NEW ORAL ANTICOAGULANTS – A REVIEW OF LITERATURE AND GUIDELINES

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Disclosures

- Honorarium from Boehringer Ingelheim

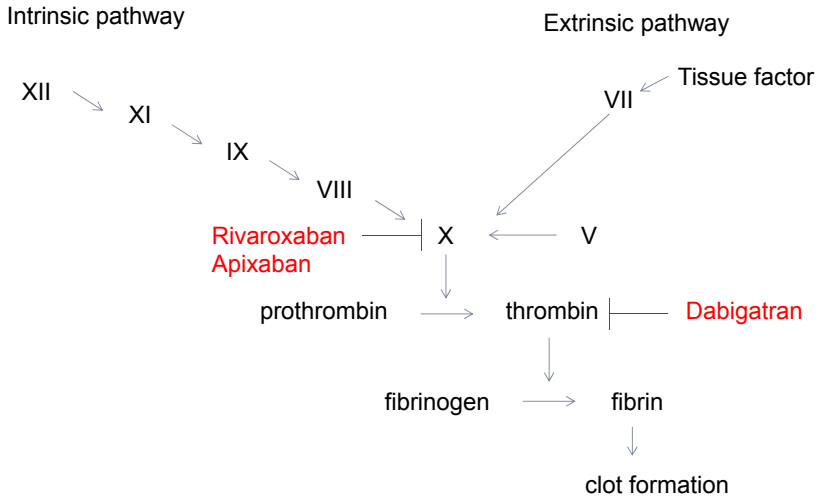
Outline

- Introduce three new oral anticoagulants: Dabigatran, Apixaban, Rivaroxaban
- Review the clinical indications of the new oral anticoagulants and the supporting evidence/guidelines
- Discuss practical issues around the use of these agents

Limitations of warfarin

- Needs INR monitoring
- Frequent dose adjustments
- Narrowing therapeutic window (INR 2-3)
- Slow onset/offset of action
- Multiple drug and food interactions

The coagulation cascade



New oral anticoagulants

	Dabigatran[1,2] (Pradax™)	Apixaban[1,3] (Eliquis™)	Rivaroxaban[1,4] (Xarelto®)
Mechanism of action	Competitive reversible direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Onset of action	0.5 to 2 hours	2 to 4 hours	1 to 3 hours
Half life	13 to 18 hours	7 to 11 hours	9 to 13 hours
Elimination	80% renal 20% fecal	66% renal 33% fecal	55% fecal; 25% renal
Drug interactions	P-glycoprotein	CYP3A4 and p-glycoprotein	CYP3A4 and p-glycoprotein

1. Eriksson et al. Clin Pharmacokinet 2009, 48:1-22
2. Dabigatran product monograph 2012
3. Apixaban product monograph 2012
4. Rivaroxaban product monograph 2008

Clinical indications of oral anticoagulants

- Stroke prevention in atrial fibrillation
- Prevention and treatment of VTE

Atrial fibrillation

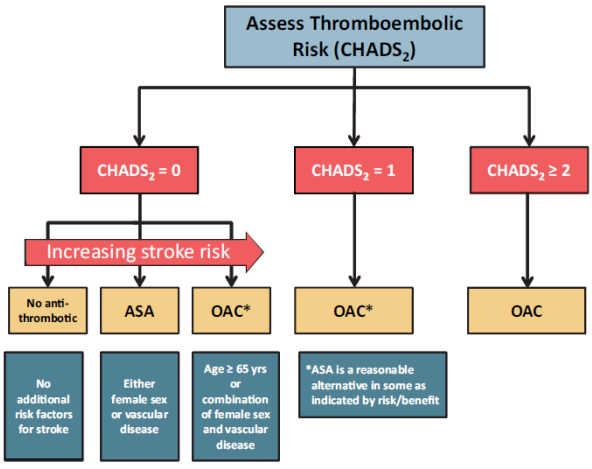
Estimation of stroke risk

- **C**ongestive heart failure (1 point)
- **H**ypertension (1 point)
- **A**ge ≥ 75 (1 point)
- **D**iabetes Mellitis (1 point)
- **S**troke/TIA (2 points)

CHADS2 score	Stroke rate (%/yr)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

Gage et al. JAMA 2001;285:2864-2870

CCS atrial fibrillation guidelines 2012



Skanes et al. Can J Cardio 2012; 28(2):125-36

Randomized **E**valuation of **L**ong-term Anticoagulation Therap**y** (RE-LY) trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RE-LY trial design

N = 18113 patients

Non-valvular atrial fibrillation ≥1 of: stroke/TIA/systemic embolus, LVEF<40%, HF (NYHA≥2), age ≥75, age 65-75 + (DM, CAD, or HTN

Excluded:
Severe valvular heart disorder
Conditions associated with high risk of bleeding
CrCl < 30ml/min
Active liver disease
pregancy

- Dabigatran 110mg BID
- Dabigatran 150mg BID
- Warfarin (INR 2-3)

Primary study outcome: rate of stroke or systemic embolism
Primary safety endpoint: Major bleeding

Connolly et al. N Engl J Med. 2009;361(12):1139-51

Baseline patient characteristics

Characteristic	Dabigatran 110 mg N=6015	Dabigatran 150 mg N= 7076	Warfarin N=6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean) **0-1 (%)** **2 (%)** **3+ (%)**	2.1 32.6 34.7 32.7	2.2 32.2 35.2 32.6	2.1 30.9 37.0 32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
HF (%)	32.2	31.8	31.9
Prior VKA (%)	50.1	50.2	48.6
% Discontinued @ 2 yrs	20.7	21.1	16.6

Connolly et al. N Engl J Med. 2009;361(12):1139-51

Primary efficacy outcome: stroke/systemic embolism

	Dabigatran (110mg)	Dabigatran (150mg)	Warfarin
Rate of stroke or systemic embolism (%/yr)	1.53	1.11	1.69

Dabigatran 110 mg met the criteria for non-inferiority compared to warfarin (relative risk 0.91, 95% CI 0.74-1.11, p<0.001 for non-inferiority)

Dabigatran 150 mg was significantly more effective than warfarin (relative risk 0.66, 95% CI 0.53-0.82) or dabigatran 110 mg (RR 0.73, 95% CI 0.58-0.91, p<0.001)

Connolly et al. N Engl J Med. 2009;361(12):1139-51

Efficacy outcomes (superiority analysis)

	Dabigatran (110mg)	Dabigatran (150mg)	Warfarin	D110 vs W RR (95% CI) P value	D150 vs W RR (95% CI) P value
Stroke (%/yr)	1.44	1.01	1.57	0.91 (0.74–1.11) p = 0.41	0.66 (0.53–0.82) p < 0.001
Ischemic stroke (%/yr)	1.34	0.92	1.20	1.11 (0.89–1.40 p = 0.35	0.76 (0.60–0.98) p < 0.03
Hemorrhagic stroke (%/yr)	0.12	0.10	0.38	0.31 (0.17–0.56) p < 0.001	0.26 (0.14–0.49) p < 0.001
Myocardial infarction (%/yr)	0.72	0.74	0.53	1.35 (0.98–1.87) p = 0.07	1.38 (1.00–1.91) p = 0.048
Death from any cause (%/yr)	3.75	3.64	4.13	0.91 (0.80–1.03) p = 0.13	0.88 (0.77–1.00) p = 0.051

Connolly et al. N Engl J Med. 2009;361(12):1139-51

Safety outcomes

	D 110mg	D 150mg	Warfarin	D 110 mg vs. W		D 150 mg vs. W	
				RR 95% CI	P value	RR 95% CI	P value
Major Bleeding	2.87 %	3.32 %	3.57%	0.80 0.70-0.93	0.003	0.93 0.81-1.07	0.32
Life-Threatening Major Bleed	1.24 %	1.49 %	1.85 %	0.67 0.54-0.82	<0.001	0.80 0.66-0.98	0.03
Intracranial Bleeding	0.23 %	0.32 %	0.76 %	0.30 0.19-0.45	<0.001	0.41 0.28-0.60	<0.001
GI Major Bleed	1.15 %	1.56 %	1.07 %	1.08 0.85-1.38	0.52	1.48 1.18-1.85	0.001

Connolly et al. N Engl J Med. 2009;361(12):1139-51

ARISTOTLE trial

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

ARISTOTLE trial design

N = 20998 patients

Non-valvular atrial fibrillation
≥1 of: stroke/TIA/systemic embolus, LVEF<40%,, age ≥75, DM, HTN

Excluded:
Moderate to severe MS
Stroke within past 7 days
Need for ASA>165mg/d or ASA and clopidogrel
CrCl < 25ml/min

→ Apixaban 5mg BID
(2.5mg BID for patients with ≥2 of: age≥80, wt≤60kg, Cr>133μmol/L)

→ Warfarin (INR 2-3)

Primary efficacy outcome: rate of stroke or systemic embolism
Secondary efficacy outcome: death from any cause, MI
Primary safety endpoint: Major bleeding

Granger et al. N Engl J Med. 2011;365(11):981-92.

Baseline patient characteristics

	Apixaban (N=9120)	Warfarin (N=9081)
Age (years)	70	70
Female (%)	35.5	35.0
$CHADS_2$ Score (mean) **≤1 (%)** **2 (%)** **≥3 (%)**	2.1 34.0 35.8 30.2	2.1 34.0 35.8 30.2
Prior Stroke / TIA / Embolism (%)	19.2	19.7
Prior Myocardial Infarction (%)	14.5	13.9
Heart Failure (%)	35.5	35.4
Prior VKA Use (%)	57.1	57.2

Granger et al. N Engl J Med. 2011;365(11):981-92.

Efficacy outcomes

	Apixaban (%/yr)	Warfarin (%/yr)	HR (95% CI)	P-value†
Primary Outcome: Stroke or Systemic Embolism	1.27	1.60	0.79 (0.66, 0.95)	<0.001 non-inferiority 0.01
Stroke **Ischemic or uncertain type**	1.19 0.97	1.51 1.05	0.79 (0.65, 0.95) 0.92 (0.74, 1.13)	0.01 0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic Embolism	0.09	0.10	0.87 (0.44, 1.75)	0.70
All Cause Mortality	3.52	3.94	0.89 (0.80,0.998)	0.047
Myocardial Infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

Granger et al. N Engl J Med. 2011;365(11):981-92.

Safety outcomes

	Apixaban (%/yr)	Warfarin (%yr)	HR (95% CI)	P-value
Primary: Major Bleeding	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial Hemorrhage	0.33	0.80	0.42(0.30,0.58)	<0.001
Major GI Bleeding	0.76	0.86	0.89(0.70,1.15)	0.37

Granger et al. N Engl J Med. 2011;365(11):981-92.

ROCKET AF trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

ROCKET-AF trial design

N = 14264 patients

Non-valvular atrial fibrillation stroke/TIA/systemic embolus, or ≥2 of LVEF<35%, age ≥75, DM, HTN

→ Rivaroxaban 20mg (15mg in patients with CrCl 30-49 ml/min)

→ Warfarin (INR 2-3)

Primary efficacy outcome: rate of stroke or systemic embolism
Primary safety endpoint: Major and nonmajor clinically relevant bleeding events

Patel et al. N Engl J Med 2011;365:883-91

Baseline characteristics

	Rivaroxaban	Warfarin
Age (years)	73	73
Female (%)	39.7	39.7
$CHADS_2$ Score (mean) **≤1 (%)** **2 (%)** **≥3 (%)**	3.48 13.0 42.9 44.1	3.46 13.1 44.3 42.6
Prior Stroke / TIA / Embolism (%)	54.9	54.6
Prior Myocardial Infarction (%)	16.6	18.0
Heart Failure (%)	62.6	62.3
Prior VKA Use (%)	62.3	62.5

Patel et al. N Engl J Med 2011;365:883-91

Primary efficacy outcome

	Rivaroxaban	Warfarin	HR (95% CI)	P value
Stroke/systemic embolism (no/100 patient/yr)	2.1	2.4	0.88 (0.75-1.03)	<0.001 (non-inferiority) 0.12 (superiority)

Intention to treat analysis

Rivaroxaban met the criteria for non-inferiority compared to warfarin in preventing stroke or systemic embolism

Patel et al. N Engl J Med 2011;365:883-91

Secondary outcomes

	Rivaroxaban (event rate)	Warfarin (event rate)	HR (95% CI)	P-value†
Vascular Death, Stroke, Embolism	4.51	4.81	0.94 (0.84, 1.05)	0.27
Stroke **Hemorrhagic** **Ischemic** **Unknown type**	 0.26 1.62 0.15	 0.44 1.64 0.14	 0.58 (0.38, 0.89) 0.99 (0.82, 1.20) 1.05 (0.55, 2.01)	 0.01 0.92 0.87
Myocardial Infarction	1.02	1.11	0.91 (0.72, 1.16)	0.46
All Cause Mortality **Vascular** **Non-vascular** **Unknown Cause**	4.52 2.91 1.15 0.46	4.91 3.11 1.22 0.57	0.92 (0.82, 1.03) 0.94 (0.81, 1.08) 0.94 (0.75, 1.18) 0.80 (0.57, 1.12)	0.15 0.35 0.61 0.20

Patel et al. N Engl J Med 2011;365:883-91

Safety outcomes

	Rivaroxaban Event Rate (per 100 patient/years)	Warfarin Event Rate (per 100 patient/years)	HR (95% CI)	P-value
Primary: Major and Non-Major Clinically Relevant Bleeding	14.9	14.5	1.03 (0.96, 1.11)	0.44
Major bleeding	3.6	3.4	1.04 (0.90, 1.20)	0.58
Intracranial Hemorrhage	0.5	0.7	0.67 (0.47, 0.93)	0.02
Major GI Bleeding	3.2 % of pts	2.2% of pts	Not reported	<0.001

Patel et al. N Engl J Med 2011;365:883-91

Summary of the three trials

- All three agents were non-inferior to warfarin in stroke/systemic embolism prevention in patients with non-valvular atrial fibrillation
- Dabigatran (150mg) and Apixaban were shown to be superior to warfarin in stroke prevention
- All three agents were associated with decreased ICH compared to warfarin

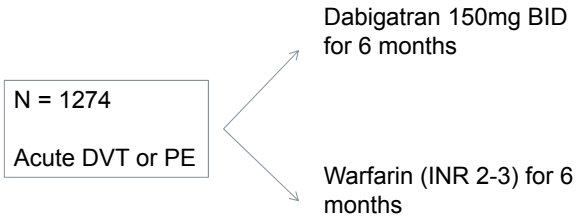
CCS 2012 recommendations

"When OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban in preference to warfarin"

Skanes et al. Can J Cardio 2012; 28(2):125-36

Treatment of VTE

RECOVER



Non-inferiority study

Primary efficacy outcome: Six-month incidence of composite of recurrent symptomatic VTE and deaths related to VTE

Safety outcomes: Bleeding events, Adverse events

Schulman et al. N Engl J Med 2009;361:2342-52

Primary efficacy outcome

	Dabigatran	Warfarin	HR (95% CI)	P value
VTE or related death (% patients)	2.4%	2.1%	HR 1.10 (0.65-1.84)	P<0.001 for non-inferiority

Schulman et al. N Engl J Med 2009;361:2342-52

Safety outcomes

	Dabigatran	Warfarin	HR (95% CI)
Major bleeding (% patients)	1.6	1.9	0.82 (0.45–1.48)
Major or clinically relevant nonmajor bleeding event (% patients)	5.6	8.8	0.63 (0.47–0.84)
Any bleeding event (% patients)	16.1	21.9	0.71 (0.59–0.85)

Schulman et al. N Engl J Med 2009;361:2342-52

Adverse events

	Dabigatran	Warfarin
Acute coronary syndrome (%)	**5 (0.4)**	**3 (0.2)**
Myocardial infarction (%)	**4 (0.3)**	**2 (0.2)**
ALT >3 x ULN (%)	**38 (3.1)**	**25 (2.1)**
AST >3 x ULN (%)	**42 (3.4)**	**46 (3.8)**
ALT >3 x ULN + bilirubin >2 x ULN (%)	**2 (0.2)**	**4 (0.4)**

Schulman et al. N Engl J Med 2009;361:2342-52

Adverse events

	Dabigatran	Warfarin
Headache (%)	**60 (4.9)**	**64 (5.3)**
Pain in extremity (%)	**59 (4.8)**	**69 (5.7)**
Nausea (%)	**43 (3.5)**	**43 (3.5)**
Diarrhea (%)	**46 (3.8)**	**34 (2.8)**
Nasopharyngitis (%)	**47 (3.8)**	**53 (4.4)**
Dyspnea (%)	**33 (2.7)**	**47 (3.9)**
Back pain (%)	**42 (3.4)**	**44 (3.6)**
Arthralgia (%)	**45 (3.7)**	**30 (2.5)**
Peripheral edema (%)	**41 (3.3)**	**45 (3.7)**
Dyspepsia (%)	**36 (2.9)***	**7 (0.6)**

*p<0.001

Schulman et al. N Engl J Med 2009;361:2342-52

EINSTEIN DVT

N = 3449

Acute proximal DVT

Rivaroxaban15 mg twice daily for 3 weeks, followed by 20 mg once daily

Enoxaparin followed by warfarin (INR 2-3)

- Non-inferiority study
- Primary efficacy outcome: recurrent VTE
- Safety outcomes: major bleeding or clinically relevant nonmajor bleeding

Bauersachs et al. N Engl J Med 2010;363:2499-510

Primary outcome

	Rivaroxaban	Warfarin	HR (95% CI)	P value
Recurrent VTE (% patients)	2.1	3.0	0.68 (0.44–1.04)	P<0.001 (non-inferiority)

Bauersachs et al. N Engl J Med 2010;363:2499-510

Safety outcomes

	Rivaroxaban	Warfarin	HR (95% CI)	P value
First major or clinically relevant nonmajor bleeding occurring during treatment (% patients)	8.1	8.1	0.97 (0.76–1.22)	0.77
Major bleeding (% patients)	0.8	1.2	0.65 (0.33–1.30)	0.21

Bauersachs et al. N Engl J Med 2010;363:2499-510

EINSTEIN PE

- Non-inferiority study
- 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis
- Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) vs enoxaparin followed by an adjusted-dose VKA
- primary efficacy outcome was symptomatic recurrent venous thromboembolism
- Rivaroxaban was non-inferior to standard therapy (P=0.003 non-inferiority) for the primary efficacy outcome, (2.1% vs 1.8% HR 1.12; 95% CI 0.75 to 1.68)
- Comparable primary safety outcome (major or clinically relevant non-major bleeding): 10.3% vs 11.4% (HR 0.90; 95% CI, 0.76 to 1.07; P=0.23).

Buller et al. N Engl J Med. 2012;366(14):1287-97

Summary

- Dabigatran and Rivaroxaban had comparable efficacy to warfarin in the treatment of VTE
- Dabigatran and Rivaroxaban were associated with similar or lower rates of bleeding compared to warfarin

ACCP guidelines 2012

Recommendations:

"In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy.

For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy.

In patients with PE and cancer, we suggest LMWH over VKA therapy.

In patients with PE and cancer who are not treated with LMWH, we suggest VKA over dabigatran or rivaroxaban for long-term therapy."

Guyatt et al. CHEST 2012; 141(2)(Suppl):7S–47S

Management of bleeding

Management of bleeding

- Currently no antidote available for the new oral anticoagulants

Minor bleeding

- Dose delay or drug discontinuation usually sufficient to stop bleeding, as half life relatively short

1. Van Ryn et al. Thromb Haemost. 2010;103(6):1116
2. Dabigatran product monograph

Life-threatening bleed

- Discontinue medication
- Consider using activated prothrombin complex concentrates or rFVIIa

1. Van Ryn et al. Thromb Haemost. 2010;103(6):1116
2. Dabigatran product monograph

Possible antidote?

- Monoclonal antibody against Dabigatran
- Factor Xa inhibitor antidote

1. Schiele et al. Blood. 2013 Mar 8
2. Lu et al. Nat Med. 2013 Apr;19(4):446-51

Periprocedural management of the new OACs

When to stop new OACs before surgery/procedure?

Anticoagulant	Renal function	Low bleeding risk surgery (2-3 t1/2 b/w last dose and surgery)	High bleeding risk surgery (4-5 t1/2 b/w last dose and surgery)
Dabigatran	CrCl>50ml/min CrCl 30-50 ml/min	2 days before surgery 3 days before surgery	3 days before surgery 4-5 days before surgery
Rivaroxaban	CrCl>50ml/min CrCl 30-50 ml/min CrCl 15-30 ml/min	2 days before surgery 2 days before surgery 3 days before surgery	3 days before surgery 3 days before surgery 4 days before surgery
Apixaban	CrCl>50ml/min CrCl 30-50 ml/min	2 days before surgery 3 days before surgery	3 days before surgery 4 days before surgery

Connolly and Spyropoulos. J Thromb Thrombolysis 2013; Mar 27

When to resume?

Drug	Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	1 day after surgery	2-3 days after surgery
Rivaroxaban	1 day after surgery	2-3 days after surgery
Apixaban	1 day after surgery	2-3 days after surgery

Connolly and Spyropoulos. J Thromb Thrombolysis 2013; Mar 27

Switching from warfarin to new OACs

- Discontinue warfarin and monitor INR
- Once INR <2, start new OAC

Connolly and Spyropoulos. J Thromb Thrombolysis 2013; Mar 27

Switching from new OACs to warfarin

Dabigatran	
CrCl (ml/min)	
>50	Start warfarin and stop dabigatran 3 days later
31-50	Start warfarin and stop dabigatran 2 days later
15-30	Start warfarin and stop dabigatran 1 day later

Rivaroxaban or Apixaban	
CrCl (ml/min)	
>50	Start warfarin and stop rivaroxaban/apixaban 4 days later
31-50	Start warfarin and stop rivaroxaban/apixaban 3 days later
15-30	Start warfarin and stop rivaroxaban/apixaban 2 days later

Connolly and Spyropoulos. J Thromb Thrombolysis 2013; Mar 27

Summary

- The new oral anticoagulants are more convenient options
- Routine anticoagulation monitoring not required due to predictable pharmacokinetics
- Less drug interactions compared to warfarin
- Comparable or superior efficacy to warfarin in stroke prevention in patients with non-valvular atrial fibrillation
- Comparable efficacy to warfarin in treatment of VTE
- Favourable safety profile
- Comparable or lower risk of bleeding compared to warfarin
- Currently no antidote for drug reversal

NEW ORAL ANTICOAGULANTS – A REVIEW OF LITERATURE AND GUIDELINES

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April 20, 2013

Summary of Dabigatran trials

Clinical trial	Trial design	Results
REMODEL (2007)	• patients undergoing total knee replacement • Dabigatran 150 mg or 220 mg od vs enoxaparin 40 mg od for 6-10 days after surgery	• No significant difference in primary outcome (VTE and mortality during treatment) • Both doses met criteria for non-inferiority compared to enoxaparin • No significant difference in bleeding risks
RENOVATE (2007)	• patients undergoing total hip replacement • Dabigatran 150 mg or 220 mg od vs enoxaparin 40 mg od for 28-35 days after surgery	• No significant difference in primary outcome (VTE and mortality during treatment) • Both doses met criteria for non-inferiority compared to enoxaparin • No significant difference in bleeding risks
REMOBILIZE (2009)	• patients undergoing total knee replacement • Dabigatran 150 mg or 220 mg od vs enoxaparin 30 mg BID for 12-15 days after surgery	• Both doses of dabigatran were shown to be inferior to BID dosing of enoxaparin in VTE rates • No difference in bleeding risks

Summary of Rivaroxaban trials

Clinical trial	Trial design	Results
RECORD 1	Patients undergoing total hip replacement Rivaroxaban 10mg od for 35d vs enoxaparin 40mg od for 35d	Rivaroxaban was superior to enoxaprain in reducing total VTE No difference in bleeding events
RECORD 2	Patients undergoing total hip replacement Rivaroxaban 10mg od for 35d vs enoxaparin 40mg od for 12d	Rivaroxaban was superior to enoxaparin in reducing total VTE No difference in bleeding events
RECORD 3	Patients undergoing total knee replacement Rivaroxaban 10mg od for 12d vs enoxaparin 40mg od for 12d	Rivaroxaban was superior to enoxaparin in reducing total VTE No difference in bleeding events
RECORD 4	Patients undergoing total knee replacement Rivaroxaban 10mg od for 12d vs enoxaparin 30mg BID for 12d	Rivaroxaban was superior to enoxaparin in reducing total VTE No difference in bleeding events