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

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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

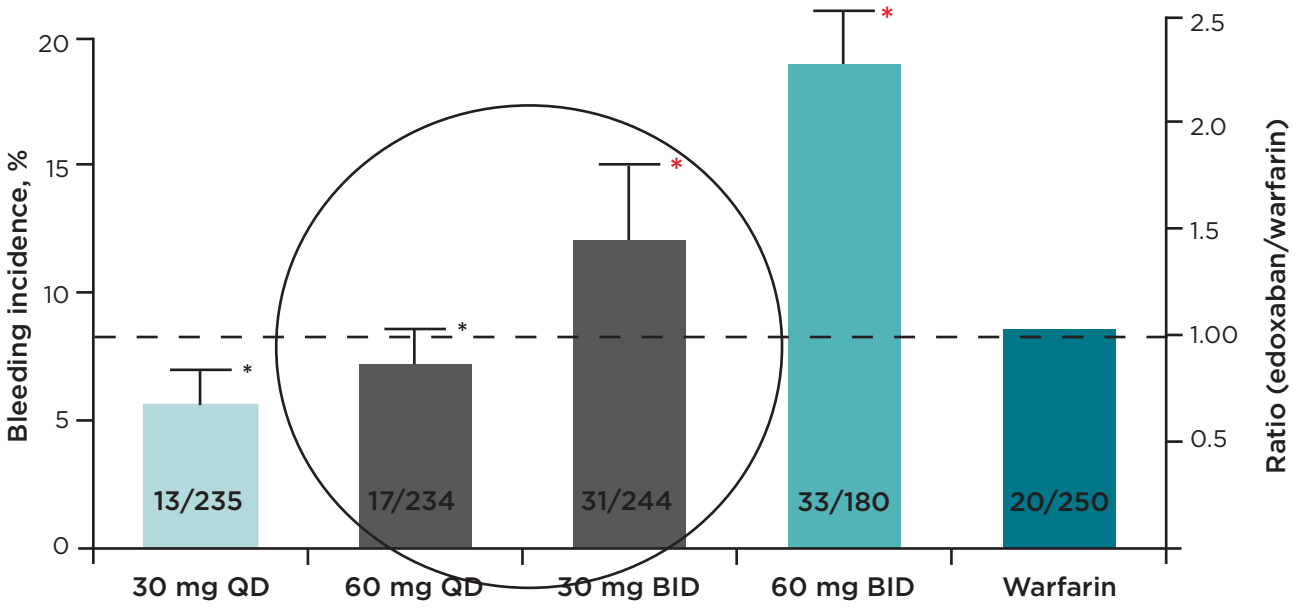

Figure 1. Edoxaban in AF (Phase II): All bleeds for edoxaban relative to warfarin.
For the same total daily dose of 60 mg, higher bleeding observed for 30 mg BID compared with 60 mg QD. *Upper bound for one-sided 67% CI for ratio of incidence rates (edoxaban/warfarin): 0.80, 1.04, 1.79 and 2.58.
Weitz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

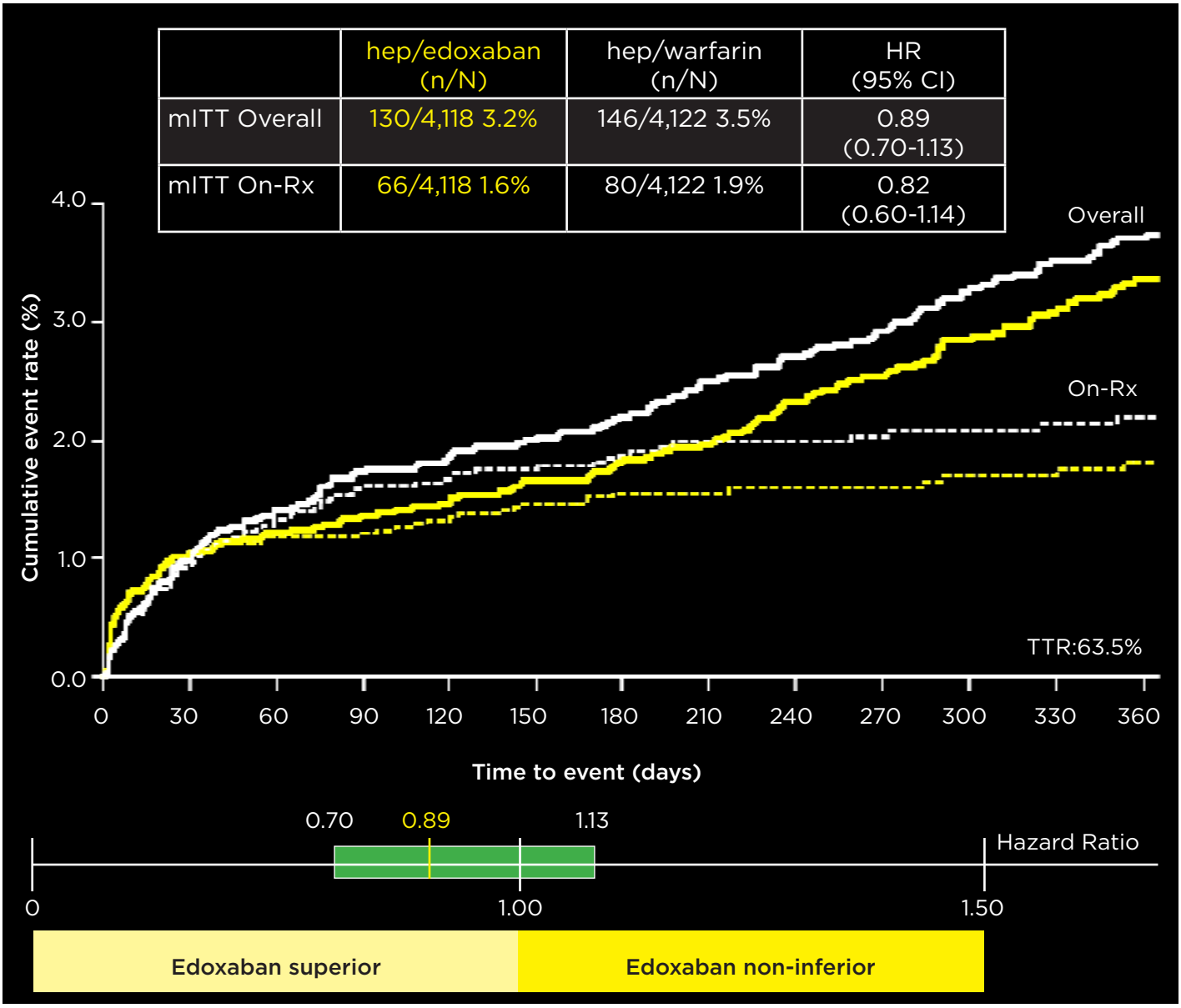

Figure 2. Hokusai-VTE study primary efficacy outcome.

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.

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