When And How To Use Dabigatran And Other New Agents

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Warfarin and AF

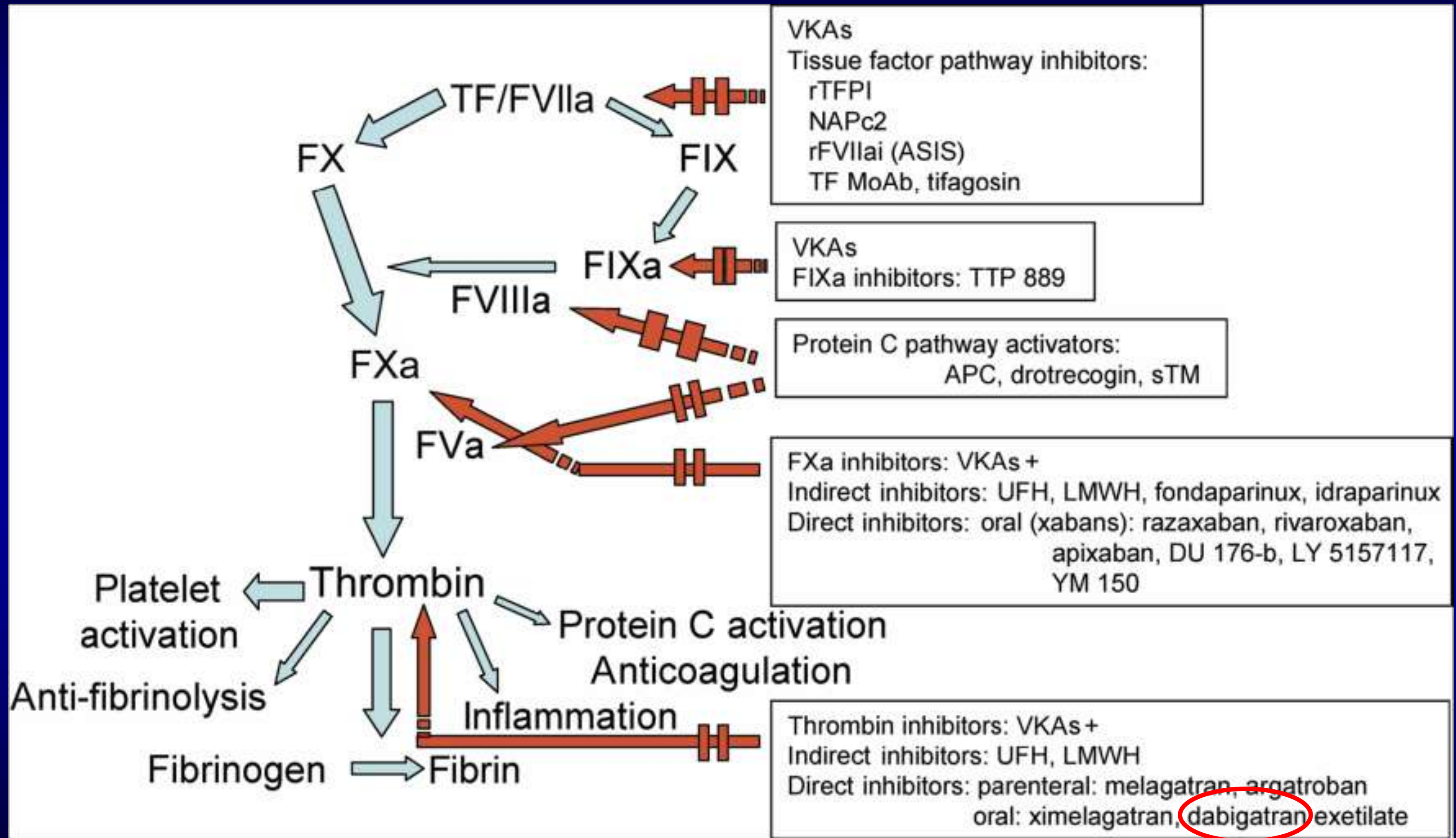
Warfarin (dose titrated to INR of 2 to 3):

- is the first-line anticoagulant treatment for prevention of stroke in patients with AF
- is exceptionally effective in stroke prevention in AF.

Wafarin

- Positive
  - Cheap
  - Vast experience
  - Effective if good control
- Negative
  - Monitoring / titration / Inconvenient
  - Doesn’t completely remove risk
  - Bleeding
  - Stigma

Anticoagulation Target



Are they better than warfarin?

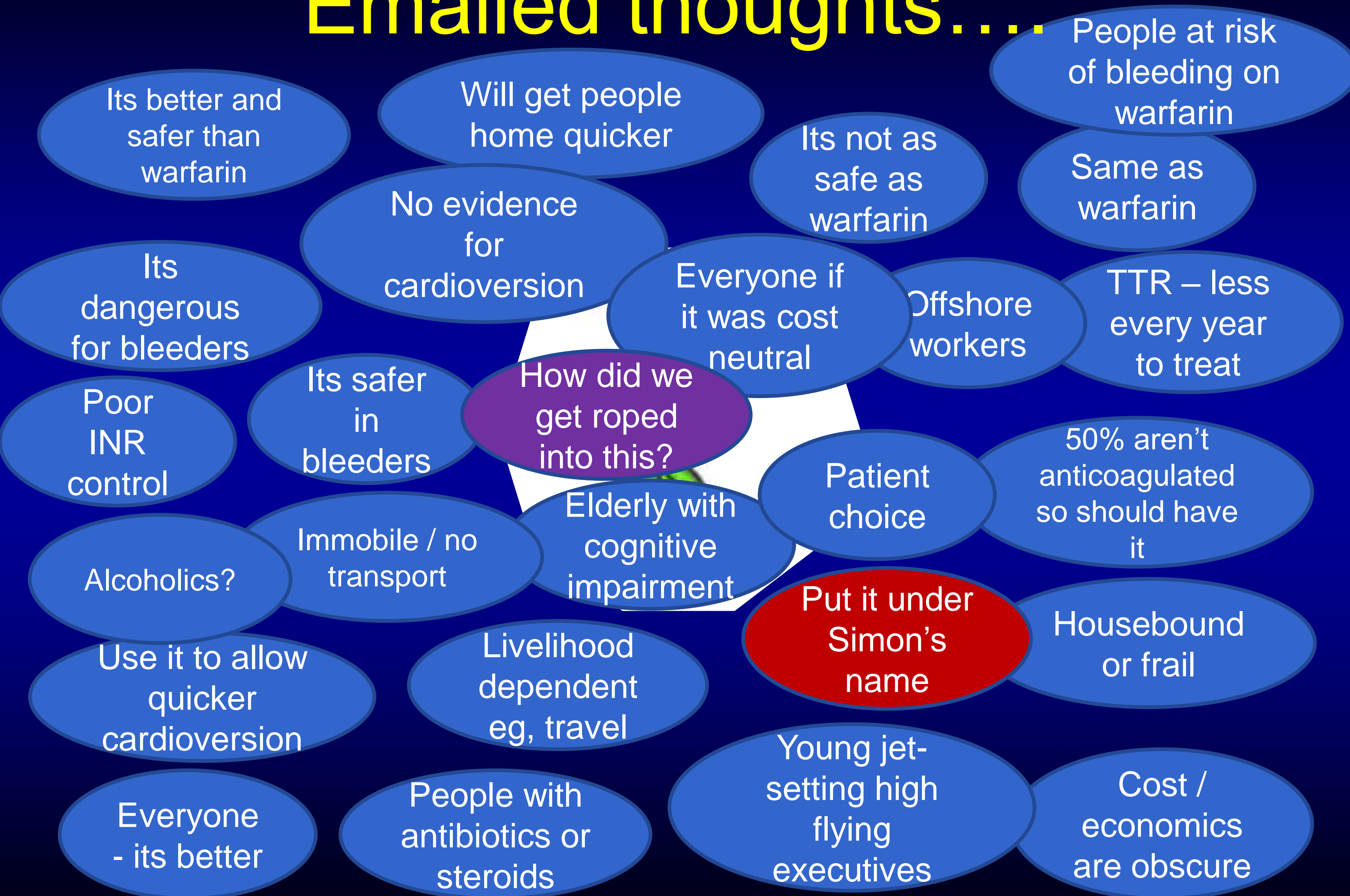
Background

- Recent local network opinion (Dabigatran)
- Volunteered to present consensus
  - Haematology / cardiology/ neurology
- Huge variation in opinion

Opinions

- Well read / relevant to their field / work
- Primary and secondary care
- Cardiology, haematology, neurology, stroke specialists
- All seen / debated same information
- Huge variation in opinions and thoughts
- Tendency to address the rare/ complex/ obscure cases for their specific area

Emailed thoughts….



General opinion

- Dabigatran is either better, worse or the same as warfarin
- Ideal patient for to have warfarin is: Elderly, cognitive impaired jet-setting young business executive with no transport, possibly alcoholic, who may or may not be at risk of bleeding
- Not a huge help really
- Clearly not everyone will agree

Data considered

- Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Study
- Various sub-studies
- Editorials derived from it

RE-LY

- 18 113 pts from 44 countries
- Designed as non-inferiority study
- Inclusion - atrial fibrillation and one of
  - Stroke / TIA
  - LV ejection fraction <40% or NYHA CCF ≥ 2
  - Age ≥ 75 years
  - Age ≥ 65 to 74 years plus
    - DM, hypertension, or coronary artery disease.

RE-LY

- Exclusion criteria
  - Valvular disease
  - CVA within 14 days or Severe CVA within 6 months
  - Previous bleed
  - Physician considers at risk of bleed

RE-LY

	D110	D150	Warfarin
Stroke (%)	1.53	1.11	1.69
Haemorrhagic stroke	0.12	0.10	0.38
Major bleed	2.71	3.11	3.36
Major GI bleed	1.12	1.51	1.02

All

- Significant?
- Small percentage but low risk already

$P < 0.05$

Opinions

- General thoughts
  - D 110 safer than warfarin, no better?
  - D 150 better than warfarin, as safe?
- Versus
  - Both non-inferior to warfarin

FDA view

- Concerned that D110 perceived as “Play it safe – less effective regime”
- “stroke prevention outweighs treatable bleeds”
- “No clear group where 110 better option”
- Unconvincing as safer bet

FDA – Role of D110 In high risk Group?

- Remember that bleeders excluded
- Looked at newly declared bleeders
- Re-bleed rate
  - D150 14 %
  - D110 16 %
  - Warfarin 12 %

“Exploratory data, not supportive in this group”

Cardioversions?

- Substudy data
- Is it safe / quicker way to get cardioversion done?

	D110	D150	Warfarin
Total	647	672	664
TOE	165 (25)	162 (24)	88 (13)
CVA	5 (0.77)	2 (0.30)	4 (0.60)
Major bleed	11 (1.7)	4 (0.6)	4 (0.6)

Only TOE significant / $P < 0.05$ but insufficiently powered to detect true difference

Cardioversion (2)

- But to further confuse things…
- “*additional oral anticoagulant to study drug*”*

	D110	D150	Warfarin
Pre DCCV	9.7	8.6	5.42
Post DCCV	19.8	16.8	13.7

P < 0.05 all

P < 0.05 D110

Other than aspirin, clopidogrel, heparins and drug randomised to

DCCV summary

- Safety / efficacy hard to assess

1. Underpowered to assess accurately
2. Inconsistent practice
3. Use of other anticoagulants

- All muddy the water

Guidelines

- Bleeders?
  - Evidence suggests possibly worse
  - Non-reversible
- Cardioversion
  - Impossible to assess whether worse, better or same as warfarin
- Ruled out a large area of suggested patients

Warfarin contraindications

- Bleeding disorder
- Recent CVA or TIA
- Uncontrolled BP
- Active bleeding
- Haemorrhagic retinopathy
- Intracranial haemorrhage
- Use of NSAID
- Chronic alcohol abuse
- Risk of GI bleed
- Planned surgery
- Pregnancy
- Psychiatric disorder or dementia
- Poor compliance / access to service

Almost all are a contraindication to anti-coagulation, not specifically warfarin

All excluded from trial

Newly declared may actually do worse – who knows?

Warfarin contraindications

- ~~Bleeding disorder~~
- ~~Recent CVA or TIA~~
- ~~Uncontrolled BP~~
- ~~Active bleeding~~
- ~~Haemorrhagic retinopathy~~
- ~~Intracranial haemorrhage~~
- ~~Use of NSAID~~
- Chronic alcohol abuse
- ~~Risk of GI~~
- ~~Planned surgery~~
- ~~Pregnancy~~
- Psychiatric disorder or dementia
- Poor compliance / access to service

? Fall, bleed or to chaotic to take tablets ?

Unable to manage?

Unable v unwilling?

Time in Therapeutic Range

- TTR
- If < 50% then little benefit from warfarin
- May be detrimental / harmful
- Cost analysis?

Cost and Economics

- Obscure, some guesswork and confusing
  - Calculated cost for warfarin
  - Health utility values
  - Cost of dabigatran
  - USA models

Other people's work

- West Yorkshire Cardiac Network
- Cost effectiveness D150 v warfarin
- Population in RE-LY
- Incremental cost per QALY by TTR
- < 56.9% £3895
- 56.9 – 65.4 £3615
- 65.4 – 72.4 £56,810
- >72.4 £245,910

Key points

- Many contraindications to anticoagulation not warfarin per se - ? LAA exclusion
- Cost effectiveness issue
- Robust data for specific patient cohort
- General guidance
- Not every possible constellation of comorbidities and circumstances
- Justifiable prescriber freedom

Others?

- Rivaroxaban – ROCKET-AF
  - ? Similar

- Apixaban - ARISTOTLE
  - Didn’t exclude bleeders

NETAG recommendation

Dabigatran is recommended for stroke prevention in non-valvular AF when:

- There is a contra-indication to warfarin due to clinical or logistical reason such that the patient is not expected to manage the variable dose regimen or the requirement for regular INR monitoring with warfarin therapy *
- Patients cannot achieve an INR Time-in-Therapeutic Range (TTR) with warfarin of at least 65%.
  - Calculated using a minimum of five consecutive months of warfarin therapy excluding the first month of warfarin therapy

Wrapping up

- Extensive discussion
  - Dr Andreas Wolff GPwSI
  - Will Horsley NETAG
  - Dr Patrick Kesteven haematology
  - Dr Simon James

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Questions?