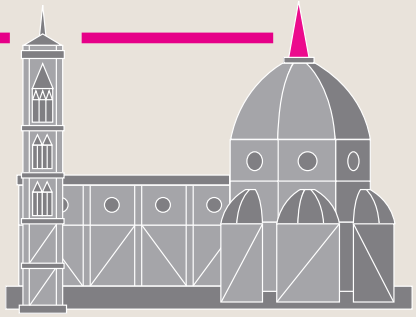
Newsletter

NEWS FROM THE 8TH EFORT CONGRESS



Advances in the surgical and clinical management of orthopaedic patients

Introduction

The spectacular Renaissance city of Florence, Italy was host to 8000 orthopaedic surgeons this week for the 8th European Federation of National Associations of Orthopaedics and Traumatology (EFORT) congress.

New technologies and emergent surgical procedures are transforming orthopaedic surgery. Particularly exciting advances are being made in the field of minimally invasive surgery (MIS), such as the MicroHip™ technique, and in the clinical development of novel, oral anticoagulants to simplify antithrombotic management after surgery.

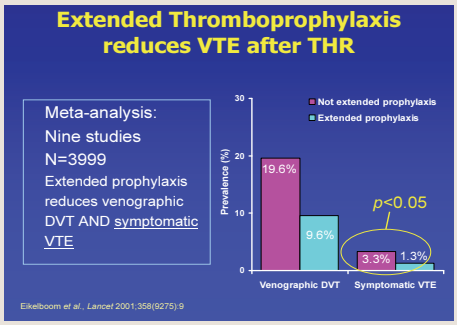
This newsletter covers the presentations from: 'Advances in the surgical and clinical management of orthopaedic patients: the future potential of oral anticoagulation with rivaroxaban – a once-daily, direct Factor Xa inhibitor' – a well-attended educational session chaired by Dr Michael Rud Lassen, and supported by Bayer HeathCare and Scios, Inc. – and other rivaroxaban presentations.

William H. Geerts, MD, FRCPC, FCCP
Professor of Medicine and Director, Thromboembolism Program, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

Guidelines for thromboprophylaxis after major orthopaedic surgery

The American College of Chest Physicians (ACCP) issue evidence-based guidelines for thromboprophylaxis after major orthopaedic surgery. While these guidelines have gone a long way towards ensuring all patients receive adequate thromboprophylaxis, there is still room for improvement according to Dr Geerts – the lead author of the ACCP guidelines.

The effectiveness of thromboprophylaxis to reduce the incidence of venous thromboembolism (VTE) after total hip arthroplasty (THA) or total knee arthroplasty (TKA) is indisputable, and it has become the standard of care. The current guidelines conclude that

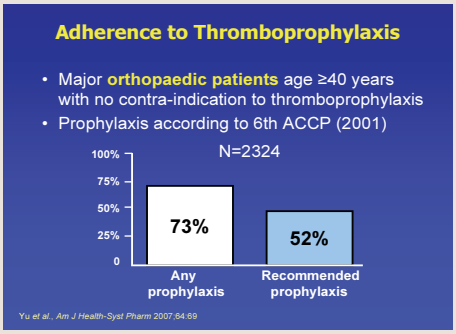


all patients undergoing THA or TKA should receive thromboprophylaxis for at least 10 days after surgery; however, Dr Geerts presented data clearly showing that extending prophylaxis up to 35 days after THA significantly reduces the incidence of both asymptomatic and symptomatic VTE. As a result of such evidence, the ACCP recommend extending prophylaxis in these patients.

'In terms of adherence to prophylaxis guidelines in hip and knee replacement, there's some good and bad news: the good news is that arthroplasty has led the way in adherence to guidelines – 73% of patients received prophylaxis; but only 52% received recommended prophylaxis; so there's still room for improvement', said Dr Geerts. In discussing strategies to improve adherence, he proposed that the following should all help:

- A local, written policy
- The involvement of pharmacy and nursing staff in the supervision of prophylaxis
- The use of pre-printed and/or computerized orders

'We need to bring VTE prevention into the culture of everyday patient care'



Anticoagulants for use after major orthopaedic surgery: the story so far …

Alexander (Ander) T. Cohen, MBBS, MSc, MD, FRACP

Department of Surgery,
Guy's, King's and St Thomas' Hospital, London, UK

'Currently available anticoagulants have significant limitations; what we need are predictable, safe, oral anticoagulants', began Dr Cohen. Low molecular weight heparins (LMWHs) and fondaparinux are limited by subcutaneous administration, and oral vitamin K antagonists have unpredictable pharmacology and require frequent monitoring.

Ideal anticoagulant versus currently available agents

	Oral	Fixed dosing	Rapid onset/ offset	Predictable response	No routine coagulation monitoring	No food/drug interactions	No thrombo-cytopenia	Inhibits free & clot-bound Factor Xa/ thrombin
IDEAL	✓	✓	✓	✓	✓	✓	✓	✓
UFH			✓			✓		
LMWH		✓	✓	✓	✓	✓		
Fondaparinux		✓		✓	✓	✓	✓	✓
Warfarin	✓						✓	

After discussing the new oral drugs in development – there are at least nine compounds in phase I or later – Dr Cohen moved on to the choice of target for novel anticoagulants – most are thrombin or Factor Xa (FXa) inhibitors. 'In theory, FXa may be a better target – it has few functions outside coagulation; also we know that rebound thrombin generation can occur with thrombin inhibitors', he said. Two novel, oral anticoagulants in advanced clinical development – dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct FXa inhibitor) – were highlighted because they have predictable pharmacology and offer fixed, once-daily dosing in orthopaedic surgery. 'However, a FXa inhibitor should have a very wide therapeutic window, whereas, with other approaches, the therapeutic window might be much narrower'. With so many drugs in development, thromboprophylaxis after orthopaedic surgery in the future will probably be very different from today.

'Simplicity is the key …'

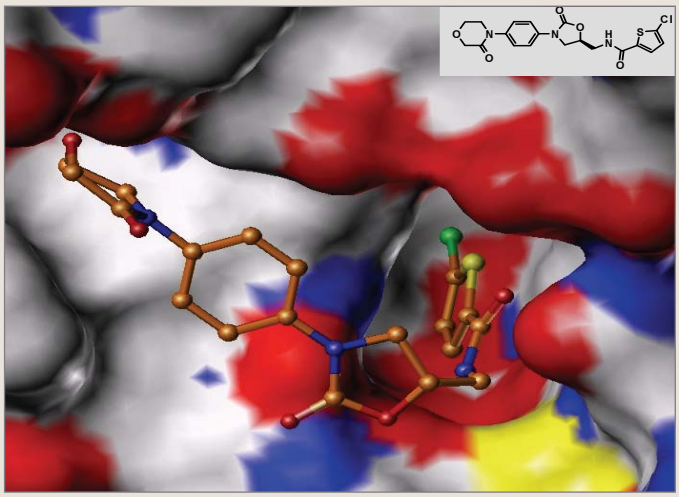
Anticoagulation with rivaroxaban – a novel, oral, direct Factor Xa inhibitor

Bengt I. Eriksson, MD, PhD

Sahlgrenska University Hospital/Östra,
Göteborg, Sweden

Dr Eriksson reviewed the promise of rivaroxaban for thromboprophylaxis after major orthopaedic surgery by discussing preclinical, phase I and phase II rivaroxaban data. Rivaroxaban has:

- A highly selective mechanism of action
- High oral bioavailability
- A rapid onset and offset of action
- Predictable pharmacokinetics and pharmacodynamics
- No accumulation
- A dual mode of excretion



'Rivaroxaban has predictable pharmacokinetics, which is very reassuring'

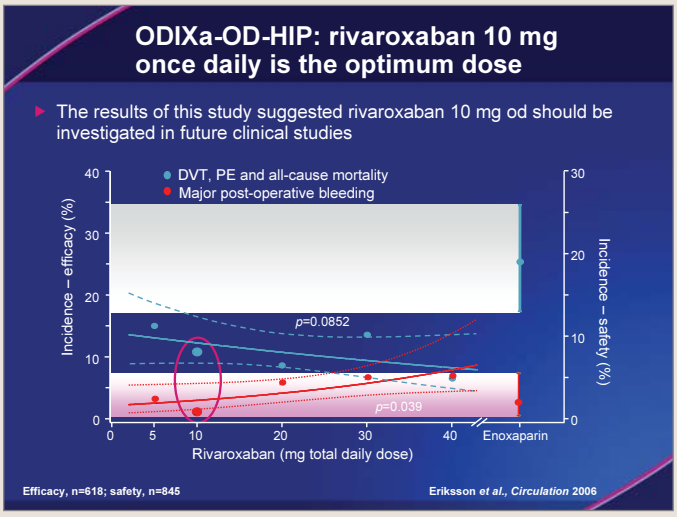
Phase I studies suggested that rivaroxaban may be given in fixed doses to all patients undergoing orthopaedic surgery; 'as orthopaedic surgeons, we like the idea of one regimen for all patients – the nurses will love us for it!', he quipped. Rivaroxaban also has a low risk of drug–drug interactions (especially with commonly used pain medications such as acetylsalicylic acid [ASA] and non-steroidal anti-inflammatory drugs).

Dr Eriksson reviewed the large phase II programme of rivaroxaban for thromboprophylaxis after major orthopaedic surgery – almost 3000 patients were included; the four studies resulted in a wealth of knowledge on rivaroxaban in this indication.

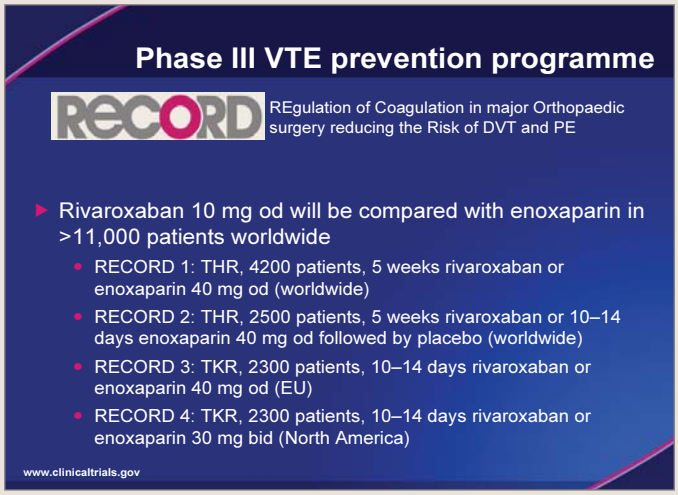
'Rivaroxaban – an oral, direct FXa inhibitor – has great promise for thromboprophylaxis after major orthopaedic surgery'

The studies had the same endpoints and central adjudication committees, and the comparator was the LMWH enoxaparin:

- An open-label study in patients undergoing total hip replacement (THR) demonstrated proof of principle for both twice-daily (bid) and once-daily (od) rivaroxaban dosing
- Two double-blind studies with bid rivaroxaban dosing – one in THR and one in total knee replacement (TKR) – demonstrated that rivaroxaban total daily doses of 5–20 mg had similar efficacy and safety to enoxaparin
- Rivaroxaban od dosing was investigated in a further double-blind study in THR patients
  - Observed incidences of deep vein thrombosis (DVT), pulmonary embolism (PE) and all-cause mortality were lower with all rivaroxaban doses than with enoxaparin
  - Major VTE (proximal DVT, PE and VTE-related death) decreased dose dependently with rivaroxaban
  - When efficacy and safety were considered together, rivaroxaban 10 mg od was selected as the optimal dose



'When you combine efficacy and safety, it seems that rivaroxaban 10 mg od – a dose within the range identified in the bid studies – is the dose of choice, and that's what is being investigated in the ongoing studies', Dr Eriksson said. The large phase III programme of rivaroxaban (RECORD) will enrol over 11,000 patients in four studies – two after THR and two after TKR. A fixed dose of rivaroxaban 10 mg od will be investigated in all studies and all patients, and extended prophylaxis with rivaroxaban will be investigated in patients undergoing THR. 'The phase III results are eagerly awaited, and the first are expected later this year', he concluded.



Other rivaroxaban presentations at EFORT

Four other presentations covered rivaroxaban data. Rivaroxaban has no clinically relevant interaction with ASA or naproxen (important co-medications in patients undergoing major orthopaedic surgery) in healthy subjects – this was the conclusion of Dr Dagmar Kubitza's poster, which was also presented as an e-poster.

Dr Kubitza also presented data from two phase I studies that suggested that fixed dosing of rivaroxaban may be possible with no restrictions for age, gender or weight. These findings were backed up in a plenary presentation given by Dr Ola Dahl, which showed that in phase II studies, the dose–response relationships between rivaroxaban and VTE or bleeding were not affected by patients' age, gender or weight. Current anticoagulants often require dose adjustment for age, gender or weight, so an oral anticoagulant that could be given in fixed doses would be a real step forward.

Finally, in a plenary presentation Dr Eriksson gave an overview of the phase II clinical data of rivaroxaban for thromboprophylaxis after THR/TKR.

‘From the drug to the knife’: advances in minimally invasive surgery

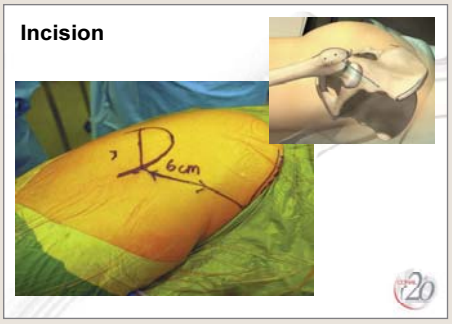
Markus C. Michel, MD

Münsingen Orthopaedic Centre, Münsingen, Switzerland

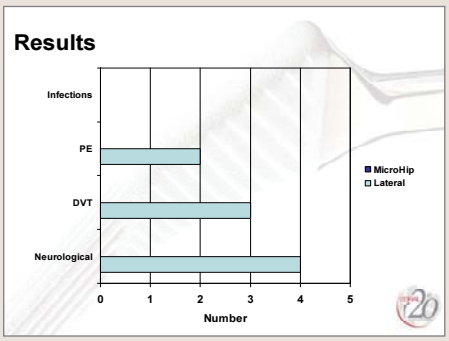
Louis M. Kwong, MD, FACS

Department of Orthopaedic Surgery, Harbor-UCLA Medical Center, Los Angeles, CA, USA

Two presenters discussed MIS – an approach that aims to reduce wound size, blood loss and recovery time.

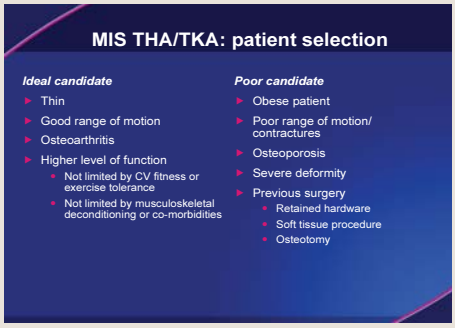


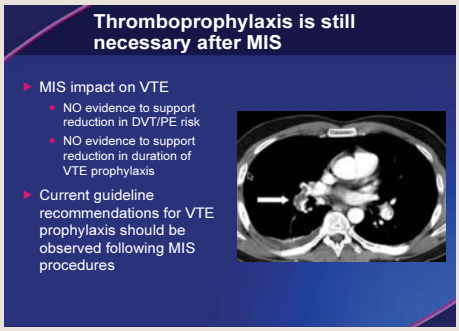
Dr Michel introduced MicroHip – a promising, new minimally invasive technique for THR based on a modified Smith-Petersen approach. An impressive multimedia presentation highlighted the small incision (6 cm) and showed that no tendons or muscles are cut or detached using this exciting technique. The joint capsule is split and left in place, and the hip joint is not dislocated; osteotomy of the femoral neck is performed *in situ*.



Dr Michel said that ‘reaming of the acetabulum and cup insertion is more or less standard, but uses special, bent instruments.’ For femur insertion, the leg is flipped backwards in hyperextension with external rotation. He then presented preliminary data, in which MicroHip was compared with a conventional, lateral approach, that showed that complications appeared to be reduced when using MicroHip: there were no fractures of the greater trochanter in the MicroHip group, compared with three in the standard group; no VTE events were observed with MicroHip, compared with five with the standard approach, despite all patients receiving the same thromboprophylaxis; and blood loss and hospital time were reduced by about 30% with MicroHip.

Dr Kwong went on to cast additional light on important issues to consider with regard to MIS. ‘A number of clinical factors have driven the development and evolution of MIS, including a decrease in post-operative pain, shorter time to rehabilitation and optimizing the clinical outcome.’ ‘The introduction of MIS total joint athroplasty was greeted with much fanfare by both the orthopaedic community and the patient population. But soon, the realities of the technical demands of these procedures dampened this enthusiasm, along with the realization that smaller is not necessarily better for all patients, nor is it easier to perform.’ He then





illustrated how, unfortunately, MIS is not suitable for all patients – obese and inflexible patients, among others, would not be suitable.

Importantly, bone trauma and vessel damage are not reduced with MIS, compared with standard procedures; therefore, the risk of VTE is likely to be as high after MIS as after standard surgery. There is no evidence that thromboprophylaxis intensity or duration should be reduced after MIS; and current recommendations should be followed.

These two presentations clearly showed that orthopaedic surgery techniques continue to evolve, with substantial benefits for the patient; however, there is as yet no proof that the risk of VTE and the need for thromboprophylaxis are reduced.

‘Physician education is needed – the eyes see only what the mind knows; if orthopaedic surgeons don’t know what they’re looking for with respect to VTE, it won’t be apparent’

Bayer HealthCare would like to thank the session Chairman and the presenters for their participation.

We look forward to seeing you in Nice, France at EFORT 2008!