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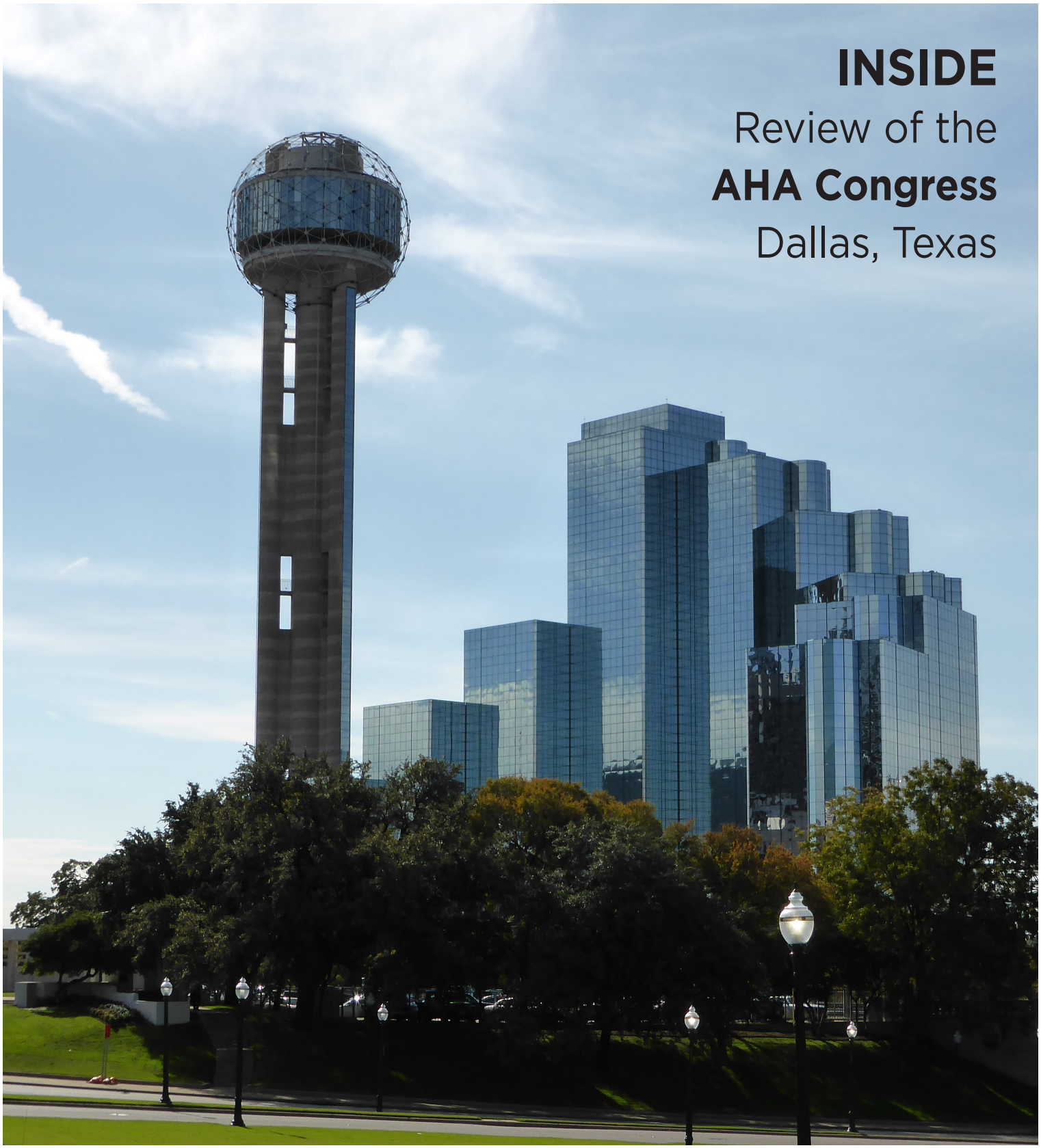

INSIDE

Review of the
AHA Congress
Dallas, Texas

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Welcome to the *European Medical Journal* review of the American Heart Association Congress 2013

THE MISSION of the American Heart Association (AHA) is: "Building healthier lives, free of cardiovascular disease and stroke. That single purpose drives all we do. The need for our work is beyond question."

The 2013 Congress was held in the home of the AHA, Dallas, and attracted 18,000 cardiovascular experts from more than 150 countries. A total of 23 million people worldwide suffer from the effects of heart failure and so now, more than ever, the need for these scientific meetings is paramount. In the opening ceremony, the President of the AHA, Dr Mariell Jessup, reflected that in 1979 heart failure was considered a terminal illness, and that since then "we have come a long way in our understanding of treatment of heart failure."

The 5-day event emphasised multidisciplinary interactions, and was accompanied by seven cardiovascular cores which reflected the evolution of scientific investigation and practice. Dr Jessup said: "Clinical trials have worked hard to demonstrate the efficiency of each new therapy, often involving hundreds or thousands of patients." All of these ground-breaking studies contribute to the understanding and improvement in treatment of cardiovascular disease.

The debate: valve replacement versus valve repair

VALVE replacement and valve repair produced similar results in patients with severe ischaemic mitral regurgitation, a randomised trial has shown.

As the guidelines pertaining to the problem of valve replacement or repair are not clear, the problem needs to be addressed. In the USA, two-thirds of patients have their defective valve repaired compared to one-third who have it replaced.

It has been the feeling of many healthcare providers that there were fewer deaths when the valve was repaired, as it provides many long-term benefits despite the operative risk.

"Practice guidelines recommend repairing or replacing mitral valves in severe cases, but there has been a lack of conclusive evidence that one approach is better than the other," said Dr Michael Acker, University of Pennsylvania Perelman School of Medicine, USA.

This is the first randomised trial to answer the question of which method is better. The study included 251 patients, randomised into either receiving mitral valve repair or mitral valve replacement.

The results from this study challenged previous ones, showing the death rate to be 14.3% after 1 year for the repair group, compared to 17.6% for the replacement group. Additionally, recurrent mitral regurgitation in the repair group was 32.6%, whereas in replacement it was 2.3%. Functional status or quality of life (QoL) was not significantly different between the two groups.

Dr Acker said: "My concern is that people will look at this and say 'Oh, I can replace the valve. I'll just do it the way I usually do it.' Don't cut out the chordae. If you don't cut out the chordae – anterior or posterior – you have a better result and less morbidity and mortality."

A new generation of pacemaker, keeping the heart on track

PACEMAKERS which only pace during an abnormal heart rhythm have proven to be a more effective way of preventing further heart damage when compared to standard pacemakers, which are continuous.

Prof Giuseppe Boriani, Professor at the Institute of Cardiology, University of Bologna, Italy, said: "If applied to all patients requiring pacemakers, the benefits could help many thousands of patients in every country."

Compared to traditional pacemakers, which can cause further heart damage, these highly-sophisticated pacemakers were able to reduce the patient's risk of death and hospitalisations by 26%. These patients also reported a better QoL and less fatigue.

Dr Giuseppe said: "This is the first study to demonstrate that this suite of algorithms can significantly reduce the progression of atrial tachyarrthymias or atrial fibrillation into permanent disturbances and the associated risk of death and hospitalisations."

The study included 1,166 patients, all of whom suffer from bradycardia. Over the course of 2 years, 15.2% of patients with smart pacemakers were hospitalised and 4.6% died, compared to 16.8% of patients without smart pacemakers who were hospitalised and 5.6% died.

Throughout this study doctors were able to discover the most effective programme, which focused on a varied off-and-on approach to the whole heart. This programme reduced the number of heart patients who developed permanent atrial fibrillation by 61%.

Although these figures are encouraging, researchers believe that more evaluation, especially concerning the peacemaker programme, is needed.

Combination therapy, the best approach for patients with leg pain

EXERCISE combined with a procedure to open clogged blood vessels has been shown to reduce leg pain, with patients able to walk up to 282 m further compared to patients using exercising alone.

The study included 212 patients with leg pain caused by intermittent claudication, a form of peripheral artery disease. The symptoms often include cramping and fatigue, and it also affects the patient's QoL as it can limit movement. In addition, it can also be an indication for more serious illnesses, such as heart disease and stroke.

Previous guidelines have recommended that patients with leg pain should only receive exercise therapy, such as walking on a treadmill. "Although guidelines recommend supervised exercise as initial therapy in patients with intermittent claudication, our data suggest that a combined therapy of the vessel-opening procedure followed by a supervised exercise programme might be the best option," said Dr Farzin Fakhry, Department of Epidemiology, Erasmus MC, University of Rotterdam, the Netherlands.

Half of the patients in the study were assigned to a supervised exercise group, while the other half underwent angioplasty or stenting procedures - to open blocked blood vessels - followed by supervised exercise.

Patients in the combination therapy group yielded the most significant improvements, the results showed. Patient QoL in this group was greatly improved as less pain was reported, especially while walking, and patients were able to increase their walking distance. On the other hand, 20% of patients in the exercise-only group needed secondary follow-up.

Heart disease is the main cause of pregnancy-related deaths

PREGNANCY-RELATED deaths in the USA are commonly associated with heart disease, however, one-third of these could be prevented through more effective diagnosis, treatment and patient awareness.

Researchers examined the medical records of 732 women who died from all causes while pregnant, or within 1 year of pregnancy. Of these, 209 deaths were pregnancy-related.

The findings of the study indicated that African-American and obese women, in addition to women who had documented substance abuse during pregnancy, were more likely to die from pregnancy-related heart disease.

Dr Afshan Hameed, the study's lead researcher, Associate Professor of Clinical Cardiology, Obstetrics and Gynecology,

University of California, Irvine, USA, said: "Healthcare providers should be referring pregnant women who complain of symptoms consistent with cardiac disease to specialists, especially when these risk factors are present. Women with evidence of substance abuse should receive early referral for treatment."

The number of deaths as a result of cardiovascular disease was around one-quarter, 6% of whom had been diagnosed with a heart condition prior to pregnancy. Of the cardiovascular-related deaths which occurred, two-thirds were the result of cardiomyopathy.

Researchers also found that one-third of patients delayed or failed to seek medical care, while 10% refused medical advice and 27% did not recognise their symptoms as cardiovascular.

While earlier intervention and diagnosis would have prevented these deaths, Dr Hameed suggested: "Missed cues to the presence of heart disease were common."

Heart risks facing childhood cancer survivors

CHILDREN who survive cancer treatment are at an increased risk of heart problems as the changes in their arteries may increase the risk of early heart disease and atherosclerosis.

Prof Donald Dengel, Professor at the University of Minnesota, USA, lead author of the study, said: "Early in life, child cancer survivors, especially leukaemia survivors, are already starting to have a higher risk for premature atherosclerosis and cardiovascular disease."

A study in 2008 showed that the blood vessels in adult survivors of acute lymphocytic leukaemia (ALL) still maintained some dysfunction even 20 years after the start of their treatment. Until now researchers had not looked at the health effects in a large population of childhood cancer survivors while they were still children.

Using ultrasound imaging, Prof Dengel and colleagues measured artery stiffness, thickness and function in 319 randomly recruited children, all of whom have survived leukaemia or cancerous tumours. This was done with 208 non-cancerous siblings as controls, with all children aged between 9-18 years of age.

After completing chemotherapy, leukaemia survivors had a 9% decrease in arterial health compared to their healthy counterparts. Moreover, decline in arterial function was more likely to occur in children who survived cancer, meaning premature heart disease would also be prevalent in this group.

As a result of these findings it has been suggested that once the cancer is cured, healthcare providers would then have to cure the effects of treatment. Prof Dengel has suggested that in the future they can "look at new ways to treat cancer, whether we reduce some of the chemotherapy agents into smaller doses or develop better ones that cause less damage."

While a lot of progress has been made within this field, researchers still have a long way to go to improve the vascular health of this population.

EFFECTIVE ANTICOAGULATION WITH FACTOR XA NEXT GENERATION IN ATRIAL FIBRILLATION – (ENGAGE AF - TIMI 48 TRIAL): PRIMARY RESULTS

Robert Giugliano

Associate Professor of Medicine, Harvard Medical School, Cambridge, Massachusetts, USA

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PRESENTATION SUMMARY

The following is an executive summary of the abstract presentation by Prof Robert Giugliano on the ENGAGE AF – TIMI 48 trial primary results. It was presented on 19th November 2013 at the American Heart Association (AHA) annual congress, held in Dallas, Texas.

Primary Results of the ENGAGE AF - TIMI 48 Trial

Prof Giugliano initially provided an overview of the therapy area and noted that while warfarin is an effective therapy for atrial fibrillation (AF) patients, reducing stroke by 64% versus placebo, it is linked to increased bleeding and has a number of other drawbacks. There are currently three novel oral anticoagulants (NOACs) that are at least as effective as warfarin in AF, reducing haemorrhagic stroke by 51%. Edoxaban is a new drug that inhibits Factor Xa; it has oral bioavailability of 62%, a fast onset of action, and a half-life of 10–14 hours. Edoxaban is taken once daily. 50% of the absorbed drug is eliminated by renal clearance, and dose reduction is recommended in patients with moderate renal impairment, low body weight and concomitant use of potent p-glycoprotein inhibitors.

Prof Giugliano described the study design of the ENGAGE AF – TIMI 48 trial, which enrolled 21,105 patients with documented AF and a moderate-to-high risk of stroke, based on a $CHADS_2$ score of ≥2. A double-blind, double-dummy design was used, and patients were randomised to one of three dosage regimens: warfarin titrated to an internationalised normalisation ratio (INR) of 2–3, high-dose edoxaban (60 mg once-daily), or low-dose edoxaban (30 mg once-daily). The edoxaban dose was halved to 30 mg once-daily and 15 mg once-daily, respectively, in patients with reduced renal function, low body weight and concomitant use of potent p-glycoprotein inhibitors. The primary endpoint was a composite of stroke or systemic embolic event (SEE). This was analysed for non-inferiority to exclude a risk ratio <1.38 (97.5% confidence interval). He outlined that the primary analysis was carried out on the modified intent-to-treat (mITT) cohort during the on-treatment period. Testing for superiority was carried out on the full ITT population, and analysed all events between randomisation and the final visit. Safety was analysed during the on-treatment period with the principal safety outcome being major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH). Prof Giugliano noted that this was the longest duration trial with a novel agent, with a median of 2.8 years follow-up.

Prof Giugliano presented the baseline characteristics of the trial population. He noted that there were no significant differences in parameters across the treatment groups, and highlighted that the median age was 72 years, 25% of participants had paroxysmal AF, and the mean $CHADS_2$ score was 2.8, with over half of patients having a score ≥3. A quarter of patients had dose-reduction at randomisation and 59% of patients had prior experience with a vitamin K antagonist.

Of the patients enrolled in the trial, 99.6% received the study drug and complete follow-up was available for 99.5% of the potential years of follow-up. Only one patient was lost to follow-up, 0.9% of patients withdrew consent, and less than 9% of patients discontinued drug use each year. The median proportion of time in the therapeutic range (TTR) for warfarin was 68.4%; this was >77% for a quarter of patients. The trial results are summarised in Table 1.

Edoxaban was considered to be better tolerated than warfarin, and there was no difference between treatments in serious adverse events or liver function abnormalities. At the end of the trial, all patients were transitioned onto a vitamin K antagonist (approximately two-thirds) or NOAC (approximately one-third). Patients transitioning onto vitamin K antagonists had frequent INR measurements. These patients were also treated with a low dose edoxaban for up to 2 weeks until the INR was ≤2.0 and patients could transition to a NOAC when the INR was below 2.0. There was no difference in stroke, SEE or major bleeding between the treatment groups during the first 30 days of transition post-trial.

By comparison to well-managed warfarin (TTR 68.4%), edoxaban once daily was non-inferior in terms of stroke or SEE in both dosing regimens, with a trend towards reduced stroke and SEE observed in the high-dose edoxaban regimen treatment arm. Both edoxaban dosing regimens significantly reduced major bleeding events, intracranial haemorrhage, haemorrhagic stroke, and cardiovascular death. In addition, both edoxaban regimens showed superior net clinical outcomes and there was no excess in stroke or bleeding during the treatment transition at the trial end.

Table 1. Summary of ENGAGE-AF trial results.

Outcome	High-dose edoxaban* HR (p-value vs warfarin)	Low-dose edoxaban* HR (p-value vs warfarin)
Primary		
Stroke/SSE, non-inferiority	0.79 (<0.0001)	1.07 (0.005)
Stroke/SSE, superiority	0.87 (0.08)	1.13 (0.10)
Secondary		
Haemorrhagic stroke	0.54 (<0.001)	0.33 (<0.001)
Ischaemic stroke	1.00 (0.97)	1.41 (<0.001)
Stroke, SEE, cardiovascular death	0.87 (0.005)	0.95 (0.32)
Death or intracerebral haemorrhage	0.87 (0.004)	0.82 (<0.001)
All-cause mortality	0.92 (0.08)	0.87 (0.006)
Cardiovascular death	0.86 (0.013)	0.85 (0.008)
Myocardial infarction	0.94 (0.60)	1.19 (0.13)
Safety**		
ISTH major bleeding	0.80 (<0.001)	0.47 (<0.001)
Fatal bleeding	0.55 (0.006)	0.35 (<0.001)
Intracranial haemorrhage	0.47 (<0.001)	0.30 (<0.001)
Gastrointestinal bleeding	1.23 (0.03)	0.67 (<0.001)
Net clinical outcomes		
Stroke, SEE, death, major bleeding	0.89 (0.003)	0.83 (<0.001)
Disabling stroke, life-threatening bleeding, death	0.88 (0.008)	0.83 (<0.001)
Stroke, SEE, life-threatening bleeding, death	0.88 (0.003)	0.89 (0.007)

ISTH: International Society for Thrombosis and Haemostasis; HR: hazard ratio; SEE: systemic embolic event.
*Dose reduction by 50% was carried out in selected patients.
**Safety cohort, all patients who received at least one dose by treatment actually received.

NOVEL ANTICOAGULANTS IN ATRIAL FIBRILLATION

Summary of the Presentations from the Daiichi Sankyo Symposium, AHA Congress 2013, Dallas, Texas, USA

Chairperson

Eugene Braunwald[1]

Speakers

Elaine Hylek,[2] Jeffrey Weitz,[3] Robert Giugliano,[4] Christian Ruff,[5] John Camm[6]

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3. Professor of Medicine and Biochemistry, McMaster University, Hamilton, Ontario, Canada
4. Associate Professor of Medicine, Harvard Medical School, Cambridge, Massachusetts, USA
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MEETING SUMMARY

This educational seminar, supported by an independent educational grant from Daiichi Sankyo, was held at the AHA congress in Dallas on 19th November 2013. The meeting provided clinicians with an update on the pharmacokinetics and pharmacodynamics of new anticoagulant drugs. The speakers also discussed how best to use these agents according to the latest evidence.

Anticoagulants in Non-Valvular Atrial Fibrillation

Prof Elaine Hylek

Prof Hylek presented an overview of AF and its treatment. It is estimated that upwards of 9 million people in the USA will have AF by 2020. AF is associated with increased risk of stroke, dementia and heart failure. In addition, overall mortality is increased by 40–90% independent of other risk factors.

Warfarin reduces stroke and systemic embolism by 64% and reduces mortality by 26% compared to placebo. However, maintaining warfarin within the therapeutic range is a challenge and many intracranial haemorrhages, the most feared complication of anticoagulant therapy, apparently occur even when patients' internationalised normalisation ratio (INR) values are between 2 and 3.

Prof Hylek briefly discussed the results of the novel oral anticoagulant (NOAC) clinical trials. The RE-LY trial found that dabigatran 150 mg, given twice-daily, was superior to warfarin for reducing strokes and systemic embolic event (SEE) and was associated with a 50% reduction in intracranial haemorrhage.[1]

The ROCKET-AF trial showed that once-daily rivaroxaban was non-inferior to warfarin in terms of primary stroke and non-central nervous system (CNS) embolic events and also reduced intracranial haemorrhage.[2]

However, there was an increased risk of major haemorrhage from a gastrointestinal site.

The ARISTOTLE trial evaluated apixaban 5 mg twice-daily.[3] The rate of intracranial bleeding was halved. However, the rate of gastrointestinal (GI) haemorrhage was the same as warfarin and Prof Hylek commented that the risk of GI bleeding is one of the main reasons why patients want to stop treatment. Prof Hylek cautioned it was inappropriate to directly compare the results across trials as the patient populations were quite different.

Clinical Pharmacology of Novel Anticoagulants

Prof Jeffrey Weitz

Prof Weitz reviewed the clinical pharmacology of NOACs, with a particular focus on edoxaban. He highlighted the limitations of warfarin treatment, including potential interactions with food and drugs, slow onset and offset of action and its narrow therapeutic window; all of which contribute to the underuse of warfarin for stroke prevention in AF. Warfarin targets multiple steps in the coagulation pathway; in contrast, NOACs target downstream enzymes in the final steps of the coagulation cascade; Factor Xa (rivaroxaban, apixaban and edoxaban) or thrombin (dabigatran).

Prof Weitz compared the pharmacological characteristics of the various NOACs and highlighted the differences in dosing frequency, renal excretion rates and potential for drug–drug interactions. Rivaroxaban (20 mg once-daily) resulted in higher peaks and lower troughs of drug plasma concentration than apixaban (2.5 mg twice-daily). While this may be considered problematic, with either agent there is a marked reduction in intracranial haemorrhage compared to warfarin and at least comparable efficacy. Phase I studies demonstrated that single-dose edoxaban produced a very dose-dependent increase in peak plasma concentrations and that prothrombin times also paralleled drug plasma levels.[4]

Prof Weitz described a Phase II safety study that compared edoxaban at four dose rates (30 mg or 60 mg, once or twice a day) with warfarin.[5] Excess bleeding was observed in both of the edoxaban twice-daily dosing regimens, but not in the once-daily regimen even though the total daily doses were the same. The main predictor of bleeding was the trough concentration of drug (higher in the split dose groups, compared with the once-daily dose), suggesting that the risk of bleeding increased once the trough concentration exceeded a threshold. Single doses of either 30 mg or 60 mg inhibited thrombin generation as effectively as heparin for at least 24 hours.[6]

There are numerous advantages for the use of NOACs over warfarin. These include their rapid onset of action, their predictable dose-response profiles, which eliminate the requirement for monitoring, and having fewer drug–drug interactions than warfarin. Dosing is fixed and simplified at once a day. On the other hand, their short half-lives mean that patient adherence could be critical. The NOACs are eliminated by renal excretion by some degree so creatinine clearance should be monitored and NOACs should not be given to patients with severe renal impairment.

Prof Weitz concluded that NOACs are just as effective but more convenient than warfarin, safer for the brain and many are safer in terms of major bleeding.

The ENGAGE AF – TIMI 48 Trial[7]

Prof Robert Giugliano

Prof Giugliano detailed the recently published results from the ENGAGE AF – TIMI 48 trial. The main objective of this trial was to determine whether two dose regimens of edoxaban were non-inferior to warfarin in preventing ischaemic and haemorrhagic strokes and SEE in patients with non-valvular AF. This double-blinded, double-dummy study involved 21,105 patients with moderate to high-risk AF with a clinical prediction risk score ($CHADS_2$) of at least 2 (mean of 2.8). Patients were randomised into one of three treatment arms: warfarin (dose adjusted to an INR of 2–3), high-dose edoxaban (60 mg once-daily) or low-dose edoxaban (30 mg once-daily). Where necessary, patients in the edoxaban groups were also dose adjusted (reduced by 50%) before and during the study, for example if they had renal impairment.

The primary endpoint was a composite of stroke or SEE. The secondary efficacy endpoint was a composite of stroke, SEE, or cardiovascular

mortality, and the principal safety outcome was major bleeding. It was a particularly rigorous trial, with a high rate of follow-up (99.1%), low discontinuation of treatment (<9% per year) and a median follow-up of 2.8 years. Both the low and high-dose edoxaban groups were shown to be non-inferior to warfarin for the primary endpoint (incidence of 1.6% and 1.1%, respectively, versus 1.5% for warfarin [p=0.005]). Haemorrhagic stroke was dramatically reduced with both dose rates of edoxaban compared to warfarin. There was no difference in ischaemic stroke between high-dose edoxaban and warfarin; however, there was a significant increase in ischaemic stroke with low-dose edoxaban compared with warfarin with a hazard ratio of 1.41. Cardiovascular mortality was significantly reduced for both dose regimens of edoxaban (reduction of 14–15% and 8–13%, for 60 mg and 30 mg, respectively). Net clinical outcomes were also assessed. Disabling stroke, life-threatening bleeding and death were all reduced significantly with both dose regimens of edoxaban (12% for 60 mg, 17% for 30 mg).

International Society on Thrombosis and Haemostasis (ISTH) major bleedings were reduced by 20% overall. There was a 20% reduction in major bleeding in the high-dose edoxaban group compared to warfarin, and a 53% reduction in the low-dose group. A significant reduction in fatal bleeding and intracranial haemorrhage was also observed in the edoxaban groups. GI bleeding was more common in the high-dose group compared to warfarin (p=0.03). However, the low-dose group had 33% less GI bleeding than the warfarin group. Patients receiving edoxaban demonstrated significantly better compliance and there were no differences in serious adverse events compared to warfarin.

Prof Giugliano summarised that in comparison to well-managed warfarin (median time in the therapeutic range [TTR] was 68.4%), once-daily edoxaban was non-inferior for stroke or SEE at both high and low doses. There was a trend towards reduced stroke and SEE observed in the high-dose edoxaban regimen treatment arm. Both dose regimens significantly reduced major bleeding, i.e. haemorrhagic stroke, and cardiovascular death. Both dose regimens of edoxaban achieved superior net clinical outcomes.

Meta-Analysis of 72,000 Patients with AF Treated with Novel Anticoagulants

Dr Christian Ruff

Dr Ruff presented the results of a meta-analysis of the four warfarin-controlled, landmark trials investigating the efficacy of NOACs for preventing stroke in AF: RE-LY,[1] ROCKET-AF,[2] ARISTOTLE,[3] and ENGAGE AF – TIMI 48.[7] The data for NOACs used at their highest dose were pooled to create a sample size of almost 72,000 patients. A separate analysis was carried out for dabigatran and edoxaban used at a lower dose rate.

As a class of drugs, NOACs significantly reduce stroke and SEE by 19% compared to warfarin. Although they are comparable to warfarin in reducing ischaemic stroke, they reduce haemorrhagic stroke by 51%, which is reflected in the reduction in intracranial haemorrhage of 52%. NOACs significantly reduce all-cause mortality by 10%, indicating that this class of drug does help patients live longer. Dr Ruff also highlighted that NOACs in general tend to reduce major bleeding. Even in the whole range of patient subgroups, those with and without adequate TTR on warfarin, the benefits of NOACs in reducing stroke and systolic embolic events are consistent. Indeed there was an even greater reduction in bleeding in patients who could not achieve an INR between 2 and 3 for 66% of the time. In terms of safety, Dr Ruff noted there was an excess of GI bleeding by approximately 25% with NOAC use, but there was heterogeneity between the different trials.

In the lower dose meta-analysis, the NOACs were similar to warfarin in terms of stroke reduction and SEE. As expected with a lower dose of anticoagulant, there tended to be more ischaemic stroke (a 28% excess), but in contrast there was an even greater reduction in haemorrhagic stroke than with the higher dose (67% compared to 51%). There was less bleeding (35% reduction) and less intracranial haemorrhage (69% reduction) associated with low-dose NOAC use.

Dr Ruff explained that there is a trade-off between the increased risk of ischaemic stroke and reduced risk of haemorrhagic stroke when using a lower dose of NOAC. He also noted that lower doses of NOACs produced a similar reduction in all-causes mortality (11%) to the higher doses.

Dr Ruff concluded that NOACs offer an effective and safe therapeutic alternative to warfarin. In comparison to warfarin, NOACs significantly reduced all-cause stroke by 19%, primarily due to a 51% reduction in haemorrhagic stroke. NOACs significantly reduced all-cause mortality by about 10%, and in addition there was a trend towards less bleeding, although there was an increase in GI bleeding.

The Future of Antithrombotic Therapy for Atrial Fibrillation

Prof John Camm

Prof Camm summarised the preceding presentations and discussed the way forward in anticoagulant therapy in AF patients, with a particular focus on edoxaban.

Most physicians have concerns that the risk of haemorrhage may outweigh the antithrombotic benefits of warfarin, which may result in underuse. He said it was important to remember that warfarin treatment is associated with a 26% reduction in mortality compared to placebo. Although there are problems keeping warfarin within the therapeutic range, patient self-testing can significantly improve dose management.[8] The major difficulty with warfarin therapy is that intracranial haemorrhage occurs even when the dosage is properly controlled.[9] Prof Camm commented that there is still a role for warfarin use. NOACs need to be used with care in patients with renal impairment and are contraindicated in patients with mechanical heart valves. There are currently no data for their use in children or adolescents, while some patients may be intolerant of NOACs.

Edoxaban has been evaluated in the largest and longest clinical trial of NOACs, in a moderate-to-high risk population with excellent warfarin control. Edoxaban treatment reduced all-cause mortality at the low dose and tended towards a reduction in all-cause mortality at the higher dose compared to warfarin. Most of the bleeding complications were reduced and there was a marked 50% reduction in intracranial haemorrhage. However, the low dose of edoxaban was associated with an increase in ischaemic stroke.

Prof Camm discussed the PINNACLE registry. The data from this study revealed that only 12% of patients are currently being treated with a NOAC. The European Society of Cardiologists guidelines point out that aspirin is not necessary for the majority of patients with AF and that when there is a thromboembolic risk and an anticoagulant can be used, then a NOAC should be the preferred treatment option. Prof Camm raised the issue of the cost of NOACs, which are approximately £5,000 per quality-adjusted life year. When this figure is taken into account, NOACs are a cost-effective therapy option in the UK. However, the overall cost of implementing a switch to NOACs for all patients currently on warfarin would be considerable. Nevertheless, Prof Camm concluded by intimating that NOACs will hopefully be gradually but fully implemented in the not too distant future.

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EVERY PATIENT IS DIFFERENT. ORAL ANTICOAGULANTS NEED TO 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] **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.[1-10]

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

Clinical trials that evaluate the effects of patient-related factors in oral anticoagulation can help provide much-needed clarity to physicians when making critical therapeutic choices.[1-10]

DAIICHI SANKYO IS DEDICATED TO ONGOING RESEARCH IN ORAL ANTICOAGULATION

Daiichi Sankyo is highly committed to conducting clinical research with the goal of providing important information that helps physicians make treatment decisions for patients.

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