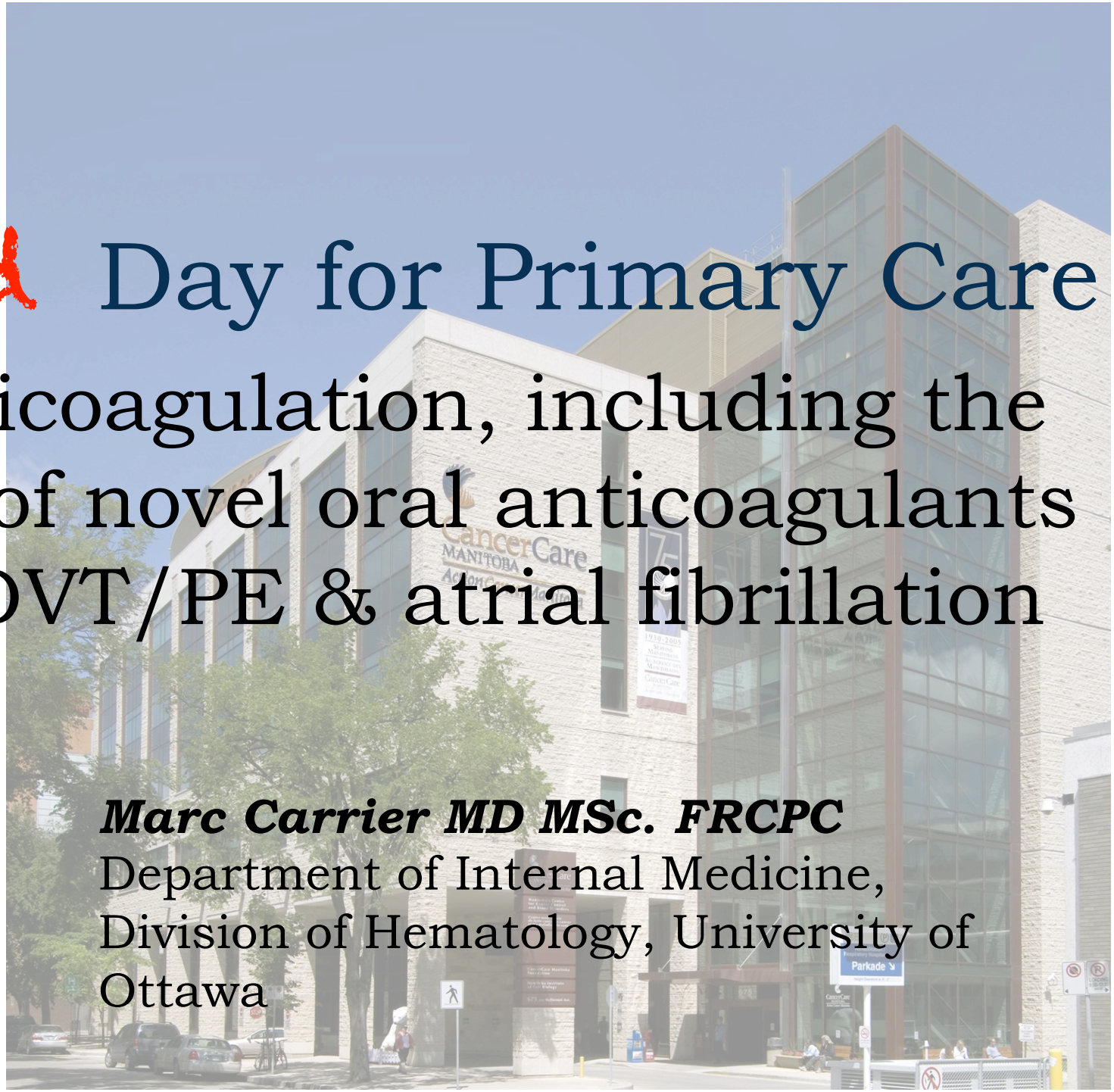
CancerCare Manitoba

Blood Day for Primary Care

Anticoagulation, including the use of novel oral anticoagulants in DVT/PE & atrial fibrillation



UPCON
Uniting Primary Care and Oncology

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Disclosures

Research Support/P.I.	**Leo Pharma (PERIOP 01 Trial)**
Employee	**No relevant conflict of interest to declare**
Consultant	**No relevant conflict of interest to declare**
Major Stockholder	**No relevant conflict of interest to declare**
Speakers' Bureau	**No relevant conflict of interest to declare**
Honoraria	**Sanofi Aventis, Pfizer, Boehringer Ingelheim, Leo Pharma, Bayer.**
Scientific Advisory Board	**Sanofi Aventis, Leo pharma.**

Objectives

1. Discuss the use of novel oral anticoagulants for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation

2. Review of the efficacy and safety data regarding the use of anticoagulation in the management of deep vein thrombosis and pulmonary embolism

Ms. MT

82 yo man with new onset atrial fibrillation

PMHx: Dementia, HTN, VRE, EtOH abuse

Allergy: NKDA

Meds: Trazodone 50 mg qhs, seroquel 50 mg BID, galantamine 24 mg daily, cipralex 10 mg PO daily.

Wt: 78 kg; BP 106/62; HR: 62

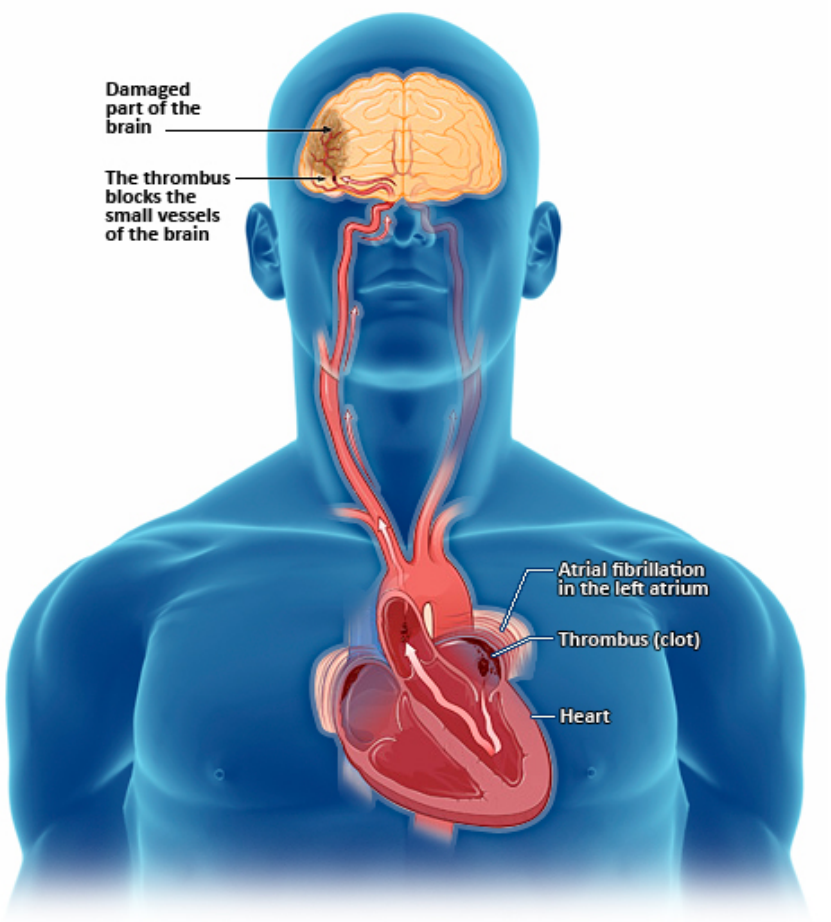
Hb: 116, eGFR: 55 cc/min

Ms. MT

What anticoagulant will you use for stroke prevention?

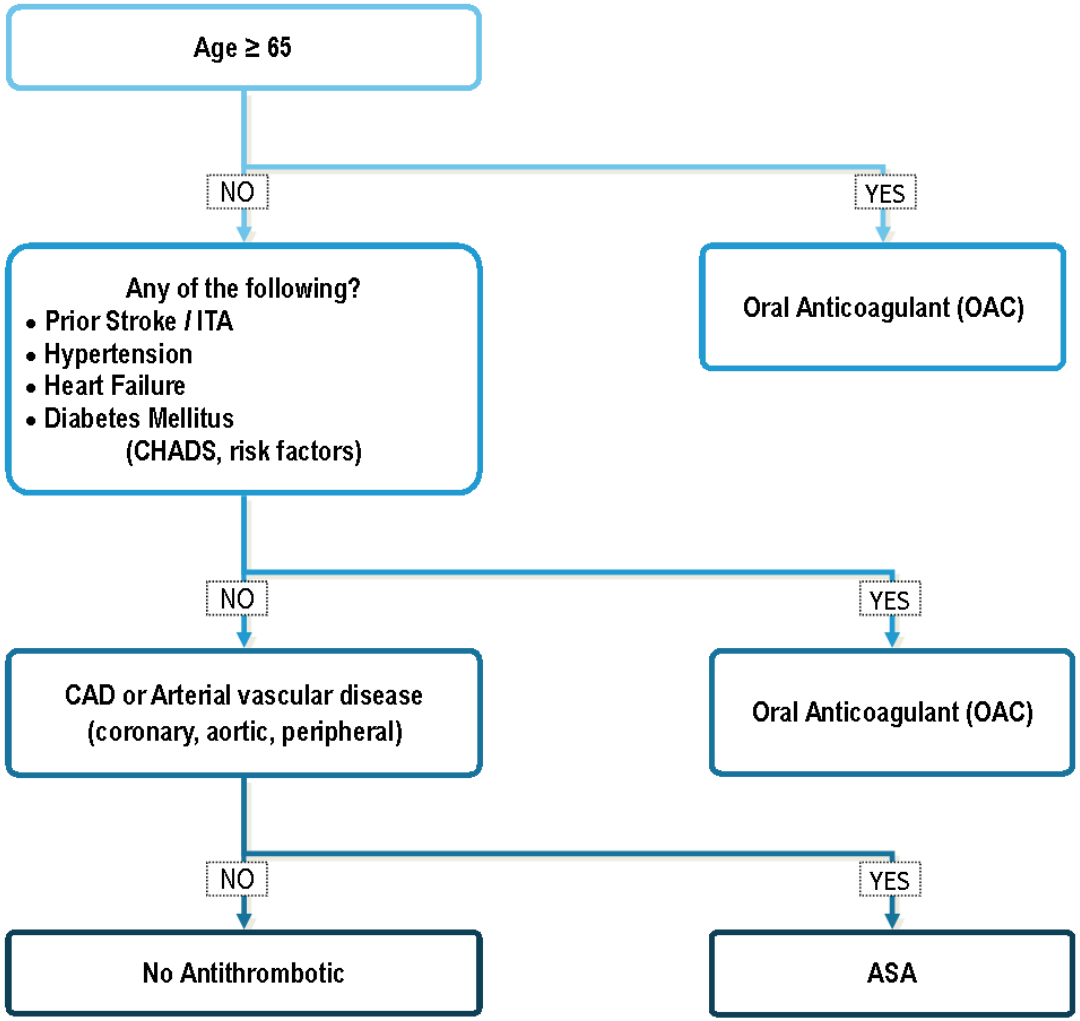
A. Warfarin (target INR 2.0-3.0)
B. Dabigatran 150 mg BID
C. Dabigatran 110 mg BID
D. Rivaroxaban 20 mg daily
E. Apixaban 5 mg BID

Atrial Fibrillation (AF)



The "CCS Algorithm" FOR OAC Therapy in AF

PRACTICE POINTS: Consider and modify (if possible) all factors influencing risk of bleeding on OAC (hypertension, antiplatelet drugs, NSAIDs, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low eGFR, age ≥ 75, low body weight)**



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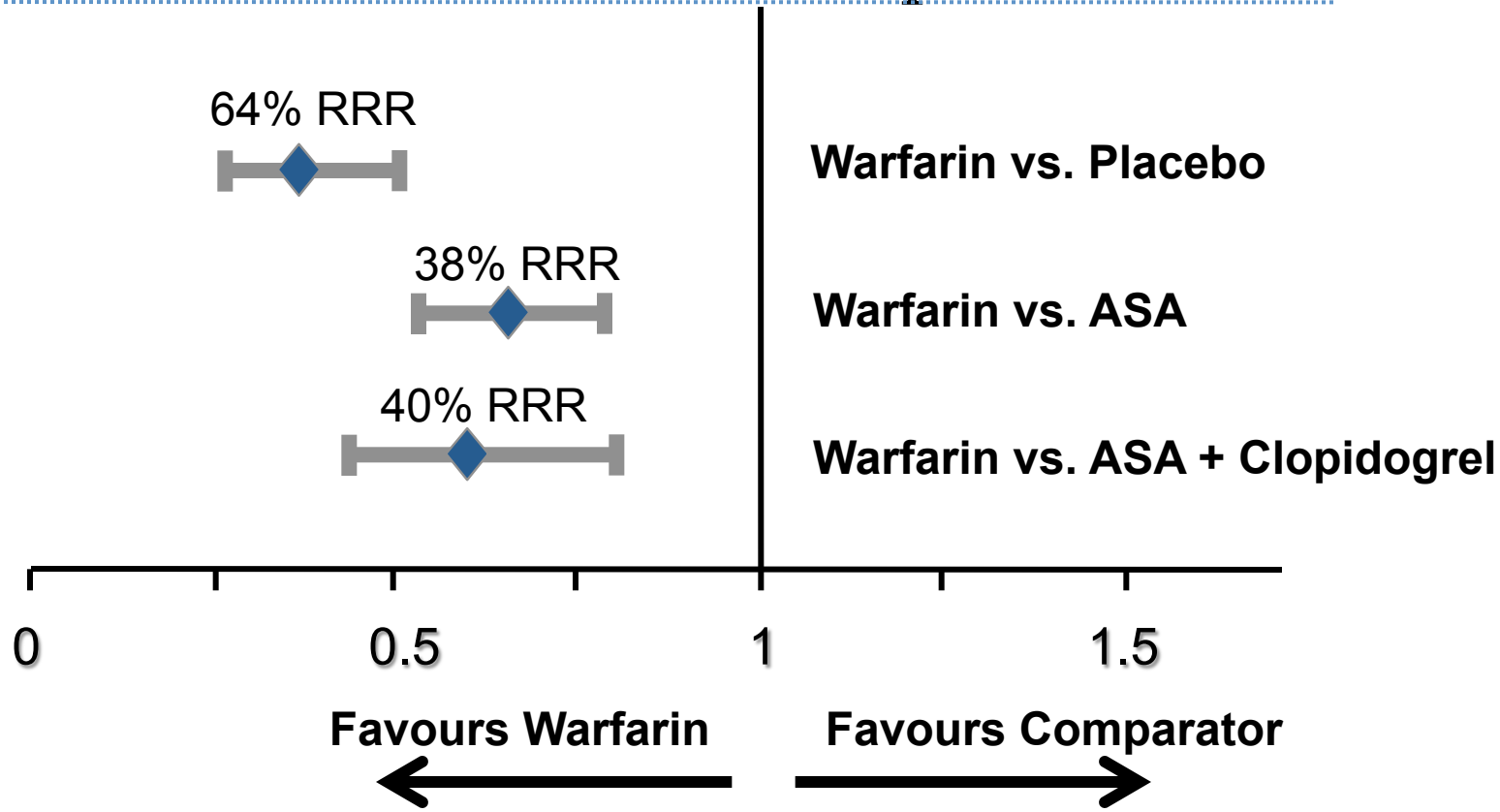
Adapted From: 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Canadian Journal of Cardiology 30 (2014) 1114 -1130

Warfarin is highly effective for the prevention of stroke in patients with AF



Hart et al Ann Intern Med. 2007;146:857-867
Connolly et al. Lancet. 2006;367:1903-12.

Warfarin

- Advantages
  - Active by oral route
  - Once daily dosing
  - Can be monitored
  - Rapidly-acting antidote available
  - Low cost
- Disadvantages
  - Delayed onset of action
  - Long-half life
    - i.e. Needs to be held for many days pre-op
  - Many drug-drug and drug-food interactions
  - Needs monitoring

New oral anticoagulants (NOACs)

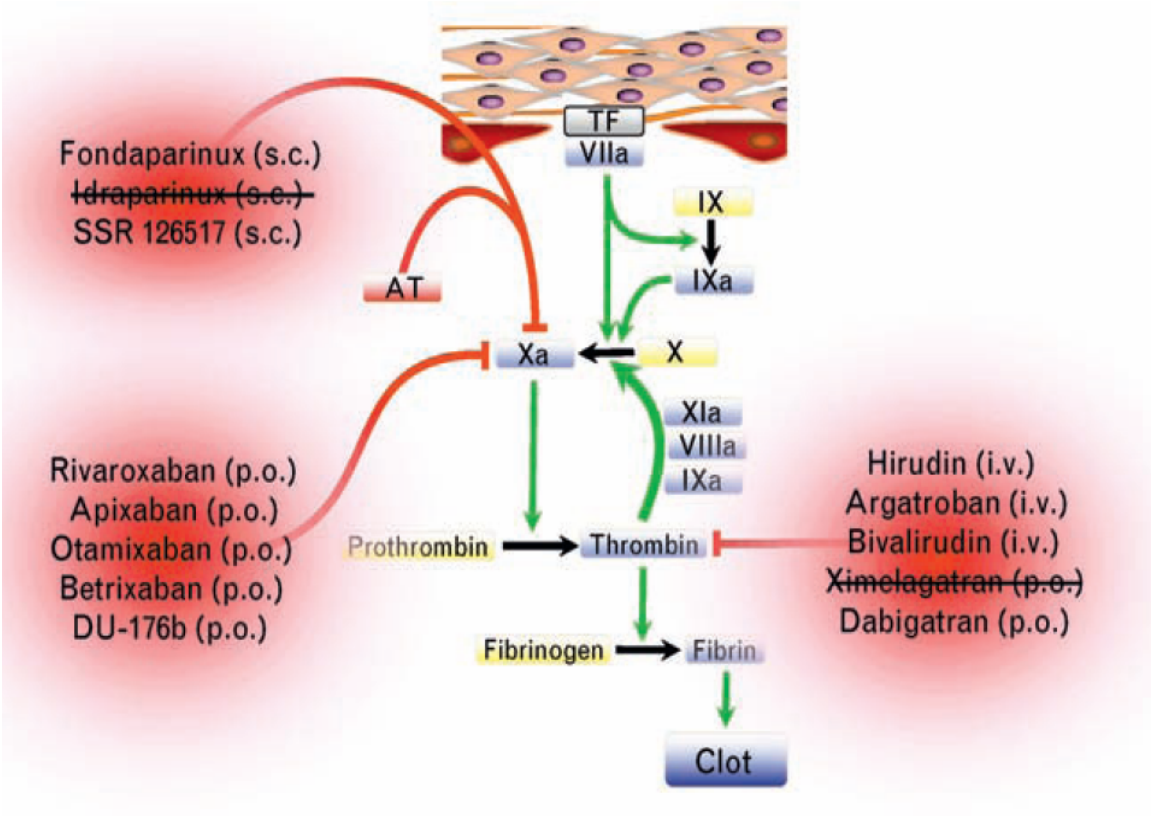


Figure from: Steffel et al. J Cardiovasc Med 2009;10:616-23

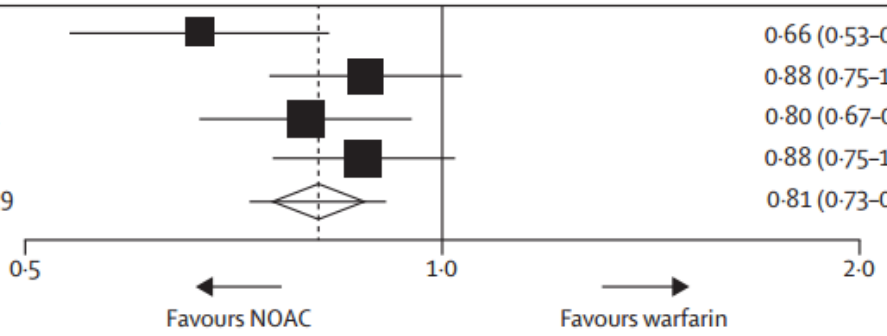
Properties of new oral anticoagulants (NOACs)

	Apixaban	Dabigatran	Rivaroxaban
Direct factor inhibition	Xa	IIa	Xa
Bioavailability (F_{rel})	80%	6%	80%
Peak action (t_{max})	1–3 hr	1–3 hr	1–3 hr
Protein binding	84%	35%	92–95%
Renal clearance	25%	80%	33%
Elimination half life with creatinine clearance > 80 ml/min	15.1 hr	13.8 hr	8.3 hr
Elimination half life with creatinine clearance 50–79 ml/min	14.6 hr	16.6 hr	8.7 hr
Elimination half life with creatinine clearance 30–49 ml/min	17.6 hr	18.7 hr	9.0 hr
Elimination half life with creatinine clearance < 30 ml/min	17.3 hr	27.5 hr	9.5 hr

Kaatz et al. Am J Hematol 2012 May;87 Suppl 1:S141-5

NOACs vs. warfarin - Stroke prevention

	NOAC (events)	Warfarin (events)	RR (95% CI)	p
RE-LY[5]*	134/6076	199/6022	0·66 (0·53–0·82)	0·0001
ROCKET AF[6]†	269/7081	306/7090	0·88 (0·75–1·03)	0·12
ARISTOTLE[7]‡	212/9120	265/9081	0·80 (0·67–0·95)	0·012
ENGAGE AF–TIMI 48[8]§	296/7035	337/7036	0·88 (0·75–1·02)	0·10
Combined (random)	911/29312	1107/29229	0·81 (0·73–0·91)	<0·0001

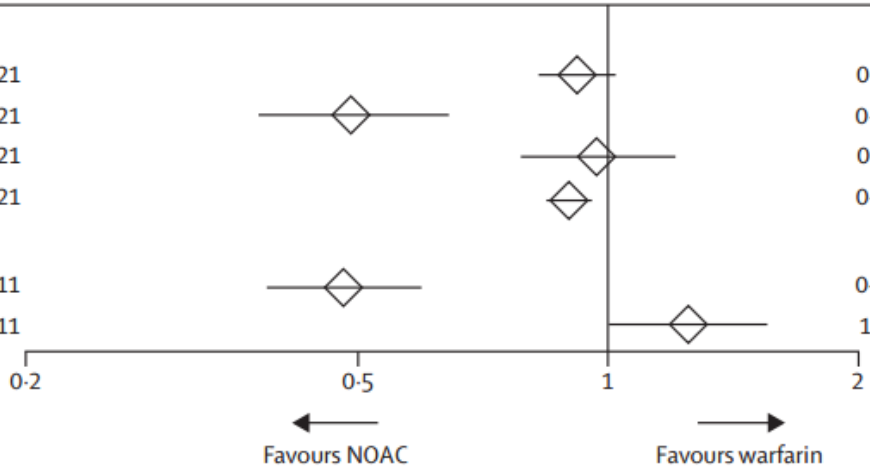


- Warfarin, rivaroxaban, dabigatran and apixaban are effective in preventing strokes and systemic embolism in patients with atrial fibrillation
- NOACs are associated with a RRR of 20% compared to warfarin

Ruff CT et al. Lancet 2014;383:955-62.

NOACs vs. warfarin - Bleeding

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	p
Efficacy				
Ischaemic stroke	665/29 292	724/29 221	0·92 (0·83–1·02)	0·10
Haemorrhagic stroke	130/29 292	263/29 221	0·49 (0·38–0·64)	<0·0001
Myocardial infarction	413/29 292	432/29 221	0·97 (0·78–1·20)	0·77
All-cause mortality	2022/29 292	2245/29 221	0·90 (0·85–0·95)	0·0003
Safety				
Intracranial haemorrhage	204/29 287	425/29 211	0·48 (0·39–0·59)	<0·0001
Gastrointestinal bleeding	751/29 287	591/29 211	1·25 (1·01–1·55)	0·043



- NOACs reduce hemorrhagic stroke, overall mortality and ICH
- …but increase GI bleeding

Ruff CT et al. Lancet 2014;383:955-62.

NOACs: All the same?

Similarities

- Non-inferior to warfarin for efficacy
- Less ICH than with warfarin
- Decrease overall mortality compared to warfarin
- No hepatic toxicity

Differences

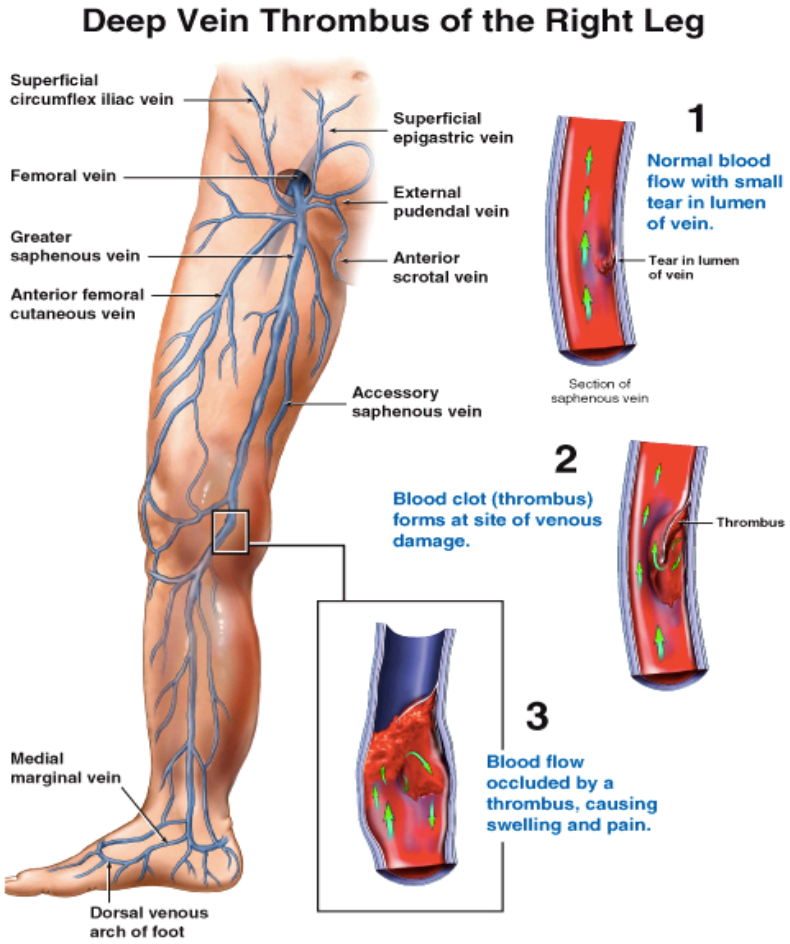
- Increase risk of MI in patients taking dabigatran compared to warfarin
- More GI bleeding with rivaroxaban and dabigatran
- Dabigatran (150 mg BID) is associated with lower risk of ischemic strokes compared to warfarin
- Apixaban is associated with both lower risk of stroke and major bleeding compared with warfarin

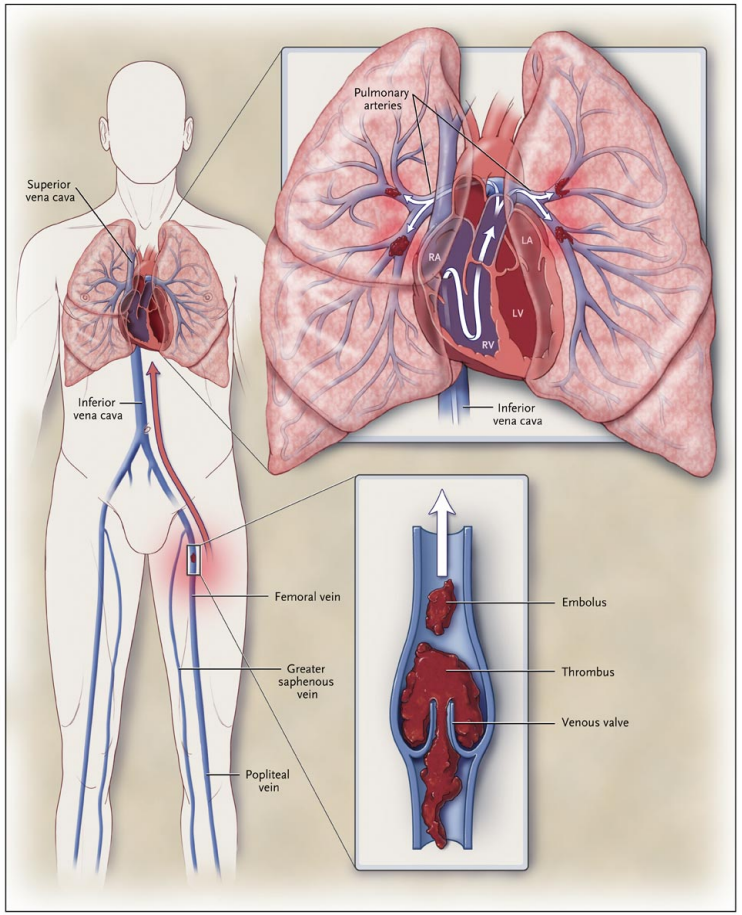
Weitz JL et al. Hematology Am Soc Hematol Educ Program;2012:536-40.

Choice of anticoagulation based on patients characteristics

Characteristic	Drug choice	Rationale
Mechanical valve or valvular atrial fibrillation	Warfarin	New agents not studied
Liver dysfunction with increased INR	Warfarin	New agents require hepatic metabolism
Poor compliance	Warfarin or nothing*	Missed doses of greater consequence with shorter-acting new agents
Stable on warfarin	Warfarin	Consider switching at patient request
CrCl less than 30 mL/min	Warfarin	Such patients were excluded from trials with new agents
CrCl of 30-50 mL/min	Rivaroxaban or apixaban	Oral factor Xa inhibitors are less affected by impaired renal function than dabigatran
Dyspepsia or upper gastrointestinal symptoms	Rivaroxaban or apixaban	Dyspepsia in up to 10% given dabigatran
Recent gastrointestinal bleed	Apixaban	More gastrointestinal bleeding with dabigatran (150 mg twice daily) or rivaroxaban than with warfarin
Recent ischemic stroke on warfarin	Dabigatran	Dabigatran (150 mg twice daily) associated with lower risk of ischemic stroke than warfarin
Recent acute coronary syndrome	Rivaroxaban or apixaban	Small myocardial infarction signal with dabigatran
Poor compliance with twice-daily dosing or request for a once-daily regimen	Rivaroxaban	Only agent given once daily

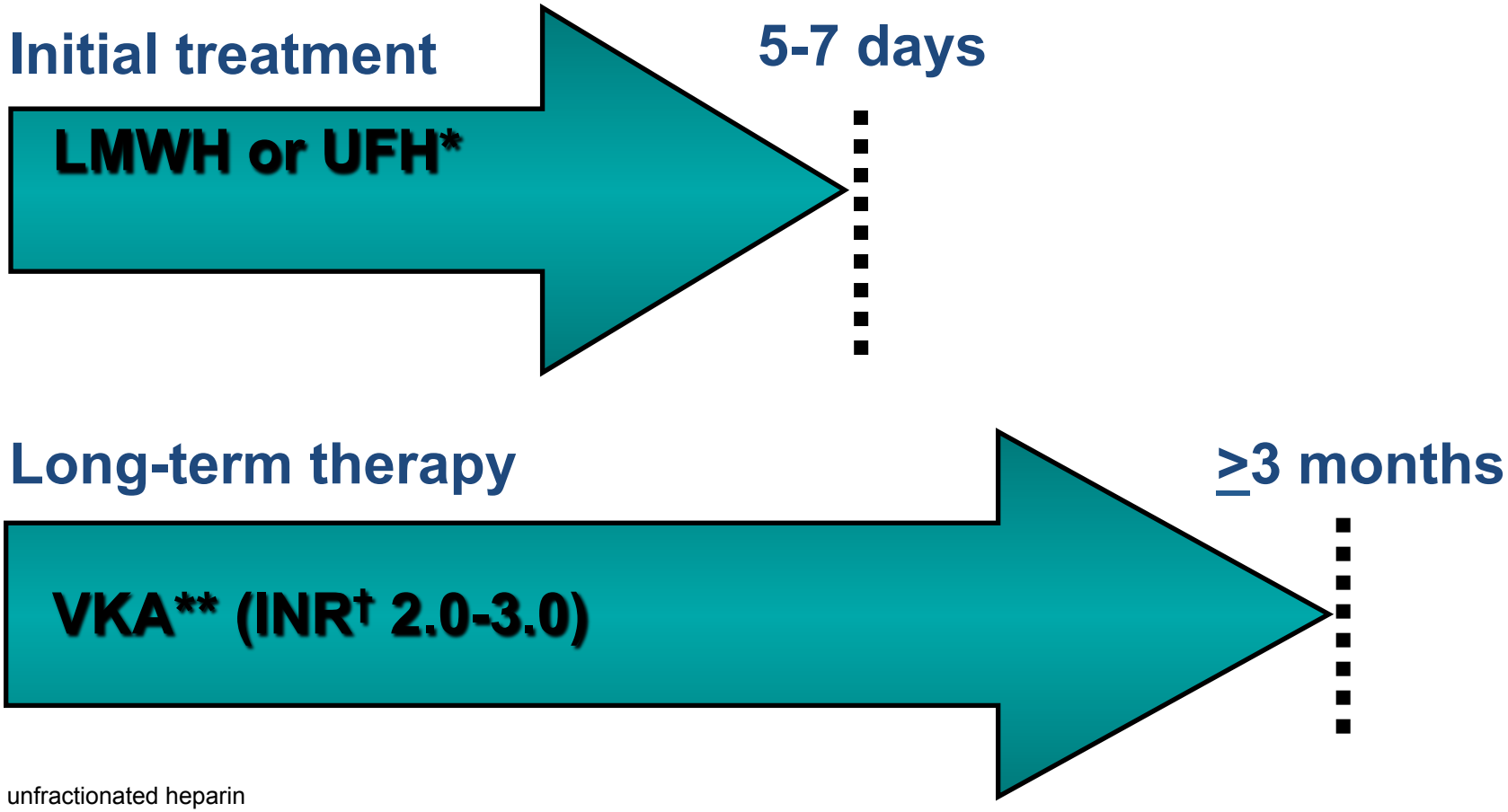
DVT and PE





Tapson VF. *N Engl J Med* 2008; 358(10):1037-52.

Traditional Treatment of VTE



*UFH = unfractionated heparin
**VKA = vitamin K antagonist
†INR = international normalization ratio

NOACs: All the same?

Figure 3. Network Meta-analysis Comparing Low-Molecular-Weight Heparin–Vitamin K Antagonist Combination for Recurrent Venous Thromboembolism and Major Bleeding

A Recurrent venous thromboembolism and major bleeding

Comparator Treatment	Hazard Ratio (95% Credible Interval)
Unfractionated heparin + vitamin K antagonist	
Recurrent VTE	1.42 (1.15-1.80)
Major bleeding	1.19 (0.90-1.58)
Fondaparinux + vitamin K antagonist	
Recurrent VTE	1.01 (0.65-1.62)
Major bleeding	1.07 (0.65-1.70)
Low-molecular-weight heparin + dabigatran	
Recurrent VTE	1.11 (0.67-1.80)
Major bleeding	0.74 (0.46-1.26)
Low-molecular-weight heparin + edoxaban	
Recurrent VTE	0.83 (0.46-1.49)
Major bleeding	0.84 (0.51-1.39)
Rivaroxaban	
Recurrent VTE	0.90 (0.57-1.41)
Major bleeding	0.55 (0.35-0.89)
Apixaban	
Recurrent VTE	0.84 (0.46-1.51)
Major bleeding	0.31 (0.15-0.62)
Low-molecular-weight heparin alone	
Recurrent VTE	0.99 (0.70-1.42)
Major bleeding	0.71 (0.42-1.31)

Castellucci L et al. JAMA. 2014;312(11):1122-1135.

Take Home Messages

- NOACs (dabigatran, rivaroxaban, apixaban) approved and covered for stroke prevention but are not recommended for:
  - Patients with valvular heart disease, mechanical valves, severe renal impairment, active bleeding
- NOACs (Rivaroxaban, apixaban and dabigatran currently approved) can be used for the initial treatment of VTE
  - Rivaroxaban only NOAC covered in MB for VTE (Part III EDS)
  - Be carful:
    - Patients with severe renal impairment, active bleeding, cancer, etc.

When to consider referral to hematology

- Unprovoked VTE
- Thrombosis at unusual sites
- Recurrent thrombosis despite adequate anticoagulation

Questions?

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