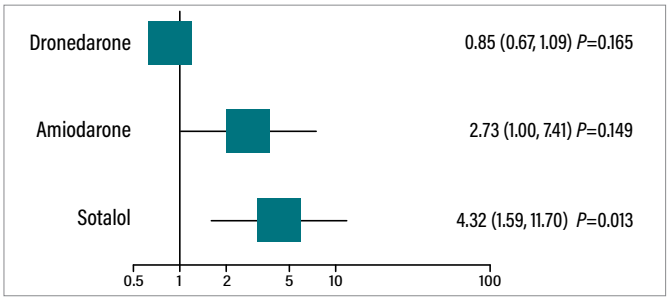

Figure 4. Mixed treatment comparison analysis: effect of antiarrhythmic drugs on all-cause mortality in studies involving 100 patients in either arm. Odds ratios and 95% confidence intervals. Reproduced with permission.

Overall, the existing literature on the efficacy of dronedarone includes a suite of recent, high-quality RCTs that highlight its competitive efficacy and favorable safety profile relative to other drugs in AF and AF sub-populations, apart from permanent AF. Even more promising, as described in the meta-analysis by Freemantle et al., dronedarone is associated with less proarrhythmic events.[34] The recent findings summarized here have presented dronedarone as a viable solution to cardiac arrhythmias across various AF patients in controlled clinical settings.

Role of Dronedarone in the Antiarrhythmic Armamentarium

According to the European Society of Cardiology (ESC) 2016 Guidelines, dronedarone is currently suggested for long-term indication in patients with (1) No or minimal signs of structural heart disease, and (2) with coronary artery disease, significant valvular heart disease, or abnormal left ventricular hypertrophy **(Figure 5)**.[35] In both indications, it is the patient's choice to decide between catheter ablation or antiarrhythmic drug therapy. Other drugs recommended for the former indication include flecainide, propafenone, or sotalol, while sotalol and amiodarone are also recommended for latter indication.

As of 2009, dronedarone has been approved for use in patients with persistent or paroxysmal AF to effectively manage disease and reduce the risk of AF-related hospitalization. Since then, dronedarone has shown impressive rate-controlling and rhythm-controlling properties.[15,18,19] The latter is especially advantageous in patients who are younger or more active and require a higher level of exercise capacity.[31]

As mentioned previously, amiodarone is the most prevalent and effective of the recommended drugs but is associated with high toxicity.[10,11] The lower toxicity associated with dronedarone is a major advantage for patients at risk of or presenting with comorbidities such as liver or thyroid disorders, or those who previously

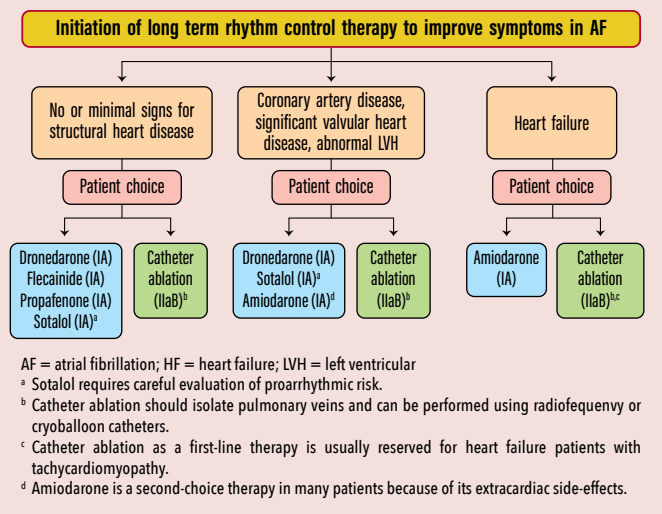

Figure 5. Algorithm for the management of atrial fibrillation in the 2016 ESC guidelines. Reproduced with permission.

experienced amiodarone thyroid toxicity and are looking for an alternative.

Finally, the promising efficacy and safety profile of dronedarone in the various AF populations described above makes it a potentially advantageous second-line treatment for patients who have failed other antiarrhythmic drugs.

Dronedarone is an antiarrhythmic drug that has been shown to preserve a large part of amiodarone efficacy but with a better safety profile. In several clinical trials, dronedarone was shown to maintain sinus rhythm and control ventricular rate during episodes of AF. It is also the first compound to demonstrate reductions in cardiovascular morbidity and mortality in AF patients. Its use, however, should be limited to patients without permanent atrial fibrillation or without heart failure or hemodynamic instability, as evidenced by ANDROMEDA.

Dronedarone shows a promising tolerability profile, as mild adverse events such as nausea, vomiting and diarrhea were the most commonly experienced. There is no clinically significant interaction with warfarin. Some patients may experience a prolongation of QTc interval, but incidence of *torsades de pointes* is rare. The drug might also cause a reversible increase in serum creatinine, but the effect is not associated with a reduction in renal function.

Given the limitation of the adverse effects of current antiarrhythmic drugs and dronedarone's excellent tolerability profile, dronedarone is a viable, effective, and safe option for patients with AF.

Author's background

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Dronedarone: A Review in Atrial Fibrillation

1. ***Which modification from amiodarone may be responsible for dronedarone reduced organ toxicity?***
   - A. Addition of methyl sulphonyl group and removal of 2 iodine radicals
   - B. Removal of methyl sulphonyl group and addition of 2 iodine radicals
   - C. Addition of methyl sulphonyl group and 2 iodine radicals
   - D. Removal of methyl sulphonyl group and 2 iodine radicals

2. ***Dronedarone***
   - A. Increases the secretion of creatinine at the tubular level
   - B. Increases the level of serum creatinine by 10-15%
   - C. Interferes with renal function
   - D. Requires dose-adjustment in renal impairment

3. ***The half-life of dronedarone is ___ hours***
   - A. 15 hours
   - B. 20 hours
   - C. 25 hours
   - D. 50 hours

4. ***The recommended daily dosage of dronedarone is _____***
   - A. 75mg BID
   - B. 100 mg BID
   - C. 200mg BID
   - D. 400mg BID

5. ***Which of the following is not rhythm -control drugs?***
   - A. Diltiazem
   - B. Dronedarone
   - C. Sotalol
   - D. Flecainide

6. ***Dronedarone is excreted mainly via the***
   - A. Kidneys
   - B. Liver
   - C. Skin
   - D. Lungs

7. ***Dronedarone is contraindicated in:***
   - A. Stage I and II NYHA compensated heart failure
   - B. Stage II and III NYHA compensated heart failure
   - C. Stage III and IV NHYA compensated heart failure
   - D. All NYHA heart failure patients

8. ***Dronedarone is indicated for which cardiac condition?***
   - A. Paroxysmal supraventricular tachycardia
   - B. Paroxysmal and persistent atrial Fibrillation
   - C. Ventricular tachycardia
   - D. Premature atrial contractions

9. ***The most common side-effect seen with dronedarone use is:***
   - A. UTI infections
   - B. Diarrhea
   - C. Headache
   - D. Muscle ache

10. ***Compared with amiodarone, dronedarone is associated with a lower incidence of:***
    - A. Skin rashes
    - B. GI side-effects
    - C. Thyroid toxicity
    - D. Bradycardia

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 254(D&T)

Idiopathic pulmonary fibrosis (IPF): 10 points to take home

1. D 2. C 3. D 4. A 5. C 6. B 7. A 8. B 9. B 10. D

A Multidisciplinary Approach to Stroke Management: from Prevention to Rehabilitation

The Hong Kong Geriatrics Society Brain Health Special Interest Group

SIU, David Chung Wah
Clinical Professor, Division of Cardiology, The University of Hong Kong, Hong Kong

At a recent symposium held on 12th January 2019 at Cordis Hong Kong, Professor David Siu Chung Wah, Clinical Professor of Division of Cardiology at the University of Hong Kong shared his knowledge of therapeutic choices for atrial fibrillation (AF)-related stroke prevention. This was followed by the presentation of Dr Shirley Li Xue, Research Assistant Professor of the Department of Pharmacology and Pharmacy at the University of Hong Kong, which discussed the safety of non-vitamin K antagonist oral anticoagulants (NOACs) in Hong Kong. The symposium was concluded by Dr Shea Yat Fung, Consultant Geriatrician of Division of Geriatric Medicine at Queen Mary Hospital, and Mr William Ng Chak Wing, Occupational Therapist at Kowloon Hospital, with a brief discussion of cognitive rehabilitation after stroke. The event was organised by the Hong Kong Geriatrics Society.

Is there a role of antiplatelet therapy for stroke prevention in AF?

Local burden and complications of AF

As the most commonly encountered arrhythmia in clinical practice, AF affects at least 4 million Chinese adults, posing an enormous threat to the healthcare system in mainland China.[1] Since the AF incidence increases with age,[1,2] Asia, with a proportionally larger elderly population, has a much higher disease burden in spite of the relatively lower prevalence of AF in the overall population when compared with the West.[2] AF causes turbulent flow within the atria, leading to a predisposition to atrial thrombus formation. The dislodging of thrombus fragments may embolise and occlude cerebral arteries, causing an ischaemic stroke.[3] As a result, AF patients are at 5-fold increased risk of developing a thromboembolic stroke.[4] Furthermore, AF patients without treatment of an anticoagulant drug were found to have a 2.1-fold increase in the risk for recurrent stroke and a 2.4-fold increase in the risk for recurrent severe stroke.[5] Such findings indicate the crucial role of antithrombotic treatment in AF-related stroke prevention.

Current guideline recommendations

Regarding the treatment pattern of AF-related stroke prevention, the global usage of aspirin was common. In the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF), 25.3% of AF patients were prescribed an antiplatelet drug as antithrombotic therapy.[6] The frequent prescription of aspirin may be related to its easy administration, and the perceived lower major bleeding risk compared to other antithrombotic agents. Nevertheless, the evidence in the benefit of aspirin for stroke prevention remains scarce.[7]

Since 2012, antiplatelet therapy has been out of sight from various international guidelines of AF.[8-11] Most guidelines recommended NOACs and vitamin K antagonists (VKAs) for stroke prevention in patients with medium to high risk of stroke (CHA_2DS_2-VASc score ≥1) and abandoned the use of antiplatelet therapy.[9-11] The only exception was from the 2014 AHA/ACC/HRS guideline, which recommended no therapy or acetylsalicylic acid (ASA) for patients with a CHA_2DS_2-VASc score of 1.[8] However, only a small minority of AF patients had such score. Furthermore, the use of antiplatelet monotherapy for stroke prevention in AF patients was considered harmful in the 2016 European Society of Cardiology (ESC) Guideline.[11] Clinicians, therefore, should reassess the decision of prescribing aspirin for AF-related stroke prevention.

Decision making for antithrombotic agents in stroke prevention

An evidence-based approach is the ideal method of determining treatment regimen for stroke prevention. Although aspirin was claimed to reduce stroke risk by overall 42% (p=0.02) in the SPAF I study in 1991,[12] the study was prematurely terminated and may not have enough statistical power to substantiate the findings. Previous studies have already proven the superiority of warfarin over aspirin as thromboprophylaxis, leaving aspirin as a less effective alternative.[7] In addition, warfarin was shown to reduce AF-related stroke by 64%

in a meta-analysis.[13] Furthermore, NOACs have been demonstrated to further reduce stroke by 19% when compared with warfarin, proving their superiority in stroke prevention.[14] For the relative efficacy of a NOAC versus aspirin, a study was conducted to compare stroke prevention efficacy between the two treatments in nonvalvular atrial fibrillation (NVAF) patients not suitable for warfarin.[15] Apixaban users were found to have a significantly lower stroke risk compared with aspirin users (1.6%/ year vs 3.7%/year, p<0.001), with a similar intracerebral haemorrhage (ICH) and severe bleeding risk.[15]

The best way to estimate the efficacy of an antithrombotic therapy is to calculate its net benefit, by balancing its effect on stroke reduction with its bleeding risk. A CHA_2DS_2-VASc score of 2 indicates an annual stroke risk of 2.2%, and the use of aspirin and a VKA will only lower the annual risk by 9% and 36%, respectively; while the use of NOACs will reduce the risk of total events by 55% **(Figure 1)**. With higher efficacy in stroke risk reduction and a similar side effect profile compared with aspirin, NOACs should be the preferred choice for thromboprophylaxis.

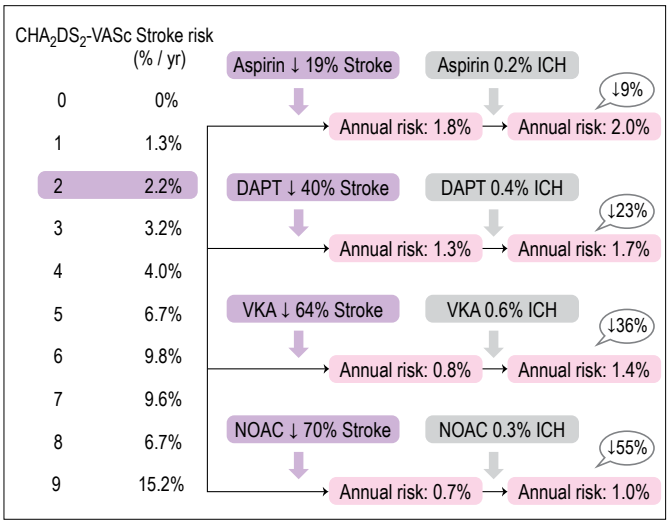

Figure 1. *Net benefit of antithrombotic therapies in stroke prevention for AF patients (ischaemic stroke prevented + ICH induced)*

Antithrombotic therapy in AF after percutaneous coronary intervention (PCI)

Around 5 to 8% of patients undergoing PCI have AF.[16-18] The treatment strategy for such patients must be carefully evaluated, to balance the risk of stroke and thrombotic events, recurrent cardiac ischaemia and/or stent thrombosis against the bleeding complications.[19] Considering the suboptimal performance of anticoagulation therapy in preventing stent thrombosis, and the inadequacy of dual-antiplatelet therapy (DAPT) in halting embolic stroke in AF, the anticoagulation therapy and DAPT should be combined to achieve the desired effect.[20] Triple therapy with warfarin and DAPT is the standard of care;[19] however, the high bleeding risk induced by the triple therapy is apparent.[21] A treatment regimen with lower bleeding risk would therefore be ideal.

In PIONEER AF-PCI study, rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months (group 1) and rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2) were compared with standard triple therapy (VKA once daily plus DAPT for 1, 6, or 12 months) (group 3) regarding the bleeding risk of antithrombotic therapy in AF patients who underwent PCI.[19] Significantly lower rates of clinically significant bleeding were recorded in the two groups receiving rivaroxaban when compared with the standard triple therapy group (group 1 vs group 3: 41% risk reduction, group 2 vs group 3: 37% risk reduction) **(Figure 2)**.[19] The reduction in bleeding in the rivaroxaban-treated patients will definitely cause less complications and medical attention.

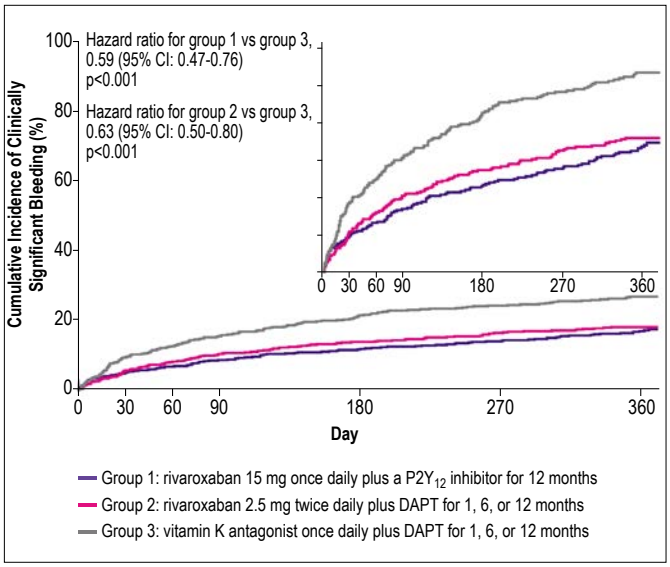

Figure 2. *Cumulative incidence of clinically significant bleeding in PIONEER AF-PCI study.*[19]

CONCLUSION

As patients suffering from AF are at heightened risk of developing stroke, appropriate treatment is needed for effective stroke prevention. Although aspirin is easy to administer with a perceived lower major bleeding risk, it is inadequate to avert embolic stroke in AF and is no longer recommended by international guidelines. On the other hand, NOACs have been demonstrated as a safe and efficacious treatment option for AF-related stroke prevention. Furthermore, with a lower clinically significant bleeding risk than the standard triple therapy, rivaroxaban in combination with a $P2Y_{12}$ inhibitor could be a safer option as the antithrombotic therapy in patients with AF undergoing PCI.

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Will NOACs increase GI bleeding risk? Insights from a local real-world perspective

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Safety concerns of anticoagulation therapy

Safety of anticoagulation therapy has been a cause for concern to many clinicians. The situation has gone so far as to influence their decision making regarding antithrombotic therapy for AF-related stroke prevention.[1,2] One of the main adverse events associated with anticoagulation therapy is gastrointestinal (GI) bleeding.[3] Warfarin, the most commonly used VKA, is also the most frequently prescribed oral anticoagulant (OAC) for prevention of AF-related stroke.[4] However, VKA has been associated with a 3-fold increase in the likelihood of GI bleeding compared with placebo or control in a meta-analysis.[3] More recently, NOACs have become available with a claimed advantage of further reducing stroke risk when compared with VKA.[5] Although the efficacy of NOACs has been demonstrated, GI bleeding risk of NOACs remains uncertain in different settings.

Current findings of GI bleeding risk of NOACs

As GI bleeding is a major concern in the usage of anticoagulation therapy, numerous studies have been conducted to investigate such risk with different OACs. However, the results are conflicting.[6,7] A meta-analysis of 43 randomised control trials (RCT) has reported no differences in major bleeding risk between NOACs and conventional anticoagulants (1.5% vs 1.3%, respectively) with an odds ratio (OR) of 0.98 (95% CI: 0.80–1.21).[6] Nevertheless, some of the NOACs were even associated with increased risk in GI bleeding when compared with conventional anticoagulants.[6] On the contrary, in a network meta-analysis comparing NOACs, warfarin and low-molecular-weight heparin in terms of the risk of major GI bleeding, NOACs (in particular factor Xa inhibitors) have been shown to reduce risk of GI bleeding at all levels of severity when compared with warfarin, with an incidence rate ratio (IRR) of 0.25 (95% CI: 0.07–0.76).[7]

With regards to such controversy, real-world analyses were conducted in the US to investigate the risk of GI bleeding in NOAC users in the real-world clinical settings. In an observational study, NOAC users exhibited lower GI bleeding rates than warfarin users. In fact, all three NOACs in this study had a lower GI bleeding rate than warfarin **(Table 1)**.[8] In addition, the incidence of blood transfusion related to GI bleeding was also less frequent in NOAC users than in warfarin users (20% vs 64.6%; p=0.04).[8] In another case-control study evaluating the severity of GI bleeding with anticoagulation therapy (defined by the need for hospitalisation, the length of stay in hospital, and the need for transfusion), the use of a NOAC was associated with fewer hospitalisation and transfusion episodes than the warfarin group, indicating a lower level of severity in terms of GI bleeding in NOAC users.[9]

Table 1. Rates of gastrointestinal bleeding for patients taking warfarin as compared with the NOACs, dabigatran, rivaroxaban, or apixaban[8]

	GI bleed rate
Warfarin	158/6,263 (2.5%)
All NOACs	5/803 (0.62%)
Dabigatran	1/165 (0.61%)
Rivaroxaban	2/383 (0.52%)
Apixaban	2/254 (0.79%)

Abbreviations: *GI=gastrointestinal; NOAC=non-vitamin K antagonist oral anticoagulants*

Prescription pattern of stroke prevention in NVAF in Hong Kong

The trends in prescription medication use in NVAF in Hospital Authority (HA) hospitals revealed a low frequency of OACs use (23%), which might be explained by the concern of bleeding risk.[10] As a result, more than half of the NVAF patients (CHA_2DS_2-VASc score ≥2) still received inappropriate treatment (61.1% receiving antiplatelet drugs alone), and 15.7% received no treatments before the year of 2014.[10]

Risk of GI bleeding with rivaroxaban comparable with aspirin from real-world evidence

In order to address clinicians' concern about the safety of NOACs and provide statistical data support for clinical decision making, a real-world analysis was conducted to compare rivaroxaban and aspirin in terms of GI bleeding risk, by using the Clinical Data Analysis and Reporting System (CDARS) from HA.[11]

This population-based cohort study looked at whether there was a difference in all-cause GI bleeding between new users of rivaroxaban and aspirin from 2010 to 2016, using the method of propensity score matching **(Figure 3)**.[11] 765 rivaroxaban users were successfully matched with 3825 aspirin users. Before propensity score matching, rivaroxaban users were one year younger than aspirin users. Although CHA_2DS_2-VASc and HASBLED scores were similar, in terms of medical conditions, aspirin users were more likely to have a history of congestive heart failure, vascular disease, GI bleeding and renal disease. The variables were well balanced after matching **(Table 2)**.[11]

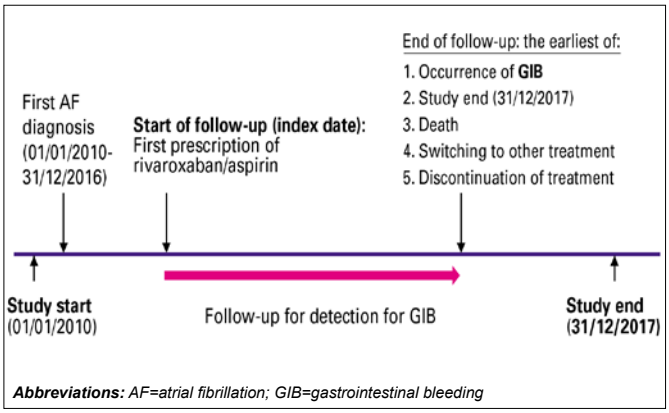

Figure 3. *Study design of the Hong Kong real-world analysis*[11]

The majority (66%) of patients initiated rivaroxaban treatment at a higher dose (20 mg), and those on rivaroxaban underwent longer follow-up than those on aspirin (313 days and 111 days, respectively). As for the time to GI bleeding, GI bleeding events appeared to occur earlier in aspirin users than rivaroxaban users (158 days vs 237 days). After propensity score matching, no significant differences in GI bleeding rates between aspirin and rivaroxaban were observed, with the absolute incidence rates of bleeding being 2.7 and 3.3 per 100 person-years for rivaroxaban and aspirin, respectively **(Table 3)**.[11] Such results indicate that rivaroxaban and aspirin have similar GI bleeding risk.

CONCLUSION

With the conflicting results about GI bleeding risk of NOACs, a real-world analysis of local data is warranted. In the matched cohort, rivaroxaban is associated with a comparable GI bleeding risk compared with aspirin in patients with NVAF in Hong Kong. Although further investigation is needed to confirm such findings, the analysis provided real-world evidence on the safety of NOACs to inform future point-of-care decisions.

Table 2. Baseline characteristics of the real-world analysis before and after propensity score matching[11]

	Before matching			After matching		
	Rivaroxaban	Aspirin	Stddiff	Rivaroxaban	Aspirin	Stddiff
N	1131	27177		765	3825	
Age, mean (SD), year	74.7 (10.8)	75.8 (12.8)	-0.10	75.5 (10.5)	76 (12.9)	- 0.04
Women	583 (51.5)	13576 (50.0)	0.03	387 (50.6)	2007 (52.5)	- 0.04
$CHADS_2$, mean (SD)	1.6 (1.3)	1.7 (1.3)	-0.07	1.8 (1.3)	1.7 (1.3)	0.04
CHA_2DS_2 -VASc, mean (SD)	3.1 (1.7)	3.2 (1.8)	-0.05	3.2 (1.7)	3.2 (1.8)	0.05
HAS-BLED, mean (SD)	1.8 (1.1)	1.9 (1.2)	-0.06	2 (1.1)	1.9 (1.1)	0.08
Medical conditions (any record on or before index date)						
Congestive heart failure	184 (16.3)	6202 (22.8)	-0.17	147 (19.2)	700 (18.3)	0.02
Hypertension	509 (45.0)	11876 (43.7)	0.03	354 (46.3)	1746 (45.6)	0.01
Diabetes	203 (17.9)	4722 (17.4)	0.02	140 (18.3)	670 (17.5)	0.02
Prior ischaemic stroke/TIA/systemic embolism	167 (14.8)	4035 (14.8)	-0.002	130 (17)	589 (15.4)	0.04
Vascular disease	116 (10.3)	4027 (14.8)	-0.14	95 (12.4)	442 (11.6)	0.03
History of peptic ulcer/gastrointestinal bleeding	147 (13)	4466 (16.4)	-0.10	126 (16.5)	555 (14.5)	0.05
Renal disease	58 (5.1)	2647 (9.7)	-0.18	56 (7.3)	250 (6.5)	0.03
Liver disease	46 (4.1)	1461 (5.4)	-0.06	38 (5.0)	168 (4.4)	0.03

Abbreviations: *Stddiff=standardised difference; SD=standard deviation; Standardised difference<0.1 indicates negligible difference*

Table 3. Real-world data of gastrointestinal bleeding risk in patients taking rivaroxaban as compared with aspirin[11]

	Rivaroxaban, N	No. of case/ Person-years	Incidence per 100 person-years	Aspirin, N	No. of case/ Person-years	Incidence per 100 person-years	Hazard ratio (95% CI)	P-value
Before PS Matching	1131	35/1359	2.6	27177	941/32206	2.9	0.83 (0.49–1.16)	0.27
After PS Matching	765	26/953	2.7	3825	110/3374	3.3	0.86 (0.37–1.36)	0.56

Abbreviation: *PS=propensity score*

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Vascular Cognitive Impairment: An update and role of atrial fibrillation

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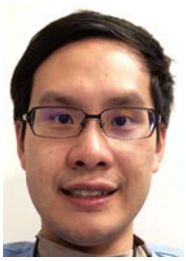

Insults in the anterior lobe of the cerebellum with a stroke usually lead to the classic motor symptoms, while on the other hand, cognitive manifestations of strokes can be contributed by tissue injury in the cerebellar posterior lobe.[1] As a result, one condition that clinicians should be aware of during the assessment of post-stroke cognitive dysfunction is the cerebellar cognitive affective syndrome (CCAS).[1]

Clinical findings of vascular cognitive impairment

CCAS is a typical representation of how the cerebellum is involved in one's cognitive function.[1] Deficits in several cognitive domains, including language, executive function, verbal and visual learning, and affect can be the signs of CCAS.[1] The problems with emotional behaviours in these patients are usually disinhibition and impulsiveness.[1]

Besides CCAS, there are still many different causes of vascular cognitive impairment (VCI) in patients after stroke or without stroke **(Figure 4)**.[2] In contrast to Alzheimer's disease (AD), vascular pathology alone accounts for not more than 10% of dementia cases,[3] and only 30% of such patients exhibit amyloid positivity.[4]

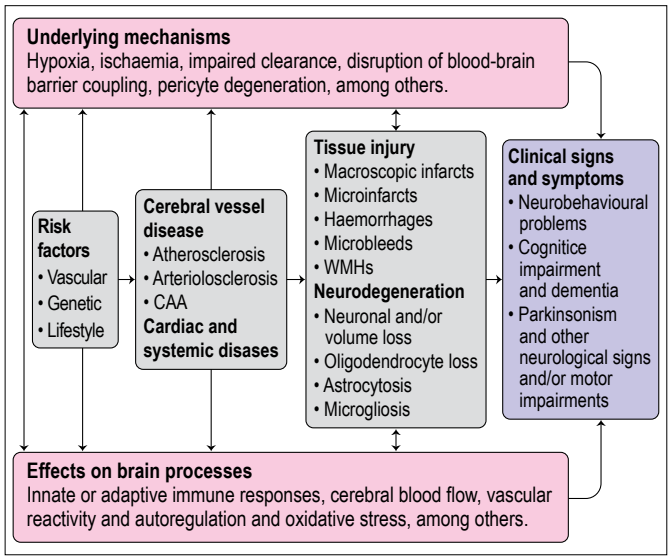

Figure 4. *Current understanding of the various factors leading to VCI[2]*

Yet vascular dementia in more advanced ages is associated with higher prevalence of amyloid positivity,[4] further complicating how it can be differentiated from AD, or if the patients have mixed dementia indeed.

Atrial fibrillation as a risk factor for dementia

AF is not only a well-known risk factor for stroke, but also a risk factor for post-stroke cognitive impairment.[5] After a stroke, AF patients are 2.4 times more likely to suffer from dementia compared to those without AF (OR; 95% CI: 1.7–3.5).5 At the same time, AF patients without stroke are also at increased risk for dementia or cognitive dysfunction (HR=1.42; 95% CI: 1.17–1.72) compared to control.[6]

Several mechanisms are proposed to explain how AF contributes to cognitive impairment **(Figure 5)**.[7] Cerebral hypoperfusion caused by reduced ejection fraction in AF can be one of the causes, while the prothrombotic state in AF can at the same time induce silent cerebral ischaemia.[7] One subclinical finding is that AF patients tend to have more cerebral microbleeds, for a not-yet-known reason, which may further signify the underlying pathological vascular changes.[7]

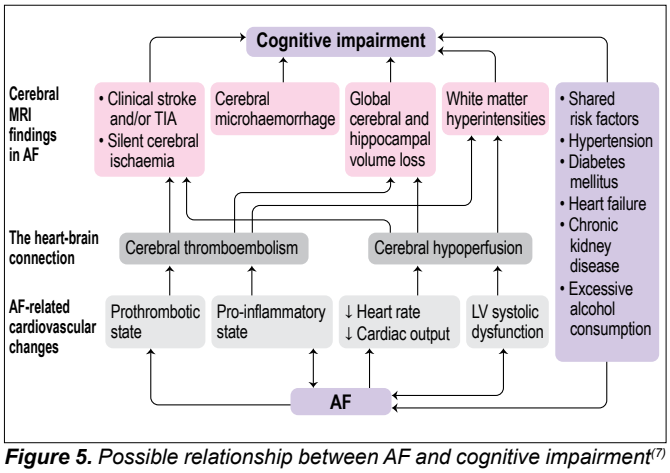

Figure 5. *Possible relationship between AF and cognitive impairment[7]*

Risk factor control for prevention of VCI?

It is intriguing to see if the control of vascular risk factors can prevent VCI, after or even before a cerebrovascular accident. However, currently there is only scant evidence showing an improvement

in surrogate endpoints for VCI.[7] The PROGRESS MRI study somehow demonstrated for patients with cerebrovascular disease, blood pressure-lowering medications can help in retarding the progression on white matter hyperintensities (WMH) volume.[8] On the other hand, in the local ROCAS trial, the use of a statin among stroke-free individuals has been shown to be associated with reduced WMH volume progression.[9] Despite these, findings of clinical cognitive endpoints are technically non-existent.7 Given the current wide use of NOACs in NVAF patients, it would be eminent if further research can demonstrate a protective effect against cognitive impairment with oral anticoagulation.[7]

CONCLUSION

Clinicians should be aware that damage in the cerebellum can have cognitive consequences.[1] Besides its stroke-causing characteristic, AF can induce cognitive impairment via different mechanisms.[2] Though the clinical course of a patient with vascular dementia is more dismal than an AD patient, we are yet to have a management strategy with definitive protective effect available.[7]

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Vascular Cognitive Impairment- Cognitive rehabilitation after stroke

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From an Occupational Therapist's perspective, cognitive rehabilitation for patients with VCI not only aims for improvement in their different cognitive domains, but also to help them regain functionality to resume their previous life roles as far as possible, for example, return to work or perform activities of daily living (ADL) in the community.[10]

Assessment of post-stroke cognitive impairment

To achieve these aims, several locally-validated tools are available for screening or assessing the severity of VCI in patients after a cerebrovascular accident. Besides the traditional Mini-Mental State Examination (MMSE),[11] healthcare workers in the public hospital setting are now well-adapted to use the Abbreviated Mental Test (AMT)[12] or the Montreal Cognitive Assessment (MoCA) for the detection of VCI.[13] These two instruments have both been translated and validated for their application in Hong Kong (known as HK-MoCA for the latter).[12, 14]

Similar to various models in cognitive science, cognitive assessment by an Occupational Therapist is performed through both "bottom-up" and "top-

down" approaches. The formulation of a rehabilitation programme for a VCI-affected patient can also be based on utilising both approaches.[10]

"Bottom-up" and "top-down" assessment approaches

A "bottom-up" approach, or a component-based approach, is built on the concept that divides one's cognition into different cognitive domains. Based on this rationale, different cognitive functions, like visuospatial function and working memory, are assessed with different validated assessment tools accordingly. For example, Behavioural Inattention Test (BIT) can help in detecting visual neglect, and memory problems can be assessed with the Rivermead Behavioural Memory Test (RBMT).

On the other hand, a "top-down" approach, or a function-based approach, aims to measure one's functional performance using standardised scales. It is expected that patients with similar cognitive profiles may demonstrate different functional presentations. Therefore, a "top-down" approach can help in identifying the interrelation among cognitive, physical, motor, psychosocial and functional performance in every individual. Assessment tools for this approach include the Functional Independent Measure (FIM) instrument[15] and the Lawton Instrumental ADL scale.[16]

Occupational Therapy approaches for cognitive rehabilitation

A thorough cognitive assessment helps in guiding the design of an individual's cognitive rehabilitation programme. This is where Occupational Therapy (OT) intervention plays its important role during post-stroke recovery.[10]

The "bottom-up" approach for cognitive rehabilitation is delivered by cognitive remediation. By making use of one's implicit learning ability, it aids the restoration of lost functions in specific cognitive domain(s).[10] Cognitive stimulation and specific cognitive training programmes are typical examples of how it applies in the clinical setting, for instance, an evidence-based intervention programme – Attention Process Training (APT).[10] Technology nowadays allows home-based and smartphone app-based cognitive remediation, which greatly expands patients' opportunity for reinforcing their cognitive training in home-based setting continually. The"top-down" approach for cognitive rehabilitation is an adaptive approach which focuses on patient's functionality and problem solving skills for daily tasks.[10] This is achieved through direct training of functional skills, by relearning alternative or compensatory methods for various tasks.[10] Different cognitive strategies can also be employed to further enhance one's independence in functional tasks.[10] Similarly, technology has brought improvement in the adaptive approach for cognitive rehabilitation. For example, nonimmersive Virtual Reality (VR) instrumental ADL software has been developed that simulates different day-to-day tasks in related environments.[17]

CONCLUSION

There are various tools that an Occupational Therapist can utilise to screen[12,14] and assess[15,16] post-stroke patients for VCI. For the assessment of VCI as well as the design of a cognitive rehabilitation programme, both the "bottom-up" and "top-down" approaches can be adopted, with the aim of promoting recovery in patients' different cognitive domains and also their real-life functional performance.[10]

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Lixiana®(edoxaban) – The Latest Kid on the Block in Anticoagulation Therapy

Prepared by ***HO, Vivian***

Anticoagulation therapy is vital to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (NVAF) and to prevent or treat arterial and venous thrombosis. Direct oral anticoagulants (DOACs), which is previously referred to as newer oral anticoagulants (NOACs), have become promising alternatives to vitamin K antagonists in recent years due to their lower risk of intracranial bleeding, fewer drug interactions, less frequent laboratory monitoring, and dose adjustments and less dietary restrictions. Edoxaban, an oral selective direct Factor Xa inhibitor approved by the Food and Drug Administration (FDA) in January 2015, has joined the DOACs family which previously included direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (apixaban and rivaroxaban).[1]

Edoxaban has been registered in Hong Kong since May 2016. In this article, the pharmacology, characteristics, risks, and benefits of edoxaban are highlighted and compared with other DOACs.

Pharmacology and Pharmacological Characteristics

Normally, factor Xa forms a complex with factor Va to allow for conversion of prothrombin to thrombin **(Figure 1)**. Edoxaban inhibits free factor Xa selectively without the need of antithrombin.[2] Inhibition of factor Xa in the coagulation cascade prevents the conversion of prothrombin to thrombin, leading to reduced thrombus formation and progression. The reduction in thrombin at the same time indirectly inhibits platelet aggregation.[2]

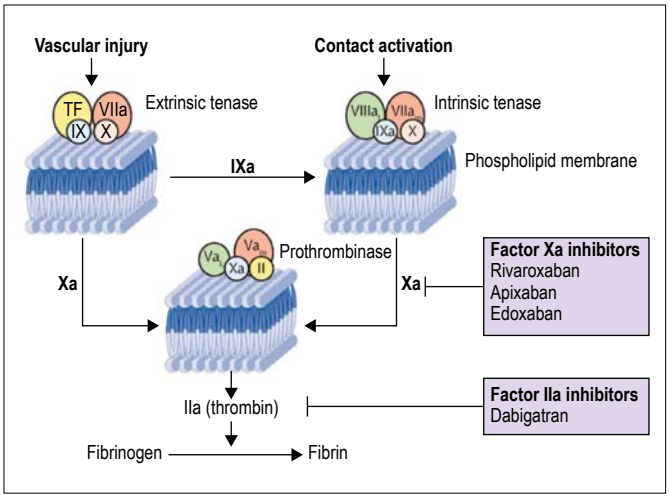

Figure 1. *Coagulation system and oral direct factor IIa and Xa inhibitors.*[2]

The pharmacological properties of edoxaban make it favourable in anticoagulant therapy. The plasma concentrations of edoxaban were closely correlated to the suppression of thrombin generation, inhibition of platelet activation parameters (e.g. fragment 1+2, thrombin-antithrombin complex, and β-thromboglobulin) and anti-factor Xa activity **(Figure 2)**. Edoxaban quickly reaches peak plasma concentrations in around 1.5 hours and has a half-life of 10-14 hours. Bioavailability is 62% which is relatively high in comparison to other DOACs **(Table 1)**.[3] It also exhibits highly selective, competitive, concentration-dependent inhibition of human factor Xa.[3] It is eliminated in the feces (60%) and urine (35%) with over 70% of the drug eliminated unchanged.

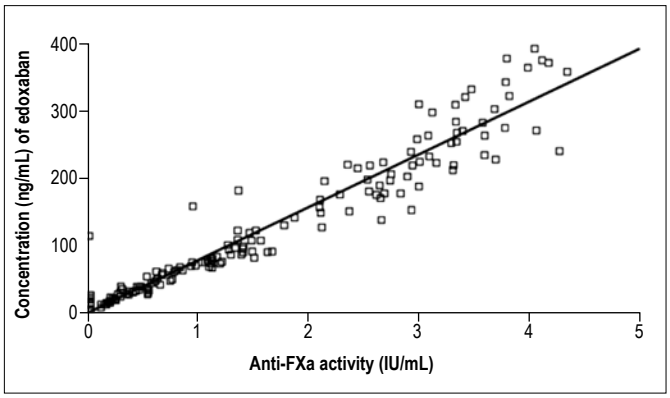

Figure 2. *Relationship between edoxaban concentration and anti-factor Xa (FXa) activity.*[3]

Clinical Efficacy

According to the Hong Kong package insert, edoxaban is indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA) at a dose of 60 mg once daily.[1] The same dosage is also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.[1]

Non-valvular Atrial Fibrillation (NVAF)

The efficacy of edoxaban in NVAF was supported by the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48) trial. It was a double-blind, double-dummy, non-inferiority trial that randomized

Table 1. Pharmacological Characteristics of Oral Direct Thrombin Inhibitors and Oral Direct Factor Xa Inhibitors.[4]				
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Bioavailability	3 to 7%	50%	62%	66% without food. Almost 100% with food
Prodrug	Yes	No	No	No
Time to maximum inhibition, h	0.5-2	1-4	1-2	1-4
Elimination half-life	12 to 17 h	12 h	10–14 h	5–9 h (young) 11–13 h (elderly)
Clearance non-renal/renal of absorbed dose (if normal renal function)	20%/80%	73%/27%	50%/50%	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Potential metabolic drug interactions	Inhibitors of P-gp: verapamil, reduce dose; dronedarone: avoid	Potent inhibitors of CYP3A4 and P-gp*: avoid	Potent inhibitors of P-gp*: reduce dose	Potent inhibitors of CYP3A4 and P-gp*: avoid
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure	+39% more
Asian ethnicity	+25%	No effect	No effect	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem

21,105 patients with documented NVAF and a creatinine clearance (CrCl) >30 ml/min to receive high-dose edoxaban (60 mg daily), low-dose edoxaban (30 mg daily), or warfarin titrated to a goal INR 2-3.[5] Patients with a creatinine clearance of 30–50 ml/min, weighing ≤60 kg, or receiving strong p-glycoprotein inhibitors at randomization or during the study received a 50% dose reduction of edoxaban or matched placebo.[5] During the treatment period, the primary outcome (stroke or systemic embolic event) occurred at an annualized rate of 1.5% in patients receiving warfarin, 1.18% with high-dose edoxaban [Hazard Ratio (HR) 0.79; 97.5% confidence interval (CI) 0.63–0.99; p<0.001] and 1.61% low-dose edoxaban [HR 1.07; 97.5% CI 0.87–1.31; p = 0.005] **(Figure 3)**.[5]

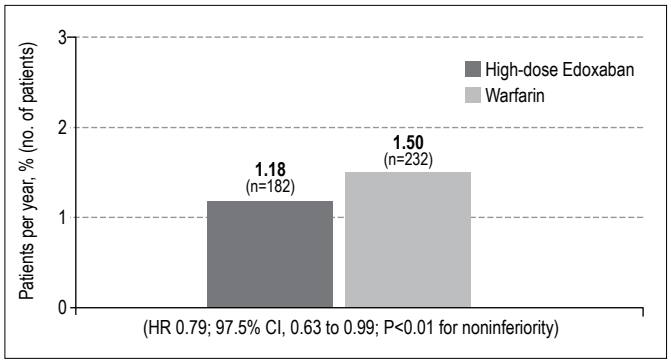

Figure 3. *Stroke or Systemic embolism in the modified intention-to-treat (mITT) population during the treatment period in the ENGAGE AF-TIMI 48 trial.*

A post-hoc analysis on East Asian population included 1,943 patients from Japan, China, Taiwan, and South Korea.[6] Significantly lower rates of stroke or systemic embolic event were observed with higher-dose edoxaban as compared with warfarin in this subanalysis population.[6] Moreover, a significantly greater proportion of East Asian patients than non-East Asian patients was observed to be qualified for a 50% dose reduction, which was associated with a greater reduction in bleeding with no apparent differences in the efficacy.[6] Despite the positive findings outlined by the investigator, it should be noted that the definition of East Asian was limited by the patient recruited in the ENGAGE AF-TIMI 48 trial. The relatively small number of East Asian patients did not provide sufficient power for statistical comparisons. The results should be interpreted with cautions.

An indirect comparison analysis suggested that there were no significant differences in efficacy endpoints between high-dose edoxaban (60 mg daily) and other DOACs, except dabigatran 150 mg BD regimen [lower stroke/systemic embolism (HR 0.75; 95% CI 0.56–0.99), stroke (HR 0.73; 95% CI 0.55–0.96) and hemorrhagic stroke (HR 0.48; 95% CI 0.23–0.99)].[7]

Venous Thromboembolism (VTE)

The efficacy in treatment of VTE was studied in the Hokusai-VTE trial. This double-blind, non-inferiority trial compared the safety and efficacy of edoxaban with warfarin in the treatment of VTE. 8292 patients, who experienced a DVT (n = 4921) and/or PE (n= 3319), received open-label enoxaparin or unfractionated heparin for at least 5 days with a median duration of 7 days and were randomized to receive edoxaban 30 or 60 mg (n= 4118) or warfarin with goal INR 2-3 (n= 4122).[8]

The recurrence of thromboembolism or VTE-related death occurred in 3.2% of edoxaban patients and 3.5% of warfarin patients (HR 0.89, 95% CI 0.70–1.13; p<0.001 for non-inferiority).[8] No differences were observed with DVT alone, non-fatal PE, or fatal PE. The non-inferiority

of edoxaban was maintained in patients receiving the 30mg daily dose when compared with warfarin (HR 0.73, 95% CI 0.42–1.26).[8]

Systematic review and network meta-analysis were conducted to compare the efficacy and safety of DOACs for the initial and long-term treatment of VTE. The indirect comparison showed statistically similar reductions in the risk of VTE or VTE related death for all DOACs, with apixaban being the only DOAC to show a significantly improved bleeding profile.[9]

The post-hoc analysis of the Hokusai-VTE study evaluated the risk–benefit of extended treatment for up to 12 months with edoxaban compared with warfarin. The incidence of recurrent VTE at the evaluation intervals, cumulative incidence of recurrent VTE and cumulative incidence of major bleeding in the edoxaban-treated patients were similar or lower than the warfarin-treated patients **(Figure 5a)**.[10] The investigators suggested that edoxaban could be a promising alternative to warfarin for patients with VTE who require extended treatment for prevention of recurrent VTE.[11]

Safety Concern

In most phase II trials, edoxaban 30 and 60 mg once daily had similar or lower bleeding risk when compared with warfarin and they resulted in treatment emergent adverse events in the same fashion as warfarin. Edoxaban was shown to have superior side effect profile in terms of less major bleedings when compared to well-controlled warfarin in the two landmark studies (ENGAGE-AF-TIMI-48 and Hokusai-VTE) **(Figure 4, 5b)**.[5,8]

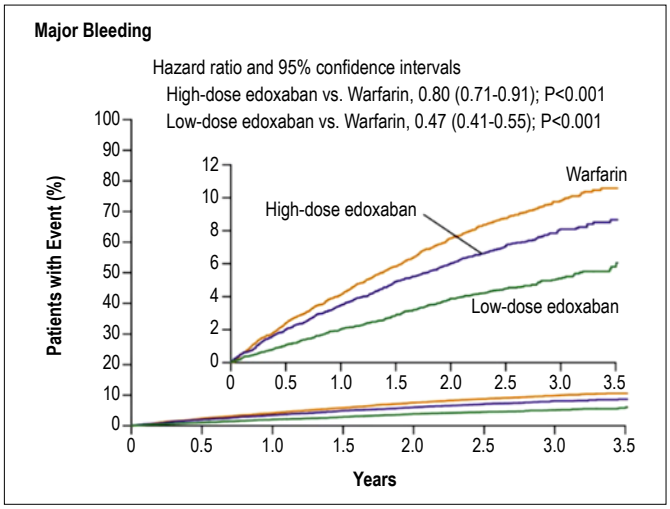

Figure 4. *Kaplan–Meier Curves for the cumulative event rate for major bleeding in the intention-to-treat (ITT) group during the study period.*

Pooled analysis of phase I and II trials suggested that renal insufficiency and concomitant P-glycoprotein (P-gp) inhibitor treatment may also influence bleeding risk. Therefore, the recommended dose for moderate or severe renal impairment (creatinine clearance (CrCl) 15 - 50 mL/min) or concomitant use of P-gp inhibitors including cyclosporin, dronedarone, erythromycin and ketoconazole, should be reduced to 30mg once daily, instead of 60 mg once daily.[1] Patients with a low body weight of less than 60 kg is another condition that requires dose reduction to 30 mg daily.[1]

Place in Therapy

DOACs are proven to be at least as effective and safe as vitamin K antagonists (VKAs). Less intracranial bleeding, food and drug interactions are associated with the use

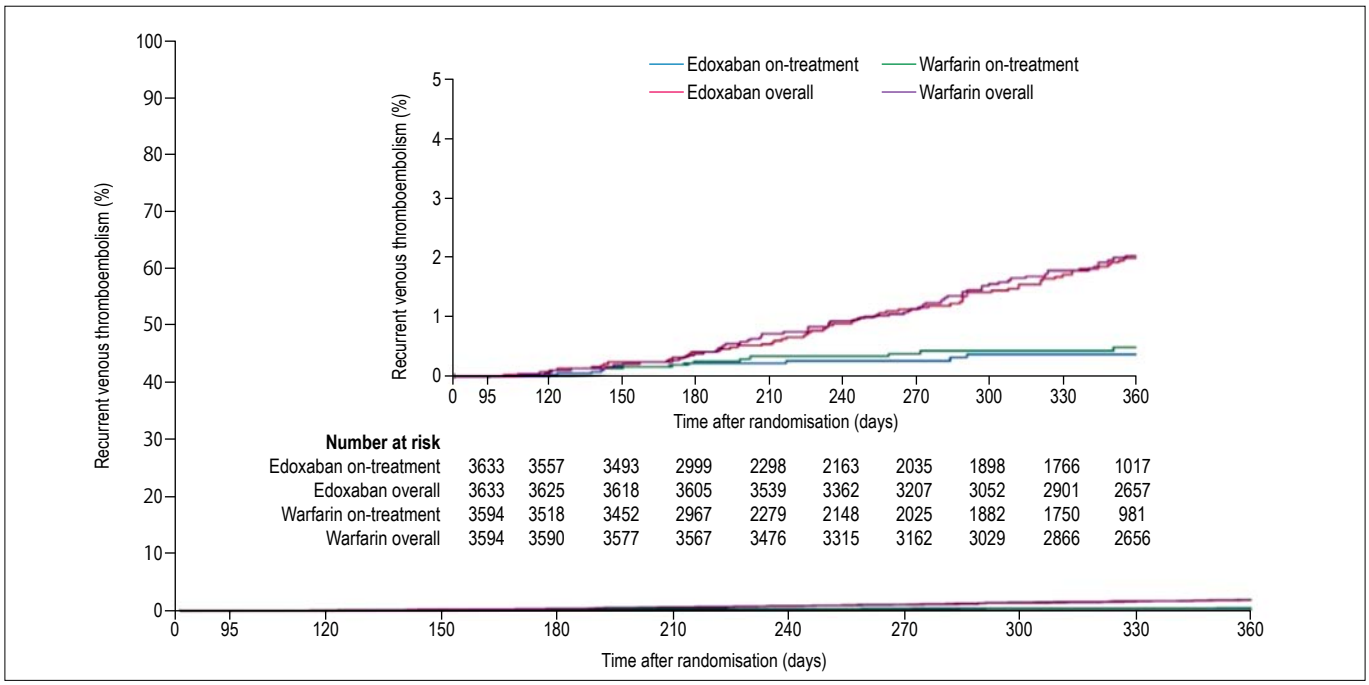

Figure 5a. *Cumulative rates of recurrent venous thromboembolism: on-treatment and modified intention-to-treat analyses starting at day 95. Both population groups are based on the modified intention-to-treat population.*

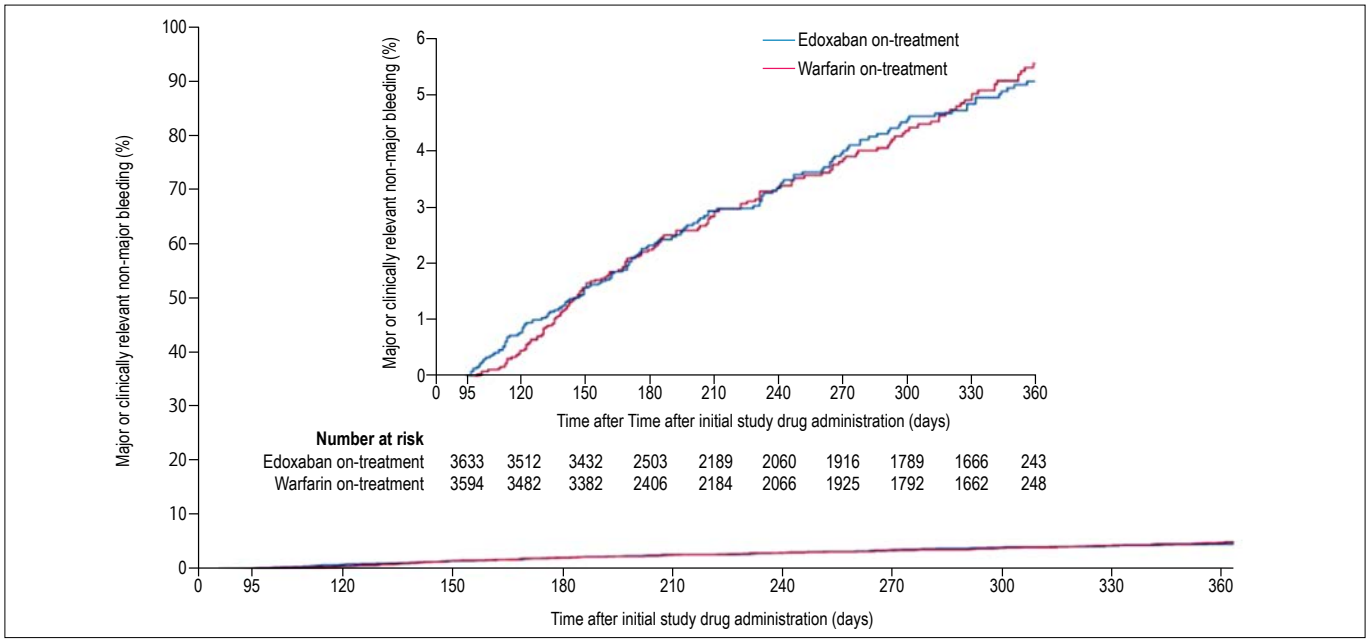

Figure 5b. *Cumulative incidences of clinically relevant bleeding (major or non-major) starting at day 95.*

of DOACs. The favorable pharmacological profiles of the DOACs contribute to the easier administration and monitoring, making them the preferred options for anticoagulation. The four DOACs have been included in the European Heart Rhythm Association Practical Guide for stroke prevention in NVAF.[11] For VTE, the American College of Chest Physicians (ACCP) suggests DOACs over VKA therapy in patients with DVT of the leg or PE and no cancer as anticoagulant therapy in the first 3 months and no change in anticoagulant are needed if the initial therapy is well-tolerated.[12]

However, due to the lack of the direct head-to-head comparison of the clinical efficacy and safety profile between edoxaban and other DOACs, the guidelines did not state any preference in the choice of DOACs. Choice of therapy should be made after throughout consideration on the clinical need, concomitant medications, and patient's characteristics such as age, renal function, weight, comorbidities etc. **(Table 2)**.[11-14]

In the ENGAGE AF-TIMI 48 trial, subgroup analysis revealed the increased stroke rates in NVAF patients with CrCl >95ml/min and the effect of thrombosis prevention appeared to diminish in this group of patients.[5] The US labelling has a black box warning that edoxaban should not be used in NVAF patients if CrCl is >95 mL/min

Table 2. Patient characteristics and drug of choice among DOACs.

Patient characteristic	Drug choice	Rationale
Not currently anticoagulated	DOAC[a]	DOACs are at least as effective and safe as VKAs, produce less intracranial bleeding and are more convenient because they do not require routine monitoring and have a low propensity for food and drug interactions
Already receiving warfarin, stable INR and satisfactory time in therapeutic range	Maintain VKA therapy or consider switching to DOAC[a]	Depends on patient and physician preference
Already receiving warfarin, unsatisfactory time in therapeutic range	Any DOAC[a]	DOACs produce a more predictable and stable anticoagulant effect and do not require routine coagulation monitoring
CrCl 30–50 ml/min	Apixaban[b], rivaroxaban[c] or edoxaban[d]	Less affected by renal impairment than dabigatran
CrCl < 15 ml/min	VKA	DOACs are not recommended for use in this patient population
Ischaemic stroke on warfarin, rivaroxaban, apixaban, or edoxaban	Dabigatran	Lower risk of ischaemic stroke with dabigatran (150 mg)
Dyspepsia or upper GI complaints	Rivaroxaban, apixaban, or edoxaban	Dyspepsia with dabigatran in up to 10% of patients
Recent GI bleed	Apixaban	Dabigatran (150 mg), rivaroxaban, and edoxaban (but not apixaban) produce more GI bleeding than warfarin
Concomitant use of strong inhibitors or inducers of both P-gp and CYP3A4	Dabigatran or edoxaban	Not restricted for concomitant use
Poor compliance with twice-daily dosing	Rivaroxaban or edoxaban	Only agents given once-daily

a) In the United States, use of edoxaban in patients with CrCl > 95 ml/min is not recommended.
b) In patients with serum creatinine ≥ 1.5 mg/l (≥ 133 μmol/l), the dose of apixaban should be reduced to 2.5 mg twice daily if age ≥ 80 years or body weight ≤ 60 kg.
c) Recommended dosing of rivaroxaban in patients with CrCl 15–50 ml/min varies across regulatory regions. Physicians should consult their region/country-specific labelling instructions.
d) Edoxaban 30 mg once daily.

CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; GI, gastrointestinal; DOAC, non-vitamin K antagonist oral anticoagulant; P-gp, P-glycoprotein; VKA, vitamin K antagonist.

due to the increased risk of ischemic stroke compared with warfarin in NVAF trial.[15] In view of the aforesaid findings, *Bohula et a*l evaluated the efficacy and safety of edoxaban versus warfarin across the range of baseline creatinine clearance (CrCl) in the ENGAGE AF-TIMI 48 trial focusing on the upper range of CrCl.[16] The relative risk of adverse events or outcomes with edoxaban versus warfarin in patients with CrCl >50 mL/min was similar to those with CrCl ≤50 mL/min. Although several exploratory analyses suggested lower relative efficacy at higher levels of CrCl, the net clinical outcome of reduced bleeding at all levels of CrCl were maintained.[16] It is therefore recommended that edoxaban could be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.[1, 16]

On the other hand, for patients who have been receiving long-term VKA treatment with well-controlled INR and no other clinical concerns, the benefits from switching to DOACs is uncertain and controversial. The decision of switching should be made based on the preference of patient and physician. It should be noted that VKAs still play a crucial role in anticoagulation therapy in certain conditions such as severely impaired renal function, intolerance of new anticoagulants and under clinical settings that efficacy and safety of DOACs have not been established.[12]

CONCLUSION

Edoxaban, the most recently approved DOAC, is non-inferior to warfarin for NVAF and treatment of VTE after parenteral anticoagulation, with the advantage of lower rates of bleeding. Edoxaban is approved for prevention of stroke and systemic embolism in patients with NVAF and treatment of VTE after 5-10 days of parenteral therapy. Indication-specific dose adjustments for edoxaban are necessary based upon creatinine clearance, weight, and concomitant administration of P-gp inhibitors. Clinical advantages of edoxaban include once daily dosing, the lack of need or bridging or routine therapeutic monitoring. Potential disadvantages when comparing to other DOACs include reduced efficacy in NVAF patients with CrCl >95 mL/min and the need of initial parenteral anticoagulation in acute VTE. Direct head-to-head comparisons of clinical efficacy and safety between edoxaban and other DOACs are awaited to determine the relative clinical benefits of the DOACs.

Author's background

HO, Vivian *is currently a pharmacist practicing at Queen Mary Hospital in Hong Kong.*

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- Higher Diploma in Pharmaceutical Dispensing (CBCC)

UNIVERSITY OF WOLVERHAMPTON

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Programme Code: HS072A

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Level 3
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Application Deadline: 17 January 2020

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* These are exempted courses under the Non-Local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognize any qualification to which these courses may lead.

The Time is Now!

Reported by ***LEUNG, Vienna***
Pharmacist of the Society of Hospital Pharmacists of Hong Kong (SHPHK)

Happy Lunar New Year!
The Hong Kong Pharmacy Conference (HKPC) 2019 was successfully held on 9-10th March. This year, the theme for the plenary session is *'The Time is Now to Reflect on Ourselves'*. Comments made by the representatives of the patient groups in panel discussion were thought-provoking:

'I remember there was a time that I tried looking for a community pharmacist for medication advice. The pharmacy staff at the front desk told me that the pharmacist was temporarily away. The same happened to another two pharmacies I visited,' recalled Mr. Yuen Siu Lam, President of Hong Kong Alliance of Patients' Organizations.

'I remember last time when I asked my doctor for medication advice in the hospital, the doctor referred me to the hospital pharmacists. But when I asked a hospital pharmacist for advice, I was referred back to the doctor,' said Mr. Lau Kim Hung, President of the Hong Kong Stroke Association.

Plenary session of HKPC 2019: The Time is Now to Reflect on Ourselves.

Perhaps, now is the time for pharmacists to reflect on ourselves and step outside of the box to reach out proactively to the general public, showing that pharmacists are always here to help!

Breakthrough! Reach out to the community to provide intranasal flu vaccination to kindergarten students

Currently, the Hong Kong Government only offers school-based vaccination to primary school students, but not to the pre-school and kindergarten students. In view of the recent flu outbreak in the kindergartens in Hong Kong, the Society has taken the lead to provide flu vaccination service to a kindergarten in Kowloon. Many positive feedbacks were received from the teachers and the parents.


Intranasal flu vaccination service for kindergarten students.

Community Vaccination Programme in Shum Shui Po and Tin Shui Wai

In early March, SHPHK was invited by the Department of Paediatrics and Adolescent Medicine, The University of Hong Kong to participate in the Community Vaccination Programme in Shum Shui Po (SSP) and Tin Shui Wai (TSW). Participated pharmacists have provided intranasal flu vaccination to more than 170 residents at the community center in SSP and TSW. The Society would like to thank our hospital and community pharmacist colleagues for their help in this programme.

Movie Night: <我不是藥神> (Dying to Survive)

A movie night was hosted by the Society on 24th January 2019 at the PALACE IFC cinema. *'Dying to Survive'* is a very touching, yet inspiring movie. The movie reflects the obstacles that patients have to go through in their treatment journey. This is definitely a must-watch movie for pharmacists!

Declaration Ceremony of Hong Kong Society for Travel Medicine Founding Group (HKSTMFG) cum Hong Kong Symposium in Travel Health 2019

A symposium on travel medicine co-organized by SHPHK, Hong Kong Society for Travel Medicine

Founding Group (HKSTMFG) and Department of Pharmacology and Pharmacy, The University of Hong Kong was held on 17th March 2019. We were particularly honored to have Group Captain Andy Green, Personal Physician to Queen Elizabeth (QHP) to share with us the importance of vaccination in disease prevention. Prior to the start of the symposium, a press conference was held to raise public awareness of the importance of travel health.

Opening Ceremony of the Hong Kong Symposium in Travel Medicine on 17th March 2019.

Mark your Calendar: The 32nd SHPHK Annual General Meeting

The 32nd SHPHK Annual General Meeting (AGM) will be held on the 22nd March, 2019 (Friday) at Shanghai Room, Cordis Hotel, 555 Shanghai Street, Mongkok, Kowloon. Before the start of the AGM, Dr. Lam King Yun Joanne, Specialist in Endocrinology, Diabetes and Metabolism will deliver a lecture on 'Novel Synergy of Insulin and GLP-1 Receptor Agonist for Management of Type-2 Diabetes Mellitus'. A Chinese set dinner will be served at 8:00pm during the AGM.

In the AGM, the General Committee Members of the Society will report to the Members on the progress of different on-going projects of the Society, including the revamp of the SHPHK Website, the Hong Kong Pharmacy e-Museum, and more.

Secure your place by signing up for the event via shphk30@gmail.com now!

See you all at the SHPHK AGM 2019!

You are most welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to learn more about the latest development of drugs in Hong Kong. To join us as member or renew your membership, please visit the Society's website: www.shphk.org.hk.

JARDIANCE®
(Boehringer Ingelheim)

Prepared and edited by Ivy Chan

Active Ingredient:
Empagliflozin

Presentation:
One film-coated tablet contains empagliflozin 10 mg or 25 mg

Pharmacological Properties:
Empagliflozin is a reversible competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC_{50} of 6278 nM), responsible for glucose absorption in the gut.
SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.
Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

Indications:
Glycaemic control
JARDIANCE is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:
Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.
Add-on combination therapy
In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Reduction of risk of cardiovascular death
JARDIANCE is indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death.

Dosage & Administration:
The recommended starting dose of JARDIANCE is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. JARDIANCE can be taken with or without food.

Patients with renal impairment
JARDIANCE is contraindicated in patients with persistent eGFR <45mL/min/1.73m2. No dose adjustment is required for patients with eGFR ≥45mL/min/1.73m2.

Patients with hepatic impairment
No dose adjustment is recommended for patients with hepatic impairment.

Elderly Patients
No dosage adjustment is recommended based on age. Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended. Patients age 75 years and older should be prescribed with caution.

Paediatric population
Safety and effectiveness of JARDIANCE in children under 18 years of age have not been established.

Combination therapy
When JARDIANCE is used in combination with a sulfonylurea or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

Forensic Classification:
P1S1S3

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: ***Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drugs & Therapeutics; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology*** and ***New Products***. It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular four issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

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Submission of a paper implies that it has not been published previously, that it is not under consideration for publication elsewhere, and that if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher. Authors are specifically discouraged from submitting papers as fragmented studies of a particular topic. A manuscript must be indicated which section it is belonged. Upon received, it will be screened by a **Sectional Editor** of HKPJ for initial consideration before it is sent out for further review or comment.

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Three copies of the manuscript are required on either 8.5"x11" or A4 paper (two copies are used for review purposes and the original is kept on file at the Section Editor). Copies must be produced on a high-quality printer, and originals and copies of all Figures and Schemes must be fully legible. Initially only send hard copies of the paper; when it has been refereed, revised if necessary, and accepted, you will be requested to send a disk containing the final version with the final hard copy to the appropriate Editor. Make sure that the disk and the hard copy match exactly. The revised manuscript must be returned to the Editors within one month, otherwise it may be deemed to be new and subject to further review. When submitting the final version with a disk please label all disks with "HKPJ", your name, software (e.g. word 2000), hardware used (e.g. PC or Macintosh) and file names with the correct extension (e.g. Fig 1.cdx, Table 1-6. xls). Save text on a separate disk from the graphics, include the text and tables in one file, and provide graphics and structures in separate numbered files. Please remember to keep a backup copy of both the electronic files and original manuscript for reference and safety since we cannot accept responsibility for damage or loss of papers. Original manuscripts are discarded three months after publication unless the Publisher is asked to return original material after use.

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Please submit, with your manuscript, the names and addresses of 2 potential referees. You may also mention persons who you would prefer not to review your paper.

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The Editors of HKPJ reserve the right to make alterations to manuscripts submitted for publication. Such alterations will be made if manuscripts do not conform with accepted scientific standards or if they contain matter which in the opinion of the Editors is unnecessarily verbose or unclear. Alterations may be queried, but this will inevitably delay publication.

Preparation of manuscript

The manuscript is required to be written in English, with numbered pages, single-spaced, using Arial 9 point font, and in a suitable word-processing format. Each page should have adequate margins (4 cm) and liberal spaces at top and bottom of the manuscript. All textual elements should begin flush left, with the second paragraphs onwards indent, and should use the wrap-around end-of-line feature, i.e. no returns at the end of each line. Place two returns after every element such as title, headings, paragraphs, figure and table call-outs. Most formatting codes will be removed or replaced on processing your article. Please do not use options such as automatic word breaking, justified layout, double columns or automatic paragraph numbering (especially for numbered references). However do use bold face, italic, subscripts, superscripts etc. The Editors reserve the right to adjust style to certain standards of uniformity. If authors are unfamiliar with HKPJ, they should consult a recent copy (or the free online sample copy available from www.HKPS.com/HKPJ) to see the conventions currently followed for guidance in preparing submissions.

The content of manuscripts must be arranged as follows: (1) a Title Page with authors name(s) and address(es); (2) an Abstract, in which contents are briefly stated; (3) a 4 to 6 Key Word Index, (4) Introduction, and (5) the Results and Discussion (preferably combined). Although each section may be separated by headings, they should form one continuous narrative and only include details essential to the arguments presented. If a discussion is separately provided, it should not include a repetition of the results, but only indicate conclusions reached on the basis of them, and those from other referred works; (6) Conclusions or Concluding Remarks; (7) the Experimental should include brief details of the methods used such that a competent researcher in the field may be able to repeat the work; (8) Acknowledgments; (9) References; (10) Legends, Formulae, Tables and Figures.

Title Page and Author Names: Titles must be as brief as possible, consistent with clarity, and should not exceed 10 words in length. Uninformative phrases such as "Chemical examination of", "Studies on", "Survey of", "New", "Novel" etc. will be deleted. If a paper is part of a series, this must not be given in the heading, but referred to in a footnote in the form: *Part 9 in the series "The Role of Pharmacists in Medical Care of Patients" followed by a numbered reference to the previous part. Author names should be typed right underneath the article title. Each author should identify himself or herself with Surname in capital letters, followed by the first name. All names are separated by a semicolon (;). An asterisk should be placed following the name of the author to whom correspondence inquiries should be made. Full postal addresses must be given for all co-authors. Superscript letters; a, b, c should be used to identify authors located at different addresses.

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ABSTRACT: The abstract should be on a separate page and briefly describe the results obtained and conclusions reached, not the methods used, or speculations on any other matter. They are not expected to be a complete summary but only an outline of the main findings. The abstract should be contained within 250 words and should be readable without reference to the rest of the paper.

Key Words: Authors must give four to six "key words" or phrases, which identify the most important subjects covered by the paper.

INTRODUCTION should give the minimum historical data needed to give appropriate context to the author's investigation and its relationship to other similar research previously or currently being conducted. Only information essential to the arguments should be presented. Much data can be taken for granted or quoted in abbreviated form. Specific term (genus, species, authority) of all experimental works must be given at first mention and preferably be in the form adopted by the International Scientific Community.

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(2) Mabry T, Markham KR, Thomas MB. (1970). *The Systematic Identification of Flavonoids.* 2nd Ed, pp. 79-105. Springer Verlag, New York.

(3) Harborne JB. (1999). Plant chemical ecology. In: Barton D, Nakanishi K, Meth-Cohn 0, (Eds.), *Comprehensive Natural Products Chemistry,* Vol. 8. pp. 137-196. Pergamon, Oxford.

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Abbreviations
About, approximately: ca.
Anhydrous: dry (not anhyd.)
Aqueous: aq.
Circular dichroism: CD
Concentrated (or mineral acids): conc.
Concentrations: ppm (or ppb), μM, mM, M, %, mol
Dry weight: dry wt; fresh weight: fr. wt
Electricity: V, mA, eV
Force due to gravity (centrifugation): g; rpm (revolutions min^{-1})
Gas chromatography: GC
Gas chromatography-mass spectrometry: GC-MS Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in ^{1}H NMR)
High performance liquid chromatography: HPLC
Infrared spectrophotometry: IR
Length: nm, μm, mm, cm, m
Literature: lit.
Mass spectrometry: m/z $[M]^{+}$ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M_r
Nuclear magnetic resonance: ^{1}H NMR, ^{13}C NMR, Hz, δ
Numbers: e.g. 1, 10, 100, 1000, 10000; per or $^{-1}$
Optical rotatory dispersion: ORD
Paper chromatography: PC
Precipitate: ppt.
Preparative thin-layer chromatography: prep. TLC
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation sec^{-1})
Repetitive manipulations: once, twice, x3, x4, etc.
RR_t (relative retention time), R_1 (Kovat's retention index), ECL (equivalent chain length- term frequently used in fatty acid work)
Saturated: satd.
Solution: soln.
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H_2O (4:1:5)
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)
Temperature: (with centigrade), mp, mps, mmp, bp
Temperature: temp.
Thin-layer chromatography: TLC, R_f
Time: s, min, h, day, week, month, year
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)
Volume: 1, (litre), μ1, ml
Weight: wt, pg, ng, μg, mg, g, kg

Inorganics, e.g. $AlCl_3$ (aluminum chloride), BF_3 (boron trifluoride), Cl., CO_3, H_2, HCl, $HClO_4$ (perchloric acid), HNO_3. H_2O, H_2O_2, H_2SO_4, H_3B0_3 (boric acid), He, $KHCO_3$ (potassium bicarbonate), $KMn0_4$ (potassium permanganate;), KOH, K-Pi buffer (potassium phosphate buffer), $LiAlH_4$ (lithium aluminium hydride), Mg^{2+}, $MgCl_2$, N_2, NH_3, $(NH_4)_2S0_4$, Na^{+}, $NaBH_4$ (sodium borohydride), NaCl, $NaI0_4$ (sodium periodate), NaOH, Na_2S0_3 (sodium sulphite), Na_2S0_4 (sodium sulphate), $Na_2S_20_3$ (sodium thiosulphate), 0_3, PPi (inorganic phosphate), SO_4^{2-}., Tris (buffer).

Organics, e.g. Ac_20 (acetic anhydride), n-BuOH (butanol), C_6H_6 (benzene), CCl_4 (carbon tetrachloride), CH_2Cl_2 (methylene chloride), $CHCl_3$ (chloroform), CH_2N_2 (diazo-methane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetra-acetic acid), Et_20 (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), $HC0_2H$ (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me_2CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran). ^{1}H NMR solvents and standards: $CDCl_3$ (deutero-chloroform), D_2O, DMSO-d_6 [deuterodimethylsulphoxide not $(CD_3)_2S0$], pyridine-d_5 (deuteropyridine), TMS (tetramethylsilane).

For further terms used in biochemistry and molecular biology the authors should see the websites of the nomenclature committees (www.chem.qmul.ac.uk/iubmb/).

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