Anticoagulation at the end of life

Rhona Maclean
Rhona.maclean@sth.nhs.uk

Content

- Anticoagulant Therapies
- Indications for anticoagulation
  - Venous thromboembolism (VTE)
  - Atrial Fibrillation
  - Mechnical Heart Valves
- How do we manage anticoagulation at the end of life?

Anticoagulants

- Injectable
  - Low molecular weight heparin
  - Fondaparinux
- Oral
  - Warfarin
  - Rivaroxaban
  - Dabigatran
  - Apixaban
  - Edoxaban etc…..

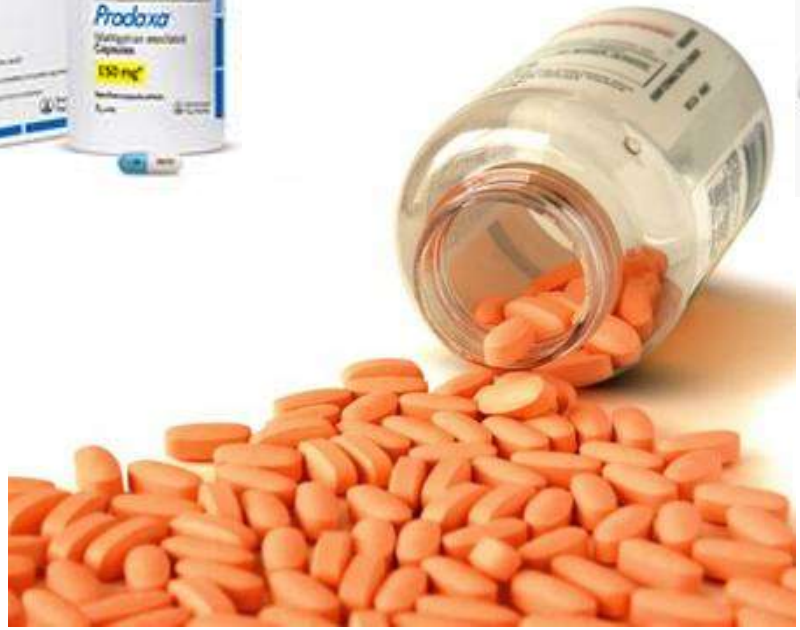
Licensed and NICE approved indications for NOACs

- **Dabigatran:**
  - **VTE prevention after elective hip or knee replacement surgery**
  - **Stroke prevention in Atrial Fibrillation**
  - DVT and PE treatment and secondary prevention (NICE Oct 2014?)

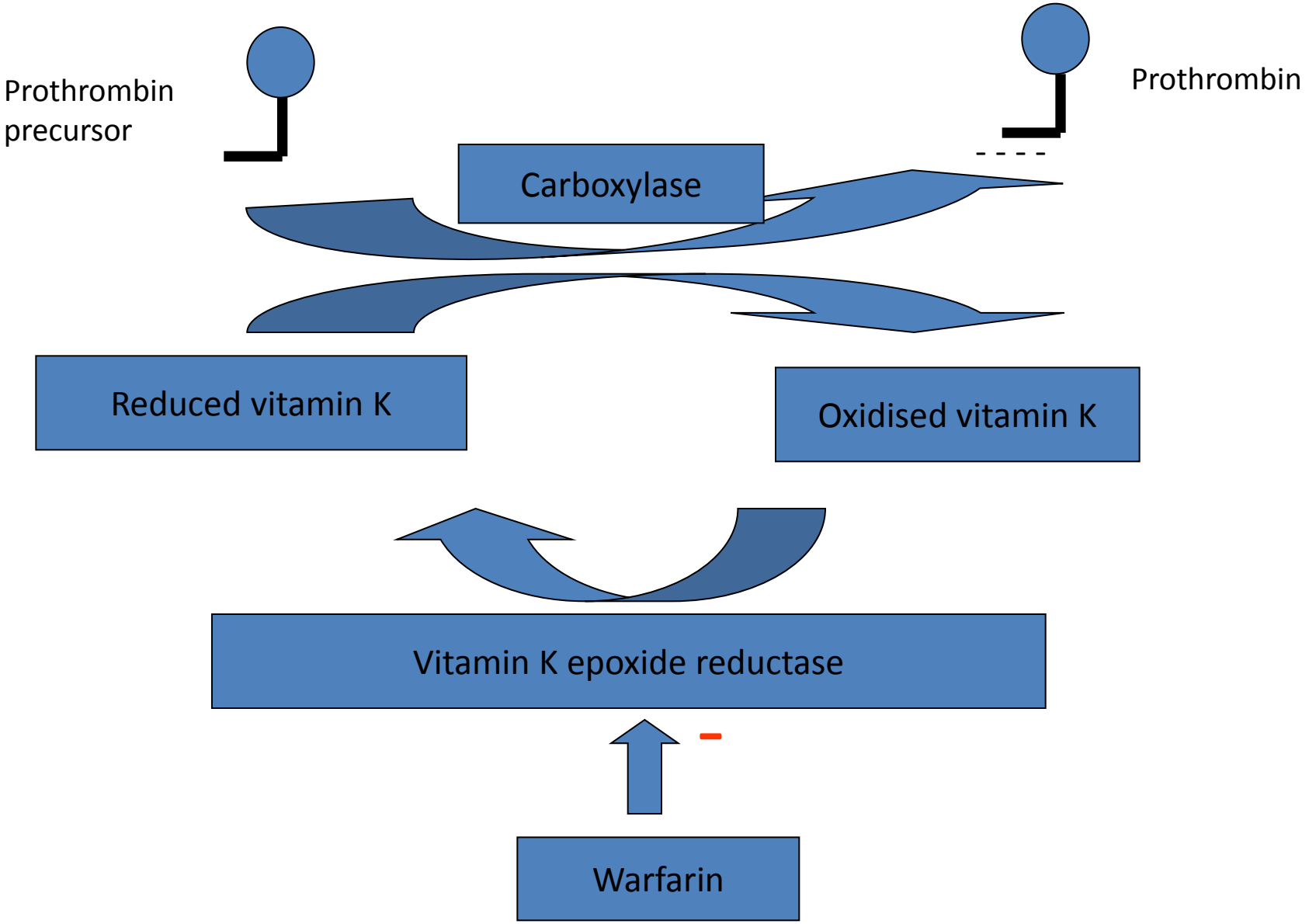
- **Rivaroxaban:**
  - **VTE prevention after elective hip or knee replacement surgery**
  - **Stroke prevention in Atrial Fibrillation**
  - **DVT and PE treatment and secondary prevention**
  - **Acute coronary syndromes**

- **Apixaban:**
  - **VTE prevention after elective hip or knee replacement surgery**
  - **Stroke prevention in Atrial Fibrillation**
  - DVT and PE treatment and secondary prevention (NICE date?)

Oral Anticoagulation 2014



Warfarin Mode of Action

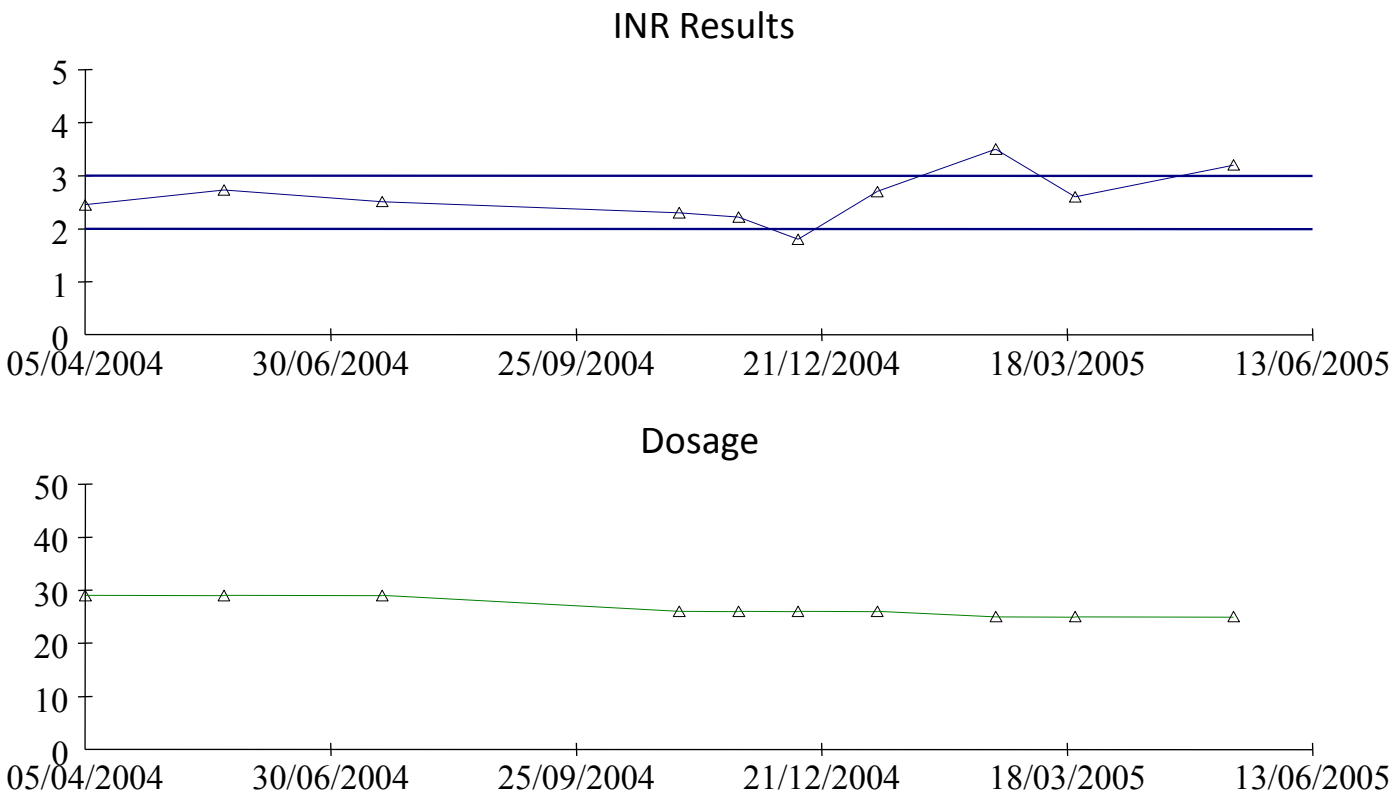


Pick a number…..

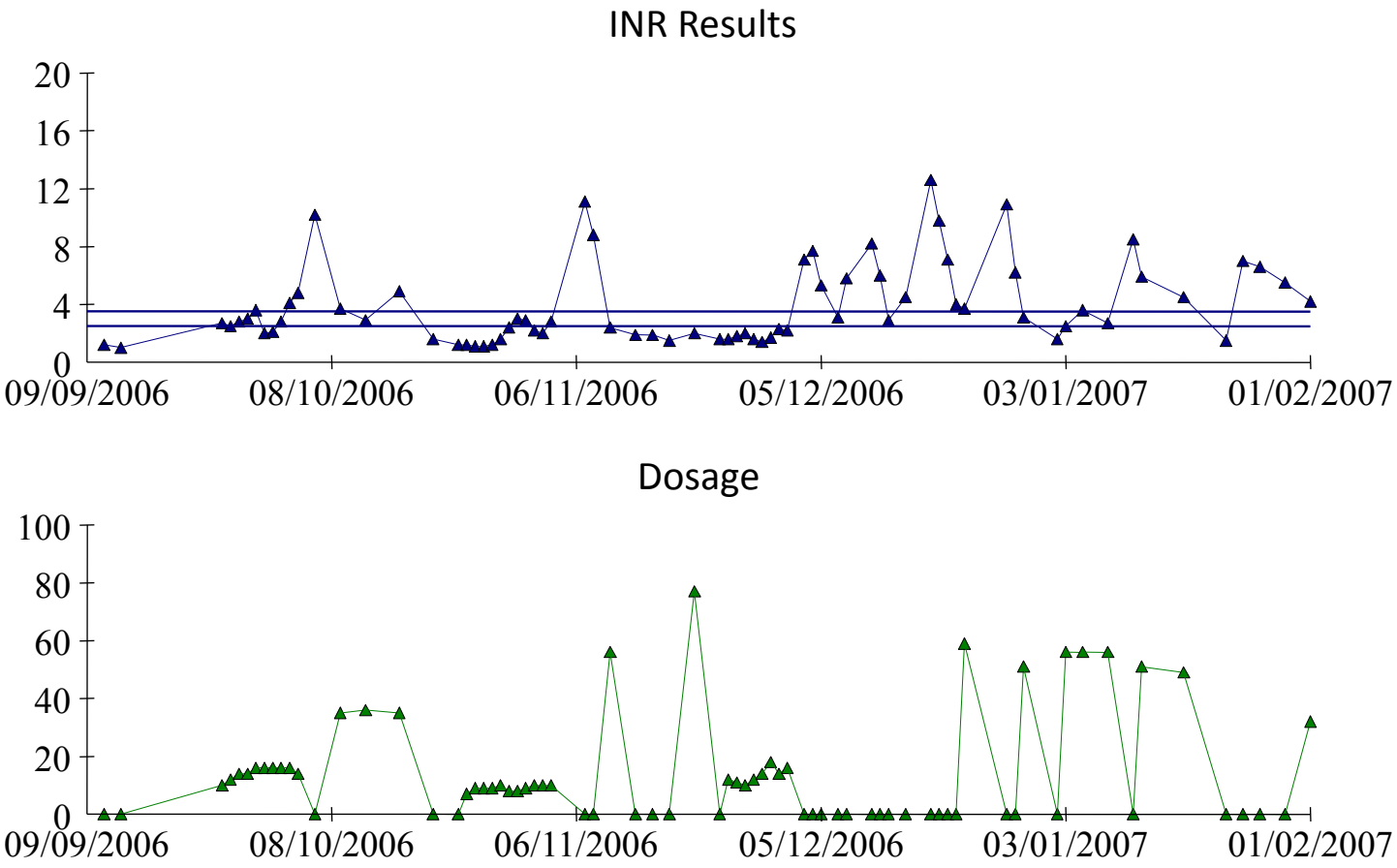
- Can you predict the dose?
  - Sex
  - Age
  - Ethnic background
  - Genetics (VKORC1 and CYP2c9 genes)
  - Comorbidities (cardiac failure, liver disease, gastrointestinal disease)
  - Other drug therapies
  - Social factors (alcohol/ diet)
  - Compliance

- Average dose 4mg for women and 6mg for men

Stable anticoagulation



Unstable anticoagulation



Can bleeding risk be assessed? HASBLED score for patients on warfarin

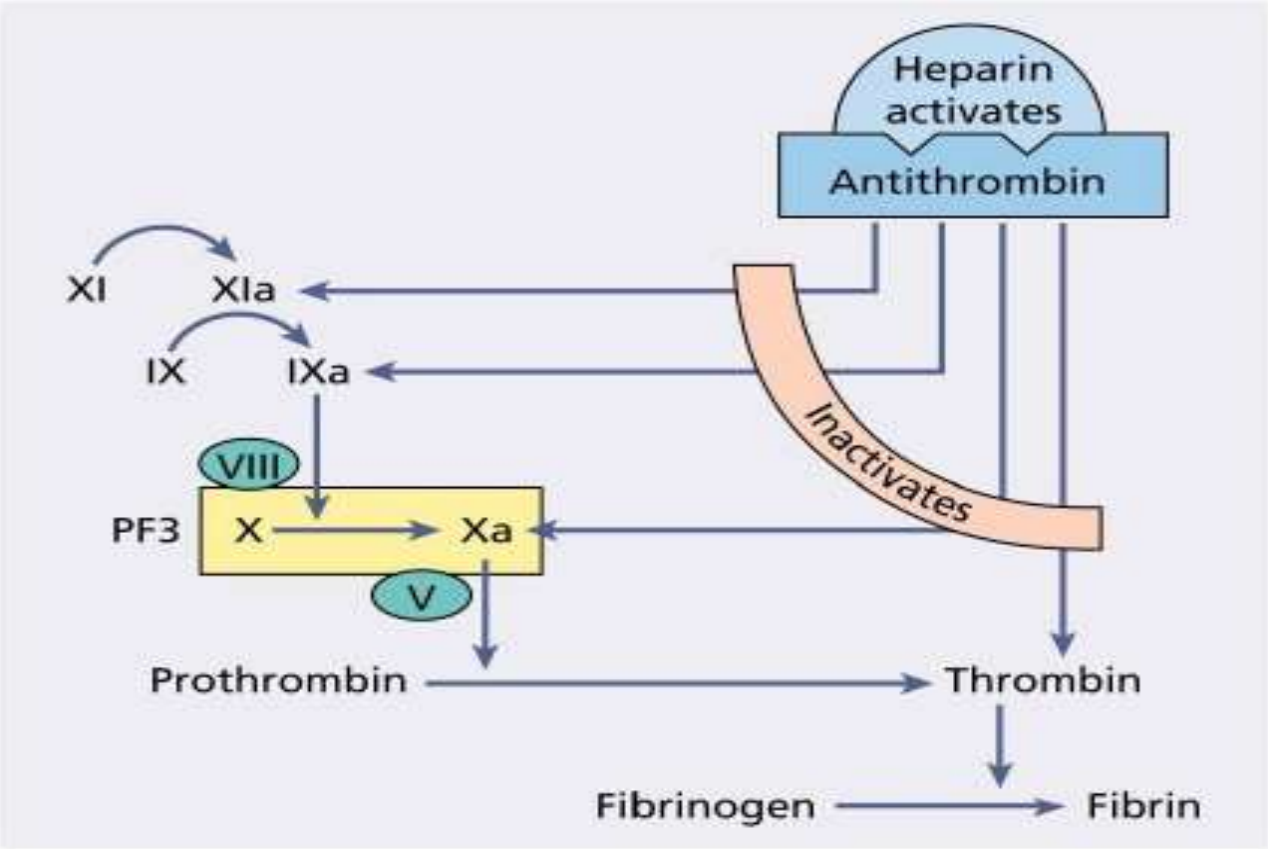
	Clinical Characteristic	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function	1 point each
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65 y)	1
D	Drugs or alcohol	1 point each
	Total	**Maximum 9 points**

Warfarin monitoring and control

- INR more unstable in ill patients
- INR influenced by diet/intake
- INR influenced by medication changes.

- When making decisions about warfarin at end of life need to consider INR stability and these other issues

Mode of action of other anticoagulant drugs



From: *Essential Haematology*, 6th Edn. © A. V. Hoffbrand & P. A. H. Moss. Published 2011 by Blackwell Publishing Ltd.

LMWH

- Used for prevention and treatment VTE
- Used for treatment VTE particularly in cancer patients (and pregnant patients)
- Used in patients with Mechanical Heart Valves when cannot use warfarin- advice from haematology
- Renally excreted- dose is weight dependent
  - May require monitoring

Novel Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
Half life	12-17h	5-13h	9-12h
Administration	Oral	Oral	Oral
Renally excreted?	+++	+/-	+/-
Heparin Induced Thrombocytopenia	-	-	-
Osteoporosis	-	-	-
Side effects	Dyspepsia in 8-10%	-	-
Monitoring?	No	No	No
Dietary/ drug interactions	+	+	+
Reversal agent?	?	?	?

Drug Interactions with NOACs

	Dabigatran	Rivaroxaban	Apixaban
Increase anticoagulant effect	Amiodarone (caution) Verapamil (caution) Azole antimycotics Tacrolimus Cyclosporin HIV protease inhibitors Dronaderone	Azole Antimycotics HIV Protease Inhibitors Dronaderone	Azole Antimycotics HIV Protease Inhibitors Dronaderone
Reduce anticoagulant effect	Rifampicin Carbamazepine Phenytoin Phenobarbital St John's wort	Rifampicin Carbamazepine Phenytoin Phenobarbital St John's wort	Rifampicin Carbamazepine Phenytoin Phenobarbital St John's wort

Advantages to new anticoagulant drugs

- Fewer drug interactions
- Reduced bleeding risk
- No monitoring
  - Reliable PK
  - Fewer drug interactions
- No lifestyle interactions
- Easier
  - Facilitates ambulatory care

Disadvantages of new anticoagulants

- Unsuitable in renal failure
  - Caution in renal impairment (dabigatran)
- Some drug interactions
- Increased risk dyspepsia (dabigatran)
- Compliance?
- Cost? (NICE approved on economic analysis)

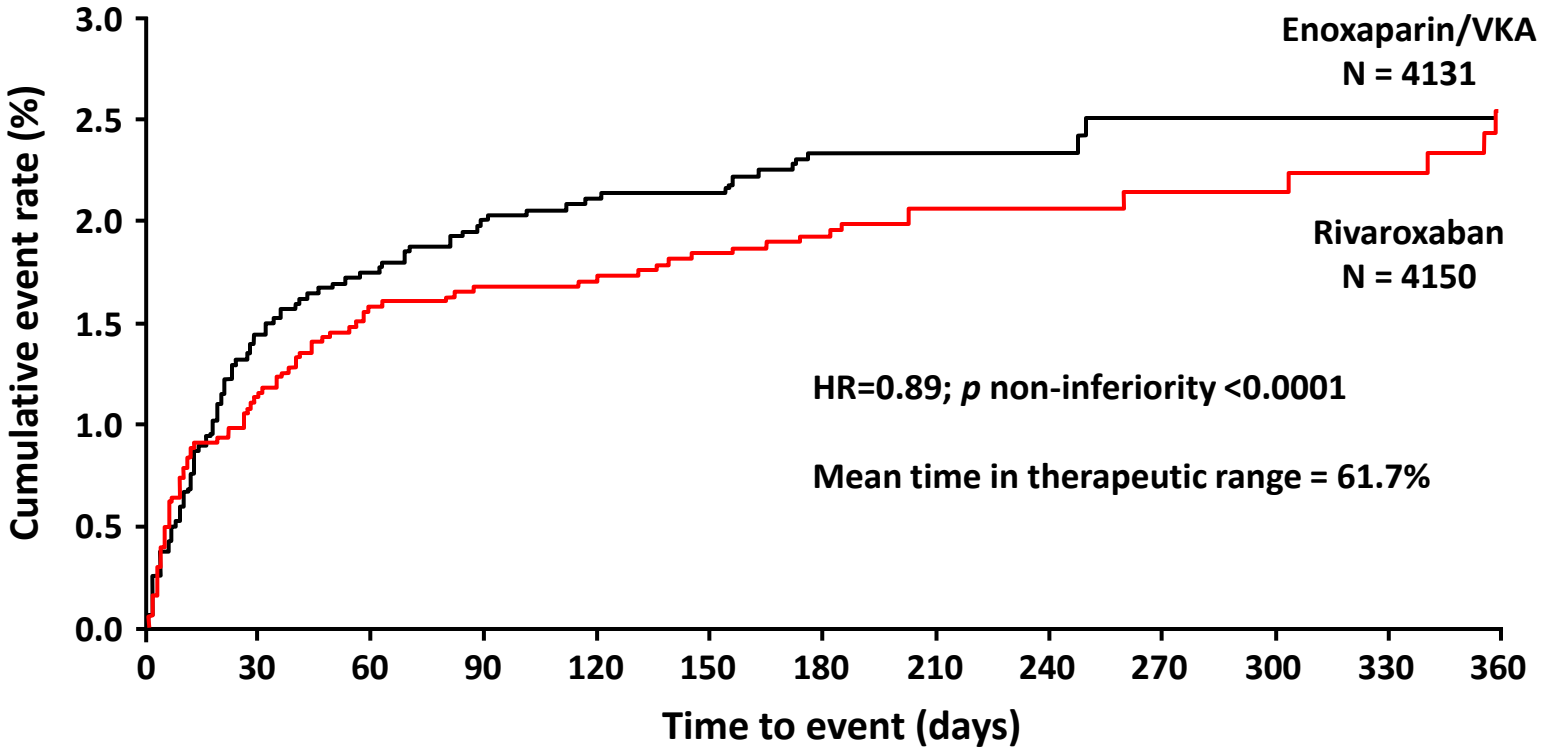
Common Indications for Anticoagulation

- Prevention of Venous Thromboembolism
- Treatment of Venous Thromboembolism
- Stroke Prevention in Atrial Fibrillation
- Anticoagulation in patients with mechanical heart valves

Venous Thromboembolism

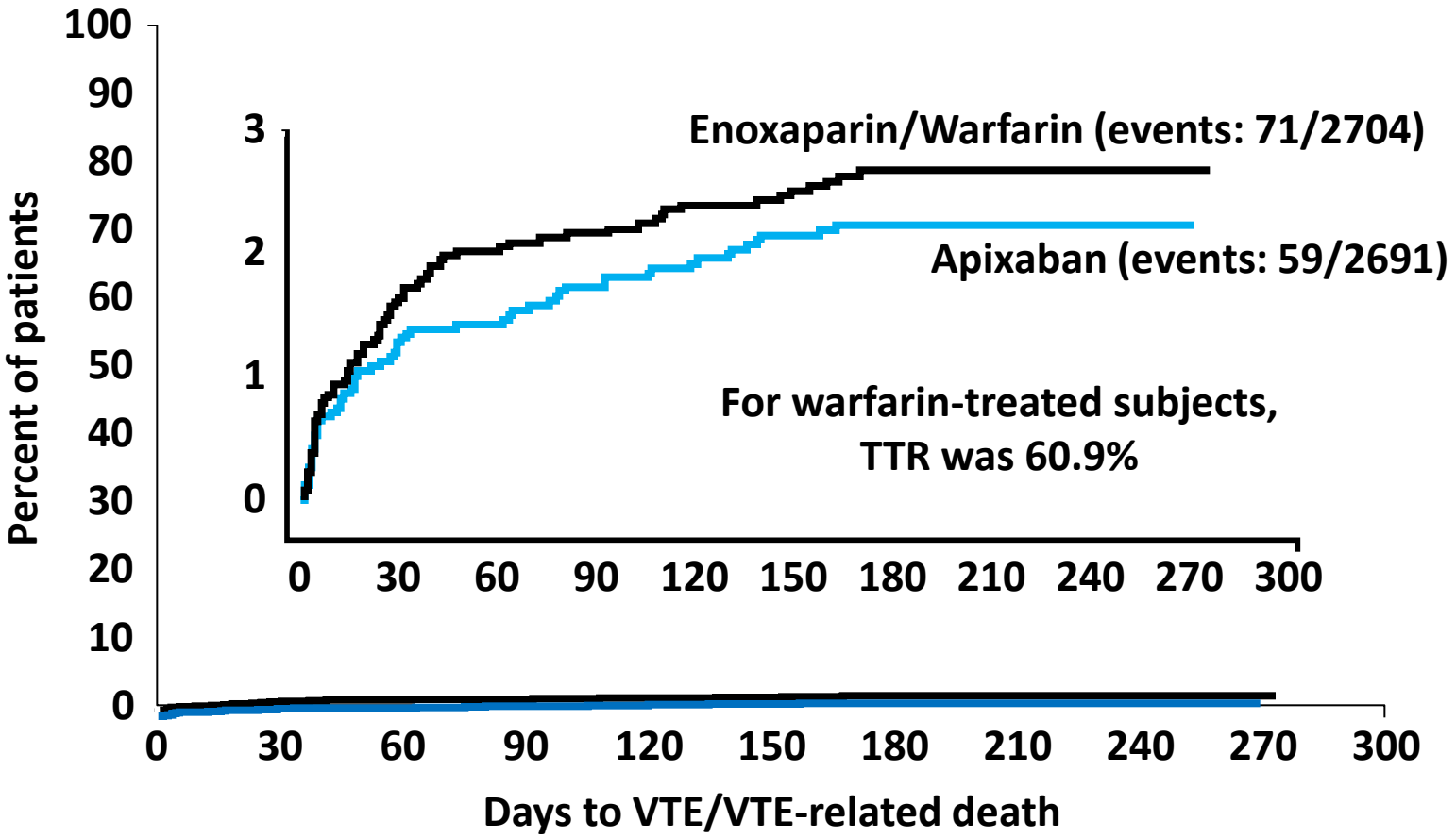
- Incidence 1-2 per 1000 per year
- ~2/3 will present with DVT
- Pulmonary embolism in >50% of those with DVT
- Mortality PE 10-25%
  - CTEPH 2-8%
- Post thrombotic syndrome
  - 50% discolouration, swelling, discomfort
  - 25% pain, ulceration
- Death in 1-2%

EINSTEIN DVT and EINSTEIN PE pooled analysis: primary efficacy outcome



Number of patients at risk													
Rivaroxaban	4150	4018	3969	3924	3604	3579	3283	1237	1163	1148	1102	1034	938
Enoxaparin/VKA	4131	3932	3876	3826	3523	3504	3236	1215	1149	1109	1071	1019	939

AMPLIFY (apixaban) First recurrent VTE / VTE-related death

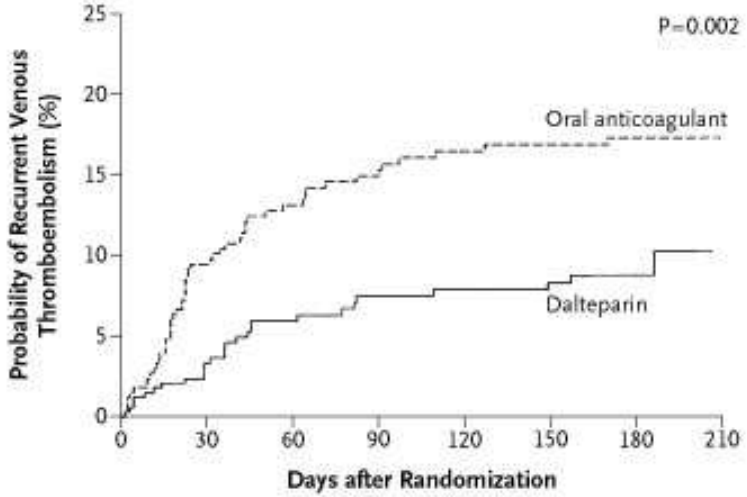


No. of patients at risk

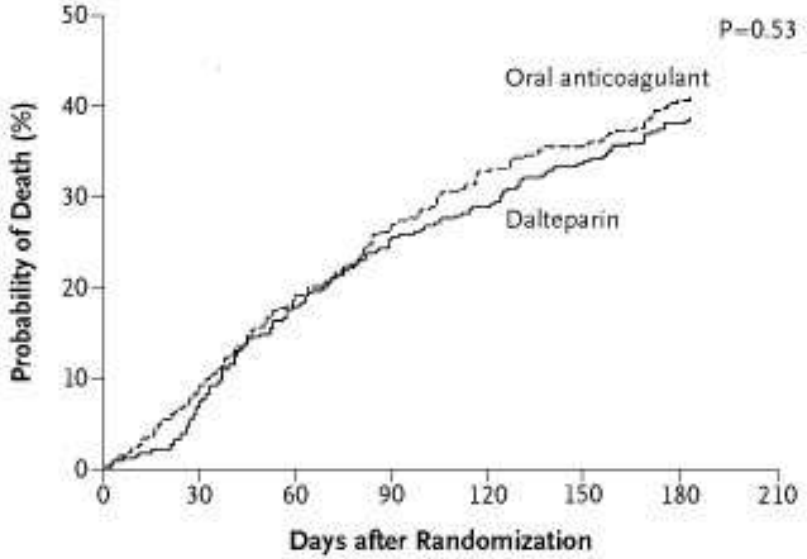
Apixaban	2691	2606	2586	2563	2541	2523	62	4	1	0	0
Eno/War	2704	2609	2585	2555	2543	2533	43	3	1	1	0

TTR, time in therapeutic range.

LMWH for patients with VTE and cancer



No. at Risk							
Dalteparin	336	301	264	235	227	210	164
Oral anticoagulant	336	280	242	221	200	194	154



No. at Risk							
Dalteparin	336	310	274	248	237	220	206
Oral anticoagulant	336	301	268	240	220	211	194

Lee A et al, NEJM 2003

Survival in patients with and without VTE in patients with prostate cancer

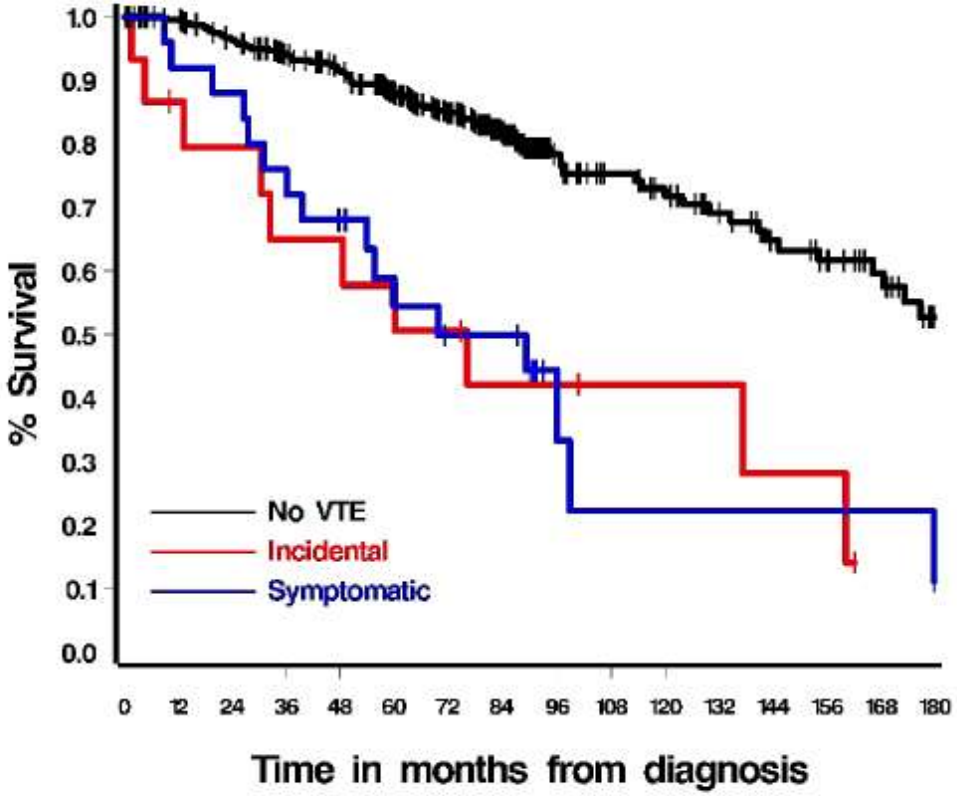


Figure 2. Survival curves depicting survival (in months) for patients with and without venous thromboembolic disease (VTE). Patients with VTE have higher mortality compared to patients without VTE [HR 6.89 (4.29–11.08), $p<0.001$]. There was no difference in mortality between patients with symptomatic or incidental VTE ($p=0.83$).

Chaturveti et al, PLOSone 2014

Incidence of death in patients with breast cancer and VTE

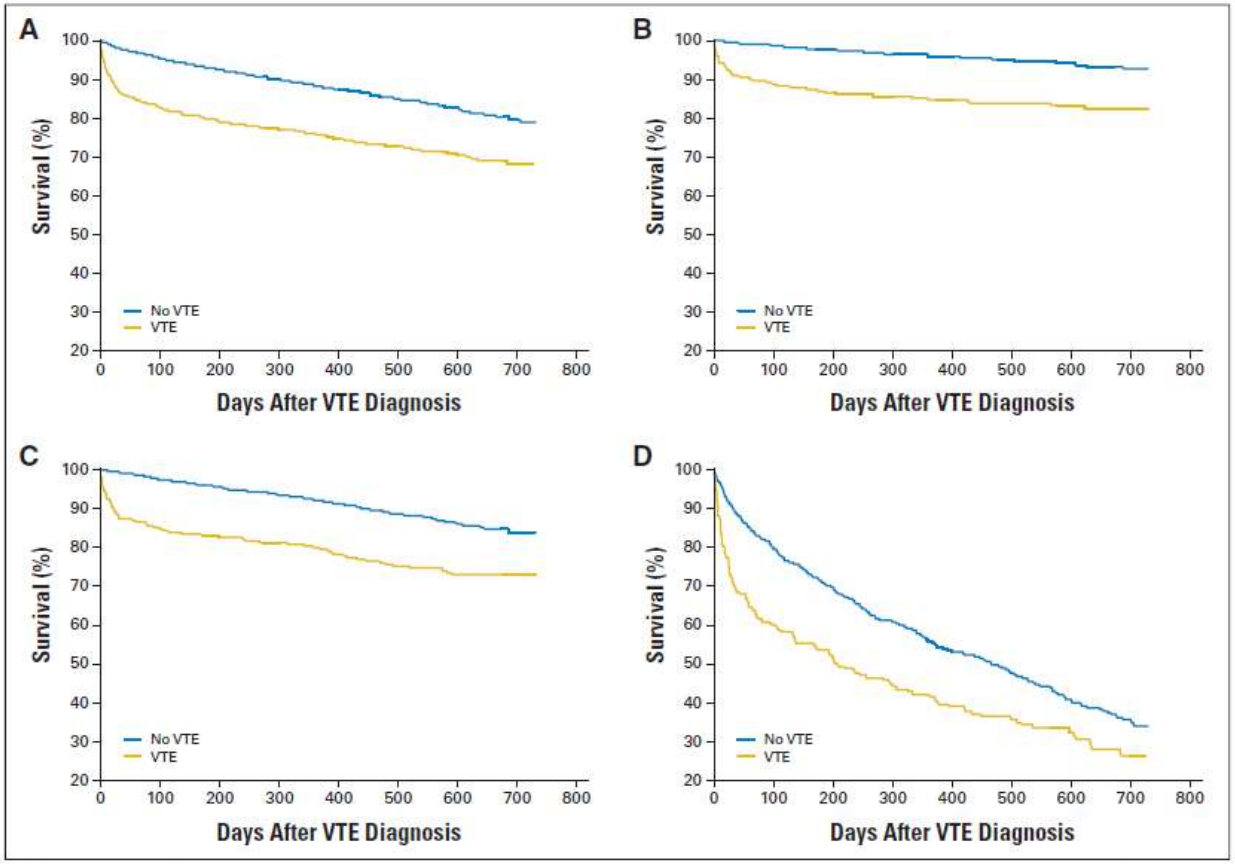
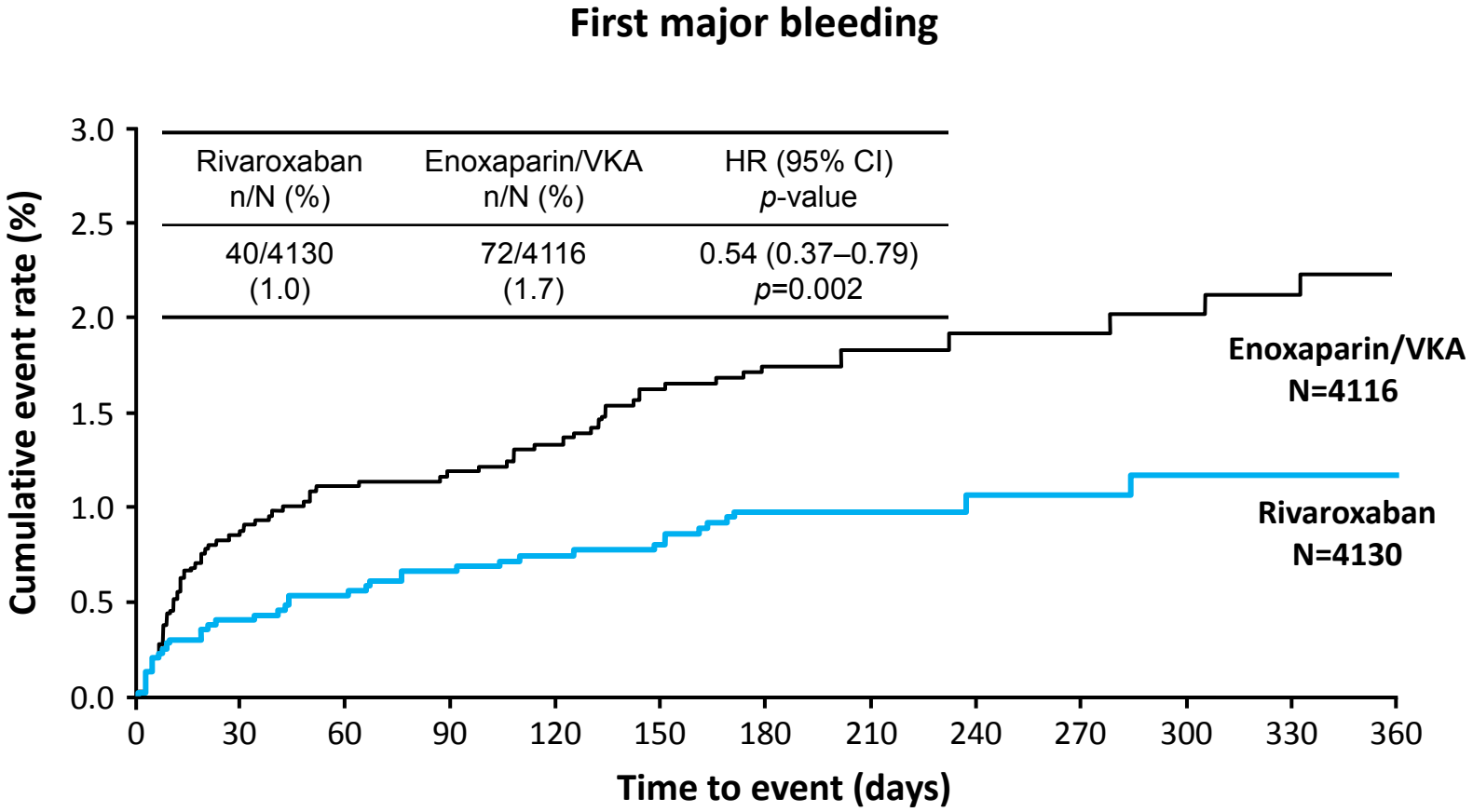


Fig 2. Kaplan and Meier plots of the incidence of death after venous thromboembolism (VTE) diagnosis and in a matched cohort without VTE, among the (A) entire cohort, and in (B) localized, (C) regional, and (D) metastatic stage breast cancer. Control and VTE patients were matched on survival from the cancer diagnosis date to the VTE diagnosis date, and survival was measured from this date.

Chew et al, JCO 2007

EINSTEIN DVT and EINSTEIN PE pooled analysis: major bleeding



Number of patients at risk													
Rivaroxaban	4130	3921	3862	3611	3479	3433	2074	1135	1095	1025	969	947	499
Enoxaparin/VKA	4116	3868	3784	3525	3394	3348	1835	1109	1065	990	950	916	409

Safety population

Acute VTE

- If symptomatic – treat
- Anticoagulant options- LMWH or Rivaroxaban
- High bleeding risk?
  - If contraindication to anticoagulation ‘consider’ IVC filter…?? Unusual in such patients
  - Consider reduced dose LMWH?

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

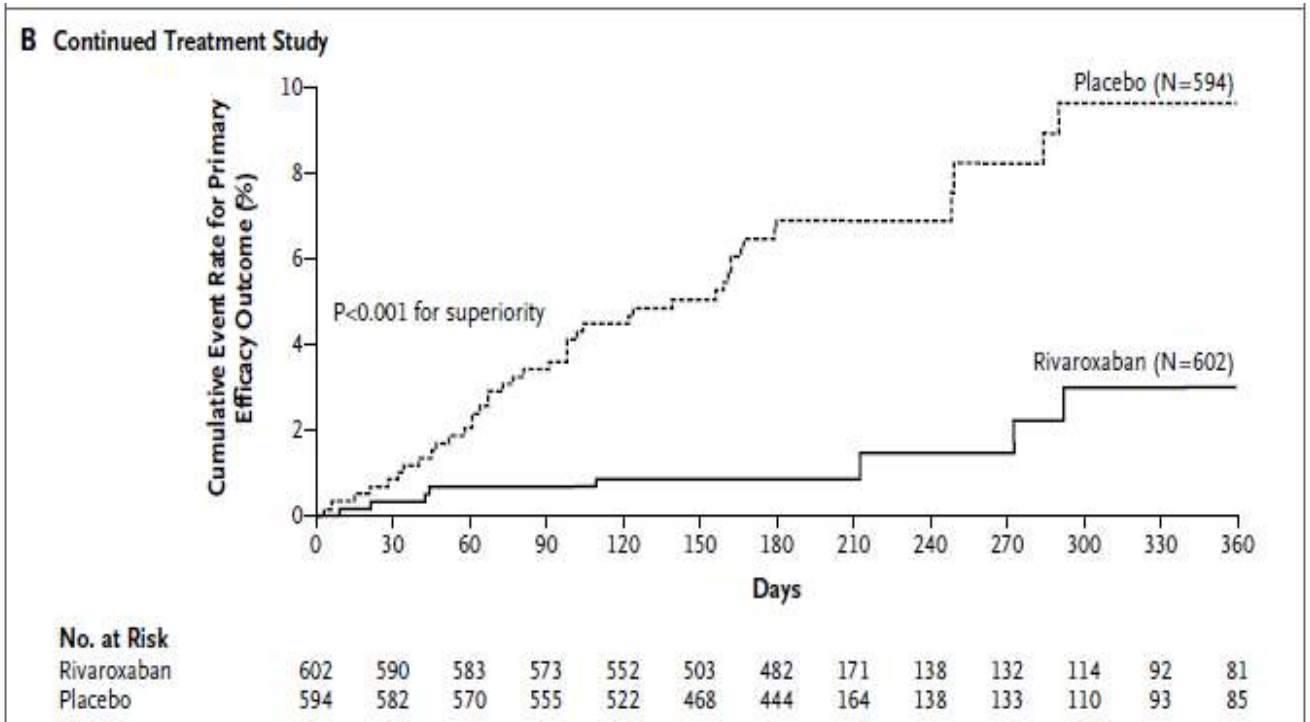


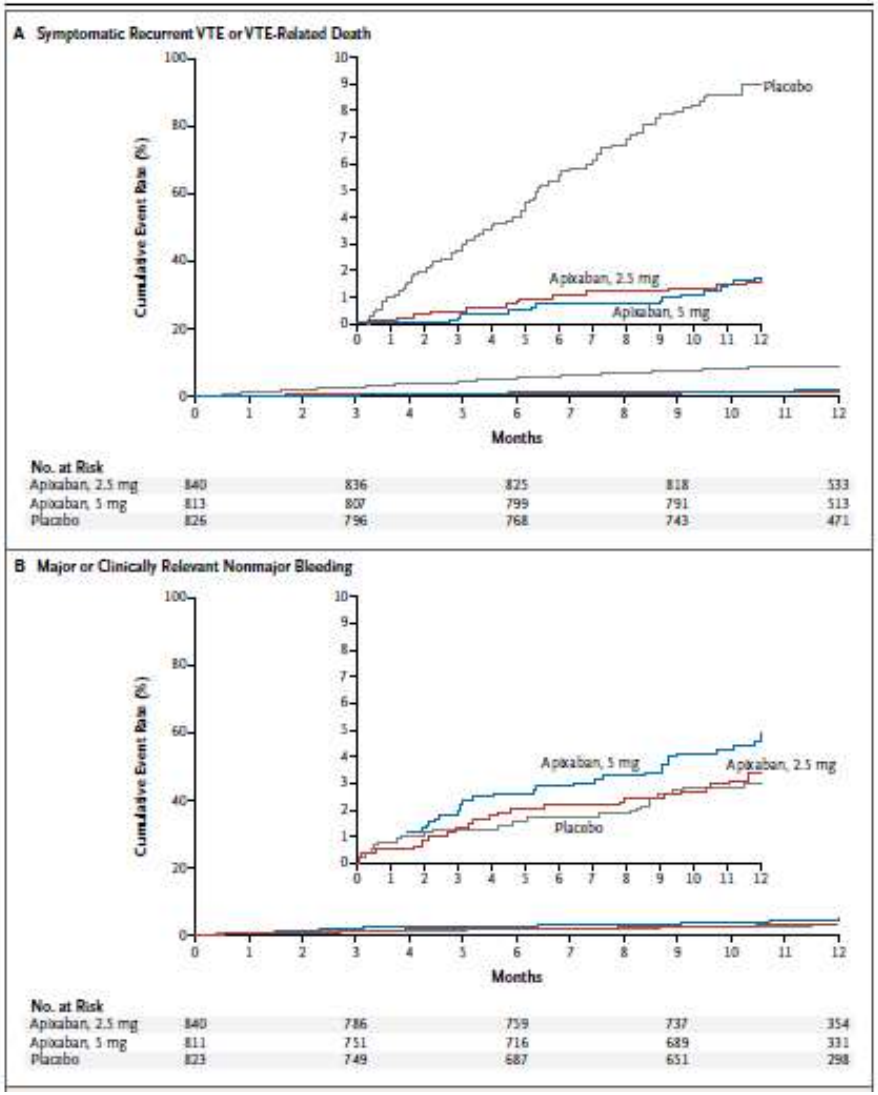
Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome in the Two Studies.

VKA denotes vitamin K antagonist.

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

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D.,



Should patients with malignant disease be given primary prophylaxis?

Table 1. Khorana's risk assessment score.

Patient characteristic		Risk score
Site of primary cancer		
• Very high risk (stomach, pancreas)		2
• High risk (lung, lymphoma, gynecologic, bladder, testicular)		1
Prechemotherapy platelet count 350×10^9/l or higher		1
Hemoglobin level less than 10 g/l or erythropoiesis-stimulating agents		1
Prechemotherapy leukocyte count higher than 11×10^9/l		1
BMI 35 kg/m^2 or higher		1
Total Score	Risk category	Risk of symptomatic VTE
0	Low	0.3–0.8%
1, 2	Intermediate	1.8–2.0%
3 or higher	High	6.7–7.1%

BMI, body mass index; VTE, venous thromboembolism.

Hogg and Carrier 2011

On anticoagulation for secondary prevention VTE

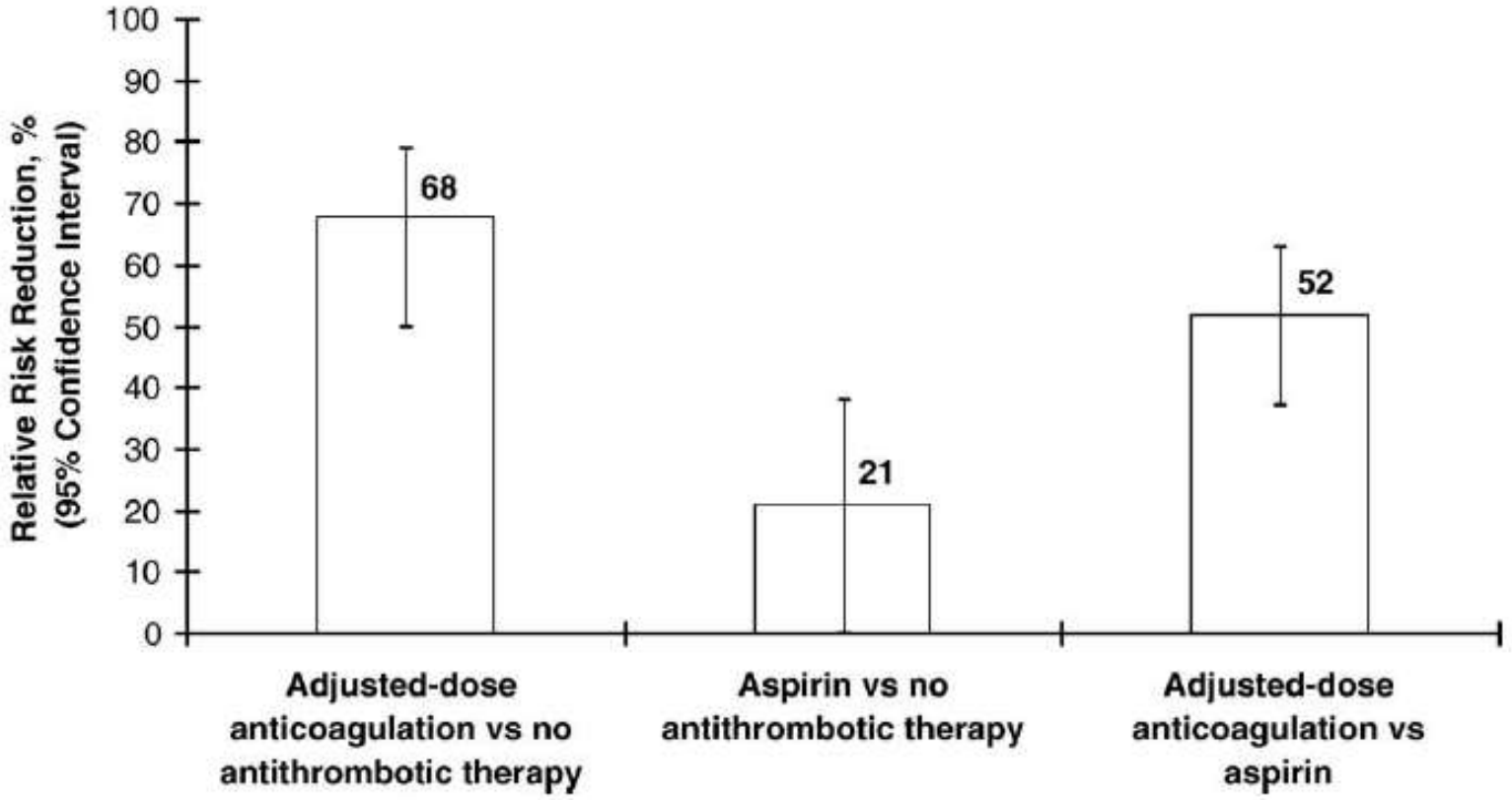
- Consider patient's wishes and those of carers, family as appropriate
- High risk recurrent VTE
  - Long history recurrent VTE, VTE with pancreatic/colorectal cancer etc..
  - Continue anticoagulation in this group?
- Lower risk recurrent VT
  - If on warfarin consider swapping to NOAC?
  - Stop anticoagulant treatment?

Stroke outcomes in AF

Pooled analysis of mortality rates after stroke in patients with and without AF		
	AF	Non-AF
30 day mortality rate (%)*	16.3%	7.5%
1 year mortality rate (%)**	37.4%	19.5%

Broderick 1992, Sandercock 1992, Lin 1996, Lamassa 2001, Kimura 2005, Ghatnekar 2008, Thygesen 2009, Hannon 2010, Saposnik 2013

Summary of Stroke Prevention



Progress in Cardiovascular Diseases, Vol 48, No 2 (September/October), 2005: pp 108-124

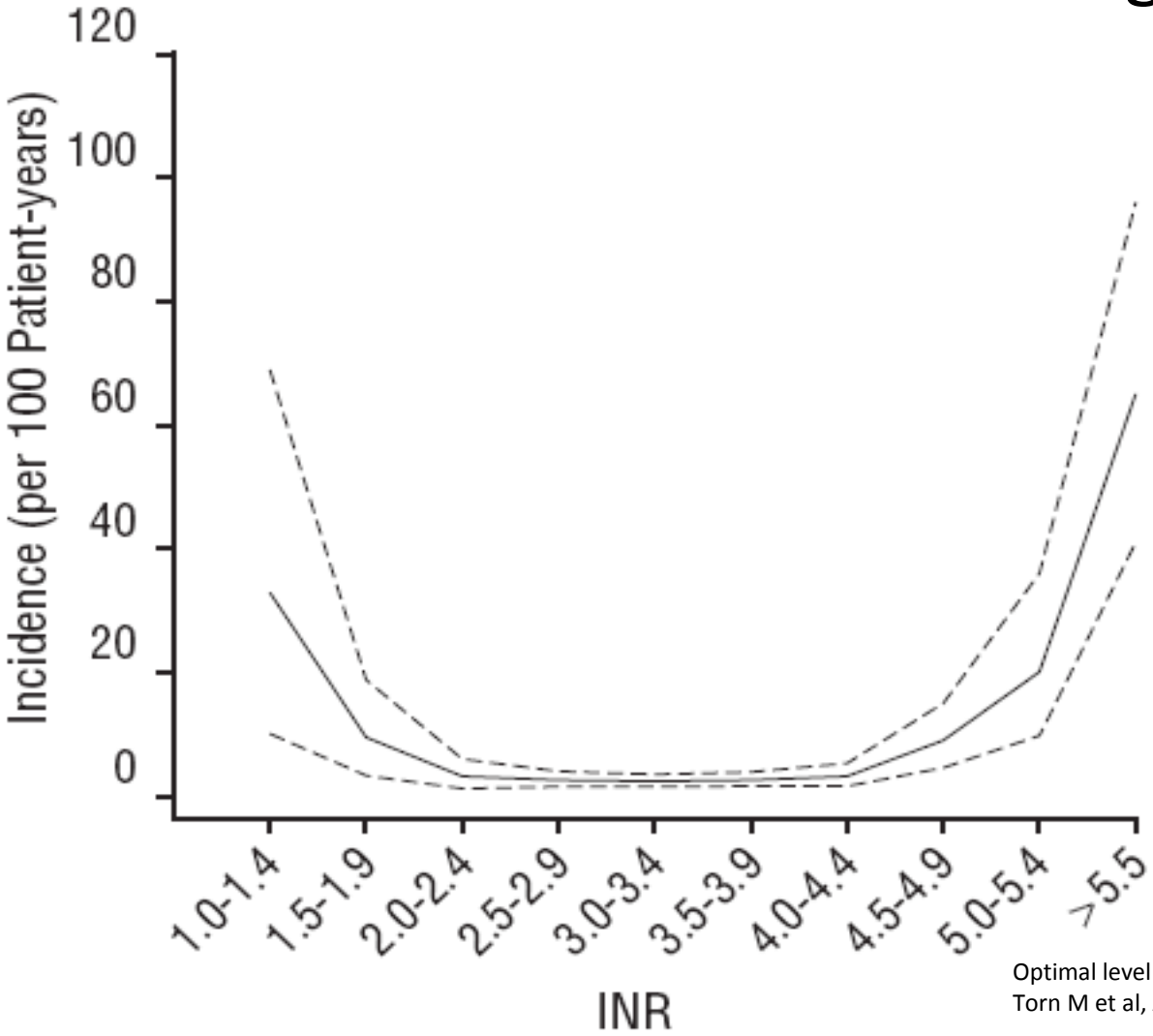
Stroke Risk Stratification- $CHADS_2$

	Score (Points)	Prevalence, %
Congestive Heart failure	1	32
Hypertension	1	65
Age >75 years	1	28
Diabetes mellitus	1	18
Stroke or TIA	2	10
Moderate-High Risk	≥2	50-60
Low Risk	0-1	40-50

$CHADS_2$ score	Patients (N = 1,733)	Adjusted Stroke Rate, %/y[a] (95% CI)
0	120	1.9 (1.2-3.0)
1	463	2.8 (2.0-3.8)
2	523	4.0 (3.1-5.1)
3	337	5.9 (4.6-7.3)
4	220	8.5 (6.3-11.1)
5	65	12.5 (8.2-17.5)
6	5	18.2 (10.5-27.4)

JAMA. 2001;285:2864-2870

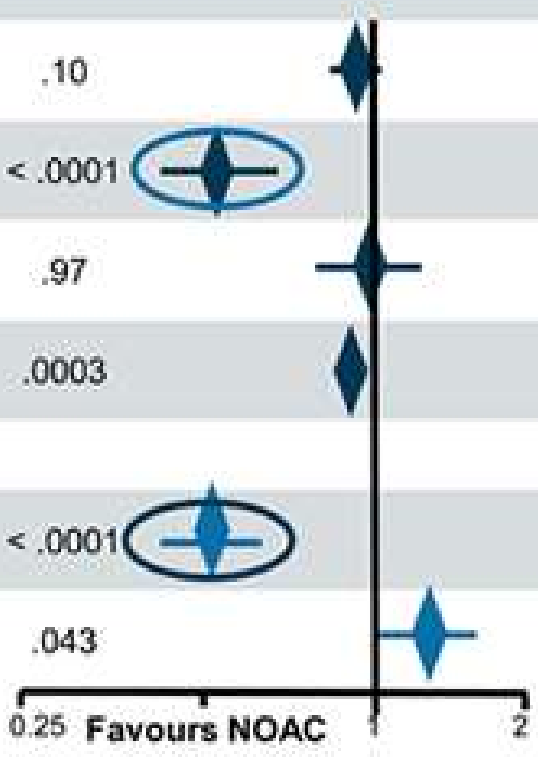
Risk of adverse events in patients with atrial fibrillation taking warfarin : Warfarin is an effective drug



Optimal level of oral anticoagulant therapy
Torn M et al, Arch Int Med 2009; 169:203-1209

Efficacy vs safety NOACs

Result	Pooled DOAC, Events/Total	Pooled Warfarin, Events/Total	Risk Ratio	95% CIs	P
Efficacy					
Ischaemic Stroke	665/29292	724/29221	0.92	0.83-1.02	.10
Hemorrhagic stroke	130/29292	263/29221	0.49	0.38-0.64	< .0001
Myocardial Infarction	413/29292	432/29221	0.97	0.78-1.20	.97
All Cause mortality	2022/29292	2245/29221	0.90	0.851-0.95	.0003
Safety					
ICH	204/29287	425/29211	0.48	0.39-0.59	< .0001
GI bleeding	751/29287	591/29211	1.25	1.01-1.55	.043



* Edoxaban is not approved for clinical use

Ruff 2013

Anticoagulation in AF

- Again, consider patient/ carers wishes
- Consider CHADSVASc score
- Unstable on warfarin/ TTR <50% stop warfarin
  - ?consider a switch to a NOAC?
  - Depends on bleeding risk/ patient preference
- Continue NOAC?

Mechanical Heart Valves

- Risk thrombosis without anticoagulation:
- Mitral valve- 22%/annum
- Aortic valve 6-8%/annum
- Risk increased if additional RF (eg. AF, previous stroke/ valve thrombosis)

Mechanical Heart Valves: NOAC studies

- Dabigatran study stopped- adverse outcomes
- Case reports of valvular thrombosis on Dabigatran (off-license use)
- No data on Rivaroxaban or Apixaban
- Do not use

Mechanical heart valves

- Again, consider patient and family wishes
- Warfarin usual anticoagulant- continue if INR stable and infrequent monitoring?
  - NPT monitoring?
- If wishes to continue on anticoagulation and INR unstable ?LMWH (watch weight and renal function)
- Consider stopping anticoagulant

Conclusions

- Decisions require to be taken on a case-by-case basis, with patient input
- Indication for anticoagulation and anticoagulant treatment will influence decision making

Table 2. Suggested use of NOACs according to patient characteristics: *All NOACs are clinically indicated for patients with AF irrespective of the estimated risk of stroke or bleeding; the suggested NOAC use in this table might not be applicable to individual patients.*

PATIENT CHARACTERISTIC	SUGGESTED NOAC REGIMEN	COMMENT
Patients with AF at high risk of stroke (eg, $CHADS_2$ score ≥3) or with previous stroke	Dabigatran, 150 mg twice daily	This dose of dabigatran conferred the greatest risk reduction in stroke compared with warfarin
	Rivaroxaban, 20 mg daily	More patients with previous stroke were studied with rivaroxaban
Patients with AF at high risk of bleeding	Apixaban, 5 mg twice daily	This dose of apixaban conferred a decrease in the risk of major bleeding compared with warfarin
	Dabigatran, 110 mg twice daily	This dose of dabigatran conferred a decrease in the risk of major bleeding compared with warfarin
Patients with dyspepsia or other gastrointestinal complaints	Apixaban or rivaroxaban	These drugs have been associated with less dyspepsia than dabigatran
Patients with AF and anticipated medication compliance problems	Rivaroxaban, 20 mg daily	Once-daily dosing might allow better compliance when there is long-term need for medication
Elderly (≥80 y) patients with impaired renal function (eg, eGFR <50 mL/min)	Apixaban, 2.5 mg twice daily	Apixaban was associated with a reduced risk of bleeding in patients with impaired renal function

Douketis et al, 2014
Canadian family physician