Extended Duration Rivaroxaban Versus Short-Term Enoxaparin for the Prevention of Venous Thromboembolism After Total Hip Arthroplasty: A Double-Blind, Randomized Controlled Trial

RECORD 2

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Lancet 2008;372:31–39

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- Issued: 26 June 2008

RECORD 2

Landmark studies RECORD1, 2 and 3 all published in one week in June 2008

RECORD1

The NEW ENGLAND JOURNAL of MEDICINE

Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty

RECORD2

THE LANCET

Articles

Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial

RECORD3

The NEW ENGLAND JOURNAL of MEDICINE

Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Total Knee Arthroplasty

Eriksson *et al*., *N Engl J Med* 2008; 358:2765–2775; Kakkar *et al*., *Lancet* 2008;372:31–39; Lassen *et al., N Engl J Med* 2008;358:2776–2785

RECORD2

Selective Factor Xa inhibition for thromboprophylaxis

Comment

Selective factor Xa inhibition for thromboprophylaxis

For over 60 years, vitamin K antagonists, such as warfarin, have been the only available oral anticoagulants. Although effective, these drugs are challenging to use. Dose requirements vary among patients and the anticoagulant response is unpredictable. Consequently, coagulation needs to be monitored and the dose frequently adjusted to ensure that a therapeutic level of anticoagulation is achieved. Such monitoring is inconvenient for patients and costly for health-care systems.

The limitations of vitamin K antagonists have prompted the development of new oral anticoagulants that target activated factor X (factor Xa) or thrombin. Rivaroxaban is a new oral direct inhibitor of factor Xa in advanced stages of development. Rivaroxaban has high oral bioavailability, rapid onset of action, and a half life of 5–9 h;[1] furthermore, it produces such a predictable anticoagulant response that no monitoring is required. Building on promising phase II results,[2] four large phase III trials, involving more than 12 500 patients, have compared rivaroxaban with enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty (table).[3–6]

In today's *Lancet*, Ajay Kakkar and colleagues report the results of the RECORD2 trial,[4] in which they compared oral unmonitored rivaroxaban, at 10 mg once daily given for 35 days, with subcutaneous enoxaparin, at 40 mg once daily given for 12 days, in 2509 patients undergoing total hip arthroplasty. The primary efficacy outcome, a composite of deep-vein thrombosis, non-fatal pulmonary embolism, and all-cause mortality at 30–42 days, occurred in 9·3% of patients given enoxaparin and 2·0% of those treated with rivaroxaban (absolute risk reduction 7·3%, 95% CI 5·2–9·4%; number needed to treat 14). Compared with enoxaparin, rivaroxaban also significantly reduced the incidence of symptomatic venous thromboembolism (1·2% and 0·2%, respectively; absolute risk reduction 1%; number needed to treat 100). Unlike most other thromboprophylaxis trials, the primary safety outcome of major bleeding in the RECORD2 trial excluded surgical-site bleeding unless it led to reoperation or death. As a result, the incidence of major bleeding was low (<0·1% in both groups); however, rates of non-major bleeding, which included surgical-site bleeding, were similar with enoxaparin and rivaroxaban (5·5% and 6·5%, respectively).

The RECORD2 results add to the evidence that an extended duration of thromboprophylaxis after total hip arthroplasty is more effective than short-term therapy.[7] Although current guidelines recommend extended thromboprophylaxis after total hip arthroplasty,[8] such treatment is underused after hospital discharge[9] because low-molecular-weight heparin and fondaparinux must be given by subcutaneous injection, whereas vitamin K antagonists need monitoring. With fixed oral dosing and no monitoring, rivaroxaban will streamline out-of-hospital thromboprophylaxis.

Another barrier to the use of extended prophylaxis is the belief held by many orthopaedic surgeons that most cases of deep-vein thrombosis after total hip arthroplasty are asymptomatic and confined to the calf and, therefore, unlikely to lead to pulmonary embolism. RECORD2 challenges this view because the reduction in any deep-vein thrombosis with rivaroxaban was associated with a parallel reduction in symptomatic venous thromboembolism.

The unequal treatment durations in RECORD2 tell us little about the relative efficacy of rivaroxaban and enoxaparin. However, RECORD1 showed that 35 days of once daily rivaroxaban was more effective than 35 days of once daily enoxaparin for prevention of venous thromboembolism after total hip arthroplasty, and RECORD3 and RECORD4 showed that 10–14 days of once daily rivaroxaban was more effective than 10–14 days of once daily or twice daily enoxaparin after knee arthroplasty (table). Importantly, the benefits of rivaroxaban over enoxaparin occurred without an increase in bleeding events. With superior efficacy, no compromise in safety,

	Setting	N	Enoxaparin dose and treatment duration	Rivaroxaban treatment duration	DVT, PE, or death		Symptomatic VTE	
					Events	RRR	Events	RRR
RECORD1[3]	THA	4541	40 mg once daily, 35 days	35 days	3·7% *vs* 1·1%	70%	–	–
RECORD2[4]	THA	2509	40 mg once daily, 10–14 days	31–39 days	9·3% *vs* 2·0%	79%	1·2% *vs* 0·2%	80%
RECORD3[5]	TKA	2531	40 mg once daily, 10–14 days	10–14 days	18·9% *vs* 9·6%	49%	2·0% *vs* 0·7%	66%
RECORD4[6]	TKA	3148	30 mg twice daily, 10–14 days	10–14 days	10·1% *vs* 6·9%	31%	1·7% *vs* 0·7%	NS

Trials compared rivaroxaban (10 mg once daily) with enoxaparin for thromboprophylaxis after hip or knee arthroplasty. N=number of participants; DVT=deep-vein thrombosis; NS=not significant; PE=pulmonary embolism; VTE=venous thromboembolism; RRR=relative risk reduction; THA=total hip arthroplasty; TKA=total knee arthroplasty.

Table: Main efficacy outcomes of the RECORD trials

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- "Another barrier to the use of extended prophylaxis is the belief held by many surgeons that most cases of deep vein thrombosis after total hip arthroplasty are asymptomatic and confined to the calf, and, therefore, unlikely to lead to pulmonary embolism. RECORD2 challenges this view because the reduction in deep vein thrombosis with rivaroxaban was associated with a parallel reduction in symptomatic venous thromboembolism"

Eikelboom and Weitz, *Lancet* 2008

RECORD2

Study background

- Heparin-based thromboprophylaxis in the perioperative period reduces fatal pulmonary embolism[1]
- Consensus guidelines recommend pharmacological prophylaxis for a minimum of 10 days and up to 35 days after elective hip replacement surgery[2–4]
- Meta-analyses indicate that extended thromboprophylaxis after elective hip arthroplasty reduces the frequency of venous thromboembolism[5,6]
- Clinicians are concerned about the clinical relevance of extended prophylaxis and the risk of bleeding[7]

[1]Kakkar *et al*., 1975; [2]Geerts *et al*., 2004; [3]SIGN Guideline 62;
[4]NICE Guideline 46; [5]Eikelboom *et al*., 2001; [6]Hull *et al*., 2001;
[7]American Academy of Orthopaedic Surgeons Guideline

RECORD 2

Rivaroxaban: the first in a new class of direct Factor Xa inhibitors

- 10 mg od was selected for investigation in the phase III RECORD programme based on an extensive phase II programme (N=2,857) that evaluated a wide dose range (total daily doses: 5–60 mg)

- Oral, one tablet, once daily
- Predictable pharmacokinetics and pharmacodynamics
- High bioavailability
- Rapid onset of action
- Fixed dose
- No requirement for coagulation monitoring

Kubitza *et al*., 2005; Turpie *et al*., 2005; Eriksson *et al.*, 2006; 2006; 2007

RECORD 2

Study question

- Is extended-duration prophylaxis with rivaroxaban (10 mg od for 31–39 days) superior to short-duration prophylaxis with a LMWH (enoxaparin 40 mg od for 10–14 days) for the prevention of VTE following THR?

Kakkar *et al.*, *Lancet* 2008;372:31–39

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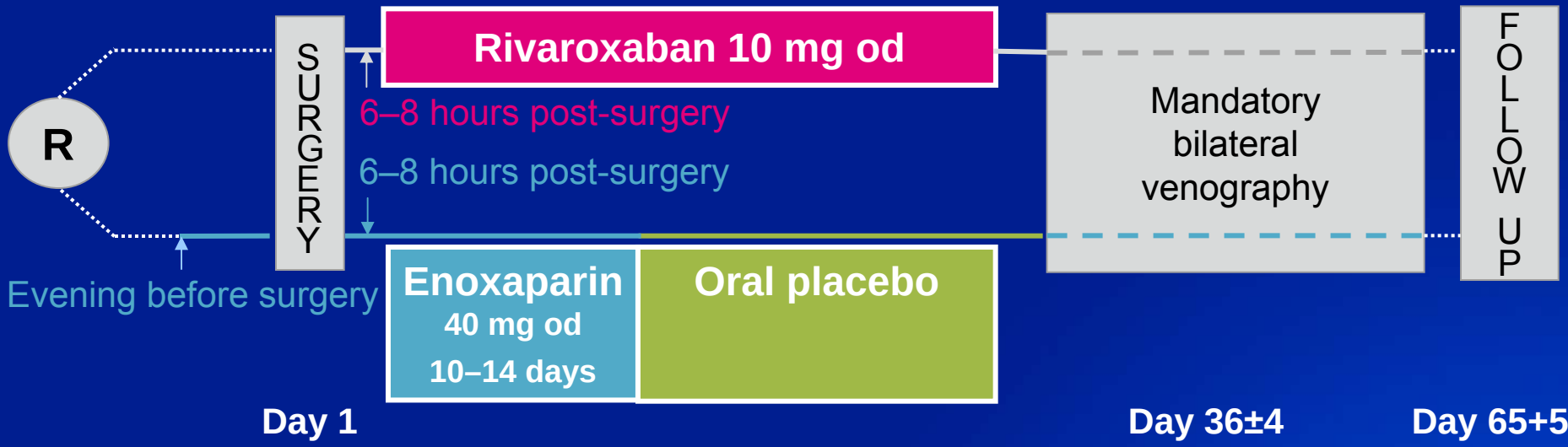
RECORD2: study design

Double blind



Inclusion criteria

- Patients aged ≥18 years, scheduled to undergo elective THR

Major exclusion criteria

- Active bleeding or high risk of bleeding
- Significant liver disease
- Anticoagulant therapy that could not be stopped
- Use of HIV-protease inhibitors

Kakkar *et al.*, *Lancet* 2008;372:31–39

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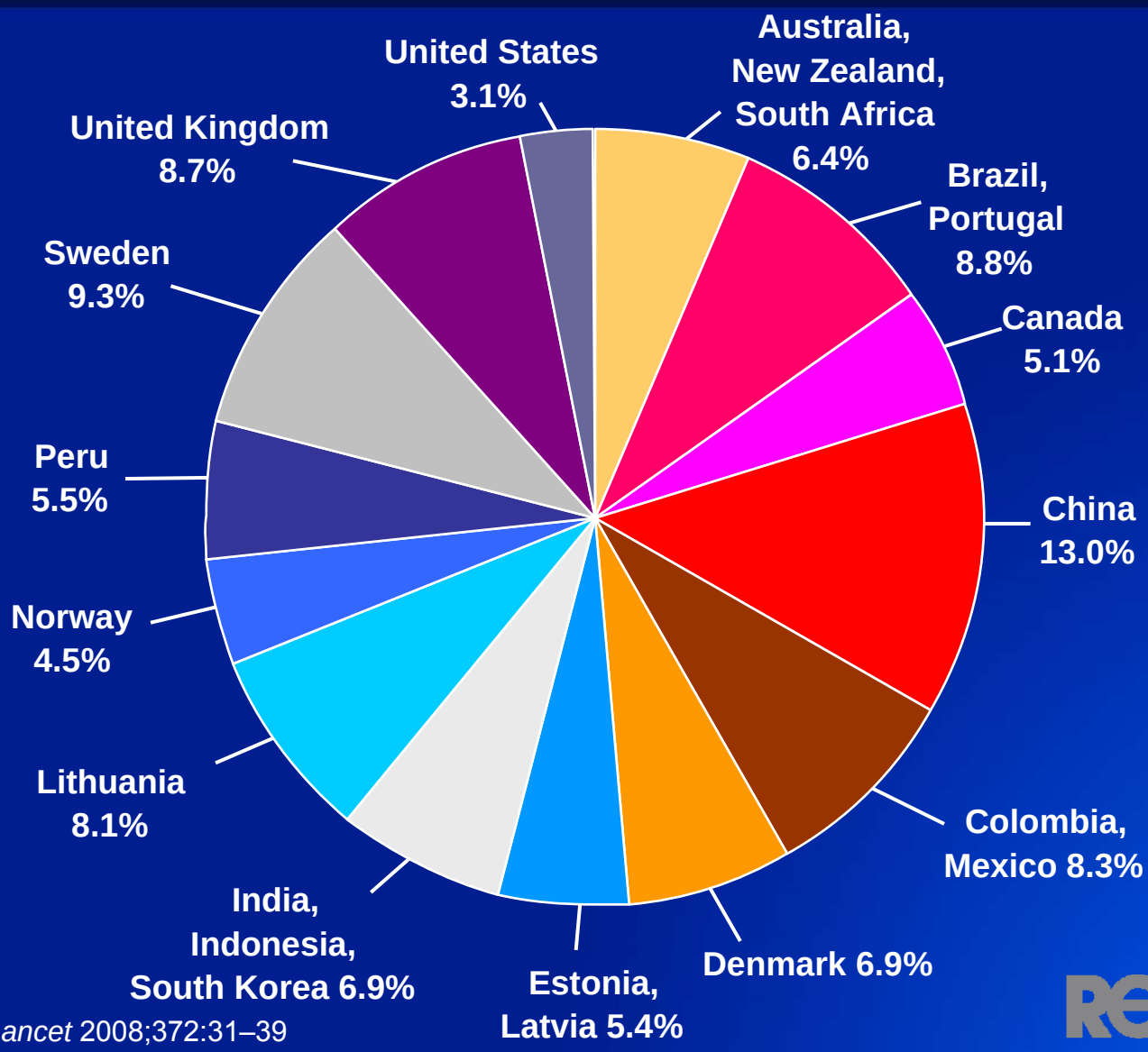
123 sites worldwide



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Efficacy endpoints

Primary

- Total VTE: any DVT, non-fatal PE and all-cause mortality up to day 30–42

Secondary

- Major VTE: proximal DVT, non-fatal PE, and VTE-related death
- DVT: any, proximal and distal
- Symptomatic VTE

All endpoints were adjudicated centrally by independent, blinded committees

Kakkar *et al*., *Lancet* 2008;372:31–39

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Safety endpoints

Main

- Major bleeding starting after the first blinded dose and up to 2 days after last dose ('on treatment')
  - Bleeding that was fatal, into a critical organ, or required re-operation
  - Extra-surgical-site bleeding associated with a drop in hemoglobin ≥2 g/dL or requiring transfusion of ≥2 units of blood

Other

- Any bleeding on treatment*
- Non-major bleeding*
- Hemorrhagic wound complications*#
- Cardiovascular adverse events
- Liver enzyme levels

All endpoints were adjudicated centrally by independent, blinded committees; *Up to 2 days after last dose of study medication; #Composite of excessive wound hematoma and reported surgical-site bleeding

Kakkar *et al*., *Lancet* 2008;372:31–39

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Sample size and pre-specified statistical analysis

Sample size

- Assumed event rate: 11% in the short-duration enoxaparin, plus placebo group
- Risk reduction: 40% in the extended-duration rivaroxaban group
- 1,828 evaluable patients (914 per group) sufficient to detect relative risk reduction (RRR) with 90% power and two-sided type 1 error rate of 5%
- Assuming 25% invalidity rate → 2,500 patients to be enrolled in total

Statistical analysis

- Primary efficacy analysis: absolute weighted risk difference between regimens, with weights based on geographic region

Kakkar *et al.*, *Lancet* 2008;372:31–39

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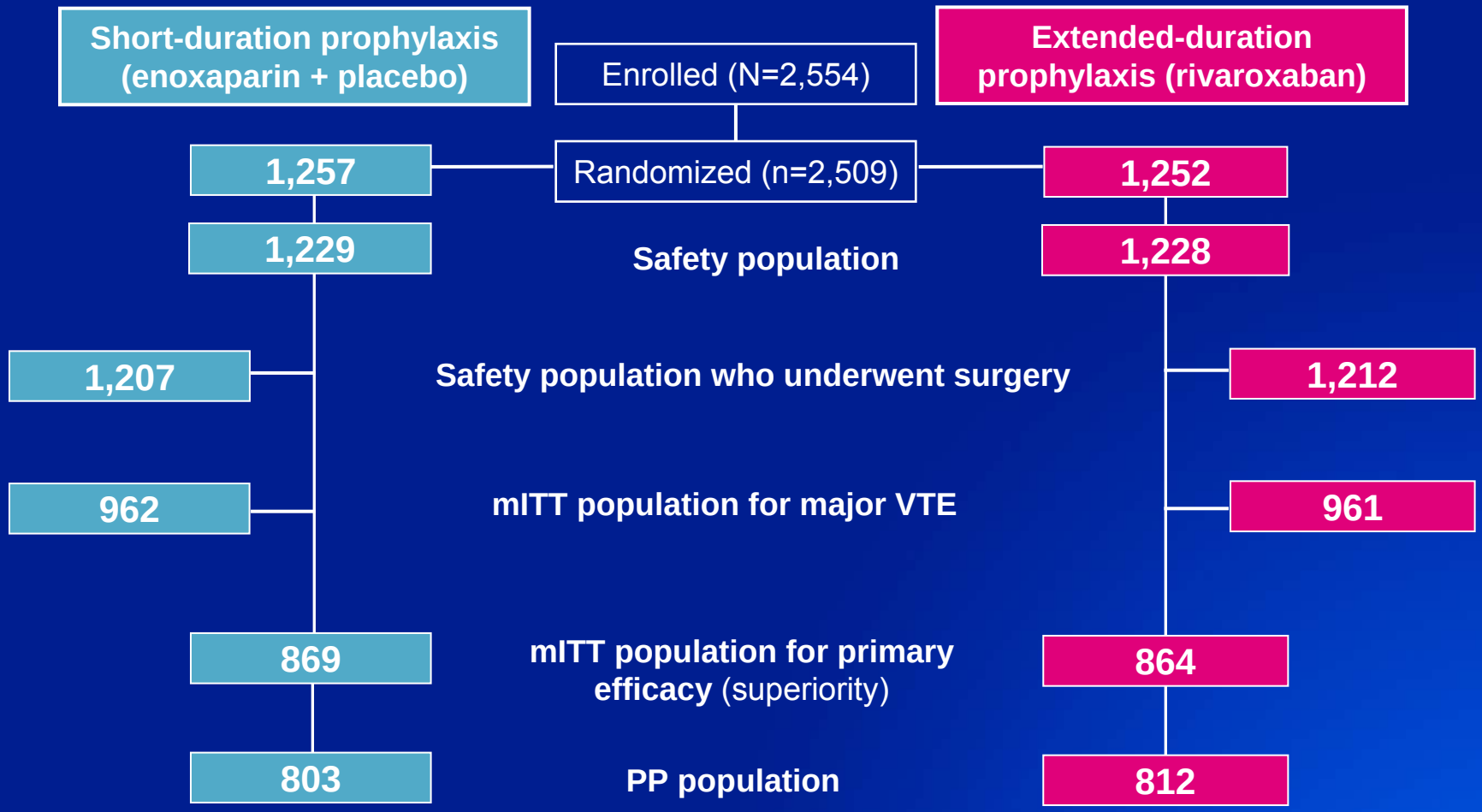
Study flow



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Reasons for exclusion

n %	Short-duration enoxaparin + placebo		Extended-duration rivaroxaban	
Randomized	1,257		1,252	
No intake of study drug	28		24	
Valid for safety analysis	1,229	97.8%	1,228	98.1%
Planned surgery not performed	22		16	
Safety population who underwent surgery	1,207	96.0%	1,212	96.8%
Inadequate assessment of thromboembolism	338	26.9%	348	27.8%
– Venography not performed	159		155	
– Unilateral venography	57		57	
– Indeterminate/non-evaluable venography	111		127	
– Not in time window*	11		9	
Valid for mITT population	869	69.1%	864	69.0%

*The time window for valid venography was day 32–36

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Patient demographics

	Short-duration enoxaparin + placebo (n=1,229)		Extended-duration rivaroxaban (n=1,228)	
Female, n %	651	**53.0%**	667	**54.3%**
Age*, years (range)	61.6	(19–93)	61.4	(18–93)
Weight*, kg (range)	75.2	(33–151)	74.3	(41–149)
Body mass index*, kg/m^2 (range)	27.1	(15.5–59.0)	26.8	(15.6–54.7)
Race, n %				
– Caucasian	798	**64.9%**	799	**65.1%**
– Asian	244	**19.9%**	247	**20.1%**
– Hispanic	142		134	
– Black	29		35	
– Other/missing	16		13	
History of VTE, n %	20	**1.6%**	10	**0.8%**

*Mean values

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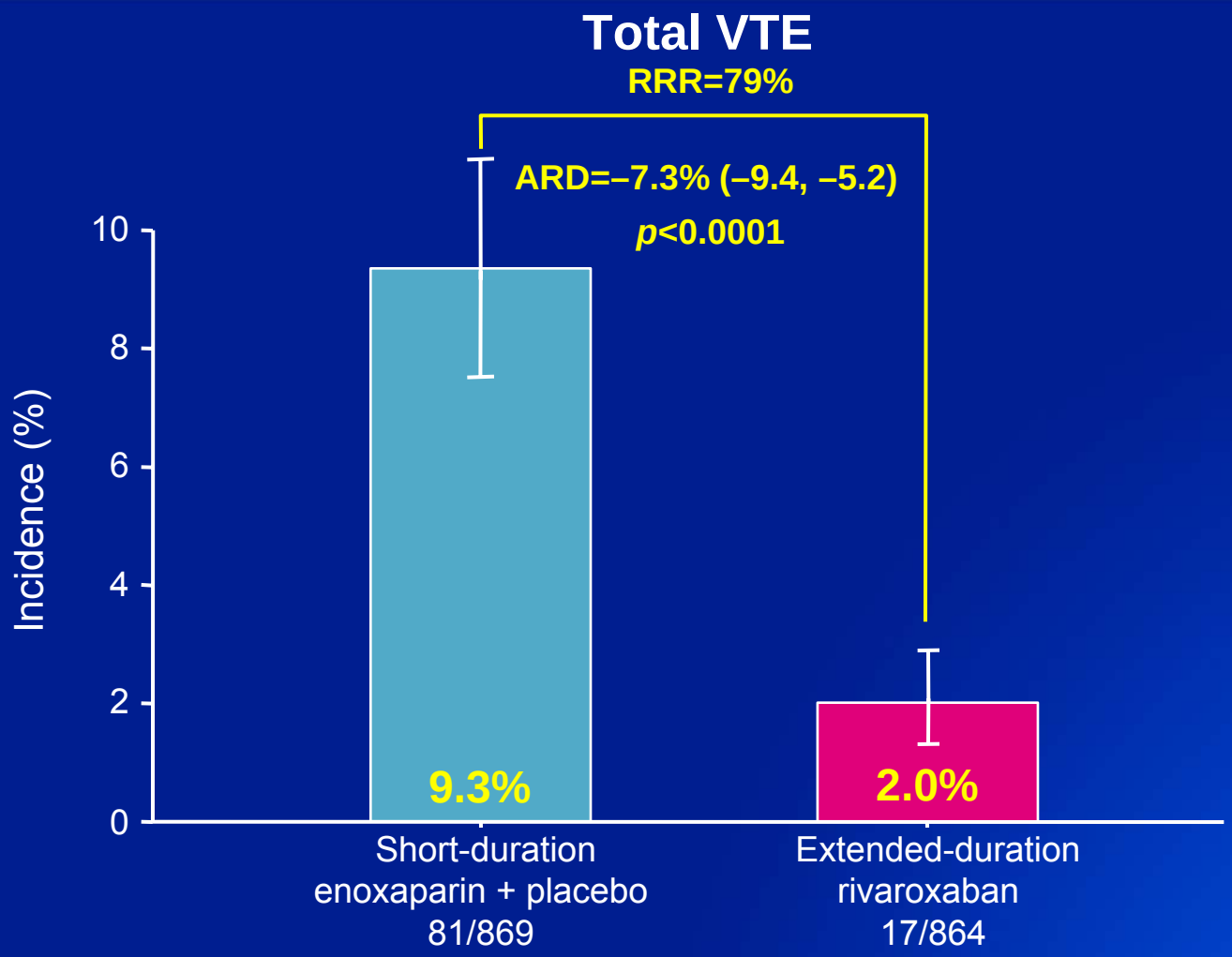
Primary efficacy endpoint



ARD (with 95% CI); mITT population, n=1,733

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Primary efficacy endpoint: individual components

n % (95% CI)	Short-duration enoxaparin + placebo (n=869)		Extended-duration rivaroxaban (n=864)		*p*-value
Primary efficacy endpoint	**81**	**9.3%** (7.5, 11.5)	**17**	**2.0%** (1.2, 3.1)	<0.0001
All-cause mortality	**6**	**0.7%** (0.3, 1.5)	**2**	**0.2%** (<0.1, 0.8)	
Non-fatal PE	**4**	**0.5%** (0.1, 1.2)	**1**	**0.1%** (<0.1, 0.6)	
DVT	**71**	**8.2%** (6.4, 10.2)	**14**	**1.6%** (0.9, 2.7)	
− Proximal only	44	**5.1%** (3.7, 6.7)	5	**0.6%** (0.2, 1.3)	
− Distal only	27	**3.1%** (2.1, 4.5)	9	**1.0%** (0.5, 2.0)	

mITT population, n=1,733

Kakkar *et al.*, *Lancet* 2008;372:31–39

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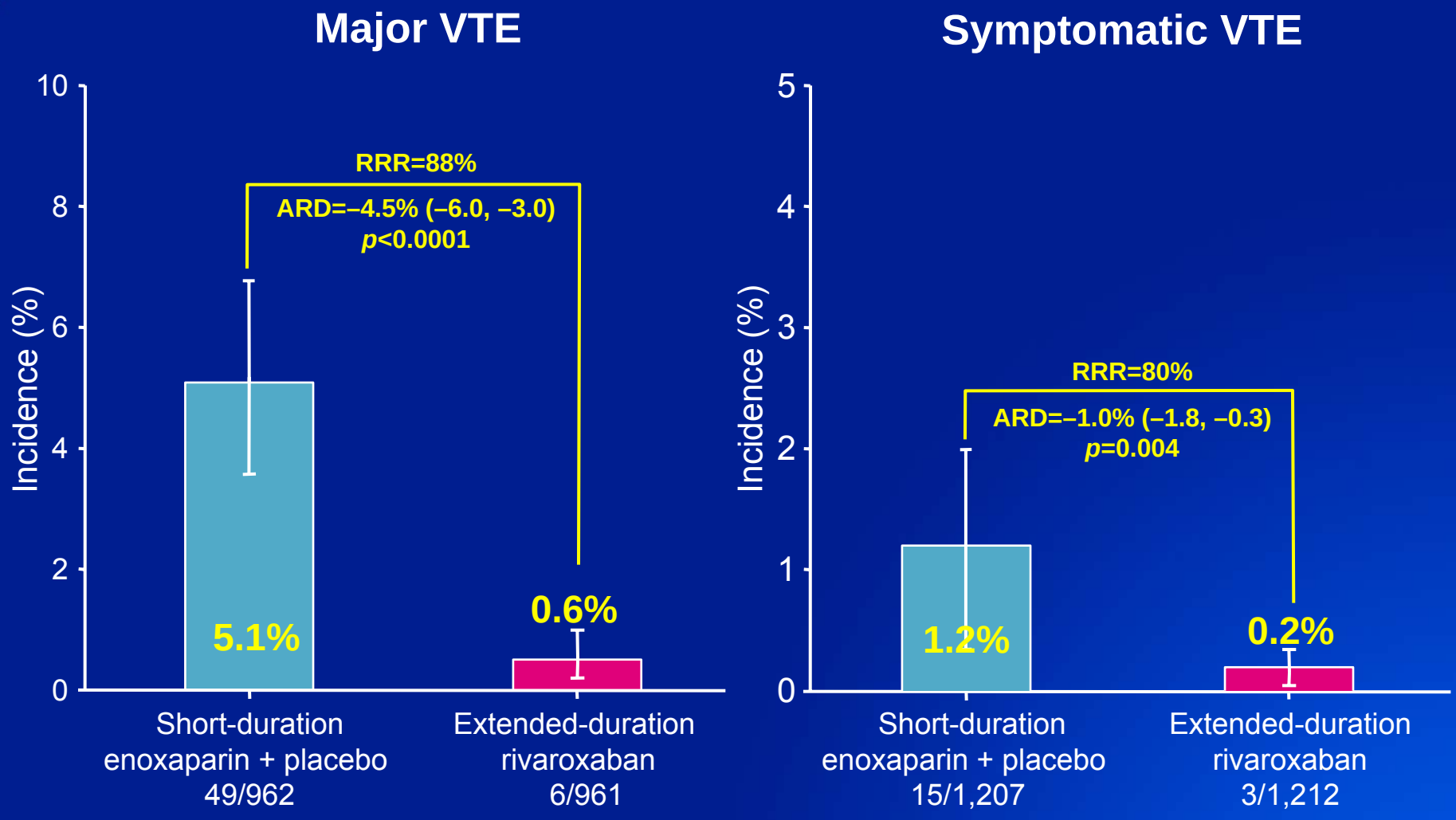
Secondary efficacy endpoints



mITT population valid for major VTE, n=1,923, and symptomatic VTE in safety population who underwent surgery, n=2,419

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Safety: components of bleeding

n %	Short-duration enoxaparin + placebo (n=1,229)		Extended-duration rivaroxaban (n=1,228)	
Major bleeding*	**1**	**<0.1%**	**1**	**<0.1%**
Fatal	0		0	
Into a critical organ	1		0	
Leading to re-operation	0		0	
Leading to fall in hemoglobin#	0		1	
Leading to transfusion of ≥2 units of blood#	0		1	
Non-major bleeding*	**67**	**5.5%**	**80**	**6.5%**
Clinically relevant, non-major bleeding	33	**2.7%**	40	**3.3%**
– Hemorrhagic wound complications‡	21	**1.7%**	20	**1.6%**
Other non-major bleeding	36	**2.9%**	43	**3.5%**
Any bleeding	**68**	**5.5%**	**81**	**6.6%**

On-treatment bleeding events; *major bleeding events could qualify for more than one subcategory; #extra-surgical-site bleeding; ‡composite of excessive wound hematoma and surgical-site bleeding; safety population, n=2,457

Kakkar *et al.*, *Lancet* 2008;372:31–39

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Adverse events

n %	Short-duration enoxaparin + placebo (n=1,229)		Extended-duration rivaroxaban (n=1,228)	
Any adverse event	**832**	**67.7%**	**790**	**64.3%**
On treatment	807	**65.7%**	768	**62.5%**
During follow-up	110	**9.0%**	107	**8.7%**
Cardiovascular adverse events	**4**	**0.3%**	**8**	**0.7%**
On treatment	4	**0.3%**	3	**0.2%**
During follow-up*	0	**0**	5	**0.4%**
Wound-related infections	**7**	**0.6%**	**8**	**0.7%**
On treatment	6	**0.5%**	8	**0.7%**
During follow-up	2	**0.2%**	0	**0**
Death	**8**	**0.7%**	**2**	**0.2%**

*Events occurring more than 1 day after the last intake of study drug; safety population, n=2,457

Kakkar *et al.*, *Lancet* 2008;372:31–39

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Liver function tests

n/N %	Short-duration enoxaparin + placebo		Extended-duration rivaroxaban	
ALT >3×ULN				
On treatment*	55/1,164	**4.7%**	19/1,167	**1.6%**
During follow-up	7/1,097	**0.6%**	6/1,101	**0.5%**
ALT >3×ULN + bilirubin >2×ULN				
On treatment*	3/1,167	**0.3%**	2/1,169	**0.2%**
During follow-up	1/1,093	**0.1%**	1/1,098	**0.1%**

*From first intake of study drug up to 2 days after the last intake of study drug

Kakkar *et al.*, *Lancet* 2008;372:31–39

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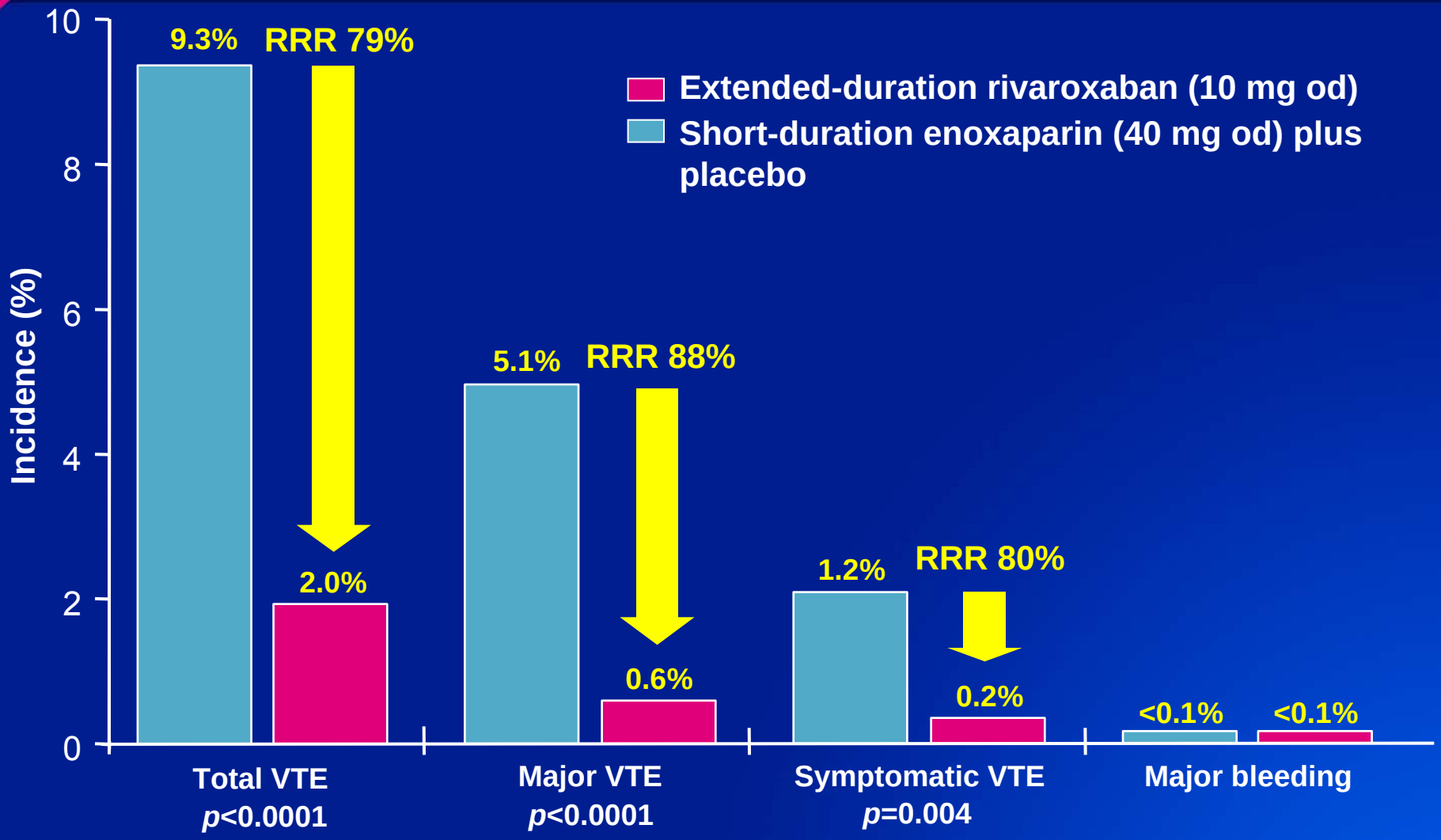
RECORD2: summary



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RECORD2: conclusions

This study comparing extended prophylaxis (rivaroxaban 10 mg od for 31–39 days) with short-term prophylaxis (enoxaparin 40 mg od for 10–14 days) followed by placebo in patients undergoing elective, total hip arthroplasty showed:

- Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin plus placebo for the prevention of venous thromboembolism, including symptomatic events
- Similar good safety profile
  - No increased risk of serious bleeding complications or other adverse events that may affect surgical outcome

Kakkar *et al.*, *Lancet* 2008;372:31–39

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Thank you to the patients, their relatives, the study nurses, and…

Independent Central Adjudication Committee*:* M Levine. **Venous Thromboembolic Event Adjudication Committee***:* H Eriksson, G Sandgren, J Wallin. **Cardiovascular Adverse Event Adjudication Committee***:* JP Bassand, C Bode, T Lüscher. **Bleeding Event Adjudication Committee***:* U Angeras, A Falk, M Prins. **Data Safety and Monitoring Board***:* H Bounameaux, S Dittmar (sponsor contact), D Larray, W Lehmacher (independent statistician), A Leizorovicz. **Study Sponsor***:* A Benson, J Curram, M Fletcher, ÁF Pap (statistical analysis); C Povesi (study management); AG Soglian (medical expert). **Investigators, Australia**: T Brighton, P Coughlin, A Curtin, I Prosser, B Richards, C Ward, S Williams; **Brazil**: G Duarte, L Gomes, E Guydes, R Ikemoto, F Maldorado, K Mesquita, R Moreira, N Ono, M Roos, E Takata; **Canada**: P Ali, L Bredo, V DeKorompay, E Dessouki, S Dolan, J Guerra, G Jasey, P Kim, K McKenzie, J Naude, D Puskas, E Wai; **China:**T Chen, W He, H Lv, K Wang, Y Wang, Y Wang, W Xu, Q Yang, B Zeng, H Zhang, M Zhang; **Colombia:** R Botero, S Escandon, C Palacios, A Reyes, M Urina; **Denmark:** J Bagger, A Borgwardt, P Gebhur, N Krarup, G Lausten, P Mikkelsen, S Mikkelsen, A Phillipsen, B Roennow Duus; **Estonia:** A Koop, A Martson; **India:** SK Becera, M Desai, SJ Mahajan, B Prasad, K Puttakemparaju, N Rajagopalan; **Indonesia:** D Roeshadi, F Tandjung; **Latvia:** U Argalis, J Dobelnieks, J Keselis; **Lithuania:** J Belickas, R Mazutaviciene, V Smilgiene, R Tarasevicius; **Mexico:** E Nafarrete, E Sanchez; **New Zealand:** S Chunilal, P Harper; **Norway:** K Griegel, B Haakan, O Hovik, H Hovind, P Stahl; **Peru:** L Arrieta, R Cotrina, C Diaz, Z Moncada, E Pastor, C Ruiz, M Salas, C Tochio; **Portugal:** L Amaral, C Moniz, J Mousinho, P Oliveira, A Rodriguez; **South Africa:** U Dhanjee, J Diedericks, F Greeff, B Jacobson, S Moodley, R Routier, O Van der Spuy, J Viljoen, GJ Vlok; **South Korea:** SY Kim, YH Kim, SH Lee, YS Park; **Sweden:** L Ahnfelt, L Bengtson, B Edshage, M Flondell, HC Hyldahl, J Johansson, H Laestander, B Paulsson, L Ryttberg; **UK:** I Brenkel, E Crawfurd, A Cohen, R Field, S Frostick, D Meek, A Ratnam, S Sadullah, P Williams; **USA:** P Comp, A Corces, S Hakki, J Papilion, J Ward.

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