DOACs: The practical side

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Overview

- Focus on stroke prevention in AF
- Getting the dose right
- Case study: back to basics
- Case study: uncertainties

Warm up

1. Mrs RD: 81 years old, AF. PMH: HF, smoker, HTN, COPD
   Creatinine 140, Wt 85kg, CrCl = 30-37ml/min;
   Treating with apixaban:
   a) 5mg BD or
   b) 2.5mg BD

2. Mr GF: 73 years old, new PE. PMH: CKD4, T2DM, HTN
   Cr 190, Wt 65kg, CrCl=28ml/min; Rx rivaroxaban
   15mg BD for 3 weeks then:
   a) 20mg OD or
   b) 15mg OD

Warm up

3. Miss AD, 76yo, PAF treated with amiodarone.

   PMH: HTN, T2DM, diverticulosis. Cr 97, Wt 66kg, CrCl=48ml/min. Treating with dabigatran:

   a) 150mg BD or
   b) 110mg BD or
   c) 75mg BD

4. Mr JB: 68yo, DVT 1992 and 2001, lifelong warfarin (2-3). Cr 83, Wt 93kg, CrCl=85-99ml/min, switch to apixaban:

   a) 5mg BD or
   b) 2.5mg BD

DOAC dosing

- More drugs
- More indications
- More criteria for dose reduction
- More errors?!

- In our quest for more accessible, convenient oral anticoagulation, **“we are now faced with […] a tyranny of choice”** [1]

1 Czuprynska J et al. *Br J Haematol* 2017;178:838-851

Dosing in NVAF

	Dabigatran[1]	Apixaban[2]	Edoxaban[3]	Rivaroxaban[4]
Standard dose	150mg BD	5mg BD	60mg OD	20mg OD
Reduced dose	110mg BD	2.5mg BD	30mg OD	15mg OD
Criteria for dose reduction	1. Age≥80 2. On verapamil 3. Consider ↓dose: • Reflux/gastritis • Age75-80 • CrCl 30-50ml/min • "Bleed risk"	**≥2 of:** • Age ≥80 • Body wt ≤60kg • Cr ≥133µmol/L **Or** CrCl 15-29ml/min	**≥1 of:** • CrCl 15-50ml/min • Body wt≤60kg • On ciclosporin, dronedarone, erythromycin, ketoconazole	CrCl 15-49ml/min
CI / NR	CrCl <30ml/min	---------- CrCl <15ml/min ----------		

1. Dabigatran SmPC. Available at www.medicines.org.uk;
2. Apixaban SmPC. Available at www.medicines.org.uk;
3. Edoxaban SmPC. Available at www.medicines.org.uk;
4. Rivaroxaban SmPC. Available at www.medicines.org.uk.

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Dosing in VTE

Dose	Dabigatran[1]	Apixaban[2]	Edoxaban[3]	Rivaroxaban[4]
Acute	LMWH ≥ 5/7	10mg BD 7/7	LMWH ≥ 5/7	15mg BD 21/7
Standard	150mg BD	5mg BD	60mg OD	20mg OD
Reduced	110mg BD	---n/a---	30mg OD	15mg OD
Criteria for dose reduction	1. Age≥80 2. On verapamil 3. Consider ↓dose: • Reflux/gastritis • Age75-80 • CrCl 30-50ml/min • "Bleed risk"		**≥1 of:** • CrCl 15-50ml/min • Body wt≤60kg • On ciclosporin, dronedarone, erythromycin, ketoconazole	CrCl 15–49 mL/min if bleeding risk is assessed to outweigh risk for recurrent VTE
> 6 months	No change	2.5mg BD	No change	10mg OD or 20mg OD
Caution		CrCl 15-29ml/min		CrCl 15-29ml/min
CI / NR	CrCl <30ml/min	---------- CrCl <15ml/min ----------		

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Is the licensed dose the right dose?

- Danish registry – reduced dose DOAC vs standard VKA[1]
- Stroke & systemic embolism
  - NS increase with apixaban (HR 1.19: 95%CI 0.95–1.49)
  - NS decrease with rivaroxaban/dabigatran (HR 0.92 / 0.93)
- Unable to confirm off/on-label dose reduction
- Significant selection bias
  - E.g. overall mean age=73: lowest mean age = warfarin (71), highest mean age = apixaban (83)
  - Higher CHADS-VASc & HAS-BLED scores and renal disease codes predicted apixaban use

1. Nielson PB, Skjøth F, Søgaard M et al. BMJ 2017;256:j510

Is the licensed dose the right dose?

- ORBIT II AF prospective registry (US)
  - ❖ 5,738 patients: 1 in 8 on wrong dose
  - ❖ **3.4% overdosed** = ↑ risk all-cause mortality: HR 1.91 (95%CI 1.02–3.60)
  - ❖ **9.4% underdosed** = ↑ risk of CV hospitalisation: HR 1.26 (95% CI 1.07–1.50) with no benefits seen in major bleeding (rates similar)

- Predictors of "off-label" dosing
  - High stroke (CHA2DS2-VASc) & bleed (ORBIT) risk
  - Moderate renal impairment (CrCl = 30-50ml/min)

1. Steinberg et al. J Am Coll Cardiol 2016;68:2597–2604

Is the licensed dose the right dose?

- Yao et al (US insurance database):
  - 14,865 patients: ?renal indication for DOAC dose reduction
  - **Overdose** (4%) = ↑ risk of major bleeding (HR 2.19; 95% CI 1.07–4.46) + similar stroke risk
  - **Underdose** (12%) = ↑ stroke risk with apixaban (HR 4.87; 95% CI 1.3–18.26) + similar bleeding rate
    - No statistical difference for dabigatran/rivaroxaban
  - 50% of apixaban underdosing in age > 80 years old

1. Yao X et al. J Am Coll Cardiol 2017;69(23):2779-2790

A potential problem…

Single centre study in the US[1]:

- 13.3% patients on reduced dose DOAC
- Overall, only 43.3% met criteria for dose reduction
  - 54.7% on rivaroxaban
  - 32.2% on dabigatran
  - **10.7% on apixaban** …met criteria for dose reduction

1. Barra M et al. *Am J Med* 2016;129:1198-1204

A potential problem…

- Apixaban 2.5mg bd
  - 4.7% of all apixaban patients in ARISTOTLE[1]
  - 24% to 55% of all apixaban prescriptions in England[2]
    - (includes all indications!)

1 Granger CB et al. NEJM 2011;365:981-992
2 Data from Openprescribing.net Feb-18 (consistent from Jan-17 to Feb-18) accessed 08MAY2018

Case One – Back to Basics

Case 1 - Opportunity calls

- Mrs EE – 93yo
- Warfarin for stroke prevention in AF
- PMH: T2DM, stroke, hyperthyroidism
- DH:
  - AM: metformin, carbimazole
  - PM: citalopram, warfarin

- CHA_2DS_2-VASc = ….

  a) 4 **b) 5** **c) 6**

- HAS-BLED = ….

  a) 1 **b) 2** **c) 3**

Stroke risk

CHA_2DS_2-VASc components	Score
Heart failure / LVSD	1
Hypertension	1
Aged ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior ACS, PAD, IHD)	1
Aged 65–74 years	1
Sex category (i.e. female)	1
Maximum score	9

Total score	Adj. stroke rate (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Camm et al. Eur Heart J 2010;31:2369–2429

Bleeding risk on OAC

Letter	Clinical characteristic[1]	Score
H	Hypertension	1
A	Abnormal renal / liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
	Maximum score	9

Total score	Major bleeds /100 PY[2]
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50
6	ND
7	ND
8	ND
9	ND

Validated in DOACs with similar intervention threshold of 2%/yr[3]

1 Pisters R et al. *Chest* 2010;138(5):1093-1100
2 Lip GY et al. *J Am Coll Cardiol.* 2011;57(2):173-180
3 Lip GY et al. *Am J Med* 2018; 131(5): 574.e13 – 574.e27

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Case 1 – But she's fine on warfarin…

- Requires DN for INR phlebotomy (wheelchair bound)
  - Poor veins

- Unstable INRs – over last 6 months:
  - 3 failed samples (poor veins)
  - Six INRs >3 (four >5), nine INRs <2
  - Admission for INR >10 (Sept 2015)
  - retest every 7-14 days
  - **TTR = 37%**

- Daughter refills dosette box weekly to include warfarin

Time in Therapeutic Range (TTR)

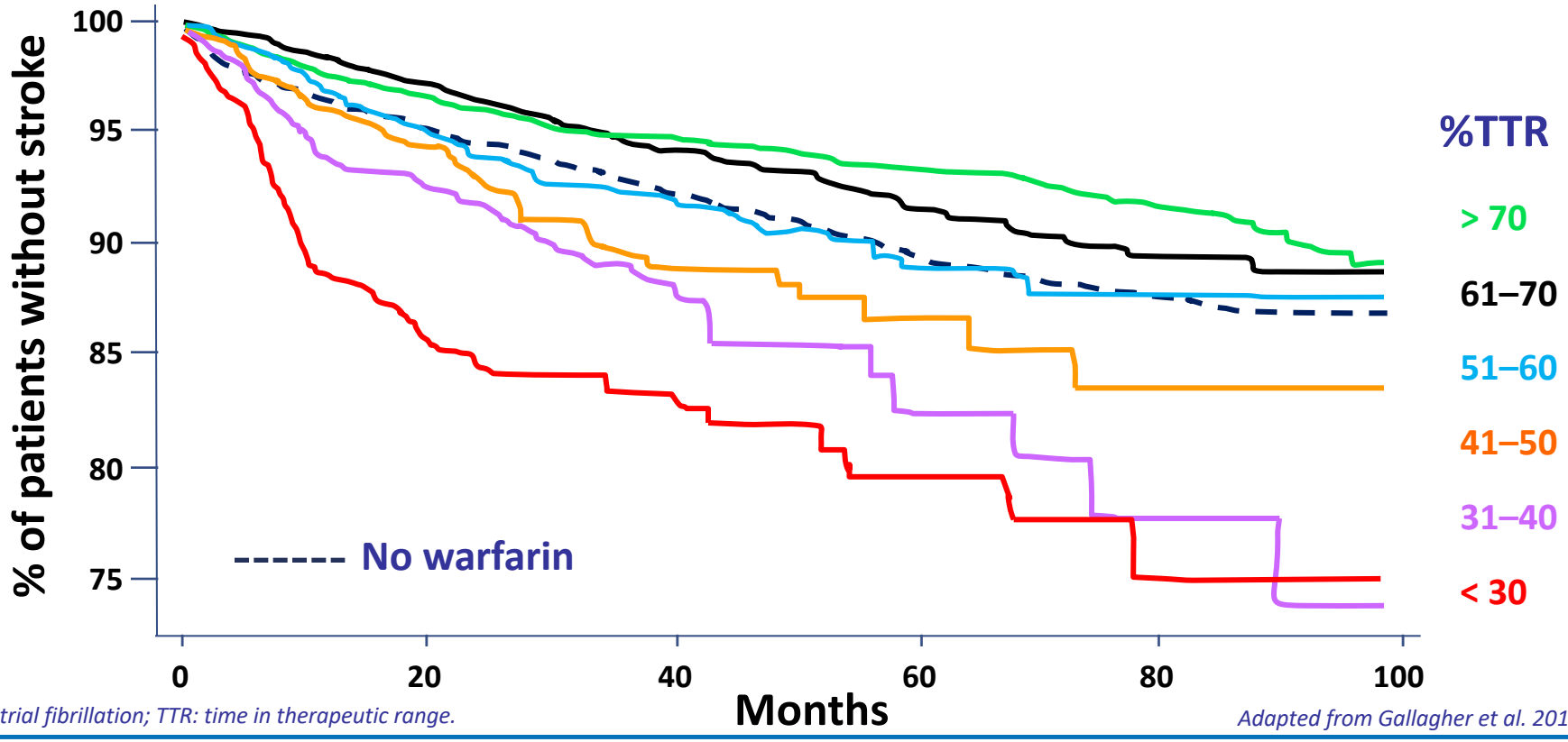
Q: What is a good TTR, who should be switched?

- Reduction in major bleeding significantly higher for DOACs vs VKA when TTR<66% (vs TTR>66%)
- Efficacy benefits heterogeneous: unable to compare
- Not identified TTR where warfarin > DOAC (efficacy or safety)

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

TTR Correlates with Stroke

Stroke survival in 37,907 AF patients – UK General Practice Research Database (27,458 warfarin users and 10,449 not treated with an antithrombotic)[1]



AF: atrial fibrillation; TTR: time in therapeutic range.

Adapted from Gallagher et al. 2011[1].

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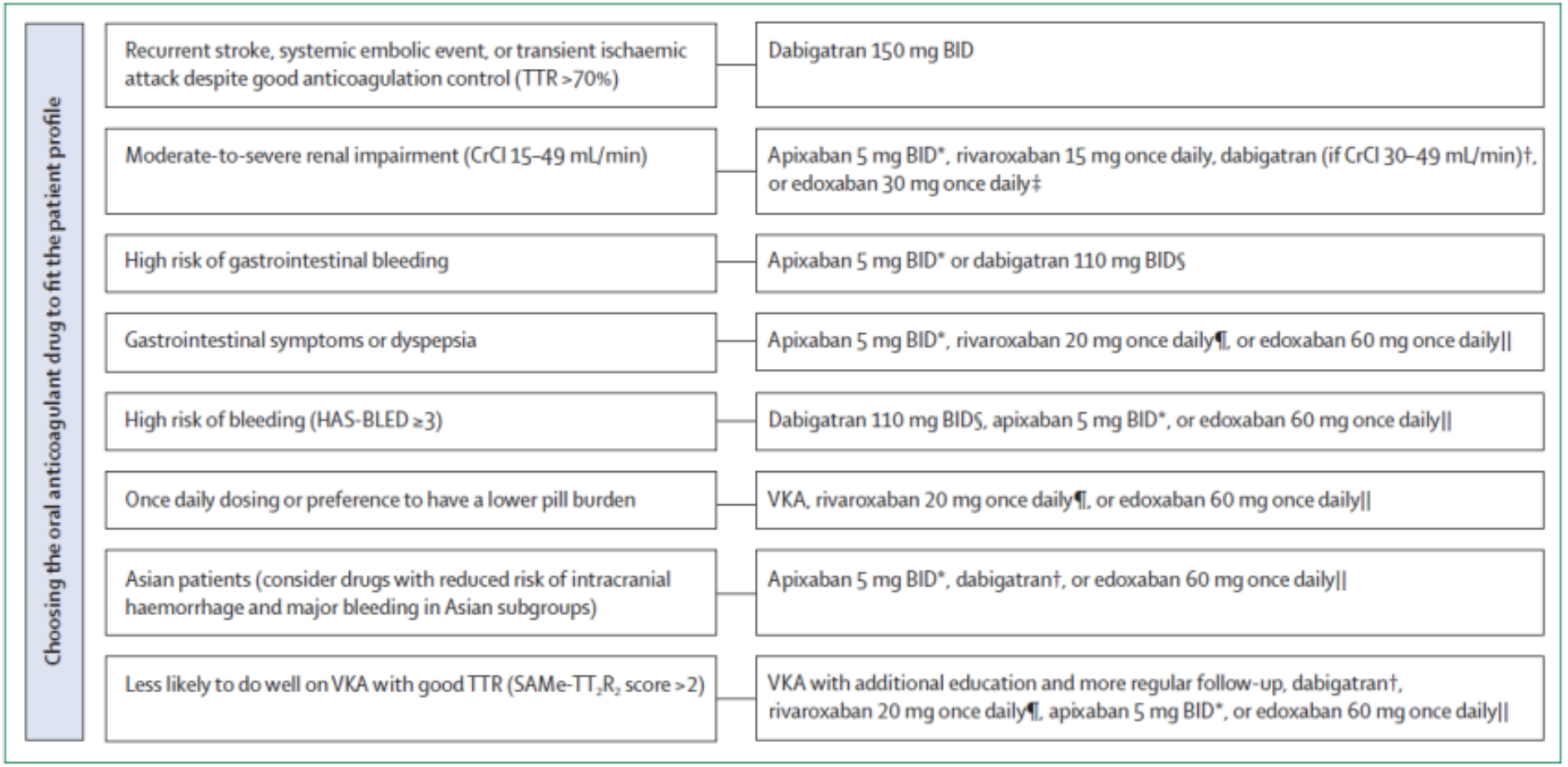
1. Gallagher et al. *Thromb Haemost* 2011;106:968–977.

Case 1 – Making the change

- Cr 71, CrCl = 47.3ml/min
- 68.5kg

1. Which drug?
2. Which dose?
3. Does it matter?
4. How to decide?

So how do I decide?



Freedman B, Potpara TS, Lip GY. *Lancet* 2016;388:806-817

Reviews & Prescribing Decision Aids

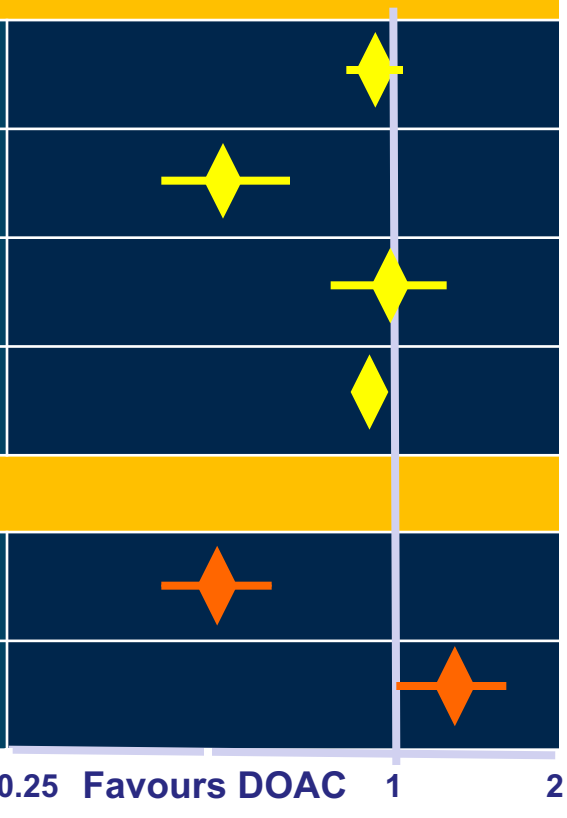
- Freedman B, Potpara TS, Lip GY. *Lancet* 2016;388:806-817
- Savelieva I, Camm AJ. *Clin Cardiol* 2014;37(1):32-47
- Shields AM, Lip GY. *J Internal Medicine* 2015;278(1):1-18
- Millar CM, Laffan MA. *Clinical Medicine* 2017;17(3):233-244

- **EHRA Practical Guide 3ed:**
  Steffel J et al. *Eur Heart J* 2018;39(16):1330-1393

- Keele University decision support tool
  https://www.anticoagulation-dst.co.uk/

AF – Efficacy & Safety: 4-Trial Meta-analysis

Measure	Pooled DOAC Events /Total	Pooled Warfarin Events /Total	Risk Ratio	95% CIs	p	Outcome
Efficacy						
Ischaemic Stroke	665 /29292	724 /29221	0.92	0.83-1.02	0.10	
Hemorrhagic stroke	130 /29292	263 /29221	0.49	0.38-0.64	<0.0001	
Myocardial Infarction	413 /29292	432 /29221	0.97	0.78-1.20	0.97	
All-cause mortality	2022 /29292	2245 /29221	0.90	0.851-0.95	0.0003	
Safety						
Intracranial hemorrhage	204 /29287	425 /29211	0.48	0.39-0.59	<0.0001	
Gastrointestinal bleeding	751 /29287	591 /29211	1.25	1.01-1.55	0.043	



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Estimating Renal Function[1,2]

- Use Cockcroft – Gault equation as per pivotal studies
  - Avoid MDRD / CKD-EPI based eGFR
- What weight?
  - Actual weight used in trials
  - Extremes of weight & age poorly represented
  - Avoid IBW –risk of underdose
  - Consider adjusted body weight in extreme of weight

1 http://www.lambethccg.nhs.uk/news-and-publications/meeting-papers/south-east-london-area-prescribing-committee/Documents/Cardiovascular%20Disease%20Guidelines/Creatinine%20clearance%20guidance%20July%202017.pdf

2 https://www.sps.nhs.uk/articles/what-factors-need-to-be-considered-when-dosing-patients-with-renal-impairment-2/

Switching – complicated?

- SmPCs: (AF) switch from VKA when…

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
INR threshold	< 2.0	< 2.0	≤ 2.5	≤ 3.0 (≤ 2.5 in VTE)

- Simplified approach in non-high risk maintenance VKA* patients, e.g.

INR	Instruction
< 2.0	Start immediately
2.0 to 2.9	Start following day
3.0 to 3.5	Start in 2 days
> 3.5	Recheck INR 2-3 days

*Not phenprocoumon!

Case 1 – Outcome

- No frequent venepuncture required
  - ↓ burden on district nurse service
  - ↓ pain from difficult phlebotomy

- Dosette from pharmacy
  - Remove daughter's commitment to weekly refill

Case Two - Uncertainties

Case 2 - Uncertainties

- Mr RG: 62yo male, truck driver, PAF, HTN, T2DM
- Switched from warfarin to rivaroxaban 20mg once daily

Assessments			
CHA_2DS_2-VASc		2	
HAS-BLED		0	
Wt	**143kg**	Height	180cm
BMI	**44.1kg/m^2**		
Cr	100µmol/L	CrCl (adj)	98ml/min
Hb	146g/L	ALT	26

Medication
Atorvastatin
Metoprolol
Metformin
Candesartan
Omeprazole
Amlodipine
Humulin I
Beconase nasal

Can we use a DOAC?

ISTH SSC[1]

- Avoid DOACs if BMI >40 or Wt >120kg
  - Available evidence suggests peaks may be reduced & clearance may be increased; risk of underdosing
- If using DOACs in above, check drug-specific plasma peak & trough
  - by anti-Xa (a/r/e) or dTT (d), or mass spec (any).
  - If out of range, change to VKA rather than dose adjust

1. Martin K, Beyer-Westendorf J, Davidson BL et al. J Thromb Haemost 2016;14:1308-1313

What do we know?

Phase II/III data:

- Clear associated between weight/BSA & Vd
- Effect on plasma levels is modest
  - <25% reduction in plasma concentrations [1]
- SPCs: “No dose adjustment necessary”

1 De Caterina R, Lip GY. *Clin Res Cardiol* 2017;106(8):565-572

Pivotal Studies

- No exclusions based on weight / BMI
- > 15% subjects >100kg

- Efficacy & safety endpoints consistent in patients >100kg
  - Also shown in meta-analysis[1]

- Limitations: sparsity of outcome data beyond:
  - Weight >120kg
  - BMI >40kg/m^2

1 van Es N et al. *Blood* 2014;124(12):1968-1975

Kinetic studies

Specifically recruiting >120kg:

- Apixaban: 30% and 20% reduction in Cmax & AUC [1]
  - Weight: mean 137kg SD +/- 18.3kg
- Rivaroxaban: No change in Cmax [2]
  - Weight: Mean 132kg SD +/- 10kg

Local data (2017) – No troughs below expected range [3]

- 30 patients (26 SPAF)
  - rivaroxaban (19) & apixaban (11)
  - Weight: mean 137kg SD +/- 22kg

1 Upreti VV et al. *Br J Clin Pharmacol* 2013;76:908-916
2 Kubitza D et al. J Clin Pharmacol. 2008;48(11):1366-1367
3 Mahir Z et al. unpublished data

"Real World Data"

Dresden registry (prospective) – AF [1]

- 9.8% patients with BMI >35kg/m^2
  - Highest BMI 57.2kg/m^2
- No dose adjustments
- Cardiovascular outcomes, major bleeding and all-cause mortality consistent with general study population

- Beware the BMI paradox!

1 Titti L et al. *Int J Cardiol* 2018;262:85-91

Case 2 – more complications

Back to Mr RG…

- Continue rivaroxaban 20mg od (with main meal!)
- Assess trough plasma level

But 2 months later…

- Chest pain – calls 999
- ECG in ambulance: STEMI
- Transferred for PPCI

What do we know?

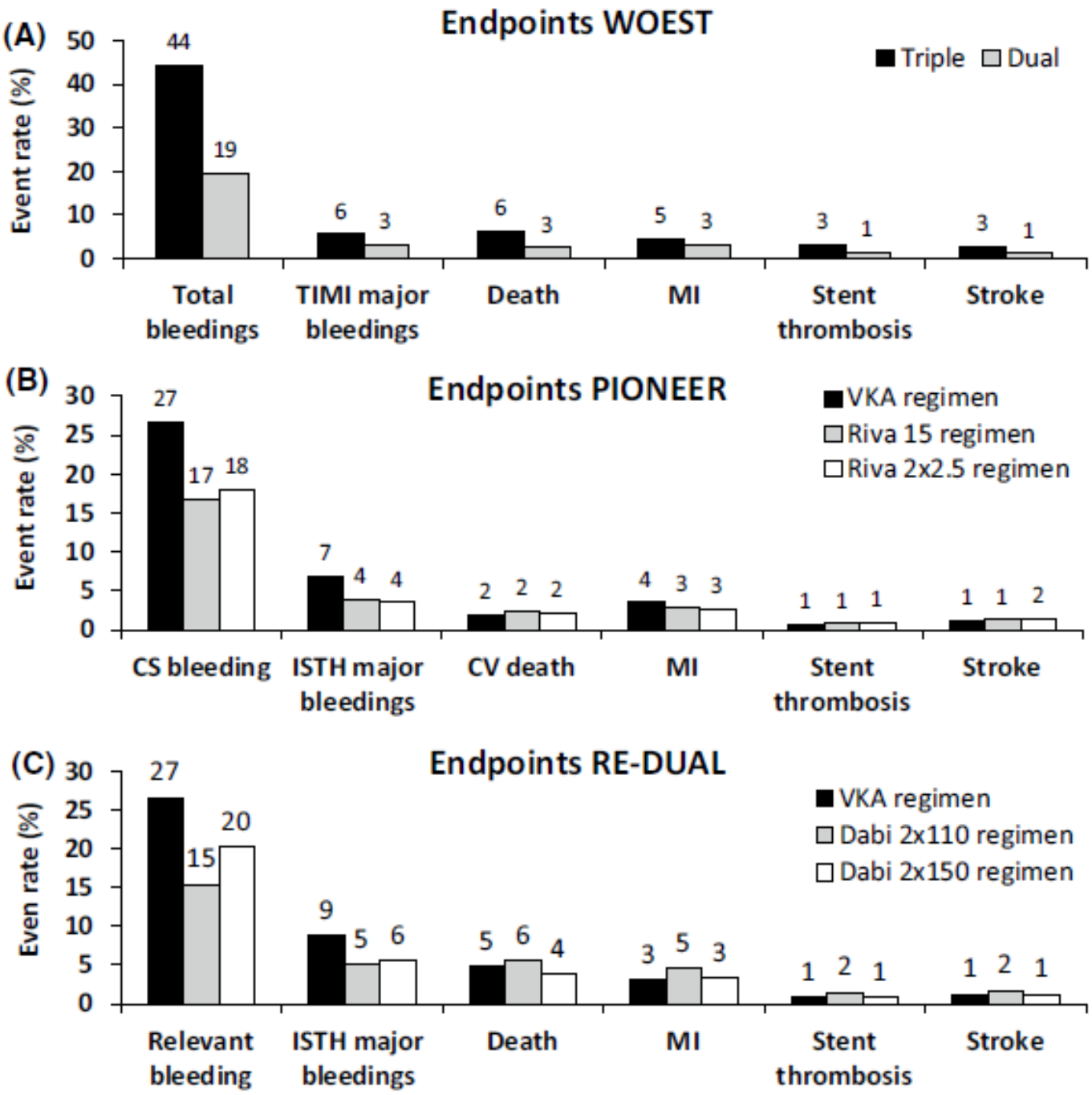
- DAPT is indicated post ACS & PCI
  - Superior to aspirin alone[1]
  - Optimal duration varies
- DAPT is inferior to OAC for stroke prevention in AF[2]
- Triple therapy significantly increases bleeding risk
  - VKA + aspirin + clopidogrel = >3 fold ↑ in non-fatal+fatal bleeding[3]

1 Roffi M et al. *Eur Heart J* 2016;37:267-315
2 Conolly S et al. *Lancet* 2006;367:1903-1912
3 Hansen ML et al. *Arch Int Med* 2010;170:1433-1441

Prospective studies

- WOEST
- PIONEER AF-PCI
- RE-DUAL PCI

- Single versus double antiplatelet
  - In combination with OAC
- Primary endpoint is “safety” only (bleeding)
  - Underpowered for “efficacy” (MACE, stent thrombosis etc)



Duerschmied D et al. *Clin Res Cardiol* 2018 epub ahead of print

WOEST

- OAC = VKA
- 65% RRR in all bleeding
  - 19.4% and 44.4% respectively
  - High rates driven by minor bleeds
  - TIMI major 3% and 6% respectively (n.s.)
- Composite efficacy endpoint
  - Death, MI, revascularisation, stroke, stent thrombosis
  - HR 0.6 (95%CI 0.38-0.94)
  - Underpowered
- Non-standard OAC: INR target 2.0

Dewilde W et al. *Lancet* 2013;381:1107-1115

PIONEER AF-PCI

- Triple therapy: VKA (2-3) + DAPT
  - 1, 3 or 12 months DAPT: 50% = 12mo
- Rivaroxaban
  - 15mg od (2/3 AF dose) + $P2Y_{12}$
  - 2.5mg bd (ACS dose) + DAPT
- 40% RRR bleeding with rivaroxaban arms
  - Composite TIMI major + clinically significant bleeding
- 12% STEMI
  - Bleeding: Riva15 = 14.6%, Triple therapy = 36%
- $P2Y_{12}$ choice: 5% ticagrelor, <2% prasugrel

RE-DUAL PCI

- Triple therapy: VKA (2-3) + DAPT
  - 1 month BMS, 3 months DES
- Dabigatran + $P2Y_{12}$
  - 150mg bd – 30% RRR bleeding
  - 110mg bd – 50% RRR bleeding
- Bleeding: ISTH Major bleed + CRNM bleed
- $P2Y_{12}$ choice: 12% ticagrelor
- Non-inferiority for composite secondary endpoint
  - MI, Stroke, SSE, death, unplanned revasacularisation
  - Combined analysis of both dabigatran arms vs warfarin

Summary

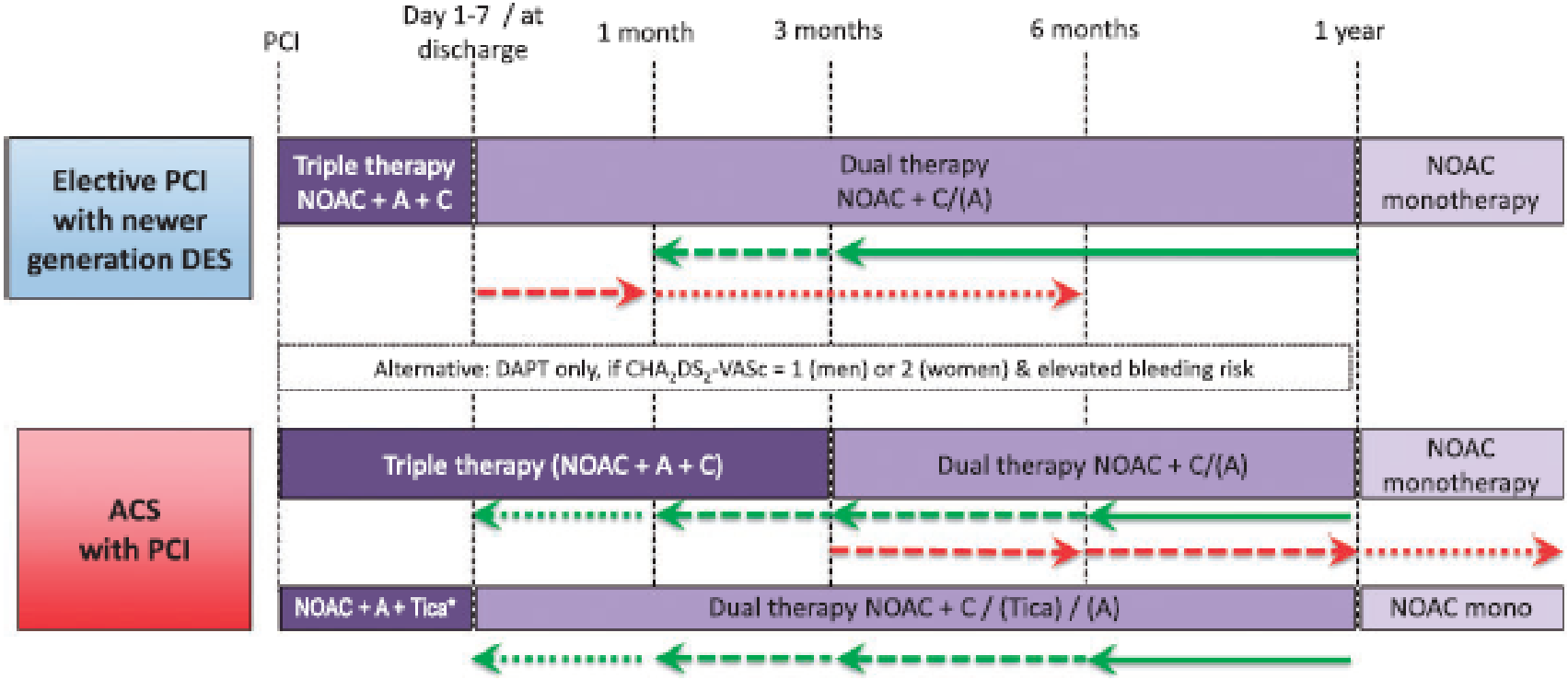
- Non-guideline INR targets
  - WOEST INR target 2.0 (1.5 to 2.5)
  - PIONEER / RE-DUAL target 2.5 (2.0 to 3.0)
  - ECS: 2.25 (2-2.5) [1]
- Not powered for efficacy
  - But no signal for loss of efficacy
- Rivaroxaban doses not proven in SPAF
  - Both dabigatran doses effective for SPAF
- Clear reduction in clinically significant bleeding
- All the evidence is for clopidogrel as $P2Y_{12}$ inh of choice
  - Registry data: increased bleeding with ticagrelor / prasugrel – avoid[1]

1 Steffel J et al. *Eur Heart J* 2018;39:1330-1393

Guidelines

- Constantly evolving
  - New antithrombotic strategies
  - New generation DES with shorter DAPT requirements
- Significantly reduced duration of triple therapy
- Practical advice
  - PPI throughout combined antithrombotic therapy (COGENT[1])
  - **Specify plan & duration prior to discharge[2]**

1 Bhatt D et al. *NEJM* 2010;363:1909-1917
2 Steffel J et al. *Eur Heart J* 2018;39:1330-1393



Factors to shorten combination therapy

- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE ≥140 if ACS)

Factors to lengthen combination therapy

- First-generation DES
- High atherothrombotic risk (scores as above ; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

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Steffel J et al. *Eur Heart J* 2018;39:1330-1393

Coming soon…

	AUGUSTUS	ENTRUST-AF-PCI	RT-AF	WOEST 2
Design	RCT	RCT	RCT	Prospective cohort registry
Primary endpoint	Safety	Safety	Safety	Efficacy & safety

Post 12 months

- Combination antithrombotics increased MB but no benefit on stroke or mortality
  - Post hoc analyses of pivotal DOAC studies in AF

- Retrospective cohort study[1]:
  - VKA + single antiplatelet in stable CAD (>12 months event free)
  - No reduction in MI or TE events
  - 50% increase in major bleeding

- Still a caveat in guidance for ***exceptionally high risk*** patients for recurrent MI / stent thrombosis

1 Lamberts M et al. *Circulation* 2014;129:1577-1585

What's the message?

- Right drug
- **Right Dose!!!**
  - Use Cockcroft-Gault CrCl calculation
- We are still exploring at the edge of the normal distribution (watch this space)
- Always have a plan for concomitant antiplatelets

Thank you for listening

London SCN AF Toolkit

http://www.londonscn.nhs.uk/publication/atrial-fibrillation-toolkit-for-london/

London SCN Excellence in anticoagulant care

http://www.londonscn.nhs.uk/publication/excellence-in-anticoagulant-care/


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