Minimising bleeding risk associated with anticoagulation use

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March 25th / 26th 2020

Disclosures

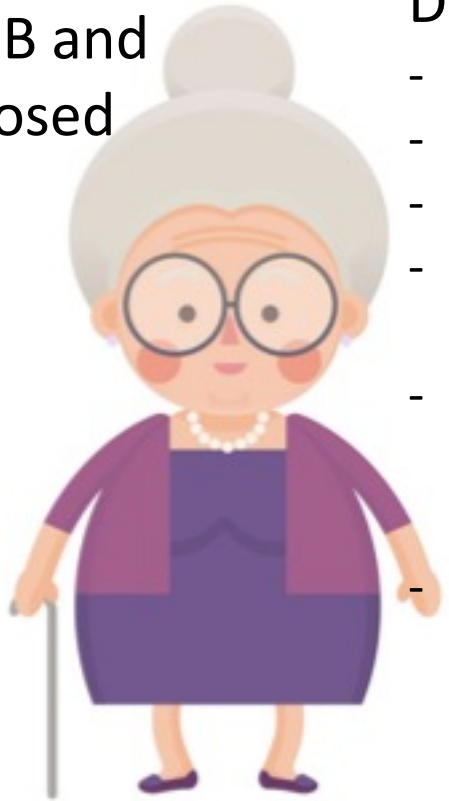
- Honorarium
  - Daiichi Sankyo

Introduction

- Risks of bleeding on anticoagulation
- Understanding bleeding risk scores / tools
- Identify and address reversible / non reversible factors for bleeding
- Applying principles to practice

Lets introduce Doris

- 81 yr old
- Admission to A&E with SoB and irregular pulse – AF diagnosed
- PMH:
  - Hypertension
  - Angina
  - Osteoarthritis
- On examination:
  - 55kg
  - BP 130/80, HR 85 bpm - AF
  - SrCr 120, eGFR 52ml/min



Drugs on admission

- Aspirin 75mg daily
- Atorvastatin 20mg daily
- Amlodipine 5mg daily
- Indapamide 2.5mg daily

- fluconazole 50mg daily (for another 5 days)

- OTC medication:
  - Ibuprofen when required
  - Ginger, Ginko, Garlic

Should we anti coagulate?

CHA_2DS_2VASc

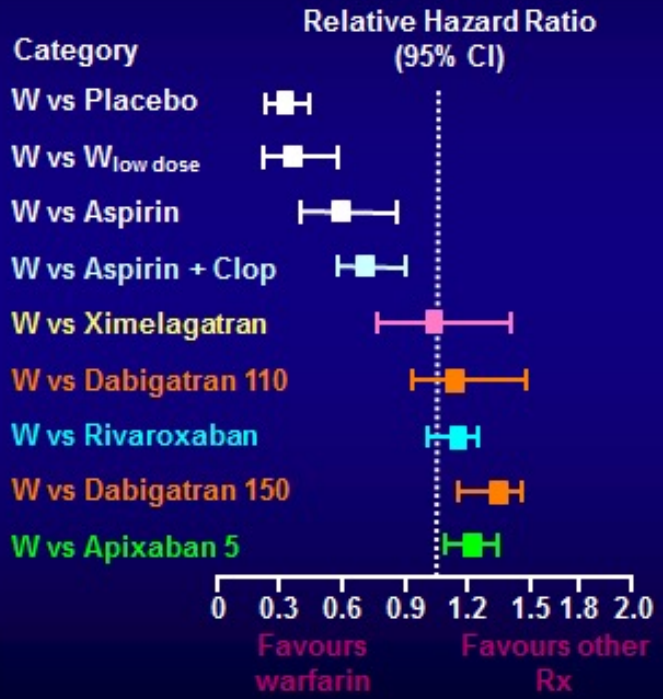
(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	Patients (*n*=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

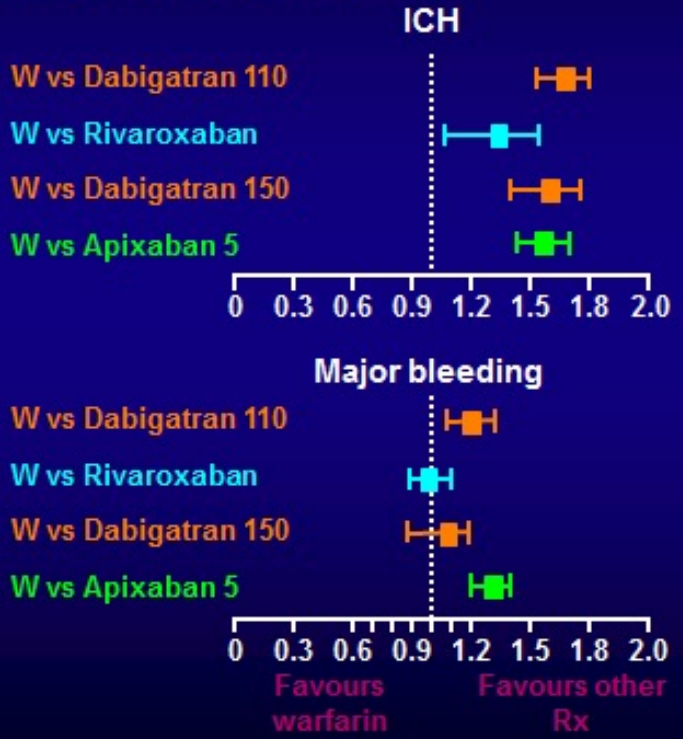
HASBLED

	Score	Bleeds per 100 patient-years
Low	0	1.13
	1	1.02
Intermediate	2	1.88
	3	3.74
High	4	8.70

Stroke Prevention
Anticoagulant Effect

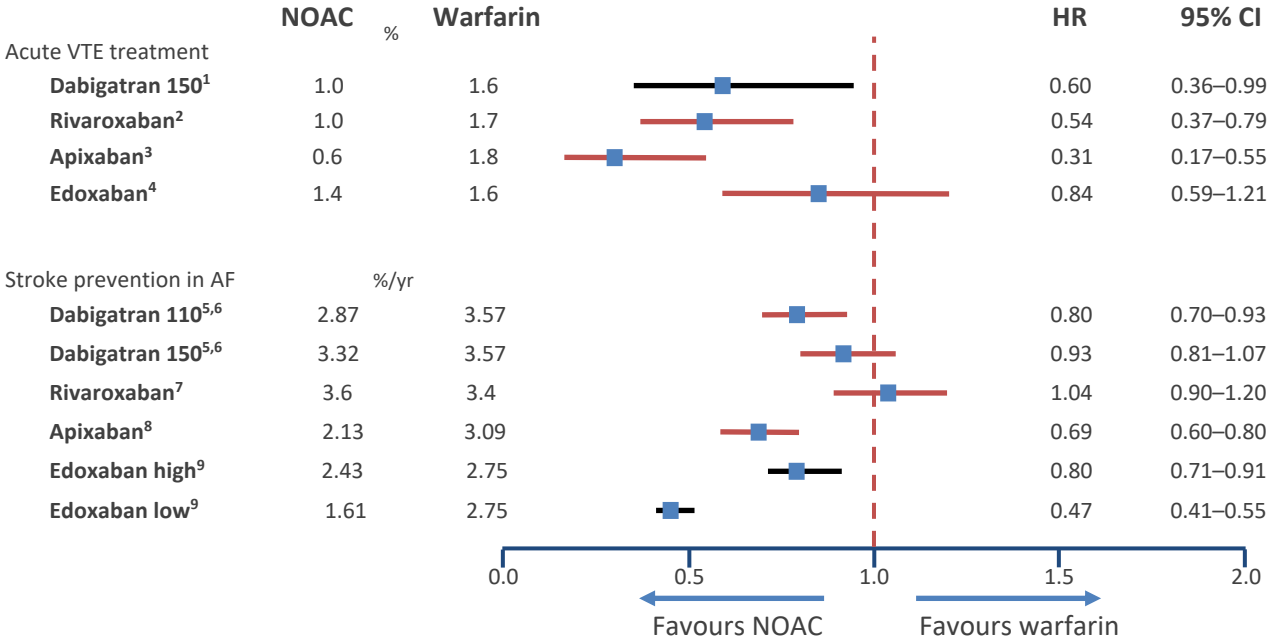
Meta-analysis of stroke or systemic embolism





Modified from Camm AJ. EHJ 2009;30:2554-5

Major bleeding rates: OACs vs VKA in phase III trials



For information purposes only, no cross trial comparisons can be drawn – adapted from references

References:
1 Schulman S et al. *Circulation* 2014;129:764–772.
2 Prins MH et al. *Thromb J* 2013;11:21.
3 Agnelli G et al. *N Engl J Med* 2013;369:799–808.
4 Hokusai-VTE Investigators et al. *N Engl J Med* 2013;369:1406–1415.
5 Connolly S et al. *N Engl J Med* 2009;361:1139–1151.
6 Connolly S et al. *N Engl J Med* 2010;363:1875–1876.
7 Patel MR et al. *N Engl J Med 2011*;365:883–891.
8 Granger CB et al. *N Engl J Med* 2011;365:981–992.
9 Giugliano RP et al. *N Engl J Med* 2013;369:2093–2104.

Risk tools validated in AF

HAS-BLED[33]	
Hypertension – uncontrolled (>160 mmHg systolic)	1
Abnormal renal function (SCr ≥200 μmol/L or dialysis or transplantation) or abnormal hepatic function[b]	1 or 2
Stroke history	1
Bleeding history or predisposition to bleeding (eg, anemia and bleeding diathesis)	1
Labile INRs	1
Elderly (>65 years old)	1
Drugs or alcohol (antiplatelet agents or NSAIDs; alcohol ≥8 units per week)	1 or 2
Maximum score	9

Potentially modifiable risk factors

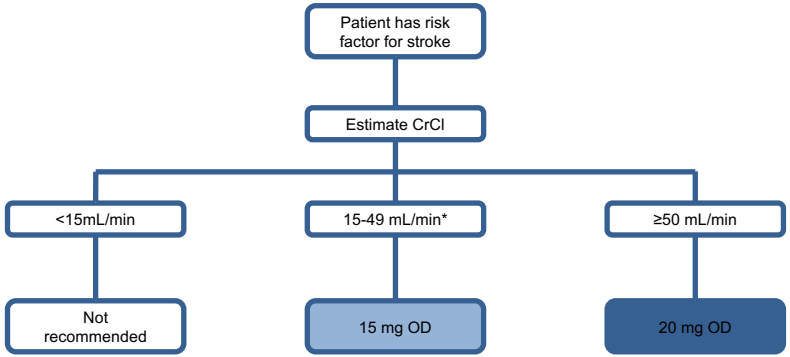
Risk factors that may mandate a dose reduction of DOAC

Ref: *International Journal of General Medicine* 2016: **9;** 337–347

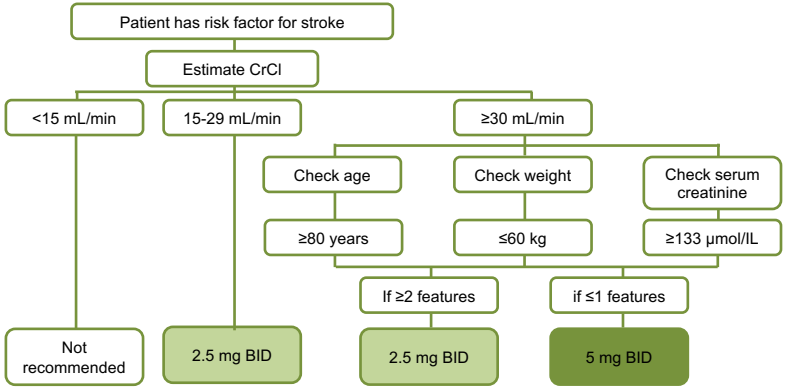
Dose adjustments in AF[1-4]

Refer to individual medicine SmPC's for dose reduction criteria

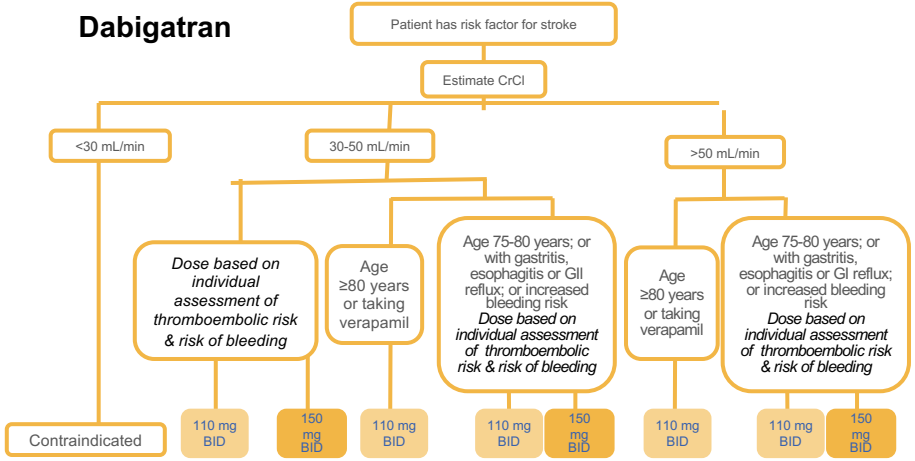
Rivaroxaban



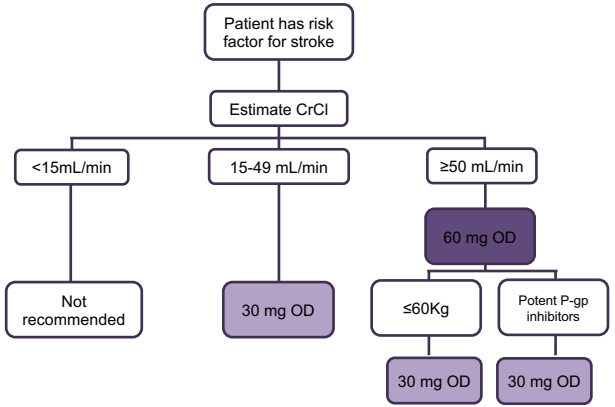
Apixaban



Dabigatran



Edoxaban



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3 Dabigatran SmPC; 4. Edoxaban SmPC.

Aid memoir to dose reduction of DOACs

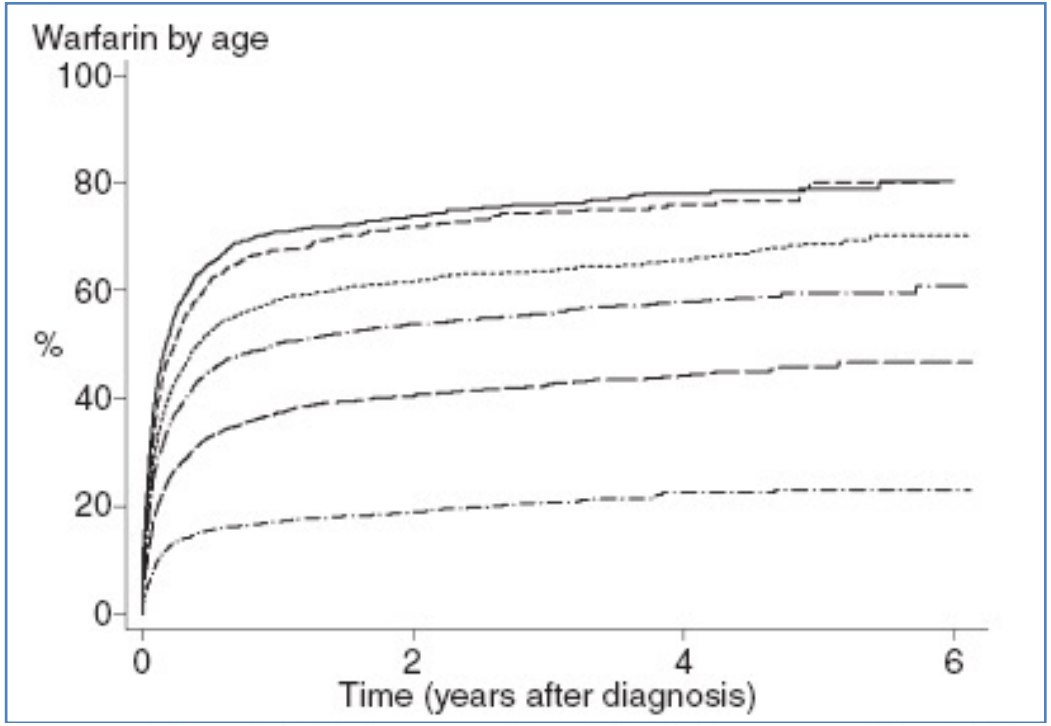
A Age

B Body weight

C Creatinine clearance

D Drugs

Older AF patients less likely to get warfarin



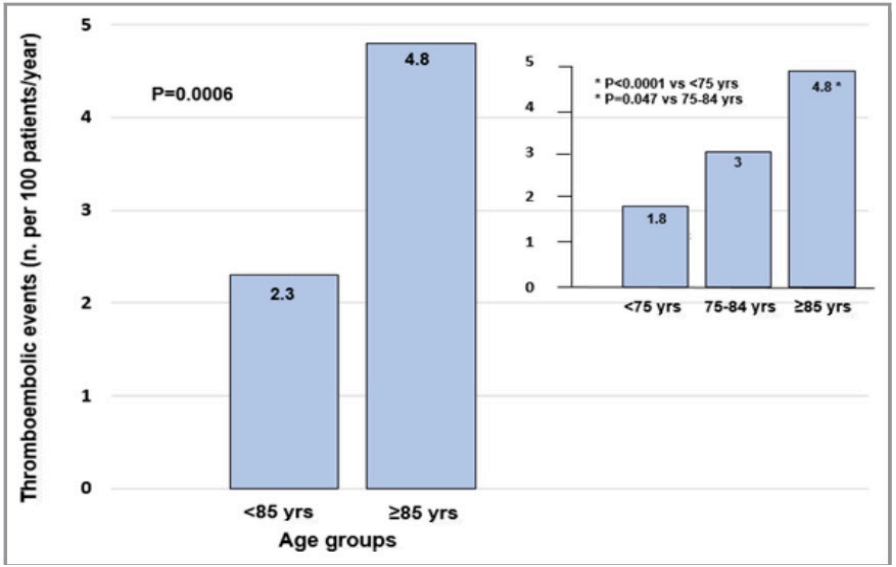
Younger

Older

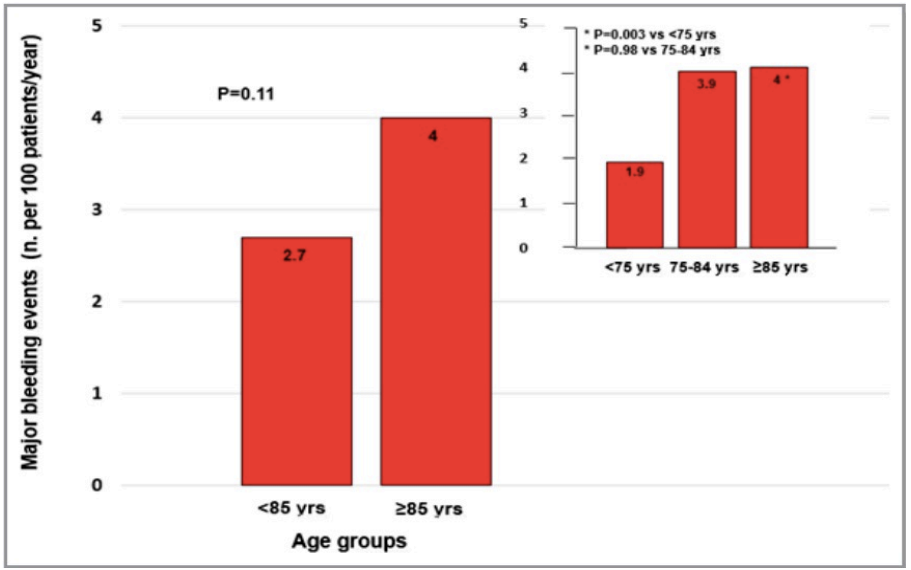
Gallagher AM *et al. J Thromb & Haem* 2008;6:1500-1506

Is age just a number?

Data from PREFER in AF
(PREvention oF thromboembolic events–European Registry in Atrial Fibrillation)



Incidence of thromboembolic events (stroke/TIA/systemic embolism) at 1 year in patients aged <85 and ≥85 years and rates of thromboembolic events according to 3 age strata (<75, 75–84, and ≥85 years)



Incidence of major bleeding at 1 year in patients aged <85 and ≥85 years and rates of major bleeding according to 3 age strata (<75, 75–84, and ≥85 years).

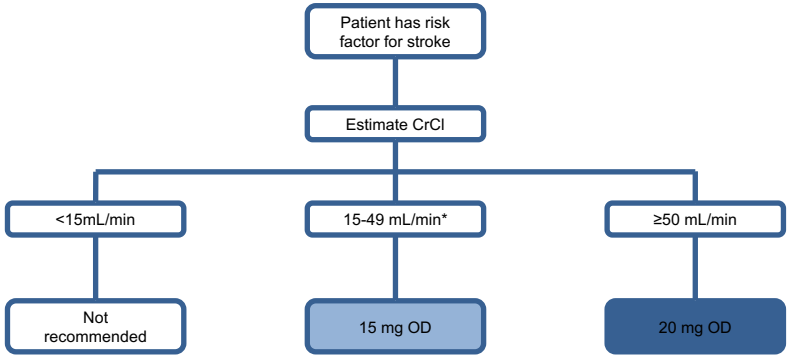
Ref: J Am Heart Assoc. 2017; 6:e005657

Dose adjustments in AF[1-4]

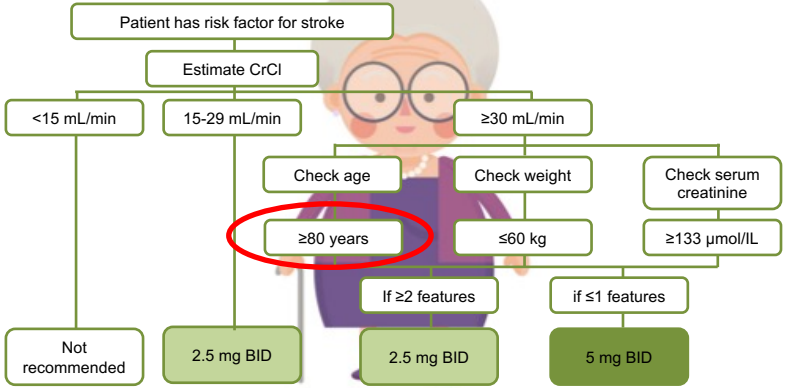
Refer to individual medicine SmPC's for dose reduction criteria

A - AGE

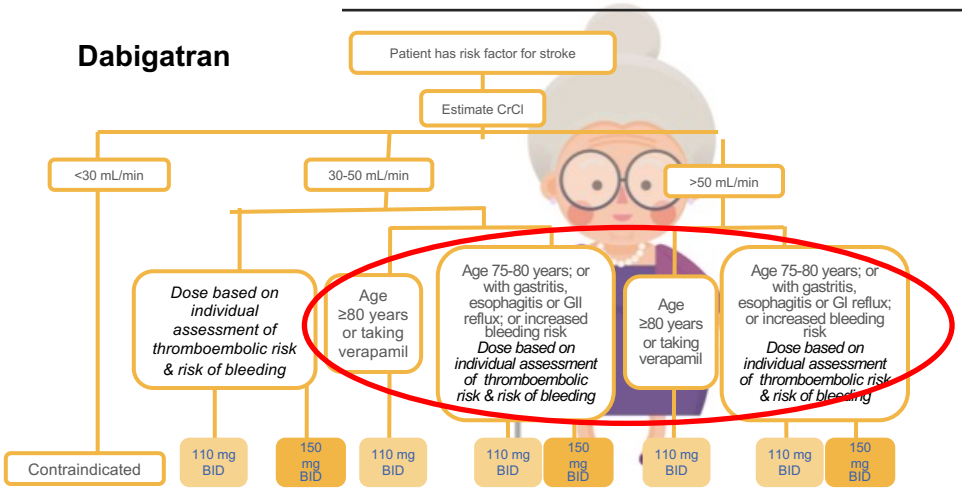
Rivaroxaban



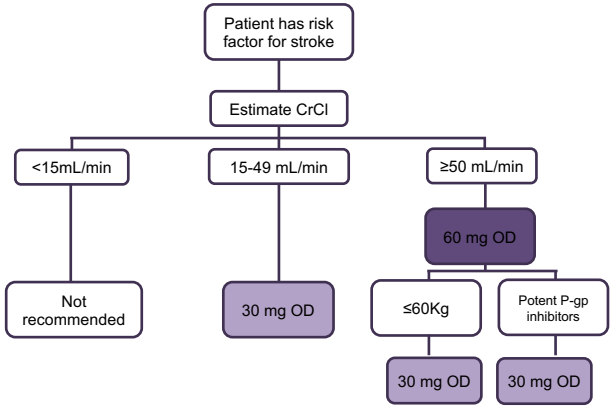
Apixaban



Dabigatran



Edoxaban



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3 Dabigatran SmPC; 4. Edoxaban SmPC.

B – Body weight

- Weight at borderlines – 59kg to 61kg
- Which NOACs to dose reduce
- Study demonstrating increase bleed risk associated with lower body weight[1]
  - Consider dose reduction if BMI < 18.5kg/m^2

    (noting this may be unlicensed)

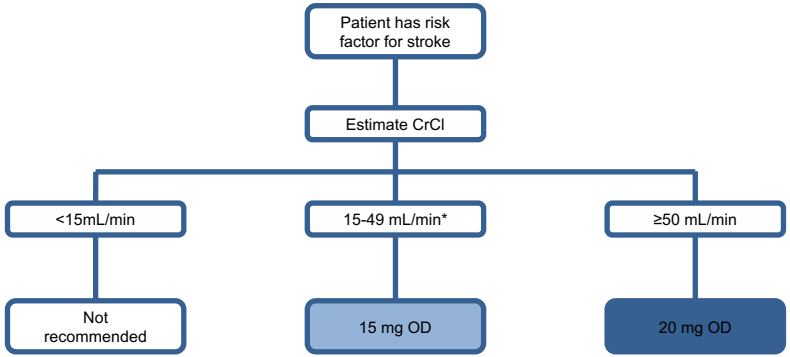
[1]Heart Rhythm http://dx.doi.org/10.1016/j.hrthm. 2016.12.036

Dose adjustments in AF[1-4]

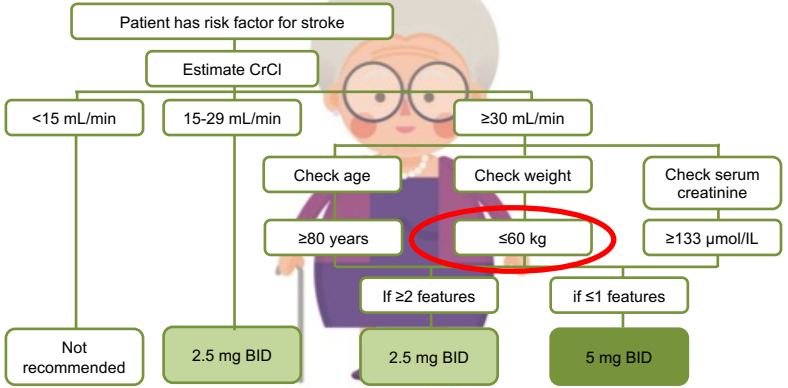
Refer to individual medicine SmPC's for dose reduction criteria

B - Body Weight

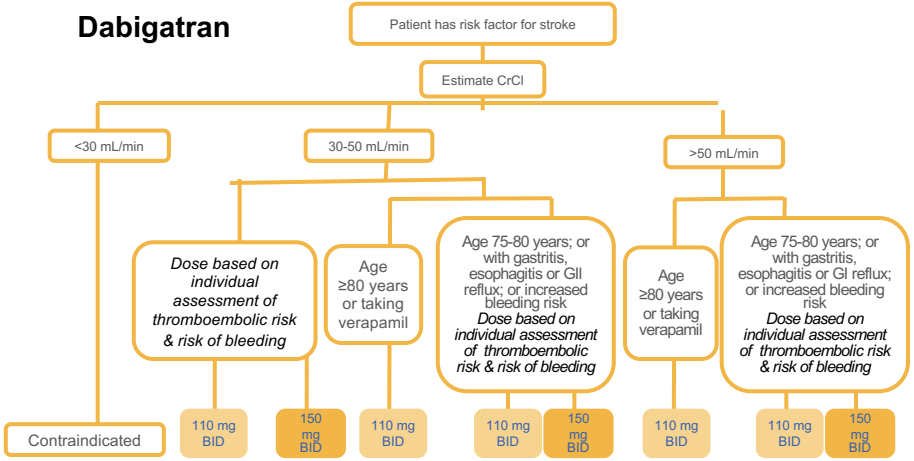
Rivaroxaban



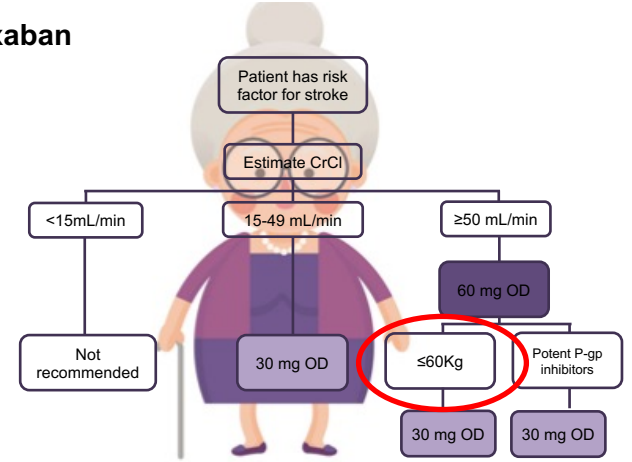
Apixaban



Dabigatran



Edoxaban



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C – Creatinine clearance

Drug Safety Update

MHRA

Advice for healthcare professionals:

- MHRA has received reports and queries related to the choice of renal function estimate used when prescribing medicines for patients with renal impairment
- for most drugs and for most adult patients of average build and height, estimated Glomerular Filtration Rate (eGFR) should be used to determine dosage adjustments
- creatinine clearance (CrCl) should be calculated using the Cockcroft-Gault formula (see below) to determine dosage adjustments for:
    - direct-acting oral anticoagulants (DOACs)

Ref: Drug Safety Update volume 13, issue 3: October 2019: 3

How to assess renal function?

- DOAC trials used CrCl to estimate renal function, hence SPCs recommend this method
- eGFR may overestimate for ages > 65yrs, CrCl may underestimate for ages >65yrs[1]

Cockcroft–Gault:

$$\text{CrCl} = \frac{\{(140 - \text{age}) * (\text{weight in kg}) * (\text{F})\}}{\text{Serum creatinine}}$$

Where F = 1.23 if male or 1.04 if female

[1] MacCallum PK et al. BMJ Open 2013;3:e003343.

Calculating Creatinine Clearance

Cockcroft–Gault:

$$\text{CrCl} = \frac{\{(140 - \text{age}) * (\text{weight in kg}) * (F)\}}{\text{Serum creatinine}}$$

Where F = 1.23 if male or 1.04 if female

- Age 81 years
- Female
- Serum creatinine 120 µmol/l
- Weight 55 kg
- Height 5 feet 7 inches (170 cm)
- eGFR 52 ml/min

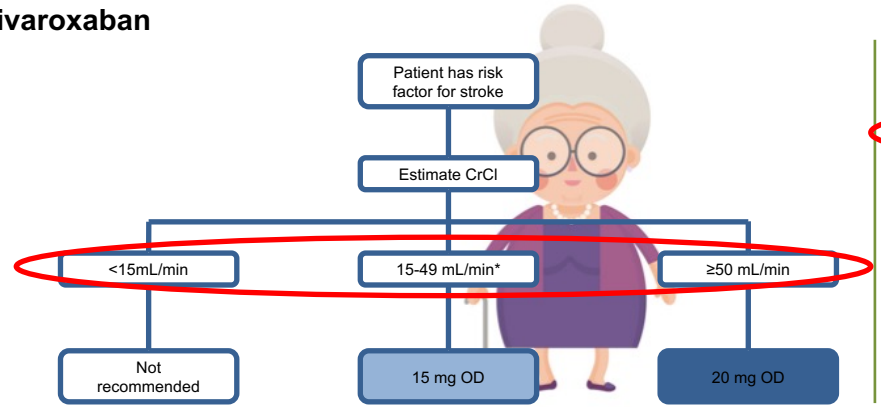
CrCl: using CG 33 ml/min

Dose adjustments in AF[1-4]

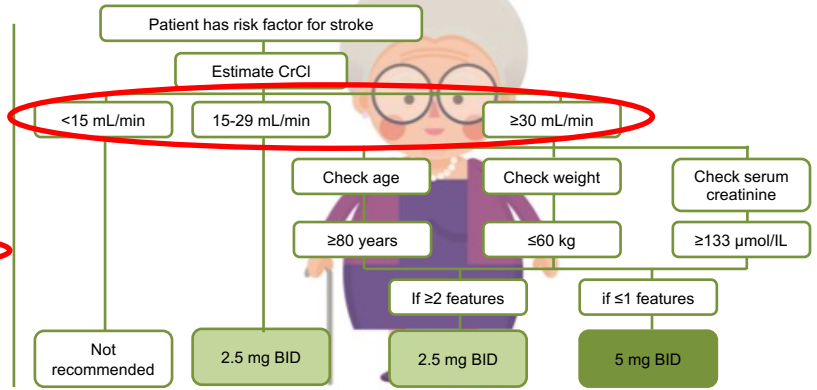
Refer to individual medicine SmPC's for dose reduction criteria

C - Creatinine clearance

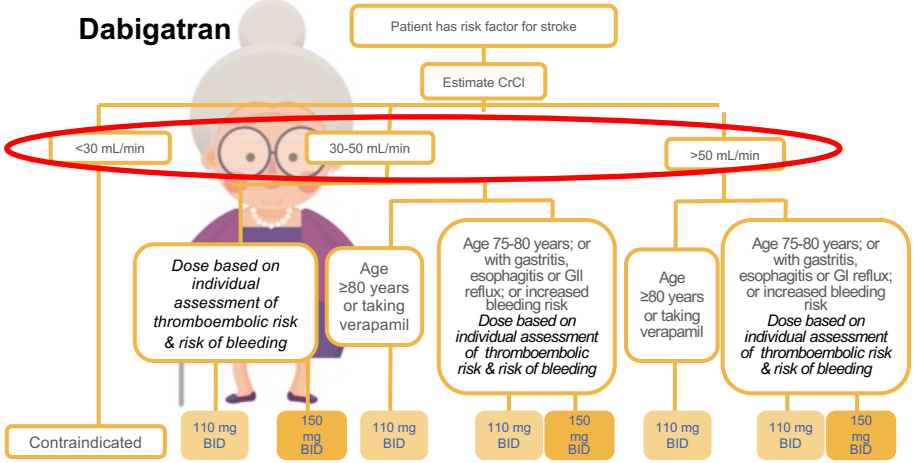
Rivaroxaban



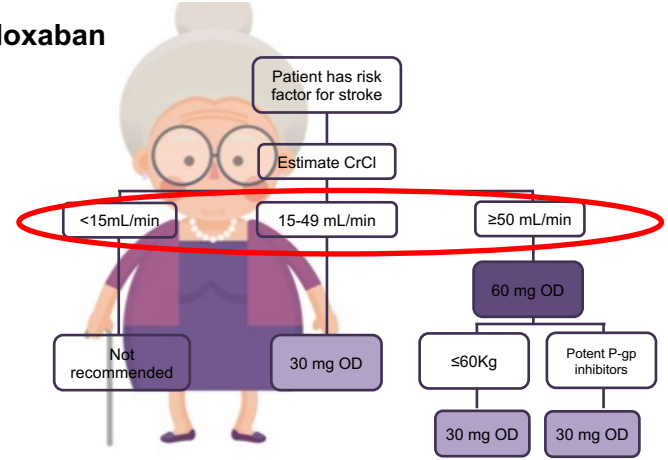
Apixaban



Dabigatran



Edoxaban



1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3 Dabigatran SmPC; 4. Edoxaban SmPC.

D - Drug Interactions

1. Pharmacodynamic (functional) interactions
   - Enhance the physiological affects through synergistic impact
   - Any antithrombotic drug or drug that increases bleeding risk

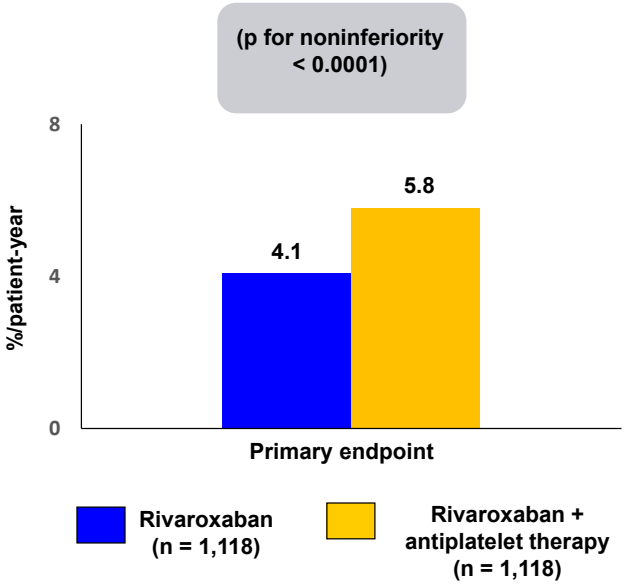
2. Phamacokinetic interactions
   - Drugs that increase or decrease drug exposure
   - Inhibitors or inducers of P-glycoprotein

AFIRE

#ESCCongress

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients with atrial fibrillation and stable coronary artery disease were randomized to rivaroxaban 15 mg daily (10 mg daily for creatine clearance 15-49 ml/min) versus rivaroxaban/antiplatelet therapy.



RESULTS

- Primary efficacy endpoint: all-cause mortality, myocardial infarction, stroke, unstable angina requiring revascularization, or systemic embolism occurred in 4.1%/patient-year in the rivaroxaban monotherapy group compared with 5.8%/patient-year in the rivaroxaban/antiplatelet therapy group (p for noninferiority < 0.0001)
- Primary safety endpoint: major bleeding (ISTH criteria) occurred in 1.6%/patient-year in the rivaroxaban monotherapy group compared with 2.8%/patient-year in the rivaroxaban/antiplatelet therapy group (p = 0.01)

CONCLUSIONS

- Among patients with atrial fibrillation and stable coronary artery disease, rivaroxaban monotherapy vs. rivaroxaban/antiplatelet therapy was noninferior for ischemia and superior for bleeding

Yasuda S, et al. N Engl J Med 2019;Sep 2:[Epub]

Drug–drug interactions with DOACs

Table 3 Effect of drug–drug interactions and clinical factors on NOAC plasma levels ('area under the curve')

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[SmPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 × 75 mg if CrCl 30–50 mL/min)	+100%[136]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPc]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC
Others					
Naproxen	P-gp competition; pharmacodynamically increased bleeding time	No data yet	+55%[139]	No effect	No data yet
H2B; PPI; Al-mg-hydroxide	GI absorption	Minus 12–30%	No effect	No effect[SmPc]	No effect[140]
St. John's wort	P-gp/BCRP and CYP3A4/CYP2J2 inducers				

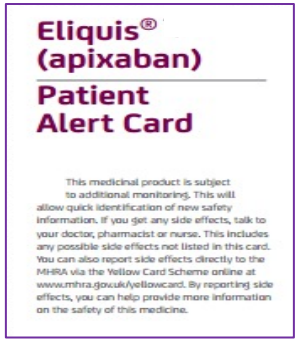
Taken from:
The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation 2018. European Heart Journal (2018) 39, 1330–1393

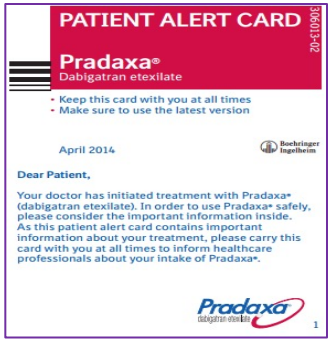
Accessed (in Feb 2020) at:
https://www.escardio.org/Guidelines/Recommended-Reading/Heart-Rhythm/Novel-Oral-Anticoagulants-for-Atrial-Fibrillation

Other considerations for reducing bleeding risk

Patient Alert Cards - audit

- Anticoagulated patients should carry their alert card at all times
- Alert cards are included as part of patient guides
- Do all your patients have them?





When to stop NOACs before a planned surgical intervention

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban		Rivaroxaban	
	No important bleeding risk and/or local haemostasis possible: perform at trough level (i.e. ≥12h or 24h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24h	≥48h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 50–80 ml/min	≥36h	≥72h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 30–50 ml/min §	≥48h	≥96h	≥24h	≥48h	no data yet	no data yet	≥24h	≥48h
CrCl 15–30 ml/min §	not indicated	not indicated	≥36h	≥48h	no data yet	no data yet	≥36h	≥48h
CrCl <15 ml/min	no official indication for use							

Low risk: surgery with low risk of bleeding. High risk: surgery with high risk of bleeding § many of these patients may be on the lower dose of dabigatran (i.e. 2x110 mg/d) or apixaban (i.e. 2x2.5 mg/d), or have to be on the lower dose of rivaroxaban (15 mg/d).

Open access Original research

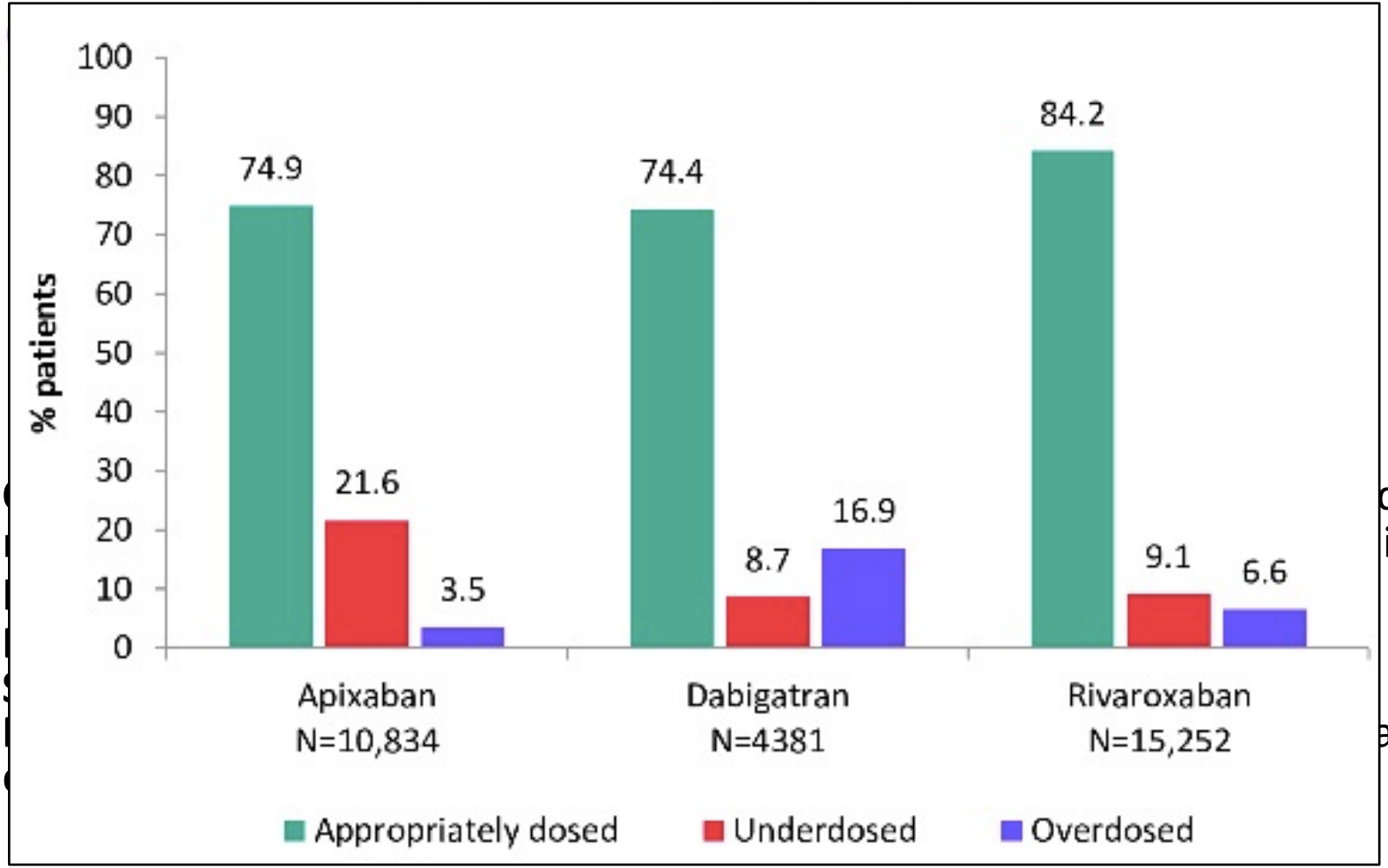
BMJ Open

Appropriateness of initial dose of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial fibrillation in the UK

Luis Alberto García Rodríguez,[1] Mar Martín-Pérez,[1] Pareen Vora,[2] Luke Roberts,[3] Yanina Balabanova,[2] Gunnar Brobert,[4] Samuel Fatoba,[5] Kiliana Suzart-Woischnik,[2] Bernhard Schaefer,[2] Ana Ruigomez[1]

- **Objective** To evaluate the appropriateness of the initial prescribed daily dose of non-vitamin K antagonist oral anticoagulants (NOACs) according to label in patients with non-valvular atrial fibrillation (NVAF) in the UK.
- **Design** Population-based cross-sectional study.
  Setting UK primary care.
  Population 30 467 patients with NVAF and a first prescription for apixaban, dabigatran or rivaroxaban between January 2011 and December 2016.

BMJ



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Final review for Doris

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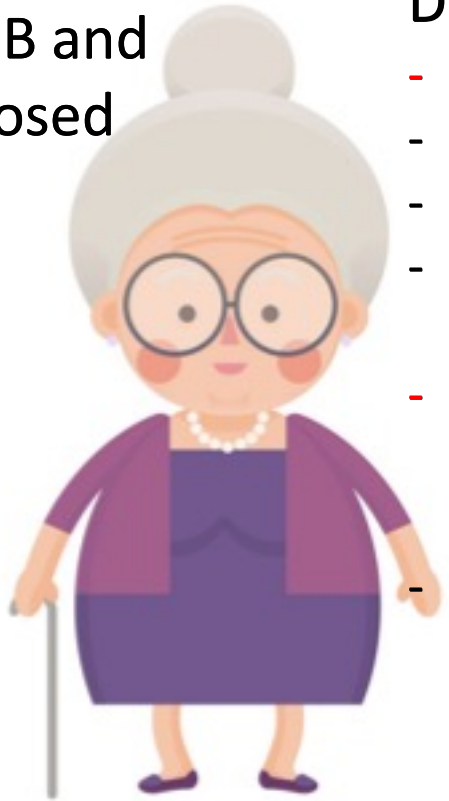

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Questions

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March 25th / 26th 2020