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CARDIOLOGY

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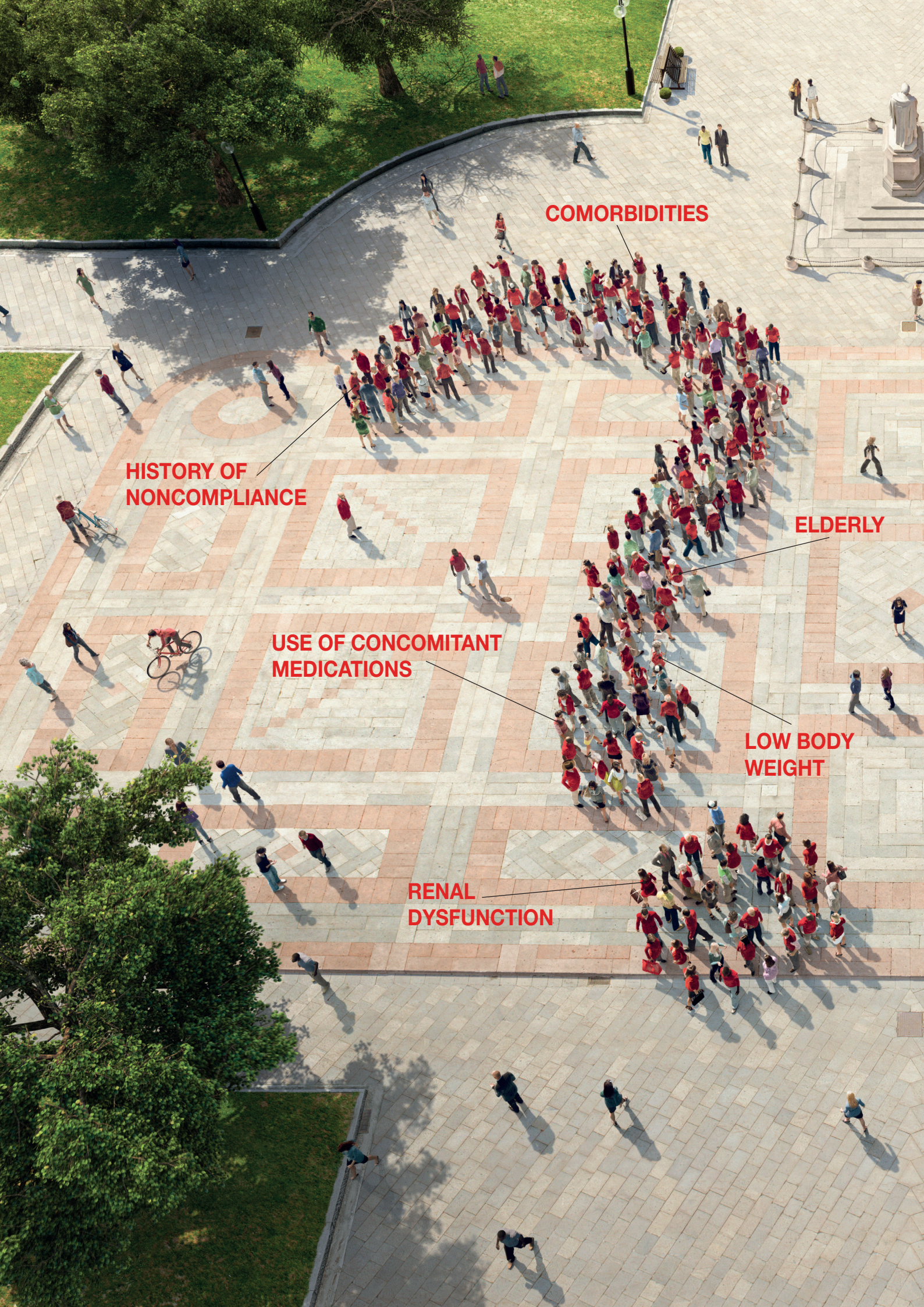
INSIDE

Review of the 61st

Annual ESC Congress 2013

Amsterdam, the Netherlands


COMORBIDITIES
HISTORY OF NONCOMPLIANCE
ELDERLY
USE OF CONCOMITANT MEDICATIONS
LOW BODY WEIGHT
RENAL DYSFUNCTION

EVERY PATIENT IS DIFFERENT. BUT DO ORAL ANTICOAGULANTS ADDRESS THIS?

ORAL ANTICOAGULATION SHOULD CONSIDER INDIVIDUAL PATIENT DIFFERENCES AND NEEDS

Patient-related factors are important considerations for determining an individual's response to oral anticoagulation therapy.[1-2] **Despite advances in oral anticoagulation, questions still remain about how patient-related factors complicate the decision of which agent to use and at what dose.**[3,4] These factors include[5-10]:

- Age
- Renal dysfunction
- Low body weight
- Concomitant medications
- Comorbidities
- Medication compliance

Patients who are exposed to the risks of over- and under-anticoagulation may require patient-specific dosing options that can confer protection against thromboembolism while minimizing bleeding risk.[11v]

ASSESSING PATIENT-RELATED FACTORS WILL HELP PHYSICIANS MAKE MORE INFORMED CLINICAL DECISIONS

Clinical trials that are designed to evaluate the effects of patient-related factors (*e.g.*, age, low body weight, comorbidities, renal dysfunction, and use of concomitant medications) in oral anticoagulation will help provide much-needed clarity to physicians when making critical therapeutic choices.[4]

DAIICHI SANKYO IS DEDICATED TO ONGOING RESEARCH IN ORAL ANTICOAGULATION

Daiichi Sankyo is highly committed to studying oral anticoagulation in a manner that considers patient-related factors. We are conducting clinical research with the goal of providing important information that helps physicians make treatment decisions for patients.

To learn more, visit our Web site at www.CoagulationCenter.com.

Daiichi-Sankyo

Passion for Innovation.
Compassion for Patients.™

References: 1. Zhu T, Martinez I, Emmerich J. Venous thromboembolism: risk factors for recurrence. *Arterioscler Thromb Vasc Biol.* 2009;29(3):298-310. **2.** Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of oral anticoagulants in atrial fibrillation: a systemic review. *Am J Med.* 2010;123:638-645. **3.** De Caterina R, Husted S, Wallentin L, et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol.* 2012;59(16):1413-1425. **4.** Kaluski E, Maher J, Gerula CM. New oral anticoagulants: good but not good enough! *J Am Coll Cardiol.* 2012;60(16):1434. **5.** Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation.* 2011;123(21):2362-2372. **6.** Black MH, Wu J, Singer DE, et al. Body mass index and outcomes among patients with atrial fibrillation from the ATRIA2-CVRN study. Poster presented at: Quality of Care and Outcomes Research 2013 Scientific Sessions; May 15-17, 2013; Baltimore, MD. **7.** DiMarco JP, Flaker G, Waldo AL, et al; AFFIRM Investigators. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study. *Am Heart J.* 2005;149:650-656. **8.** Goto S, Lip GYH, Goldhaber SZ, et al; for the GARFIELD Investigators. Impact of renal function on use of antithrombotic therapy in atrial fibrillation: real-world perspective from the Global Anticoagulant Registry in the FIELD. *Eur Heart J.* 2012;33(Abstract suppl):967-968. Abstract 5290. http://spo.escardio.org/abstract-book/presentation.aspx?id=108231. Accessed June 12, 2013. **9.** Skov J, Bladbjerg EM, Sidelmann J, Vamosi M, Jespersen J. Plenty of pills: polypharmacy prevails in patients of a Danish anticoagulant clinic. *Eur J Clin Pharmacol.* 2011;67:1169-1174. **10.** Kimmel SE, Chen Z, Price M, et al. The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Arch Intern Med.* 2007;167:229-235. **11.** Grip LT, Giugliano RP. Importance of dose selection in novel oral anticoagulants for atrial fibrillation. *Arch Cardiol Mex.* 2012;82(4):308-311.

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CONTENTS

CARDIOLOGY

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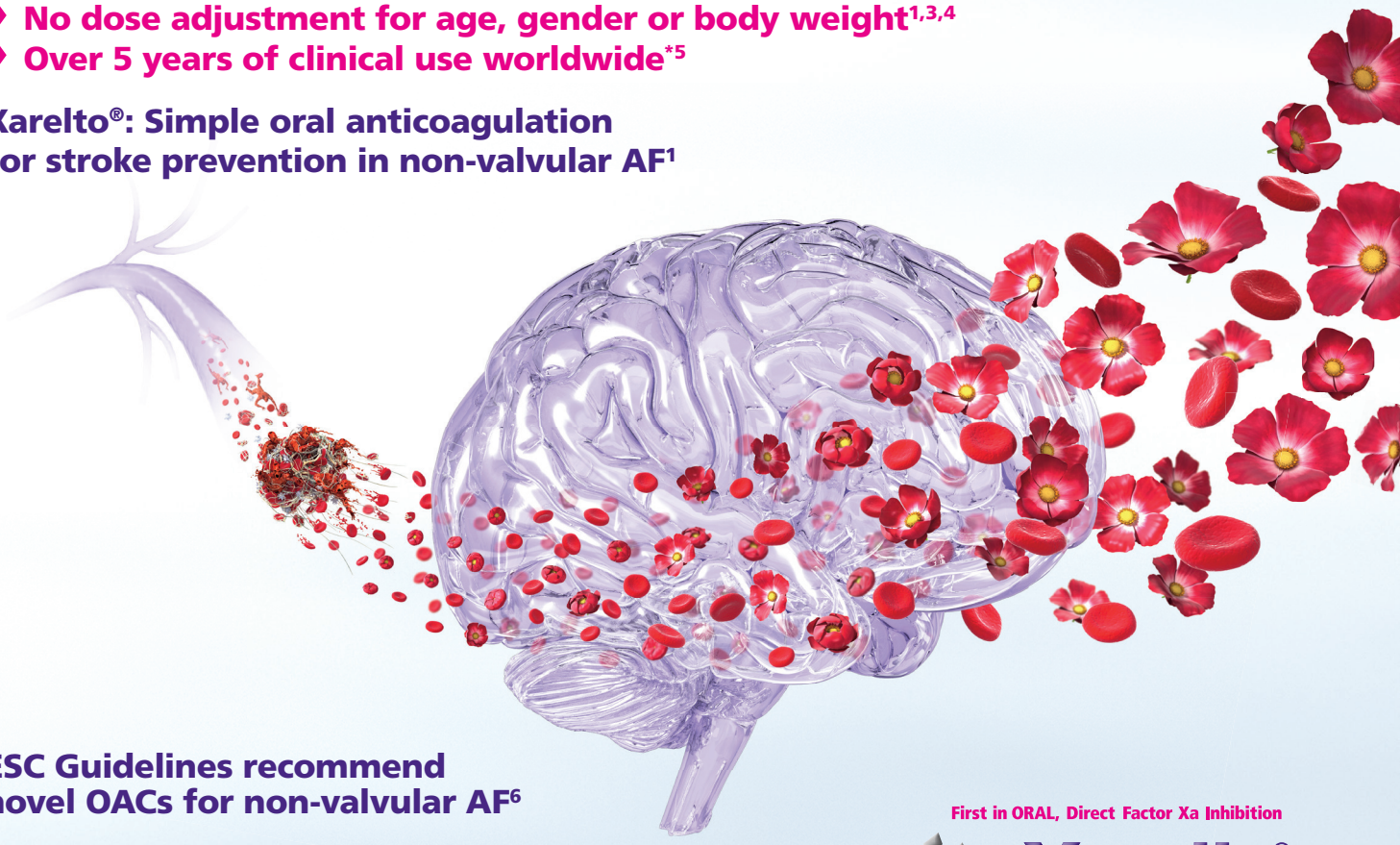
Reduce Stroke Risk

Protect Your Patients

- **One tablet, once daily for effective stroke prevention[1,2]**
- **No dose adjustment for age, gender or body weight[1,3,4]**
- **Over 5 years of clinical use worldwide*[5]**

Xarelto®: Simple oral anticoagulation for stroke prevention in non-valvular AF[1]



ESC Guidelines recommend novel OACs for non-valvular AF[6]

Xarelto® is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular AF with one or more risk factors[1]

AF: Atrial Fibrillation, OACs: oral anticoagulants, * Across all indications

First in ORAL, Direct Factor Xa Inhibition

Xarelto® rivaroxaban

Simple, proven, predictable anticoagulation

Xarelto® 15 and 20 mg film-coated tablets (rivaroxaban) Prescribing Information (Refer to full Summary of Product Characteristics (SmPC) before prescribing) **Presentation:** 15mg/20mg rivaroxaban tablet **Indication(s):** 1. Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). 2. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **Posology & method of administration:** *Dosage 1 (SPAF):* 20 mg orally *o.d.* with food. *Dosage 2 (DVT & PE):* 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; take with food. Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) - no dose adjustment; moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29 ml/min) - limited data indicate rivaroxaban plasma concentrations are significantly increased, use with caution – *SPAF:* reduce dose to 15mg *o.d.*, - *DVT & PE:* 15 mg *b.i.d.* for 3 weeks, thereafter 20mg *o.d.* Consider reduction from 20mg to 15mg *o.d.* if patient's bleeding risk outweighs risk for recurrent DVT & PE; Creatinine clearance <15 ml/min - not recommended. ***Hepatic impairment:*** Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C patients. ***Paediatrics:*** Not recommended. **Contra-indications:** Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except when switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **Warnings & precautions:** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment – haemoglobin/haematocrit testing may be of value to detect occult bleeding. The following sub-groups of patients are at increased risk of bleeding & should be carefully monitored after treatment initiation so use with caution: in patients with severe renal impairment or with renal impairment concomitantly receiving potent inhibitors of CYP3A4 (PK models show increased rivaroxaban concentrations); in patients treated concomitantly with medicines affecting haemostasis. Not recommended in patients: with creatinine clearance <15 ml/min; with an increased bleeding risk (refer to SmPC); receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors; with prosthetic heart valves; with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. If invasive procedures or surgical intervention are required stop Xarelto use at least 24 hours beforehand. Restart use as soon as possible provided adequate haemostasis has been established. See SmPC for full details. *Elderly population* – Increasing age may increase haemorrhagic risk. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as clinically relevant increased rivaroxaban plasma concentrations are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving other anticoagulants, NSAIDs or platelet aggregation inhibitors due to the increased bleeding risk. Strong CYP3A4 inducers should be used concomitantly with caution as they may reduce rivaroxaban plasma concentrations. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive and use machines:** Adverse reactions like syncope (uncommon) & dizziness (common). Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage, renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, allergic reactions, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, abnormal hepatic function, hyperbilirubinaemia, jaundice, vascular pseudoaneurysm. Prescribers should consult SmPC in relation to full side effect information. Overdose: No specific antidote is available. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** *15mg* – 14 tablets: £29.40, 28 tablets: £58.80, 42 tablets: £88.20, 100 tablets: £210.00; *20mg* – 28 tablets: £58.80, 100 tablets £210.00 **MA Number(s):** EU/1/08/472/011-21 **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. **Date of preparation:** August 2013.

Xarelto® is a trademark of the Bayer Group.

References: 1. Xarelto® 15mg and 20mg Summary of Product Characteristics. United Kingdom: Bayer HealthCare AG. **2.** Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Xarelto versus warfarin in non-valvular atrial fibrillation. *N Engl J Med* 2011; **365**(10): 883-891. **3.** Kubitza D, Becka M, Roth A, Mueck W. The Influence of Age and Gender on the Pharmacokinetics and Pharmacodynamics of Rivaroxaban-An Oral, Direct Factor Xa Inhibitor. J Clin Pharmacol. 2013 Mar; **53**(3):249-55. **4.** Kubitza D, Becka M, Roth A, et al. The influence of age and gender on the pharmacokinetics and pharmacodynamics of rivaroxaban-an oral, direct factor xa inhibitor. J Clin Pharmacol. 2013;**53**(3):249-255. **5.** Health Canada, Drugs and Health Products, Summary Basis of Decision (SBD) for Xarelto®, Submission Control Number 119111, Date Issued: 2009/02/13 **6.** Camm AJ et al. *Eur Heart J.* 2012; **33**(21):2719–2747.

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Bayer plc.
Tel.: 01635 563500, Fax.: 01635 563703,
Email: phdsguk@bayer.co.uk

September 2013 L.GB.08.2013.3504a

Ischaemic stroke: the most common thromboembolic complication in patients with AF[1]

Ischaemic stroke devastates

Who's your next Pradaxa® patient?

Prescribing Information (SPAF – UK) PRADAXA® (dabigatran etexilate)

Capsules containing 110 mg or 150 mg dabigatran etexilate (as mesilate) **Action:** Direct thrombin inhibitor **Indication:** Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: Previous stroke, transient ischaemic attack, or systemic embolism (SEE); Left ventricular ejection fraction < 40 %; Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; Age ≥ 75 years; Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension **Dose and Administration:** Renal function should be assessed by calculating CrCL prior to initiation to exclude patients with severe renal impairment (CrCL < 30 mL/min). Recommended daily dose 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term. In case of intolerability to dabigatran, patients should be instructed to immediately consult their doctor. Elderly: Aged ≥ 80 years 220 mg taken as one 110 mg capsule twice daily; 75 – 80 years consider 220 mg taken as one 110 mg capsule twice daily. As renal impairment may be frequent in the elderly (> 75 years), assess renal function by calculating CrCL prior to initiation to exclude patients with severe renal impairment (CrCL < 30 mL/min). Renal function should also be assessed at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate. Patients with an increased risk of bleeding: closely monitor clinically looking for signs of bleeding or anaemia. Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test may help identify increased risk patients. Patients with gastritis, oesophagitis, or gastroesophageal reflux consider 220 mg taken as one 110 mg capsule twice daily due to the elevated risk of major gastro-intestinal bleeding. Renal impairment: contraindicated in severe renal impairment (CrCL < 30 mL/min); patients with renal impairment and a high risk of bleeding consider 220 mg taken as one 110 mg capsule twice daily. Close clinical surveillance is recommended in patients with renal impairment. As above assess renal function prior to initiation to exclude patients with severe renal impairment and assess renal function at least once a year or more frequently as needed. Concomitant verapamil 220 mg taken as one 110 mg capsule twice daily; Pradaxa and verapamil should be taken at the same time. No dose adjustment required but close clinical surveillance in patients < 50 kg. Not recommended if liver enzymes > 2 Upper Limit of Normal (ULN). If switching from Pradaxa to parenteral anticoagulant wait 12 hours after the last dose of Pradaxa; if switching from parenteral anticoagulants to Pradaxa then Pradaxa should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment; if switching from Pradaxa to VKA adjust the starting time of the VKA based on CrCL; if switching from VKA to Pradaxa stop VKA and give Pradaxa once INR <2.0. Cardioversion patients can stay on Pradaxa whilst being cardioverted. No relevant use of Pradaxa in the paediatric population in the indication. Pradaxa should be swallowed whole with water, with or without food. Patients should be instructed not to open the capsule as this may increase the risk of bleeding. **Contraindications:** Hypersensitivity to any component; severe renal impairment (CrCL < 30 mL/min); active clinically significant bleeding; lesion or condition, if considered a significant risk factor 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; 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, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; hepatic impairment or liver disease expected to have any impact on survival; concomitant systemic ketoconazole, cyclosporine, itraconazole, tacrolimus, dronedarone; prosthetic heart valves requiring anticoagulant treatment. **Warnings and Precautions:** Not recommended if liver enzymes > 2 ULN. Haemorrhagic risk: Close clinical surveillance (signs of bleeding or anaemia) is recommended throughout the treatment period, especially when haemorrhagic risk is increased or risk factors combined. Factors which may increase haemorrhagic risk: age ≥ 75 years; moderate renal impairment (CrCL 30 – 50 mL/min); P-glycoprotein inhibitor co-medication; body weight < 50 kg; acetylsalicylic acid (aspirin); NSAID; clopidogrel; selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs); other drugs which may impair haemostasis; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, recent biopsy, major trauma, bacterial endocarditis, oesophagitis, gastritis or gastroesophageal reflux. Concomitant use of ticagrelor. The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Patients who develop acute renal failure must discontinue Pradaxa. If severe bleeding occurs, discontinue treatment and investigate the source of the bleeding. Avoid or use with caution medicinal products which may increase the risk of haemorrhage. The use of fibrinolytic medicinal products for the treatment of acute ischaemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the ULN according to the local reference range. Avoid concomitant administration with P-gp inducers. Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate; prescribers should consult the Summary of Product Characteristics for further information. Procedures such as spinal anaesthesia may require complete haemostatic function. The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate; these patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma. Treat with caution patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events. Myocardial infarction. Contains Sunset Yellow (E110) which may cause allergic reactions. **Interactions:** Anticoagulants and antiplatelet aggregation medicinal products; P-gp inhibitors e.g. amiodarone, quinidine, verapamil, clarithromycin, ticagrelor co-administration (close clinical surveillance); verapamil co-administration - reduce Pradaxa dose to 220 mg (see above); not recommended for concomitant treatment posaconazole, protease inhibitors including ritonavir and its combinations with other protease inhibitors; avoid with P-gp inducers e.g. rifampicin, St John's wort, carbamazepine, phenytoin; SSRIs or SNRIs. Dabigatran etexilate and dabigatran are not metabolised by cytochrome CYP450 system, therefore related medicinal product interactions not expected. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa. Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran. **Fertility, pregnancy and lactation:** Avoid pregnancy during treatment. Do not use in pregnancy unless clearly necessary. Discontinue breast-feeding during treatment. **Undesirable effects:** Most commonly reported adverse reactions are bleedings occurring in total in approximately 16.5 % in patients with atrial fibrillation treated for the prevention of stroke and SEE. Common (≥ 1/100 to <1/10): anaemia; epistaxis; gastrointestinal haemorrhage; abdominal pain; diarrhoea; dyspepsia; nausea; skin haemorrhage; genitourological haemorrhage, including haematuria. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price**: *110 mg* 60 capsules £65.90 *150 mg* 60 capsules £65.90 **Legal category** POM **MA numbers:** *110 mg* EU/1/08/442/007 (60 capsules) *150 mg* EU/1/08/442/011 (60 capsules) **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Str. 173, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** July 2013.

Boehringer Ingelheim

Pradaxa® dabigatran etexilate

Stroke prevention in atrial fibrillation

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

Reference

1. Dweck M, Shah A, *et al.* Anticoagulation in atrial fibrillation: the present and the future. *J R Soc Med Cardiovasc Dis* 2012; 1(13):1-7.

Date of preparation: October 2013 **Job code:** UK/DBG-131349

For more information, including an educational pack, go to www.pradaxa.co.uk/SPAFeducationalpack or call the Pradaxa® information line on 0845 601 7880

EMJ GORELY NEW MEDIA

European Medical Journal
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www.emjreviews.com
31-34 Railway Street
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Welcome

I would like to offer you all a warm welcome to the inaugural edition of *European Medical Journal – Cardiology* in which we aim to provide the most up-to-date reviews of new technologies and techniques currently being developed in the field of Cardiology.

In this edition we provide extensive coverage of the European Society of Cardiology (ESC) Congress, held in the vibrant capital of the Netherlands, Amsterdam, from the 31st August–4th September 2013. The ESC Congress is the largest and most influential annual cardiovascular event, whose goal is to give healthcare professionals the opportunity to share top scientific data. The Past President of the ESC, Prof Panos Vardas, said: "New treatments and devices presented at the ESC Congress 2013 show that cardiologists continue working hard to make patients' lives better." This is in line with the mission statement of the ESC, which is to reduce the burden of cardiovascular disease in Europe. At *EMJ* we also hope that our *Cardiology* edition will contribute to this through readership of our Congress Review, published articles and 'What's New' section.

Within the Congress Review we also report on the role of music and exercise in improving endothelial function in patients with coronary artery disease. One of our featured articles, written by Dr Roselien Buys, also focuses on the positive cardiovascular benefits of exercise. Her article entitled 'Prescribing physical activity for the prevention and treatment of hypertension in patients with aortic coarctation. A review,' describes how patients with aortic coarctation who partake in endurance exercises can benefit from a decrease in blood pressure.

In our 'What's New' section, which focuses on human interest stories, and also new developments within cardiology, one of our articles highlights the difficulties that patients - who have suffered from a heart attack, a stroke, or have received a heart transplant - may have in resuming their sex life, as their fitness may not be sufficient, and focuses on the doctor's role in ensuring that patients feel confident in pursuing this.

The use of technology, not only in our everyday lives, but also in a patient-centred setting, is constantly growing and evolving and is strongly embraced by cardiologists. See our 'What's New' section for a report on the use of three-dimensional holograms and their future in hospitals and in the hands of cardiologists. This section also includes an article concerning the world's first self-contained and leadless pacemaker, which will greatly benefit the cardiac industry.

We hope that this first edition of *EMJ – Cardiology* will provide a great insight into the changing world of Cardiology, and will provide a new base of information for the hardworking and ever-busy cardiology healthcare-providers. From everyone at *EMJ*, we would like to thank our Editorial Board for their co-operation and support in maintaining a high standard of data to be conveyed to our readership, which we hope that you will find an invigorating read.

Kelly-Ann Lazarus

Editor, European Medical Journal

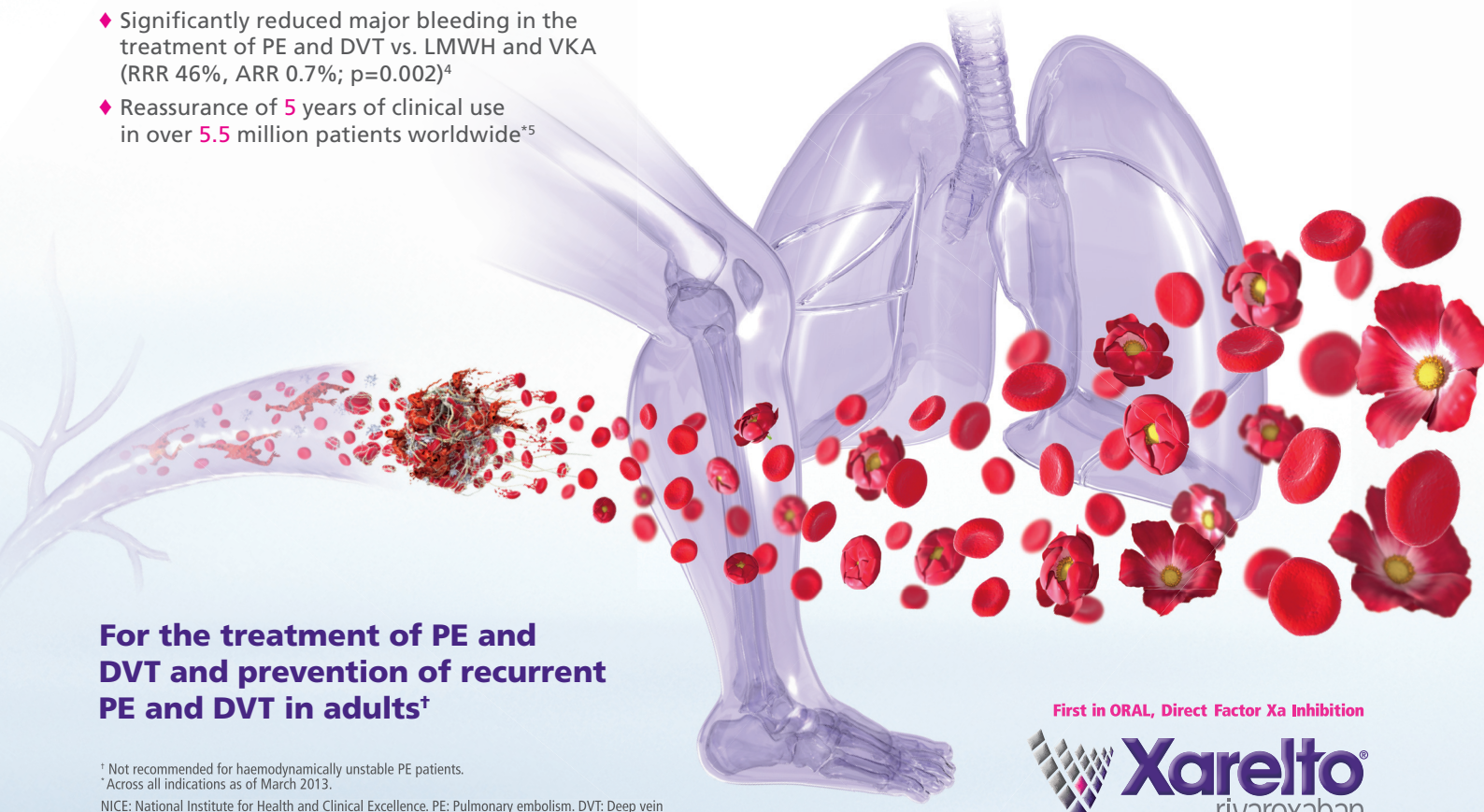
150 Years
Science For A Better Life

Now NICE RECOMMENDED for treatment of PE & DVT and prevention of recurrent PE and DVT in adults[1,2]

Treat PE and DVT Protect Your Patients

Xarelto: The Single-Drug Solution Matters

- The only novel oral anticoagulant licensed to both treat PE and DVT and prevent recurrent PE and DVT[3]
- Significantly reduced major bleeding in the treatment of PE and DVT vs. LMWH and VKA (RRR 46%, ARR 0.7%; p=0.002)[4]
- Reassurance of 5 years of clinical use in over 5.5 million patients worldwide*[5]



For the treatment of PE and DVT and prevention of recurrent PE and DVT in adults†

† Not recommended for haemodynamically unstable PE patients.
* Across all indications as of March 2013.

NICE: National Institute for Health and Clinical Excellence. PE: Pulmonary embolism. DVT: Deep vein thrombosis. LMWH: Low molecular weight heparin. VKA: Vitamin K antagonist. RRR: Relative risk reduction. ARR: Absolute risk reduction.

First in ORAL, Direct Factor Xa Inhibition

Xarelto® rivaroxaban

Simple, proven, predictable anticoagulation

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Consider reduction from 20 mg to 15 mg o.d. if patient's bleeding risk outweighs risk for recurrent DVT & PE; Creatinine clearance <15 ml/min – not recommended. ***Hepatic impairment:*** Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C. ***Paediatrics:*** Not recommended. **Contraindications:** Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except when switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breastfeeding. **Warnings & precautions:** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Discontinue if severe haemorrhage occurs. In studies, mucosal bleedings & anaemia were seen more frequently during long-term rivaroxaban treatment compared with VKA treatment – haemoglobin/haematocrit testing may be of value to detect occult bleeding. The following subgroups of patients are at increased risk of bleeding & should be carefully monitored after treatment initiation, so use with caution: in patients with severe renal impairment or with renal impairment concomitantly receiving potent inhibitors of CYP3A4 (PK models show increased rivaroxaban concentrations); in patients treated concomitantly with medicines affecting haemostasis. Not recommended in patients: with creatinine clearance <15 ml/min; with an increased bleeding risk (refer to SmPC); receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors; with prosthetic heart valves; with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. If invasive procedures or surgical intervention are required, stop Xarelto use at least 24 hours beforehand. Restart use as soon as possible provided adequate haemostasis has been established. See SmPC for full details. *Elderly population* – Increasing age may increase haemorrhagic risk. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as clinically relevant increased rivaroxaban plasma concentrations are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving other anticoagulants, NSAIDs or platelet aggregation inhibitors due to the increased bleeding risk. Strong CYP3A4 inducers should be used concomitantly with caution as they may reduce rivaroxaban plasma concentrations. **Pregnancy & breastfeeding:** Contraindicated. **Effects on ability to drive and use machines:** Adverse reactions like syncope (uncommon) & dizziness (common). Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage, renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, allergic reactions, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, muscle), haemarthrosis, which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, abnormal hepatic function, hyperbilirubinaemia, jaundice, vascular pseudoaneurysm. Prescribers should consult SmPC in relation to full side-effect information. **Overdose:** No specific antidote is available. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** *15 mg* – 14 tablets: £29.40, 28 tablets: £58.80, 42 tablets: £88.20, 100 tablets: £210.00; *20 mg* – 28 tablets: £58.80, 100 tablets £210.00 **MA Number(s):** EU/1/08/472/011-21 **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. **Date of preparation:** August 2013.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bayer plc. Tel.: 01635 563500, Fax.: 01635 563703, Email: phdsguk@bayer.co.uk

References
1. National Institute for Health and Clinical Excellence. Technology appraisal guidance 287. June 2013. 2. National Institute for Health and Clinical Excellence. Technology appraisal guidance 261. July 2012. 3. Xarelto 15mg and 20mg Summary of Product Characteristics. United Kingdom: Bayer HealthCare AG. 4. Büller HR, on behalf of the EINSTEIN Investigators. Oral Rivaroxaban for the Treatment of Symptomatic Venous Thromoembolism: A Pooled Analysis of the EINSTEIN DVT and EINSTEIN PE Studies. ASH 2012. Oral presentation 20. 5. Data on file. Bayer HealthCare AG, Berlin, Germany.

September 2013
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Foreword

Dr Carl J. Lavie

Professor of Medicine, Medical Director,
John Ochsner Heart and Vascular Institute

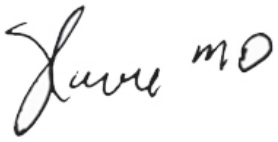
Dear Colleagues,

It is my distinct pleasure to introduce the inaugural issue of the *European Medical Journal – Cardiology*. As with the other *European Medical Journals*, this journal is dedicated to reporting on major European cardiovascular (CV) conferences, including the recent European Society of Cardiology meeting in August, 2013 in Amsterdam, the Netherlands. As with our other CV-related journal (*EMJ-Interventional Cardiology*), this journal aims to publish high quality peer-reviewed research, reviews, case reports, and state-of-the-art articles in all aspects of CV diseases (CVD). This journal joins the growing trend of open access journals in medical publishing, with all articles easily accessible and without charge to our readership, which represents a large range of primary care clinicians, scientists, as well as specialists and sub-specialists in CVD.

The journal encourages the submission of a broad range of CV topics from across the globe. Although certainly the journal will represent the European CV community, as evidenced by the Editorial Board, this journal hopes to serve the European, American, and internal communities.

This certainly is an exciting time in the area of CVD, including prevention, coronary artery disease, valvular heart disease, arrhythmias, heart failure, congenital heart disease, as well as all aspects of CV imaging. Certainly, my colleagues and I on the Editorial Board look forward to an innovative forum for the propagation of a vast range of CV knowledge to our readership across the globe.

Regards,



Dr Carl J. Lavie

Professor of Medicine, Medical Director, Cardiac Rehabilitation and Prevention; Director, Stress Testing Laboratory, John Ochsner Heart and Vascular Institute, Ochsner Clinical School - The University of Queensland School of Medicine, New Orleans, Louisiana, U.S.A.

ESC ANNUAL CONGRESS 2013

AMSTERDAM RAI EXHIBITION AND CONVENTION CENTRE, AMSTERDAM, THE NETHERLANDS

31ST AUGUST-4TH SEPTEMBER 2013

Welcome to the *European Medical Journal* review of the Annual European Society of Cardiology Congress

EMJ EUROPEAN MEDICAL JOURNAL

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Welcome to the *European Medical Journal* review of the Annual European Society of Cardiology Congress 2013

HELD in the heart of Amsterdam, the European Society of Cardiology (ESC) 2013 Congress brought an already vibrant city to life, as attendees and abstracts from 82 different countries travelled from across the globe to attend the event.

Under the roof of the Amsterdam RAI Exhibition and Convention Centre, thousands of delegates and professionals bustled inside the vast event. Symposia halls, quirkily named after the prominent cities of Europe, embodied the broad-reaching community atmosphere.

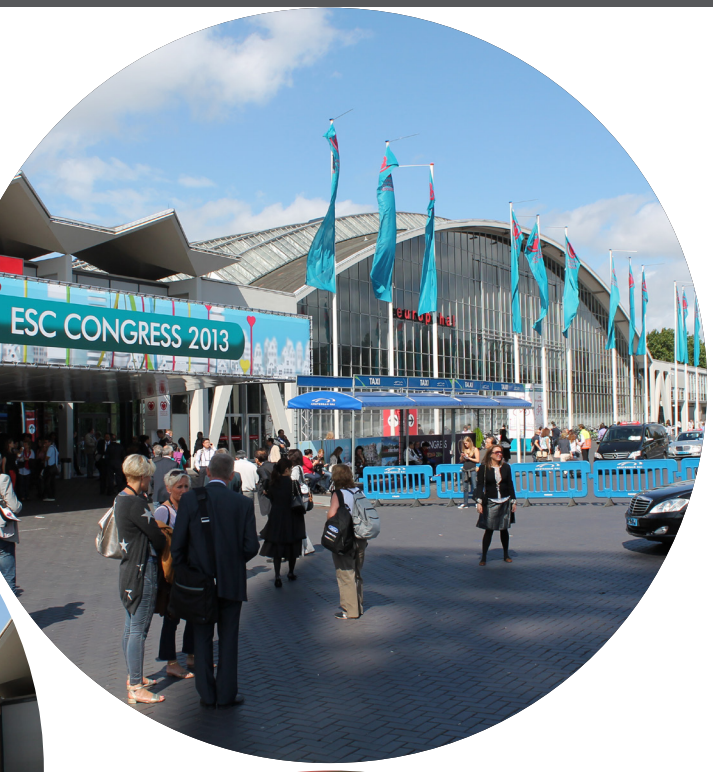
The President of ESC, Professor Panos Vardas, highlighted in his pre-Congress statement: "There is simply nothing like the ECS Congress. It is unique, not only in terms of the quality of its science, but in the diversity of the people you meet and connections you make. ESC President or not, as a health professional, the ESC Congress is an unforgettable experience that I would not miss."

This over-arching sense of diversity extended to the topics on show, with results from studies covering a multitude of different subjects presented throughout, including the world's first self-contained leadless pacemaker, as seen in the following pages with exclusive quotes from Dr Petr Neuzil of the LEADLESS study.

Whether it was research on the health and mortality of Tour de France cyclists compared to the general French population, the effect of listening to one's favourite music on the endothelial function concerning coronary artery disease, or the examination of the Dutch model of emergency pre-hospital cardiac care, all were observed with intense interest.

"It is the complete experience – you eat, drink, sleep, breathe the most exciting science on the planet."

Professor Panos Vardas, President, European Society of Cardiology



Ongoing issues were approached with both open-mindedness and enthusiasm, with presentations on known problems such as heart and stroke, everyday life, smoking, rhythmology, obesity, and aortic stenosis, all successfully covered over the five days from 31st August to 4th September.

The society proudly announced the launch of their ESC Guidelines app for mobile devices, in a bid to further embrace the digital world and encourage cardiologists to have constant access to the most up-to-date information. This was alongside the increasing development of their eLearning platform – an online, 'life-long' learning tool based on the European Curriculum which was demonstrated during the event.

The industry exhibition accompanied this unspoken theme, seeing such enchanting entertainment as virtual reality visors and Wii Golf projections featured at a number of company stands for attendees to enjoy.

Professor Vardas, speaking on the engrossing nature of ESC 2013, summarised his pride by saying: "For me, it is the complete experience – you eat, drink, sleep, breath the most exciting science on the planet."

In doing so, he described the draw of the Congress most effectively: all-encompassing. It is with this impressive scope that the organisation carries both itself and its 80,000 professionals forward into the future, ensuring that if one thing is certain, it is that the world of cardiology is in safe hands.

Should we all follow in the footsteps of the Dutch emergency response team?

THE length of emergency response times have often been criticised. The Dutch model of emergency pre-hospital cardiac care however, has challenged this preconception, at the ESC Congress 2013 in Amsterdam.

The project began in 2008, when it was clear that the standard ambulance response times were too long and so did not provide an effective CPR service. The Director of ambulance services for the North Holland North region, where the project originated, Dr Martin Smeekes, said: "We had to do something different, and that meant bringing in the public and making AEDs [automated external defibrillators] more widely available."

In the North Holland North region, there are 500 members of the public trained to perform CPR, and more than 600 AEDs available. Commenting that it is the involvement from the public which is key, Dr Smeekes said: "Now, from the moment we receive the first alarm call, the dispatch centre can send an immediate alert to local AED centres and lay rescuers, and they respond more quickly than the police or ambulance ever could."

The involvement from the public has single-handedly increased survival rates by up to 23% from out-of-hospital cardiac arrests.

Dr Smeekes explained how the involvement of local people has "made an enormous difference in just a few years; cardiologists are now seeing far more cardiac arrest cases brought to hospital with a good chance of survival."

"The dispatch centre can send an immediate alert to local AED centres and lay rescuers, and they respond more quickly than the police or ambulance ever could."

Dr Martin Smeekes, Director of Ambulance Services

As the project has been so successful in cutting down response time by 4 or 5 minutes, from the average response time of 15 minutes, it has attracted international attention. Based on data from 2011, the overall survival rate is 23%. For those with an initial rhythm of ventricular fibrillation it is 42%, and those with any other rhythm is 5%. Whereas in 2006, the rates were 18%, 32%, and 4% respectively.

This programme is especially important in rural regions where a fast response time is not feasible, which is why, according to Dr Smeekes, it was important to ensure every town was involved with public education in CPR and AEDs. Although more lay volunteers and AEDs are desirable, the programme has been very successful, and owing to this success, Dr Smeekes hopes that every town in the Netherlands will have the same results.

Music can help rehabilitation process of CAD

A NEW study presented at ESC, found that listening to your favourite music, as well as exercising, will improve endothelial function in patients with coronary artery disease (CAD).

Professor Marina Deljanin of the Ilic Institute of Cardiology, Medical Faculty University of Niš, Serbia, said: "Exercise training has been shown to improve endothelial function and is the cornerstone of a multifaceted programme of cardiovascular rehabilitation. However, little is known about the role of music in cardiovascular rehabilitation or the effects of listening to favourite music on endothelial function."

The study assessed 74 patients with stable CAD over a period of 3 weeks. The researchers evaluated the effects of listening to favourite music on endothelial function through changes of circulating blood markers of endothelial function.

Professor Ilic said: "In the setting of cardiovascular risk factors and cardiovascular disease, the endothelium loses its normal function. Since endothelium-derived nitric oxide is necessary to maintain an adequate vascular response, correction of endothelial dysfunction has become a goal of therapy."

After 3 weeks, the results showed that those who were in the group that listened to music as well as exercising had improved their heart function by 39%, compared to the group which only listened to music alone whose heart function only improved by 19%.

"The combination of music and exercise training led to the most improvement in endothelial function. Improvements in endothelial function were associated with significant improvements in exercise capacity," Professor Ilic said.

It is the view of the researchers that the vascular health benefits associated with listening to music may be associated with brain function which may, when we listen to music we like, release endorphins or endorphin-like compounds.

> "Little is known about the role of music in cardiovascular rehabilitation or the effects of listening to favourite music on endothelial function."
>
> *Professor Marina Deljanin, Ilic Institute of Cardiology.*

World's first leadless pacemaker presented

A REVOLUTIONARY new pacemaker technology is set to innovate the cardiac industry, as results from studying the world's first self-contained, leadless cardiac pacemaker were presented at ESC 2013.

With a 4.5 cm length and 5 mm diameter, the device is less than 10% of the size of a conventional pacemaker, allowing itself to be implanted directly into the heart via a percutaneous, catheter-based procedure using the femoral artery.

Done without the need for a lead or surgical pocket, the device is inherently MRI compatible and boasts an average total procedure time of 28 minutes.

Dr Petr Neuzil, Head of Cardiology at Homolka Hospital, Prague, Czech Republic, argues that one of the key benefits is the leadless capabilities of the device, meaning the pacemaker is practically a new platform for cardiologists.

"We are now missing all the troubles that you potentially get from the leads. Lead troubleshooting could be technical issues with the rupture, the fracture, inhalation troubles, and also infection," he said. "So with a platform like the leadless pacemaker, you don't need to worry about this."

> "If you consider the longevity was supposed to be 6 or 7 years, now we estimate it will probably be much longer, because we have now got really exciting data."
>
> *Dr Petr Neuzil, Holmolka Hospital, Czech Republic*

A conventional pacemaker operation involves an incision made in the upper chest, with one or more leads guided through the vein into the heart. The pacemaker is then connected to the leads, inserted beneath the skin, and the incision is closed. Through the new, less invasive option, patient comfort is also greatly improved, with no visible lump and no scarring around the pectoral.

Battery life also matches the current conventional pacemakers, with an average lifespan of 8.5 years at 100% pacing, which was noted during the LEADLESS study.

"If you consider the longevity was supposed to be 6 or 7 years, now we estimate it will probably be much longer, because we have now got really exciting data," Dr Neuzil continued.

"So we estimate [longevity to be] over 10 years now for our very first patients, which is exciting. But still, since the very start we have been developing a retrieval system, because logically, at the same time you put the device in, you need to think: 'How can I get it back if something is wrong?'"

A hospital in Prague had two patients in the trial who needed the retrieval during their original procedure. In one of the procedures, the pacemaker entered the left ventricle, rather than the right as planned, therefore having to be retrieved immediately, and placed in the right

ventricle. The retrieval is done through the use of a clever catheter, and has also been put into use throughout the study.

Devices were implanted at the Czech Republic's Homolka Hospital and the Institute for Clinical and Experimental Medicine (IKEM) Hospital, both in Prague, and the Academic Medical Center (AMC) Hospital in Amsterdam, The Netherlands.

Following implementation, patients will continue to be monitored for the first year at every quarter. The first patient group were implanted early in December 2012, and after 10 months of follow-up the device is set for CE mark approval as soon as the next couple of months.

"We're excited with these outstanding preliminary results," said Drew Hoffmann, Chief Executive Officer of Nanostim, Inc. "We remain confident that the LEADLESS study will further our understanding of the benefits of this innovative, minimally-invasive technology and look forward to making this important technology available to patients and physicians worldwide."

McCain's can benefit cardiometabolic health

POTATOES are regularly consumed but poorly understood. If consumed in the right quantity and with the right food, not only can they be part of a healthy diet but they will also have a positive effect on certain measures of cardiometabolic health, according to studies revealed at ESC.

The direct benefits of a healthy, balanced diet are very well-known. The direct benefits of potatoes on cardio metabolic diseases however, are not very well-known. In fact, potatoes can have an impact on blood pressure, cholesterol, inflammation, glycaemic response, body weight, and other risk factors in both humans and animals.

Professor Jean-Davignon highlights that they are a good source of vitamin C, potassium, and dietary fibre, saying: "They contain a host of macro and micronutrients that are indispensable to life, including amounts of vitamin C that can be equal or sometimes higher than what is found in oranges, and potassium levels that rival with those contained in bananas."

Cardiometabolic diseases are one of the leading causes of premature deaths, so it is important to understand which foods could prevent this. In the view of Jean Bernou, President of McCain Europe, it is important to promote both the nutritional benefits and the environmental aspects.

Professor Anton Haverkort, of Plant Research International – Wageningen University and Research Centre in the Netherlands, highlighted: "Potato is a very well-performing crop in that it is most efficient when it comes to sustainable utilisation of soil, water and nutrients and its possible benefits from climate change."

Although more extensive research and studies need to be undertaken, these findings are very significant and may go a long way to help towards cardiometabolic diseases.

Cardiologists and patients will welcome cangrelor

RESEARCHERS have discovered that cangrelor is an effective antiplatelet drug that reduces periprocedural ischaemic events during percutaneous coronary intervention (PCI), according to the results from three Phase III trials testing cangrelor, revealed at the ESC Congress.

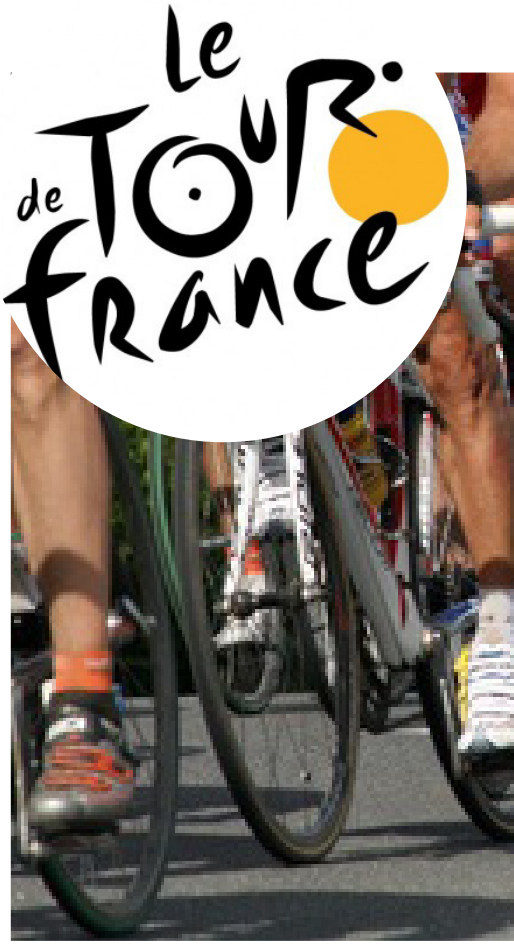
Professor Phillipe Gabriel Steg, Director of Coronary Care Unit, Bichat-Claude Bernard Hospital, Paris, France, suggested: "The results of this analysis provide a wealth of data that intravenous cangrelor reduces thrombotic events and angiographic complications during the procedure, a totality of evidence that will have impact on guideline recommendations."

> "The results of this analysis provide a wealth of data...a totality of evidence that will have an impact on guideline recommendations."
>
> *Professor Phillipe Gabriel Steg, Bichat-Claude Bernard Hospital*

Cangrelor is different from andenosine diphosphate (ADP) receptor antagonists as it is administered intravenously and produces rapid platelet inhibition. It also reduces the odds of death, myocardial infarction (MI), ischaemia-driven revascularisation or stent thrombosis, at 48 hours after randomisation, by 19%.

CHAMPION programme co-chair Dr Robert A. Harrington, Professor of Medicine and Chairman of Medicine at Stanford University, said: "Angiographic complications during the procedure were significantly reduced by cangrelor with a marked reduction in new or suspected thrombus, in acute stent thrombosis, and in the need for bailout glycoprotein IIb/IIIa inhibitor."

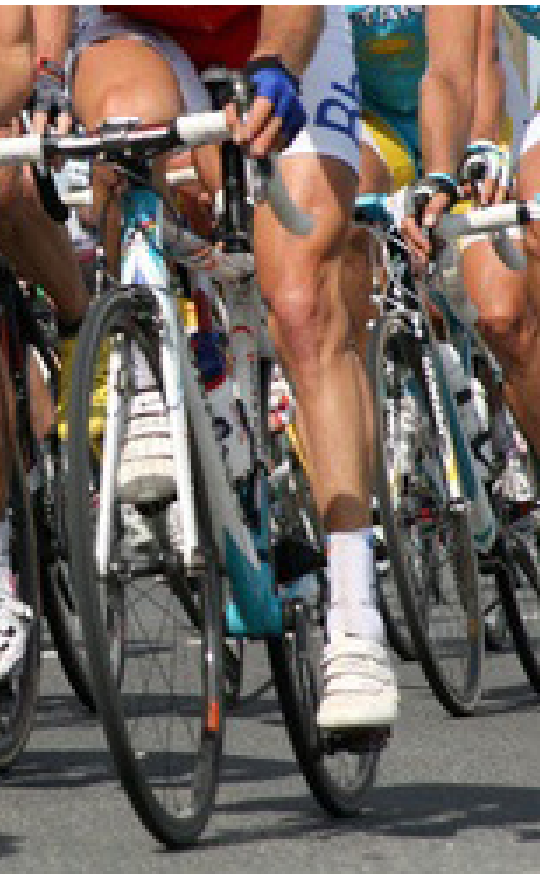
Currently, The Medicine Company is in the process of approving the drug for use in America, and will file for European use in the last quarter of 2013. These trials have not only shown the success of the drug in preventing platelet activation and aggression, but also in it's cost-effectiveness, and, as such, will be welcomed by both cardiologists and patients alike.



Tour de France riders have better mortality rates

MARKING the 100th anniversary of the Tour de France, new research has shown that French cyclists who have participated in the Tour de France race have a better mortality rate compared to the general French male population.

Cycling is one of the toughest endurance sports, being not just physically, but also psychologically demanding. This study assessed 786 French cyclists who participated in at least one Tour de France between 1947 and 2012, and compared them to the general French male population of the same age.



Dr Xavier Jouven, from the Sudden Death Expertise Centre in Paris, France said: "In the context of recent concerns regarding performance-enhancing techniques and the potential negative health effects of excessive high-level physical activity, data on the long-term outcomes and causes of death in elite endurance cyclists is of particular interest."

The results of the study found that there was a 41% lower mortality rate compared to the general population. Dr Jouven commented that although these results are reassuring, no death has been observed since 1990, adding: "We have to remain careful since we cannot directly assess the potential harmfulness of doping through our analyses and results."

The use of doping or other performance-enhancing techniques has undergone three eras: the first in 1947-1970 using cocaine and amphetamines, 1971-1990 using androgens and anabolic steroids, and finally, 1991-2012, growth hormones and erythropoietin. Dr Jouven stressed that these types of doping "may have attenuated the association between participation in the Tour de France and lower long-term mortality."

The main causes of death amongst cyclists, which occurred less frequently in the general population, included neoplasms and cardiovascular diseases, which accounted for 32.2% and 29% of deaths, respectively.

Many trauma-related deaths, which were as responsible for 15.8%, were also apparent. This percentage was roughly the same as that which occurs in the general population.

It should be stressed however, that these results are deemed to be encouraging, and the mortality ratio was consistent across all age groups. Furthermore, it shows that high-level endurance sports should be encouraged as the positive effects outweigh the negatives.

A decrease in the risk of ischaemic stroke after AMI

IT has been discovered that over a 10-year period there has been a 7.1% decrease in risk of ischaemic stoke after acute myocardial infarction (AMI) in diabetic patients. This decline has happened due to the use of reperfusion therapy and secondary prevention drugs, according to results published at ESC.

The study enrolled 173,233 patients who had their first AMI during 1998-2008. Stina Jakobsson, Herzzentrum Ludwigshafen, Ostersund, Sweden said: "Ischaemic stroke following an acute myocardial infarction is a fairly uncommon but devastating event with high mortality. It has long been recognised that patients with diabetes mellitus are at a particularly high risk of complications after an AMI but, until now, the risk of ischaemic stroke after an AMI in patients with diabetes has been uncertain."

Of the 33,503 (19%) patients in the register who had a previous diagnosis of diabetes, 5.5% had an ischemic stroke within 1 year after the AMI. Miss Jakobsson said: "We believe that an important mechanism behind the increased risk for ischaemic stroke after an AMI, especially in diabetic patients, may be increased inflammation and platelet reactivity seen with an AMI."

It is thought that the reduction of ischaemic stroke rate decreased because the researchers increased the use of secondary preventive treatments after AMI. Therefore, these positive results highlight that the use of secondary preventive treatments should be utilised more, especially when treating diabetic patients.

"Ticking bomb" threatens 5% of untreated 75-76 year olds

IT was announced, following the results of mass screening presented at ESC on Saturday 31st August, that 5% of 75-76-year-olds were at an increased risk of stroke, due to atrial fibrillation (AF).

The STROKESTOP trial screened all 75-76 year olds in Stockholm County and Region Halland, with 90% of the newly diagnosed placed on oral anticoagulation.

Though stroke associated with AF often proves to be fatal, with survivors finding themselves further disabled and at a higher risk of reoccurrence, Dr Emma Svennberg, of Sweden, maintains that hope is on the horizon.

"Oral anticoagulant (OAC) medication reduces the risk of AF-related stroke by 64-70%. But more than 50% of high-risk patients with AF do not receive any treatment. We are looking at

an epidemic of AF-related strokes if nothing is done to improve treatment levels," she said.

Patients were split to a ratio of 1:1 into either an AF or control group, and were followed prospectively for 5 years for thromboembolic events, bleeding, and mortality. Screening was done at home with a handheld ECG device, taking merely 1 minute per day for 2 weeks.

Professor Mårten Rosenqvist, chair of the STROKESTOP Steering Committee, said: "Without appropriate treatment, atrial fibrillation is a ticking bomb. We hope the STROKESTOP study will show that screening for atrial fibrillation reduces the risk of stroke."

Dr Svennberg stated that after starting OAC, patients should enjoy a 70% reduction in the risk of stroke, though data on patients with known AF but not on OAC are still being collected. The final results of the study are expected to be made available by November 2018.

Put on pounds, expert warns underweight CAD patients

UNDERWEIGHT women suffering from coronary artery disease (CAD) are twice as likely to die as other CAD patients, and should look to gain weight, according to research presented on Tuesday 3rd September.

Researchers also found that maintaining weight actually lowered the risk of death in obese women with CAD, with both weight gain and loss not appearing to affect their risk of CAD death compared to the normal weight group.

The study, looking to examine the effect of weight change on the survival in CAD-suffering women with various body weight classes, oversaw 1,685 women diagnosed with CAD through coronary angiography.

Patients were divided into four weight classes, according to body mass index (BMI): underweight (<20 kg/m^2), normal weight (20-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (>30 kg/m^2). Changes were also placed into three classes: no change, weight loss, and weight gain, all depending on whether the patient had gained or lost 2 kg per year.

> "Weight management should be individual due to their medical condition."
>
> *Dr Aziza Azimi, Genofte Hospital, Hellerup, Denmark*

The risk of death was then calculated, using the normal weight group as a reference. Afterwards it was adjusted for age, smoking, diabetes, previous heart surgery, and previous percutaneous coronary.

"Obese women are more likely to be treated early with statins, antihypertensive or diabetic drugs, and this may reduce their risk. Weight management should be individual due to their medical condition," Dr Azimi said.

New technology developed to detect CVD early

MANY deaths, caused as a result of cardiovascular disease (CVD) can be easily prevented, however, it is the early detection of CVD which remains a challenge. In 2008, CVD was responsible for the loss of 17.3 million lives; it is for this reason that the early detection and also future advances against CVD is vital.

It has been suggested that early detection of peripheral arterial disease (PAD), a manifestation of systemic atherosclerosis, would reduce the risk of cardiovascular morbidity and mortality.

Therefore, using ankle brachial index (ABI), which is considered to be the most effective, accurate, and practical method of detecting PAD, will identify those at risk of the disease, it was shown at ESC. Moreover, current guidelines have recommended that the same strategy should be used for managing cardiovascular risks, as well as those with coronary artery disease (CAD).

Traditionally, a hand-held Doppler machine is used. This device however, is very time-consuming and requires a vast amount of training. In order to revolutionise the process, Huntleigh's Dopplex® ABIlity has been designed.

This device provides pulse volume recordings for each leg, as well as measuring the blood pressure in both arms, before calculating the ABI; this complies with current guidelines. These readings, which are produced within 3 minutes, are easily interpreted, which means that minimal training is need. In addition to the ABI reading, PAD can also be diagnosed, provided that the reading is ≤0.9.

The dopplex® ABIlity provides automatic, easy, fast, and accurate ABI measurements, while also significantly reducing health costs. It has proven itself to be an accurate method of detecting cases of PAD, which could result in a reduction of deaths.

$CHADS_2$ new stroke risk measurement for patients

RESULTS revealed at ESC showed additional criteria, when added to $CHADS_2$ stroke risk score assessments for patients with atrial fibrillation (AF) reclassified 53.8% of patients with $CHADS_2$ scores 0 or 1 to a CHA_2DS_2-VASc score of 2 or higher, where oral anticoagulation is the recommended treatment.

The CHA_2DS_2-VASc score, which takes the age of 65-74, vascular disease, and female sex into account as stroke risk factors for the $CHADS_2$ score, has been suggested to improve risk stratification in patients at a low risk of stroke, and is now the recommended risk stratification scheme for AF in the ESC Guidelines.

Findings are supported by the fact that only eight strokes and other thromboembolic events were observed in patients classed with a CHA_2DS_2-VASc rating of 0 during the follow-up period.

Professor Michael Näbauer, of Munich University Hospital Großhadern, Germany, said: "While oral anticoagulation is very effective in preventing ischaemic strokes in AF, it increases bleeding risk. Identification of patients with low risk of stroke not requiring oral anticoagulation is important to maximise anticoagulation benefit while avoiding the cost, hassle, and bleeding risk."

Professor Näbauer added: "A $CHADS_2$ score of 0 or 1 does not appear to be suitable to identify patients with AF at low risk for stroke while CHA_2DS_2-VASc picks up these patients. The risk of stroke in patients with a CHA_2DS_2-VASc score of 0, over a mean follow-up of 5.1 years, was very low. Our data support the current recommendation that oral anticoagulation is not beneficial in patients with 'lone AF' or a CHA_2DS_2-VASc score of 0."

Heart attacks rise as temperature lowers

COLD weather increases the risk of heart attacks, it was announced on Sunday 1st September at the ESC Congress.

Nearly 16,000 patients were examined weekly for potential environmental acute myocardial infarction (AMI) triggers, including air pollution, black smoke, temperature, and relative humidity. However, multivariate analysis revealed that only temperature truly affected AMI numbers, with the risk increasing by 7% for every 10°C drop in temperature.

Professor Marc Claeys, University Hospital Antwerp, Belgium said: "In a global environmental model, low temperature is by far the most important environmental trigger for AMI, whereas air pollution has a negligible effect. People at risk of AMI – for example, elderly patients with diabetes and hypertension – can minimise their risk by avoiding big changes in temperature.

"This means wearing suitable clothes when going from the warm indoors to the colder outdoors, even beyond winter time."

Professor Claeys suggested the results could be due to the stimulation of cold receptors in the skin and the sympathetic nervous system, leading to a rise in catecholamine levels. An increase in platelet aggregation and blood viscosity during exposure to the cold, thereby promoting thrombosis and clot formation, also has an effect.

Correlated with average weekly meteorological data obtained from the daily measurements in 73 evenly-distributed sites in Belgium, 15,964 patients who had undergone primary percutaneous coronary intervention (pPCI) from 2006 to 2009 were taken on. The group, who saw an admission rate of 77+/-11, had a mean age of 63 years, while 24.8% were female.

"Epidemiologic studies have focused mainly on one environmental condition, but most environmental triggers are related to each other and may attenuate or reinforce the triggering effect of a single environmental factor," Professor Claeys added.

"Better knowledge of the impact of environment on AMI will help medical care providers and policy makers to optimise prevention strategies for a target risk population."

Healthcare systems more effective in richer countries despite higher risk

THE ongoing PURE (Prospective Urban Rural Epidemiology) study has found that major cardiovascular diseases (CVD), such as myocardial infarction, stroke, and heart failure, are more prevalent among low income countries, even though there is a far greater risk in high income countries.

Over 4 years, the study – presented at ESC – enrolled 155,245 people, of whom 16,110 came from high income countries, 104,206 from middle income countries, and 34,875 from low income countries. The primary outcome of the study was to assess the influence of cardiovascular risk factors on actual disease and mortality.

Using the INTERHEART Risk Score (IHRS), researchers found that CVD risk factors, as well as hospitalisations for CVD, were common in high income countries as opposed to middle and low income countries where the IHRS was the lowest.

Co-author Koon Teo, who presented the results at a Hot Line press conference, said: "PURE emphasises how important access to good healthcare is likely to be."

These findings suggest that, in the view of the principal investigator, Dr Salim Yusuf from McMaster University's Michael G. DeGroote School of Medicine, Hamilton, Canada, it is access to good healthcare which is vital in the differing mortality rates.

"Healthcare matters." Dr Yusuf said. "The gurus of cardiovascular disease prevention have kept emphasising the control of risk factors with very little recognition that healthcare matters, but this is telling us that healthcare matters at least as much as risk factor control."

> "PURE emphasises how important access to good healthcare is likely to be."
>
> *Dr Koon Teo, PURE Study Co-Author*

It is also important that CVD is found earlier in high income countries than in lower income countries, where, by the time it is discovered, it is either too severe or the patient dies.

Dr Yusuf emphasised that the key aspects within healthcare which are effective need to be identified so they may be applied, in a more economical way, to middle and low income countries.

PaceWave™ a positive step for sleep-disordered breathing in patients

ON the 3rd September, ResMed announced at ESC that they have enrolled 1,325 participants in their SERVE-HF randomised study. The aim of the study is to investigate the effect of PaceWave™ on patients with heart failure and sleep-disordered breathing (SDB), and assess the improvement of mortality rates.

The co-principle investigator, Professor Martin Cowie of the Royal Brompton Hospital in London, emphasised that the level of recruitment of SERVE-HF has been "an important milestone in this landmark trial."

It is estimated that, along with the 14 million people in Europe who have heart problems, 30-50% of these patients are also diagnosed with central SDB. This condition often means a poorer quality of life, and also increases mortality.

> "An important milestone in this landmark trial."
>
> *Professor Martin Cowie, Royal Brompton Hospital, London*

Professor Cowie said: "The aim of SERVE-HF is to not only assess survival rates, but also to see if adaptive servo-ventilation (ASV) improves quality-of-life, sleep, and physiological changes associated with heart failure. Additionally, a health economic analysis will be performed to evaluate the potential economic benefits of therapy."

The SERVE-HF study will provide specialists with conclusive evidence highlighting the direct benefits of effectively treating patients with central SDB. RedMed thus far, have shown that the use of PaceWave™ ASV will control SDB and improve cardiac function, which in turn, may lead to improved survival rates and a better quality-of-life.

To date, there has been limited involvement of cardiologists in diagnosing, treating and managing SDB, Professor Cowie said: "We owe much to the commitment and dedication of SERVE-HF investigators and to a strong collaboration between sleep specialists and cardiologists."

Professor Cowie expressed that he looks forward to results in 2016 and to a fuller understanding of how important the treatment of central SDB is in heart failure patients.

The study also aims to promote a greater collaboration of cardiologists in managing SDB in heart failure patients. The completion of the trial is expected in mid 2015, with results available in early 2016.

ESC release new guidelines on treating CVD and diabetes

THE European Association for the Study of Diabetes (EASD) and the ESC have come together in the creation of the 2013 guidelines for diabetes, pre-diabetes and cardiovascular disease (CVD).

In 2011, it was estimated that 360 million people had diabetes mellitus (DM), with the number expected to increase to 550 million by 2030. Therefore, according to the EASD and ESC, it is critical that definitions and implications of DM, pre-diabetic states, and CVD are discussed.

The main focus of the 106-page document concerns the management of patients with these conditions, while also discussing the diagnostic criteria, the risk stratification, lifestyle modifications, glucose control, maintaining a good level of blood pressure, and primary prevention.

The criteria for diagnosing CVD or DM is somewhat in line with the World Health Organisation (WHO) and the American Diabetes Association (ADA) recommendations, which have all placed an emphasis on using fasting plasma glucose combined with HbA1c, or using glucose test tolerance if there is still doubt.

It has been suggested however, that glucose control should be individualised, and should take into account several factors such as the duration of DM, comorbidities, and age. Type 1 DM, for example, should be treated differently than type 2. Type 1 DM should include frequent glucose monitoring, whereas for Type 2, metformin should be the first-line therapy.

In accordance with both the ESC and the European School of Haematology (ESH) 2013 guidelines, blood pressure control is crucial in hypertensive DM patients. In order to do this, an ACE-inhibitor takes precedent over any other drug which lowers blood pressure. Hyperglycaemia in CVD patients is another major concern, and it is recommended that screening should be used to target high-risk individuals.

An individualised approach should also be taken when concerning primary prevention. These guidelines suggest that the use of aspirin should be prohibited in patients with DM and low CVD risk, although this approach could be considered in those who have a very high risk, but only on an individual basis.

There is a large chapter which details the importance of lifestyle modifications for patients with DM.

It recommends that patients should partake in frequent physical exercise, as well as stopping smoking. It also recommended that the total amount of fat intake should be <35%, while a low carbohydrate diet is not advised.

If all these lifestyle changes have occurred then dyslipidaemia, one of the major risk factors for patients with DM, should fail to occur. However, if it does occur then it should be treated aggressively with an LDL-C target of <1.8 mmol/L, or at least a ≥50% LDL-C reduction in patients at very high-risk.

These guidelines offer a patient-centred care-model, one which focuses on the patient as an individual and facilitates their priorities and goals so they can change their lifestyle and their outcome. The guidelines, which are based on current evidence, are intended to help physicians make better informed decisions. This will help them in everyday clinical decision-making.

NEW INSIGHTS INTO THE DEFINITIVE MANAGEMENT OF VENOUS THROMBOEMBOLISM

Summary of the Presentations from the Daiichi Sankyo Symposium, ESC Congress 2013, Amsterdam, the Netherlands

Chairperson

Valentin Fuster[1]

Speakers

Ajay K. Kakkar,[2] Gregory Y. H. Lip,[3] Ander Cohen,[4] Harry R. Büller[5]

1. Director of Mount Sinai Heart at the Mount Sinai Medical Center, Chicago, USA
2. Professor of Surgery, University College London, UK
3. Professor of Cardiovascular Medicine, University of Birmingham, UK
4. Honorary Consultant Vascular Physician, Kings College Hospital, London, UK
5. Professor of Internal Medicine, Academic Medical Center, University of Amsterdam, the Netherlands

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INTRODUCTION

This educational symposium, supported by an unrestricted educational grant from Daiichi Sankyo, was given at the European Society of Cardiology (ESC) Congress, held between 31st August and 4th September 2013 in Amsterdam, the Netherlands. This meeting highlighted the global burden of venous thromboembolism (VTE), and discussed the available therapies, both new and old.

Understanding the Burden of VTE

Prof Ajay K. Kakkar

Prof Ajay Kakkar began by discussing the high incidence of VTE. Population data from the USA and Europe indicate annual incidence rates of 120–180 per 100,000 adults.[1-3] This constitutes a significant burden of disease which has a large impact on public health. Pulmonary embolism (PE) is the third leading cause of cardiovascular death after myocardial infarction and stroke.[4]

Much research has focused on hospitalised populations as they are at a high risk of VTE. Medical patients have a 10–15% increased risk of thrombosis and patients undergoing major orthopaedic surgery have a 40–60% risk of thromboembolism.[5] However, one study found that only half of hospitalised patients at high risk for VTE were receiving thromboprophylaxis.[6] Prof Kakkar presented data showing that more than 12% of patients presenting with PE have died 3 months after diagnosis.[7] In addition, data from the Computerised Registry of Patients with Thromboembolism (RIETE) shows that despite receiving treatment, 17% of medical ward patients (6% of surgical patients) have died 3 months after presenting.[8] Medical patients were also more likely to have major and fatal bleeds than surgical patients during long-term anticoagulation therapy.

Recurrent thrombosis occurs in over 20% of patients despite receiving early anticoagulation measures for their first thrombotic event.[9] The highest risk of recurrence (≥10%) is seen in patients who present with an initial idiopathic VTE.[10]

Studies suggest that extending treatment with anticoagulants for 6–12 months is associated with a lower risk of recurrent thromboembolism.[11] In patients presenting with idiopathic thromboembolism, the risk of recurrence is renewed when anticoagulants are ceased; however, if maintained on anticoagulant medication long-term, there is a heightened risk of major bleeding.[11]

Another risk identified was the development of long-term complications such as post-thrombotic syndrome, which occurs in 5–40% of patients.[9] Post-thrombotic syndrome is characterised by ulceration, induration and pigmentation in the lower limbs as a result of destruction of the venous valvular architecture and development of venous hypertension. A recent study showed that the frequency of post-thrombotic syndrome was greater in patients whose anticoagulation was suboptimal in the 6 months following presentation.[12] Chronic thromboembolic pulmonary hypertension occurs in 3–4% of patients within 2 years of presentation with a PE, and is an extremely debilitating illness.[13]

Prof Kakkar concluded that there is a substantial economic burden associated with VTE in terms of its acute presentation, management, long-term complications of disease, and associated morbidity and mortality.[14–16]

Anticoagulant Profiles: What You Need To Know

Prof Gregory Y. H. Lip

Prof Gregory Lip discussed the targets of the classic anticoagulant medications, heparin and vitamin K antagonists. Heparin targets various stages of the coagulation pathway – initiation, amplification and thrombin activity.[17] Vitamin K antagonists, like warfarin, target vitamin K-dependent coagulation factors II, VII, IX and X.[17]

The target international normalised ratio (INR) for patients receiving warfarin is 2–3. Above this level, there is a substantially increased risk of serious bleeding, while below 2 there is an increased risk of stroke.[18,19] A balancing act is therefore required in in order to minimise risk and maximise benefit to the patient. The quality of anticoagulation control is determined by the time in the therapeutic range (TTR), which is time spent within an INR of 2–3.

Limitations associated with vitamin K antagonists include variability in response between individuals, risk of haemorrhage (particularly intracranial bleeds), a narrow therapeutic window, multiple food and drug interactions and slow onset and offset of action.

Studies of patients with atrial fibrillation (AF) receiving warfarin showed that those who had at least 70% TTR had a substantially reduced risk of stroke, haemorrhage and thromboembolism.[20,21] Patients who were suboptimally treated fared worse than patients who were untreated. The key message identified by Prof Lip was that the quality of anticoagulation control, as measured by TTR, should be considered at an individual level in order to improve outcomes. These data demonstrate that vitamin K antagonists such as warfarin are limited by the need for good quality INR control.

The SAMe-TT_2R_2 score uses clinical risk factors to predict those patients who would benefit from warfarin.[22] It takes into account sex (S, one point), age (A, one point), medical history (Me, one point), treatment – especially interacting medicines such as amiodarone (T, one point), tobacco use in the previous two years (T, two points) and race (R, two points). The maximum score is 8, and patients scoring 0–1 are most likely to benefit from warfarin since they are also more likely to have ≥70% TTR, indicating good quality anticoagulation control. Patients with a score above 2 are at risk of suboptimal anticoagulant control.

Prof Lip then discussed novel oral anticoagulants (NOACs). The four main NOACs available are the direct thrombin inhibitor dabigatran and the Factor X inhibitors apixaban, edoxaban and rivaroxaban. (Edoxaban is currently available only in Japan). These target various stages of the coagulation pathway.[17]

There are relevant pharmacokinetic differences between the NOACs. Dabigatran has the lowest bioavailability (3–7%), while only 27% of apixaban is excreted renally, compared to 80% of dabigatran, 50% of edoxaban and 35% of rivaroxaban.[23] The half-lives of dabigatran, edoxaban and apixaban are approximately 10 to 12 hours, whereas for rivaroxaban it is 5–9 hours in the young, and longer in the elderly. The half-life of dabigatran is markedly increased in patients with chronic kidney disease, therefore renal function must be observed closely in these patients.[23]

Prof Lip presented data from his research group concerning the change in renal function in a cohort of patients with AF who were receiving anticoagulants.[24] A low glomerular filtration rate was associated with increased frequency of thrombotic/vascular events, bleeding and mortality. Renal function declined in approximately one in five patients over the follow-up period, highlighting the need for regular checking of renal function.

Prof Lip concluded that older vitamin K antagonists are subject to diet, drug and alcohol interactions, and as such their administration needs to be monitored to maintain an INR of 2–3. NOACs such as direct thrombin inhibitors and factor Xa inhibitors are less subject to food and drug interactions, and therefore require less monitoring.

At the Crossroads: Deciding Factors for Optimising VTE Treatment

Dr Ander Cohen

Dr Ander Cohen compared the design of phase III acute VTE studies; RE-COVER (dabigatran), EINSTEIN (rivaroxaban), AMPLIFY (apixaban) and Hokusai-VTE (edoxaban).[25–30] All studies were double-blind, except the EINSTEIN study that evaluated quality of life. EINSTEIN evaluated DVT and PE separately while the other studies evaluated combined VTE. There were variations in study duration and in the use of a heparin bridge.

The RE-COVER I and II studies evaluated dabigatran in comparison to warfarin. In RECOVER-I the level of recurrent VTE was 2.4% for dabigatran-treated patients and 2.1% for warfarin-treated patients. Major bleeding was observed in 1.6% versus 1.9% of dabigatran-treated patients versus warfarin-treated patients. RECOVER-II had very similar results.[29,30] RE-MEDY was an extension study of dabigatran that monitored recurrent VTE (1.8% in dabigatran-treated patients versus 1.3% in warfarin-treated patients) and major bleeding (0.9% in the dabigatran group versus 1.8% in the warfarin group).[31] The RE-SONATE study evaluated dabigatran versus placebo and demonstrated an 80–90% reduction in recurrent VTE with dabigatran treatment, with a small (0.3%) increase in major bleeding.[31]

The EINSTEIN-DVT study demonstrated recurrence rates of 2.1% versus 3.0% and major bleeding of 0.8% versus 1.2% in rivaroxaban versus conventional therapy.[26] In the EINSTEIN-PE study, rivaroxaban led to an approximately 50% reduction in major bleeding.[27] The EINSTEIN extension study demonstrated an 82% reduction in recurrence in those treated with rivaroxaban versus conventional therapy and major bleed rates of 0.7% (rivaroxaban) versus 0.1% (conventional).[26]

The AMPLIFY study showed non-inferiority for apixaban in VTE (both DVT and PE) with a reduction in major and clinically relevant non-major bleeding.[28] The AMPLIFY extension study compared 2.5 mg or 5 mg apixaban twice-daily to placebo.[28] The risk of recurrence was reduced by 80% in the apixaban groups, with no significant difference in major bleeding.

While there were similarities in the studies, there were also some differences, including variations in dosage and side-effect profile. Overall, NOACs show similar efficacy to warfarin but are safer and easier to administer. Dr Cohen commented that there are still a number of areas that require further study. There is limited information on the use of NOACs in cancer patients, and it is unknown whether the dose of NOACs can be lowered, in particular for secondary embolism prevention. It is also necessary to define which patients are the most suitable candidates for NOACs. Patients with poor INR control on warfarin would be candidates, however only if poor INR control was not due to poor compliance.

Areas of uncertainty regarding NOACs include their use in severe PE and DVT patients, as some clinicians advocate longer use of low molecular weight heparin. Dr Cohen noted that all the reported studies included patients with moderately severe PE, however there is a need to know more about the co-medications, the role of p-glycoprotein, and the impact of inducers and inhibitors and Cyp3A/4. There is a need for more information regarding fragile patients; those who are elderly, of low body weight or with renal impairment.

Dr Cohen suggested that the use of NOACs represents an opportunity to simplify therapy and streamline the transition from hospital to home, saving money and improving patient quality of life. Challenges of NOAC therapy include collecting follow-up information on these unmonitored therapies, and the lack of monitoring tests for these drugs. Another challenge is that unlike for warfarin, there are no specific

antidotes. However, a phase II study of the Portola antidote is currently ongoing, which may prove effective in reversing the pharmacodynamic effects of Xa inhibitors.

Dr Cohen concluded that there is a need for more information on NOAC use in patients with severe VTE, cancer, low- and high-weight patients, patients with renal impairment and on the effect of comedications and optimal dosing schedules.

Recent Clinical Trial Data: Future Opportunities for VTE Prophylaxis and Treatment

Prof Harry Büller

Prof Harry Büller presented the results of the global Hokusai-VTE study.[25] This study aimed to evaluate the use of edoxaban versus warfarin in patients with VTE. The inclusion of more patients with extensive VTE as they may not have been represented adequately in previous studies, distinguishes Hokusai-VTE from previous NOAC trials. Patients were treated with initial parenteral heparin, followed by three months of edoxaban (60 mg) treatment, after which it was continued at the treating physician's discretion. All patients were followed for 12 months.

The primary efficacy outcome was symptomatic recurrent VTE, comprising deep vein thrombosis (DVT), non-fatal PE and fatal PE. There were multiple secondary outcomes: recurrent VTE in the on-treatment period; recurrence of DVT and PE separately; severe PE with right ventricular dysfunction; and TTR quartiles. The primary safety outcome was a composite of major or clinically relevant non-major bleeding in the treatment period.

Prof Büller highlighted that 40% of patients in the study had a qualifying diagnosis of PE. A high proportion of patients had more extensive disease; in 42% of DVT patients the thrombus extended into the femoral or iliac vein, while 45% of PE patients had extensive disease. Thirty percent of patients with PE had right ventricular dysfunction defined by NT-pro B type natriuretic peptide (NT-pro BNP) of 500 pg/mL.

The rate of VTE recurrence was 3.2% in the edoxaban group and 3.5% in the warfarin group, which confirmed non-inferiority of the NOAC ($p<0.001$). This was valid both for patients with DVT and those with PE. In patients with PE and elevated NT-pro BNP, the recurrence rate for VTE in the warfarin group was 6.2%, while those treated with edoxaban had a recurrence rate of 3.3%; equivalent to an almost 50% risk reduction.

Edoxaban therapy was associated with significantly improved safety; 8.5% of patients treated with edoxaban had a major or clinically relevant non-major event compared with 10.4% of warfarin patients (hazard ratio [HR] 0.81, $p<0.004$). There were also fewer fatal and non-fatal bleeds in patients treated with edoxaban.

Prof Büller noted that there was a higher proportion of patients with more severe disease in the Hokusai-VTE study compared to other studies of NOACs. In the EINSTEIN-PE study, in which 25% of patients had more severe disease, the HR for patients treated with rivaroxaban was 1.12.[27] In the Hokusai-VTE study, the HR was 0.73, and in those patients with more severe PE, the HR was 0.52.

In the Hokusai-VTE study, the rate of VTE in patients with >70% TTR was 3.7% in the warfarin group and 2.5% in the edoxaban group, demonstrating non-inferiority of edoxaban and showing that patients treated with warfarin were receiving an optimal treatment regimen, since outside of the clinical trial setting, Prof Lip noted that the TTR for warfarin patients is usually 40–50%.

The 60 mg dose of oral factor Xa inhibitor edoxaban was chosen for investigation. However, in certain situations (such as moderate renal impairment, low body weight, concomitant use of p-glycoprotein inhibitors) this dose should be reduced to 30 mg in order to prevent patients from overexposure and bleedings. Edoxaban 30 mg was shown to be comparable in efficacy to the 60 mg dose. In addition, there were almost 40% fewer cases of clinically relevant bleeding in patients treated with edoxoban 30 mg compared to those treated with warfarin. Thus the dose adaption to 30 mg was shown to be effective and safe in patients treated for VTE.

Prof Büller concluded that low molecular weight heparin plus edoxaban was non-inferior to low molecular weight heparin plus warfarin therapy, and demonstrated a significant reduction of VTE in patients with right ventricular dysfunction.

Panel Discussion

The main presentations were followed by a panel discussion with chair Prof Valentin Fuster and the four speakers. Prof Kakkar commented that cardiologists will be key in providing education about NOACs and VTE. Dr Cohen considered it unlikely that there would be head-to-head comparisons of NOACs, and that differentiation between individual therapies would not be of value. He emphasised the importance of the positive results from NOACs in general over those for individual treatments, advocating that this should be the take-home message from the symposium.

REFERENCES

1. Heit JA et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160:761–768.

2. Nordström M et al. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992;232:155–160.

3. Oger E for the EPI-GETBO Study Group. Incidence of venous thromboembolism: a community-based study in Western France. Thromb Haemost. 2000;83:657–660.

4. Goldhaber SZ & Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379:1835–1846.

5. Geerts WH et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:338S–400S.

6. Cohen AT et al for ENDORSE investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet. 2008;371:387–394.

7. Goldhaber SZ et al for ICOPER. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386–1389.

8. Monreal M et al for the RIETE registry. The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients. Findings from the RIETE registry. J Thromb Haemost. 2004;2:1892–1898.

9. Prandoni P et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996;125:1–7.

10. Kearon C. Natural history of venous thromboembolism. Circulation. 2003;107:I22–I30.

11. Hutten BA & Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. Cochrane Database Syst Rev. 2006;1:CD001367.

12. Chitsike RS et al. Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study. J Thromb Haemostasis. 2012;10:2039–2044.

13. Pengo V et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257–2264.

14. MacDougall DA et al. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. Am J Health Syst Pharm. 2006;63:S5–S15.

15. Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. Angiology. 1997;48:67–69.

16. Jantet G. [The socioeconomic impact of venous pathology in Great Britain]. Phlebologie. 1992;45:433–437.

17. De Caterina R et al. General mechanisms of coagulation and targets on anticoagulants (Section I). Thromb Haemost. 2013;109:569–579.

18. Hylek EM et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med. 1996;335:540–546.

19. Odén A et al. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. Thromb Res. 2006;117:493–499.

20. Gallagher AM et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost. 2011;106:968–977.

21. Wan Y et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008;1:84–91.

22. Apostolakis S et al. Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin: The SAMe-TT2R2 (Sex female, Age less than 60, Medical history, Treatment strategy [rhythm control], Tobacco use [doubled], Race [doubled] score. Chest. 2013; doi 10.1378/chest.13-0054.

23. Heidbuchel H et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15:625–651.

24. Roldán V et al. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). Am J Cardiol. 2013;111:1159–1164.

25. The Hokusai-VTE investigators. Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. N Engl J Med. 2013;369:1406–1415.

26. EINSTEIN investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499–2510.

27. EINSTEIN investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287–1297.

28. Agnelli G et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2012;368:699–708.

29. Schulman S et al. Dabigatran versus warfarin in the treatment of acute

venous thromboembolism. N Engl J Med. 2009;361:2342–2352.

30. Schulman S et al. Dabigatran or warfarin for extended maintenance therapy of venous thromboembolism. ISTH 23–28 July 2011, Kyoto, Japan. Abstract O-TH-033.

31. Schulman S et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368:709–718.

ACE-INHIBITORS AND CARDIOPROTECTION OPEN ISSUES AND FUTURE SOLUTIONS

Summary of Presentations from the Menarini Symposium, ESC Annual Congress 2013, Amsterdam, the Netherlands

Chairperson

Giuseppe Mancia[1]

Speakers

Krzysztof Narkiewicz,[2] Athanasios J. Manolis,[3] Claudio Borghi[4]

1. Department of Internal Medicine and Cardiovascular Prevention, S. Gerardo Hospital, Milan, Italy
2. Medical University of Gdansk, Poland
3. Director, Cardiology Department, Asklepeion Hospital, Athens, Greece
4. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

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Pharmacodynamics of Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors: From Laboratory to Clinical Practice

Prof Krzysztof Narkiewicz

The current management of patients with hypertension, especially those with a high risk of coronary artery disease should take into account the role of angiotensin II in the development of hypertension and cardiovascular disease.

There are several ways that the RAAS might contribute to high cardiovascular risk. However, the RAAS might affect several other mechanisms underlying both the development of hypertension and the development of cardiovascular disease. This includes the effect on the endothelial function, the increased risk of inflammation, the effect on lipids, which are a very important component of cardiovascular risk and the effect on fibrinolysis. All these factors may contribute to both cardiovascular morbidity and mortality.

The new 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines[1] stress that the role of target organ damage assessment is not only evident cardiovascular disease, but the subclinical evidence of target organ damage which in the vast majority of patients would put them in the category of high cardiovascular risk.

The activation of the RAAS contributes to the development of target organ damage and it is inter-related with other mechanisms that contribute to target organ damage. For example, the positive relationship between the RAAS and the sympathetic nervous system, the effect of inflammation (oxidative stress) on endothelial dysfunction and the input of insulin and leptin resistance (which are important in terms of sodium handling and volume retention). To date, the evidence is that the RAAS contributes to target organ damage, which includes both blood pressure dependent and blood pressure independent mechanisms that are of clinical importance.

A large amount of research has been performed to discover the most effective way to inhibit the RAAS and this has indicated that there are several ways that the RAAS can be potentially blocked;[2] angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and renin inhibitors (the newest component in terms of clinical management). There is no doubt that blocking the RAAS provides substantial clinical benefit.

The evidence base for this is comprehensive; ACE inhibitors have been used successfully for decades and effective innovative drugs are becoming available, in addition there is increased understanding of the pathophysiology and pharmacology, all of which contribute to improved management of high risk patients.

The ESH/ESC guidelines present the various types of asymptomatic organ damage (left ventricular hypertrophy, asymptomatic atherosclerosis, micro albuminuria, renal dysfunction) various clinical cardiovascular (CV) events (previous stroke, previous myocardial infarction [MI] angina pectoris, heart failure, aortic aneurysm, atrial fibrillation prevention, atrial fibrillation ventricular rate control, end stage renal disease/proteinuria, peripheral artery disease) and other co-morbidities (isolated systolic hypertension [elderly], metabolic syndrome, diabetes mellitus). In many of these conditions ACE inhibitors are listed in the guidelines as the drugs of preferred choice. There is increasing evidence suggesting that ACE inhibitors could be beneficial in patients at risk of coronary artery disease, they not only provide management for hypertension, but also for congestive heart failure and more recently for different stages of coronary artery disease, including acute coronary events.[3]

ACE inhibitors differ in chemical structure and functional group (primarily the sulfhydryl [SH] group), prodrug nature, potency and duration of effect. Different structural profiles may include additional pharmacological properties which may provide significant benefits as well as different clinical pharmacokinetic profiles.

The ACE inhibitors captopril and Zofenopril are at the top of the SH-group. Captopril provides several benefits but has the disadvantage of having a short mode of action. Zofenopril is the most recent drug in the ACE inhibitor group. The major difference of Zofenopril compared with other drugs is that Zofenopril is converted into the active form (zofenoprilat) both in serum and different tissues, especially the cardiac tissue. It is highly lipophilic which possibly provides important benefits in terms of the reduction of the activity of the RAAS and there is evidence[4] of increased

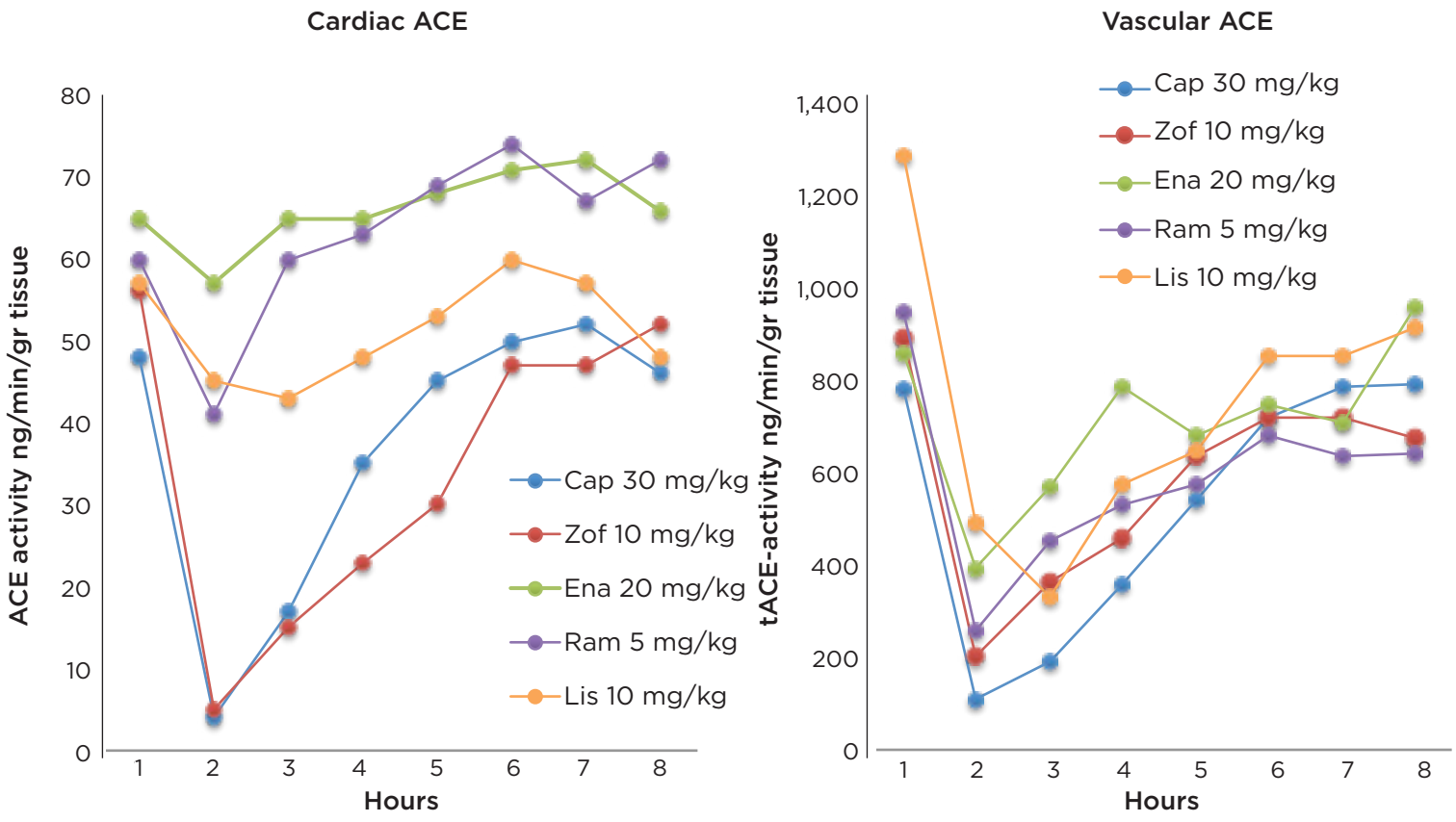

Figure 1. Inhibition of tissue ACE activity over time after equivalent oral doses of Zofenopril and ramipril. *Cushman DW et al.*[6]

cardiac uptake, and a greater rate of conversion to its active inhibitor by local cardiac esterases. In contrast to captopril and many other ACE inhibitors, Zofenopril has a long mode of action.

Borghi et al. (1993)[5] showed that the use of Zofenopril compared with placebo in patients with acute MI produced a dramatic decrease in ACE activity. When Zofenopril is compared with other ACE inhibitors (including ramipril) vascular ACE inhibition is similar. However, unlike other ACE inhibitors, cardiac ACE inhibition with Zofenopril produces a decrease in the ACE activity and marked long-lasting inhibition sustained for up to 24 hours (Figure 1).[6] This potentially provides benefit in terms of target organ damage. In addition the prevention of cardiac tissue necrosis, which is related to acute coronary ischaemia and acute coronary syndrome, has been shown to be significantly reduced with Zofenopril when compared with a control group ($p<0.05$).[7]

Zofenopril may have an effect beyond blood pressure control; it has a beneficial vasculoprotective effect on endothelial function that is partly mediated by its action on nitric oxide (NO). An experimental study using bovine aortic endothelial cells demonstrated that Zofenopril stimulates NO release from these cells to a significantly greater extent ($p<0.001$) than both captopril and enalapril.[8] Pasini et al. (2007)[9] compared the vasculoprotective effects of Zofenopril with ramipril and atenolol in hypertensive subjects and found endothelium-dependent dilation was significantly increased ($p<0.001$) in the Zofenopril treated group when compared with the ramipril and atenolol treated groups. These results indicate that Zofenopril has important advantages in reducing endothelial activation.

The role of the SH-group in the improvement of endothelial dysfunction with ACE inhibitors was evaluated in an experimental model of heart failure in myocardial infarcted rats treated with Zofenopril or lisinopril. Following 11 weeks of treatment, the aortas were studied as ring preparations for endothelium dependent and independent dilation. At the end of the study, Zofenopril (but not lisinopril) additionally potentiated the vasodilator effect of endogenous NO after A23187-induced release from the

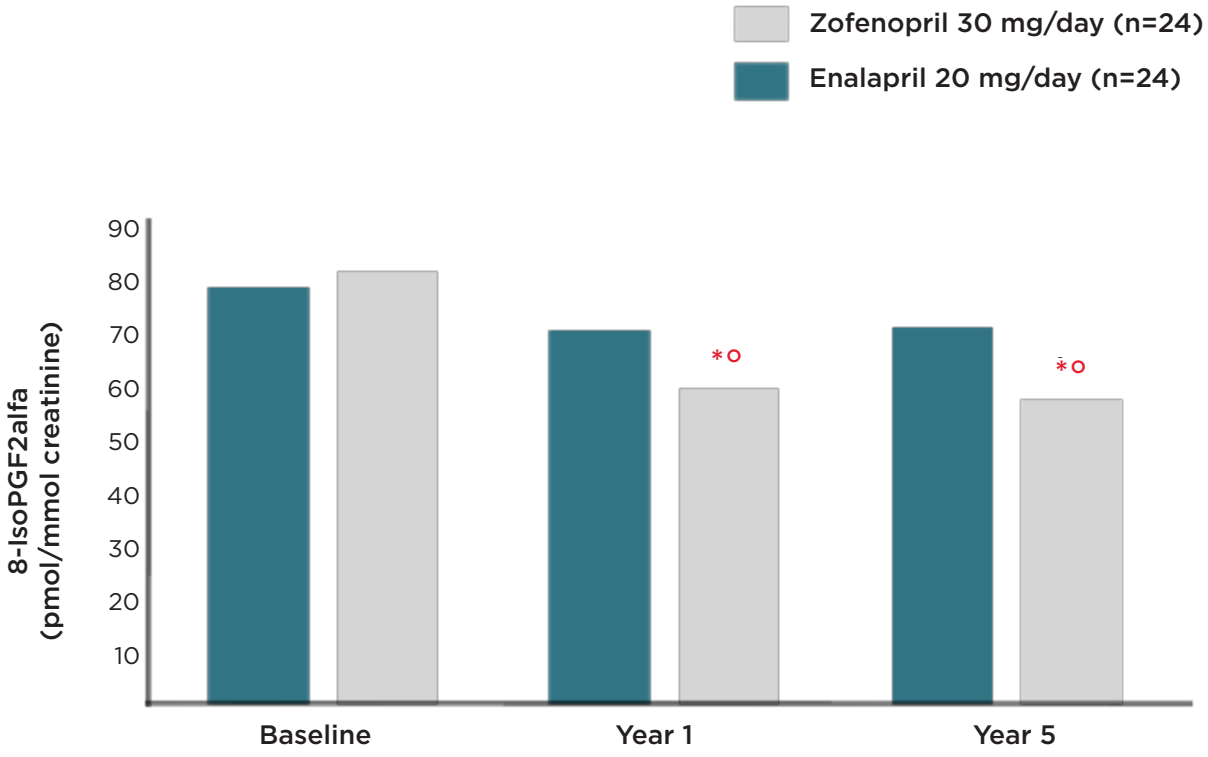

Figure 2. Antioxidant activity of ACE inhibitors after 5 years of treatment.
*p<0.01 versus respective baseline; °p<0.05 versus enalapril.
Napoli C et al.[12]

endothelium (+100%).[10] This demonstrates a potential advantage in improvement of endothelial dysfunction through increased activity of NO after release from the endothelium into the vessel wall.

The oxidative stress potentially exposes hypertensive patients to both arterial sclerosis and atherosclerosis. Healthy subjects were compared with: hypertensive subjects before treatment; hypertensive subjects who received 12 weeks of treatment with enalapril; and hypertensive subjects who received 12 weeks treatment of Zofenopril. The results showed that isoprostanes were similar after Zofenopril treatment ($p<0.03$) compared to the healthy control subjects ($p<0.01$) whereas enalapril was ineffective.[11] These results are sustained in long-term follow-up, in a randomised, prospective study, 48 newly diagnosed mildly hypertensive patients with no additional risk factors for atherosclerosis (e.g. hyperlipidaemia, smoking habit, family history of atherosclerosis-related diseases or diabetes) were enrolled and randomly assigned to 5 years of treatment with either enalapril 20 mg/day (n=24) or Zofenopril 30 mg/day (n=24).[12] The objective was to evaluate the effect of treatment with Zofenopril and enalapril on systemic oxidative stress. The isoprostane 8-iso-PGF2 was measured at baseline and at 1 and 5 years of treatment. The results showed the reduction of 8-iso-PGF2a levels were greater in the Zofenopril group, suggesting a sustained antioxidant efficacy (Figure 2). This indicates there is no rebound effect for patients after long-term treatment.

There have been some novel developments in terms of cardiovascular risk; these include reduced platelet accumulation in atherosclerosis. In a rabbit model of atherosclerosis, platelets were labelled to assess their distribution in the atherosclerotic plaque. Zofenopril reduced platelet accumulation in the abdominal aorta and common carotid ($p<0.01$).[13] The reduced accumulation of labelled platelets induced by Zofenopril indicates less atherosclerotic plaque progression and lower probability of plaque rupture with consequent vessel occlusion, suggesting that Zofenopril may play an important role in the prevention of cardiovascular events.

Ferrari R et al. (1992)[14] assessed the effect of captopril and Zofenopril on reperfusion and determined that Zofenopril influences the release

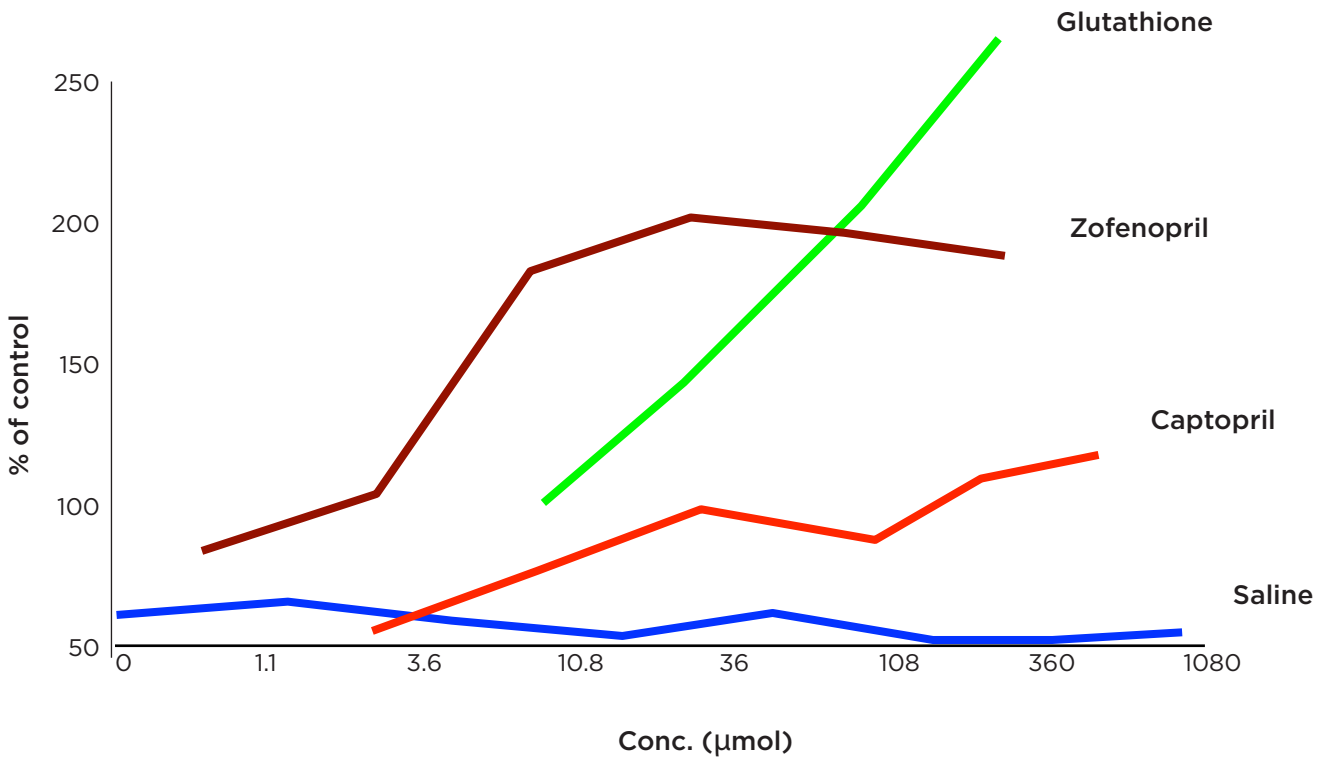

Figure 3. Dose response curve of captopril, Zofenopril and glutathione effects on coronary flow of isolated rat hearts.
Van Gilst WH et al.[15]

of lactate and creatinine phosphokinase from the heart. The study concluded that captopril had no effect on the occurrence of oxidative stress during reperfusion, whereas Zofenopril reduced it. The dose response curve of captopril, Zofenopril and glutathione on the coronary flow of isolated rat hearts showed that Zofenopril is considerably more powerful than captopril[15] (Figure 3).

The interaction between hypertension, cardiovascular disease and metabolic factors and the RAAS possibly predisposes patients to diabetes, metabolic syndromes and other abnormalities. The blockade of the system with ACE inhibitors, particularly the in light of the evidence shown by Zofenopril, could provide beneficial effects in terms of the metabolic risk.

In summary, Zofenopril is differentiated from other drugs in its class by the presence of the SH-group due to its ability to reduce oxidative stress. It has high lipophilicity producing high myocardial and vascular uptake that provides improved blockade at the level of the cardiac tissue (increasing coronary flow) and reduced cellular hypertrophy. Zofenopril has a high level of ACE inhibition providing the additional benefits of plasma ACE blockade. Including reduced angiotensin II and increased bradykinin level beyond classic ACE inhibitor levels. This reduces ischaemia and improves left ventricular fraction. Consequently there is an improved CV outcome for the patient.

Zofenopril has been tested in a series of randomised trials looking at the different aspects of ACE inhibition;[16-25] this provides a carefully tested evidence base that demonstrates the beneficial effects of the drug.

ACE-Inhibitors Pharmacological Effects: Just a Matter of mmHg?

Prof Athanasios J. Manolis

The fundamental questions in the treatment of patients with cardiac disease are:

Are there beneficial effects in blood pressure reduction? Are drugs in all classes the same? Are drugs of the same class equally effective in cardiovascular prevention?

The ESH/ESC hypertension guidelines[1] - choice of antihypertensive drugs, conclude that the main benefits of antihypertensive treatment are due to lowering the blood pressure per se and are largely independent of the drug employed. Although meta-analyses occasionally claim superiority of one class of drug the outcome largely depends on selection bias of the trials and the largest meta-analyses do not show clinically relevant class differences. The current guidelines reconfirm that the drugs classes: diuretics (thiazides, chlorthalidone, indapamide); beta-blockers; calcium antagonists; ACE-inhibitors and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as a monotherapy or in various combinations with each other. The guidelines propose the combinations between some classes of antihypertensive drugs (ACE-inhibitors or angiotensin receptor blockers plus diuretics or calcium antagonists) produce a pronounced antihypertensive effect, CV protection and optimal tolerability.

Previous clinical trials have shown promising data and excellent results using ACE inhibitors in the treatment of chronic heart failure and post-MI.[17,26-34] ACE inhibitors are the preferred drug in the treatment of most conditions in the cardiovascular continuum (heart failure, LV dysfunction, post-MI, diabetic nephropathy, non-diabetic nephropathy, LV hypertrophy, carotid atherosclerosis, proteinuria/microalbuminuria, atrial fibrillation, metabolic syndrome), and in most of these conditions are the gold standard treatment.

There is continued debate concerning ACE inhibitors and ARBs and which group is the best choice of treatment. Staessen et al.[35] reviewed the outcome of six trials evaluating blood-pressure lowering drugs in 74,524 hypertensive or high risk patients. The review concluded that because ARBs might offer less protection against MI than ACE inhibitors, ACE inhibitors should remain the preferred renin system inhibitor for cardiovascular prevention in ACE inhibitor tolerant patients. The protective attributes of ACE inhibitors are due to the cardioprotective properties of bradykinin. The actions of bradykinin include vascular contraction and relaxation, participation in the process of inflammatory reactions, interaction with central and peripheral neural structures, stimulation of synthesis and release of various vasoactive substances, and enhanced insulin-dependent glucose transport utilisation. Recent studies have shown that the

activation of the β-2 receptor has beneficial effects in terms of both functional and structural cardioprotective actions.[36]

In CV prevention the main target is blood pressure reduction. However, there are drugs that provide beneficial effects beyond blood pressure reduction, mainly in the field of high risk factors, these include; prevention of diabetes, target organ regression and prevention, prevention of atrial fibrillation or coronary artery disease, congestive heart failure, stroke and cognitive dysfunction dementia.

A meta-analysis of randomised, controlled trials of left ventricular hypertrophy (LVH) regression in essential hypertension showed that there are significant differences between the different classes of drugs in the regression of LVH[37] (Figure 4).

The LIFE study[38] showed that in patients with LVH (ascertained by electrocardiography) there was similar blood pressure reduction in both systolic and diastolic measurements in patients receiving atenolol based treatment or losartan based treatment. However, the primary composite endpoint results showed losartan prevents more cardiovascular morbidity and death than atenolol for a comparable reduction in blood pressure and has greater tolerability.

The ACCOMPLISH study[39] found that treatment with the combination of an ACE inhibitor plus a diuretic, or a calcium channel blocker plus an ACE inhibitor resulted in a similar blood pressure reduction (within 1 mmHg). However, there was a 20% (p=0.0002) risk reduction of cardiovascular events in patients treated with an ACE inhibitor plus a calcium channel blocker. These results clearly show that treatment with an ACE inhibitor plus a calcium channel blocker has beneficial effects beyond blood pressure reduction. Likewise, the ASCOT trial[40] compared amlodipine plus perindopril versus atenolol plus thiazide and the results showed a significant reduction in cardiovascular events in patients who were treated with an ACE inhibitor plus a calcium channel blocker. Furthermore, the results of the CAFÉ trial[41] have shown that despite a similar reduction in the peripheral systolic blood pressure in patients

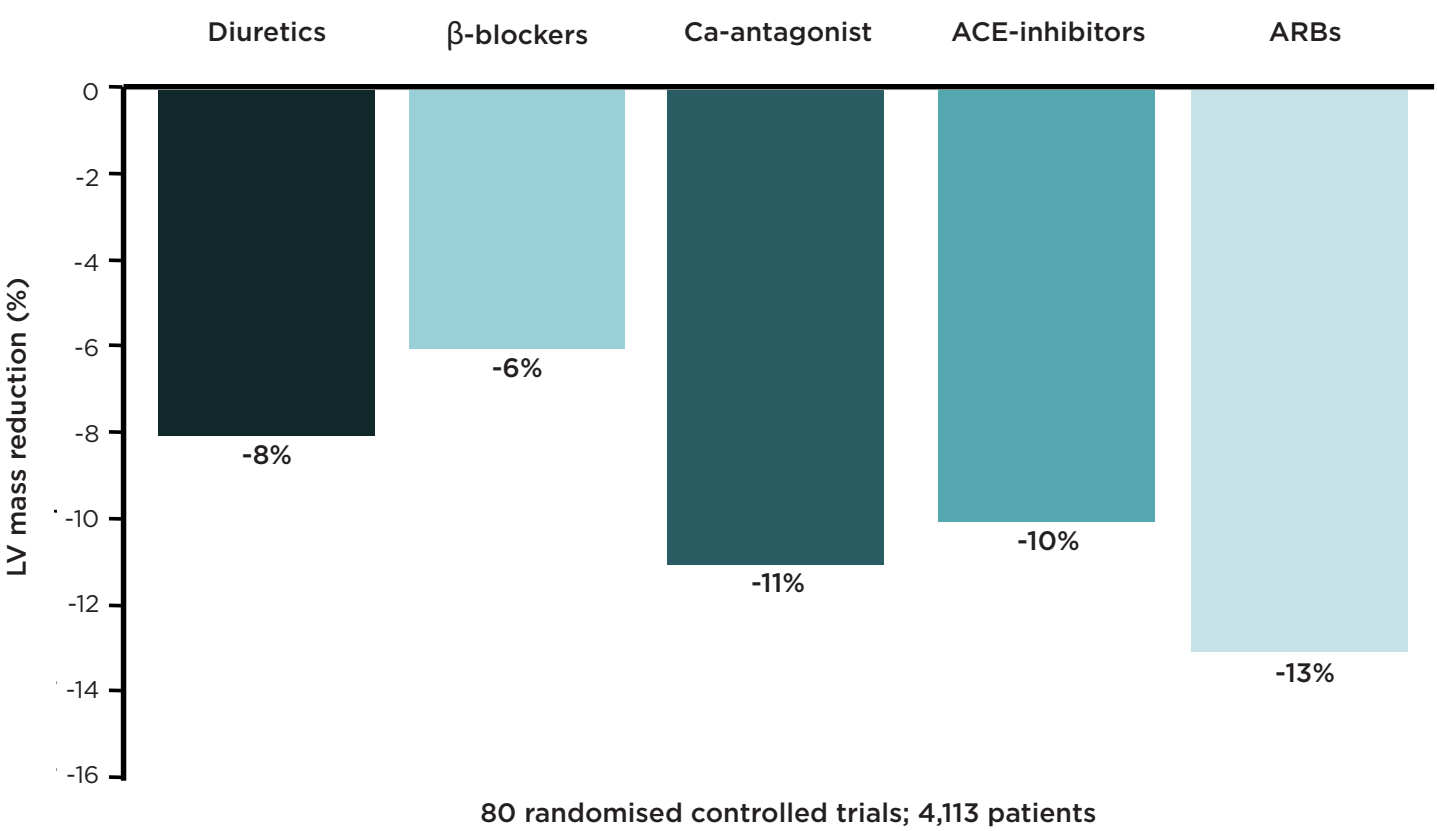

Figure 4. Meta-analysis of randomised, controlled trials of the treatment of LVH regression in essential hypertension.
Schmieder RE at al.[37]

treated with an ACE inhibitor plus a calcium channel blocker, and patients treated with a β-blocker plus a diuretic, there was a significant difference in the central systolic blood pressure. This difference was shown in patients treated with the combination of an ACE inhibitor and a calcium channel blocker.

ACE inhibitors have been shown to produce a greater reduction in central aortic pressure compared with other antihypertensive drug classes.[42] In addition, pulse wave velocity (PWV) measured in normotensive patients with diabetes mellitus showed a significant reduction in PWV in patients treated with ACE inhibitors compared with placebo ($p<0.003$).[43] McEniery et al.[44] compared nebivolol and atenolol and found that atenolol caused an increase in PWV and conversely nebivolol caused a reduction in PWV.

It is clear that in the same class there are differences between drugs. For example, nebivolol when compared with other beta-blockers demonstrates improvements in central blood pressure and sexual dysfunction that are not shown in other beta-blockers. Moreover, nebivolol is one of the preferred beta-blockers in chronic obstructive pulmonary disease. This is due to its NO-mediated vasodilating properties and beta-1 selectivity, and it does not decrease glucose tolerance as demonstrated by the low occurrence of new onset diabetes in seniors versus placebo.[1]

Two studies; the PEACE trial45 and the EUROPA trial[46] evaluated patients with coronary artery disease who had experienced a previous MI. Patients in the PEACE trial were treated with either trandolapril or placebo and in the EUROPA trial patients were treated with perindopril. The PEACE study found no difference in cardiovascular events between trandolapril and placebo whereas the EUROPA trial found that perindopril significantly reduced cardiovascular events ($p=0.003$). An editorial comment on the PEACE trial results[47] stated that *'the possibility that not all ACE inhibitors are equally effective for all indications should also be considered.....I will continue to use ACE inhibitors that have been shown to be effective for this indication in several groups of patients.'*

It is evident that there are distinctions in the mode of action of different ACE inhibitors. Within this class Zofenopril shows promising results.

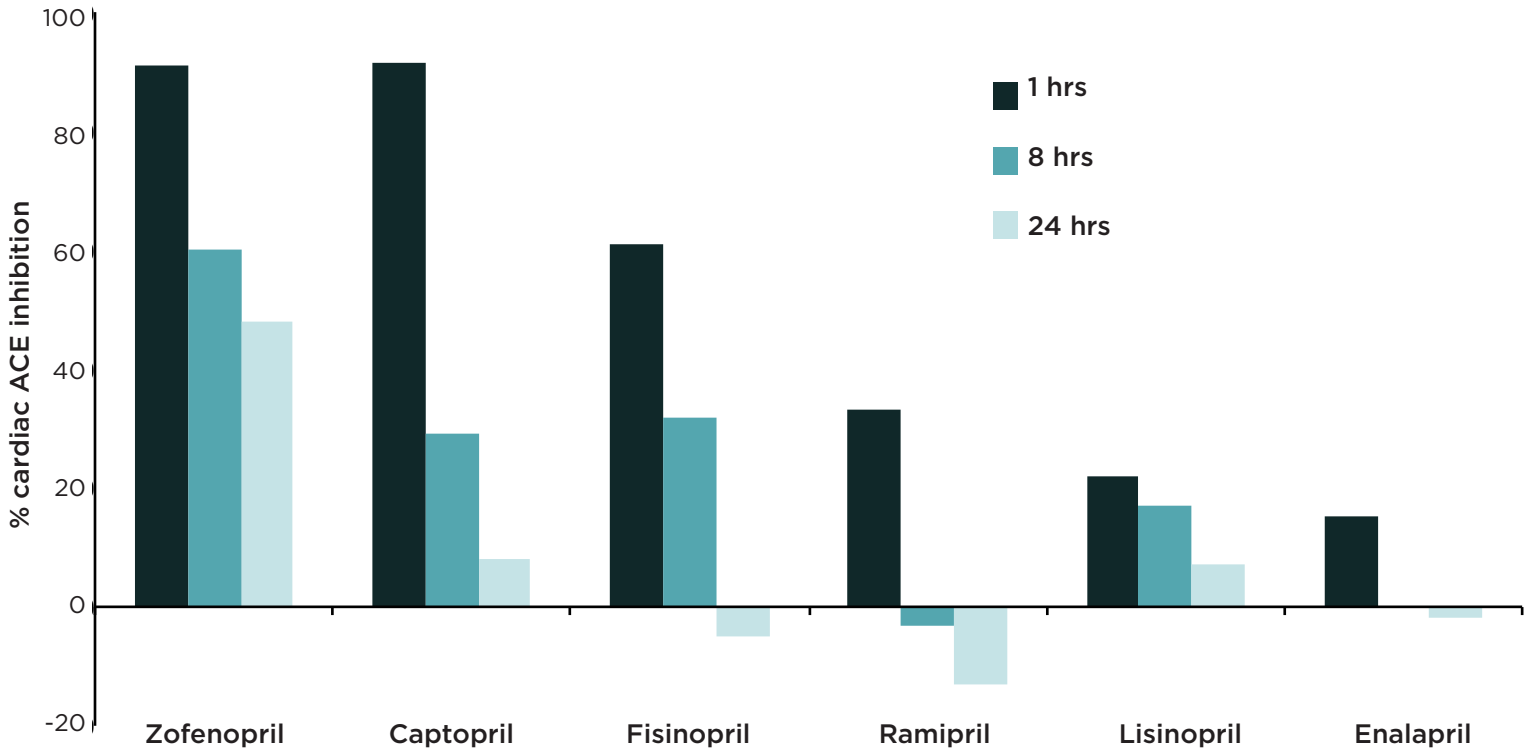

Figure 5. Cardiac tissue ACE inhibition by equivalent oral doses of ACE inhibitors.
Cushman DW et al.[6]

In Watanabe heritable hyperlipidaemic rabbits Zofenopril significantly reduced atherosclerosis in the abdominal aorta and common carotid arteries ($p<0.05$).[13] In addition, cardiac ACE inhibition by equivalent oral doses of ACE inhibitors in spontaneously hypertensive rats showed that Zofenopril has a longer activity in comparison with other ACE inhibitors[6] (Figure 5).

Napoli et al.[11] compared the effect of the two ACE inhibitors enalapril and Zofenopril on low density lipoprotein (LDL). The results of the study found that there were differences in oxidisability, LDL from hypertensive patients had enhanced oxidation compared with control subjects ($p<0.05$). Following 12 weeks of treatment malondialdehyde levels were significantly reduced by Zofenopril ($p<0.05$) but not enalapril treatment (p=not significant). This suggests that Zofenopril reduces oxidative stress and improves the NO pathway in patients with essential hypertension.

In a study of patients with essential hypertension,[9] differences were observed between Zofenopril, ramipril and atenolol in relation to the molecules related to inflammation (intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1] and E-selectin), a significant reduction in these molecules was seen in patients treated with Zofenopril but not in patients treated with ramipril or atenolol. This suggests that through sustained antioxidant activity Zofenopril has advantages in reducing endothelial activation. A further study compared Zofenopril with other ACE inhibitors and found that there was an increase in the release of NO ($p<0.01$ versus control; $p<0.02$ Zofenopril versus other ACE inhibitors) showing that when compared with other ACE inhibitors, Zofenopril has superior efficacy in improving the endothelin-1/nitric oxide balance in human vascular endothelial cells due to its greater antioxidant properties.[48]

Zofenopril has further potential in the field of diabetes, when compared with enalapril Lupi et al.[49] found that Zofenopril had increased potency in promoting insulin secretion from human pancreatic cells ($p<0.05$ versus glucose 22.2 mmol/L; $p<0.05$ versus enalapril; $p<0.01$ versus glucose 5.5 mmol/L). These results indicate that Zofenopril protects human islets from glucotoxicity.

Not all ACE inhibitors are equivalent, pharmacology classifies ACE inhibitors in three

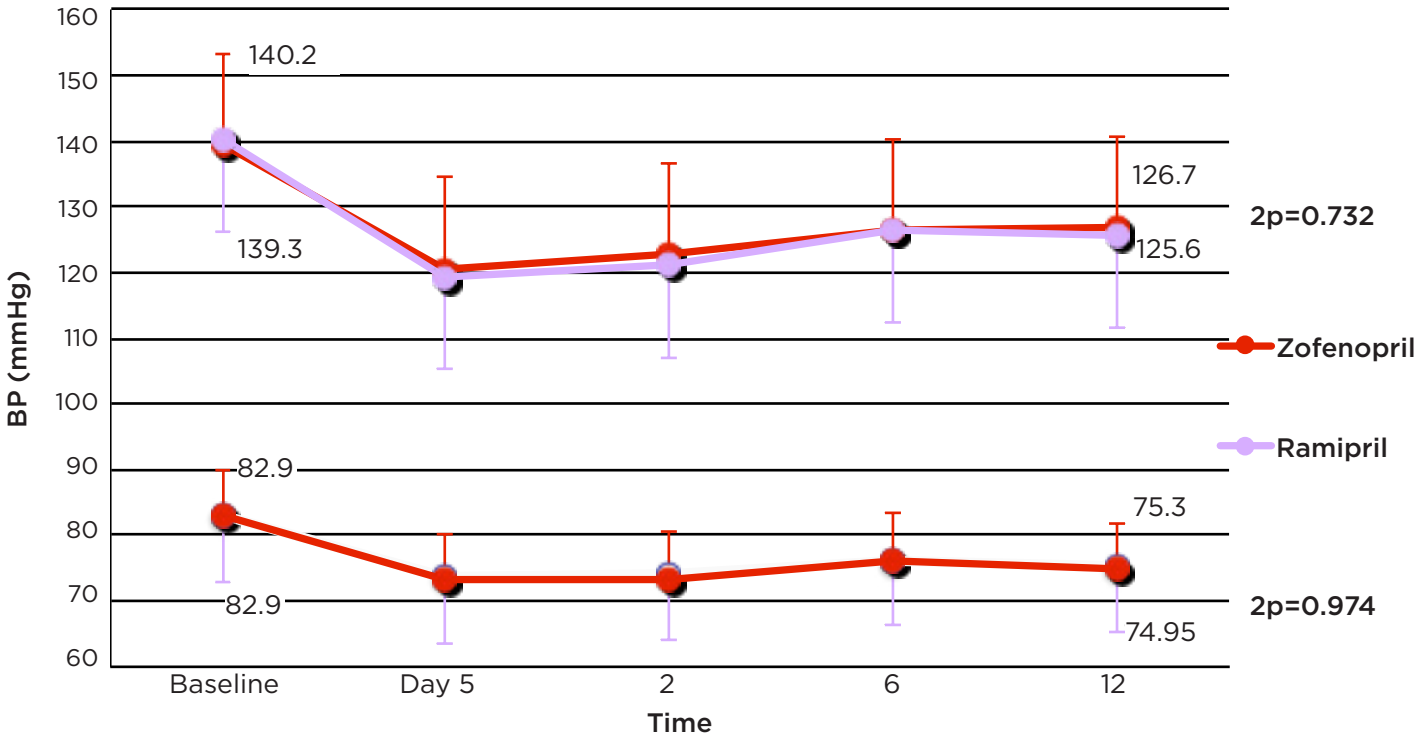

Figure 6. Changes in systolic and diastolic blood pressure – Zofenopril compared with ramipril.
Borghi C et al.[25]

groups; prodrugs (captopril, lisinopril, Zofenopril), SH-group (captopril, Zofenopril) and high lipophilicity group (quinapril, ramipril, Zofenopril). As a third generation ACE inhibitor Zofenopril has the advantage of demonstrating the properties of all three groups. It is a prodrug and therefore has a long duration of action and is effective in patients with renal and hepatic impairment. In addition it has the SH-group properties of a free radical scavenger and reduces oxidative stress, prevents endothelial dysfunction, has anti-ischaemic, anti-inflammatory and anti-atherogenic effects, reverses apoptosis and increases NO. Furthermore, Zofenopril has high lipophilicity which produces high myocardial and vascular uptake, a high tissue ACE blockade, increases coronary flow and reduces cellular hypertrophy.

Likewise data in human trials show the benefits of using Zofenopril. In post-MI patients Zofenopril was compared with ramipril (SMILE-IV trial).[25] The results concluded that a similar systolic and diastolic blood pressure reduction was seen using either ramipril or Zofenopril but a significant reduction of cardiovascular events was seen in patients treated with Zofenopril (Figure 6).

The primary endpoint of one year CV mortality and hospitalisation for CV causes in the same trial showed there was a significant reduction in those treated with Zofenopril ($p<0.05$) compared with those treated with ramipril. Furthermore, a retrospective analysis of post-MI patients with left ventricular systolic dysfunction compared Zofenopril and ramipril and acetylsalicylic acid. The results showed that the survival rate was significantly improved in those treated with Zofenopril compared with those treated with ramipril (normotensive patients $p=0.631$; hypertensive patients $p=0.041$).[50]

Based on the editorial comments on the SMILE study[25] that emphasised the possibility that not all ACE inhibitors are equally effective for all indications, it appears judicious to use ACE inhibitors that have been shown to be effective for the particular indication as opposed to using other ACE inhibitors that are effective in several groups of patients.

Zofenopril in Post-MI: Can We SMILE Again?

Prof Claudio Borghi

It is a matter of fact that extensive activation of the renin angiotensin system is deeply involved in the pathophysiology of cardiovascular disease. This gives a robust rationale for the successful use of drugs inhibiting the renin angiotensin system in the prevention and treatment of cardiovascular disease. This is particularly true for ACE inhibitors whose clinical efficacy has been clearly demonstrated in several clinical trials[51] and recently emphasised by the publication of two large meta-analyses[52,53] that show the superiority of ACE inhibitors even when compared with other drugs belonging to the inhibition of the same renal angiotensin system.

In the SMILE programme[16-25] the efficacy of ACE inhibitors in has been demonstrated in both chronic disease[24,45,46,54] and acute coronary syndrome either when patients are treated within 24 hours of the onset of symptoms[17-22,32,33,55] or later on when MI is complicated by left ventricular dysfunction.[27,29-31] A huge amount of evidence has been generated from the SMILE program.[16-25] The SMILE program is a long-standing investigative programme to address the role of ACE inhibitors and in particular Zofenopril in the treatment of patients with coronary artery disease and specifically acute MI. The programme started almost 20 years ago with the pilot study.[16] The results of the SMILE-1 trial[17] showed that early treatment with Zofenopril in patients with acute anterior MI was followed by a significant reduction in the combined incidence of severe congestive cardiac failure and death. Most importantly the results of this trial showed that the early benefit observed in this group of patients was extended over one year in terms of reduction of mortality (overall mortality $p=0.0083$). This clearly supports the mandatory role of ACE inhibition in patients with acute MI. The mechanistic view shows that the benefits shown by Zofenopril in the treatment of patients post-MI can be due to the effect expected from other ACE inhibitors e.g. improvement in blood pressure control, the prevention of left ventricular failure and improvement of left ventricular function. However, the results of this program have clearly

shown that one of the enhanced benefits of Zofenopril treatment in post-MI patients is conceivably due to its anti-ischaemic effect. This has been demonstrated in the SMILE ischaemic study.[56] The primary objective of the study was ischaemic burden. A group of patients with preserved left ventricular function following MI were treated with Zofenopril and compared with patients treated with placebo. The results showed that treatment with Zofenopril displayed a significant reduction in the overall rate of ischaemic burden. The clinical importance of these results is that such a prevention of cardiovascular complications was associated with a significant reduction in major cardiovascular events (Figure 7). This clearly suggests that this mechanism of action (which has not been demonstrated for any other ACE inhibitors) can significantly contribute to the overall benefits of Zofenopril in post-acute MI patients.

A recent editorial supports the findings of the SMILE ischaemia study by clearly suggesting that the best drugs for the treatment of post-MI patients are those that are able to prevent or effectively treat myocardial ischaemia and not just the symptoms of myocardial ischaemia.[57]

The benefits of Zofenopril treatment seen in the SMILE trial extend to an important sub-group of patients, those with hypertension. The study showed that the reduction of the major cardiovascular endpoint of long-term mortality was more prevalent in Zofenopril treated patients with a history of hypertension (p=0.041) compared with placebo.[19] In addition the SMILE trial found that in another subgroup of patients, those with dysmetabolic disease (including patients with diabetes, metabolic syndrome and dyslipidaemia), the extent of reduction of the relative risk of the major category primary endpoint outcome was

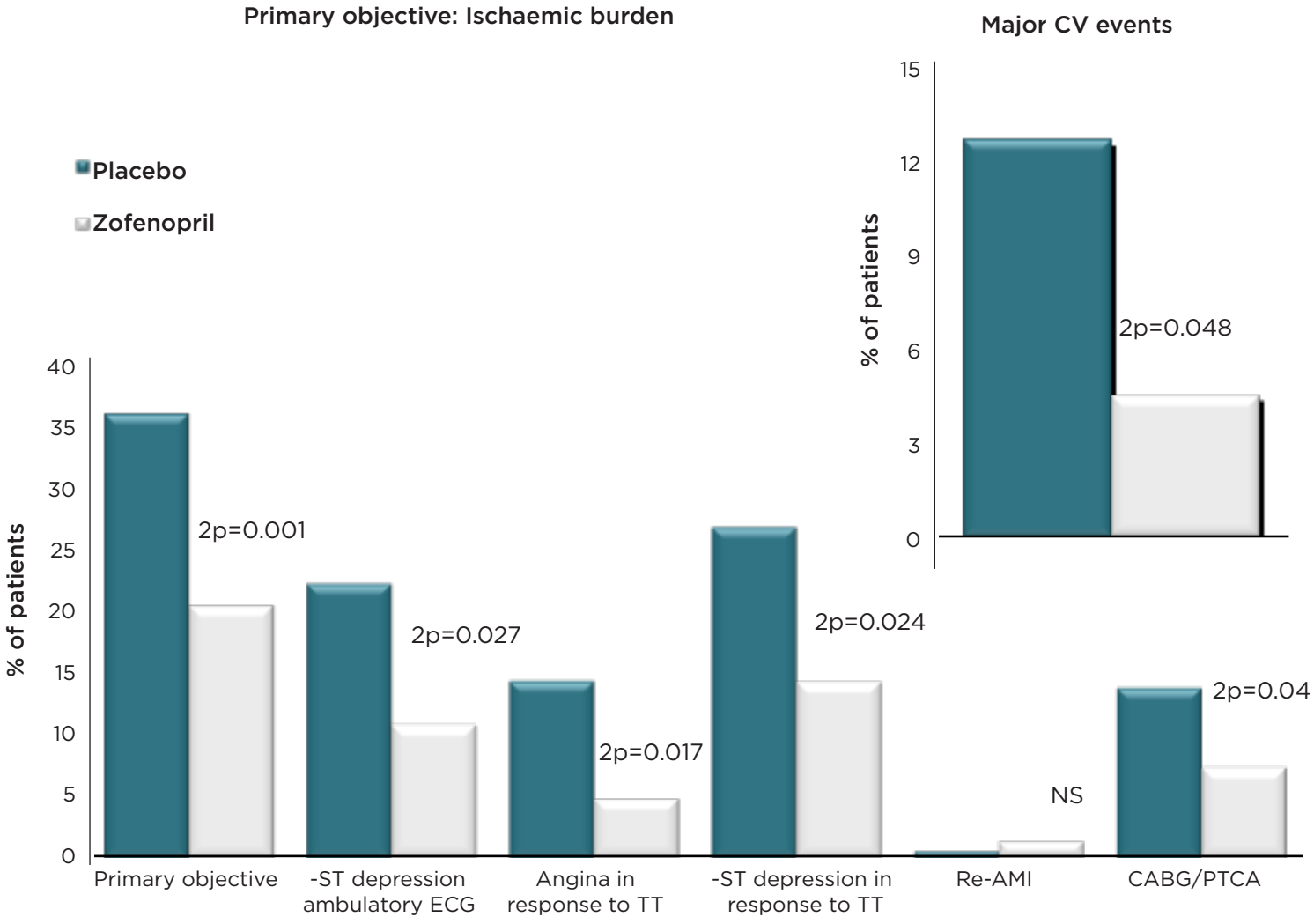

Figure 7. SMILE Ischaemia study: primary objective and clinical outcome.
Borghi C et al.[56]

Comparison	Hazard ratio (95% CI)
Zofenopril vs placebo	0.36 (0.29-0.45)
Ramipril vs placebo	0.57 (0.43-0.77)
Lisinopril vs placebo	0.49 (0.35-0.70)

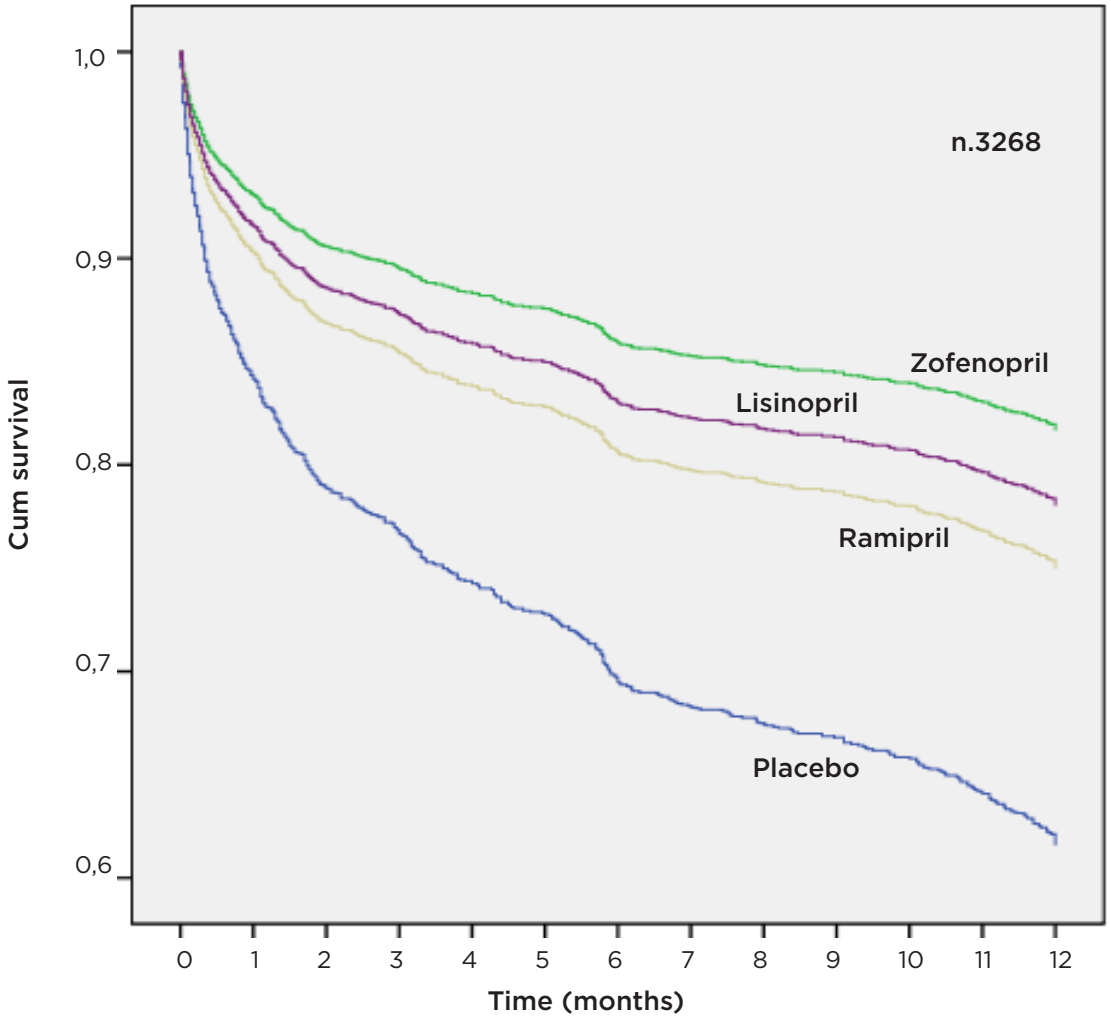

Figure 8. SMILE overall: ACE inhibitors vs. placebo. 1 year adjusted* event free survival (CV mortality and hospitalisation for CV causes).

**Cox Regression model with treatment, age, gender, country and baseline CV risk factor as covariates. SMILE Pooled Analysis[58]*

more evident in these patients treated with Zofenopril than in patients without metabolic abnormalities. This is important because it suggests that the benefits observed in the SMILE trial are probably due to Zofenopril's favourable interaction with some of the mechanisms that are responsible for excessive cardiovascular events in patients with high blood pressure and abnormalities of the metabolic profile.

The efficacy of Zofenopril has been compared with other drugs of the same class[58] (Figure 8). The results of the SMILE pooled analysis, which included over 3,000 patients in the SMILE trials, has confirmed that ACE inhibitors are better than placebo in the treatment of post MI patients. The results also demonstrate that there are some differences between ACE inhibitors. The most striking observation from this huge amount of pooled data is that when Zofenopril is compared with lisinopril and ramipril, event free survival is improved in patients treated with Zofenopril. The difference between Zofenopril and other ACE

inhibitors is that Zofenopril appears to produce superior efficacy. This is an important observation that should be taken into consideration in clinical practice when choosing treatment for post MI patients.

Many of the differences seen when comparing Zofenopril and other ACE inhibitors in terms of clinical outcome have arisen from the results of the SMILE-4 trial.[25] Two different populations of patients were treated with Zofenopril or ramipril in combination with aspirin. The objective was to evaluate the problem of possible interaction between ACE inhibitors and aspirin in patients with acute MI, and particularly in patients where MI was complicated by left ventricular dysfunction. The primary endpoint showed that treatment with Zofenopril was more effective than ramipril ($p<0.05$) in terms of cardiovascular mortality and hospitalisation for cardiovascular causes. A great proportion of the benefit was due to the reduction in hospitalisation for cardiovascular causes (RR [95% CI] =0.64 [0.46-0.89]; adjusted p=0.009). The SMILE trial also assessed the difference in benefit between Zofenopril and ramipril in pre-specified subgroups. In patients with hypertension treatment with Zofenopril appears to achieve better results than ramipril. Another very important subgroup is patients with preserved left ventricular function. Despite the clinical signs of congestive heart failure a significant improvement was seen in patients treated with Zofenopril compared with those treated with ramipril. This suggests that the choice of ACE inhibitor should be decided on by the appropriateness to the particular disease characteristics of the patient.

There are differences in the mechanistic action of ACE inhibitors, in particular Zofenopril, in cardiovascular prevention. The four most important properties that differentiate Zofenopril from other ACE inhibitors are: 1) the presence of an SH-group producing an antioxidant effect. 2) High lipophilicity allowing a greater tissue drug concentration. 3) High tissue ACE blockade. 4) A favourable balance between reduced A-II and increased bradykinin levels. Indeed the mechanism of action of Zofenopril appears less dependent on the bradykinin system while it promotes a prominent increase in the NO availability that compensate for the lesser BK activation. The combination of these four properties demonstrates that Zofenopril is very different from other drugs belonging to the same class.

The evidence obtained from the SMILE studies show that when compared with drugs of the same class Zofenopril is firstly, more effective than any other ACE inhibitor in the treatment of post-MI patients complicated by left ventricular dysfunction. Secondly, the efficacy of Zofenopril is less affected in terms of negative interaction by the concomitant administration of aspirin because of the difference in the extent of the bradykinin contribution to the overall mechanism of action of the drug. Thirdly, Zofenopril has additional properties that play a clinical role, particularly the anti-ischaemic effect, which can have some advantage in terms of clinical outcome when compared with other drugs of the same class. Finally, Zofenopril has a more favourable interaction with the concomitant drugs which are usually given in combination with ACE inhibitors, in particular diuretics. This has been demonstrated as a working hypothesis in an experimental situation in which two different ACE inhibitors lisinopril and Zofenopril were given to rats in an attempt to understand the changes in plasma and tissue concentration.[59] The results showed that plasma concentration particularly at the left ventricular level was higher in rats treated with Zofenopril (Figure 9). The ability to achieve higher plasma concentration plays an important role in target organ protection and clinical prognosis.

The SMILE programme is set to continue to further develop understanding of the mechanism of Zofenopril particularly in cardio protection and increase the amount of data concerning the anti-ischaemic effect.

Based on the evidence to date it is clear that ACE inhibitors favourably affect CV outcomes and have a remarkable cardioprotective effect in patients with coronary artery disease. The benefit can be demonstrated from the acute phase of MI and is related to specific drug properties, particularly those seen in Zofenopril. The cardioprotective benefit of ACE inhibitors is enhanced in Zofenopril as a result of its haemodynamic and anti-ischaemic effects. The peculiar mechanism of action of Zofenopril when compared with other ACE inhibitors might improve the treatment of a wide range of patients with coronary artery disease and patients with hypertension with or without left ventricular dysfunction and congestive cardiac failure.

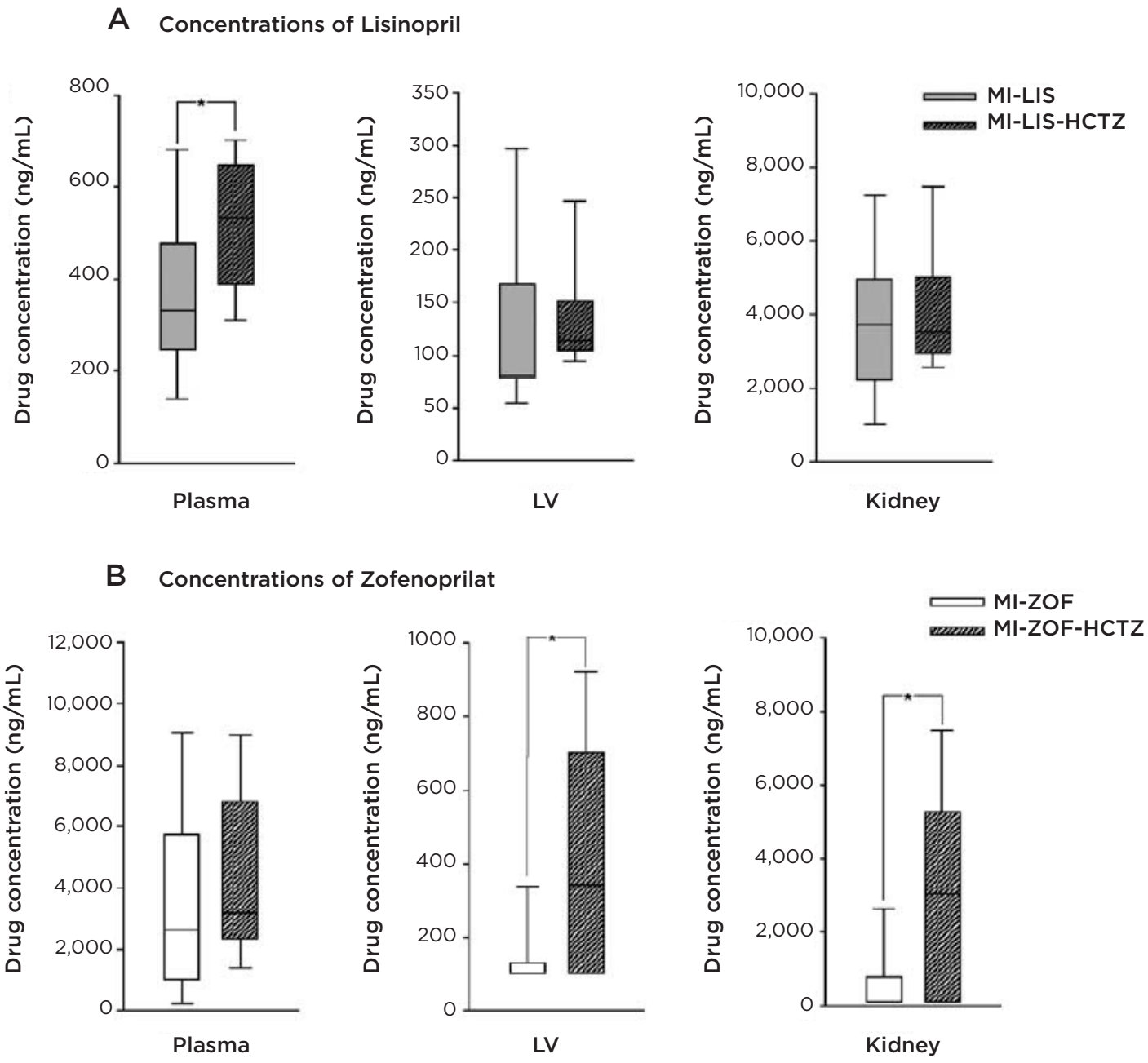

Figure 9. Plasma, left ventricular and kidney tissue concentrations of different ACE-inhibitors in rats with MI treated or not with hydrochlorothiazide.
Westendorp B et al.[59]

Panel Discussion

Question: In SMILE Zofenopril was used twice a day (30 mg dose) while the advice is to give it once a day. Should Zofenopril be given twice a day at 30 mg or 60 mg once a day?

Prof Claudio Borghi: In the SMILE trial we have tried to follow the suggested dose of other ACE inhibitors used in other trials in post MI patients e.g. captopril or enalapril. In these trials the drugs had been given twice a day. In the SMILE trial we needed to have careful control of blood pressure values. Actually we have achieved a good result using the drug twice a day so my suggestion is try to use the drug twice a day for the first 6 weeks and later on the drug can be given once a day.

Question: Nebivolol has advantages in terms of organ damage and blood pressure control. Is there an outcome trial with nebivolol?

Prof Claudio Borghi: There is the Seniors trial which is a trial where the study population's mean age was 68 whereas in previous trials the mean age was 62. In the Seniors trial we saw that by adding nebivolol at the start of treatment showed a significant reduction of cardiovascular events and in the prevention of coronary artery disease there was a significant reduction even of cardiac death. And there are some promising data for congestive cardiac failure. On the other hand despite what has been seen, beta blockers increase the nuances of diabetes despite that 85% of heart failure patients receive high doses of diuretics there is a reduction of nuances of diabetes instead of an increase of nuances of diabetes

Question: The title of the discussion is also to look for solutions. The question of differences between drugs and different ACE inhibitors, there are mechanistic differences no question about that. But how can we move further than we already have in terms of proving differences because you don't have proof that there are differences in addition to blood pressure we need to be sure that the effect on blood pressure is the same. Now the picture is complicated because we need to be sure that the effect on office blood pressure is the same, out of office blood pressure is the same in other words you have to remove all blood pressure related effects which have prognostic significance, this is going to be a very difficult step.

Prof Krzysztof Narkiwicz: This is a very difficult question we had a discussion during the presentation about the guidelines and we stressed the role and the need for a trial in younger patients with stage 1 hypertension because I am convinced that the evidence is overwhelming that the cardiovascular complications need to be caught very early. The data coming from Sweden with 1.2 million subjects observed for many years which indicate that those effects might be observed in the earlier stages of hypertension of the cardiovascular continuum suggests that mild alteration of the mechanism and all the potential benefits will be I think observed in younger patients. It will be extremely important to explore this as it can not only prevent heart endpoints in very high risk older patients but that we can prevent or delay the development of target organ damage. Such a study would provide evidence of the benefit of the newer ACE inhibitors.

Question: Is there any comparison on the efficacy of Zofenopril and ramipril? Of course ramipril is still considered by many cardiologists as the gold standard because of the data.

Prof Claudio Borghi: Basically I think there is some evidence in the basic literature, there are some comparisons that seem to suggest that what we have shown and what we have supposed from the clinical point of view can be confirmed in an experimental setting. We have published a paper after the publication of SMILE-4 at the very beginning of this year in which we have extrapolated from our population of out-patients with chronic heart failure patients treated with Zofenopril, patients treated with ramipril and we have found over ten years follow-up the difference in survival in patients treated with Zofenopril compared with patients treated with ramipril. So I think the basic is probably if we talk about the treatment of hypertension the two drugs behave in exactly the same way but if we talk about the protection of organ damage and in particular we talk about the possibility to protect the myocardium in any condition related to myocardial ischaemia there are some differences between the two drugs and all the data we have and the literature seems to report exactly the same way.

REFERENCES

1. Mancia G et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219.

2. Verdecchia P et al. The renin angiotensin system in the development of cardiovascular disease: role of aliskiren in risk reduction. Vasc Health Risk Manag. 2008;4(5):971–81.

3. Khalil ME et al. A remarkable medical story: benefits of angiotensin-converting enzyme inhibitors in cardiac patients. J Am Coll Cardiol. 2001;37(7):1757-64.

4. Grover GJ et al. Effects of different angiotensin-converting enzyme (ACE) inhibitors on ischemic isolated rat hearts: relationship between cardiac ACE inhibition and cardioprotection. J Pharmacol Exp Ther. 1991:257(3);919-29.

5. Borghi C et al. Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. J Clin Pharmacol. 1993;33(1):40-5.

6. Cushman DW et al. Differentiation of angiotensin-converting enzyme (ACE) inhibitors by their selective inhibition of ACE physiologically important target organs. Am J Hypertens. 1989;2(4):294-306.

7. Frascarelli S et al. Cardioprotective effect of zofenopril in perfused rat heart subjected to ischemia and reperfusion. J Cardiovasc Pharmacol. 2004;43(2):294-9.

8. Scribner AW et al. The effect of angiotensin-converting enzyme inhibition on endothelial function and oxidant stress. Eur J Pharmacol. 2003;482(1-3):95-9.

9. Pasini AF et al. Effects sulfhydryl and non-sulfhydryl angiotensin-converting enzyme inhibitors on endothelial function in essential hypertensive patients. Am J Hypertens. 2007;20(4):443-50.

10. Buikema H et al. Comparison of zofenopril and lisinopril to study the role of the sulfhydryl-group in improvement of endothelial dysfunction with ACE-inhibitors in experimental heart failure. Br J Pharmacol. 2000;130(8):1999-2007.

11. Napoli C et al. Sulfhydryl angiotensin-converting enzyme inhibition induces sustained reduction of systemic oxidative stress and improves the nitric oxide pathway in patients with essential hypertension. Am Heart J. 2004;148(1):e5.

12. Napoli C et al. Long-term treatment with sulfhydryl angiotensin-converting enzyme inhibition reduces carotid intima-media thickening and improves the nitric oxide/oxidative stress pathways in newly diagnosed patients with mild to moderate primary hypertension. Am Heart J. 2008;156(6):1154.e1-8.

13. Napoli C et al. Beneficial effects of ACE-inhibition with zofenopril on plaque formation and low-density lipoprotein oxidation in watanabe heritable hyperlipidemic rabbits. Gen Pharmacol. 1999;33(6):467-77.

14. Ferrari R et al. Protection of the ischemic myocardium by the converting-enzyme inhibitor zofenopril: insight into its mechanism of action. J Cardiovasc Pharmacol. 1992;20(5):694-704.

15. van Gilst WH. Captopril-induced increase in coronary flow: an SH-dependent effect on arachidonic acid metabolism? J Cardiovasc Pharmacol. 1987;9 suppl 2:S31-6.

16. Ambrosioni E et al. Early treatment of acute myocardial infarction with angiotensin-converting enzyme inhibition: safety considerations. SMILE pilot study working party. Am J Cardiol. 1991;68(14):101D-110D.

17. Ambrosioni E et al. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The survival of myocardial infarction long-term evaluation (SMILE) study investigators. N Engl J Med. 1995;33(2):80-5.

18. Borghi C et al. Effects of the early administration of zofenopril on onset and progression of congestive heart failure in patients with anterior wall acute myocardial infarction. The SMILE study investigators. Survival of myocardial infarction long-term evaluation. AM J Cardiol. 1996;7(8):317-22.

19. Borghi C et al. Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension. SMILE study investigators. Survival of myocardial infarction long-term evaluation. Am J Hypertens. 1999;12(7):665-72.

20. Borghi C et al. Effects of the early ACE inhibition in diabetic nonthrombolyzed patients with anterior acute myocardial infarction. Diabetes Care. 2003;26(6):1862-8.

21. Borghi C et al. Effects of early treatment with zofenopril in patients with myocardial infarction and metabolic syndrome: the SMILE study. Vasc Health Risk Manag. 2008;4(3):665-71.

22. Borghi C et al. Serum cholesterol levels on admission and survival in patients with acute myocardial infarction treated with zofenopril: a post hoc analysis of the Survival of Myocardial Infarction Long-Term Evaluation trial. Fundam Clin Pharmacol. 2009;23(5):641-18.

23. Borghi C et al. Double-blind comparison between zofenopril and lisinopril in patients with acute myocardial infarction: results of the Survival of Myocardial Infarction Long-term Evaluation-2 (SMILE-2) study. Am Heat J. 2003;145(1):80-7.

24. Borghi C et al. Effects of early angiotensin-converting enzyme inhibition in patients with non-ST-elevation acute anterior myocardial infarction. Am Heart J. 2006;152(3):470-7.

25. Borghi C et al. Comparison between zofenopril and ramipril in combination with acetylsalicylic acid in patients with left ventricular systolic dysfunction after acute myocardial infarction: result of a randomized, double-blind, parallel-group, multicenter. European study (SMILE-4). Clin Cardiol. 2012;35(7):416-23.

26. The Consensus trial study group. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative North Scandinavian enalapril survival study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987;316:1429-53.

27. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325:293-302.

28. Packer M et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999;100(23)2312-8.

29. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infraction with clinical evidence of heart failure. The acute infarction ramipril efficacy (AIRE) study investigators. Lancet. 1993;342;(8875):821-8.

30. Pfeffer MA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327:669-77.

31. Køber L et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril cardiac evaluation (TRACE) Study Group. N Engl J Med. 1995;333:1670-6.

32. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo sudio della sopravvivenza nell'infarto miocardico. Lancet. 1994;7343(8906):1115-22.

33. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute mycocardial infarction. ISIS-4 (fourth international study of infarct survival) Collaborative group. Lancet. 1995;345(8951):669-85.

34. Swedberg K et al. Effects of the early administration of enalapril on mortality in patietns with acute myocardial infarction. Results of the cooperative new Scandinavian enalapril survival study II (CONSENSUS II). N Engl J Med. 1992;327(10):678-84.

35. Staessen JA et al. Implications of recently published trials of blood pressure-lowering drugs in hypertensive or high-risk patients. Hypertension. 2010;55(4):819-31.

36. Manolis AJ. Cardioprotective properties of bradykinin: role of the B(2) receptor. Hypertens Res. 2010;33(8):772-7.

37. Schmieder RE et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med. 2003;115(1):41-6.

38. Dahlöf B et al. Cardiovascular mobidity and mortality in the Losartan Intervention for endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet. 2002;359(9311):995-1003.

39. Jamerson K et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in High-Risk Patients. N ENgl J Med. 2008;359:2417-28.

40. Dahlöf B et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895-906.

41. Williams B et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the conduit artery function evaluation (CAFÉ) study. Circulation. 2006;113(9):1213-25.

42. Morgan T et al. Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens. 2004;17(2):118-23.

43. Manolis AJ et al. Arterial compliance in diabetic normotensive patients after angiotensin-converting enzyme inhibition therapy. Am J Hypertens. 2005;18(1):18-22.

44. McEniery CM et al. Nebivolol increases arterial distensibility in vivo. Hypertension. 2004;44(3):305-10.

45. Braunwald E et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351:2058-68.

46. Fox KM et al. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362(9386):782-8.

47. Pitt B. ACE inhibitors for patients with vascular disease without left ventricular dysfunction-may they rest in PEACE? N Engl J Med. 2004;351(20):2115-17.

48. Desideri G et al. Different effects of angiotensin converting enzyme inhibitors on endothelin-1 and nitric oxide balance in human vascular endothelial cells: evidence of an oxidant-sensitive pathway. Mediators Inflamm. 2008;2008:305087.

49. Lupi R et al. The direct effects of the angiotensin-converting enzyme inhibitors, zofenoprilat and enalaprilat, on isolated human pancreatic islets. Eur J Endocrinol. 2006;1542(2):355-61.

50. Borghi C et al. Zofenopril and ramipril and acetylsalicylic acid in postmyocardial infarction patients with left ventricular systolic dysfunction: a retrospective analysis in hypertensive patients of the SMILE-4 study. J Hypertens. 2013;31(6):1256-64.

51. McMurray JJ. ACE inhibitors in cardiovascular disease – unbeatable? N Engl J Med. 2008;358(15):1615-6.

52. Savarese G et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. J Am Coll Cardiol. 2013;61(2):131-42.

53. van Vark LC et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J. 2012;33(16):2088-97.

54. Verma J et al. Plasma renin activity predicts cardiovascular mortality in the heart outcomes prevention evaluation (HOPE) study. Eur Heart J. 2011;32(17):2135-42.

55. Oral captopril versus placebo among 14,962 patients with suspected acute myocardial infarction: a multicentre, randomized, double blind, placebo controlled clinical trial. . Chinese Cardiac study (CCS-1) Collaborative Group. Chin Med J. (Engl) 1997;110(11):834-8.

56. Borghi C et al. Effects of zofenopril on myocardial ischemia in post-myocardial infarction patients with preserved left ventricular function: the Survival of Myocardial Infarction Long-term Evaluation (SMILE)-ISCHEMIA study. Am Heart J. 2007;153(3):445.e7-14.

57. Stone PH. Ischemia dictates outcome, not symptoms. J Am Coll Cardiol. 2013;61(7):712-3.

58. SMILE Pooled Analysis, J Am Coll Cardiol 2013 (abstract).

59. Westendorp B et al. Hydrochlorothiazide increases plasma or tissue angiotensin-converting enzyme-inhibitor drug levels in rats with myocardial infarction: differential effects on lisinopril and zofenopril. Eur J Pharmacol. 2005;527(1-3):141-9.

Disclaimer

THE CHANGING LANDSCAPE IN ORAL ANTICOAGULATION – THE LAST PIECES OF THE PUZZLE

Summary of Presentations from the Daiichi Sankyo Symposium, ESC Annual Congress 2013, Amsterdam, the Netherlands

Chairpersons

A. John Camm,[1] Jeffrey I. Weitz,[2]

Speakers

Raffaele De Caterina,[3] Hein Heidbüchel,[4] Robert P. Giugliano,[5] Harry R. Büller[6]

1. Professor of Clinical Cardiology, St George's Hospital, London, UK
2. Professor, Division of Haematology and Thromboembolism, Department of Medicine, McMaster University, Ontario, Canada
3. Professor and Director, University Cardiology Division, "G. d'Annunzio" University, Chieti, Italy
4. Professor of Cardiology and Electrophysiology, University of Leuven, Belgium
5. Assistant Professor, Harvard Medical School, Massachusetts, USA
6. Professor of Internal Medicine, Academic Medical Center, University of Amsterdam, the Netherlands

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The Changing Landscape in Oral Anticoagulation

Introduction

Prof Jeffrey I. Weitz

Dabigatran, rivaroxaban, apixaban and edoxaban are four new oral anticoagulants (NOACs). There are an increasing number of indications for which these agents are licensed or under consideration for approval. Dabigatran is licensed for venous thromboembolism (VTE) prevention in the orthopaedic setting in most countries except the United States and there is an application in progress for licensing in VTE treatment. Dabigatran is also licensed for stroke prevention in atrial fibrillation (AF) and it has been investigated in a Phase II study for the indication of acute coronary syndrome (ACS). Rivaroxaban is licensed for VTE prevention, VTE treatment, stroke prevention in AF and, in Europe, for secondary prevention in patients with ACS. Apixaban is licensed in most countries, except the US, for VTE prevention in the orthopaedic setting, application is in progress for licensing for VTE treatment. Apixaban is also licensed for stroke prevention in AF but not for ACS. Edoxaban is licensed in Japan for VTE prevention after elective hip or knee surgery and the Phase III studies in VTE treatment and stroke prevention in AF have been completed.

The NOACs are divided into two groups; those that target factor Xa, rivaroxaban, apixaban and edoxaban, and the drug that targets thrombin, dabigatran. All of the NOACs have certain advantages over warfarin; they have a rapid onset of action (peak onset within 1-4 hours), they can be given in fixed doses, and there is no effect of dietary vitamin K intake on their pharmacological activity. There are few drug-drug interactions, they produce a very predictable anticoagulant response and have an extremely wide therapeutic window, which renders routine coagulation monitoring unnecessary. In addition, the NOACs all have a half-life of approximately 12 hours and with this relatively short half-life their anticoagulant effect wears off rapidly. The short half-life of the NOACs is an advantage in cases where there is serious bleeding

or a patient requires urgent surgery or intervention because this obviates the need for an antidote in most circumstances. Due to these advantages over warfarin, there is an increasing uptake of these new agents.

Anticoagulation in Atrial Fibrillation – Recent Steps and Open Questions

Prof Raffaele De Caterina

AF is a common cause of stroke, heart failure, hospitalisations, and death in affected patients.[1-3] The management of AF has seen marked changes in recent years with the availability of new anticoagulants, antiarrhythmic drugs, and the wider availability of catheter ablation.[3] These changes have resulted in new or updated management guidelines published in Europe, Canada and the US.[4-7] Although most of the recommendations in the guidelines for the management of AF are based on sound evidence, they are not totally consistent[8] and are not always fully implemented into practice.[9-11] Therefore, it is important to ascertain how these guidelines are being translated into practice. This is the purpose of the registries that have flourished in recent years. The focus of the registry is to address the current situation pertaining to a particular medical condition and predict how it may change.

The Prevention of Thromboembolic Events – European Registry (PREFER) in AF is a multi-national, multi-centre, prospective disease registry with the objective of gaining a detailed insight into the characteristics and management of patients with AF. The main focus is the prevention of thromboembolic events. Subjects have completed a baseline visit and will receive a follow-up visit 12 months after baseline. This will provide the opportunity to monitor the changes that occur in the pattern of treatment of AF within a year, at a time of rapid changes in the anticoagulation landscape in Europe.

The registry is based in several European countries including Austria, France, Germany, Italy, Spain Switzerland, and the United Kingdom. For regional comparisons, Austria, Switzerland and Germany were combined into one pre-specified region.

The PREFER registry incorporated all-comers with AF as long as the subjects met the inclusion criteria. The inclusion criteria were that subjects were at least 18 years of age, gave written informed consent for participation, and had a history of AF documented by electrocardiography (ECG) or by an implanted pacemaker or defibrillator within the preceding 12 months. No explicit exclusion criteria were defined in order to avoid a biased selection of patients and achieve a cohort as close to 'real-life' as possible. Inclusion of patients was consecutive at each site in order to reduce selection bias. All data were captured through an electronic case report form, which included a wide range of plausibility checks in order to ensure the best possible data collection. There was on-site source data verification in 5% of the sites. This was an extensive registry involving 7,243 patients distributed relatively homogenously throughout the various macro regions of Europe. The mean CHA_2DS_2VASc score[12] was 3.4 and the mean HAS-BLED score,[13] used to assess the bleeding risk of the patients, was 2.0.

In the study population the intersection between the types of AF - paroxysmal, persistent, long-standing persistent, and permanent - in relation to the CHA_2DS_2VASc score showed there was a significant prevalence of low CHA_2DS_2VASc score for paroxysmal AF. This low score for paroxysmal AF usually occurs in younger people who have fewer risk factors for thromboembolism. The pattern of use of antithrombotic therapy, according to AF clinical presentation, shows that the category of paroxysmal AF has a greater percentage of use of antiplatelet (AP) agents, while in the other patient categories there is a more distributed use of anticoagulants. This includes the use of the NOACs which accounts, at the time of the first registry snapshot, for about 5% of antithrombotic drugs.

The use of antithrombotic treatment in Europe according to the CHA_2DS_2VASc score shows that there is good implementation of the guidelines in the category of thromboembolic risk of ≥2. There is also adequate use of oral anticoagulants, mainly vitamin K antagonists (VKA). In the category of patients with a CHA_2DS_2VASc score of one, there is a large use of AP agents despite the fact that the European guidelines on AF recommend the use of anticoagulants in this patient category.

In Europe, the time in therapeutic range (TTR) is still suboptimal in a substantial proportion of patients; approximately 30% have a suboptimal international normalised ratio (INR) control as objectively determined by the TTR assessed in the registry, by recording data on the last three INR measurements. The perception of the physician on

the adequacy of anticoagulation is usually better than the reality. There is a smaller percentage of patients judged by the physicians to be not well controlled compared with patients with suboptimal INR control.

Physicians are therefore inclined to overestimate their ability to control anticoagulation with VKAs. In AF anticoagulation, warfarin is the most often discussed drug, but in Europe there are several other VKAs that are used, including phenprocoumon used mainly in German speaking countries; acenocoumarol which is the prevailing VKA in Spain and widely used in Italy; and fluindione, widely used in France. The data recorded in the PREFER registry show that the quality of anticoagulation is relatively homogenous irrespective of the type of VKA used.

One of the aims of the PREFER registry was to address the issue of the concomitant use of AP agents and anticoagulants in AF patients. The data showed that 9.9% of patients received combined treatment with VKA and one or more AP agents. The data was broken down according to the use of VKA plus a single AP agent, which in most cases was aspirin (ASA); and VKA plus dual antiplatelet agents, in most cases a combination of ASA and clopidogrel. The appropriateness or inappropriateness of treatment with ASA or ASA plus clopidogrel in combination with VKA, was evaluated. The results showed that in 95.6% of patients, the combined use of ASA and VKA is not justified in light of the recommendations of the European guidelines.[4] The guidelines to this regard state that if patients do not have an acute coronary syndrome (ACS) and but are stable coronary heart disease (CHD) patients with AF, they are best successfully treated with warfarin only.

The PREFER registry demonstrated that a higher ($p<0.0001$) occurrence of risk factors for CHD, or the presence of CHD itself, characterised the category of patients treated with dual AP therapy, compared with those not receiving such therapy. The choice of dual AP treatment for this category of patients was to a large extent inappropriate. No significant differences were observed in the other patient characteristics.

The appropriateness of the combined use of VKA plus ASA plus clopidogrel (triple therapy) was evaluated in the PREFER registry patient population. There were approximately 100 patients that were captured in the database (excluding patients with insertion of a bare metal stent ≤1 month, a drug-eluting stent ≤1 year or ACS ≤1 year before the visit) and 67% of the patient population receiving triple therapy were receiving such therapy inappropriately. This choice of treatment is mainly driven by the presence of CHD, which in most cases is a previous myocardial infarction or a stent inserted years ago. No significant differences were observed in the other patient characteristics.

The PREFER registry shows that the current situation in Europe in the management of AF patients is that physicians are adapting treatment to recent evidence and to guideline recommendations. Oral anticoagulant therapy is mainly with VKA, or to a lesser extent with NOACs, and is given to over 80% of eligible patients, including those at risk of bleeding. This indicates a good overall implementation of the guideline recommendations. Paroxysmal AF is relatively more prevalent in classes of lower thromboembolic risk, in which most of the use of AP agents is concentrated. Adequate INR control is achieved in approximately 70% of patients on VKAs; however physicians tend to overestimate the control of the INR. The quality of anticoagulation does not appear to be different between the various VKAs used in different European countries. Approximately 10% of AF patients are treated with a combination of an anticoagulant and one or two AP agents, and in most cases this treatment is considered inappropriate.

The Use of Novel Oral Anticoagulants in Clinical Practice

Prof Hein Heidbüchel

There are NOACs for different indications; these are very powerful drugs and show encouraging outcomes. An understanding of how to work with these new drugs in clinical practice is required; there are many scenarios where an adaption of work flow is required to change treatment regimens to these novel drugs. The summary of product characteristics (SmPC) offers some guidance. These are leaflets or booklets made by the company, offering healthcare professionals information on how to use the medication. However, the problem is that there are three or four different drugs on the market. The SmPCs for the drugs are similar in many ways; however, there are important differences which may present

confusion rather than help. The documents produced by the company are legally bound in many respects and do not always give physicians the answers that are required for appropriate and effective use in clinical practice. For this reason the European Heart Rhythm Association (EHRA) produced some unified information that is as practical as possible and attempts to provide answers where they are needed (even if all the information is not available).[14] As more information becomes available, updates will be made accordingly.

The EHRA Practical Guide on the use of NOAC drugs in patients with non-valvular AF covers all four NOACs side by side. Apart from the writing group of 9, 14 reviewers provided comments and contributed to the final document. In addition, all four pharmaceutical companies contributed to the guide to ensure that the latest pharmacological information was available. This approach enabled the document to be as complete and up-to-date as possible.

The document answers 15 different very practical clinical topics:

1. Start-up and follow-up.
2. How to interpret coagulation tests.
3. Drug-drug interactions and pharmacokinetics of NOAC.
4. Switching between anticoagulant regimens.
5. Ensuring compliance of NOAC intake.
6. How to deal with dosing intake errors.
7. Patients with chronic kidney disease.
8. What to do if (suspected) overdose without bleeding.
9. Management of bleeding complications.
10. Planned surgical intervention or ablation.
11. Urgent surgical intervention.
12. Patients with both AF and coronary artery disease.
13. Cardioversion in a NOAC treated patient.
14. Patients presenting with acute stroke while on NOAC.
15. NOAC versus VKA in AF patients with a malignancy.

The topics covered in the practical guide are part of a wider project, i.e. the development of a website (www.NOACforAF.eu); the website enables physicians to download PDFs of the practical guide documents. In addition, a new anticoagulation card is available which is translated into 11 languages (more translations are underway); the PDF of the anticoagulation card can be downloaded and printed for use in clinical practice. There is an area to provide feedback which will be taken into account when updates are made to the guide. Furthermore, a slide kit and a key message pocket guide are available. Regular updates will be presented on the site allowing access to the most recent information.

NOACs are absorbed in the gut, some of them require metabolisation and all of them require elimination. The bio-availability of NOACs is not equal[14] and they range from very low, to very high bio-availability.

There are different pathways of elimination which can be renal or liver related; there is a difference between the drugs in the proportion of the absorbed dose that is eliminated via a renal or liver pathway.[14] Edoxaban (which has no European Medicines Agency approval at present) is somewhere in the middle, with a 50:50 elimination between the liver and kidney. Knowledge of the absorption, metabolisation and elimination pathways is required for drug-drug interactions. In contrast to VKAs, it was anticipated that there would be no drug-drug interactions with NOACs but a few have been observed.[14] Dabigatran, apixaban, edoxaban and rivaroxaban react differently to concomitant medication.

There is some missing information regarding the drug-drug interactions of NOACs. However, the missing data is required in clinical practice to make informed decisions for the treatment of patients. Hopefully it will be provided by the manufacturers soon. In addition, there are other factors that affect drug-drug interaction, e.g. patient weight, age and other drugs that have a pharmacodynamic interaction. It is important that this information is available and is as complete as possible.

Physicians require a range of doses to choose from in order to treat patients effectively with a NOAC. Edoxaban has been studied at three different dosages; in the ENGAGE-AF trial, pharmacokinetic data and biomarker measurements in all patients over a wide dose range (15-60 mg) have been generated, providing substantial information that

relates to clinical factors.[15] The dosing regimen of edoxaban is consistent across all indications studied, providing promising evidence for its use in clinical practice.

Edoxaban has been studied in patients with severe renal impairment with CrCl 15-30 ml/min.[16] For most other NOACs only extrapolations from the data were used. Edoxaban was evaluated in 93 patients with non-valvular AF; 50 patients with CrCl 15-30 ml/min were given a reduced dose of 15 mg once a day (QD). No major bleeding or serious adverse events were seen. The plasma levels of patients with CrCl 15-30 ml/min receiving a 15 mg dose were similar to the plasma levels in patients receiving a 30 mg dose with better renal function. This shows that the same plasma levels can be achieved with a dose reduction in patients with severe renal impairment, and provides the evidence to make an informed decision in the treatment of these patients.

Another practical aspect relating to anticoagulants is the concern of bleeding, especially as the NOACs do not have antidotes available for rapid reversal. The information provided from the studies of NOACs indicates that the concerns surrounding bleeding and NOACs should not be over-interpreted. All NOAC trials have shown less major bleeding complications (even though reversal agents are not available) in NOAC-treated patients. Moreover, there is no certainty that when coagulation is restored with antidotes, this will impact outcome. However, only limited data from animal experiments or *in vitro* experiments are available. The pocket guide suggests possible measures to take when major bleeding occurs (Table 1).[14] The difference between dabigatran, a direct thrombin inhibitor, and apixaban, edoxaban and rivaroxaban, which are FXa inhibitors, is that maintaining diuresis and/or dialysis is an option for dabigatran but probably not for the FXa inhibitors. There are no specific reversal agents for the NOACS so if there is major bleeding non-specific reversal agents are required.

There is incomplete data in the literature and no clinical data concerning the treatment of patients with major bleeding who are receiving NOACs, nonetheless, it is thought that prothrombin complex concentrates (PCCs) or activated prothrombin concentrates (APCCs), which are preferred to PCCs, are a good choice of treatment because they are readily available in the clinical setting. There is some suggestion that recombinant factor VII should be used, however this has not been shown to be superior and it is a much more expensive choice.

Dialysis is not usually an option for NOACS but it has been shown that edoxaban is slightly cleared by dialysis (6-20%). In a recent abstract, 10 patients undergoing dialysis for end-stage renal disease were investigated.[17] The patients were treated with 15 mg of edoxaban 2 hours prior to a 4 hour dialysis session, versus on a day without planned dialysis. The plasma exposure was comparable – AUC 692±150 versus 676±221 ng.h/ml - indicating that dialysis is ineffective in eliminating the drug in cases of bleeding. Furthermore, the results implicate that dose adjustment is not needed when a patient undergoes dialysis. However, it should be noted that these patients are not indicated for treatment with NOACs.

There are clinical studies in progress examining specific edoxaban reversal agents including recombinant protein and small molecules; a Phase II study in healthy volunteers with FXa inhibitor antidote PRT4445 (andexant alfa) a recombinant protein,[18] and a Phase I study with FXa inhibitor antidote PER977, a synthetic small molecule that directly binds to heparin and circulating FXa- and IIa-inhibitors.[19] In addition there are ongoing clinical studies with 3-factor and 4-factor PCC. Therefore, more information will be provided offering better tools for reversal.

For planned surgery, it is important to know when to cease NOACs and to correctly advise the patient. The guide incorporates a scheme of cessation before planned surgery for NOACs (Table 2),[14] and specific guidance on how to switch between anticoagulants.[14]

Trial data have shown that switching periods are associated with increased thrombo-embolic risks, therefore, switching needs to be carried out diligently. The guide[14] contains the following recommendations:

For switching from a VKA to a NOAC:

• INR <2
start NOAC

• INR 2-5
start NOAC immediately or the next day

• INR >2.5
estimate new INR check depending on VKA half-life

For switching from NOAC to VKA:

• Administer concomitantly until INR >2

Table 1: Bleeding complications and possible measures to take.

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-life-threatening bleeding	Inquire last intake + dosing regimen. Estimate normalisation of haemostasis: Normal renal function: 12-24 hours CrCl 50-80 ml/min: 24-36 hours CrCl 30-50 ml/min: 36-48 hours CrCl <30 ml/min: ≥48 hours Maintain diuresis. Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60x109/L or thrombopathy). FFP as plasma expander (not as reversal agent). Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy). Consider dialysis (preliminary evidence: -65% after 4 hours). Charcoal haemoperfusion not recommended (no data).	Inquire last intake + dosing regimen. Normalisation of haemostasis: 12-24 hours. Local haemostatic measures. Fluid replacement (colloids if needed). RBC substitution if necessary. Platelet substitution (in case of thrombocytopenia ≤60x109/Lor thrombopathy). FFP as plasma expander (not as reversal agent). Tranexamic acid can be considered as adjuvans. Desmopressin can be considered in special cases (coagulopathy or thrombopathy).
Life-threatening bleeding	All of the above. Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence). Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit and expensive (only animal evidence).	All of the above. Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence). Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 µg/kg) no data about additional benefit and expensive (only animal evidence).

Table 2. Cessation of NOACs before planned surgery.

	Dabigatran		Apixaban		Edoxaban*		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)							
	Low risk	**High risk**	**Low risk**	**High risk**	**Low risk**	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥24h	≥48h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 50-80 ml/min	**≥36h**	**≥72h**	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 30-50 ml/min§	**≥48h**	**≥96h**	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 15-30 ml/min§	not indicated	not indicated	**≥36h**	**≥48h**	no data yet	no data yet	**≥36h**	**≥48h**
CrCl <15 ml/min	no official indication for use							

*: no EMA approval yet. Needs update after finalisation of SmPC.
§: many of these patients should be on the lower dose of the drug, for example: 2x110 mg/d dabigatran or 15 mg/d rivaroxaban.
Heidbüchel et al.[14]

(checked before NOAC intake)

• Retest INR 24 hours after last NOAC intake

• Monitor INR closely within the first month (goal of 3 consecutive INRs between 2 and 3).

For switching from low molecular weight heparin (LMWH) to NOAC:

• Start NOAC at the time of next LMWH administration

For switching from unfractionated heparin to NOAC:

• Administer NOAC at time of discontinuation of intravenous heparin (cf. $t_{1/2}$±2h).

In conclusion, in the practical use of NOACs, choice is important; apart from the trial data on outcomes, physicians have to consider some interactions based on metabolism and patient characteristics when deciding on the NOAC drug and its dosing. Edoxaban appears to offer a wide range of dosing choices. Moreover, it allows for a consistent regimen across all indications. In addition, edoxaban has a once daily dose which has the potential for higher intake adherence, which may result in improved clinical efficacy, although this requires confirmation in clinical practice. A simple dosing scheme is an important preventive for bleeding and is associated with a consistent cessation plan before planned surgery. As mentioned, In the near future it is likely that there will be selective and unselective reversal when required in specific situations that require rapid restoration of coagulation.

ENGAGE AF-TIMI (Thrombolysis in Myocardial Infarction) 48: What Does (Will) it Add to Current Knowledge?

Prof Robert P. Giugliano

[NB. Dr Giugliano has referenced unlabelled/unapproved uses of drugs or products]

There has been rapid introduction of NOACs in patients with AF over the last 4 years, starting with the RE-LY trial[20] (dabigatran) in 2009, the ROCKET trial[21] (rivaroxaban) in 2010, and the ARISTOTLE trial[22] (apixaban) in 2011. The ENGAGE AF-TIMI 48 trial[15] with edoxaban[23] is expected to report in November 2013. A recent meta-analysis of the completed trials of NOACs versus warfarin in 51,896 patients with AF[24] pooled the results from the 3 mega-trials. The primary endpoint of stroke or systemic embolic events (SEE) was significantly reduced by 18%, with a borderline statistically significant reduction in ischaemic stroke of 13%, and a large significant reduction of 51% in haemorrhagic stroke with the NOACs. The major advantage of these novel agents appears to be a large reduction in intracranial bleeding. In addition, the meta-analysis showed significant reductions of 9% in mortality and of 18% in major bleeding.

The ENGAGE AF-TIMI 48 trial incorporated the information gathered from the development phases of edoxaban, in particular the edoxaban in AF Phase II trial where four dosage regimens were compared to warfarin[25] (Figure 1).

The Phase II trial results showed an important difference in bleeding with 60 mg once daily as compared to 30 mg twice daily (BID), despite the identical total daily dose. Pharmacokinetic modelling demonstrated that the bleeding rate with edoxaban was best correlated with the trough levels of the drug – thus since 30 mg BID had higher trough levels than 60 mg QD, higher bleeding rates were seen with 30 mg BID compared with a dose of 60 mg QD (which had lower trough levels of edoxaban). For this reason, the two doses taken forward for study in Phase III were 30 mg and 60 mg QD in the ENGAGE AF-TIMI 48 trial.

In the Phase III ENGAGE AF-TIMI 48 trial,[23] 21,105 patients with AF were randomised. AF had to have been documented by electrical recording within 12 months prior to enrolment. All patients (and physicians) had to agree to anti-coagulation for

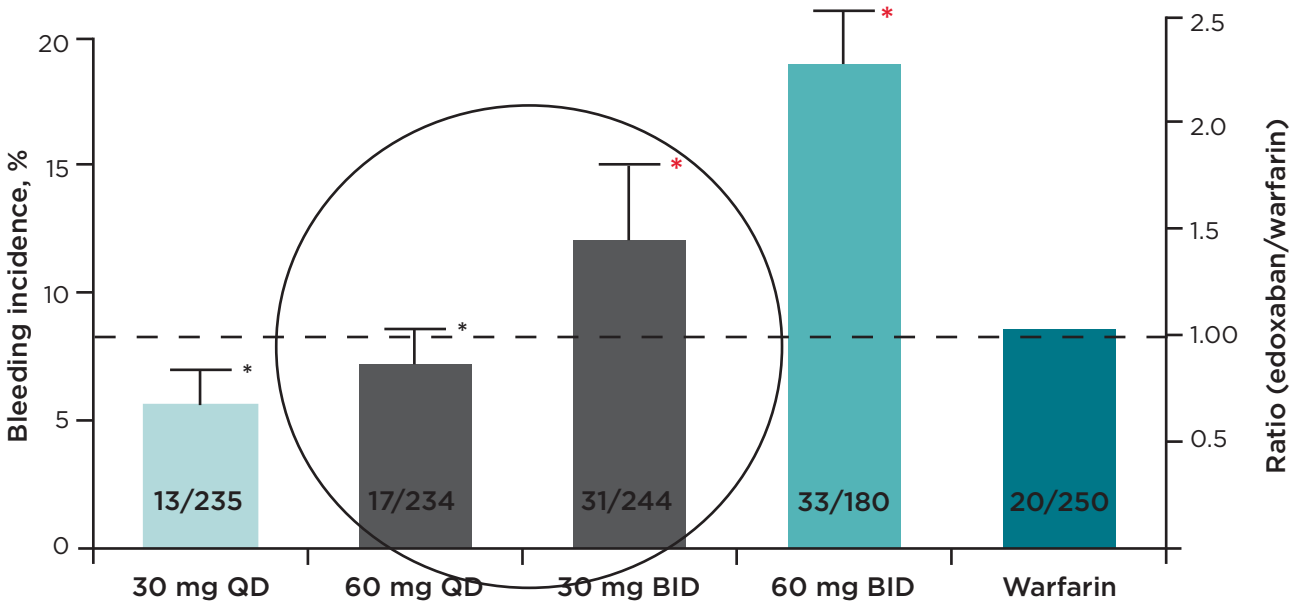

Figure 1. Edoxaban in AF (Phase II): All bleeds for edoxaban relative to warfarin.
For the same total daily dose of 60 mg, higher bleeding observed for 30 mg BID compared with 60 mg QD. *Upper bound for one-sided 67% CI for ratio of incidence rates (edoxaban/warfarin): 0.80, 1.04, 1.79 and 2.58.
Weitz JI et al.[25]

the duration of the trial. Patients were at moderate to high risk for stroke as defined by the $CHADS_2$ of ≥2. This was a double-blind, double-dummy trial and patients were randomised to one of three dose regimens; a low dose regimen of 30 QD (n≈7,000), a high dose regimen of 60 mg QD (n≈7,000), and an active control group (n≈7,000) who were treated with warfarin titrated to an INR of 2-3. The primary objective was to assess whether edoxaban was therapeutically equivalent to warfarin. The trial was event driven and the median duration of follow-up was anticipated to be approximately 24 months. The primary endpoint of stroke or SEE was assessed using non-inferiority approach with an upper boundary HR of 1.38. The secondary endpoint was stroke, SEE or cardiovascular mortality. The principle safety endpoint was ISTH major bleeding.

The dose selection of edoxaban for this trial was considered very carefully. There were two dosing regimens compared to warfarin: a high-dose regimen of 60 mg once daily (dose reduced to 30 mg once daily in selected patients), and a low-dose regimen of 30 mg once daily (dose reduced to 15 mg in selected patients). Analyses of the pharmacokinetic data from phase II had identified three patient subpopulations who achieved a higher blood level of edoxaban, and thus would require dose reduction. These three subpopulations were patients with: moderate renal dysfunction defined as CrCl 30-50 mL/min (patients with a CrCl below 30 mg/dL were excluded from the trial), very low body weight of ≤60 kg, and concomitant use of a strong P-glycoprotein (P-gp) inhibitor. In patients with any one (or more) of these three features, a dose reduction was mandated by the protocol at randomisation.

The protocol also mandated dynamic dose adjustment (this could be downward or upward) after randomisation if one of the three issues noted above had changed during the trial.[25,26] For example, if a patient was taking verapamil at randomisation and the dose of edoxaban was reduced at the start of the trial, but after randomisation verapamil was discontinued, then the dose of edoxaban was restored to the full dose. This type of dynamic dose adjustment was one of the novel features of the ENGAGE AF-TIMI 48 trial. It was implemented with the notion that this better reflected what actually happens in clinical practice when patients have major changes in factors that affect the clearance of a medication. Another novel feature of the trial is the broad range of doses studied; because of the high and low-dosing regimens and the permitted dose reductions with each of these regimens, there were a total of three different doses of edoxaban included in this trial (60, 30, and 15 mg), spanning a 4-fold range of doses.

One of the adjustment factors incorporated in the study was the interaction with P-gp system. There are a large number of cardiovascular medications that can act as substrates or inhibitors of P-gp transport system, including several antiarrhythmics, antihypertensives, antiplatelets, and statins. An even greater number of non-cardiovascular medications interact with the P-gp system, including multiple anti-neoplastic, anti-microbial, gastrointestinal, rheumatologic/immunosuppressive, protease inhibitors, and neurologic agents.[27] Of these drugs, the three cardiovascular agents (verapamil, quinidine, dronedarone) with the largest effect on the clearance of edoxaban were identified, and dose reductions were implemented if they were used concomitantly during the trial. Prior studies with other NOACs did not incorporate such dose adjustment when potent P-gp inhibitors were used, in part because of such interactions were only recently appreciated. Of note, the potential for interactions between the prior NOACs and potent P-gp are increasingly being incorporated with each new iteration of the prescribing information in post-marketing of these NOACs.

A comparison of the trial designs of the RE-LY, ROCKET-AF, ARISTOTOLE and ENGAGE AF-TIMI 48 trials[28-31,33] identifies important differences across the four trials (Table 3). The trials are all large trials although the ENGAGE AF-TIMI 48 trial is the largest. Two studies evaluated QD dosing (edoxaban and rivaroxaban) and two of the trials studied two different dose levels (RE-LY and ENGAGE AF-TIMI 48), but ENGAGE AF-TIMI 48 is the only trial that studied both the drug given QD as well as different dosing regimens.

Three of the four studies allowed for initial dose reduction, however very few patients in the ARISTOTOLE trial with apixaban (less than 5%) qualified for dose reduction compared with 21% in the ROCKET-AF trial and 25% (at randomisation) in the ENGAGE AF-TIMI 48 trial. There was no dose reduction in the RE-LY study. The ENGAGE AF-TIMI 48 trial is unique in the fact that it was

Table 3. Phase III AF trials - dose comparisons.

	RE-LY[28]	ROCKET-AF[29]	ARISTOTLE[30]	ENGAGE AF-TIMI 48[23]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
N	18,113	14,266	18,201	21,105
Dose (mg)	**150,110**	20	5	**60,30**
Frequency	BID	**QD**	BID	**QD**
Initial dose reduction	No	**20 →15 mg**	**5 →2.5 mg**	**60 →30 mg 30 → 15 mg**
Dose reduction (%)	0	21	4.7	25
Dose change after randomisation	No	No	No	Yes
Design	**PROBE**	2x blind	2x blind	2x blind

PROBE: prospective, randomised, open-label, blinded end point evaluation.

the only study that allowed for dose reduction after randomisation. The ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials used a double-blind design, which is superior and more rigorous than the prospective, randomised, open-label, blinded endpoint, evaluation (PROBE) design of the RE-LY trial.

The baseline characteristics of the four trials show that the ROCKET-AF trial enrolled a higher risk population with 87% of patients having a $CHADS_2$ score ≥3. The populations enrolled in RE-LY and ARISTOTLE were lower risk (the percentage of patients with $CHADS_2$ score ≥3 were 32% and 30%, respectively), whereas the ENGAGE AF-TIMI 48 trial enrolled 53% of patients with a $CHADS_2$ score ≥3 (preliminary data for the ENGAGE AF-TIMI 48 trial). Thus the population in ENGAGE AF-TIMI 48 was at moderate to high risk for stroke.

The results to date of the Phase III AF trials show that dabigatran (both doses of 110 mg BID and 150 mg BID), rivaroxaban (20 mg QD) and apixaban (5 mg BID) are superior or similar to warfarin. In addition, both dabigatran 150 mg BID and apixaban were superior to warfarin with regard to the primary endpoint. All therapies substantially reduced intracranial haemorrhage. Major bleeding was favourably reduced with dabigatran 110 mg BID and apixaban compared to warfarin. Mortality tended to be lower with the high dose of dabigatran as well as with apixaban, while only the high dose of dabigatran reduced ischaemic stroke. Thus, there are several safe and effective NOACs already available and the bar is set quite high for edoxaban.

The quality of a study is an important consideration when evaluating new therapies. Three critical metrics that reflect the quality of a study comparing a NOAC to warfarin, include the TTR in the warfarin arm, the percentage of patients who prematurely stopped drug intake before the end of the trial, and the percentage of patients who had missing data due to withdrawal of consent (WD) or loss to follow-up (LTFU). It is important when comparing a NOAC to warfarin that warfarin is used in an expert fashion with a high TTR to ensure a fair comparison. If warfarin is not carefully titrated and patients are out of range most of the time, then it would be easy to show better results using a NOAC. The median TTR varied across the three NOAC versus warfarin trials to date, ranging from 58-66%, reflecting fair-good warfarin titration.

One of the common challenges across these three trials was a relatively high proportion of patients that stopped the drug early, with rates ranging from 21-23% (over a 1-2 year follow-up period). Premature discontinuation of a NOAC is particularly problematic for a clinical trial since these drugs only work while the patient is taking them. Unlike some other drugs in cardiovascular medicine, e.g. statins where the effect can remain for weeks or months after discontinuation, the effect of a NOAC wears off in just a few days, and high rates of premature discontinuation can greatly effect trial results. For example, in the ROCKET-AF trial, if the data are analysed when the patients were on treatment, there is a 21% reduction in the primary endpoint, which is statistically significant favouring rivaroxaban. However, if the entire time in the follow-up period is analysed, including time when patients were off treatment, there was a more modest 12% reduction with rivaroxaban and the results are no longer statistically significant.[29] Therefore keeping patients on anticoagulation therapy is critically important in a trial, as is also true of clinical practice.

Clinical trialists and regulatory authorities are placing increasing attention on the quantity of missing data in a clinical trial. One important component of missing data is reflected by the number of patients who withdraw consent to follow-up. The RE-LY and ROCKET-AF trials had rates of WD consent of 7.6% and 8.7% respectively, whereas in ARISTOTLE, only 1.1% of patients WD consent. This low rate of WD consent has set a new bench mark for trials in this area.

There were some concerns raised regarding an increased risk of stroke observed at the end of trials as patients transitioned off the study drug. The Food and Drug Administration has placed black box warnings in the prescribing information for rivaroxaban and apixaban, stating that these medications should not be stopped without a plan to continue anticoagulation. At the end of the ROCKET-AF trial, there was a three-fold increase in stroke in the next 30 days. It is thought that the most likely explanation was a longer time to reach a therapeutic level of warfarin in those patients who had been randomised to rivaroxaban during the randomised treatment period. Of the patients who had been randomised to warfarin, about two-thirds were in range at the end of the trial and these were largely protected from stroke during the subsequent 30-day period.[29,32] However, among those randomised to rivaroxaban, fewer than half achieved an INR of 2.0 or greater by 30 days after the end of the double-blind portion of the study.

A similar pattern of excess strokes in the 30-day 'transition period' was seen in the ARISTOTLE trial with apixaban. There were 21 patients who experienced stroke or systemic embolism between 1 and 30 days after the last dose of apixaban as compared with only 5 patients among

Table 4. ENGAGE AF-TIMI 48: Additional scientific investigations.

Name	Objective
Pharmacokinetics/ Pharmacodynamics in all patients	Characterise the relationship between exposure and response to edoxaban
Health economics/Quality of life	Cost-effectiveness of edoxaban therapy
Pharmacogenetics	Identify genetic polymorphisms that identify patients at higher risk for recurrent AF, thromboembolism and bleeding
Biomarker	Correlate concentrations of biomarkers of thrombosis, inflammation, necrosis and hemodynamic status with efficacy and safety
Continuous and static electrocardiography	Determine the varying risk associated with different burdens of AF
Echocardiography*	Improve risk stratification*, Determine if left atrial size predicts thromboembolic risk

AF: atrial fibrillation.
Ruff et al.[23]
**Gupta et al.*[34]

those who had been randomised to warfarin. Unlike ROCKET-AF, there was a brief period of overlap of approximately 36 hours of apixaban and open-label anticoagulant during the first 2 days of the transition. During these first 2 days only one patient in each group experienced a stroke or systemic embolism. Thereafter, there was no further overlap in therapy, and an excess of strokes was observed in those patients who had been randomised to apixaban compared with those randomised to warfarin.[33] These findings support the recent guidelines on antithrombotic treatment,[4-7] which recommend that anticoagulant therapy is overlapped until the warfarin or other VKA is within therapeutic range.

With this knowledge, the protocol for the ENGAGE AF-TIMI 48 study was modified to include an end-of-study transition, aiming to avoid an excess of strokes at the end of the trial. A detailed protocol amendment was instituted and the investigators and monitors underwent intensive training. First, all patients were required to transition to an open-label oral anticoagulant. Transition to antiplatelet monotherapy or to no antithrombotic therapy was not permitted because the patients had been receiving an anticoagulant for several years during the trial and at the start of the trial the patient and the investigator agreed that the patient required anticoagulant treatment. Therefore, unless there was an absolute contraindication to anticoagulant therapy, the logical extension is to continue anticoagulant treatment at the end of the trial. In the ENGAGE AF-TIMI 48 trial transition was permitted to a VKA or NOAC. If a patient was transitioning to an open-label VKA, an overlap of treatment with edoxaban plus the open-label VKA was required until the INR was at least 2.0. At least 3 INR tests were mandated in the first 2 weeks, as was the use of an approved VKA dosing algorithm to adjust the dose of the VKA.

In addition, built into the protocol were additional scientific investigations covering a variety of topics; not only the traditional pharmacokinetics and pharmacodynamics, but information on health economics, quality of life, pharmacogenetics, biomarkers, analyses of electrocardiograms,[25] and data on ECG[34] (Table 4).

It is anticipated that the ENGAGE AF-TIMI 48 trial will enhance current knowledge as it is the largest (21,105 patients) randomised controlled trial in AF with a NOAC performed to date, and has the longest median follow-up (median 2.8 years). Two QD dosing regimens (60 and 30 mg) were studied and this allows the evaluation of another QD dose NOAC compared with warfarin, as well as two very different levels of anticoagulation. The ENGAGE AF-TIMI 48 study is the first study that will assess continual dose adjustment (60↔30 mg; 30↔15 mg) even after randomisation, and will provide information on three doses spanning a four-fold range in dose. With the benefit of hindsight, intense efforts have been made to minimise missing data, to implement a careful transition on/off edoxaban/open label OACs, and to be cautious with the titration of warfarin, aiming to get patients into therapeutic range as quickly as possible. This trial should also add to the understanding of the science of the disease state by virtue of the ancillary studies on echocardiography, electrocardiograpy, and genetics of AF, as well as further our understanding of the pharmacology and mechanism of action of the factor Xa inhibitor edoxaban.

Hokusai-VTE – What it Adds to VTE Management

Prof Harry R. Büller

In December 2009, the first Phase III trial with NOACs in VTE was published and we now have Phase III data from four NOACs in a period of less than 4 years. Receiving, digesting and putting this amount of information into clinical practice is not going to be easy because the field is moving so quickly.

The first NOACs and VTE trials were Recover I and II;[35] these trials used a heparin lead-in. These were followed by two studies - the Einstein Deep vein thrombosis (DVT)/pulmonary embolism (PE)[36,37] and the Amplify[38] - without a heparin lead-in. These two studies started from day 0 with the NOAC. The latest study is Hokusai-VTE,[39] which has a heparin lead-in and three unique features. Firstly the heparin lead-in has been left in place because the impression from the previous studies was that if physicians could use heparin at the start of the trial they were much more willing to include the full spectrum of patients, including patients with large DVTs and large PEs. Therefore, LMWH was included in order to attract and obtain information on this subgroup of patients. The second feature of the Hokusai-VTE study is that the 60 mg dose was reduced to 30

mg actively, at randomisation or during the trial, in circumstances of low body weight, renal insufficiency or concomitant use of P-gp inhibitors. The third unique feature is that it is known that patients are treated for 3, 6 or 10 months; accordingly a priority of this study was to ensure all patients were followed-up for 12 months, regardless of the duration of treatment.

The Hokusai-VTE was a Phase III, randomised, parallel-group, multi-centre, multi-national study for the evaluation of efficacy and safety of (low molecular weight) heparin/edoxaban versus (low molecular weight) heparin/warfarin in subjects with symptomatic DVT and/or PE. The primary outcome was symptomatic recurrent VTE. The objective was to include at least 40% of patients with primary PE, and this was achieved. At baseline, two-thirds of the patients had experienced unprovoked VTE, and approximately one-fifth of the patients required dose reduction for low body weight, renal insufficiency or concomitant use of P-gp. It has been implied that the need for dose reduction is rare in this patient population; however, the large proportion of patients that required dose adjustment in this study suggest that it is not a rare occurrence. The study included patients with DVTs at various sites and PEs with different degrees of anatomical extent (Table 5) achieving the objective of including the full spectrum of severity.

The most proximal site at study entry was the femoral or iliac vein and occurred in approximately 40% of all patients; this is the only known study that has such a large proportion of patients in this group. One of the concerns with previous studies was that physicians and investigators were reluctant to include patients without initial heparin. In the Hokusai-VTE study, 47% of patients had quite extensive PE; one way to quantify the extent of PE is to assess N-terminal pro-brain natriuretic peptide (NT-proBNP), in this case with a 500 cut-off. This test indicates that patients with PE have right ventricular dysfunction, this was present in approximately one-third (28-29%) of patients in the PE subgroup of this study. Therefore, there was a sufficiently large group of patients in which to analyse the new treatment regimen of LMWH followed by a fixed dose of edoxaban (60 mg in most patients and 30 mg in the reduced group).

The efficacy outcome of the trial at 12 months showed that the first recurrence of VTE in the edoxaban group was 130 (3.2%) compared with 146 (3.5%) in the warfarin group, with a hazard ratio of 0.89 (95% confidence interval [CI]; 0.70-1.13), the upper margin for non-inferiority was pre-set at 1.5, this is because LMWH followed by vitamin K is associated with a 90% reduction. So the 1.5 that was pre-set really preserves 70% of that effect. The results show that the upper margin was 1.13, indicating that LMWH followed by a fixed dose of edoxaban is clearly non-inferior to the current standard treatment.

Table 5. Severity index of the Hokusai-VTE study.

	Edoxaban (n=4118)	Warfarin (n=4122)
DVT – no. (%)	2468 (60)	2453 (60)
Most proximal site – no. (%)		
Popliteal Vein	603 (24)	596 (24)
Superficial Femoral Vein	795 (32)	773 (32)
Femoral or Iliac Vein	1035 (42)	1049 (43)
PE – no. (%)	1650 (40)	1669 (40)
Anatomical extent – no. (%)		
Limited	128 (8)	123 (7)
Intermediate	679 (41)	682 (41)
Extensive	743 (45)	778 (47)
Concomitant DVT – no. (%)	410 (25)	404 (24)
NT pro-BNP ≥500 pg/ml – n/N (%)	454/1484 (28)	484/1505 (29)
Right Ventricular Dysfunction – n/N (%)	172/498 (35)	179/504 (36)

The efficacy outcomes during the on-treatment period of the study were 1.6% in the edoxaban group and 1.9% in the warfarin group with a hazard ratio that is comparable (<0.001 noninferiority). However, if patients stop treatment the disease comes back, the 1.6% in the edoxaban on-treatment period increases to 3.2% in the overall study period, and from 1.9% in the on-treatment period to 3.5% in the overall study period in the warfarin group. In the subgroup of severe PE, more than 480 patients entered the study with evidence of right ventricular dysfunction; there was a recurrence rate in the edoxaban group of 3.3% and 6.2% in the warfarin group. These results show that the regimen of LMWH followed by edoxaban is extremely effective in this subgroup of patients and is superior to LMWH/warfarin. This group of patients are haemodynamically stable and many physicians around the world would treat them with standard VKA treatment, which has been shown to have a much higher recurrence rate.

The TTR was 63.5% (Figure 2), which is a very encouraging result in the setting of venous thromboembolism.

A comparison of the anatomical extent of PE at baseline in the Einstein, Hokusai and Amplify studies shows that in the Einstein PE study, extensive PE was seen in approximately a quarter of the patients (25% in the NOAC treatment group and 24% in the standard treatment group). The Hokusai study had almost double the number of patients with extensive

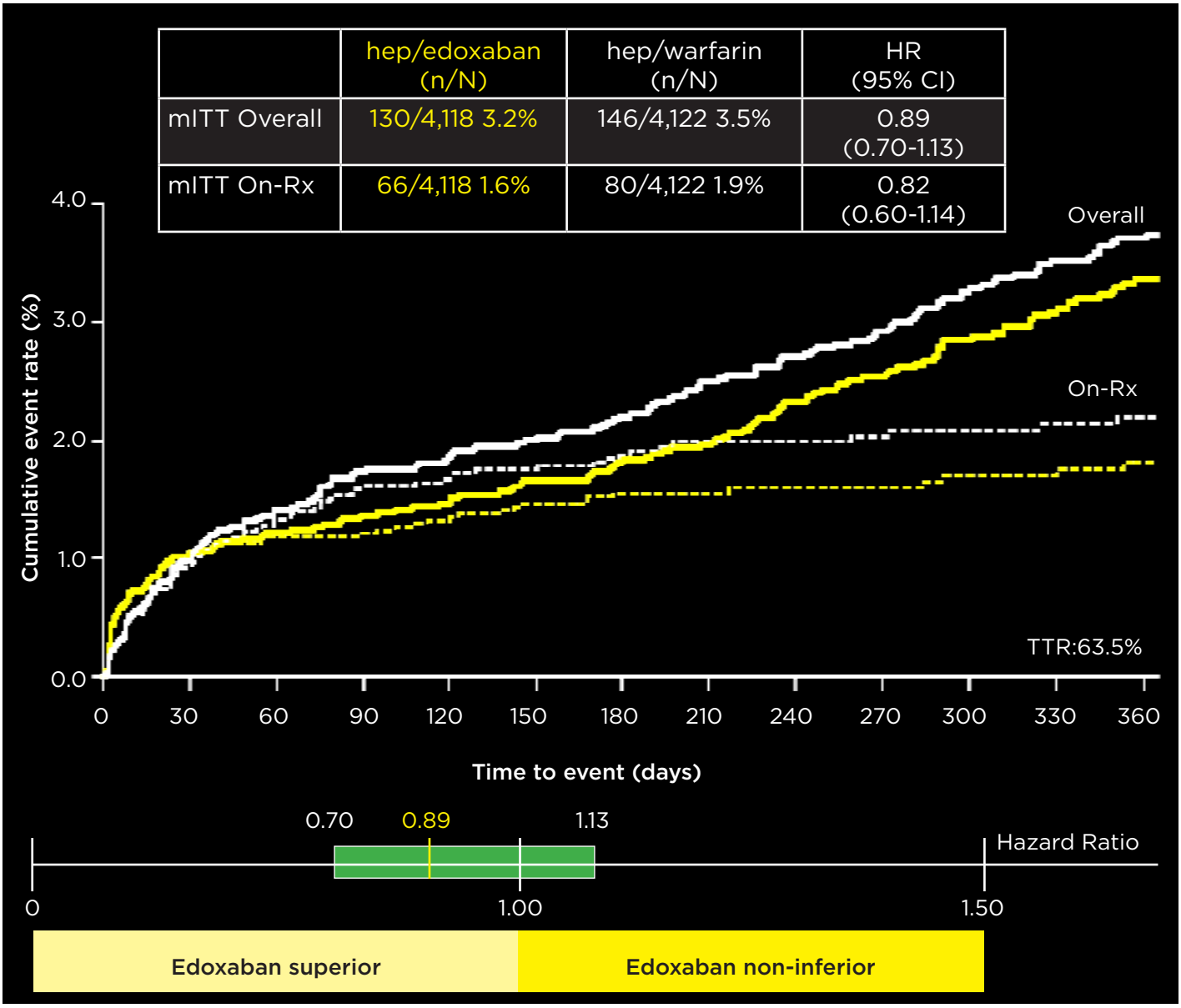

Figure 2. Hokusai-VTE study primary efficacy outcome.

disease (45% in the NOAC treatment group and 47% in the standard treatment group) compared with the Einstein study. The Amplify study used a different method to define extensive PE so is not comparable but similar to the findings in Einstein.

In the Hokusai study, NT-proBNP was assessed in all PE patients at baseline and in a random sample of 1,000 patients a qualifying spiral CT with a 4 chamber view was used; the results were assessed in an independent blinded review. The efficacy outcomes in the PE subgroup showed 2.8% in the experimental treatment group and 3.9% in the standard treatment group (hazard ratio 0.73 [95% CI] 0.50-1.61). In the Einstein study 2.1% of patients on experimental treatment had recurrence, compared with 1.8% on standard treatment (hazard ratio 1.12; [95% CI] 0.75-1.68). The Amplify study PE subgroup showed 2.3% in the experimental treatment group compared with 2.6% in the standard treatment group (relative risk 0.90 [95% CI] 0.50-1.61).

Right ventricular dysfunction was defined by NT-proBNP and spiral CT in the Hokusai study. When the data is analysed and compared with the NT-proBNP group and the diameters from spiral CT group the relative difference is minimal between the two methods when comparing the results of edoxaban versus standard treatment. In those with a NT-proBNP ≥500, the recurrence rate was 3.3% in the edoxaban group compared with 6.2% in the warfarin group (hazard ratio [95% CI] 0.52 [0.28 to 0.98]), and using spiral CT R/L diameter ≥0.9, these rates were 2.9% in the edoxaban group compared with 6.7% in the warfarin group (hazard ratio [95% CI] 0.42 [0.15-1.20]), showing that the overall results are similar regardless of the method used to assess right ventricular dysfunction.

In the Hokusai study, the results show that in recurrent VTE in subjects with severe PE (NT-proBNP ≥500), there is little difference between the edoxaban and warfarin arms during the period from day 0 to day 180, however, edoxaban significantly lowers the risk when compared with warfarin from day 180 onwards. These results should not be over interpreted but are useful because the question of right ventricular dysfunction has not been addressed in either the standard or the new treatments.

The Hokusai study aimed to show improved safety. The safety outcomes show that the first major, or clinically-relevant non-major, event following commencement of treatment was 8.5% in the edoxaban group compared with 10.3% in the warfarin group (hazard ratio [95% CI] 0.81 [0.71-0.94]p=0.004 for superiority).

The results for major bleeding events show a similar trend: 1.4% in the edoxaban group and 1.6% in the warfarin group (hazard ratio [95% CI] 0.84 [0.59-1.21] p=0.35 for superiority). However, there are types of bleeding that are associated with warfarin; e.g. fatal intracranial bleeding was seen in 6 patients (0.1%), compared with 0 in the edoxaban group, and fatal bleeding was seen in 10 patients (0.2%) in the warfarin group compared with 2 patients (<0.1%) in the edoxaban group. Non-fatal intracranial bleeding was seen in 12 patients (0.3%) in the warfarin group and 5 patients (0.1%) in the edoxaban group.

The results of relative efficacy/safety in the 30 mg dose subgroup (who had received a dose reduction for body weight <60 kg, CrCL 30-50 mL/min or receiving strong P-gp inhibitors) showed that in the edoxaban recipients, the first recurrent VTE rate was 3.0% compared with 4.2% in the warfarin group (hazard ratio [95% CI] 0.73 [0.42-1.26]). This shows that efficacy was maintained in the 30 mg subgroup. The reason for dose reduction was to lower the risk of bleeding, and the results showed that the clinically-relevant non-major or major bleeding rate was 7.9% in the edoxaban group compared with 12.8% in the warfarin group. This is an almost 40% reduction in bleeding in the edoxaban group, showing that bleeding is lower in patients treated with edoxaban when compared with standard treatment.

The Hokusai-VTE study adds to VTE management because there is convincing evidence that the efficacy is non-inferior to standard therapy. The heparin lead-in attracted more severe VTE patients, providing solid data for analysis and subsequent conclusions. In PE patients with right ventricular dysfunction the regimen of LMWH followed by edoxaban was superior to standard therapy. The dose reduction was shown to be beneficial and there was less bleeding seen in patients treated with edoxaban.

Panel Discussion

Question: What are the numbers needed to harm in both groups in terms of major bleeding?

Prof Harry R. Büller: You need to treat 55 patients in order to prevent one clinically relevant or major bleed.

Question: What about the results, how much are you going to put down to the heparin use?

Prof Harry R. Büller: I am going to be honest since I was involved in the Einstein and the Amplify studies. We looked at what had been done in the past and when designing the Hokusai-VTE we thought where can we improve, and one impression we had was that to leave out the heparin lead-in was quite acceptable but the general community was reluctant. I changed my mind; I thought based on the Einstein and on the Amplify that VKAs and the low molecular weights were on their way out. I think these data should make us reconsider. I still think VKAs are on their way out but for LMWH in a subset of patients we should really re-consider. At least in my mind this is what the study adds, and science is about changing your mind from time to time.

Question: What about the patients with right ventricular dysfunction, how much do they contribute to the overall result? Why did you do CT scans on all the patients and so on?

Prof Harry R. Büller: The CT scans analyses were done in a random sample of 1,000 patients; we are in the process of adding another 1,000. Blood sampling was easy because that was done in everybody. The reason to do it is because we wanted to have information in that particular subgroup. As you can see the current standard is to give LMWH and vitamin K antagonists and you end up with a recurrence rate of 6% over 12 months. I think the message here is that, for reasons we do not completely understand, Edoxaban is just more effective in this group and one hypothesis that I learnt from one of the suggestions Jeff Weitz made is that if you see that curve in the warfarin group, probably those are the patients that are very difficult to get into therapeutic range with warfarin. We are going to look into that in great detail. The kinetics and dynamics with Edoxaban has apparently, when you look at the data, an advantage.

Question: A few questions about the Edoxaban ENGAGE trial. With regard to the down-scaling or down-grading or reduction of dose in ENGAGE, you mentioned a few characteristics, but can you also down grade the dose or reduce the dose if patients have bleeding complications?

Prof Robert P. Giugliano: We did not do that in this trial protocol, though I agree that that would be a rational consideration for therapies in practice and it's not unlike what we do with many of our medications, but it wasn't permitted in the protocol.

Question: How did you define non-valvular AF in the ESC guidelines and specifically what about Grades II, III and IV micro regurgitations, is it valvular or non-valvular?

Prof Hein Heidbüchel: It is a recurring question; valvular AF is understood by the fact that AF is the incompetence in the prosthetic heart valve or haemodynamically severe valvular disease, which is mostly stenotic disease, mitral stenosis, or aortic stenosis relating to the regurgitation that is not usually considered as severe valvular disease. This is because there is some indication, although there is conflicting evidence, that thromboembolic risk may be even lower in those patients. Although you could say that if the valvular disease, even the mitral regurgitation by itself, is a predominant problem other than the AF that could also be included in lunar valvular damage.

Prof A. John Camm: I think that is very reasonable. I know that contributors to both the ESC guidelines and the American guidelines, which are currently under way, are reviewing the clinical trials to see how much mitral regurgitation was present in the major clinical trials comparing NOACs with warfarin and also looking at trials of warfarin against placebo and so on in order to try and define whether there are any characteristics of natural mitral regurgitation, I mean non-prosthetic valve mitral problems that would make it more favourably treated with a NOAC, and we just don't have the answer to that. On the other hand, I think most people, from a clinical perspective, regard mitral regurgitation as not a great differentiator between patients who have so-called valvular and non-valvular AF, in that it is more consequential than contributory to the diagnosis. Whereas, clearly with prosthetic valves, it is a completely separate requirement for anticoagulation, and the same is true rheumatic mitral stenosis. I think that is the position we find ourselves in now.

Question: My institution will restrict hospital use of NOACs to a single drug, which one should it be?

Prof Raffaele De Caterina: Of course to be politically correct I would not give one answer and I hope that physicians will never be confronted with the need for restriction because there are differential features that may impact the choice and I think it is very healthy to have a plethora of drugs rather than one.

Prof Jeffrey I. Weitz: With all the different NOACs it would be really wrong to switch them to the one that you have and then switch them back and forth; it is really problematic. So what we have done in our hospital is we have got them all on the formulary because we want to avoid that switching back and forth, which is going to lead to problems with both thrombolic events and bleeding events.

Prof A. John Camm: We have also argued very strongly with our drugs and therapeutics committee that, since we have received patients from all other jurisdictions, it would be ridiculous for us to have a restriction to a single drug because of that very problem, and I think that everyone should argue against restriction to a single drug because they do have specific pros and cons. If you want to practice as good personalised medicine as possible, you want to have a good choice between these NOACs.

Question: Were any patients treated with thrombolitics before being switched to edoxaban?

Prof Harry R. Büller: No, patients that qualified for thrombolitic therapy because of haemodynamic instability were excluded.

Question: This question refers to the ventricular dysfunction group, how do you interpret this; the fact that the sick patients were particularly well catered for in this trial?

Prof Harry R. Büller: At this point in time it's speculation, but the Kaplan Myer curve really suggests that in that subgroup, getting it right with LMWH and vitamin K is much more difficult than getting it right with LMWH and edoxaban.

Question: We have now seen a number of trials with new agents in VTE and these studies have emphasised DVT and PE. I think it is important to point out that we do not have data on patients for example who have upper extremity DVT, particularly upper extremity DVT in association with central venous catheters, whether they be hick lines or quarter caths, and we also don't have data on other forms of thrombosis, whether portal vein thrombosis or splenic vein thrombosis or cerebral vein thrombosis. So how far can we actually extrapolate from the data we have to other situations? What would your word of caution be at this point?

Prof Harry R. Büller: I think we can extrapolate maybe to some other sites of thrombosis, so a straight forward arm thrombosis that we now treat with LMWH and vitamin K antagonists may also be well treated with regimen. But on the whole I think it is much better to get data. Where I do think we do need data is in the cancer population at the present time. I have used LMWH in these ones and I think a head to head comparison of an oral drug like edoxaban with an initial LMWH over a couple of days, is of paramount importance because LMWH works but these are already sick patients and they have big problems. Superficial vein thrombosis is another area we would like to get more data and then the splenic and the other ones it would be fantastic but in those situations you have less trouble in extrapolating.

Prof Jeffrey I. Weitz: I just want to put in a word of caution about the upper extremity DVT in association with indwelling devices. As we have seen at this meeting, RE-LY trial showed that dabigatran was ineffective in patients with mechanical valves, and you have here a blood-contacting medical device that also incites the generation of high concentration of Factor Xa and thrombin, and I would be very cautious about the use of these single target agents in those patients until we have more data.

Question: How are you going to handle the analysis of the three dosing strategies in the ENGAGE trial?

Prof Robert P. Giugliano: The first analysis is the regimens as a strategy because that is the way that the trial was designed but then, in exploratory analyses, I think we might look at each of the three doses we want to look at all the patients who received 30 mg. The patients who were downwardly adjusted could be compared, so those who went from 60 to 30 mg could be compared with those that went from 30 to 15 mg, but obviously those who were downwardly adjusted as opposed to those who were not adjusted are very different patients because they will be on average younger, healthier, heavier, and have better renal function, so that kind of analysis is priceless.

Question: How are we going to treat older patients who are in their 80's into their 90's with AF, what is the advantage here for the NOACs versus warfarin?

Prof Harry R. Büller: One of the classical responses is I am not going to use it in older patients. Now we have very good data from the Einstein DVT and PE in those patients that are frail, either defined by body weight or aged above 75 or renal insufficiency; it is exactly in that group that you see the greatest advantages of safety. If you look in the Hokusai it is exactly the same trend albeit of course that in those ones of course the dose was reduced to 30 mg, but the same pattern is there. The classical reaction of 'these new drugs are not good for the elderly', I think is something we have to consider a mistake, probably it is that group that is going to be greatly benefitting from it, particularly in terms of safety.

REFERENCES

1. Heeringa J et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006;27:949-53.

2. Lloyd-Jones DM et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circ. 2004;110:1042-46.

3. Kirchhof P et al. Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options. Executive summary of the report from the 3rd AFNET/EHRA consensus conference. Thromb Haemost. 2011;106:1012-9.

4. Camm AJ et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369-429.

5. Camm AJ et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719-47.

6. Fuster V et al. 2011 ACC/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circ. 2011;123:e269-367.

7. Skanes AC et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol. 2012;28:125-36.

8. Kirchhof P et al. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society, and the Canadian Cardiovascular Society. Eur Heart J. 2013;34:1471-4.

9. Bo s et al. Implementing hospital guidelines improves warfarin use in non-valvular atrial fibrillation: a before-after study. BMC Pub H. 2007;7:203.

10. Zimetbaum P et al. Impact of a practice guideline for patients with atrial fibrillation on medical resource utilization and costs. Am J Cardiol. 2003;92:677-81.

11. Frykman V et al. Management of atrial fibrillation: discrepancy between guideline recommendations and actual practice exposes patients to risk for complications. Eur Heart J. 2001;22:1954-9.

12. The CHA2DS2VASc score is a refinement of CHADS2 score (a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic AF) and extends the latter by including additional common stroke risk factors.

13. The HAS-BLED score is a therapeutic bleeding risk stratification score for those on oral anticoagulants in AF.

14. Heidbüchel H et al. European heart rhythm association practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15:625-51.

15. http://clinicaltrials.gov/ct2/show/NCT00781391

16. Koretsune Y et al. Evaluation of edoxaban in patients with atrial fibrillation and severe renal impairment. ESC Congress

Abstract P529. Eur Heart J. 2013;34:S95.

17. Parasrampuria D et al. Safety, tolerability, and pharmacokinetics of edoxaban in end-stage renal disease subjects undergoing hemodialysis. ISTH Congress Abstract OC 79.1. Presented at ISTH Congress 2013, Amsterdam, The Netherlands, on Thursday 4th July 2013.

18. Crowther M, Portola Pharmaceutics. A Phase 2 Randomized, double-blind, placebo-controlled trial of PRT4445, a novel, universal antidote for direct and indirect Factor Xa inhibitors. New developments in treatment of venous thrombosis. ISTH Congress Abstract AS 20.1. Presented at the ISTH Congress 2013, Amsterdam, The Netherlands, on Tuesday 2nd July 2013.

19. http://clinicaltrials.gov/show/NCTO1826266

20. http://clinicaltrials.gov/show/NCT262600

21. http://clinicaltrials.gov/show/NCT00403767

22. http://clinicaltrials.gov/ct2/show/NCT00412984

23. Ruff CT et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J. 2010;160:635-41.

24. Dogliotti A et al. Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. Clin Cardiol. 2013;36:61-7.

25. Weitz Jl et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost. 2010;104:633-41.

26. Salazar DE et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. Thromb Haemost. 2012;107:925-36.

27. Wessler JD et al. The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol. 2013;61:2495-502.

28. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.

29. Patel MR et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91.

30. Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.

31. Grip LT et al. New oral antithrombotic strategies: 2013 update on atrial fibrillation. Hot Top Cardiol. 2013;31:7-18.

32. Piccini JP. Outcomes of discontinuing rivaroxban compared with warfarin in patients with nonvalvular atrial fibrillation: Analysis from the ROCKET AF trial. American Heart Association Emerging Science Series April 25, 2012 webinar. Abstract 114.

33. Piccini JP et al. Events after discontinuation of randomized treatment at the end of the ARISTOTLE trial. Eur Heart J. 2012;33(supplement 4045):685-6.

34. Gupta D et al. Cardiac structure and function and CHADS2 risk score in patients with atrial fibrillation: the effects anticoagulation with factor XA next generation in afthrombolysis in myocardial infarction 48 (ENGAGE AF – TIMI 48) echocardiographic study. J Am Coll Cardiol. 2013;61(10_S):doi:10.1016/S0735-1097(13)60964-X.

35. Schulman S et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl Med. 2009;361:2342-52.

36. http://clinicaltrials.gov/show/NCT00440193

37. http://clinicaltrials.gov/show/NCT00439777

38. Agnelli G et al. Oral Apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799-808.

39. http://clinicaltrials.gov/show/NCT00986154

PRACTICAL GUIDANCE FOR STROKE PREVENTION IN ATRIAL FIBRILLATION – INTERACTIVE CASE STUDIES

Summary of Presentations from the Boehringer Ingelheim Symposium, ESC Annual Congress 2013, Amsterdam, the Netherlands

Chairpersons

Gregory Y.H. Lip,[1] Michael Brainin[2]

Speakers

Jonas Oldgren,[3] Hans-Christoph Diener,[4] John Eikelboom[5]

1. Professor of Cardiovascular Medicine, University of Birmingham, UK
2. Head, Department of Clinical Neurosciences and Preventive Medicine, Danube-University Krems, Austria
3. Associate Professor of Cardiology, Uppsala University Hospital, Sweden
4. Professor of Neurology, University Hospital of Essen, Germany
5. Associate Professor of Medicine, McMaster University, Canada

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INTRODUCTION

This Boehringer Ingelheim sponsored satellite symposium was held on 2nd September 2013 as part of the ESC conference, which was hosted this year in Amsterdam, the Netherlands. In light of recent advances within the field of stroke prevention in atrial fibrillation (AF), the scientific programme contained an overview of the updated guidelines, with a subsequent focus on their everyday implementation, through interactive case studies in order to address some of the practical issues that have arisen.

The meeting was co-chaired by Professors Gregory Lip and Michael Brainin, who were supported by a distinguished faculty of Professor Jonas Oldgren, Professor Hans-Christoph Diener and Dr John Eikelboom.

Stroke Prevention in Atrial Fibrillation: From Guidelines to 'Real-World' Practice

Prof Gregory Y.H. Lip

Prof Lip began his presentation by highlighting the importance and risk of developing AF. It was stated that AF is the most commonly occurring cardiac rhythm disorder, and those aged over 40 years have a lifetime risk of 1 in 6, which increases to 1 in 4 in individuals who have suffered a heart attack or heart failure during their lifetime. The field of AF is of particular therapeutic interest owing to the burden it creates due to the increased risk of stroke.

The international normalised ratio (INR) range recommended for patients at risk of stroke was discussed. An INR of >3 leads to an increased risk of bleeding, whereas an INR of <2 leads to a risk of thromboembolism and stroke. It is therefore important to maintain a patient's INR between 2 and 3. The quality of anti-coagulant control is reflected by the time in therapeutic range (TTR), with a TTR of >70% regarded as ideal with respect to favourable stroke and mortality outcomes. Conversely, it has been demonstrated that when

TTR is <50%, these outcomes are in fact worse than in untreated patients thus highlighting the importance of optimal anti-coagulant control.[1] The use of warfarin and vitamin K antagonists is further limited for a variety of reasons, including lack of adherence due to an increased risk of bleeding, as well as the impact of required lifestyle changes, such as regular monitoring and diet modification. As a consequence, warfarin and vitamin K antagonists are associated with suboptimal treatment outcomes, which emphasised the need for the development of alternative and improved strategies.

As a result of this, it was noted that there have been significant changes, which culminated in a focused update to the ESC guidelines in August 2012. These changes reflect the advances within this field, such as the availability of new anti-coagulant therapies beyond warfarin, as well as improved management strategies involving patient risk stratification. An algorithm for the management of AF and assessment of risk of stroke was subsequently delineated. The first stage is to identify AF patients at low risk of stroke, namely those who have a CHA_2DS_2-VASc score of 0 or who are under 65 and have lone AF. These patients are not prescribed anti-coagulant therapy. Patients with a CHA_2DS_2-VASc score of ≥2 are recommended for anti-coagulation therapy and those with a score of 1 for oral therapy. The HAS-BLED score is then used to assess the risk of bleeding, and following this, specific anti-coagulants are chosen. The ESC guidelines state that novel oral anti-coagulants (NOACs) offer improved safety, efficacy and convenience compared to vitamin K antagonists; these NOACs include dabigatran, rivaroxaban and apixaban. Since some of these novel therapies have a degree of renal excretion, it is vital to monitor renal function in patients receiving NOACs.

The importance of adhering to guidelines was emphasised through the presentation of improved outcomes in clinical practice following guideline implementation. For example, in the RE-LY trial of warfarin and dabigatran, the use of EU label and ESC guideline-recommended dosages (110 mg and 150 mg) of dabigatran resulted in a reduction in the primary endpoints of stroke and systemic embolism.[2] The successful crossover of this treatment into everyday practice was demonstrated with an analysis of 5,000 patients in Denmark who, after receiving the same doses of dabigatran, had achieved similar results. In addition, reduced mortality, from factors such as myocardial infarction, was also observed when compared to the 9,000 patients receiving warfarin.[3]

Prof Lip concluded his presentation by reiterating that these are new drugs and thus have a lot of questions associated with them. The European Heart Rhythm Association (EHRA) practical guide on the use of NOACs in patients with AF, which also contains follow-up guidance, was therefore strongly recommended.

Initiating and Maintaining Optimal Anticoagulation: Practical Considerations

Prof Jonas Oldgren

Prof Oldgren began his presentation with a case study of a 72-year-old woman with AF, who was a previous smoker and had well-controlled hypertension. She was currently receiving warfarin treatment and wanted to discuss alternative anti-coagulation therapies since these require less monitoring. The audience were asked to state whether they would continue with warfarin or prescribe a new anti-coagulant; a third chose the former option while two-thirds preferred the latter. The range of anti-coagulants that could be considered for treatment was subsequently discussed.

Dabigatran, rivaroxaban and apixaban are three NOACs; the first targets thrombin, while the latter two target factor Xa. Compared to warfarin, the time for these drugs to reach peak concentration is fairly short, and the anti-coagulation effect is rapid onset. In addition, the half-life of these drugs is much shorter than warfarin. However, renal excretion for these drugs is higher, since, unlike warfarin, they are not metabolised.

These NOACs have been compared to warfarin in clinical trials.[4-7] With respect to the primary outcomes of these trials, all three are non-inferior to warfarin. Dabigatran 150 mg twice daily and apixaban 5 mg daily are superior to warfarin.[8] In terms of ischaemic stroke reduction, dabigatran is superior to warfarin whilst rivaroxaban and apixaban are non-inferior.[6,9,10] Each of the three NOACs have comparable safety profiles, with respect to major bleeding events, compared to

warfarin. It was highlighted that, from the results of the RE-LY[4,5] ROCKET[6] and ARISTOTLE[7] trials, the three NOACs demonstrated much improved safety profiles regarding intracranial bleeds, compared to warfarin.

The case of the 72-year-old woman was revisited and the audience were asked whether they would prescribe 110 mg or 150 mg dabigatran taking into consideration that she had normal kidney function and that her INR had dropped to 1.9 after cessation of warfarin treatment. Two-thirds of the audience chose the 150 mg dose, which was the speaker's preferred option since the patient's bleeding risk was low. The hypothetical situation of the patient subsequently developing an irregular heart rhythm, dyspnoea, as well as an elevated heart rate, requiring beta blocker medication and elective cardioversion was presented to the audience, they were then asked to vote whether they would continue dabigatran therapy or switch to warfarin until commencement of cardioversion therapy. Of the two options, 90% chose the former, which was discussed as safe, since the results of the RE-LY trial show that stroke rates were comparable in both dabigatran and warfarin-treated patients after cardioversion. A final question of whether to prescribe long-term dabigatran for this patient was posed to the audience; 93% correctly chose to continue her on anti-coagulation therapy since she had a CHA_2DS_2-VASc score of 3.

Prof Oldgren concluded that NOACs are the preferred option for stroke prevention in patients with AF according to the EHRA Practical Guide and 2012 ESC update,[11] and that patients switching from warfarin may start these drugs if their INR is <2. Available data suggest that elective cardioversion can be safely performed on patients treated with dabigatran.

Shielding the Brain from Ischaemic Stroke: Anticoagulant Strategies for Secondary Stroke Prevention

Prof Hans-Christoph Diener

Prof Diener started his presentation by discussing the effects of AF and stroke from his perspective as a neurologist dealing with prevention of secondary strokes. Due to various factors, 90% of patients admitted to Prof Diener's stroke unit are untreated, undertreated or mistreated for the prevention of secondary strokes. Only 10% of patients were reported to have received warfarin and achieved a recommended INR score of between 2 and 3. In the majority of cases patients are receiving aspirin, sub-optimal doses of warfarin, or no treatment at all, which highlights the major challenge of providing all patients with optimal treatment.

The case of a 70-year-old patient with AF, well-controlled hypertension and well-controlled diabetes, who received sub-optimal warfarin treatment and subsequently suffered a stroke, was described and the audience were asked to choose the best course of further anti-thrombotic therapy. Of the available options, 59% of the audience chose to administer 150 mg dabigatran, which was the correct option since the other options, such as continuing warfarin or switching to aspirin, would not be effective at raising the INR. The audience were subsequently asked how this therapy would be modified if the patient was 78 years old and had a creatinine clearance of 50 ml/min; 50% chose the correct option of prescribing 110 mg dabigatran.

Through presentation of a meta-analysis comparing the three NOACs to warfarin, it was stated that, for secondary stroke prevention, both doses of dabigatran are superior to warfarin.[12] Rivaroxaban was less effective in secondary compared to primary stroke prevention, although this was not statistically significant.[13] Apixaban was superior to warfarin in secondary stroke prevention.[14] Overall, across the three anti-coagulants; the risk reduction was 15% for secondary strokes, 56% for haemorrhagic strokes, and 14% for bleeding complications. In terms of absolute values, the risk reduction in stroke and systemic embolism was 0.7%, and 0.8% for major bleeds.[15]

Prof Diener summarised his presentation by reiterating that AF increases the risk of stroke with an associated 20% mortality rate and 50% permanent disability rate. A major problem with warfarin is intracerebral and intracranial bleeds, which have high mortality rates. This may be one of the main reasons for the high number of patients refusing to take the medication or receiving a sub-optimal dose. It was concluded that the NOACs, 150 mg dabigatran in particular, are superior to warfarin.

Optimising Periprocedural Protection with NOACs

Prof John Eikelboom

In his presentation, Prof Eikelboom discussed the importance of optimal management of patients undergoing procedures. It was stated that as many as 10% of patients every year have their anti-coagulation therapy interrupted in order to undergo a procedure. There is a well-established procedure for interrupting vitamin K antagonist treatment; anti-coagulation is stopped for 5 days, during which heparin is administered to patients deemed to be at a high risk of thromboembolic complications. NOACs have a shorter half-life and more rapid offset compared to warfarin, leaving the question of how they should be managed.

The audience were asked which factors should be considered before a surgical procedure on a patient receiving a NOAC; 90% voted that renal function, type of surgery and bleeding risk should be considered together, since renal function determines drug half-life, and bleeding risk is partly a function of the type of surgery.

The interventions that lead to an increased risk of bleeding were outlined; low-risk interventions included endoscopy with mucosal biopsy, prostate or bladder biopsy, electrophysiological study, angiography, and the insertion of a device. High-risk interventions included complex left-side ablation, spinal or epidural anaesthesia, surgery, liver or kidney biopsy, and transurethral prostate resection.

The timing of when to stop NOACs before interventions was addressed using a case study as an example. The patient in question had AF and was treated with 150 mg dabigatran twice daily. She required a colonoscopy with polypectomy, and the surgery was associated with a standard bleeding risk. She had a creatinine clearance rate of 90 ml/min. The audience were asked to select the appropriate time to stop dabigatran before surgery. From the possible options, 62% of the audience chose the preferred option of ceasing dabigatran 24 hours before surgery, since this is approximately two half-lives of the drug. In cases of reduced creatinine clearance rates, anti-coagulant administration should cease earlier, details are available in the EHRA guidelines.

It was noted that these recommendations on anti-coagulation cessation come from the RE-LY trial; where around 4,500 patients experienced an interruption in their treatment during a two-year period. The rates of thromboembolisms and bleeding in these patients in the 7 days prior to interruption and the 30 days after interruption were analysed. The rates of thromboembolic events for warfarin, 110 mg and 150 mg dabigatran were similar; although it was highlighted that warfarin had comparable bleeding rates to the two doses of dabigatran. In patients who underwent surgery within 24 hours of stopping, bleeding rates for warfarin were significantly higher than for dabigatran. It was further noted that dabigatran is also superior to warfarin in regards to bleeding rates in patients who require urgent interruption.[16]

Regarding the resumption of NOACs following an intervention, it was recommended to use the same principles as the resumption of warfarin; if immediate anti-coagulation is required NOACs can be started the next day, otherwise they can be started the second or third day after the procedure.

Prof Eikelboom concluded that due to their faster offset and shorter half-life, NOACs allow a shorter periprocedural interruption of anti-coagulation than warfarin. In the RE-LY trial, approximately one half of all patients who required an interruption in dabigatran had surgery within 48 hours of stopping; a much higher proportion than those on warfarin. Dabigatran has overall similar rates or perioperative bleeding and thrombotic complications to warfarin, but the former is more favourable for those who require urgent interruption.

This satellite symposium provided a platform for discussion on the updated guidelines as well as an opportunity for the esteemed faculty to present their translation into real-life practice. Following a stimulating and interactive session, there were several questions posed by the audience, which continued the theme of the use of these new treatments and associated guidelines in a real-world setting.

REFERENCES

1. Gallagher AM et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost. 2011;106:968–77.

2. Lip GYH et al. Guidance adherent dabigatran etexilate treatment versus warfarin in the RE-LY population: an analysis onthe basis of the European label recommendations for dabigatran etexilate Poster presented at ESC, August 31–September 4 2013, Amsterdam, the Netherlands. Poster P4278.

3. Larsen TB et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol. 2013;61:2264–73.

4. Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.

5. Connolly SJ et al. Newly identified events in the RE-LY trial. N Engl J Med. 2010;363:1875–6.

6. Patel MR et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.

7. Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.

8. De Caterina R et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. J Am Coll Cardiol. 2012;59:1413–25.

9. European Medicines Agency. Pradaxa Summary of Product Characteristics 2012.

10. Lopes RD et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet. 2012;380:1749–58.

11. Heidbuchel H et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J. 2013;34:2094–106.

12. Diener HC et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010;9:1157–63.

13. Hankey GJ et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012;11:315–22.

14. Easton JD et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012;11:503–11.

15. Ntaios G et al. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke. 2012;43:3298–304.

16. Healey JS et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation. 2012;126:343–8.

Disclosure

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MANAGING THROMBOEMBOLIC RISKS OF ATRIAL FIBRILLATION: CAN WE AFFORD INCREASED EFFICACY OF THE NOVEL ANTICOAGULANTS AND DEVICES?

Bela Merkely,[1] Eszter M. Vegh,[2] Attila Roka[2]

1. Director, Heart Center, Semmelweis University, Budapest, Hungary
2. Massachusetts General Hospital, Boston, MA, United States

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ABSTRACT

Ischaemic/embolic complications are the most common severe consequences of atrial fibrillation. Although chronic anticoagulation with warfarin has been available for decades, it was consistently shown to be underutilised; multiple drug interactions and dietary issues further complicate its use. Recently, several pharmacological and non-pharmacological alternatives have been shown to have an efficacy that is similar or slightly superior to warfarin. Novel anticoagulant agents (dabigatran, rivaroxaban, apixaban) have the advantage of a fixed dose, without the need of regular monitoring. Non-pharmacological options include left atrial appendage ligation or percutaneous closure. Although all these options are more expensive than warfarin, they have the potential of being more cost-effective – preventing very expensive complications or having less side-effects (such as haemorrhagic stroke), requiring less or no monitoring, and having fewer interactions with diet, thus, improving quality of life. Multiple studies of simulated cost-efficacy analyses have been published recently, addressing these questions, which will be reviewed in this paper. In the era of cost-conscious utilisation of healthcare resources, these new treatment options may increase the number of patients benefitting from effective therapies, reducing the number of ischaemic complications of atrial fibrillation.

Keywords: Atrial fibrillation, new oral anticoagulants, non-pharmacological treatment, cost efficiency.

THROMBOEMBOLIC RISK MANAGEMENT IN ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting around 2.7 million people in the United States.[1] By 2050, this number will exceed 12 million in the United States alone. Despite advances in rhythm control strategies over the last decade, the majority of these patients today still live with either recurrent or chronic AF.

The main goal of therapy is to decrease the risk of complications arising from AF. On average, patients with AF have a mortality which is approximately double the age-appropriate population without AF. The risk for ischaemic stroke is increased 4 to 5-fold, however, the actual risk varies approximately 20-fold in the AF group. Various scoring methods have been developed for risk stratification, including $CHADS_2$ and CHA_2DS_2-VASc. For decades, the cornerstone of treatment was the vitamin K antagonist, warfarin (and a few of its derivatives in select countries). Primary prevention studies showed a consistent benefit trend of warfarin compared to placebo, revealing a relative risk reduction of 68%, a reduction in annual stroke rate from 4.5% to 1.4%, and 31 ischaemic strokes prevented each year for every 1,000 patients treated.[2] Warfarin was superior to antiplatelet agents in multiple controlled studies. However, warfarin is a difficult medication to take long-term, due to the need of regular monitoring (INR measurement), which adds to the cost of utilisation and impairs the patient's lifestyle. Less than 60% of patients have an INR that is consistently within the therapeutic

range – this was demonstrated in multiple clinical trials and did not change much overall, despite significant efforts to mitigate responsible factors (improving compliance, point-of-care INR checking and testing for genetic variability).[3]

NEW ORAL ANTICOAGULANT AGENTS

Dabigatran is a direct, competitive inhibitor of thrombin. It is administered in a prodrug form, which is promptly metabolised. It can be administered at a fixed dose and does not require coagulation monitoring. Pharmacokinetics are affected by renal function, as 80% is excreted renally. While it is not metabolised by the cytochrome P450 system, several drug interactions exist with p-glycoprotein inhibitors (dronedarone, amiodarone, verapamil, quinidine and ketoconazole increase dabigatran concentration). Dabigatran was evaluated in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, which compared open-label warfarin with two fixed doses of dabigatran (110 or 150 mg twice daily, D110 and D150) in patients with AF and at least one additional stroke risk factor. For the primary outcome of stroke or systemic embolism, both D110 and D150 were non-inferior to warfarin (1.53%, 1.11% and 1.69% per year, respectively). The risk of haemorrhagic stroke was lower with both D110 and D150, compared to warfarin. A difference in overall survival did not attain statistical significance between the three groups; however, there was a trend towards the superiority of D150. The rate of gastrointestinal bleeding was higher with D150 (1.15%/year) than with D110 (1.12%) or warfarin (1.02%). Life-threatening bleeding was lower in the D150 (1.45%) and D110 groups (1.22%), compared to warfarin (1.80%) respectively. A similar trend was seen with intracranial bleeds. Rates of early drug discontinuation was higher with dabigatran (16% vs. 10% warfarin at 1 year), mostly due to dyspepsia.[4] The incidence of myocardial infarction was higher with D150 than with warfarin (relative risk increased by 33%) in a large meta-analysis of dabigatran trials.[5]

Rivaroxaban is a direct factor Xa inhibitor, which is metabolised by the CYP3A4 system. The ROCKET AF trial showed non-inferiority to warfarin in 14,264 patients with non-valvular AF who were at moderate to high risk of stroke (mean $CHADS_2$ score 3.5). 55% of patients had ischaemic events prior to enrolment. The primary endpoint was composite ischaemic/haemorrhagic stroke and systemic embolism (1.7%/year with rivaroxaban, 2.2%/year with warfarin, $p<0.001$ for non-inferiority). Lower rates of intracranial haemorrhage and fatal bleeding occurred in the rivaroxaban group than in the warfarin group, however, there was no difference in the composite major bleeding rate.[6]

Apixaban is also a direct and factor Xa inhibitor, which is metabolised by the CYP3A4 system. The half-life is shorter than rivaroxaban's (8-15 hours), requiring twice daily administration. The ARISTOTLE trial compared apixaban to warfarin for the prevention of stroke (ischaemic or haemorrhagic) or systemic embolisation among patients with AF and at least one additional risk factor for stroke. It achieved superiority regarding the primary endpoint (stroke or systemic embolisation, 1.27% for apixaban versus 1.6% for warfarin at 1.8 years). Main reduction ways observed in the rate of haemorrhagic strokes, while ischaemic or uncertain strokes were affected less. The study also showed a mortality benefit with apixaban (3.52% versus 3.94%).[7] So far there have been no large randomised, prospective studies completed comparing the new agents against each other.

COST-EFFECTIVENESS

The most common serious complications from AF itself or its management (ischaemic stroke, major bleeding) are expensive to treat, and even with optimal treatment may impair the quality of life. A new drug may be superior to an older one in several respects: it may be more effective in the treatment of the targeted condition, may have less side-effects or require less monitoring, etc. The new oral anticoagulant agents have at least the efficacy of warfarin in stroke prevention, with a simpler dose administration and no need for regular monitoring. Most of these factors can be accounted for and included in cost-efficacy analyses. For new treatments, a way to summarise these events is to calculate the incremental cost-effectiveness ratio (ICER) - the cost of an additional quality-adjusted life-year (QALY) over the old medication. This method integrates the cost of the treatment with the drug, differences in therapeutic efficacy (mortality and morbidy from the disease and its complications), side-effect profile (risk of bleeding issues), and other factors (such as cost of monitoring).

Most data regarding cost-efficiency of the new oral anticoagulant agents (NOACs) are from

models simulating drug use in patients with event rates and drug effects calculated from the large randomised studies. Several factors affect the results of such calculations: characteristics of the typicial patient profile (age, comorbidities), geographical setting (price of medications, costs regarding INR monitoring, travel), time horizon of simulated follow-up (may be required for up to 40 years after initiation of treatment), and the presumed event rates and their distribution. Most commonly, a Markov cohort model is generated to run the calculations on a large number of simulated patients.

Recently, several studies have been published regarding the NOACs. Most data are available for dabigatran and implies that it is a cost-effective alternative to warfarin.[8-19] Both rivaroxaban[18-20] and apixaban[19,21,22] have a smaller number of completed studies so far, however, the results are similarly encouraging. Comparison of the results from these simulated cost-effectiveness studies is often not straightforward due to the differences in models used, currencies used in the calculations, characteristics of simulated patients enrolled, and geographical settings (Figure 1). Overall, the cost for each QALY gained was less than $50,000 (USD) in the majority of these studies for the NOACs versus warfarin, which is the presumed threshold for willingness-to-pay in most simulation settings.

As this patient population is not homogenous, regarding the risk of thromboembolic complications, the cost-effectiveness should be stratified accordingly. Three studies reported models stratified by $CHADS_2$ score. In two simulations, higher $CHADS_2$ score resulted in more projected cost and those patients benefitted less from the NOAC therapy.[19,20] However Lee et al.[20] found rivaroxaban was cost-effective in the full range of patients. In a study of apixaban, two-way analysis for various baseline risks of stroke and ICH was performed. Apixaban was described as cost-effective in a wide range of those risk factors, and became more beneficial in higher $CHADS_2$ score values.[21] A Canadian comparative analysis with apixaban, rivaroxaban, warfarin, and two doses of dabigatran, showed that dabigatran 150 mg dominated (more QALYs, less cost) over

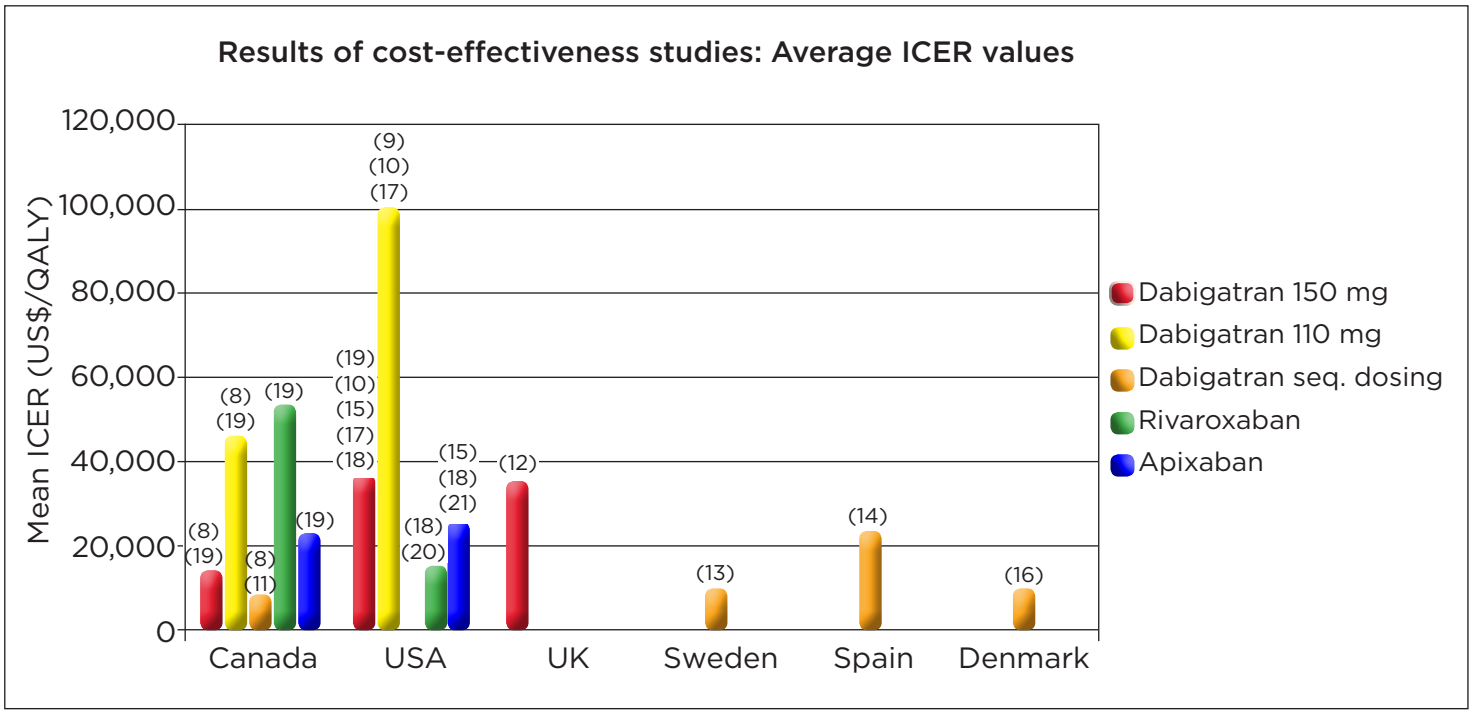

Figure 1. Cost-effectiveness of dabigatran, rivaroxaban and apixaban in studies simulated in various healthcare systems (versus warfarin).

The incremental cost-effectiveness ratio (ICER) is favourable; less than $50,000 (USD) for each quality-adjusted life year (QALY) increment for each medication in all healthcare systems. Dabigatran with sequential dosing (150 mg bid for patients <80 years, 110 mg bid for patients ≥80 years) was found to be highly cost efficient $25,000 (USD) or less per QALY increment).

most other agents, independent of the $CHADS_2$ score.[19]

Non-pharmacological prevention of stroke

Numerous novel devices and procedures are in various stages of clinical testing, aiming to prevent AF-related stroke on a non-pharmacological basis, by excluding the left atrial appendage from the circulation. Epicardial suture ligation (capturing the orifice with a snare and suturing it) does not leave any permanent endocardial implants.[23-25] Closing devices could be implanted with a catheter-based, transseptal approach under fluoroscopic and transoesophageal echocardiography (TOE) guidance, placing a self-expanding metal-frame covering the orifice of left atrial appendage.[26,27] The Watchman® Left Atrial Appendage (LAA) Closure Technology system (Atritech, Inc., Plymouth, MN) was compared to continuous oral anticoagulation with warfarin in the PROTECT AF prospective, unblinded, randomised trial: 707 patients with at least one risk factor (age >75 years, hypertension, heart failure, diabetes, or prior stroke/TIA) were enrolled and followed-up for a mean 2.3 years. The Watchman® device was non-inferior to warfarin (3.0% versus 4.3% per 100 patient-years for the primary endpoint: composite of stroke, systemic embolism and cardiovascular death). Safety events (pericardial tamponade, procedure-related stroke) were specific to the procedure itself, thus they were mostly observed in the device group;[28] however, the improvement of the quality of life was higher in this group at 12 months: the physical score improved in 34.9%, unchanged in 29.9% of the device treated patients, while 24.7% improved and 31.7% were unchanged in the warfarin group.[29] Single and multicentre studies confirmed the safety of the Amplatzer® Cardiac Plug (St. Jude Medical Inc, St. Paul, MN, USA).[27,30,31] In comparision to the Watchman device, implantation of the Amplatzer® device seems to have similar procedural time and complication rate.[32] The new Lifetech LAmbre™ Device was recently announced, that has a thinner sheath (8-10 French) for easier access and the ability to be recaptured and repositioned (Lifetech Scientific Corp., Shenzhen, China).[33]

Due to the relatively low number of overall procedures performed and a learning curve, which is steeper for devices than for new medications, cost-efficiency for non-pharmacological options may be significantly affected by these facts alone. Review of data will be required once more clinical experience is gained, allowing a more robust estimate of complications, which could be used to develop reliable models to estimate cost-efficacy (similarly to the NOACs).

CONCLUSION

The new oral anticoagulant agents have been shown to be cost-effective in a wide range of healthcare systems in simulated models. Given the significant expense of the management of atrial fibrillation and its complications, their use should be encouraged. The first feasibility and safety experiences with non-pharmacological treatments are promising, the Watchman® device was proven to be non-inferior to warfarin in the prevention of stroke. Further prospective studies, comparing the efficacy of the new agents against each other, may identify subsets of patients where one of the new agents or a non-pharmacological option may be more advantageous. Periodic review of registry data, may reveal specific issues or additional benefits that may affect the cost-effective utilisaton of these new treatment options.

Table 1. Treatment options for long-term prevention of stroke in non-valvular atrial fibrillation.

Pharmacological	Non-pharmacological
Warfarin	Epicardial suture ligation of atrial appendage
Dabigatran	Watchman® system
Rivaroxaban	Amplatzer® Cardiac Plug
Apixaban	Lifetech LAmbre™ device
ASA	

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127:e6-245.
2. Furie KL, Goldstein LB, Albers GW, Khatri P, Neyens R, Turakhia MP, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:3442-53.
3. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008;118:2029-37.
4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
5. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012;172:397-402.
6. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91.
7. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.
8. Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thromb Haemost. 2011;105:908-19.
9. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med. 2011;154:1-11.
10. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation. 2011;123:2562-70.
11. Kansal AR, Sorensen SV, Gani R, Robinson P, Pan F, Plumb JM, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart. 2012;98:573-8.
12. Pink J, Lane S, Pirmohamed M, Hughes DA. Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses. BMJ. 2011;343:d6333.
13. Davidson T, Husberg M, Janzon M, Oldgren J, Levin LA. Cost-effectiveness of dabigatran compared with warfarin for patients with atrial fibrillation in Sweden. Eur Heart J. 2013;34:177-83.
14. González-Juanatey JR, Álvarez-Sabin J, Lobos JM, Martínez-Rubio A, Reverter JC, Oyagüez I, et al. Cost-effectiveness of dabigatran for stroke prevention in non-valvular atrial fibrillation in Spain. Rev Esp Cardiol (Engl Ed). 2012;65:901-10.
15. Kamel H, Johnston SC, Easton JD, Kim AS. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke. 2012;43:881-3.
16. Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-valvular atrial fibrillation. Applying RE-LY to clinical practice in Denmark. J Med Econ. 2012;15:695-703.
17. You JH, Tsui KK, Wong RS, Cheng G. Cost-effectiveness of dabigatran versus genotype-guided management of warfarin therapy for stroke prevention in patients with atrial fibrillation. PLoS One. 2012;7:e39640.
18. Harrington AR, Armstrong EP, Nolan PEJ, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke. 2013;44:1676-81.
19. Coyle D, Coyle K, Cameron C, Lee K, Kelly S, Steiner S, et al. Cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. Value Health. 2013;16:498-506.
20. Lee S, Anglade MW, Pham D, Pisacane R, Kluger J, Coleman CI. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. Am J Cardiol. 2012;110:845-51.
21. Lee S, Anglade MW, Meng J, Hagstrom K, Kluger J, Coleman CI. Cost-effectiveness of apixaban compared with aspirin for stroke prevention in atrial fibrillation among patients unsuitable for warfarin. Circ Cardiovasc Qual Outcomes. 2012;5:472-9.
22. Kamel H, Easton JD, Johnston SC, Kim AS. Cost-effectiveness of apixaban vs warfarin for secondary stroke prevention in atrial fibrillation. Neurology. 2012;79:1428-34.
23. Singh SM, Dukkipati SR, d'Avila A, Doshi SK, Reddy VY. Percutaneous left atrial appendage closure with an epicardial suture ligation approach: a prospective randomized pre-clinical feasibility study. Heart Rhythm. 2010;7:370-6.
24. Bruce CJ, Stanton CM, Asirvatham SJ, Danielsen AJ, Johnson SB, Packer DL, et al. Percutaneous epicardial left atrial appendage closure: intermediate-term results. J Cardiovasc Electrophysiol. 2011;22:64-70.
25. Bartus K, Bednarek J, Myc J, Kapelak B, Sadowski J, Lelakowski J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. Heart Rhythm. 2011;8:188-93.
26. Park JW, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv. 2011;77:700-6.
27. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2007;49:1490-5.
28. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation. 2013;127:720-9.
29. Alli O, Doshi S, Kar S, Reddy V, Sievert H, Mullin C, et al. Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2013;61:1790-8.
30. Meerkin D, Butnaru A, Dratva D, Bertrand OF, Tzivoni D. Early safety of the Amplatzer Cardiac Plug for left atrial appendage occlusion. Int J Cardiol. 2013;doi:10.1016/j.ijcard.2013.06.062.
31. Urena M, Rodes-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol. 2013;62(2):96-102.
32. Chun KJ, Bordignon S, Urban V, et al. Left atrial appendage closure followed by 6 weeks of antithrombotic therapy: A prospective single-center experience. Heart Rhythm. 2013;doi:10.1016/j.hrthm.2013.08.025.
33. Lam YY. A new left atrial appendage occluder (Lifetech LAmbre Device) for stroke prevention in atrial fibrillation. Cardiovasc. Revasc Med. 2013;14(3):134-6.

ATRIAL FIBRILLATION IN CHILDHOOD WITH FAMILIAL HYPERTHYROIDISM IN AFRO-CARIBBEANS

Sandra Williams-Phillips

Consultant Paediatric, Adolescent and Adult Congenital Cardiologist, Andrews Memorial Hospital, Jamaica

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ABSTRACT

Atrial fibrillation (AF) associated with familial hyperthyroidism (FH) spanning three generations concomitantly, is rare. The index case was 10 years old when he started having AF secondary to hyperthyroidism, and is the youngest case documented. His mother was diagnosed at 31 years of age, 8 years after giving birth to him; and his maternal grandmother was diagnosed with the same goitre problem, hyperthyriodism, and palpitations at 49 years of age. The index case also has a restrictive perimembranous ventricular septal defect, which makes it a clinically challenging and more interesting case.

Keywords: Atrial fibrillation, hyperthyroidism, goitre, ventricular septal defect, gene.

INTRODUCTION

In 1936, Orgain and Wolf et al.[1] first recorded a familial incidence of atrial fibrillation (AF) and hyperthyroidism after the onset of atrial fibrillation in a patient with a normal heart. Brugada et al.[2] (1997) and Chen et al.[3] (2003) identified Spanish families and Chinese families with atrial fibrillation with a common autosomal dominant chromosomal link on 10q22-24 and 11p15.5 respectively.

The incidence of AF is rare in childhood, and even more so when concomitant hyperthyroidism occurs, as seen in the index case.[4] Sick Kids Hospital in 1977 noted 35 cases of AF in 22 years. There have also been documented cases of AF in foetuses.[4,5]

AF can present as, or be the presenting feature with palpitations, syncope, dizziness, fainting, shortness of breath, dyspnoea, chest pain, angina, lethargy, cerebrovascular accident (i.e. stroke), or as myocardial infarction. AF can also present with overt or subclinical hyperthyroidism, valvular heart disease of congenital or rheumatic origin, hypertension, biventricular heart failure, dilated cardiomyopathy, atrial tumours, Thyrotropin (TSH)-secreting pituitary adenoma, carney syndrome and use of specific thyrotoxic drugs like amiodarone, electrolyte disturbance, and carnitine deficiency.[1-22]

Drugs associated with AF are highly caffeinated beverages, alcohol, steroids, marijuana and illicit drugs.[6-15]

'Maladie de Roger' perimembranous ventricular septal defects (VSD), have no statistically significant aetiology of AF which the index case has.[16]

CASE REPORT

An Afro-Caribbean 10-year-old male presented with goitre (Figure 1), intermittent palpitations, diaphoresis, increased appetite, weight loss, intermittent hand and eyelid tremors, feeling warm, and mood changes for 3 months prior to being seen. There was a complete cessation of symptoms when a course of beta-blocker propranolol and anti-thyroid drug NeoMercazole was started. 2 years later, at 12 years of age, there was a continuation of propranolol but an inadvertent reduction of anti-thyroid NeoMercazole given, from 25 mg three times daily to 10 mg three times daily. Palpitations started on the third day of reduced dosage of the anti-thyroid medication, with complete resolution when the appropriate dosage was recommenced.

The index case was diagnosed at 6 months of age with a small restrictive perimembranous VSD, now partially closed with tricuspid valve tissue as

well as mild pulmonary valve stenosis. At 2 years of age he was diagnosed with autism and mild developmental delay.

He is the second of four children for his mother. All the other siblings, two boys and one girl, aged 14 years, 6 years and 3 months old, born before and after the mother was diagnosed with hyperthyroidism, are normal.

The index case's mother was diagnosed with hyperthyroidism presenting with goitre (Figure 2) and the first palpitations in the family at 31 years of age, when the index case was 8 years old. She is controlled completely on the same beta-blocker and anti-thyroid medication. The maternal grandmother of the index case was diagnosed at 49 years of age, a few months before the index case, with a goitre (Figure 3) and palpitations at a peripheral hospital, and is also controlled with the same medications. There are currently no clinical signs of ophthalmopathy in any of the hyperthyroid family members. There is no other family member with congenital heart disease or electrophysiological disorder, except the index case. There was no history of any medical or illicit drug usage in any family member, except those prescribed.

On examination, at 12 years of age, the index case's weight was 36.8 kg and height was 154 cm. Cardiovascular examination revealed a normal pulse volume and no collapsing pulse. His apex beat was in the fifth left intercostal space in the midclavicular line, thrusting in character. A pansystolic murmur, grade 4/6, was noted at the mid left sternal border. There were no signs of heart failure or pulmonary hypertension.

Investigations before recommencing the appropriate dose of anti-thyroid medication revealed increased levels of free T4 82.5 pmol/L (normal 10.3-26.0) and free T3 17.0 pg/mL (normal 1.4-4.2), and low level thyroid stimulating hormone 0.1 ulU/mL (normal 0.39-6.82). The erythrocyte sedimentation rate was 2. The only abnormality on the resting electrocardiogram was a heart rate of 104/minute.

A Holter monitor showed sinus tachycardia with a maximum heart rate of 192 bpm. There were intermittent episodes of AF (Figure 4) with 20% supraventricular ectopy. There were four isolated premature ventricular ectopic beats of no clinical significance.

Transthoracic echocardigraphy showed a restrictive perimembranous VSD partially closed by tricuspid valve tissue. The maximal velocity of the left to right shunt across the VSD was 5.39 m/s. There was mild pulmonary valve stenosis of 1.79 m/s. There were normal ventricular function, right ventricular pressure and pulmonary artery pressure.

Thyroid ultrasound showed a diffusely enlarged, hypoechoic, hypervascular gland. The right lobe measured 28 mls, left lobe 23 mls and isthmus had an anterior-posterior diameter of 1.5 cms. No discrete nodule or cervical lymphadenopathy was noted.

Fig. 1 **Fig. 2** **Fig. 3**

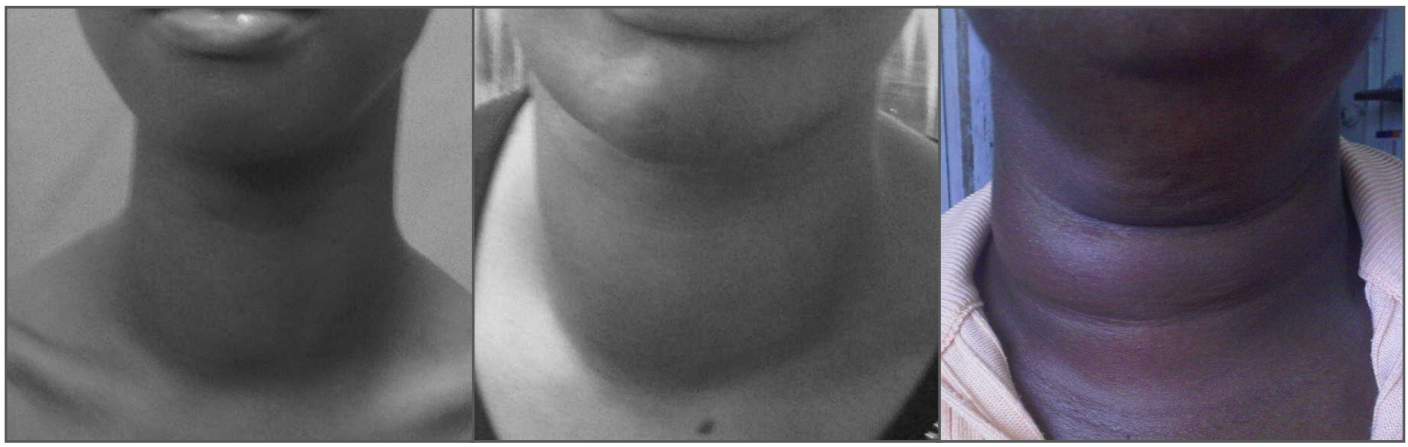

Figure 1. Goiter 12-year-old male patient.
Figure 2. Goiter 34-year-old mother of patient.
Figure 3. Goiter 49-year-old maternal grandmother.

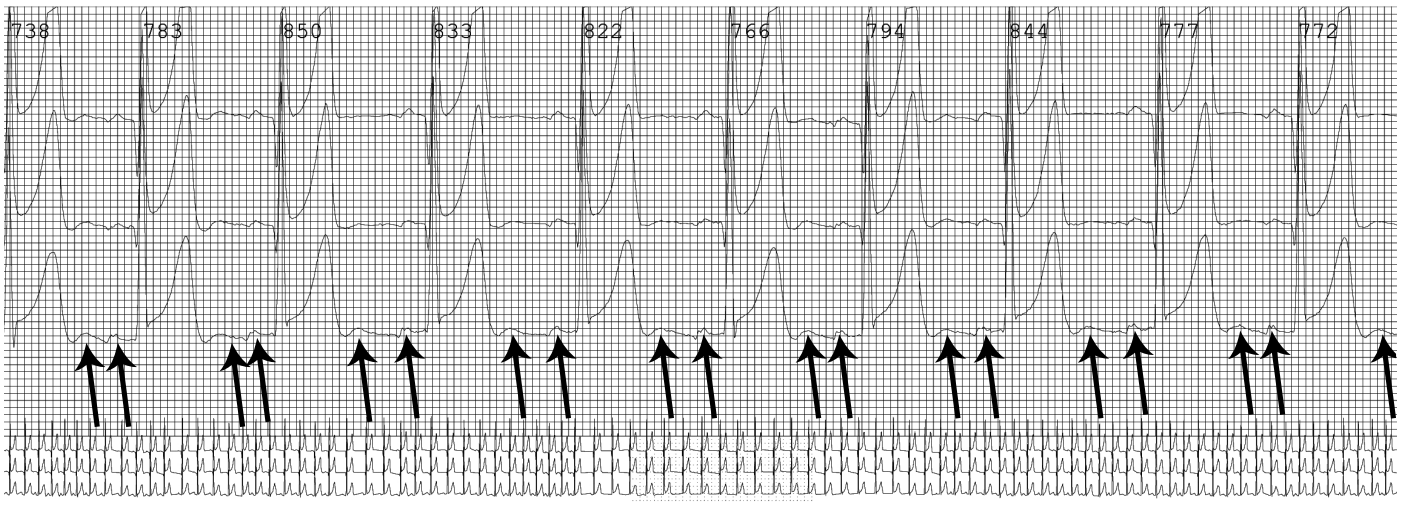

Figure 4. Holter monitor reading with intermittent episodes of atrial fibrillation with 20% supraventricular ectopy.

DISCUSSION

The incidence of AF in hyperthyroidism is between 10% to 54.7%, noted by Traube et al.[6] Bielecka-Dabrowa et al.[9] and Donatelli et al.,[7] as compared to 4% of the population. Takasugi et al.[17] and Perry et al.[18] documented the youngest cases of AF associated with hyperthyroidism at 14 years of age.

The effect of hyperthyroid states on the heart predisposing it to AF has been documented to be at various levels by varied researchers, and can be genetic and non-genetic (i.e. mechanical) via dilatation of the atria.[19] Chen et al.[20] proved that thyroid hormones have been shown to cause electrophysiological changes in the pulmonary vein cardiomyocytes. Bielecka-Dabrowa et al.[9] noted a chronotropic, dromotropic effect in the development of AF, ultimately postulating that it leads to an increased heart rate, multiple ectopic foci and, shortening of the refractory period, leading to re-entry phenomenon.[6,15,19]

Thyroid hormones have an effect on the calcium-activated ATPase and phospholamban, leading to an increase in myocardial contraction. New advances have indicated that the genome alteration affects the ionic transfer of potassium, and the calcium channel is affected in cases of hyperthyroid atrial myocytes. Activation of the renin angiotensin system, peripheral vasodilatation by triiodothyronine, and metabolic increases, leads to an increased cardiac output.[6,9,15,19] There have been documented abnormalities in the fibrinogen levels (factor VIII and factor X) with decrease in partial thromboplastin time and increased fibrinogen levels, suggesting susceptibility to thromboembolic phenomenon, in hyperthyroidism. There are documented cases of AF in children who have had a stroke and pulmonary embolism.[6,9,23-25]

For the past 180 years, the medical literature has been replete with documented genes e.g. LMNA and SCNRA, and chromosomes, which can be autosomal dominant e.g. 10q22-24, and autosomal recessive e.g. 5p13, and ways that hyperthyroid states may affect the heart. These data point to multifactorial reasons, indicating the need for more chromosomal and genetic studies, especially in patients who are familial, to further elucidate the specific reasons which will facilitate optimum management and treatment.[2-4,6,9,15,19]

The phenotypic presentation of the index case's family members supports an autosomal dominant gene with variable expression.[1-5] A genetic study of this Afro-Caribbean family would be groundbreaking.

This case report identifies an index family who have made history with the onset of AF secondary to FH at 10 years of age, the youngest case documented, and the concomitant occurrence in three generations of an Afro-Caribbean family, which has also never been documented before, in the English medical literature.

One consistent finding is that a return to an euthyroid state leads to cessation of AF associated with hyperthyroidism, as demonstrated in this index case. The literature is not consistent in the need for

anticoagulation in hyperthyroid patients with AF, with no useful studies focusing on anticoagulants in childhood. Use of anticoagulation in the index patient was deferred following a discussion with the family, until it had been confirmed the risk of stroke in the index case, with a CHA_2DS_2-VASc score of 0, is considered statistically significant in this group, warranting the risk associated with anticoagulants in an active teenager.

REFERENCES

1. Orgain ES, Wolff L, White PD. Uncomplicated auricular fibrillation and auricular flutter. Archives of Internal Medicine. 1936;493-513.

2. Brugada R, Tapscott T, Czernuszewicz GZ, Marian AJ, Iglesias A, Mont L, et al. Identification of a genetic locus for familial atrial fibrillation. N Engl J Med. 1997;336:905–11.

3. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science. 2003;299:251–4.

4. Radford DJ, Izukawa T. Atrial fibrillation in children. Pediatrics. 1977;59:250-6.

5. Orbeti C, Wang L, Dong J, Rao S, Du W, Wang Q. Genome-wide linkage scan identifies a novel genetic locus on chromosome 5p13 for neonatal atrial fibrillation associated with sudden death and variable cardiomyopathy. Circulation. 2004;110(25):3753-9.

6. Traube E, Coplan NL. Embolic risk in atrial fibrillation that arises from hyperthyroidism. Tex Heart Inst J. 2011;38(3):225-8.

7. Donatelli M, Abbadi V, Bucalo ML, Russo V, Traina M, Compagno V et al. Atrial fibrillation and hyperthyroidism. The results of a retrospective study. Minerva Cardioangiol. 1998;46(5):157-62.

8. Fuster V, Ryden LE, Cannom DS, Crijins HJ, Curtis AB, Ellenbogen KA et al. ACC/AHA/ESC Practice Guidelines: ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. Circulation. 2006;114:257-354.

9. Bielecka-Dabrowa A, Mikhailidis DP, Rysz J, Banach M. The mechanism of atrial fibrillation in hyperthyroidism. Thyroid Res. 2009;2(1):4-10.

10. Jain SKA, Patel KP, Alexander P, David S. Biventricular heart failure, an early sign of thyrotoxicosis. Int J Coll Res Intern Med Pub Health. 2012:4(6):1297-304.

11. Opris M, Maler A, Dinesch M, Bilca V, Moldovan E, Mitre A et al. Atrial fibrillation, the first manifestation of atrial myxoma. Acta Medica Marisiensis. 2011;57(6):769.

12. Jyothirmayi GN, Zaitz J, Vadehra V, Zuckier LS, Raghuwanshi M. Man, 62, with new-onset atrial fibrillation. Clinician Reviews. 2012;22(5):10-2.

13. Azabagic S, Cickusic AJ, Zukic E. Effects of short-term octreotide therapy on TSH adenoma with atrial fibrillation-Case report. HealthMED. 2012;6(3):1081-6.

14. Ahmed S, Van Gelder IC, Wiesfeld ACP, Van Veldhuisen DJV, Links TP. Determinants and outcome of amiodarone-associated thyroid dysfunction. Clinical Endocrinol (Oxf). 2011;75:388-94.

15. Rocco D, During A, Morelli PJ, Heyden M, Biancaniello TA. Atrial fibrillation in healthy adolescents after highly caffeinated beverage consumption: two case reports. J Med Case Rep. 2011;5:18.

16. Gillette PC, Garson A. In Pediatric Arrhythmias: Electrophysiology and Pacing. Philadelphia: WB Saunders Company; 1990.

17. Takasugi H, Ao K, Sato T, Maeda A, Okada T, Wakiguchi H. Atrial fibrillation with hyperthyroidism in a 14-year-old male. Pediatr Cardiol. 2006;27(6):772-4.

18. Perry LW, Hung W. Atrial fibrillation and hyperthyroidism in a 14-year-old boy. J Pediatr. 1971;79:668-71.

19. Boos CJ, Lip GY. Inflammation and atrial fibrillation: cause or effect? Heart. 2008;94:133-4.

20. Chen YC, Chen SA, Chen YJ, Chang MS, Chan P, LinCI. Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes. J Am Coll Cardiol. 2002;39(2):366-72.

21. Shimizu T, Koide S, Noh JY, Sugino K, Ito K, Nakazawa H. Hyperthyroidism and the management of atrial fibrillation. Thyroid. 2002;12(6):489-93.

22. Nikulina S, Shulman V, Dudkina K, Chernova A, Gavrilyuk O. New candidate genes in atrial fibrillation polymorphism of the alpha 2-beta-adrenoceptor and the endothelial NO synthetase genes in atrial fibrillation of different etiological origins. In Intech; 2013:Chapter 4;59-77.

23. Olesen MS, Refsgaard L, Holst AG, Larsen AP, Grubb S, Haunse S et al. A novel KCND3 gain-of-function mutation associated with early-onset of persistent lone atrial fibrillation. Cardiovas Res. 2013;98(3):488-95.

24. Szwast A, Hanna B, Shah M. Atrial fibrillation and pulmonary embolism. Pediatr Emerg Care. 2007;23(11):826-8.

25. Camm AJ, Gregory YH, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. European Heart Journal. 2012;33:2719-47.

CONSISTENCY VERSUS EQUITY - CARDIOVASCULAR DISEASE MANAGEMENT FOR SOUTH ASIANS IN THE UNITED KINGDOM

Jeetesh V. Patel,[1,2] Paul Flinders,[1] Brian D.A. Gammon,[2] Girish S. Dwivedi,[3] Richard P. Steeds[3]

1. School of Medicine, University of Nottingham, Nottingham, UK
2. Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
3. Department of Cardiology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

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ABSTRACT

An increased risk of coronary heart disease was an immediate healthcare concern following the mass arrival of South Asian immigrants to the UK, and it has since contributed as a persistent source of health inequality. The process of risk assessment and management in the UK has been backed by a strong body of scientific evidence, but there are limitations. For example, the cardiovascular risk profile amongst South Asians appears different to Whites. Health policies, which strive for consistency in risk assessment and management, can exaggerate such weaknesses, contributing to inequalities in healthcare. There is an urgent need for scientific proof that can improve the availability of tailored prevention and intervention services. Deficit in communication is a key concern for many South Asians and non-English speaking patients, which not only impacts on the access to services, but also creates critical delays with respect to diagnosis and treatment for acute myocardial infarction. Linguistic tools and language education perhaps play an undervalued role in coronary heart disease management.

Keywords: South Asian, coronary heart disease, language, health inequality.

INTRODUCTION

The elevated burden of coronary heart disease (CHD) amongst South Asians in the United Kingdom is a complex and multifactorial phenomenon whereby simplistic policies for risk assessment and management contribute to damaging health inequalities, which are worsened by failures to initiate or improve effective cross-cultural communication.

Perceptions of impartiality, equity and accessibility, within the UK National Health Service, repeatedly arise when serving members of ethnic minority groups.[1] Individuals from these groups must compete with the general population for finite health resources if they are to benefit from the often foreign workings of a healthcare system. Given this degree of unfamiliarity, the temptation must surely be to become frustrated with marginalised, generally non-indigenous persons for their failure to acquaint themselves with the NHS. Evidence suggests, however, that Central and Eastern European migrants,[2] the homeless,[3,4] asylum seekers[5] and drug dependent persons,[6] add to the diversity of an evolving landscape of patients for whom the provision of healthcare is not sufficiently sensitive. These groups experience limited access to the full range of healthcare services.[2,5,6] The situation is further complicated by language differences[5] and the hazard of consultation delays, for which the evidence of a negative impact is widespread and includes: antenatal care,[7] life limiting diseases,[8] falls in the elderly,[9] tuberculosis,[10] and organ donation.[11]

These themes of 'barriers to healthcare' and 'language difficulties' continue as recurring issues

for more established migrant groups, such as South Asians in Britain.[8] The mass immigration of people from India, Pakistan, Bangladesh, and Sri Lanka (South Asia) to the UK, particularly from the 1960s onwards, began the formation of a legacy of health needs,[12] unique due to the scale of migration. The increased coronary heart disease (CHD) risk and its management among South Asians provide an important and instructive example of the difficulties faced in the provision of equitable healthcare.

CORONARY HEART DISEASE RISK IN SOUTH ASIANS

Myocardial infarction is disproportionately more common amongst South Asians living in the UK.[13] Not only does this group develop CHD earlier,[14] but their increased risk persists despite conventional antihypertensive and lipid lowering therapy.[13] Indeed, CHD in South Asians represents a long-standing public health concern,[15] in part because the origins of this increased risk, estimated to be 40% greater than that of the indigenous British population,[1] are poorly understood. Moreover, this risk may be even higher amongst newer generations of British South Asians.[16] This burden of CHD is also mirrored by both a higher prevalence of diabetes and a higher risk of its associated complications.[17-19] Retinopathy and renal failure are both more common[18,20] and more progressive[21] than in the general population, whilst diabetic nephrophathy has been reported to be 40-fold higher than in White diabetics.[20] Such co-morbidities are likely to complicate clinical and radiological assessment, which may, perhaps in part, explain why South Asians presenting with chest pain in UK hospitals experience greater delays with respect to diagnosis and treatment for acute myocardial infarction.[22,23]

There are also more subtle disparities with respect to CHD risk. Low density lipoprotein (LDL) cholesterol is, for example, reportedly lower in South Asians compared to Whites, but at similar levels between the two groups, the risk of CHD among South Asians is still higher.[24] Similarly, cardiovascular events in South Asians occur when blood pressure is well within clinically accepted normal levels.[25,26] Furthermore, whilst evidence suggests that South Asians living in Britain have experienced a significant advance in blood pressure, obesity and total cholesterol associated with migration from the Indian subcontinent, such deleterious changes are difficult to discern against reference ranges which are based upon the general UK population.[27]

TAILORED HEALTH PROMOTION

Whilst the health prospects for South Asians appear to be relatively bleak, healthcare advances, the early identification and treatment of CHD, and the improved awareness of cardiovascular risk factors amongst the wider population, underpin a decreasing trend in CHD mortality in the UK.[28] Such trends are, however, less apparent in South Asians.[29] Hence, while national strategies for cardiovascular health promotion and risk assessment appear justified,[30] a key concern is that much of the scientific evidence that has been used to develop guidelines and policies for CHD are derived predominantly upon material which is extrapolated from data derived from the White population.

These policies thus fail to acknowledge the uniqueness of the cardiovascular risk profile amongst South Asians, which does not appear to exhibit those same CHD risk factors that are manifested in other groups.[31,32] There have been attempts to provide the redress to this problem. For example, ethnic adjustments in the approximation of cardiovascular risk. QRISK2 offers an improvement over the standard Framingham equation approach. However, this is a changing area and until new evidence emerges, current guidelines recommend that the estimated CHD risk for men with a South Asian background should be increased by a factor of 1.4.[33] ETHRISK[34] is another web-based CHD risk score available, but this needs further validation amongst South Asians. These proposed increments and 'ethnicity-related' adjustments to CHD risk prediction scores are popular. However, such adjustments can lead to ambiguity – a high risk South Asian identified using such adjusted risk scores typically has CHD risk factors at levels unworthy of intervention. What is needed is a focused cohort study that develops a validated risk assessment approach.

Furthermore, the reducing trend of CHD mortality amongst minority groups in the UK may also be a result of community and charity-based initiatives that have attempted to improve the quality of service provision and equality of access

among South Asian patients. Whilst it is often asserted that the increased availability of tailored prevention and intervention services will help to reduce such damaging disadvantages in healthcare, the efficacy of such approaches remains largely unproven. Given this greater disease burden amongst South Asians, national policies that strive for consistency and simplicity in risk assessment and service design may paradoxically increase health inequality amongst UK South Asians.

IMPROVING COMMUNICATION

Factors that influence migrant health inequalities are widespread and varied and are related to the patient, the healthcare organisation and to socioeconomic factors. These include: fears about treatment side-effects, lack of social support, perceived lack of confidentiality, the fear of social stigma associated with some illnesses, difficulty accessing transport (including cost), as well as the lesser priority sometimes afforded to female family member's healthcare.[35] Cultural discordance can arise from a failure of the healthcare organisation to accommodate traditional culture, a lack of translated patient education materials, and for female patients by fearing not being able to consult with a female clinician.[35]

Organisational factors which adversely influence migrant groups from properly engaging with the healthcare provided include the difficulty providing translators and the difficulty of three-way communication, even when they are present.[35] For example, conversational 'small talk' between the patient and interpreter is rarely translated, even when clinically relevant.[36] Moreover, institutional and even personal racism are still experienced by patients from migrant populations.[8]

Evidence indicates that these disparities in outcome are exacerbated by organisational and cultural barriers faced by such communities when attempting to access services.[37] There is an urgent need to understand how these delays influence patients and contribute to delays in seeking medical care, as well as delaying accurate and timely assessment and treatment. Whilst socio-economic and cultural influences are likely to play a key role, such influences are likely to be exacerbated by deficits in communication skills,[38,39] which are fundamental when marginalised groups attempt to access services and facilities embedded within a health system that is skewed towards the majority population.

Strategies that are used within hospitals to bridge language gaps appear to be only partially successful. Effective communication is paramount during consultations between healthcare professionals and patients due to the importance of verbal and non-verbal clues in cross-cultural exchange of information. Such initiatives may be doomed to fail as communication becomes less effective as time constraints increase. The presence of an interpreter, though often advocated as a panacea, may not improve effective information exchange as the three-way consultation between the patient, clinician and interpreter adds additional layers of cultural complexity. Moreover, interpretation may involve a degree of manipulation of which the doctor, for example, may be unaware.[40] One possibility would be to promote national initiatives, which equip individuals with those linguistic tools necessary to engage in meaningful and timely therapeutic consultations before coming into contact with services. One proposal would be, for example, to provide access to language courses as part of the coronary rehabilitation process for South Asians with language difficulties, thereby minimising delay in treatment associated with re-admission. Another, more universal option is advocating for English language course availability at the initiation of contact with a family physician or family practice.

Researchers have shown how it is possible to engage with South Asian groups by developing community-based health promotion initiatives.[41-43] Such community and charity-based initiatives have attempted to improve the quality of service provision and equality of access among South Asian patients. There is evidence that community-based approaches do impact on markers of disease risk, health behaviour and beliefs in target groups.[42] However, the clinical efficacy of such approaches remains largely unproven. A targeted response to the higher South Asian CHD risk may serve to address the disparities in the provision of services for CHD prevention, but in the current climate of austerity, such measures may impose an added burden on health services requiring as they do, increased financial commitments. Furthermore, such a reverse-discriminatory approach may be construed to

be counter-productive in promoting a sense of separate lives, separate communities and thus increased isolation.

Flanagan and Hancock argue that 'the voluntary and community sector has arguably been more successful in penetrating some of the barriers for the 'hard to reach' and has an important role to play in the understanding of service delivery provision.'[44]

CONCLUSION

Although the UK Government appears committed to maximising best practice through infusing policy decisions with objective data derived, for example, from clinical trials, it is clear that much more needs to be done to maximise integration of services and access to those services. Community-based or voluntary and community sector initiatives may prove to be particularly efficacious. A review of the literature indicates that initiatives to improve communication and raise the profile of services amongst marginalised communities has paid dividends in a series of small local victories[45] but more needs to be done at the national level.

As a now established minority group in the UK, measures have begun to be more sensitive to health problems experienced by South Asian patients. For example, South Asian specific body mass index (BMI) and waist measurement cut-offs are included in recent NICE Guidance.[46] This demonstrates that, over time, progress is made. However this is a small, comfort for more recent migrant populations such as the Yemeni, Eastern European, and Somali communities, each of whom may face similar struggles with the healthcare system.[43] Improved communication, a responsibility that is shared by both the doctor and the patient, may be a more efficient and effective way to provide equitable care to diverse and varied communities within Britain.

REFERENCES

1. Gill PS, Kai J, Bhopal RS, Wild S. Health care needs assessment: black and minority ethnic groups. In: Raftery J, ed. Health Care Needs Assessment: The Epidemiologically Based Needs Assessment Reviews, 3rd Series. Abingdon: Radcliffe Medical Press 2007.

2. Burns FM, Evans AR, Mercer CH et al. Sexual and HIV risk behaviour in central and eastern European migrants in London. Sex Transm Infect. 2011;87(4):318-24.

3. Evans AR, Parutis V, Hart G et al. The sexual attitudes and lifestyles of London's Eastern Europeans (SALLEE Project): design and methods. BMC Public Health. 2009;9:399.

4. Collinson S, Ward R.A nurse-led response to unmet needs of homeless migrants in inner. Br J Nurs. 2010;19(1):36-41.

5. Blackwell D, Holden K, Tregoning D. An interim report of health needs assessment of asylum seekers in Sunderland and North Tyneside. Public Health. 2002;116(4):221-6.

6. Calvin C, Moriarty H. A special type of 'hard-to-reach' patient: experiences of pregnant women on methadone. J Prim Health Care. 2010;2(1):61-9.

7. Parsons L, Day S. Improving obstetric outcomes in ethnic minorities: an evaluation of health advocacy in Hackney. J Public Health Med. 1992;14(2):183-91.

8. Worth A, Irshad T, Bhopal R et al. Vulnerability and access to care for South Asian Sikh and Muslim patients with life limiting illness in Scotland: prospective longitudinal qualitative study. BMJ. 2009;338:b183.

9. Perry L, Kendrick D, Morris R et al. Completion and Return of Fall Diaries Varies With Participants' Level of Education, First Language, and Baseline Fall Risk. J Gerontol A Biol Sci Med Sci. 2012;67(2):210-4.

10. Sreeramareddy CT, Panduru KV, Menten J, et al. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. BMC Infect Dis. 2009;9:91.

11. Perera S, Mamode N. South Asian patients awaiting organ transplantation in the UK. Nephrol Dial Transplant. 2011;26(4):1380-4.

12. Bivins R. "The English disease" or "Asian rickets"? Medical responses to postcolonial immigration. Bull Hist Med. 2007;81(3):533-68.

13. Patel JV, Lim HS, Gunarathne A et al. Ethnic differences in myocardial infarction in patients with hypertension: effects of diabetes mellitus. QJM. 2008;101:231-6.

14. Patel JV, Dwivedi S, Hughes EA et al. Premature coronary artery disease: an inferred cardiovascular variant or a South Asian genetic disorder? Thromb Haemost. 2008;99:991-2.

15. Tunstall-Pedoe H, Clayton D, Morris JN et al. Coronary heart-attacks in East London. Lancet. 1975;2(7940):833-8.

16. Harding S. Mortality of migrants from the Indian Subcontinent to England and Wales: effect of duration of residence. Epidemiology. 2003;14(3):287-92.

17. Patel JV, Vyas A, Prabhakaran D et al. Nonesterified fatty acids as mediators of glucose intolerance in Indian Asian populations. Diabetes Care. 2005;28(6):1505-7.

18. Burden AC, McNally PG, Feehally J et al. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med. 1992;9(7):641-5.

19. Stolk RP, van Schooneveld MJ, Cruickshank JK et al. Retinal vascular lesions in patients of Caucasian and Asian origin with type 2 diabetes: baseline results from the ADVANCE Retinal Measurements (AdRem) study. Diabetes Care. 2008;31(4):708-13.

20. Middelkoop BJ, Kesarlal-Sadhoeram SM, Ramsaransing GN et al. Diabetes mellitus among South Asian inhabitants of The Hague: high prevalence and an age-specific socioeconomic gradient. Int J Epidemiol. 1999;28(6):1119–23.

21. Chandie Shaw PK, Baboe F, van Es LA et al. South-Asian type 2 diabetic patients have higher incidence and faster progression of renal disease compared with Dutch-European diabetic patients.

Diabetes Care. 2006;29(6):1383-5.

22. Chaturvedi N, Rai H, Ben-Shlomo Y. Lay diagnosis and health-care-seeking behaviour for chest pain in south Asians and Europeans. Lancet. 1997;350(9091):1578-83.

23. Kendall H, Marley A, Patel JV, et al. Hospital delay in South Asian patients with acute ST-elevation myocardial infarction in the UK. Eur J Prev Cardiol. 2013;20:737-42.

24. Karthikeyan G, Teo KK, Islam S, et al. Lipid profile, plasma apolipoproteins, and risk of a first myocardial infarction among Asians: an analysis from the INTERHEART Study. J Am Coll Cardiol. 2009;53(3):244-53.

25. Cruickshank JK, Beevers DG. Is blood pressure really worse in Black people? Lancet. 1980;2(8190):317-2.

26. Raleigh VS, Kiri V, Balarajan R. Variations in mortality from diabetes mellitus, hypertension and renal disease in England and Wales by country of birth. Health Trends. 1997;28:122–127.

27. Patel JV, Vyas A, Cruickshank JK et al. Impact of migration on coronary heart disease risk factors: comparison of Gujaratis in Britain and their contemporaries in villages of origin in India. Atherosclerosis. 2006;185(2):297-306.

28. Müller-Nordhorn J, Binting S, Roll S et al. An update on regional variation in cardiovascular mortality within Europe. Eur Heart J. 2008;29(10):1316-26.

29. Scarborough P, Bhatnagar P, Wickramasinghe K et al. Coronary heart disease statistics 2010 edition. British Heart Foundation: London, 2010.

30. NHS health check. http://www.healthcheck.nhs.uk (accessed 1/09/2011).

31. Shaper AG. Cardiovascular disease in the tropics. IV. Coronary heart disease. BMJ. 1972;4(5831):32-5.

32. Bhopal R, Hayes L, White M et al. Ethnic and socio-economic inequalities in coronary heart disease, diabetes and risk factors in Europeans and South Asians. J Public Health Med. 2002;24(2):95-105.

33. National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London: NICE, 2008.

34. Ethrisk website. http://www.epi.bris.ac.uk/CVDethrisk/ (accessed 20/08/2012)

35. Penn C, Watermeyer J. When asides become central: small talk and big talk in interpreted health interactions. Patient Educ Couns. 2012;88:391-8.

36. Lobb R, Pinto AD, Lofters A. Using concept mapping in the knowledge-to-action process to compare stakeholder opinions on barriers to use of cancer screening among South Asians. Implement Sci. 2013;8:37.

37. Merrell J, Kinsella F, Murphy F et al. Accessibility and equity of health and social care services: exploring the views and experiences of Bangladeshi carers in South Wales, UK. Health Soc Care Community. 2006;14(3):197-205.

38. Gill P, Shankar A, Quirke T et al. Access to interpreting services in England: secondary analysis of national data. BMC Public Health. 2009;9:12.

39. Neal RD, Ali N, Atkin K et al. Communication between South Asian patients and GPs: comparative study using the Roter Interactional Analysis System. Br J Gen Pract. 2006;56(532):869-75.

40. Greenhalgh T, Robb N, Scambler G. Communicative and strategic action ininterpreted consultations in primary health care: a Habermasian perspective. Soc Sci Med. 2006;63(5):1170-87.

41. Farooqi A, Bhavsar M. Project Dil: A co-ordinated primary care and community health promotion programme for reducing risk factors of CHD amongst the South Asian community of Leicester - experiences and evaluation of the project. Ethnicity Health. 2001;6(3-4):265-70.

42. Mathews G, Alexander J, Rahemtulla T et al. Impact of a cardiovascular risk control project for South Asians (Kush Dil) on motivation, behaviour, obesity, blood pressure and lipids. J Public Health. 2007;29(4):388-97.

43. Patel JV, Gunarathne A, Lane D et al. Widening access to cardiovascular healthcare: community screening among ethnic minorities in inner-city Britain - the Healthy Hearts Project. BMC Health Serv Res. 2007;7:192.

44. Flanagan SM, Hancock B. 'Reaching the hard to reach' - lessons learned from the VCS (voluntary and community Sector): a qualitative study. Flanagan and Hancock. BMC Health Services Research. 2010;10:92.

45. Randhawa G. Promoting organ donation and transplantation among South Asians in the United Kingdom: the role of social networks in the South Asian community. Prog Transplant. 2005;15(3):286-90.

46. National Institute of Clinical Effectiveness. Assessing body mass index and waist circumference thresholds for intervening to prevent ill health and premature death among adults from black, Asian and other minority ethnic groups in the UK (PH46). http://publications.nice.org.uk/assessing-body-mass-index-and-waist-circumference-thresholds-for-intervening-to-prevent-ill-health-ph46 (accessed 6/10/13).

PRESCRIBING PHYSICAL ACTIVITY FOR THE PREVENTION AND TREATMENT OF HYPERTENSION IN PATIENTS WITH AORTIC COARCTATION - A REVIEW

Roselien Buys

Postdoctoral Researcher, Department of Rehabilitation Sciences, Catholic University of Leuven, Belgium

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ABSTRACT

Patients who have been treated for aortic coarctation (CoA) have increased late cardiovascular morbidity and mortality, which is partly due to the development of arterial hypertension occurring in up to 70% of patients. Primary prevention measures are important in order to delay or prevent the onset of hypertension as much as possible. So far, hypertension management in this population has mainly focused on the early detection of hypertension and the antihypertensive drug treatment. Even though a physically active lifestyle is recognised as a cornerstone in the prevention, treatment, and management of hypertension, exercise prescription in this context for patients with CoA is not common practice. Studies on the safety and efficacy of sports and exercise training in patients with CoA, both before and after repair, are lacking. However, decreasing blood pressure can be obtained through exercise training, in both healthy subjects and patients with hypertension. Moreover, patients with CoA are not restricted from all physical activities. Therefore, it seems that endurance exercise, supplemented by resistance exercise without isometric exercises on most days of the week, should be prescribed, but only after thorough and regularly repeated medical check-ups, including cardiopulmonary exercise testing.

Keywords: Aortic coarctation, blood pressure, hypertension, exercise, physical activity.

INTRODUCTION

Coarctation of the aorta, or CoA, is a congenital condition in which the aorta narrows in the area where the ductus arteriosus inserts. It occurs in approximately 0.34 per 1,000 live births.[1] When the narrowing has haemodynamic repercussions, surgical or percutaneous treatment is required. Patients who have been treated for CoA, require lifelong follow-up because of increased late cardiovascular morbidity and mortality, which is mainly due to the development of arterial hypertension and the occurrence of vascular complications.[2-7]

HYPERTENSION IN PATIENTS WITH COA

The late development of hypertension is common in patients with CoA, even after excellent repair.[8] Recently, Caniffe et al.[9] summarised the prevalence of hypertension in patients with CoA and reported the median prevalence to be 32.5%, which is based on studies reporting the prevalence between 25% and 68%.[9] The patterns for late hypertension have their origins in childhood, with preterm changes of the vascular bed that are both congenital and acquired.[8] These changes are demonstrated by endothelial dysfunction, arterial stiffness, a reduced arterial response to glyceryl trinitrate, increased carotid intima-media thickness, higher forearm pulse wave velocities, and by abnormal spontaneous baroreceptor sensitivity.[9] Moreover, renal and neurohormonal control mechanisms may also contribute to the development of hypertension.[9]

Even though the underlying mechanisms that lead to hypertension need to be further elucidated, it is important that all post-coarctation patients with hypertension are quickly identified and

managed in order to minimise their risk of hypertension-related complications.[9] In this light, the usefulness of exercise testing as a predictive tool for future hypertension has been reported in patients who underwent coarctation repair of the aorta.[10] Furthermore, it is suggested that aortic arch geometry can identify patients post-coarctation repair who are at a higher risk of developing hypertension.[11]

It is important to emphasise primary prevention measures in order to delay or prevent the onset of hypertension as much as possible.[10] So far, hypertension management in this population has mainly focused on early detection of hypertension and antihypertensive drug treatment, whereas lifestyle measures are less often investigated. However, a physically active lifestyle is recognised as a cornerstone for the prevention, treatment and management of hypertension.[12]

Beneficial Effects of Physical Activity on Blood Pressure

Previous epidemiological studies have demonstrated that physical activity and cardiorespiratory fitness are independent predictors of incident hypertension.[13-17] Therefore, people should be physically active by participating in regular physical activity and maintain/improve their fitness for the primary prevention of hypertension, as well as cardiovascular diseases in general.[18] This healthy lifestyle, with the primary prevention of atherosclerotic disease, should begin in childhood.[19]

The beneficial effects of exercise training on blood pressure have been shown both in normotensive and hypertensive persons.[20-22] It seems a decrease in blood pressure can be obtained through a reduction of vascular resistance, in which the sympathetic nervous system and the renin-angiotensin system appears to be involved, and favourably affects concomitant cardiovascular risk factors.[20]

When the prevention or management of hypertension is aimed in subjects with cardiovascular risk factors, endurance exercise, supplemented by resistance exercise on most - preferably all - days of the week, should be prescribed.[23]

Benefits of Physical Activity for Blood Pressure Improvement in Patients with CoA

There is an urgent need for well-designed studies investigating the effect of exercise-based interventions on exercise capacity, cardiovascular risk factors, quality of life, and long-term outcome in patients with coarctation of the aorta.

However, it is not unlikely that findings from studies on healthy and hypertensive persons can be extended towards patients with CoA. Exercise could possibly ameliorate endothelial function and the quality of the vascular bed in these patients and, therefore, reduce blood pressure and its response to exercise. This might eventually reduce the incidence of high blood pressure.

PHYSICAL ACTIVITY FOR PATIENTS WITH COA

Patients with CoA are more prone to adopt a sedentary lifestyle because of fear or overprotection by the parents and the environment.[24] Indeed, a recent study by our group showed that adult patients with CoA are less active than the general population, and less active than recommended.[25] However, the 2010 guidelines of the European Society of Cardiology states: "Patients without residual obstruction who are normotensive at rest and with exercise, can usually lead normally active lives without restriction, except for extensive static sports at competition level. Patients with arterial hypertension, residual obstruction or other complications should avoid heavy isometric exercises, in proportion to the severity of their problems."[3]

Hence, patients with CoA should comply with public health recommendations. Children are encouraged to participate every day in 60 minutes of moderate-to-vigorous physical activity that is developmentally appropriate as well as enjoyable, and involves a variety of activities. Moreover, they should perform less than 2 hours per day of sedentary activities.[26] For adults, it is recommended that healthy people should choose enjoyable physical activities, which fit into their daily routine, preferably for 30–45 minutes, 4-5 times a week, in order to prevent or delay the onset of cardiovascular disease.[27]

With a lack of studies on sports and exercise training in patients with CoA both before and after repair, it is only possible to extrapolate from the recommendations for arterial hypertension. As stated above, endurance exercise supplemented by resistance exercise, should be prescribed when prevention or management of hypertension is aimed.[23] Nevertheless, in patients with CoA, one has to be cautious with the

prescription of resistance programmes with isometric exercises.

The participation of patients with aortic coarctation in exercise programmes and sport activities always has to be judged individually, and needs to be based on and evaluated by regular medical surveillance, including cardiopulmonary exercise testing in order to rule out an abnormal blood pressure response to exercise. Medical exercise prescription and supervision are strongly recommended.[28] This way, the nature of the original coarctation, the type of coarctation repair, the aortic arch anatomy, rest gradient, presence of a bicuspid aortic valve, etc., is taken into account.

CONCLUSIONS

It is recommended that specialised health professionals should more actively counsel their patients with CoA to be physically active, by having them participate in regular physical activity such as walking, jogging, bicycling, swimming, and playing sports, as well as to improve their fitness both for the primary prevention and the treatment of hypertension. Based on evidence in healthy subjects and patients with hypertension, it seems that endurance exercise, supplemented by resistance exercise without isometric exercises on most days of the week, should be prescribed, but only after thorough and regularly repeated medical check-ups, including cardiopulmonary exercise testing.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58(21):2241-7.

2. Luijendijk P, Bouma BJ, Vriend JW, et al. Usefulness of exercise-induced hypertension as predictor of chronic hypertension in adults after operative therapy for aortic isthmic coarctation in childhood. Am J Cardiol. 2011;108(3):435-9.

3. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC guidelines for the management of grown-up congenital heart disease. Eur Heart J. 2010;31(23):2915-57.

4. Hager A, Kanz S, Kaemmerer H, et al. Coarctation Long-term Assessment (COALA): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material. J Thorac Cardiovasc Surg. 2007;134(4):738-45.

5. Vriend JW, Mulder BJ. Late complications in patients after repair of aortic coarctation: implications for management. Int J Cardiol. 2005;101(3):399-406.

6. Swan L, Kraidly M, Vonder Muhll I, et al. Surveillance of cardiovascular risk in the normotensive patient with repaired aortic coarctation. Int J Cardiol. 2010;139(3):283-8.

7. Meyer AA, Joharchi MS, Kundt G, et al. Predicting the risk of early atherosclerotic disease development in children after repair of aortic coarctation. Eur Heart J. 2005;26(6):617-22.

8. Hager A. Hypertension in aortic coarctation. Minerva Cardioangiol. 2009;57(6):733-42.

9. Canniffe C, Ou P, Walsh K, et al. Hypertension after repair of aortic coarctation - A systematic review. Int J Cardiol. 2012;epub ahead of print. doi:10.1016/j.ijcard.2012.09.084.

10. Buys R, Van De Bruaene A, Müller J, et al. Usefulness of cardiopulmonary exercise testing to predict the development of arterial hypertension in adult patients with repaired isolated coarctation of the aorta. Int J Cardiol. 2013; epub ahead of print. doi:10.1016/j.ijcard.2013.01.171.

11. Ou P, Celermajer DS, Mousseaux E, et al. Vascular remodelling after "successful" repair of coarctation. J Am Coll Cardiol. 2007;49(8):883-90.

12. Cornelissen V, Fagard R. "Hypertension", Saxton J. (Ed.), Exercise and chronic disease: an evidence-based approach (2011), United States of America: Taylor and Francis Books, Chapter 3.

13. Blair SN, Goodyear NN, Gibbons LW, et al. Physical fitness and incidence of hypertension in healthy normotensive men and women. JAMA. 1984;252(4):487–90.

14. Chase NL, Sui X, Lee DC, et al. The association of cardiorespiratory fitness and physical activity with incidence of hypertension in men. Am J Hypertens. 2009;22(4):417–24.

15. Paffenbarger RS Jr, Jung DL, Leung RW, et al. Physical activity and hypertension: an epidemiological view. Ann Med. 1991;23(3):319–27.

16. Paffenbarger RS Jr, Lee IM. Intensity of physical activity related to incidence of hypertension and all-cause mortality: an epidemiological view. Blood Press Monit. 1997;2(3):115–23.

17. Pereira MA, Folsom AR, McGovern PG, et al. Physical activity and incident hypertension in black and white adults: the Atherosclerosis Risk in Communities Study. Prev Med. 1999;28(3):304–12.

18. Vanhees L, De Sutter J, Geladas N, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health within the general population. Recommendations from the EACPR (Part I). Eur J Cardiovasc Prev Rehabil. 2012;19(4):670-86.

19. Kavey RE, Daniels SR, Lauer RM, et al. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation. 2003;107(11):1562–6.

20. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension. 2005;46(4):667–75.

21. Cornelissen VA, Fagard RH, Coeckelberghs E, et al. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. Hypertension. 2011;58(5):950-8.

22. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2(1):e004473.

23. Vanhees L, Geladas N, Hansen D, et al.; for the EACPR writing group. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors (Part II). Eur J Prev Cardiol.

2012;19(5):1005-33.

24. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. Eur J Cardiovasc Prev Rehabil. 2005;12(5):498-502.

25. Buys R, Budts W, Delecluse C, et al. Exercise Capacity, Physical Activity, and Obesity in Adults With Repaired Aortic Coarctation. Journal of Cardiovascular Nursing. 2013;28(1):66-73.

26. Takken T, Giardini A, Reybrouck T, et al. Recommendations for physical activity, recreation sport and exercise training in pediatric patients with congenital heart disease: a report from the Exercise, Basic & Translational Research Section of the European Association of Cardiovascular Prevention and Rehabilitation, the European Congenital Heart and Lung Exercise Group, and the Association for European Paediatric Cardiology. Eur J Cardiovasc Prev Rehabil. 2012;19(5):1034-65.

27. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J. 2007;28(19):2375–414.

28. Vanhees L, Rauch B, Piepoli M, et al; on behalf of the writing group of the EACPR. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (part III). Eur J Prev Cardiol. 2012;19(6):1333-56.

INITIAL EVIDENCE IN THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE) TREATMENT WITH BOSENTAN

Joaquín de Haro, Silvia Bleda, Francisco Acin

Vascular Surgery and Angiology Department, Hospital Universitario Getafe, Madrid, Spain

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ABSTRACT

Thromboangiitis obliterans (TAO) is a vascular disease that affects small and medium-sized arteries and veins of both upper and lower extremities. Distal ischaemic lesions and digital necrotic ulcers, as well as major amputation rates, among these patients are not negligible. So far, no treatment option has been demonstrated to be completely effective for this disease. Endothelin-1 (ET-1) has been increasingly associated to vascular damage. Furthermore, elevated levels of ET-1 have been proved in TAO patients. Thus, ET-1 receptor antagonists may be considered as a treatment option in this disease.

Consistently, initial results from open-label studies or case reports show promising efficacy of bosentan for treatment and prevention of digital ulcers in TAO with a favourable safety profile. In any case, bosentan should be further investigated in TAO patient management. To confirm initial promising findings, larger controlled randomised trials with a control group are needed. In the meantime, bosentan should be considered as a hopeful investigational agent for treating these patients.

Keywords: Thromboangiitis obliterans, endothelin, endothelial dysfunction, bosentan, nitric oxide.

INTRODUCTION

Thromboangiitis obliterans (TAO) or Buerger´s disease is a thrombotic, occlusive, non-atherosclerotic segmental vasculitis that affects small and medium-sized arteries and veins, which may involve distal vessel of upper and lower extremities.[1] TAO usually occurs in people around the age of 45, and is more frequent in male smokers. Intermittent claudication and, in more advanced cases, pain at rest are the predominant clinical symptoms. Involvement of both the upper and lower extremities and the size and location of affected vessels help distinguish it from atherosclerosis. Distal ischaemic lesions, as ulcers, are also frequently observed. Raynaud's phenomenon is present in >40% of patients with TAO and may be asymmetrical. Skin disorders, such as migrating thrombophlebitis, may be associated with TAO, may predate the onset of ischaemic symptoms caused by arterial occlusive disease, and frequently parallel disease activity. Although most common in the extremities, TAO may also involve the cerebral, coronary, renal, mesenteric, and pulmonary arteries. Clinical course is characterised by alternating periods of exacerbation with periods of remission. Angiographic studies reveal a distal and segmental involvement of the vasculature of the extremities. Recanalisation is frequently demonstrated, showing a typical image (corkscrew collateral vessels).

Recently, novel pathways have been implicated in the physiopathology of the disease. Endothelin-1 (ET-1) has been associated in these aetiological processes by provoking endothelial dysfunction, causing complications such as vascular damage and vessel occlusion.[2,3]

Interestingly, an impaired endothelium-dependent vasodilatation in the peripheral vasculature, even in the non-diseased limbs, has been shown in patients with TAO.[4]

ET-1 is an endothelium-derived peptide, which is involved in the regulation of vascular function under normal physiological conditions by targeting two transmembrane receptors (ETA and ETB).[5] On the other hand, it plays a key role in vascular

pathologies by exerting various deleterious effects. These include hypertrophy of vascular smooth muscle cells, cellular proliferation, fibrosis, increasing of vascular permeability, activation of leukocytes, and induction of cytokine and adhesion molecule expression.[5] Moreover, ET-1 is the most potent natural vasoconstrictive mediator. In fact, it has been demonstrated that its exogenous administration in healthy volunteers produces a marked dose-dependent reduction of the blood flow[6] (Figure 1).

Elevated circulating levels of ET-1 have been repeatedly observed in TAO and scleroderma, as well as in various other pathologies of the vascular endothelium.[7-9] An increase has been detected in plasma levels of ET-1 in situations of chronic or acute coronary ischaemia, stroke, and peripheral arterial disease.[10,11]

Meanwhile, experimental studies in animal models of hypertension[12,13] and atherosclerosis[14] have shown an improvement in the endothelial function of large arteries, following short-term administration of endothelin receptor antagonists. In any case, these data indicate that some of the endothelin-mediated deleterious effects on the vasculature may be reversible.

BUERGER'S DISEASE PATHOPHYSIOLOGY

Effects of Bosentan

Bosentan, an oral dual ET-1 receptor antagonist, can exert a selective vasodilator effect on the diseased vascular bed in addition to its antifibrotic, anti-inflammatory and antiproliferative effects[15] (Figure 2). Otherwise, endothelial dysfunction is considered to be an early event in the onset stages of vasculitis, such as Buerger's disease, and peripheral arterial disease.[11,16] Nitric oxide (NO), in turn, is also involved in the homeostasis of endothelial function.[17] An increase in ET-1 activity has been associated to an inhibition of NO synthesis.[18]

Moreover, recent investigations have suggested that an improvement in endothelial function would be achieved by enhanced NO production.[16] Thus, the treatment with bosentan may improve NO synthesis in patients with TAO due to its inhibitory action on endothelin receptors. Accordingly, several studies have shown that bosentan can improve endothelial function after 4 weeks of treatment, indirectly demonstrated by the increasing of the flow-mediated dilation (FMD) measurements in the brachial artery in patients with systemic sclerosis, diabetes mellitus, microalbuminuria, and peripheral artery disease[11,16,19] (Figure 3).

These data allow us to hypothesise that the improvement of endothelial dysfunction, after bosentan treatment, may not only be associated with haemodynamic changes, anti-inflammatory processes, or activated-endothelium effects, but rather may be due to the enhancement of NO production following inhibition of ET-1, as has previously been seen in pulmonary hypertension.[20] These findings prove that the endothelin receptor system is an important molecular pathway that is directly involved in certain reversible aspects of vascular injury.

Efficacy of Bosentan

Bosentan efficacy has been demonstrated, with a favourable safety profile, in two randomised controlled clinical trials, RAPIDS-1 and RAPIDS-2, for the treatment and prevention of digital ulcers in patients with systemic sclerosis.[21,22] These results suggest that it may be beneficial for the treatment of Raynaud's phenomenon. Moreover, there is increasing evidence that bosentan exerts a selective vasodilator effect and anti-inflammatory effects in patients affected by TAO,[23] comparable to such effects observed in connective tissue diseases.

To date, the only treatment that has been shown to be effective in TAO is complete abstention from smoking. Both clinical improvement and complete healing of the ulcers have been achieved in the majority of patients after quitting smoking. In spite of this, the disease progresses in up to 30% of cases, finally resulting in limb amputation.[24] Furthermore, quitting smoking is achieved in a very low number of these patients; inferior to 30% in most studies.[23] This unsatisfactory rate, in accordance with previous reports, highlights the fact that it is extremely difficult for patients who are heavy smokers to give up smoking despite having been strongly advised to do so, as well as having received full information about the benefits of quitting smoking, especially in terms of avoiding amputations.[25]

Only a few pharmacological and surgical options (of controversial efficacy) are available to encourage healing of ulcers in TAO.[26] Vasodilators, antiplatelet agents, anticoagulants, and corticosteroids appear to be of no use.[26] Prostaglandin analogues are beneficial when administered intravenously, although their efficacy is controversial on oral administration. A randomised clinical trial of intravenous iloprost

versus aspirin[27] has shown that the healing of ulcers is higher in patients who have received treatment with intravenous prostaglandins. In contradiction to this, other randomised trials have proven an oral formulation of iloprost not to be better than placebo with regard to this outcome.[28] Therefore, the efficacy results shown by prostacyclin analogues when used for the management of TAO are far from satisfactory.

Meanwhile, lumbar sympathectomy may alleviate the pain and improve superficial ulcers, but it does not prevent or reduce the ratio of amputations.[26] Surgical revascularisation is not usually feasible because of the diffuse and segmental character of the disease. Thus, new therapeutic options with a higher efficacy than the current ones are clearly needed in order to properly manage patients affected by TAO. However, the low incidence and lack of effective treatments contribute to serious difficulties in carrying out large prospective studies that confirm the efficacy of novel therapy in this particular disease, in controlled randomised clinical trials.

There are few articles published regarding the treatment of TAO with bosentan. However, they have increasingly shown that bosentan therapy is associated with several clinical and endothelial function-related outcomes in patients with TAO, which may be promising.

The anti-inflammatory, antifibrotic and selective vasodilator properties of bosentan have been shown to alleviate pain at rest and reduce the size of ischaemic ulcers caused by damage mainly to the microcirculation.[7,15,23] Recently, a single-centre clinical study has been published where 12 patients (13 extremities) previously diagnosed with TAO received treatment with bosentan in a compassionate use programme.[23] Bosentan therapy consisted of a month's treatment with 62.5 mg twice a day followed by a 125 mg BID dose after the first month. The full-dose regimen was maintained for the following 3 months or until total healing of the ulcers. Prior to the treatment with bosentan, 10 of 12 patients had previously been treated with a 21-days prostaglandin regimen, 3 had undergone revascularising procedures and 3 patients had a lumbar sympathectomy; all of those treatments with lack of success. Clinical improvement was observed in 12 extremities treated (92%), while only one extremity required major amputation below the knee. 10 extremities (77%) achieved complete clinical therapeutic success (healing or complete pain relief). A minor amputation of one toe was performed with conservation of the extremity. Also, a significant statistical improvement of the endothelial function, assessed by means of the FMD, was observed.

Several case reports have also been published in the literature. All of them provide information on TAO patients with a history of insidious necrotic ulcers with poor outcomes despite smoking cessation and conventional medical treatment, including intravenous prostaglandins.[29-31] Their results show that treatment with bosentan is able to obtain a favourable clinical and angiographic response with healing of ulcers, as well as the disappearing of the rest pain. Furthermore, most patients remained asymptomatic for 6 months after treatment cessation. Therefore, beneficial effects of bosentan in TAO patients have been reported not only during the acute phase of ulcers and rest pain, but also to extend over time.

Although these results are from a small study and case reports and are not comparable with those from randomised trials, they seem to be hopeful.

A likely explanation for the bosentan pharmacodynamic effect on endothelial function has been related on its capacity of improving endothelial function based on the endothelial function impairment observed in patients with peripheral arterial disease in general,[11] and in TAO patients in particular,[23] after treatment. Moreover, an elevated serum ET-1 level has been observed in patients with TAO, supporting a possible mechanistic explanation of the clinical benefit of bosentan in these patients.[32] Additionally, bosentan can exert a selective vasodilatory and anti-inflammatory effect on the vascular bed in patients affected by TAO, comparable to the effects observed in connective tissue diseases such as scleroderma, with the added complication of digital ulcers and peripheral arterial disease[21-23,33] (Figure 3).

CONCLUSION

In summary, bosentan should be investigated further with regard to TAO patient management. The hypothesis that bosentan treatment in TAO patients results in an improvement of clinical, angiographic and endothelial function outcomes is supported by the results of a small pilot study and several case reports that have been recently published. However, larger prospective studies and comparative randomised trials are needed to confirm this initial evidence.

Fig. 1

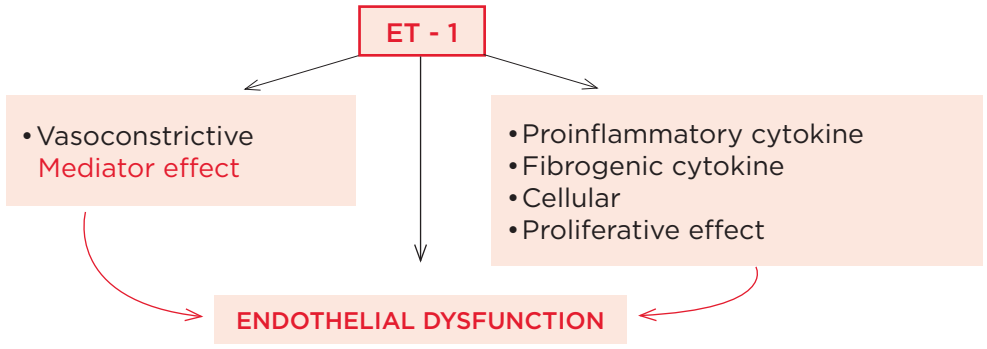

Fig. 2

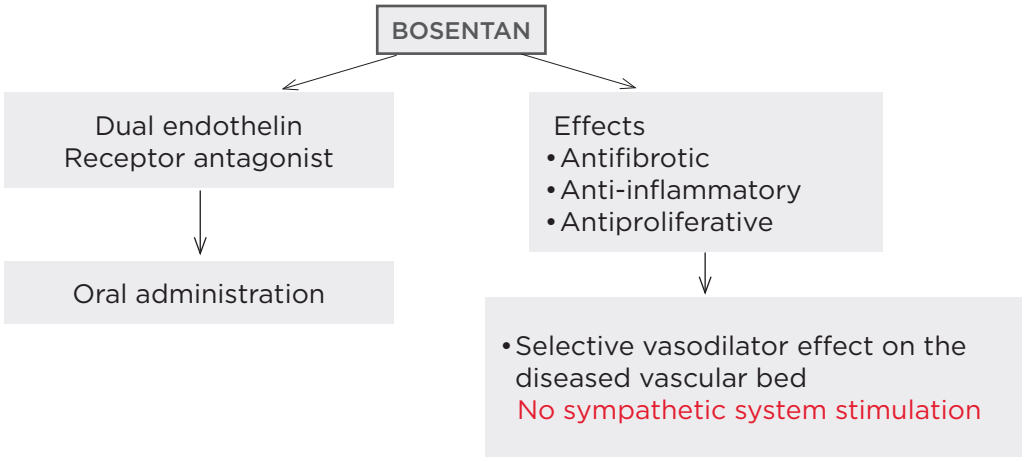

Fig. 3

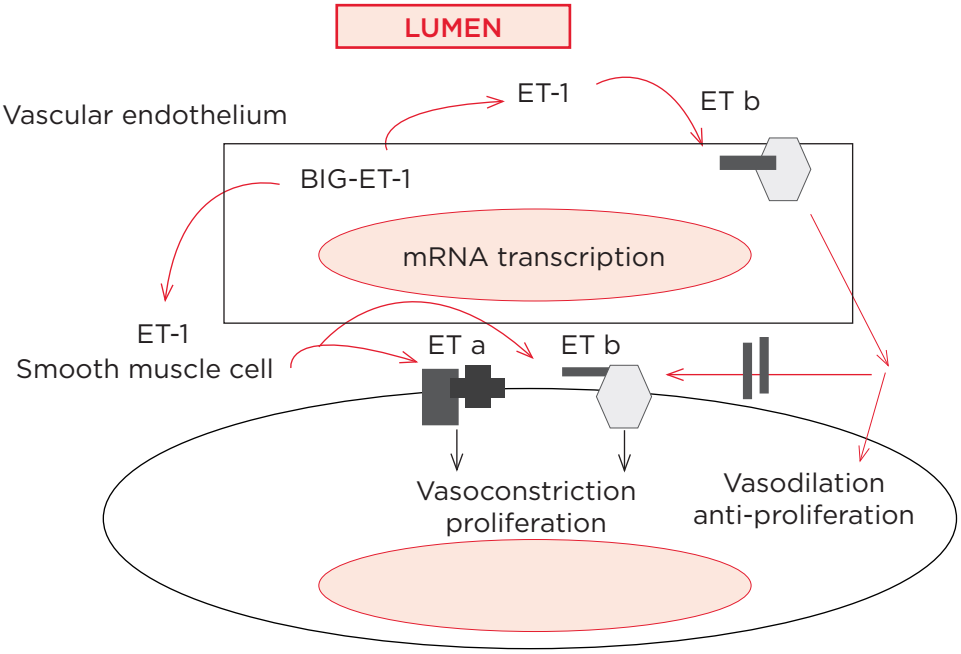

Figure 1. Major determinants of the relationship between increased plasma concentrations of endothelin-1 (ET-1) and endothelial dysfunction.

Figure 2. Effects of bosentan on vascular etiopathogeny.

Figure 3. Biology of the endothelin system and its receptors on endothelium and smooth muscle cells. The ET-A and ET-B are both present on smooth muscle cells, where they mediate vasoconstriction. The ET-B receptor is also present on the endothelium, where it exerts numerous effects: clearence of circulating endothelin, inhibition of endothelin synthesis, production of vasodilators, and production of vasoconstrictors. (Modified from Dupuis J. The Lancet. 2001;358:1113-4).

REFERENCES

1. Olin JW. Thromboangiitis obliterans (Buerguer's disease). N Engl Med. 2000;343(12):864-9.

2. Iglarz M, Clozel M. Mechanisms of ET-1-induced endothelial dysfunction. J Cardiovasc Pharmacol. 2007;50(6):621-8.

3. Ferri C, Latorraca A, Catapano G, Greco F, Mazzoni A, Clerico A, et al. Increased plasma endothelin-1 immunoreactive levels in vasculitis: a clue to the use of endothelin-1 as a marker of vascular damage? J Hypertens Suppl. 1993;11(5):S142-3.

4. Makita S, Nakamura M, Murakami H, Komoda K, Kawozoe K, Hiramori K. Impaired endothelium-dependent vasorelaxation in peripheral vasculature of patients with thromboangiitis obliterans (Buerger's disease). Circulation. 1996;94(9Suppl):II211-5.

5. Thorin E, Clozel M. The cardiovascular physiology and pharmacology of endothelin-1. Adv Pharmacol. 2010;60:1-26.

6. Clarke JG, Benjamin N, Larkin SW, Webb DJ, Davies GJ, Maseri A. Endothelin is a potent long-lasting vasoconstrictor in men. Am J Physiol. 1989;257:H2033–5.

7. Mayes MD. Endothelin and endothelin receptor antagonists in systemic rheumatic diseases. Arthritis Rheum. 2003;48:1190–9.

8. Kim NH, Rubin LJ. Endothelin in health and disease: endothelin receptor antagonists in the management of pulmonary artery hypertension. J Cardiovasc Pharmacol Ther. 2002;7:9–19.

9. Schiffrin EL. Role of endothelin-1 in hypertension and vascular disease. Am J Hypertens. 2001;14:S83–9.

10. Tsui JC, Dashwood MR. A role for endothelin-1 in peripheral vascular disease. Curr Vasc Pharmacol. 2005;3(4):325-32.

11. De Haro Miralles J, Florez Gónzalez A, Varela Casariego C, Acin García F. Onset of peripheral arterial disease: role of endothelin in endothelial dysfunction. Interact Cardiovasc Thorac Surg. 2010;10(5):760-5.

12. Barton M, d'Uscio LV, Shaw S, Meyer P, Moreau P, Luscher TF. ET(A) receptor blockade prevents increased tissue endothelin-1, vascular hypertrophy, and endothelial dysfunction in salt-sensitive hypertension. Hypertension. 1998;31:499–504.

13. Spiers JP, Kelso EJ, Siah WF, Edge G, Song G, McDermott BJ, et al. Alterations in vascular matrix metalloproteinase due to ageing and chronic hypertension: effects of endothelin receptor blockade. J Hypertens. 2005;23:1717–24.

14. Barton M, Haudenschild CC, d'Uscio LV, Shaw S, Munter K, Luscher TF. Endothelin ETA receptor blockade restores NO-mediated endothelial function and inhibits atherosclerosis in apolipoprotein E-deficient mice. Proc Natl Acad Sci USA. 1998;95:14367–72.

15. Clozel M, Salloukh H. Role of endothelin in fibrosis and anti-fibrotic potential of bosentan. Ann Med. 2005;37(1):2-12.

16. Sfikakis PP, Papamichael C, Stamatelopoulos KS, Tousoulis D, Fragiadaki KG, Katsichti P, et al. Improvement of vascular endothelial function using the oral endothelin receptor antagonist bosentan in patients with systemic sclerosis. Arthritis Rheum. 2007;56(6):1985-93.

17. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, et al. Nitric oxide is responsible for flow-mediated dilatation of human peripheral conduit arteries in vivo. Circulation. 1995;91:1314–9.

18. Allanore Y, Borderie D, Hilliquin P, Hernvann A, Levacher M, Lemarechal H, et al. Low levels of nitric oxide (NO) in systemic sclerosis: inducible NO synthase production is decreased in cultured peripheral blood monocyte/macrophage cells. Rheumatology (Oxford). 2001;40:1089–96.

19. Kahaleh MB. Vascular involvement in systemic sclerosis (SSc). Clin Exp Rheumatol. 2004;22 (Suppl 33):S19–23.

20. Girgis RE, Champion HC, Diette GB, Johns RA, Permutt S, Sylvester JT. Decreased exhaled nitric oxide in pulmonary arterial hypertension: response to bosentan therapy. Am J Respir Crit Care Med. 2005;172:352–7.

21. Launay D, Diot E, Pasquier E, Mouthon L, Boullanger N, Fain O, et al. Bosentan for treatment of active digital ulcers in patients with systemic sclerosis. Presse Med. 2006;35:587-92.

22. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2011;70(1):32-8.

23. De Haro J, Acin F, Bleda S, Varela C, Esparza L. Treatment of thromboangiitis obliterans (Buerger's disease) with bosentan. BMC Cardiovasc Disord. 2012;14:12-5.

24. Ohta T, Ishioashi H, Hosaka M, Sugimoto I. Clinical and social consequences of Buerger Disease. J Vasc Surg. 2004;39:176-80.

25. Puéchal X, Fiessinger JN. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. Rheumatology (Oxford). 2007;46(2):192-9.

26. Jaff MR. Thromboangiitis obliterans (Buerguer's disease). Curr Treat Options Cardiovasc Med. 2000;2(3):205-12.

27. Fiessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. The TAO study. Lancet. 1990;335(8689):555-7.

28. The European TAO Study Group. Oral iloprost in the treatment of thromboangiitis obliterans (Buerguer's disease): a double-blind, randomised, placebo-controlled trial. Eur J Vasc Endovasc Surg. 1998;15(4):300-7.

29. De Haro J, Florez A, Fernandez JL, Acin F. Treatment of Buerger disease (thromboangiitis obliterans) with bosentan: a case report. BMJ Case Rep. 2009;2009.pii:bcr08.2008.0691.

30. Palomo-Arellano A, Cervigón-González I, Torres-Iglesias LM. Effectiveness of bosentan in the treatment of ischemic lesions in a case of thromboangiitis obliterans (Buerguer's disease): a case report. Dermatol online J. 2011;17(7):4.

31. Todoli Parra JA, Hernández MM, Arrebola López MA. Efficacy of bosentan in digital ischemic ulcers. Ann Vasc Surg. 2010;24(5):690.

32. Czarnacki M, Gacka M, Adamiec R. A role of endothelin 1 in the pathogenesis of thromboangiitis obliterans (initial news). 2004;61(12):1346-50.

33. De Haro J, Bleda S, Varela C, Esparza E, Lopez de Maturana I, Acin F. Abstract 19723: Randomized comparison of bosentan in intermittent claudication in peripheral arterial disease: the clinical and endotelial function assessment after endothelin receptor antagonism (CLAU). Randomized controlled trial. Circulation. 2012;126:A19723.

NATIONWIDE FAMILY STUDIES OF CARDIOVASCULAR DISEASES - CLINICAL AND GENETIC IMPLICATIONS OF FAMILY HISTORY

Bengt Zöller

Associate Professor of Internal Medicine, Faculty of Medicine, Lund University, and Family Physician, Centre for Primary Health Care Research, Lund University/Region Skåne, Malmö, Sweden

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ABSTRACT

Studies of family history (FH) have long been used to estimate the heritability of cardiovascular diseases (CVDs). Genome-wide association studies (GWAS) of several CVDs, such as coronary heart disease (CHD), stroke, aortic aneurysm (AA), atrial fibrillation (AF), and venous thromboembolism (VTE), have found several novel gene loci and have revealed new biological mechanisms. However, most of the heritability for common CVDs remains to be discovered. Studies of FH will continue to be the easiest way to measure the inherited and non-genetic component of a CVD, as FH represents the sum of interactions between environmental and genetic factors. Many past FH studies of CVDs were hampered by recall and selection bias, small study sizes, retrospective case-control study designs, and a lack of follow-up data. Large nationwide register-based follow-up studies of FH have become possible in countries such as Sweden, Denmark, and Iceland. For instance, nationwide family studies of CVDs such as CHD, stroke, AA, AF, and VTE have been published. Such nationwide family studies may be very helpful for the planning of genetic studies to identify the missing heritability of CVDs. Moreover, reliable estimates of the familial risks of CVDs may be helpful for clinical risk assessment. In this article, the design, methodology, results, clinical and genetic implications, and pros and cons of nationwide FH studies are reviewed. The focus is on studies based on Swedish healthcare data. New findings from these studies will be summarised, and future opportunities will be presented.

Keywords: Cardiovascular disease, coronary heart disease, stroke, venous thromboembolism, genetics.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death and disability in the world.[1] Of the 17.3 million deaths from CVDs in 2008, coronary heart disease (CHD) was responsible for 7.3 million and stroke for 6.2 million.[1] All common CVDs are complex diseases where both environmental and genetic factors are important in the pathogenesis.[2] Genome-wide association studies (GWAS) have uncovered new genetic loci, not only for CHD, myocardial infarction (MI) and stroke, but also for other CVDs such as aortic aneurysm (AA), atrial fibrillation (AF), heart failure (HF), and venous thromboembolism (VTE).[2] VTE is the third most common CVD after CHD and stroke, and its most severe complication, pulmonary embolism (PE), is potentially lethal.[3] Though GWAS have been successful in identifying a vast number of novel genetic variants associated with CVDs, most new variants are weak and have so far not turned out to be clinically useful for risk assessment.[4] For common CVDs, only a fraction of the estimated heritability is explained by the new variants.[4] The term 'missing heritability' has therefore been introduced.[4] Several explanations for the missing heritability have been proposed, such as the presence of multiple undetected variants of smaller effect, rarer but possibly strong variants that are poorly detected by available genotyping arrays, structural variants, low power to detect gene–gene interactions, and inflated familial risks due to inadequate accounting for sharing of environments by relatives.[4]

At the moment, clinicians usually have to rely on the classic tool of family history (FH) in order to estimate whether a patient has an increased genetic risk of CVD.[5] However, many studies of FH are small case-control studies suffering from recall, selection, and ascertainment bias. There have been few prospective risk prediction studies.[5] Moreover, FH is not a binary trait.[6] The risk associated with FH is dependent on age, genetic distance to the affected relative, and number of affected relatives.[6] However, most family studies are too small to be able to give firm estimates. Nationwide family studies using official healthcare and population registers are relatively new possibilities in countries such as Sweden, Denmark, and Iceland.[7] Nationwide FH studies may not only be important for clinical risk assessment but may also be helpful for the planning of genetic studies aimed at discovering the cause(s) of missing heritability. An overview of these nationwide family studies will be presented, with a special focus on Sweden.

METHODS FOR STUDYING FAMILIAL RISKS

A central theme in genetic epidemiology is the study of diseases within families.[8] Familial aggregation of a trait is a necessary, though insufficient, condition to infer the importance of genetic susceptibility.[9] As well as genes, environmental and cultural influences may also aggregate in families, leading to familial clustering and increased familial risks.[9,10] However, without familial aggregation, which indicates a small genetic contribution to a particular disease, a further hunt for a genetic cause might not be successful.[6] If the phenotype is binary, the familial relative risk (FRR, i.e. the ratio of the risks of those with and without an FH) may be expressed as a recurrence risk ratio (λ), which is the prevalence of the disease in relatives with affected relatives divided by the prevalence in the general population.[6] Another way to express the FRR of binary phenotypes is the SIR, (standardised incidence ratio i.e. incidence rate of the disease in individuals with an FH compared with the incidence rate in those without an FH).[10] SIR is the standard method for cohort studies.[10] Other commonly used measures of the FRR are the odds ratio (OR, the ratio of the odds of disease of those with and without an FH) and hazard ratio (HR, the ratio of rates).[10] In the present review, the term FRR will be used to describe all these measures, although ORs and HRs are ratios and not relative risks.

An FRR of around two in first-degree relatives is seen in many complex diseases.[6] Although an FRR of two might appear modest, it suggests that uncovering the familial aggregation might be worthwhile.[6] However, the non-genetic contribution to familial aggregation might often be underestimated, and familial aggregation of a disease is no guarantee of success in finding causative gene variants. There are different methods for trying to disentangle genetic and environmental influences.[6,9,10] A commonly used design is the twin study. Identical twins (monozygotic) inherit identical genetic material, while dizygotic twins have the same genetic relationship as full siblings (50% shared genes) but share the same environmental factors. Another powerful method is to study risk in biological relatives of affected adoptees compared to control adoptees, because adoption creates a separation between an individual´s biological and environmental influences.[9] Studying FRRs in spouses is a way to estimate the effect of adult shared family environment (Table 1).[9-11] FRRs in spouses are low for many, but not all, complex diseases in the Swedish population. A high spousal risk suggests important familial non-genetic influences. Thus, a low spousal risk is a prerequisite for estimating biologically relevant (i.e. genetic) familial risks using nationwide registers (Table 1).[12-20] Studies of half-siblings can also help to disentangle genetic and non-genetic contributions to FH.[21] Moreover, an increased risk in second and third-degree relatives supports the interpretation that genetic factors influence familial aggregation, since individuals outside the nuclear family are less likely to have shared the same environmental exposure(s).[22] Another possibility to test for the extent of environmental sharing is to calculate FRRs according to age difference between siblings.[16] Large age differences indicate less shared environment and vice versa.

Nordic Twin and Adoption Studies

The Nordic countries have twin registers that may be used to estimate the heritability of disease.[23-26] Many important studies on CVDs have come from these registers.[27-35] While few adoption studies have been published, a recent nationwide Swedish study of 80,214 adoptees found that the familial transmission of CHD risk is related to CHD in biological parents and not in adoptive parents.[36] Though twin and adoption studies are very important for disentangling genetic and environmental influences, they are of little help for clinical risk assessment for the vast majority of patients. This report will focus on nationwide studies of the importance of family history in first, second, and third-degree relatives, which becomes possible after a nation becomes a cohort, as has happened in Sweden.[37]

Table 1. Swedish nationwide familial relative risks (FRRs) for several cardiovascular diseases (CVDs) and type 2 diabetes mellitus and Graves' disease, among spouses.

	Spouse FRR (95% CI)
CHD[12]	1.05 (1.05-1.06)
Ischaemic stroke[13]	1.06 (1.00–1.13)*
Haemorrhagic stroke[13]	0.99 (0.85–1.15)*
Subarachnoid haemorrhage[14]	1.06 (0.64–1.66)
Atrial fibrillation[15]	1.16 (1.13–1.19)
VTE[16]	1.07 (1.04–1.10)
PE[17]	1.09 (1.03–1.14)
Varicose veins[18]	1.69 (1.59–1.80)*
Type 2 diabetes mellitus[19]	1.32 (1.29–1.35)
Graves' disease[20]	2.75 (1.93–3.82)

*For wives

FRR for ischaemic stroke in husbands 1.08 (1.02–1.14)

FRR for haemorrhagic stroke in husbands 1.01 (0.86–1.17)

FRR for varicose veins in husbands 1.68 (1.58–1.79)

Nationwide Swedish Registers

Denmark,[37] Iceland,[38] and Sweden[39,40] have nationwide registries that allow individuals to be linked to their relatives. Central to performing nationwide studies in Sweden is the unique 10-digit personal identity number (PIN) assigned to each resident of Sweden for life.[41] These PINs are used to link individual data from several registers, such as the Total Population Register, the Swedish Multi-generation Register, and Swedish Inpatient Register (see below). The Multi-generation Register allows an individual to be linked to his/her relatives.[39] Statistic Sweden and the National Board of Health and Welfare maintain these registers. The most commonly used registers are listed below:

1. The Swedish Multi-generation Register contains information on the family relationships[39,40,42] of more than 9 million individuals born from 1932 onwards, with data on mothers for 97% of index persons and on fathers for 95% of index persons.

2. The Total Population Register (TPR)[42,43] contains data on place of residence, sex, age, civil status, place of birth, citizenship, immigration, and relations (married couples, offspring–parents).

3. The Swedish National Census Register[42] contains data from coordinated nationwide censuses that were completed in Sweden every fifth year between 1960 and 1990. For each individual, the register includes information on their PIN, occupation, residence, and educational level.

4. The Swedish Inpatient Register (IPR), also called the Hospital Discharge Register, contains all hospital diagnoses for all people in Sweden from 1987 onwards.[44-46] Between 1964 and 1987, the coverage was incomplete but increased steadily (1964: 6%; 1972: 36%; 1982: 71%; 1984: 86%). Every record includes the main discharge diagnosis. The validity in the IPR is generally 85-95% for the primary diagnosis.[44-46] For several CVDs, such as MI, stroke, VTE, AF, and HF the validity is around 95% for the primary diagnosis.[47-51] There is also good agreement between the Swedish National Registry for Vascular Surgery (Swedvasc) and the IPR regarding the validity for carotid, infrainguinal bypass, and abdominal AA repair (93.4%, 93.0%, and 93.1%, respectively).[52]

5. The Swedish Outpatient Care Register[46] holds information from all outpatient clinics in Sweden from 2001 onwards (not primary health care).

6. The Swedish Cause of Death Register contains data on cause and date of death from 1961 onwards and is fairly valid for a number of diagnoses.[53,54]

7. The Swedish Cancer Registry covers all diagnosed cancers since 1958.[55]

8. The Medical Birth Register holds information on practically all births in Sweden since 1973.[56]

9. The National Prescription Database contains data on drugs dispensed at pharmacies in Sweden since July 2005 (exposure data) to individuals receiving ambulatory care.[57]

10. The Swedish Conscript Register contains medical data on all Swedish conscripts born in, or since 1946, including data on height, weight, blood pressure, vision, hearing, fitness, and muscle strength, as well as psychological test results.[58]

Besides these registers there are a large number of nationwide quality registers, such as the Swedvasc,[52] the SWEDEHEART register (formerly RIKS-HIA),[59] and the Swedish stroke register (Riks-Stroke).[60]

NATIONWIDE FAMILY STUDIES

Coronary Heart Disease

GWAS have identified a large number of genetic variants with small effects on CHD.[61] However, the clinical utility of the novel GWAS findings remains uncertain.[61] A large number of family studies of CHD and MI risk in first-degree relatives have also been published (reviewed by Banerjee).[5] According to Banerjee, more long-term prospective studies are needed to determine the generalisability of FH and to quantify the risk associated with FH in asymptomatic individuals.[5] Nationwide family studies may help to fill these gaps. An example is a recent nationwide Danish study of MI in Danish citizens diagnosed in 1978-2010.[62] A high FRR (rate ratio: 4.30, 95% confidence interval, CI 3.53–5.23) was found in siblings. For offspring, the risk was dependent on the sex of the affected parent: the FRR was 2.40 (95% CI 2.20–2.60) for offspring of maternal cases and 1.98 (95% CI 1.98–2.09) for offspring of paternal cases. This supports two previous studies that found a higher parent-offspring transmission of CHD for maternal cases.[63,64] The cause of this maternal preponderance is unclear and a number of mechanisms have been suggested.[63,64] FH was also a prognostic predictor of survival in patients with MI, according to a Swedish nationwide family study by Ekberg et al.[65]

Another nationwide family study from Sweden found very high familial risks of hospitalisation and death from CHD in families with two or more affected siblings.[12] The concordant SIRs (same disease in proband and case) for hospitalised CHD patients are presented in Table 2, for individuals with one affected sibling (SIR=1.49), two affected siblings (SIR=6.92), and an affected spouse (SIR=1.05).[12] The SIR for death in individuals with two affected siblings was 7.31 (95% CI 4.76–11.19). Thus, having multiple affected siblings is a strong predictor for CHD, with relative risk that is higher than those for many established genetic and acquired risk factors.

Another possibility is to study whether different diseases share familial susceptibility.[66] Pleiotropy occurs when one gene influences multiple phenotypic traits. A mutation in a pleiotropic gene may have an effect on several traits simultaneously. It has been hypothesised that genetic variants affecting the coagulation system and the risk of VTE are also involved in the pathogenesis of CHD,[67] but previous association studies of haemostatic factors and CHD have produced varying results.[67] Zöller et al.[66] therefore determined whether CHD and VTE share familial susceptibility. However, VTE and CHD (and MI) do not aggregate in families to any great degree in Sweden (Table 2).[66] The FFR for biological relatives were similar to those for spouses. Table 2 also shows nationwide concordant (i.e same disease in proband and case) risks from a study of CHD in families with multiple affected siblings[12] and from a nationwide study of VTE.[16] The high concordant and low discordant (i.e different disease in proband and case) risks in biological relatives make it clear that CHD and VTE have completely different familial and genetic causes.[12,16,66] Thus, CHD and VTE are unlikely to share strong genetic risk factors.

Table 2. Concordant (same disease)[12,16] and discordant (different disease)[66] risks of hospitalisation for CHD and VTE among siblings and spouses.

Family history of CHD	CHD SIR (95% CI)	VTE SIR (95% CI)
One affected sibling	1.49 (1.04–2.13)	1.09 (0.75–1.59)
Two affected siblings	6.92 (4.77–10.03)	1.08 (0.72–1.62)
Affected spouse	1.05 (1.05–1.06)	1.03 (1.02–1.03)
Family history of VTE		
One affected sibling	1.18 (0.82–1.71)	2.27 (1.54–3.35)
Two affected siblings	0.70 (0.45–1.09)	51.87 (31.47–85.00)
Affected spouse	1.02 (1.01–1.03)	1.07 (1.04–1.10)

Stroke

Epidemiologic evidence supports a genetic predisposition to stroke.[68] Recent advances, primarily using the GWAS approach, are helping researchers to identify novel stroke genes.[68] However, the genetic variants identified so far are not currently useful in predicting risks for the individual patient. There is therefore, a need for large prospective nationwide family studies of stroke.[69] A Swedish nationwide study by Kasiman et al.[70] determined the FRR for ischaemic stroke in siblings. The overall familial risk of incident ischaemic stroke was significantly increased among all siblings (FRR=1.61, 95% CI 1.48–1.75). The familial risk was higher in full siblings (FRR=1.64, 95% CI 1.50–1.81) than in half-siblings (FRR=1.41, 95% CI 1.10–1.82). Familial risk of early ischaemic stroke was especially high in the siblings of individuals with stroke at a young age (FRR=1.94, 95% CI 1.41-2.67). Another nationwide family study by Sundquist et al.[13] found that ischaemic and haemorrhagic stroke do not share familial susceptibility, which suggests that familial and genetic factors for these two entities are not identical.

It has been hypothesised that genetic variants affecting the coagulation system and the risk of VTE also are involved in the pathogenesis of ischaemic stroke.[71-73] This is in analogy with the above hypothesis that thrombotic coagulation variants and CHD are associated.[67] Previous association studies of haemostatic factors and ischaemic stroke have produced varying results (just as for haemostatic variants and CHD).[67,71-73] However, a recent nationwide study found only weak familial associations between VTE and ischaemic stroke in first-degree relatives.[74] The same strengths of the associations were observed among spouses, suggesting a non-genetic contribution to the observed weak familial associations. Thus, not only CHD[66] but also ischaemic stroke is unlikely to share strong genetic risk factors with VTE.[74]

Nationwide family studies have also found an increased familial risk of subarachnoid haemorrhage in siblings and in multiplex families.[14,75]

Aortic Aneurysm

AA is a complex disease with known environmental influences, such as smoking.[76] A number of studies have shown that AA is frequently familial.[76] The pathobiology of AA is complex and largely unsolved. GWAS are now being used to elucidate the genetic basis of AA.[76] Two nationwide family studies from Sweden have been published.[77,78] The risk of AA was very high in the siblings of individuals diagnosed with AA before 50 years of age (SIR=19.69).[77] This suggests that relatives of individuals with AA should be screened for AA.[77]

Table 3. Familial relative risks (FRRs) for several CVDs (atrial fibrillation, CHD, VTE, varicose veins) and non-CVDs (type 2 diabetes mellitus, Graves' disease, and breast cancer) according to number of affected siblings.

	One affected sibling FRR (95% CI)	Two affected siblings FRR (95% CI)
CHD[12]	1.49 (1.04–2.13)	6.92 (4.77–10.03)
Atrial fibrillation[15]	2.78 (2.69–2.87)	5.72 (5.28–6.19)*
VTE[16]	2.27 (1.54–3.35)	51.87 (31.47–85.00)
PE[17]	2.49 (1.62–3.83)	114.29 (56.57–223.95)
Varicose veins[18]	2.86 (2.76–2.97)	5.88 (5.28–6.53)*
Type 2 diabetes mellitus[19]	2.77 (1.87–4.11)	36.86 (20.96–64.10)
Graves' disease[20]	5.04 (3.03–8.33)	310.34 (99.49–836.75)*

*Two or more affected siblings

Atrial Fibrillation

A large number of genetics studies of AF have been performed, and many genetic variants have been identified. However, much of the heritability of AF is still missing.[79] Arnar et al.[80] performed the first nationwide study of AF in Iceland and presented evidence of an important genetic influence on the familial risks of AF in an extended family study of first to fifth-degree relatives. High familial risks were also found in a Danish study of lone AF (LAF).[81] A Swedish nationwide family study determined the risk of AF in families with multiple affected relatives and found high familial risks in multiplex sibling families (Table 3).[15]

The relevance of family history of AF for prediction of recurrent hospitalisation for AF was previously unknown. A Swedish family study[82] determined that the familial risk of recurrent hospitalisation for LAF was 1.23 (95% CI 1.17–1.30) for individuals with affected parents, and 1.30 (95% CI 1.22–1.38) for those with affected siblings. The risk of recurrent hospitalisation for LAF in individuals with two affected parents was 1.65 (95% CI 1.44–1.90). FH was a stronger predictor for recurrent AF in younger age groups. The familial risk for recurrent hospitalisation for LAF was, however, much lower than the risk for initial LAF hospitalisation (FRR=2.08, 95% CI 2.02–2.15 for offspring and FRR=3.23, 95% CI 3.08–3.39 for siblings), suggesting that familial and possibly genetic influences are more important for initial hospitalisation for LAF than for recurrent hospitalisation for LAF.[82]

Venous Thromboembolism

Familial thrombophilia—aggregation of VTE in families—has been associated with deficiencies of antithrombin, protein C and protein S, resistance to activated protein C (APC resistance or presence of factor V Leiden=rs6025), and the prothrombin 20210G to A variant (=rs1799963).[83] However, the predictive value of FH for finding any of these defects is low.[84] The association between FH in first-degree relatives and risk of VTE has been assessed in a few case-control studies.[84-86] The FRRs in these studies of FH of VTE ranged from 2.2 to 2.7.[84-86] No family studies that used follow-up data had been published until Swedish and Danish nationwide studies assessed the familial risk in siblings, with very similar results (overall FRR=2.45 and 3.08, respectively).[16,87] The Swedish study also determined the risk of VTE when two siblings were affected and found a very high risk of VTE (FRR=51.87) (Table 2).[16] The risk among spouses was low (Table 1). Another study determined the familial risks in the offspring of affected parents (overall FRR=2.00) (Table 4).[88] When both parents were affected, the FRR was 3.97 (Table 4).[88] One Swedish study showed that VT of the legs, PE, and other types of VTE (OVTE) all share familial susceptibility.[89] Moreover, even unusual forms of VTE have increased familial risks.[90]

In another study, the familial age-specific and sex-specific risks were determined separately for VT, PE, and OVTE (Figure 1).[91] All manifestations of VTE were highly age-dependent. Family history was important for VT, PE, and OVTE at all studied ages (0-76 years), except for the first 10 years of life.[91] This is in line with the literature showing that VTE rarely occurs before 10 years of age in families with thrombophilia.[92,93] In small children, VTE is very rare and is often associated with the presence of multiple risk factors simultaneously.[94] An increased risk of fatal PE was detected in individuals with an FH of PE (FRR=1.76, 95% CI 1.38–2.21).[17] Especially high risks of PE were observed in families with multiple affected siblings (Table 3).[17] Another nationwide Swedish study by Kristinsson et al.[95] found that FH of VTE is a predictor of VTE even for patients with multiple myeloma.

Recently the familial risks of VTE in first, second, and third-degree relatives were estimated.[96] The familial OR for VTE among first-degree relatives was 2.49 in siblings (95% CI 2.40–2.58), 2.65 in offspring (95% CI 2.50–2.80), 2.09 in parents (95% CI 2.03–2.15). Among second-degree relatives, the familial OR was 2.34 in paternal half-siblings (95% CI 2.00–2.73), and 1.52 in maternal half-siblings, and 1.69 in nieces/nephews (95% CI 1.57–1.82). Among cousins (third-degree relatives), the risk was 1.47 (95% CI 1.33–1.64). Familial clustering was stronger at young ages. According to data from the national censuses, the majority of maternal half-siblings in Sweden were registered as living in the same home as each other (83%); only 3% of paternal half-siblings lived in the same home.[97] The high risk in paternal half-siblings therefore suggests a strong genetic contribution.[96] Moreover, the increased VTE risk among second and third-degree relatives indicates that the genetic component of the familial clustering of VTE is important. Familial clustering was slightly stronger for males compared with females, but was only significant for siblings and parents of probands.[96] The stronger clustering among males is in agreement with a Danish twin study,[29] but its cause is unclear.

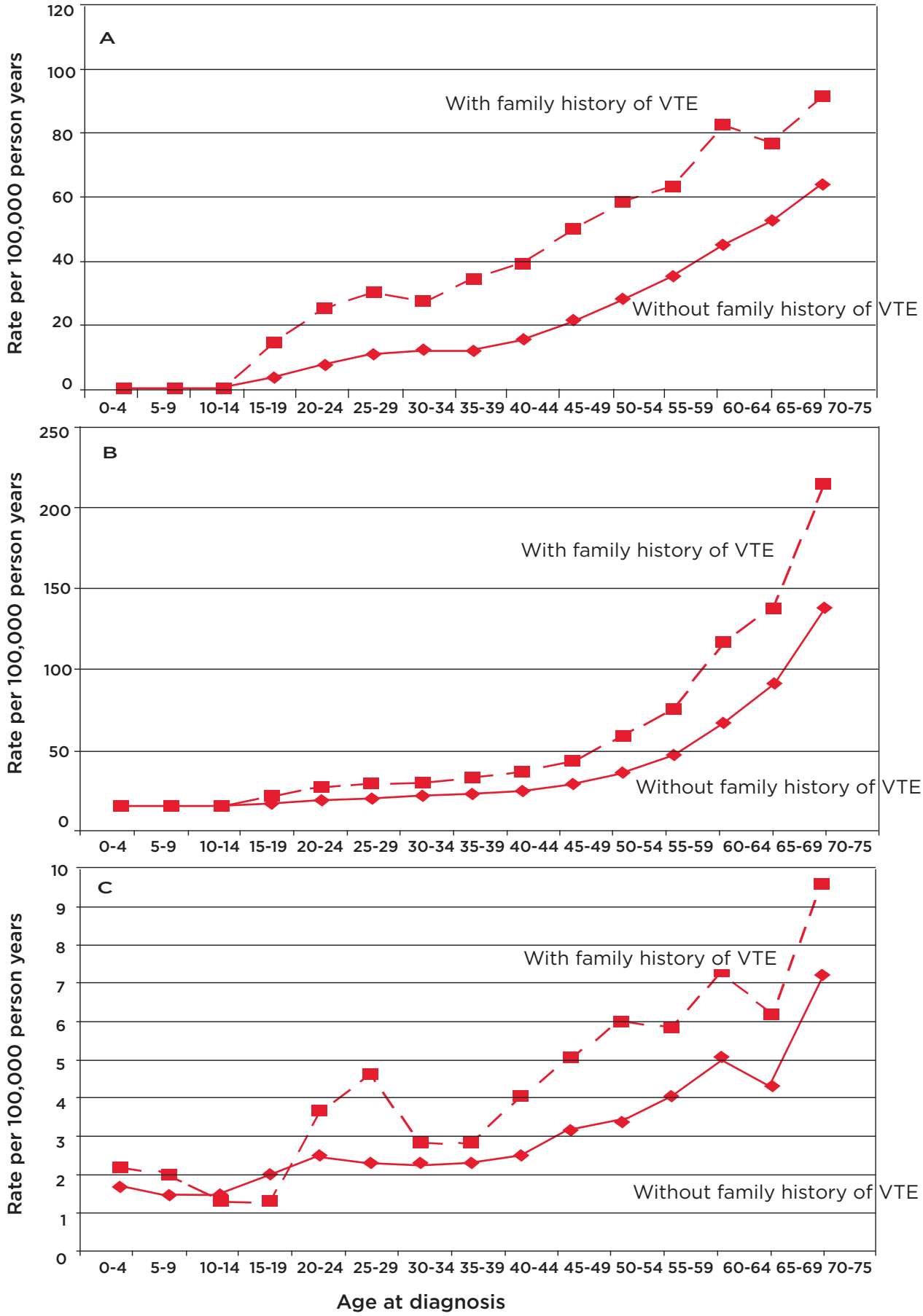

Figure 1. Age-specific incidence rates for (A) venous thrombosis of the lower extremities (VT), (B) pulmonary embolism (PE), and (C) other types of venous thromboembolism (OVTE), by family history of VTE in parents and siblings.

Reproduced from Zöller et al.[91] with permission from Thrombosis and Haemostasis (Schattauer GmbH).

Table 4. Familial relative risks (FRRs) for several CVDs (atrial fibrillation, VTE, PE, varicose veins) and non-CVDs (type 2 diabetes mellitus and Graves' disease) in offspring according to number of affected parents.

	One affected parent FRR (95% CI)	Both parents affected FRR (95% CI)
Atrial fibrillation[15]	1.95 (1.89–2.00)	3.60 (3.30–3.92)
VTE[16]	2.00 (1.94-2.05)*	3.97 (3.40–4.61)
PE[17]	1.95 (1.85–2.06)	2.74 (1.70–4.20)
Varicose veins[18]	2.39 (2.32–2.46)	5.52 (4.77–6.36)
Type 2 diabetes mellitus[19]	2.03 (1.98–2.08)	5.35 (4.56–6.24)
Graves' disease[20]	4.49 (3.82–5.24)*	4.51 (0.43–16.60)**

*One or both affected parents
**Both parents plus a sibling affected

Families with Multiple Affected Relatives (Multiplex Families)

Family history of CVD is especially important for individuals with multiple affected siblings (Table 3). Having two affected siblings was associated with high risks of AF, CHD, VTE, PE, and varicose veins (Table 3). The FRRs for VTE and PE were exceptionally high (Table 3), compared to the risks in offspring with two affected parents (Table 4). Few other nationwide studies have reported familial risks for complex diseases in families with multiple affected siblings. However, for diabetes mellitus type 2 and Graves' disease, similarly high risks in multiplex sibling families were reported (Table 3).[19,20] For AF and varicose veins, the differences between the multiplex familial risks for siblings and offspring were not so large (Tables 3 and 4). Although higher risks among multiplex families have been described for complex diseases,[6] the cause is unclear and could be different for different diseases. Among families with familial thrombophilia, interactions between rare genetic disorders, such as protein S, protein C or antithrombin deficiencies, and the more common rs6025 and rs1799963, variants have been described.[93,98-100] A 50-100 times increased risk of VTE was estimated for individuals with both protein S deficiency and the rs6025 variant.[100] Homozygosity for the rs6025 variant is also associated with a very high risk of VTE.[101] It remains to be determined whether such strong gene-gene interactions exist for other complex diseases with high multiplex sibling risks.

DISCUSSION

The nationwide family studies presented in this review serve as a good example of the possibilities that exist when a whole country becomes a cohort.[37] Nationwide health databases are invaluable for probing contradictions raised by smaller studies and for following disease progression.[102] Sweden, like Denmark, has become a dream for epidemiologists.[102] Recent nationwide family studies with long-term follow-up have shown that FH of several CVDs is a strong and clinical relevant risk factor for being affected by CVD. This sets the focus on the clinical importance of FH. It is obvious from these nationwide studies that FH of CVDs is not a binary trait; it is dependent on age, sex, number of affected relatives, and the relatedness of the affected relatives. Precise estimates of relative and absolute risks in relation to age, sex, relatedness, and number of affected relatives can be determined. Nationwide family studies may also help in the planning of genetic studies. The high risk of disease (Table 3) in multiplex sibling families suggest that selecting individuals with two or more affected siblings will increase the chance of identifying new variants considerably.

Nationwide family studies in the GWAS era

Though GWAS have been successful in identifying a large number of new genetic variants associated with CVDs, most novel variants are weak and have so far not been clinically useful for risk assessment.[4] Family history studies remain the most accessible way of measuring the hereditary component of a

disease and they represent the overall interaction between environmental, epigenetic and genetic factors.[4] It is therefore possible that even when sequencing a patient's genome may cost less than $1,000, family history will remain highly relevant for years to come.[103]

Pros and cons

The major advantage of nationwide studies is their large size. Moreover, nationwide family studies may be conducted cheaply and quickly as long-term follow-up data already exist for the entire population. Data in several Swedish registers are almost complete.[40] Thus, it is easy to test hypotheses and generate new ideas using nationwide registers, and to predict long-term follow-up risks.

There are important limitations of the Swedish databases. There is no information about individual risk factors such as smoking, weight, height, body mass index, blood pressure, and cholesterol levels. However, there is access to socioeconomic data on income, education, and occupation, which correlate with lifestyle factors.[11,42] Adjusting for socioeconomic data and comorbidities could help to diminish confounding by these factors. However, as in any observational cohort study, residual confounding remains a concern in nationwide studies.[104] Another limitation is the lack of information on the diagnostic methods used. However, many validation studies have been performed, and the validity for many CVDs is high in the Swedish Inpatient Register.[44-52]

A further limitation is that the nationwide studies are restricted to Sweden, Denmark, or Iceland and mainly reflect familial risks in the Swedish, Danish or Icelandic population, respectively. However, the Swedish population is, for instance, genetically closely related to German[105] and British[106] people and the results from Swedish nationwide family studies are likely to be valid for many individuals of Caucasian origin in Europe and the USA. However, Sweden, like many countries, has experienced dramatic demographic changes due to increasing global migration. Today, approximately 20% of all people living in Sweden are first or second-generation immigrants.[107] This large immigrant population, together with the nationwide health and sociodemographic data available, provides a unique opportunity to study the risk of many diseases among first and second-generation immigrants from multiple countries and regions around the world, and to compare the risk of different diseases in these groups with that in two corresponding generations of native-born Swedes.[108] For instance, a nationwide study of VTE risk in first and second-generation immigrants found that the country of birth affects the risk of VTE in several immigrant groups.[108]

Ethical considerations

The data in the nationwide registers mentioned here are anonymised and, as for all other research, ethics codes and laws regulate the research process.[109] Still, there is an ongoing debate about using official registers for research.[37] The majority of the Swedish population has a positive attitude towards genetic research.[110] This positive attitude is driven by altruism, and depends on the public being well informed and having trust in experts and institutions.[110]

Future opportunities

Linking nationwide quality registers[52,59,60] and data from large population-based cohort studies with the Multi-generation Register would allow incorporation of both FH and traditional risk factors in risk assessment models. Another possibility is linking nationwide registers, including the Multi-generation Register, with large biobanks. For instance, neonatal blood collected on filter paper (Guthrie cards) for screening purposes is routinely stored for decades in the Swedish National Phenylketonuria (PKU) register.[111] This could allow for nationwide genetic linkage studies with coverage of a whole country.

CONCLUSIONS

Nationwide registries are enormous and unique scientific assets and research on them will benefit society in general. Nationwide family studies have contributed much new knowledge, and may continue to be an important source of new knowledge regarding the clinical risks and genetics of CVDs.

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REFERENCES

1. World Health Organization. Cardiovascular Disease: Global atlas on cardiovascular disease prevention and control: policies, strategies and interventions. Mendis S, Puska P, Norrving B [eds]. Geneva: WHO. 2012.

2. O'Donnell CJ, Nabel EG. Genomics of cardiovascular disease. N Engl J Med. 2011;365:2098-109.

3. Goldhaber SZ. Venous thromboembolism: epidemiology and magnitude of the problem. Best Pract Res Clin Haematol. 2012;25:235-42.

4. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461:747-53.

5. Banerjee A. A review of family history of cardiovascular disease: risk factor and research tool. Int J Clin Pract. 2012;66:536-43.

6. Burton PR, Tobin MD, Hopper JL. Key concepts in genetic epidemiology. Lancet. 2005;366:941-51.

7. Hemminki K, Li X, Sundquist K, et al. Familial risks for common diseases: etiologic clues and guidance to gene identification. Mutat Res. 2008;658:247-58.

8. Hopper JL, Bishop DT, Easton DF. Population-based family studies in genetic epidemiology. Lancet. 2005;366:1397-406.

9. Risch N. The genetic epidemiology of cancer: interpreting family and twin studies and their implications for molecular genetic approaches. Cancer Epidemiol Biomarkers Prev. 2001;10:733-41.

10. Thomas DC. Statistical Methods in Genetic Epidemiology. (2004). New York: Oxford University Press, pp. 684-5.

11. Family Matters: Designing, analysing and understanding family-based studies in life-course epidemiology. Lawlor DA, Mishra GD (eds.), (2009). New York: Oxford University Press.

12. Zöller B, Li X, Sundquist J, et al. Multiplex sibling history of coronary heart disease is a strong risk factor for coronary heart disease. Eur Heart J. 2012;33:2849-55.

13. Sundquist K, Li X, Hemminki K. Familial risk of ischaemic and hemorrhagic stroke: a large-scale study of the Swedish population. Stroke. 2006;37:1668-73.

14. Sundquist J, Li X, Sundquist K, et al. Risks of subarachnoid hemorrhage in siblings: a nationwide epidemiological study from Sweden. Neuroepidemiology. 2007;29:178-84.

15. Zöller B, Ohlsson H, Sundquist J, et al. High familial risk of atrial fibrillation/atrial flutter in multiplex families: a nationwide family study in Sweden. J Am Heart Assoc. 2012;2:e003384.

16. Zöller B, Li X, Sundquist J, et al. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. Circulation. 2011;124:1012-20.

17. Zöller B, Li X, Sundquist J, et al. A nationwide family study of pulmonary embolism: identification of high risk families with increased risk of hospitalized and fatal pulmonary embolism. Thromb Res. 2012;130:178-82.

18. Zöller B, Ji J, Sundquist J, et al. Family history and risk of hospital treatment for varicose veins in Sweden. Br J Surg. 2012;99:948-53.

19. Hemminki K, Li X, Sundquist J, et al. Familial risks for type 2 diabetes in Sweden. Diabetes Care. 2010;33:293-7.

20. Hemminki K, Li X, Sundquist J, et al. The epidemiology of Graves' disease: evidence of a genetic and an environmental contribution. J Autoimmun. 2010;34:J307-13.

21. Tierney C, Merikangas KR, Risch N. Feasibility of half-sibling designs for detecting a genetic component to a disease. Genet Epidemiol. 1994;11:523-38.

22. Kerber RA. Method for calculating risk associated with family history of a disease. Genetic Epidemiology. 1995;12:291-301.

23. Lichtenstein P, De Faire U, Floderus B, et al. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. J Intern Med. 2002;252:184-205.

24. Skytthe A, Kyvik K, Holm NV, et al. The Danish Twin Registry: 127 birth cohorts of twins. Twin Res. 2002;5:352-7.

25. Bergem AL. Norwegian Twin Registers and Norwegian twin studies-an overview. Twin Res. 2002;5:407-14.

26. Kaprio J, Koskenvuo M, Rose RJ. Population-based twin registries: illustrative applications in genetic epidemiology and behavioral genetics from the Finnish Twin Cohort Study. Acta Genet Med Gemellol (Roma). 1990;39:427-39.

27. Marenberg ME, Risch N, Berkman LF, et al. Genetic susceptibility to death from coronary heart disease in a study of twins. N Engl J Med. 1994;330:1041-6.

28. Bak S, Gaist D, Sindrup SH, et al. Genetic liability in stroke: a long-term follow-up study of Danish twins. Stroke. 2002;33:769-74.

29. Larsen TB, Sørensen HT, Skytthe A, et al. Major genetic susceptibility for venous thromboembolism in men: a study of Danish twins. Epidemiology. 2003;14:328-32.

30. Zdravkovic S, Wienke A, Pedersen NL, et al. Genetic susceptibility of myocardial infarction. Twin Res Hum Genet. 2007;10:848-52.

31. Zdravkovic S, Wienke A, Pedersen NL, et al. Genetic influences on angina pectoris and its impact on coronary heart disease. Eur J Hum Genet. 2007;15:872-7.

32. Christophersen IE, Ravn LS, Budtz-Joergensen E, et al. Familial aggregation of atrial fibrillation: a study in Danish twins. Circ Arrhythm Electrophysiol. 2009;2:378-83.

33. Korja M, Silventoinen K, McCarron P, et al. Genetic epidemiology of spontaneous subarachnoid hemorrhage: Nordic Twin Study. Stroke. 2010;41:2458-62.

34. Wahlgren CM, Larsson E, Magnusson PK, et al. Genetic and environmental contributions to abdominal aortic aneurysm development in a twin population. J Vasc Surg. 2010;51:3-7.

35. Wahlgren CM, Magnusson PK. Genetic influences on peripheral arterial disease in a twin population. Arterioscler Thromb Vasc Biol. 2011;31:678-82.

36. Sundquist K, Winkleby M, Li X, et al. Familial [corrected] transmission of coronary heart disease: a cohort study of 80,214 Swedish adoptees linked to their biological and adoptive parents. Am Heart J. 2011;162:317-23.

37. Frank L. Epidemiology. When an entire country is a cohort. Science. 2000;287:2398-9.

38. Tulinius H. Multigenerational information: the example of the Icelandic Genealogy Database. Methods Mol Biol. 2011;675:221-9.

39. Ekbom A. The Swedish Multi-generation Register. Methods Mol Biol. 2011;675:215-20.

40. Rosen M, Hakulinen T. "Use of disease registers," Wolfgang A, Iris P (eds.), Handbook of epidemiology. (2005), Berlin:Springer-Verlag, pp.231-51.

41. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24:659-67.

42. Statistics Sweden. SCB-data för forskning 2011. (Microdata at Statistic Sweden for research purposes). (2011) Örebro:Statistics Sweden.

43. Johannesson I. The Total Population Register of Statistics Sweden. New Possibilities and Better Quality. Örebro: Statistics Sweden. 2002.

44. National Board of Health and Welfare: Validity of the Diagnoses from the Swedish In-Care Register 1987 and 1995. Stockholm: Epidemiologiskt Centrum. Socialstyrelsen. 2000.

45. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

46. Forsberg L, Rydh H, Jacobsson A, et al. Kvalitet och Innehåll i Patientregistret. Utskrivningar Från Slutenvården 1964-2007 och Besök i Specialiserad Oppenvård (exklusive primärvårdsbesök) 1997-2007. Quality and Content of the Patient Register. 2009.

47. Lindblad U, Råstam L, Ranstam J, et al. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med. 1993;21:3-9.

48. Hammar N, Alfredsson L, Rosen M, et al. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. Int J Epidemiol. 2001;30:S30-4.

49. Ingelsson E, Arnlöv J, Sundström J, et al. The validity of a diagnosis of heart failure in a hospital discharge register. Eur J Heart Fail. 2005;7:787-91.

50. Rosengren A, Fredén M, Hansson P-O, et al. Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. J Thromb Haemost. 2008;6:558-64.

51. Smith JG, Platonov PG, Hedblad B, et al. Atrial fibrillation in the Malmö Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. Eur J Epidemiol. 2010;25:95-102.

52. Troëng T, Malmstedt J, Björck M. External validation of the Swedvasc registry: a first-time individual cross-matching with the unique personal identity number. Eur J Vasc Endovasc Surg. 2008;36:705-12.

53. de Faire U, Friberg L, Lorich U, et al. A validation of cause-of-death certification in 1156 deaths. Acta Med Scand. 1976;200:223–8.

54. Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. Int J Epidemiol. 2000;29:495-502.

55. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol. 1984;23:305–13.

56. National Board of Health and Welfare, Centre for Epidemiolog. The Swedish Medical Birth Registry—a Summary of Content and Quality. 2003.

57. National Board of Health and Welfare. Fyra år med Läkemedelsregistret. 2003.

58. Rekryteringsmyndigheten. http://www.rekryteringsmyndigheten.se/service-och-e-tjanster/centrala-lakarhandlingsarkivet/ [2013].

59. Stenestrand U, Wallentin L. Fibrinolytic therapy in patients 75 years and older with ST-segment-elevation myocardial infarction: one-year follow-up of a large prospective cohort. JAMA Intern Med. 2003;163:965-71.

60. Asplund K, Hulter Åsberg K, Appelros P, et al. The Riks-Stroke story: building a sustainable national register for quality assessment of stroke care. Int J Stroke. 2011;6:99-108.

61. Swerdlow DI, Holmes MV, Harrison S, et al. The genetics of coronary heart disease. Br Med Bull. 2012;102:59-77.

62. Nielsen M, Andersson C, Gerds TA, et al. Familial clustering of myocardial infarction in first-degree relatives: a nationwide study. Eur Heart J. 2013;34:1198-203.

63. Sundquist K, Li X. Differences in maternal and paternal transmission of coronary heart disease. Am J Prev Med. 2006;30:480-6.

64. Banerjee A, Silver LE, Heneghan C, et al. Sex-specific familial clustering of myocardial infarction in patients with acute coronary syndromes. Circ Cardiovasc Genet. 2009;2:98-105.

65. Ekberg S, Ploner A, de Faire U, et al. Familial effects on survival after myocardial infarction: a registry-based sib-pair study. Eur J Epidemiol. 2012;27:911-4.

66. Zöller B, Li X, Sundquist J, et al. Venous thromboembolism does not share strong familial susceptibility with coronary heart disease: a nationwide family study in Sweden. Eur Heart J. 2011;32:2800-5.

67. Ye Z, Liu EH, Higgins JP, et al. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66 155 cases and 91 307 controls. Lancet. 2006;367:651-8.

68. Markus HS. Stroke genetics: prospects for personalized medicine. BMC Med. 2012;10:113.

69. Flossmann E, Schulz UG, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischaemic stroke. Stroke. 2004;35:212-27.

70. Kasiman K, Lundholm C, Sandin S, et al. Familial effects on ischaemic stroke: the role of sibling kinship, sex, and age of onset. Circ Cardiovasc Genet. 2012;5:226-33.

71. Casas JP, Hingorani AD, Bautista LE, et al. Meta-analysis of genetic studies in ischaemic stroke: thirty-two genes involving approximately 18,000 cases and 58,000 controls. Arch Neurol. 2004;61:1652–61.

72. Bentley P, Peck G, Smeeth L, et al. Causal relationship of susceptibility genes to ischaemic stroke: comparison to ischaemic heart disease and biochemical determinants. PLoS One. 2010;5:e9136.

73. Juul K, Tybjaerg-Hansen A, Steffensen R, et al. Factor V Leiden: The Copenhagen City Heart Study and 2 meta-analyses. Blood. 2002;100:3–10.

74. Zöller B, Li X, Ohlsson H, et al. Venous thromboembolism does not share strong familial susceptibility with ischaemic stroke: a nationwide family study in Sweden. Circ Cardiovasc Genet. 2011;4:484-90.

75. Bor AS, Rinkel GJ, Adami J, et al. Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study. Brain. 2008;131:2662-5.

76. Kuivaniemi H, Elmore JR. Opportunities in abdominal aortic aneurysm research: epidemiology, genetics, and pathophysiology. Ann Vasc Surg. 2012;26:862-70.

77. Hemminki K, Li X, Johansson SE, et al. Familial risks of aortic aneurysms among siblings in a nationwide Swedish study. Genet Med. 2006;8:43-9.

78. Larsson E, Granath F, Swedenborg J, et al. A population-based case-control study of the familial risk of abdominal aortic aneurysm. J Vasc Surg. 2009;49:47-50.

79. Liu X, Wang F, Knight AC, et al. Common variants for atrial fibrillation: results from genome-wide association studies. Hum Genet. 2012;131:33-9.

80. Arnar DO, Thorvaldsson S, Manolio TA, et al. Familial aggregation of atrial fibrillation in Iceland. Eur Heart J. 2006;27:708-12.

81. Oyen N, Ranthe MF, Carstensen L, et al. Familial aggregation of lone atrial fibrillation in young persons. J Am Coll Cardiol. 2012;60:917-21.

82. Zöller B, Ohlsson H, Sundquist J, et al. Family history as a risk factor for recurrent hospitalization for lone atrial fibrillation: a nationwide family study in Sweden. BMC Cardiovasc Disord. 2012;12:121.

83. Rosendaal FR. Risk factors for venous thrombotic disease. Thromb Haemost. 1999;82:610-9.

84. Bezemer ID, van der Meer FJ, Eikelboom JC, et al. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med. 2009;169:610-5.

85. Dowling NF, Austin H, Dilley A, et al. The epidemiology of venous thromboembolism in Caucasians and African-Americans: the GATE Study. J Thromb Haemost. 2003;1:80-7.

86. Noboa S, Le Gal G, Lacut K, et al. Family history as a risk factor for venous thromboembolism. Thromb Res. 2008;122:624-9.

87. Sørensen HT, Riis AH, Diaz LJ, et al. Familial risk of venous thromboembolism: a nationwide cohort study. J Thromb Haemost. 2011;9:320-4.

88. Zöller B, Li X, Sundquist J, et al. Parental history and venous thromboembolism: a nationwide study of age-specific and sex-specific familial risks in Sweden. J Thromb Haemost. 2011;9:64-70.

89. Zöller B, Li X, Sundquist J, et al. Shared familial aggregation of susceptibility to different manifestations of venous thromboembolism: a nationwide family study in Sweden. Br J Haematol. 2012;157:146-8.

90. Zöller B, Li X, Sundquist J, et al. Familial risks of unusual forms of venous

thrombosis: a nationwide epidemiological study in Sweden. J Intern Med. 2011;270:158-65.

91. Zöller B, Li X, Sundquist J, et al. Determination of age-specific and sex-specific familial risks for the different manifestations of venous thromboembolism: a nationwide family study in Sweden. Thromb Haemost. 2011;106:102-12.

92. Allaart CF, Poort SR, Rosendaal FR, et al. Increased risk of venous thrombosis in carriers of hereditary protein C deficiency defect. Lancet. 1993;341:134-8.

93. Zöller B, Berntsdotter A, García de Frutos P, et al. Resistance to activated protein C as an additional genetic risk factor in hereditary deficiency of protein S. Blood. 1995;85:3518-23.

94. Parasuraman S, Goldhaber SZ. Venous thromboembolism in children. Circulation. 2006;113:e12–6.

95. Kristinsson SY, Goldin L, Turesson I, et al. Family history of venous thromboembolism is associated with increased risk for thrombosis in multiple myeloma: a population-based study. J Thromb Haemost. 2012;10:962-4.

96. Zöller B, Ohlsson H, Sundquist J, et al. Familial risk of venous thromboembolism in first-, second- and third-degree relatives: a nationwide family study in Sweden. Thromb Haemost. 2013;109:458-63.

97. Frisell T, Pawitan Y, Långström N, et al. Heritability, assortative mating and gender differences in violent crime: results from a total population sample using twin, adoption, and sibling models. Behav Genet. 2012;42:3-18.

98. Koeleman BP, Reitsma PH, Allaart CF, et al. Activated protein C resistance as an additional risk factor for thrombosis in protein C-deficient families. Blood. 1994;84:1031-5.

99. van Boven HH, Reitsma PH, Rosendaal FR, et al. Factor V Leiden (FV R506Q) in families with inherited antithrombin deficiency. Thromb Haemost. 1996;75:417-21.

100. Zöller B, García de Frutos P, Hillarp A, et al. Thrombophilia as a multigenic disease. Haematologica. 1999;84:59-70.

101. Zöller B, Svensson PJ, He X, et al. Identification of the same factor V gene mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated protein C. J Clin Invest. 1994;94:2521-4.

102. Frank L. Epidemiology. The epidemiologist's dream: Denmark. Science. 2003;301:163.

103. Guttmacher AE, Collins FS, Carmona RH. The family history--more important than ever. N Engl J Med. 2004;351:2333-6.

104. Jepsen P, Johnsen SP, Gillman MW, et al. Interpretation of observational studies. Heart. 2004;90:956-60.

105. Nelis M, Esko T, Mägi R, et al. Genetic structure of Europeans: a view from the North-East. PLoS One. 2009;4:e5472.

106. Price AL, Butler J, Patterson N, et al. Discerning the ancestry of European Americans in genetic association studies. PLoS Genet. 2008;4:e236.

107. Statistics Sweden. http://www.scb.se (2013).

108. Zöller B, Li X, Sundquist J, et al. Risk of venous thromboembolism in first- and second-generation immigrants in Sweden. Eur J Intern Med. 2012;23:40-7.

109. CODEX. Welcome to the CODEX website - rules and guidelines for research. http://codex.vr.se/en/index.shtml (2013).

110. Kettis-Lindblad A, Ring L, Viberth E, et al. Genetic research and donation of tissue samples to biobanks. What do potential sample donors in the Swedish general public think? Eur J Public Health. 2006;16:433-40.

111. Gauffin F, Nordgren A, Barbany G, et al. Quantitation of RNA decay in dried blood spots during 20 years of storage. Clin Chem Lab Med. 2009;47:1467-9.

THE BENEFITS OF RIVAROXABAN (XARELTO®) ACROSS MULTIPLE INDICATIONS AND THE RELEVANCE TO CARDIOLOGISTS

Ingo Ahrens, Christoph Bode

Cardiology and Angiology I, Heart Center Freiburg University, Freiburg, Germany

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ABSTRACT

Oral anticoagulation with vitamin-K-antagonists has well known limitations and requires routine clinical monitoring of coagulation parameters. The new oral anticoagulants represent novel direct-acting inhibitors of the coagulation factors IIa (thrombin) or Xa. The compound with the currently widest clinical approval for oral anticoagulation in the group of the Xa inhibitors (also known as the –xabans) is the direct oral factor Xa inhibitor rivaroxaban (Xarelto®). Rivaroxaban was the first direct factor Xa inhibitor with clinical approval for long-term oral anticoagulation in patients with non-valvular atrial fibrillation and has since gained additional approval for the treatment and prevention of deep vein thrombosis and pulmonary embolism. Furthermore, low-dose rivaroxaban, in addition to standard antiplatelet therapy, has been shown to reduce cardiovascular mortality in patients following a recent acute coronary syndrome and recently gained approval for the prevention of atherothrombotic events after acute coronary syndrome by the European Medicines Agency (EMA). This review article discusses the clinical use and benefits of rivaroxaban for multiple indications.

Keywords: Rivaroxaban, novel oral anticoagulants, atrial fibrillation, deep vein thrombosis, pulmonary embolism, acute coronary syndrome.

NOVEL ORAL ANTICOAGULANTS

The introduction of new oral anticoagulants (NOACs) has been eagerly awaited for decades, as the choice of anticoagulation has been restricted to vitamin-K-antagonists, which have well-known shortcomings. With the approval of the direct factor IIa (thrombin) inhibitor dabigatran and the direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) for a variety of clinical indications where oral anticoagulation is deemed necessary, there are now drugs available that may be easier to use compared to vitamin-K-antagonists and more importantly these drugs significantly lower the risk for life-threatening intracranial bleeding events.[1,2] Among the factor Xa inhibitors (also named the –xabans), rivaroxaban was the first of its class to gain clinical approval for the use as an oral anticoagulant for stroke prevention in patients with non-valvular atrial fibrillation (AF) and for the acute treatment of deep vein thrombosis (DVT) and secondary prevention of recurrent venous thromboembolism (VTE) in 2011. Soon thereafter, rivaroxaban was also approved for the acute treatment of pulmonary embolism (PE) and secondary prevention of recurrent VTE in 2012. Very recently, in 2013, the European Medicines Agency (EMA) approved twice-daily low-dose rivaroxaban in combination with standard antiplatelet therapy for secondary prevention of atherothrombotic events in patients that suffered from a recent acute coronary syndrome (ACS).

DIRECT INHIBITION OF FACTOR Xa WITH RIVAROXABAN

Any new oral anticoagulant has undergone an extensive phase of clinical development, which

always includes the clinical scenarios with the highest risk for thromboembolism. This is especially given after total knee and hip replacement surgery, therefore it is understandable that clinical trials in patients undergoing this surgery were the starting points for each of the novel oral anticoagulants. Rivaroxaban has been assessed in the extensive RECORD 1-4 clinical study program in 12,729 patients undergoing either elective total knee or hip replacement surgery. Across the RECORD studies, a 10 mg once-daily dose of rivaroxaban was used to prevent VTE compared to 40 mg once-daily (30 mg twice-daily in RECORD 4) enoxaparin. Rivaroxaban demonstrated superiority over enoxaparin for the prevention of total VTE and was clinically approved for this indication in 2008.[2-6]

The small molecule direct factor Xa inhibitor rivaroxaban has a high oral bioavailability and a competitive mechanism of binding to factor Xa. The affinity of rivaroxaban to factor Xa is >10.000-fold greater as compared to other serine proteases thereby potently inhibiting the conversion of prothrombin to thrombin which occurs downstream of factor Xa activation within the coagulation cascade. The maximum inhibition of factor Xa occurs within 3 hours of oral intake[7,8] corresponding to maximum plasma concentrations reached 2-4 hours after oral administration. The elimination of rivaroxaban occurs partially via the kidney (one third is excreted unchanged) and the mean terminal half-life after multiple oral doses is between 7-11 hours.[7,8] The anticoagulative effects of rivaroxaban in human plasma may be detected by the prothrombin time (PT), but results are variable depending on the reagents used for the clotting assays and the timing of blood sampling after oral intake.

ORAL ANTICOAGULATION WITH RIVAROXABAN ACROSS MULTIPLE INDICATIONS

Atrial Fibrillation

Rivaroxaban is clinically approved for the prevention of stroke or systemic embolism in patients with non-valvular AF with one or more risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, or transient ischaemic attack. Patients with AF requiring oral anticoagulation should receive 20 mg rivaroxaban once-daily. Routine measurement of coagulation parameters is not necessary when patients are treated with rivaroxaban. A reduced dose of 15 mg once-daily rivaroxaban has been specifically and successfully tested and should be used in patients with impaired renal function (creatinine clearance 15-49 ml/min).[9] Rivaroxaban should be used with caution in patients with a creatinine clearance of 15-29 ml/min and should not be used in patients with a creatinine clearance <15 ml/min.

Rivaroxaban is not recommended in patients with mechanical heart valves that require anticoagulation. There are limited interactions with concomitant medication; these include strong inhibitors of CYP3A4 and P-glycoprotein that lead to increased plasma concentrations of rivaroxaban which are therefore not recommended, and with any other anticoagulant as it may increase the bleeding risk and which is therefore contraindicated. Due to limited clinical and safety data, the concomitant use of dronedarone with rivaroxaban is not recommended.

The randomised, double-blind clinical Phase III trial ROCKET AF led to the approval of rivaroxaban for stroke prevention in AF and comprised 14,264 patients with non-valvular AF and a moderate-to-high risk for stroke or systemic embolism (mean $CHADS_2$ score of 3.5).[10] In ROCKET AF patients were either randomised to rivaroxaban 20 mg once-daily (or to 15 mg once-daily in case of a creatinine clearance of 30-49 ml/min), or to dose-adjusted warfarin. Treatment was blinded with mock INR values in the rivaroxaban group. The composite primary efficacy endpoint of ROCKET AF was all-cause stroke and non-central nervous system systemic embolism. In the primary analysis of the per-protocol on-treatment population, the event rates for the primary efficacy endpoint were 1.7 and 2.2 per 100 patient-years for rivaroxaban and warfarin, respectively ($p<0.001$ for non-inferiority in this population and $p=0.02$ for superiority in the pre-specified analysis of the safety on-treatment population).[10] The primary safety outcome of major and non-major clinically relevant bleedings was similar in both treatment groups. Major bleeding events occurred with a rate of 3.6 and 3.4 per 100 patient-years ($p=0.44$) in the rivaroxaban and warfarin treated patients, respectively. However, decreases in haemoglobin

levels of ≥2 g/dl and transfusions were more common among patients in the rivaroxaban group, whereas fatal bleeding and bleeding into critical anatomical sites were less frequent. Rates of intracranial haemorrhage were also significantly lower in the rivaroxaban group than in the warfarin group (rivaroxaban 0.5 versus warfarin 0.7 per 100 patient-years, p=0.02).[10]

Deep Vein Thrombosis

The acute treatment of DVT requires immediate sufficient anticoagulation to prevent further thrombus growth and embolisation. The prevention of VTE after DVT requires oral anticoagulation for a duration of several months, depending on the individual's risk for a recurrence, outbalanced against the individual's bleeding risk. Before the introduction of rivaroxaban for the treatment and prevention of DVT, initial anticoagulation required the use of parenteral anticoagulation (e.g. unfractionated heparin, enoxaparin, or fondaparinux) followed by a VKA. With the approval of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT and PE, it is now possible to initiate treatment immediately with an oral anticoagulant without the need for initial parenteral anticoagulation. The recommended dose of rivaroxaban for the treatment of acute DVT is 15 mg twice-daily for a period of 3 weeks. Thereafter, oral anticoagulation is continued with a once-daily dose of 20 mg of rivaroxaban.[2]

The clinical approval of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT or PE is based on the results of the randomised Phase III open label EINSTEIN-DVT trial. A total of 3,449 patients with acute symptomatic DVT were randomised in EINSTEIN-DVT to either rivaroxaban 15 mg twice-daily for 3 weeks followed by once-daily rivaroxaban 20 mg for a duration of 3, 6, or 12 months, or weight-adjusted enoxaparin twice-daily for a minimum of 5 days followed by dose-adjusted vitamin-K-antagonist.[11] The primary efficacy endpoint of symptomatic recurrent VTE occurred in 2.1% of rivaroxaban treated patients versus 3.0% of enoxaparin plus vitamin-K-antagonist treated patients (p<0.001 for non-inferiority). Rates of major plus non-major clinically relevant bleedings, the primary safety outcome, were similar in both groups. Rates of major bleedings were also similar in both groups (0.8% and 1.2% for rivaroxaban- and enoxaparin plus vitamin-K-antagonist-treated patients, respectively, p=0.21).[11]

Pulmonary Embolism

Pulmonary embolism relies on the formation of venous thrombi and is therefore often accompanied by the clinical evidence for DVT. In contrast to asymptomatic DVT, PE can be a life-threatening event, therefore an immediate and reliable anticoagulation therapy is deemed necessary. Rivaroxaban as a single oral anticoagulant drug (without the need for additional initial parenteral anticoagulants) has gained clinical approval for the treatment of PE and the prevention of recurrent DVT or PE, if the patient is haemodynamically stable and does not require systemic lysis therapy. In this indication, rivaroxaban is administered at a dose of 15 mg twice-daily for a period of 3 weeks following acute PE. Thereafter oral anticoagulation is continued with a single 20 mg daily dose of rivaroxaban.

The EINSTEIN PE trial was the clinical Phase III assessment leading to the approval of rivaroxaban as a single oral anticoagulant for the treatment of PE and the prevention of DVT or PE. In EINSTEIN PE, 4,832 patients with acute PE (with or without DVT) were randomised to either oral anticoagulation with rivaroxaban 15 mg twice-daily for 3 weeks followed by 20 mg once-daily for 3, 6, or 12 months, or to weight-adjusted enoxaparin twice-daily for a minimum of 5 days followed by oral anticoagulation with a vitamin-K-antagonist.[12] The event rates for the primary efficacy endpoint of symptomatic recurrent VTE were 2.1 versus 1.8 (p=0.003 for non-inferiority) in the rivaroxaban and enoxaparin plus vitamin-K-antagonist treated patients, respectively. While there were no significant differences in the composite primary safety outcome of major bleedings plus non-major clinically relevant bleedings (10.3% versus 11.4% for rivaroxaban and enoxaparin plus vitamin-K-antagonist treatment, respectively, p=0.23) there was a significant reduction of major bleeding events in the rivaroxaban treated patient group (1.1% versus 2.2% for rivaroxaban versus enoxaparin plus vitamin-K-antagonist, respectively, p=0.003).[12]

Acute Coronary Syndrome

Major determinants of the long-term clinical outcome after an ACS in patients undergoing percutaneous coronary intervention and stent implantation, are recurrent acute coronary artery occlusion/stenosis and major bleeding events under antithrombotic therapy. While the ischaemic cardiovascular event rates were dramatically reduced following the clinical introduction of the second generation (clopidogrel) and third generation (prasugrel and ticagrelor) P2Y12 antagonists,[13] there is still an unmet need for an optimal antithrombotic regimen (consisting of dual antiplatelet and anticoagulant therapy) in patients with ACS as residual rates of recurrent cardiovascular events despite therapy are still high. The major obstacle of antithrombotic therapy in ACS is the increase in bleeding risk, especially in older patients, caused by the synergy of dual antiplatelet therapy and anticoagulant therapy. An ideal antithrombotic therapy in patients with ACS would provide an effective inhibition of platelet activation and attenuation of the coagulation system without an accompanying increase in bleeding. An attenuation of the coagulation system could be provided by the recently EMA approved low-dose (2.5 mg twice-daily) rivaroxaban therapy, to be co-adminstered with aspirin alone or with aspirin plus clopidogrel or ticlopidine, in patients after an ACS with elevated cardiac biomarkers.

The randomised, double-blind ATLAS ACS 2 TIMI 51 Phase III clinical trial in 15,526 patients was the basis for the 2013 EMA approval of low-dose rivaroxaban (2.5 mg twice-daily) added to standard antiplatelet therapy (aspirin alone or aspirin plus clopidogrel or ticlopidine) in patients with a recent ACS with elevated cardiac biomarkers.[14] This trial evaluated two different low-dose rivaroxaban treatment strategies (2.5 mg and 5 mg twice-daily) on top of antiplatelet therapy (either aspirin alone or aspirin and clopidogrel or ticlopidine) in comparison to placebo on top of antiplatelet therapy. The 2.5 mg twice-daily dose was associated with a significant reduction of the combined primary efficacy endpoint of cardiovascular death, myocardial infarction or stroke (9.1% versus 10.7% for rivaroxaban versus placebo, respectively, p=0.02). Furthermore, rivaroxaban 2.5 mg twice-daily also significantly reduced cardiovascular and all-cause death (2.7% versus 4.1% and 2.9% versus 4.5%, respectively, both p=0.002), while increasing the risk for thrombolysis in myocardial infarction (TIMI) major bleeding events not associated with coronary artery bypass grafting (1.8% versus 0.6%, p<0.001)14 and of intracranial haemorrhage (0.4% versus 0.2%, p=0.04). But importantly it did not increase the rates of fatal bleeding (0.1% versus 0.2%, p=0.45) or fatal intracranial haemorrhage (0.1% versus 0.1%).[15]

The low-dose rivaroxaban therapy did significantly reduce cardiovascular death in patients with ACS when it was co-administered with standard platelet therapy consisting of low-dose aspirin alone or in combination with clopidogrel or ticlopidine in ATLAS ACS 2 TIMI 51.[14] Patients included in this trial had a mean age of 62 years, which is younger than the typical patient requiring oral anticoagulation for atrial fibrillation and therefore would have a lower risk for bleeding events compared to patients that were exposed to higher doses of rivaroxaban in the ROCKET AF trial. Furthermore, these patients were not treated with third generation P2Y12 inhibitors (prasugrel or ticagrelor), which are known to be associated with a higher rate of bleeding events compared to clopidogrel.[16,17] Therefore, the significance of a long-term attenuation of the coagulation system with the direct factor Xa inhibitor rivaroxaban after a recent ACS remains to be determined in the current clinical setting of antithrombotic therapy with a low-dose. It also remains to be examined whether a reduction from dual to single antiplatelet therapy in combination with low-dose factor Xa inhibition could provide an even better protection from ischaemic cardiovascular events, without a substantial increase in bleeding risk. This potentially paradigm-shifting novel strategy in antithrombotic therapy in ACS would need to be explored by future clinical trials.

PATIENT CONSIDERATIONS

While elderly patients with atrial fibrillation do have a higher risk for systemic thromboembolism and stroke, they also exhibit a higher risk for major bleeding events. Recent meta-analyses including major clinical trials with the novel oral anticoagulant rivaroxaban conclude that the beneficial effects of anticoagulation are preserved in the elderly population.[18,19] However, reductions in daily dosing may be necessary based on the individual bleeding risk of the elderly

patient, including regular assessment of renal function.[18,19] There is currently no special dosing recommendation for obese patients. In a study with healthy obese subjects with a bodyweight >120kg, the maximum plasma concentration of a fixed dose of rivaroxaban was unaffected.[20]

When interruption of anticoagulation with rivaroxaban is necessary due to surgical procedures, it is recommended to stop rivaroxaban intake at least 24 hours prior to surgery.[21] Depending on the balance of the bleeding risk associated with the surgical procedure and on the individual risk for thromboembolic complications without anticoagulation, it may be deemed necessary to withhold rivaroxaban for 48 hours before the surgical procedure.[22] There is broad agreement that, due to the pharmacology of the novel oral anticoagulants, there is no need for a bridging therapy with parenteral anticoagulants when oral anticoagulation needs to be interrupted for planned surgical procedures.[21,22]

SUMMARY AND CONCLUSION

The direct oral factor Xa inhibitor rivaroxaban is currently the compound with the widest clinical approval within the group of the oral direct factor Xa inhibitors. It was the first oral factor Xa inhibitor to gain clinical approval in 2008 for the prevention of VTE after elective hip or knee replacement surgery, and also the first with clinical approval for long-term oral anticoagulation for stroke prevention in patients with non-valvular AF in 2011. Since then, rivaroxaban was also approved for the treatment and secondary prevention of DVT and PE, and just recently a low-dose rivaroxaban has gained approval when added to standard antiplatelet therapy in patients after an ACS with elevated cardiac biomarkers. Across the clinical indications, AF, DVT and PE, oral anticoagulation with rivaroxaban demonstrated non-inferior efficacy as compared with dose-adjusted vitamin-K-antagonist.

The dosing of rivaroxaban for oral anticoagulation is without the need for routine measurements of coagulation parameters. With the exception of the first 3 weeks after an acute PE or DVT, where rivaroxaban is given twice-daily at a dose of 15 mg, rivaroxaban is used at a once-daily dose of 20 mg for treatment and secondary prevention of DVT and PE, and for stroke prevention in AF (15 mg if creatinine clearance is 15-49 ml/min). For prevention of VTE after elective hip or knee replacement, a once-daily dose of 10 mg is administered. The role of the recently EMA-approved low-dose rivaroxaban therapy (2.5 mg twice-daily) in combination with aspirin and clopidogrel or ticlopidine after ACS, still needs to be determined in the current setting of the wide clinical usage of the third generation P2Y12 inhibitors prasugrel and ticagrelor.

REFERENCES

1. Ahrens I et al. New oral anticoagulant drugs in cardiovascular disease. Thromb Haemost. 2010;104(1):49-60.

2. Ahrens I et al. Development and clinical applications of novel oral anticoagulants. Part I. Clinically approved drugs. Discov Med. 2012;13(73):433-43.

3. Eriksson BI et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008;358(26):2765-75.

4. Kakkar AK et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372(9632):31-9.

5. Lassen MR et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358(26):2776-86.

6. Turpie AG et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676):1673-80.

7. Kubitza D et al. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939--an oral, direct Factor Xa inhibitor--after multiple dosing in healthy male subjects. Eur J Clin Pharmacol. 2005;61(12):873-80.

8. Perzborn E et al. Rivaroxaban: a new oral factor Xa inhibitor. Arterioscler Thromb Vasc Biol. 2010;30(3):376-81.

9. Fox KA et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-vavluar atrial fibrillation and moderate renal impairment. Eur Heart J. 2011;32(19):2387-94.

10. Patel MR et al, and the ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;385(10):883-91.

11. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-510.

12. The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-97.

13. Ahrens I, Bode C. Novel antiplatelet therapies following percutaneous coronary interventions. Curr Opin Investig Drugs. 2009;10(9):902-11.

14. Mega JL et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.

15. Gibson M. ATLAS ACS 2 TIMI 51 trial results presented at the American Heart Association Scientific Sessions 2011; Nov 12-16; Florida, USA.

16. Wallentin L et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.

17. Wiviott SD et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001-15.

18. Lip GY, Lane DA. Stroke prevention with oral anticoagulation therapy in patients with atrial fibrillation - focus on the elderly. Circ J. 2013;77:1380-8.

19. Barco S et al. New oral anticoagulants in elderly patients. Best Pract Res Clin Haematol. 2013 Jun;26:215-24.

20. Kubitza D et al. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol. 2007;47:218-26.

21. Turpie AG et al. Management consensus guidance for the use of rivaroxaban - an oral, direct factor Xa inhibitor. Thromb Haemost. 2012;108:876-86.

22. Ferrandis R et al. The perioperative management of new direct oral anticoagulants: a question without answers. Thromb Haemost. 2013;110:515-22.

Safe, fast, copeptin-based rule-out of acute myocardial infarction

A NOVEL strategy developed to rule out acute myocardial infarction (AMI) more rapidly, allowed the direct discharge of 66% of patients presenting chest pain and/or other possible symptoms, and low-intermediate overall clinical risk of AMI, from the emergency department (ED). The strategy relied on single baseline measurements of both a novel plasma biomarker, copeptin, and a conventional blood biomarker, cardiac troponin (cTn).

By contrast, only 12% of patients diagnosed without copeptin results could be directly discharged from the ED. These were key findings of the prospective, randomised, multicentre, interventional 'Biomarkers in Cardiology-8' (BIC-8) study, reported by Dr Martin Möckel of the Charité University Hospital, Berlin, at the European Society of Cardiology 2013 Congress.

Additional key observations reported by Dr Möckel suggested that the discharge benefits of the copeptin strategy were achieved while preserving patient safety. BIC-8's main finding was that the study arm, using the copeptin-based strategy, achieved the trial's primary endpoint: non-inferior safety to that of the conventional approach, pre-defined as a ≤5% absolute difference in the major cardiovascular events (MACE) rate in the 30 days post-ED presentation. MACE were confirmed by two independent expert cardiologists, blinded to the patients' study arm.

In intention-to-treat analysis, MACE rates observed during the 30-day period were 5.46% for the copeptin group (n=421), versus 5.50% for controls (n=418). Thus, the patients managed using the copeptin-based algorithm had a similarly low MACE rate compared to that of patients undergoing multiple laboratory tests and long observation in the ED. The copeptin group also had 100% 30-day survival.

BIC-8 addressed an important medical and pharmacoeconomic problem: although considered safe, conventional methods of diagnosing AMI in patients with ambiguous initial electrocardiography (ECG) findings and low initial cTn require several hours. During this time, patients must remain under surveillance in the ED. The delay occurs because cTn generally has a 'silent period' of several hours post-AMI before becoming elevated. Therefore, initial low cTn must be verified in a second cTn measurement 3 hours later, according to current guidelines.[1] The wait for results leads to ED overcrowding, which may delay care delivery to other patients, thereby worsening outcomes.[2] This wait also entails a wasteful use of monitoring equipment and ED staff time, as some 90% of chest pain patients are ultimately found not to have AMI.

Copeptin, an easier-to-measure surrogate for arginine vasopressin (AVP), is a marker of endogenous stress, and almost immediately becomes elevated in patients with AMI. Unlike AVP, copeptin is highly stable and can be measured with Thermo Scientific B·R·A·H·M·S copeptin laboratory tests. In previous larger observational studies[3-5] involving >4,000 patients altogether, combined copeptin and cTn results at presentation demonstrated a >99% negative predictive value for AMI.

BIC-8 enrolled 902 consecutive eligible patients who were randomised 1:1 to the control study arm or the experimental arm, at six participating study centres in Germany, Austria, and Switzerland. In both arms, patients received conventional diagnostic exams, including cardiac monitoring, serial ECG and initial cTn testing. Study sites used their routine ultra-sensitive, point-of-care, or 4th generation cTn I or cTn T assay methodology.

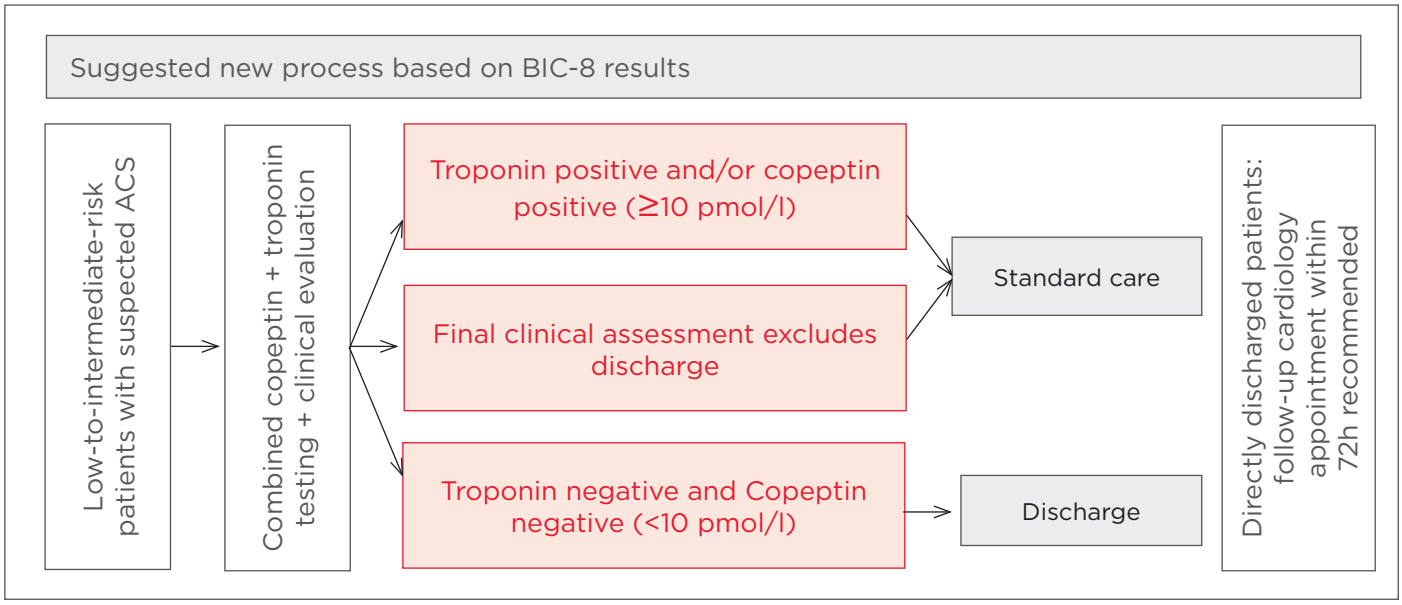


Figure 1. Suggested new process based on BIC-8 results.
M Möckel et al. Hot Line Session IV, ESC 2013, Amsterdam, 03.09.2013.

All patients underwent copeptin determination performed at hospital laboratories, using the commercially available, automated Thermo Scientific™ B·R·A·H·M·S™ Copeptin us KRYPTOR assay. However, it was only in the experimental group that the treating physician was given the copeptin results to help rule-out AMI. In the control group, physicians were to rely on the conventional diagnostic strategy, multiple cTn tests.

Patients in the experimental group with copeptin ≥10 pmol/L were hospitalised and received standard guideline-based care. Those with copeptin <10 pmol/L received the study intervention, and were directly discharged from the ED. Directly discharged patients were scheduled for an outpatient cardiologist appointment within 1-3 days post-discharge.

In a Discussant Statement regarding Dr Möckel's presentation, Dr Bertil Lindahl of the Uppsala Clinical Research Center, Uppsala, Sweden, praised BIC-8 as "important and well-performed," noting that the study's randomised, controlled design was "precisely what is needed in the era of evidence-based medicine." Additionally, according to Dr Lindahl, the BIC-8 concept of having a specific rule-out strategy for AMI besides a rule-in strategy offers "the possibility to change clinical practice."

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14:803-69.

2. Guttmann A, Schull MJ, Vermeulen MJ, Stukel TA. Association between waiting times and short term mortality and hospital admission after departure from emergency department: population based cohort study from Ontario, Canada. BMJ. 2011;342:d2983.

3. Reichlin T, Hochholzer W, Stelzig C, et al. Incremental value of copeptin for rapid rule out of acute myocardial infarction. J Am Coll Cardiol. 2009;54:60-8.

4. Keller T, Tzikas S, Zeller T, et al. Copeptin improves early diagnosis of acute myocardial infarction. J Am Coll Cardiol. 2010;55:2096-106.

5. Maisel A, Mueller C, Neath SX, et al. Copeptin Helps in the early detection of patients with acute myocardial infarction: the primary results of the CHOPIN trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction). J Am Coll Cardiol. 2013;62:150-60.

Intercourse from the bedroom to the doctor's surgery

"Patients are anxious and often afraid sex will trigger another cardiac event"

Professor Elaine Steinke, Wichita State University, Kansas

SEX life after a cardiac event has been the focus of a joint statement published by the American Heart Association journal *Circulation,* and the *European Heart Journal*, to urge healthcare professionals to counsel patients on this sensitive matter.

"Patients are anxious and often afraid sex will trigger another cardiac event – but the topic sometimes gets passed over because of embarrassment or discomfort," said Professor Elaine Steinke, Professor of Nursing at Wichita State University, Kansas, USA.

The statement specifically caters to patients who have suffered a heart attack, heart transplant, stroke, or have received a heart transplant device. Some of the recommendations include the routine assessment of patients after a cardiac event, to establish that they are healthy enough to partake in sexual activities. Individual attention and specially structured counselling sessions are based on their specific needs and requirements. Information is also given regarding sexual positions, intimacy without sexual intercourse, and when to resume sexual activity. This will be available to all patients regardless of gender, age and sexual orientation.

"There are many barriers or misconceptions that inhibit discussions about sex. Some healthcare professionals may believe the patient does not want this information, but we have found it is easier for the healthcare provider to start the discussion than for the patient to bring up these issues," said Professor Tiny Jaarsma, Linköping University, Sweden and co-chair of the task force acting on behalf of the European Society of Cardiology's Council on Cardiovascular Nursing and Allied Professions.

To determine if the patient's fitness is sufficient for sexual activity, exercise stress testing is recommended. Activities such as brisk walking can be suggested to patients before any sexual activities. It is also suggested that patients who are in an extramarital relationship could pose additional stress on the heart.

"Starting a conversation about sex can be easily included in patient discussions, particularly when discussing sex as part of recommendations for exercise. All healthcare providers should be ready and willing to address these areas," Professor Steinke said, adding that this includes cardiologists, primary care practitioners, nurses, nurse practitioners, and physical therapists.

3D holography:

The future of cardiology

THREE-DIMENSIONAL holograms could find their way into the heart of hospitals in the near future in order to assist cardiologists by projecting 3D models of a heart, rather than flat 2D images.

This vision was proposed by Dr Partho P. Sengupta of the Mount Sinai Medical Center, who presented a widely praised lecture at the American Society of Echocardiography's (ASE) 24th Annual Scientific Sessions 2013, Minnesota, USA. The lecture also included holograms of projected 3D digital images animations to showcase the latest technology and future applications of functional echocardiography to more precisely analyse structure, function and flow patterns of the cardiovascular system.

The definite highlight of the lecture was the interactive discussion between Dr Sengupta and a holographic projection of his mentor, James Seward, a retired former Director of echocardiography at the Mayo Clinic.

Patricia Pellikka, a past President of ASE and the current director of the echocardiography lab at Mayo, said: "The holographic presentation at ASE was absolutely spectacular! [Dr Sengupta] presented an insightful and futuristic lecture about the massive amounts of data available with echocardiography and how this information should be managed and harnessed to improve patient care."

> "The holographic presentation at ASE was absolutely spectacular!"
>
> *Patricia Pellikka, Director, Echocardiography Lab, Mayo*

Dr Sengupta predicted that the incorporation of holographic projections in healthcare will experience exponential growth of technology due to its potential diagnostic accuracy. He also added that the impact of robotics and wearable computers can revolutionise healthcare, citing an example of a paramedic in the field wearing Google glasses to receive advice from a remotely-based physician about a trauma or cardiac arrest case.

Lab-grown human heart tissue beats on its own

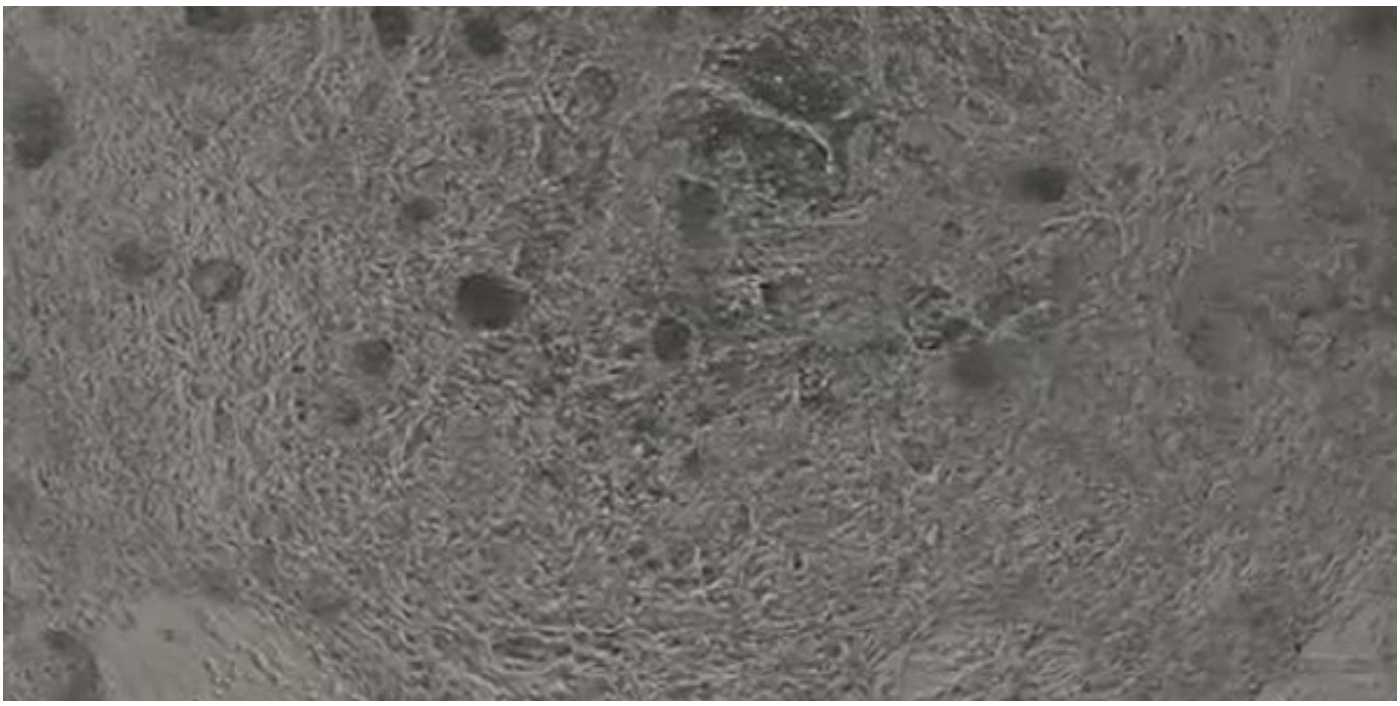
A RESEARCH team from the University of Pittsburgh, Pennsylvania, USA, has grown human heart tissue that can beat autonomously in a petri dish. This significant breakthrough could be the answer to the organ shortage, as research may yield transplantable replacement organs.

This was achieved via the use of induced pluripotent stem cells (iPS cells), matured human cells that are 'reprogrammed' to an embryonic state, before being spurred to develop into a specialised type of cell. In this investigation, iPS cells obtained from human skin were induced to become multipotential cardiovascular progenitor (MCP) cells: heart cells that can differentiate into the three specialised types of heart tissue.

These cells were then transplanted onto a mouse heart that had been stripped and turned into a scaffold. The transplanted cells then proliferated and differentiated rebuilding scaffolding into a functional organ capable of beating independently. Currently, the heart contracts to the equivalent of a human's resting rate of 40 to 50 beats per minute. More studies need to be carried out to enhance contraction rate so it is capable of beating strongly enough to distribute blood around the body and to meet the demands of the body during high level of activity or at rest.

In the past, scientists have created lab-grown beating hearts and human heart tissue, but these relied mainly on embryonic system cells. These cells cannot be derived from a specific patient for subsequent personalised transplant, but this new technique overcomes these limitations.

The possibility of a fully functioning lab-grown heart could become a reality in the future, but scientists hope that techniques utilised could in fact produce 'patches' of the human heart to repair damaged organs, opening new possibilities in the treatment of cardiovascular diseases.



Ranexa® reduces angina in patients with type 2 diabetes

GILEAD Sciences announced that in a Phase IV trial, Ranexa® (ranolazine) reduced the frequency of weekly angina episodes in type 2 diabetes patients, compared to placebo and background antianginal therapy.

"Given the high prevalence of angina in patients with diabetes, there is a need for effective therapeutic strategies in this difficult-to-treat population," the study's lead author Dr Mikhail Kosiborod, stated.

The trial showed that 927 randomised patients received either Ranexa® or the placebo twice daily, along with background antianginal therapy for an 8-week duration. The data observed that, between weeks 2-8, an average weekly angina frequency was 3.8 episodes among patients under the Gilead's therapy compared to the 4.3 episodes among the placebo group. It was also noted that weekly sublingual nitroglycerin use was relatively lower in the Ranexa® group compared to the placebo group.

Commenting on the data, Dr Kosiborod noted that: "While ranolazine was shown to be effective in reducing angina in prior studies, this is the first time it has been prospectively evaluated in patients with diabetes, a high-risk and therapeutically challenging group." He added: "If the glucose lowering action of ranolazine is confirmed in future studies, patients with diabetes and angina may derive dual benefit from this drug."

Ranexa® is currently approved for the treatment of chronic angina. The recent trial is one of many used to evaluate the role of therapy for patients with chronic angina and/or type 2 diabetes, and to determine the effects of Ranexa® on glycaemic control as monotherapy and in combination with other anti-diabetic therapies.

New drugs that target cell nucleus may treat heart failure

A TEAM of researchers from Case Western Reserve University School of Medicine and Dana-Farber Cancer Institute, Ohio, USA have discovered a new molecular pathway responsible for causing heart failure and showed that a prototype drug, JQ1, can block this pathway, protecting the heart from damage. JQ1 specifically targets the cell's nucleus to prevent damaging stress responses, with ground-breaking research potentially laying a new foundation in the treatment of heart diseases.

"As a practicing cardiologist, it is clear that current heart failure drugs fall alarmingly short for countless patients. Our discovery heralds a brand new class of drugs which work within the cell nucleus and offers promise to millions suffering from this common and lethal disease," said Dr Saptarsi Haldar, a senior author on the paper, Assistant Professor of Medicine at Case Western Reserve and Cardiologist at University Hospitals Case Medical Center.

The team discovered a new family of genes called BET bromodomains, which cause hyperactive stress responses in the nucleus, resulting in heart failure. The laboratory of Dr James Bradner, the paper's senior author and researcher at the Dana-Farber, Harvard Medical Center, developed the direct-acting inhibitor, JQ1, which prevents genetic actions leading to enlargement and damage to the heart, even in stressful situations.

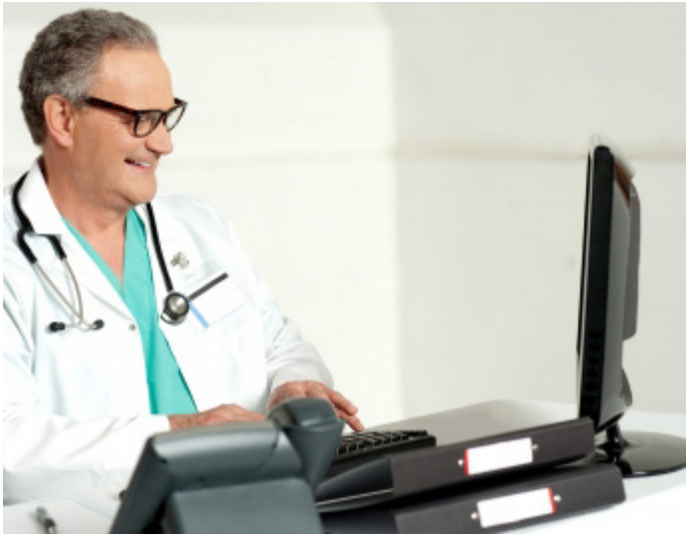
"While it's been known for many years that the nucleus goes awry in heart failure, potential therapeutic targets residing in this part of the cell are often dubbed as 'undruggable', given their lack of pharmacological accessibility," said Dr Jonathan Brown, Cardiologist at Brigham and Women's Hospital and co-first author on the paper. "Our work with JQ1 in pre-clinical models shows that this can be achieved successfully and safely."

The team, led by Dr Halder and Dr Bradner, studied mice models who develop classic human features of human heart failure, including massively enlarged hearts that are full of scar tissue and have poor pumping function. For a month's duration, the sick mice received a single daily dose of JQ1 and were protected from precipitous declines in heart function in a matter of days. There was a 60% improvement in comparison to the untreated control group.

"Remarkably, at the end of the experiment, the hearts of many JQ1 treated mice appeared healthy and vigorous, despite being exposed to persistent and severe stress," said Priti Anand, a researcher in Haldar's lab and co-first author on the paper. "We knew we were on to something big the first time we saw this striking response."

"So much has been learned from this molecule," Dr Bradner said. "The fundamental similarity between the biology of cancer cell growth and heart enlargement following extraordinary stress connects these mature fields of study in new and exciting ways, of immediate relevance to drug development. This study best exemplifies the power of open-source approaches to drug discovery."

In the future, more preclinical models of various cardiovascular conditions will be tested and the research team hopes to progress onto clinical trials.



Children still risk mutations regardless of parent's history

STUDIES have suggested that new genetic mutations can be present in children even when it is absent in the parents, accounting for 10% of severe congenital heart disease (CHD) according to findings published in *Nature*.

Genetic analysis of more than 1,800 individuals carried out by researchers at the Yale Medical School of Medicine, found hundreds of mutations linked to CHD, and further analysis has shown that genes that modify histones cause the most frequent mutations.

Genetic analysis of more than 1,800 individuals found hundreds of mutations linked to congenital heart disease.

Zaidi S et al.
Nature. 2013;498:220-3.
doi:10.1038/nature12141

The use of state-of-the-art whole sequencing and genome mapping techniques were used in the analysis which found that *de novo* mutations cause the pathogenesis of severe CHD. These mutations were found to be the cause of a specific pathway, which is crucial to human development, particularly the brain and the heart. The research revealed that protein histones are involved in the regulation of genes and are not just seen as inert packing material. The mutations can occur at the same site, which can both increase and decrease the modification of histone proteins, with a potential to be influenced by environmental factors. This brings us one step closer to fully understanding the pathogenesis at molecular level.

"These findings provide new insight into the causes of this common congenital disease," said Professor Richard Lifton, Sterling Professor and Chair of the Department of Genetics, investigator for the Howard Hughes Medical Institute, and a senior author of the paper. "Most interestingly, the set of genes mutated in congenital heart disease unexpectedly overlapped with genes and pathways mutated in autism."

"These findings suggest there may be common pathways that underlie a wide range of common congenital diseases," Professor Lifton noted.

This discovery highlights the importance of sequencing and mapping technologies in research and also the role of *in utero* environment in the development of mutations. Overall, this discovery accounts for 10% of cases linked to mutations, but the remaining 90% of CHD is still unknown. Formulations of many hypotheses will mould the future of research and hopefully more technologies will provide much needed answers.

Cardiovascular screening every 5-10 years for chest radiation patients

CANCER patients who receive chest radiation should be screened every 5-10 years, according to the European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology (ESC) and the American Society of Echocardiography (ASE).

Approval for the screening for radiation-induced heart disease (RIHD) was outlined in a consensus statement, published in the European Heart Journal - *Cardiovascular Imaging*. High-risk patients are those that receive high doses of radiation (often young people), breast cancer patients (particularly on the left side), high doses of chemotherapy, and those that have cardiovascular risk factors such as smoking, obesity, and inactivity.

"RIHD affects approximately 10-30% of patients who receive chest radiation within 5-10 years."

Professor Patrizio Lancellotti, President, European Association of Cardiovascular Imaging

Professor Patrizio Lancellotti, chair of the Expert Task Force and President of the EACVI, said: "The prevalence of radiation-induced heart disease is increasing because the rate of cancer survival has improved. It's a long-term risk, and RIHD manifests 5-20 years after the radiation dose."

It is estimated that RIHD affects approximately 10-30% of patients who receive chest radiation within 5-10 years. Structural changes to the heart after radiation can be detected initially via echocardiography, cardiac computed tomography (CT), cardiac magnetic resonance (CMR), and nuclear cardiology. Unfortunately, screening for RIHD is not routinely performed.

Professor Lancellotti added: "Survivors of Hodgkin's lymphoma and breast cancer received high doses of radiation on their chest under the old treatment regimes. Over time, these patients can develop RIHD in the heart valves, myocardium, vessels including the aorta, the pericardium, and the coronary arteries. Their risk of death from coronary artery disease, myocardial ischaemia and myocardial infarction is increased."

According to Professor Lancellotti, radiotherapy is now given in lower doses but patients are still at increased risk of RIHD, particularly when the heart is in the radiation field. This applies to patients treated for lymphoma, breast cancer and oesophageal cancer. Patients who receive radiotherapy for neck cancer are also at risk because lesions can develop on the carotid artery and increase the risk of stroke.

The report includes guidelines such as screening patients for RIDH risk factors before any chest radiation. Breast or lymphoma cancer patients should receive cardiac screening 5 years after treatment if there is a cardiac abnormality, or additional risk factors, and receive a follow-up scan after 10 years if there are no abnormalities. Every 5-10 years, cardiovascular screening should be carried out based on the extent of cardiac abnormalities and level of risk. It is also recommended that all patients who receive chest radiation should have a cardiac examination initially with an echocardiography.

Professor Lancellotti added: "Echocardiography is the first line of imaging assessment, but in some patients we need other examinations including stress imaging, CT, and CMR. For instance, we can precisely assess the presence of myocardial fibrosis using CMR and more accurately assess cardiac calcification using CT." He concluded that a registry of RIHD is needed in Europe to determine the true prevalence of the disease and collect outcome data.

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Boehringer Ingelheim is a global group of companies embracing many cultures and diverse societies, covering such business areas as human pharmaceuticals, biopharmaceuticals, and animal health. The objectives and beliefs of Boehringer Ingelheim can be summed up in a single phrase: 'value through innovation'. Headquartered in Ingelheim, Germany, it operates globally with 140 affiliates and more than 46,000 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing, and marketing novel medications of high therapeutic value for human and veterinary medicine.

In Europe, Daiichi Sankyo is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified unmet medical needs of patients. Daiichi Sankyo's European headquarters are located in Munich, Germany. The company currently does business in 12 European countries. Through licensing and sales agreements, its products are available in almost every European market. With more than 2,450 employees, Daiichi Sankyo has been one of the strongest Japanese pharmaceutical companies located in Europe, and also provides pharmaceuticals to patients in many North- or West-African countries such as Algeria, Burkina Faso, Cameroon, Congo, Morocco, Niger, Senegal and Togo, through its French affiliate.

MENARINI is dedicated to delivering innovative healthcare solutions to enhance the lives of patients worldwide, employing over 16,500 people. Its five research centres across Europe are actively involved in the development of cutting-edge drugs for cardiovascular diseases, oncology, and the asthma/pain/inflammation area, through the study of receptor antagonists.

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WORLD HEART FEDERATION

4th Congress of the Croatian Association of Cardiology Nurses (CACN 2013)

November 13-15, 2013

Zagreb, Croatia

The main purpose of this association is to help cardiac nurses and allied professionals in the education and acquisition of new knowledge. Our conferences are an excellent opportunity for this, as well as for exchanging new ideas and findings, and the main goal is to achieve excellence in professional nursing practice. Wide variety of professional matters with global issues in nursing practice, interdisciplinary sessions and topics on legislation in the nursing practice, will certainly inspire creative discussion.

9th Echo Hong Kong

November 21-24, 2013

Hong Kong

'Live & Acute Cardiac Imaging' is the theme of this year's conference. The conference will receive the generous support from Prof Bijoy Khandheria, Prof Gerald Maurer, Prof Smadar Kort, Dr Jonathan Chan, Dr Dominic Leung, Dr Joseph Selvanayagam and Mrs Bonita Anderson.

EuroEcho-Imaging 2013

December 11-14, 2013

Istanbul, Turkey

Once again EuroEcho-Imaging 2013 is intent on being a multidisciplinary congress, covering a large range of topics focusing on this year's main themes: Heart Failure & Imaging in Interventional Cardiology.

Rome Cardiology Forum 2014, an ESC Update Programme in Cardiology

January 29-31, 2014

Rome, Italy

An ESC Update Programme - vascular biology, cardiovascular risk factors, chronic ischaemic heart disease, acute coronary syndromes, arrhythmias, heart failure, cardiac valve diseases, cardiomyopathies, pulmonary hypertension, innovative treatments, presentations and interactive discussion of clinical cases.

17th International Congress on Advances in Cardiac Ultrasound

February 24-27, 2014

Davos, Switzerland

This International Congress will concentrate on the recent advances in cardiac ultrasound and their relevance for clinical problem solving in every day practice. State-of-the-art lectures will provide cardiologists and those interested in cardiac ultrasound a review of all current uses and new developments and how to implement them in daily practice.

Particular emphasis will be on quantitative doppler haemodynamics and some sessions will be entirely devoted to presentations of clinical studies/cases with interactive discussions between participants and faculty.

EuroHeartCare 2014

April 4-5, 2014

Stavanger, Norway

The preparations for the upcoming EuroHeartCare 2014 congress in Stavanger, Norway, already started in September of 2012 with the Programme Committee working together with the Norwegian Society of Cardiovascular Nurses to put an exciting programme together. The theme of the conference will be 'Heart and Mind'.

World Congress of Cardiology Scientific Sessions (WCC2014)

May 4-7, 2014

Melbourne, Australia

This major international conference addresses the importance of cardiovascular health and disease on a global scale by attracting a strong and renowned international faculty of experts. Working alongside our national members, it also focuses on the cardiovascular disease problems of the region, in which it is hosted, for 2014 this will be the Australian continent and sub-regions of Asia.

Frontiers in CardioVascular Biology (FCVB, 2014)

Scientific programme endorsed by Council on Basic Cardiovascular Science

July 4-6, 2014

Barcelona, Spain

The Core Scientific Committee, the Programme Committee and the Local Organising Committee take pleasure in organising a meeting that will bring the best and most novel cardiovascular science to participants. We will especially focus on fostering the needs of younger attendees by stimulating scientific exchange, oral presentations, travel grants and special social functions.