Anticoagulation Issues in Atrial Fibrillation

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Case

- A 72 year-old woman with a history of myocardial infarction presented to the emergency department with palpitations. ECG on admission documented atrial fibrillation (AF), which subsequently reverted spontaneously to sinus rhythm. Echocardiography revealed mild systolic impairment (LV ejection fraction 45%), mild left atrial enlargement, and normal valves.
- Additional medical history:
- Hyperlipidemia
- No hypertension or diabetes mellitus

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Case

- She returned to clinic 4 weeks later reporting intermittent palpitations. Her BP was 130/75 mmHg, and a 30-day cardiac monitor demonstrated AF which coincided with her symptoms of palpitations.
- What is the most appropriate stroke prophylaxis for this patient?

Talk Outline – Anticoagulation Issues in AF

- New scoring systems for stroke prediction and bleeding risk
- New anticoagulants for AF
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)

Atrial Fibrillation

- ***Scope of the problem:***
  - AF affects 1 – 2% of the population
- Prevalence of AF increases with age:
  - <0.5% at 40 – 50 years
  - 5 – 15% at 80 years
- Lifetime risk of developing AF is ~ 25% in those who have reached the age of 40

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Atrial Fibrillation and Stroke

- All-cause stroke rate with AF is ~ 5% per year
- 15% of all strokes are caused by AF
- A leading cause of death and long-term disability in patients with AF

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Atrial Fibrillation and Stroke

- Over 87% of AF-related strokes are thromboembolic
- AF-related strokes:
  - Larger
  - Higher mortality

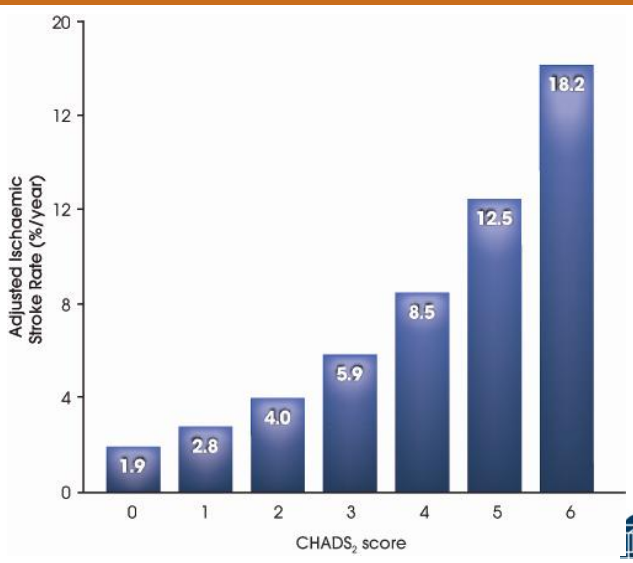
Back to our patient…

- 72 year-old woman with a prior myocardial infarction and paroxysmal AF
- $CHADS_2 = 0$
- ***Should she be anticoagulated?***

$CHADS_2$ Score

	$CHADS_2$ Risk Criteria	Score
C	CHF/LV dysfunction (EF < 40%)	1
H	Hypertension	1
A	Age ≥ 75 years	1
D	Diabetes mellitus	1
S	Stroke, TIA, or embolic event	2

$CHADS_2$ Score



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$CHADS_2$ Score – *OLD* Guidelines

Score	Risk	Anticoagulation Therapy
0	Low	None or Aspirin
1	Intermediate	Aspirin *or* Warfarin
≥ 2	Moderate/High	Warfarin, OAC

Stroke Risk Stratification

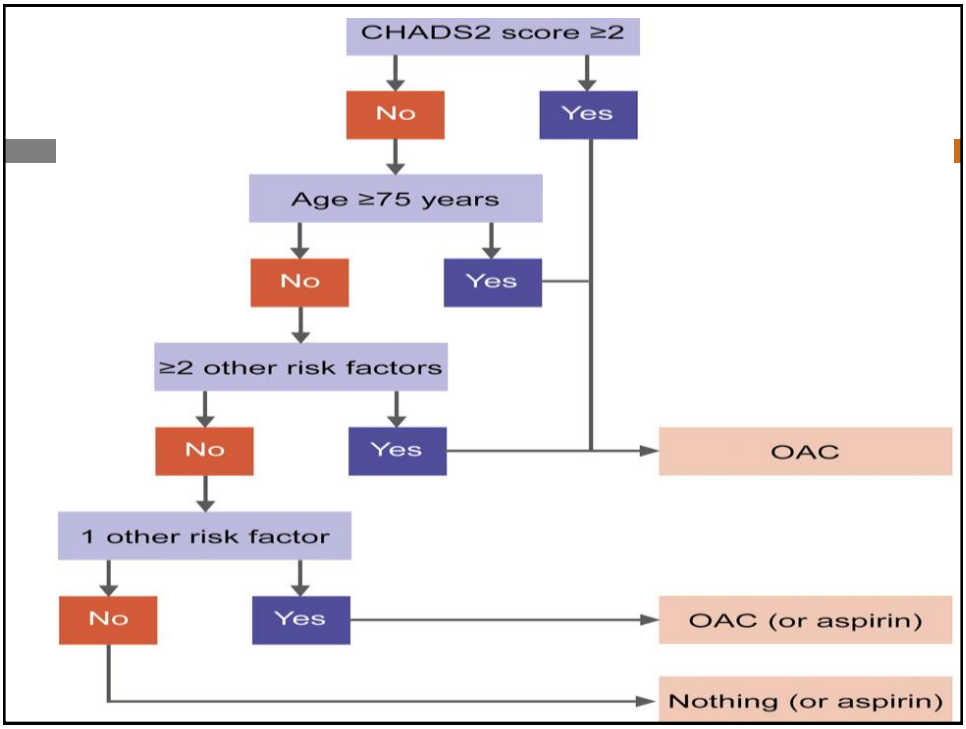
- ***Limitations of $CHADS_2$***:
- Does not include other known AF stroke risk factors
- Are $CHADS_2$ 0 or 1 patients really "low risk"?
  - $CHADS_2$ score 0 = 2% stroke risk/year
    - 20% risk over 10 years
  - $CHADS_2$ score of 1 = 2.8% stroke risk/year
    - ~ 30% risk of stroke over 10 years

Modified $CHADS_2$ Score

- ***CHA_2DS_2-VASc:***
  - ***Modifications***:
    - 2 points for age ≥ 75
  - ***Additions*** (1 point each):
    - Vascular disease (coronary, peripheral, or aortic plaque)
    - Age 65 – 74
    - Sex category (female)

CHA_2DS_2-VASc Stroke Risk

Stroke risk by CHA_2DS_2-VASc		
CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%



Bleeding Risk – *HAS-BLED*

	Clinical Characteristic	Points Awarded
H	Hypertension	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age > 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Max = 9 points

Our patient…

- Has a $CHADS_2$ of 0
- Previously deemed "low risk" (2% risk of stroke/year)

- ***However***, her CHA_2DS_2-VASc score is 3 (vascular disease; age 65 – 74; female gender)
- HAS-BLED = 1 (age)
- Her yearly stroke risk is 3.2% (~ 30% over 10 years)
- ***Current guidelines recommend OAC***

Our patient…

- Based on a CHA_2DS_2-VASc score of 3, we have decided to start an oral anticoagulant…

- What are our options?

Atrial Fibrillation

- Warfarin has been the standard therapy for stroke prevention in AF
  - 60 – 70% risk reduction vs no treatment
  - 30 – 40% risk reduction vs aspirin

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Limitations of Warfarin

- Warfarin is prescribed to only 2/3 of appropriate candidates:
  - Inconvenience in monitoring the INR
  - Risk of hemorrhage
  - Drug and dietary interactions

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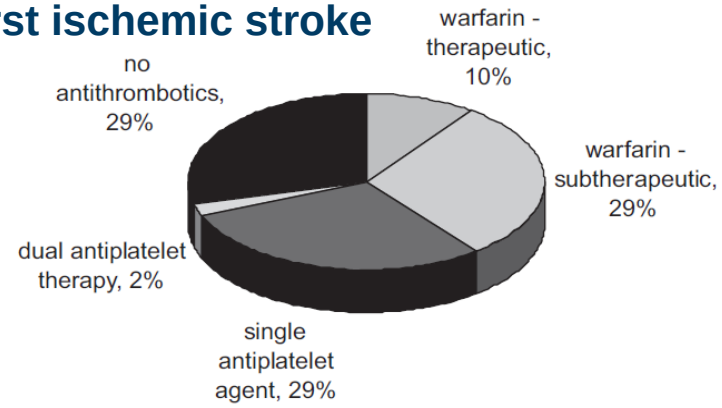
Warfarin for Stroke Prevention

- INR is outside the recommended therapeutic range 30 – 50% of the time
- INR 1.5 – 1.9 reduces its protective efficacy by a factor of 2 – 3.6
- Risk of ICH: 2.7% at values of 4 – 4.5; 9.4% at INRs > 4.5

AF – Anticoagulation for Stroke Prevention

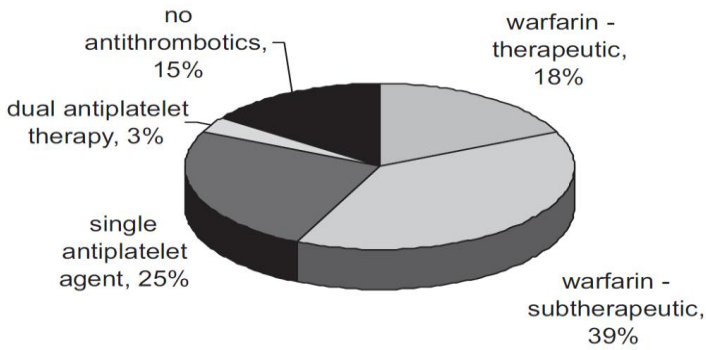
597 patients with AF presenting with a first ischemic stroke



Gladstone DJ et al. Stroke 2009; 40: 235 – 240.

AF – Anticoagulation for Stroke Prevention

323 patients with AF and prior stroke/TIA admitted with an ischemic stroke



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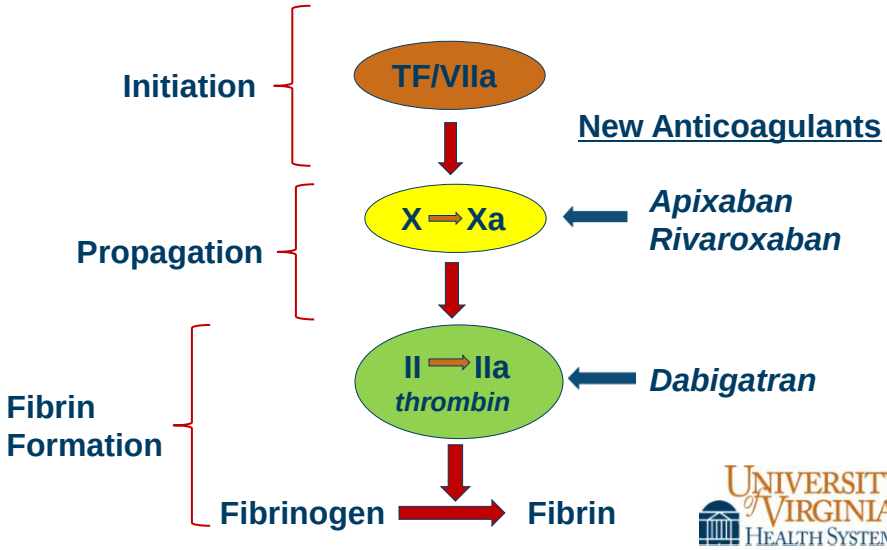
New Anticoagulants for AF



New Oral Anticoagulants for AF

	Dabigatran	Rivaroxaban	Apixaban
Target	Direct Thrombin Inhibitor	Factor Xa	Factor Xa
Half-life (hours)	14 – 17	12	9 (12 in the elderly)
Standard Dosing	150 mg twice daily	20 mg once daily	5 mg twice daily
Metabolism/ Excretion	80% renal	66% renal	67% hepatic
Major studies	RE-LY	ROCKET	ARISTOTLE AVERROES

New Anticoagulants

- ***Dabigatran (Pradaxa):***
  - Rapidly-acting, reversible inhibitor of thrombin
  - Maximum effects are achieved w/in 2 hours of administration
  - Major trial: ***RE-LY*** (NEJM 2009)

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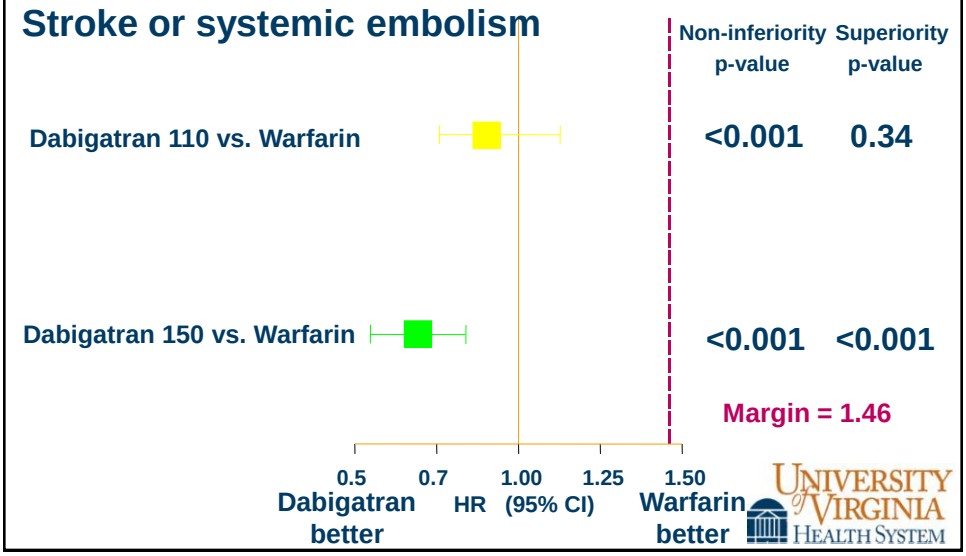
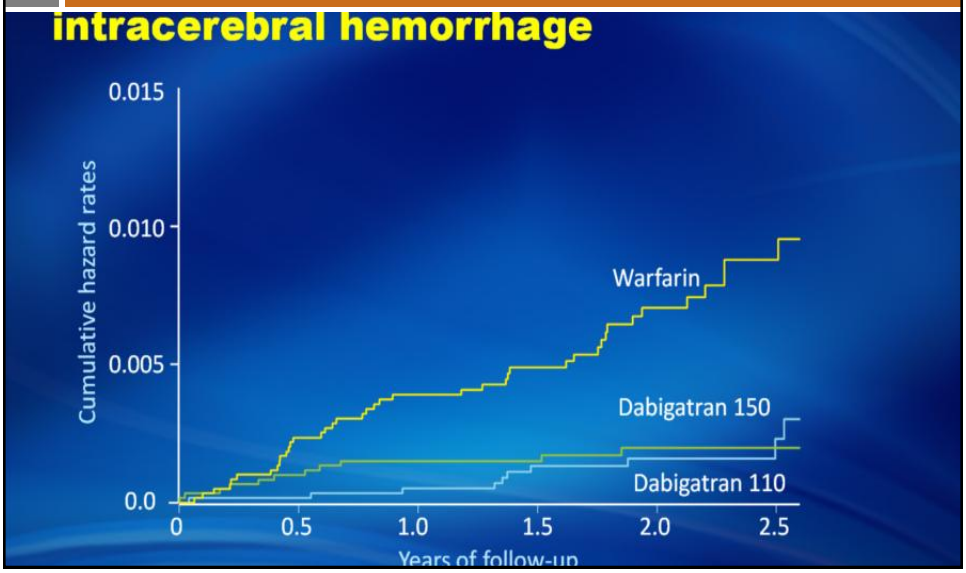
Dabigatran (Pradaxa) *RE-LY* Study

Stroke or systemic embolism



Dabigatran (Pradaxa)



Dabigatran (Pradaxa)

- Dabigatran 150 mg bid, *compared with warfarin*, results in:
  - 24 - 28% relative risk reduction for stroke and recurrent stroke
  - 60% reduction in intracranial hemorrhage
  - Fewer hemorrhagic complications overall

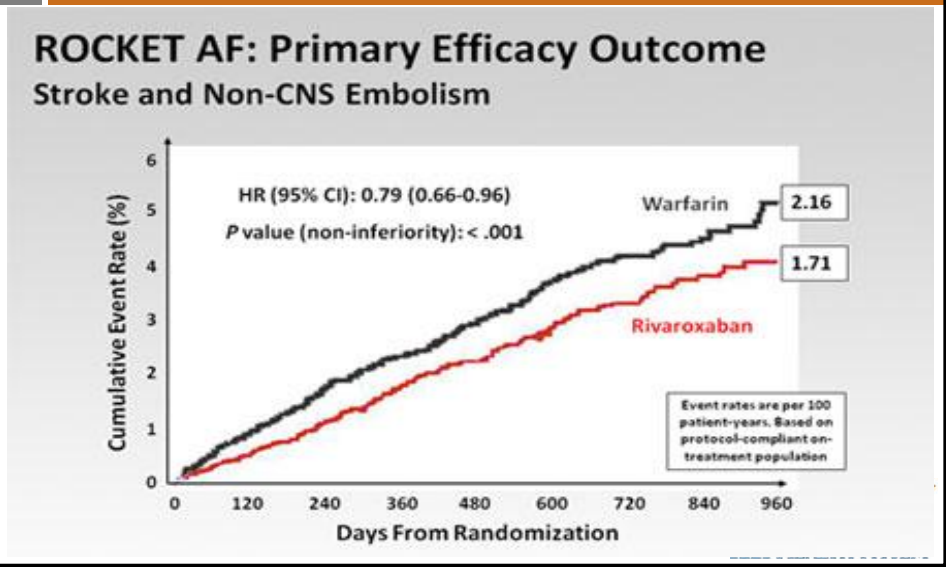
Rivaroxaban (Xarelto)

- Oral inhibitor of factor Xa
- Maximum inhibition of factor Xa occurs 4 hours after a dose
- Effects last 8 – 12 hours
- But, factor Xa activity does not return to normal for ~ 24 hours ⟶ once-daily dosing

Rivaroxaban (Xarelto)

- Major trial: ***ROCKET-AF***
- Randomized, double-blind trial involving > 14,000 patients
- Rivaroxaban 20 mg daily (15 mg daily if CrCL 30 – 49 ml/min) vs warfarin

Rivaroxaban (Xarelto)



Rivaroxaban (Xarelto)

- ***Rivaroxaban compared with warfarin***:
  - Non-inferior with regard to stroke prevention
  - No significant differences in major bleeding events
  - Less intracranial and fatal bleeding
  - Higher rate of GI bleeding

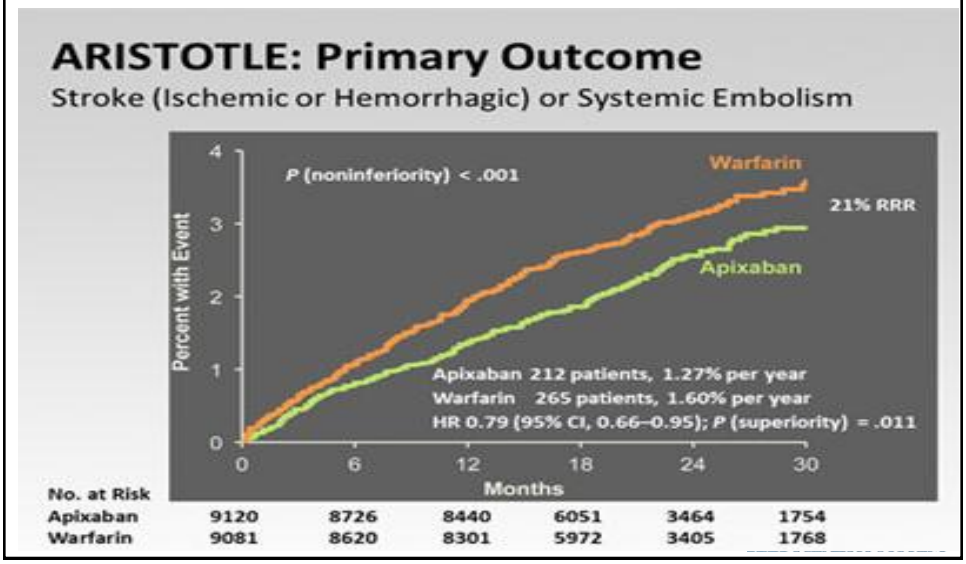
Rivaroxaban (Xarelto)

- ***ROCKET-AF caveat***:
  - In the warfarin arm, time in therapeutic range (TTR, INR 2 – 3) was < 60%
  - Among patients with TTR > 68%, there was a relative increase in stroke/embolic events with rivaroxaban
  - Poor warfarin control biased the study in favor of rivaroxaban

Apixaban (Eliquis)

- Oral direct factor Xa inhibitor
- ***Major Trials***:
  - ***AVERROES***: apixaban (5 mg twice daily) vs aspirin (not candidates for warfarin)
  - Stroke rates per year:
    - Aspirin – 3.7%
    - Apixaban – 1.6%
  - Major bleeding similar

Apixaban (Eliquis)



Comparison of New Anticoagulants to Warfarin

Properties	Warfarin	New Agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Drug-Food Interactions	Yes	No
Drug-Drug Interactions	Many	Few
Monitoring Required	Yes	No
Assays for Monitoring	Yes	No
Specific Antidote	Yes	No
Need for Bridging	Yes	No

Comparing New Anticoagulants

- No head-to-head trials comparing these agents
- Consider if patient is unwilling to commit to regular INR monitoring or INR is labile
- If INR is well-maintained, little advantage to switching from warfarin to a new anticoagulant

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Back to our patient…

- Opted for a new anticoagulant to avoid regular INR monitoring
- Started dabigatran 150 mg twice daily

Conclusions

- CHA_2DS_2-VASc > $CHADS_2$
  - Particularly for low-intermediate risk patients
- HAS-BLED helps estimate risk with anticoagulation
- New anticoagulants offer several advantages over warfarin
  - Rapid onset/no need for bridging
  - Few interactions
  - Fixed dosing
  - No monitoring

Additional Material

New Anticoagulants for AF

- Who should be switched from coumadin to a new agent?
  - Patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran

New Anticoagulants for AF

- *Consider switching from warfarin*:
  - Recurrent ischemic events/strokes despite therapeutic doses of warfarin
  - Labile INRs/difficult maintaining a stable INR
  - Patient preference
- How should we switch from warfarin to one of the new agents?
  - INR 2 or less – can switch immediately
  - INR > 2 – switch once it is ≤ 2

Dabigatran

- *Switching from dabigatran to warfarin*:
  - For CrCl > 50, start warfarin 3 days before discontinuing dabigatran
  - For CrCl 31 – 50: start warfarin 2 days prior
  - For CrCl 15 – 30: start warfarin 1 day prior
  - For CrCl < 15: no recommendation

Rivaroxaban

- Switching from rivaroxaban to warfarin:
  - Start warfarin 4 days prior to stopping rivaroxaban

Periprocedural Anticoaguation

CrCl	Half-life (hrs)	Last dose before surgery– standard risk of bleeding	Last dose – high risk of bleeding
Dabigatran			
80 ml/min	13	24 hours	2 days
> 30 to < 50 ml/min	18	2 days	4 days
< 30 ml/min	27	4 days	6 days
Rivaroxaban			
> 30 ml/min	12	24 hours	2 days
< 30 ml/min	unknown	2 days	4 days

Standard risk **of bleeding = cardiac cath; ablation; colonoscopy; laparoscopic procedure**
High risk **– cardiac surgery; insertion of pacemakers or defibrillators; neurosurgery; major abdominal surgery**