Anticoagulation: From AF to CVD Risk Reduction

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Declaration of interests

- The Westcliffe Partnership has received funding from: Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Dawn, INRStar, Medtronic, Oberoi Consulting, Pfizer, Roche, Sanofi-Aventis, Servier.

- An advisor to: Anticoagulation UK, Arrhythmia Alliance, Heart Valve Voice, National Stroke Association, Syncope Trust

- A trustee of Thrombosis UK and AF Association

Who is this?

The Yellow Emperor

‘When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades’

Huang Ti Nei Ching Su Wen

As lessons from ancient history are still pertinent in today’s society, the saying of the Yellow Emperor is unfortunately still daily practice:

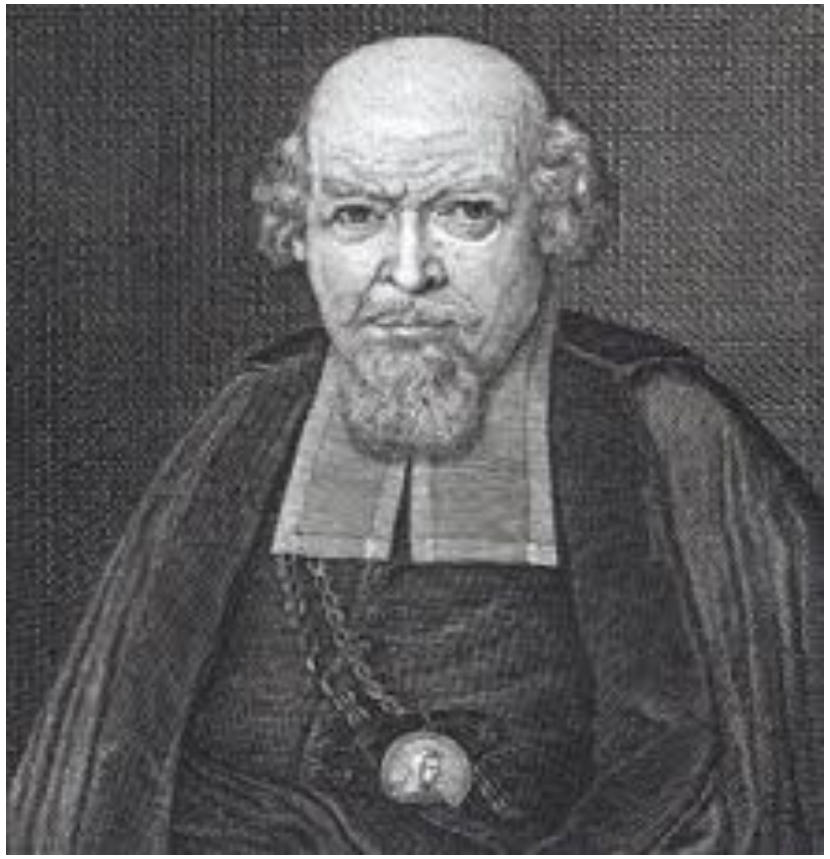
AF patients have a doubled mortality risk.

Who is this?

William Harvey

- 1628 Published *De Motu Cordis*
  - *Anatomical Account of the Motion of the Heart and Blood*
- Incited considerable controversy within the medical community.
- Some doctors affirmed they would "rather err with Galen than proclaim the truth with Harvey

Who is this?



Johann Jakob Wepfer

- 1658-Shows intracerebral haemorrhage is the cause of apoplexy
- Defined
  - sanguineous apoplexy
  - serous apoplexy
- In his declining years he suffered from a slow irregular pulse, breathlessness and orthopnoea
- Before his death asked his son in law, Johann Conrad Brunner to ensure he underwent a post mortem
  - Fluid in chest and abdomen
  - Enlargement of the heart
  - Hardening of the aorta and other major arteries
  - Diagrams are probably the first demonstration of atherosclerosis

Atrial Fibrillation-Stroke

- c 4000- Yellow Emperor
- c 1600's Sir William Harvey
  - observed chaotic motion of atria in open chest animal
- c 1650's Wepfer
- 1909 Sir Thomas Lewis
  - "irregular or fibrillatory waves and irregular ventricular response"
  - "absent atrial activity with grossly irregular ventricular response"

Atrial Fibrillation-Clinical Practice

Age (Yrs)	**Manitoba F/U Study**		**Framingham**	
	Prevalence	Incidence	Prevalence	Incidence
20	0	0	-	-
30	0	0	-	-
40	1.1	0.3	0.4	0
50	5.1	0.7	0.8	0.4
60	18.0	3.5	1.9	0.9
70	54.4	8.6	9.1	4.5
80	92.7	16.3	21.9	12.5
90	105	-	-	-

Incidence per 100,000 patient years. Prevalence per 1000,000 patients

Atrial Fibrillation-Stroke

- First half 20th century Harvey and Levine demonstrated AF with mitral stenosis increased the incidence of auricular (atrial) thrombosis
- Series of autopsy by Hey and Levine demonstrated that those with mitral stenosis and AF had increased thrombus compared with those without AF
- Further 1970s, the Framingham study was the first to demonstrate that the risk of stroke extended to those with AF and without mitral stenosis (although lower risk 5- vs 17 fold increase)
- 1980s brought early attempts to delineate the association between paroxysmal AF and stroke
- Connection between stroke and nonrheumatic AF led to trials evaluating the role of anticoagulation for stroke prevention (anticoagulation seen to be of value in rheumatic valvular AF)
- Adjusted-dose warfarin reduced stroke by 62%
  - absolute risk reductions 2.7% per year for primary prevention and
  - Absolute risk reduction 8.4% per year for secondary prevention.
  - Major extracranial bleeding was increased by warfarin therapy (absolute risk increase, 0.3% per year)
- Aspirin reduced stroke by 22%
  - Absolute risk reductions 1.5% per year for primary prevention
  - Absolute risk reduction 2.5% per year for secondary prevention

Warfarin

- 1920’s Dead cows on the prairies of north America and Canada died from internal bleeding
- Fed of spoilt sweet clover hay, contaminated with mould
- Frank W. Schofield and Lee M. Roderick showed removing the hay or transfusing blood from healthy cows aided recovery
- 1940: Link and colleagues show natural substance called coumarin was oxidized in mouldy hay to produce as dicoumarol
- 1945: Link considered using a coumarin derivative as a rodenticide, took 42 modifications to develop Warfarin that was marketed in 1948
- 1951:US Army inductee attempted suicide warfarin in rodenticide, but fully recovered after being treated with vitamin K in hospital
- 1955:US president Dwight D. Eisenhower prescribed the drug after a myocardial infarction
- 1978: John W. Suttie and colleagues demonstrated that warfarin disrupts vitamin K metabolism by inhibiting the enzyme epoxide reductase.

Atrial Fibrillation-Case Finding

SAFE study

- 50 practices, total 14,802 patients over 65 over 12 months
- 25 intervention practices
  - Systematic screening – invited for ECG
  - Opportunistic screening – pulse check at routine appt and ECG if pulse irregular
- 25 control practice
  - No screening

SAFE study

- Number of new cases of AF identified:
  - Intervention practices 1.63%
  - Control practices 1.04%
  - Difference 0.59% (95%CI 0.20%-0.98%)
- Screening
  - Systematic screening 1.62%
  - Opportunistic screening 1.64%
  - Difference 0.02% (95%CI –0.5%-0.5%)

- Screening is effective to identify new cases of AF
- Opportunistic screening equivalent to systematic screening at lower costs (no recall and fewer ECGs needed)

NHS

Screening for Atrial Fibrillation in People aged 65 and over

A report

for the National Screening Committee

May 2014

www.sph.nhs.uk

SPH

Solutions for Public Health

Atrial Fibrillation-Stroke risk reduction

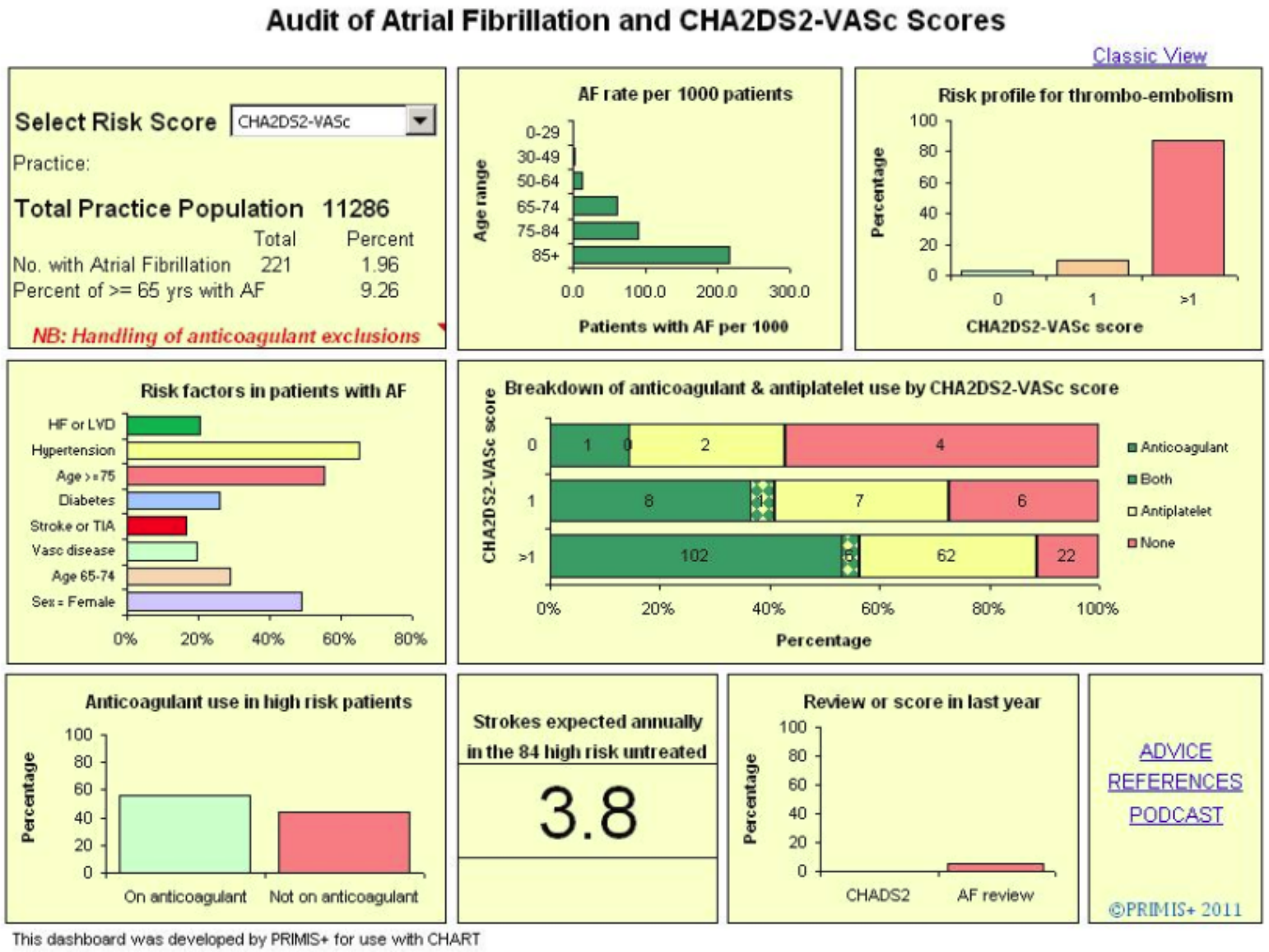
BAFTA study

- BAFTA: RCT of warfarin vs aspirin for stroke prevention in AF in a primary care population aged over 75
  - Aim: To compare the incidence of fatal and non-fatal disabling stroke (ischaemic and haemorrhagic), intra-cranial haemorrhage and other significant arterial embolism in patients randomised to warfarin (target INR 2-3) or aspirin (75mg)
  - 973 patients ≥ 75 yrs with AF assigned to warfarin (INR 2–3) vs aspirin (75 mg/day)

- Primary endpoint – fatal or disabling stroke, ICH or systemic embolism
  - **Risk per year**
  - Warfarin: 1.8%;
  - Aspirin: 3.8%
  - Relative risk warfarin vs aspirin: 0.48; $P = 0.003$
- Major extracranial hemorrhage
  - **Risk per year**
  - Warfarin: 1.4%:
  - Aspirin: 1.6%
  - Relative risk warfarin vs aspirin: 0.87

GRASP Tool and NHS-Improvement Heart

GRASP Tool and NHS-Improvement Heart



GRASP Tool and NHS-Improvement Heart

ORIGINAL ARTICLE

The use of anticoagulants in the management of atrial fibrillation among general practices in England

Campbell Cowan,[1,2] Richard Healicon,[1] Ian Robson,[1] W Robert Long,[3] James Barrett,[4] Matthew Fay,[1,5] Keith Tyndall,[2] Chris P Gale[3,6]

Marked under use of a cheap and effective intervention that cuts stroke risk by c60%

This is not news.

“overuse” of anti platelet medicine

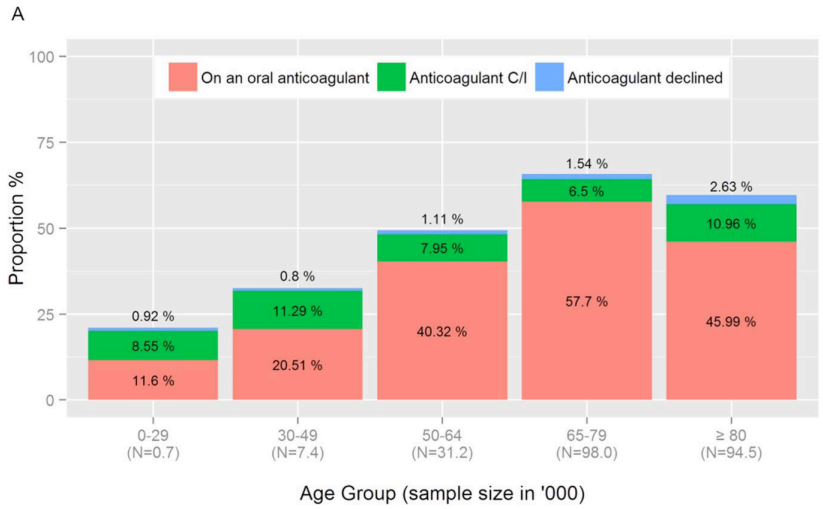


Figure 3 The proportion of atrial fibrillation patients prescribed anticoagulant therapy (A) and antiplatelet therapy (B) by age group.

GRASP Tool and NHS-Improvement Heart

ORIGINAL ARTICLE

Associations with anticoagulation: a cross-sectional registry-based analysis of stroke survivors with atrial fibrillation

Azmil H Abdul-Rahim,[1] Jao Wong,[2] Christine McAlpine,[3] Camilla Young,[3] Terence J Quinn[1]

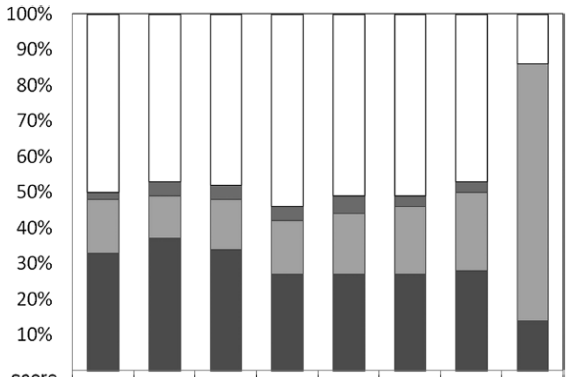
Even in really high risk patients

34% anticoagulated

Community dwelling AF stroke survivors

N=3500.

NNT = 10-12



CHA_2DS_2-VAS_C score	2	3	4	5	6	7	8	9
No treatment	50	47	48	54	51	51	47	14
VKA and antiplatelet	2	4	4	4	5	3	3	0
Antiplatelet-only	15	12	14	15	17	19	22	72
VKA-only	33	37	34	27	27	27	28	14

Figure 2 Proportion of patients treated with VKA, antiplatelet, combination or no treatment at various levels of stroke risk. Data are proportion of patients (expressed as percentage of total patients) at each level of $CHA_2DS_2VAS_C$ score from 2 to 9. VKA, vitamin K antagonist.

Occam’s Razor

- *The solution that requires the fewest steps should be preferred*

The Bradford AF Quality Improvement Program (QIP)

Acknowledgement:
- Greg Fell (@Felly500) Public Health Consultant Bradford LA
- Maciek Gwozdziewicz South & West Yorkshire and Bassetlaw CSU
- Bradford Districts, Bradford City and ACW CCG

Approach was simple

- Clear quality standard
- Measurable at practice
- Make data available and public to all practices
- Achievable benchmark of care target for each practice – what level are the 2nd quintile performers achieving
- Ten evidence based strategies were consistently applied to the practices that were participating to encourage improvement.
- Bespoke support and advice to practice and more widely - Q&A / Expert events / training / Practice visits / IT tools
- 18 months.

Management of Stroke Risk a

Patient confirmed to have Atrial Fibril
All forms of Atrial Fibrillation (Paroxysmal, Persiste
require Stroke Risk As

Is the patient less than 65 years old with r
Such as diabetes, hypertension, PV

NO

Undertake a CHA_2DS_2VASc score to define low risk patients

SCORE 0

SCORE >0

Discuss anticoagulation with the patient with AF, this
Remember that published evidence suggests that pati
of bleeding than clinicians t

Can the patient take Warfarin therapy (no previo

YES

Is the patient willing to trial Warfarin therapy?

YES

Initiate Warfarin therapy under the direction of an anticoagulation clinic with a target INR of 2.0-3.0 (tolerance up to INR 4.0)

After 3 months **consider** a switch to a NOAC if the INR >5, OR 2 consecutive INRs <1.8, OR frequent INR testing required

After 3 months is the Warfarin well controlled with an Individual Time in Therapeutic Range (iTTR) of >65%

YES

Continue oral anticoagulation indefinitely with annua
consideration of iTTR and

Buckinghamshire Healthcare NHS
NHS Trust

Contraindications to The Initiation of Oral Anticoagulant

in Patients with Atrial Fibrillation in Pr

As a patient's relative stroke & bleeding risk can change, it is essential tha
annually for a re-assessment of their stroke versus bleeding risk & the anti-

Contraindications listed below apply to **BOTH** anti-platelet a
dipyridamole) & **ALL** oral anticoagulants (e.g. warfarin, phenindione, dab
indicated.

Absolute Contraindications

- Known large oesophageal varices.
- Significant thrombocytopenia (platelet count < 50 x 10^9/L) - *refer to hae*
- Within 72 hours of major surgery with risk of severe bleeding - *defer &*
- Previously documented hypersensitivity to either the drug or excipients
- Acute clinically significant bleed - *defer & re-assess stroke versus blee*
- Decompensated liver disease or deranged baseline clotting screen
  /Hepatology. ***Contraindication applies to oral anticoagulants only***
- Pregnancy or within 48 hours post partum - *seek urgent haematologic*
  oral anticoagulants only.
- Severe renal impairment (GFR < 30 mL/min/1.73 m2 or on dialysis). ***Contraind***

Relative Contraindications

- Previous history intracranial haemorrhage - *as some AF patients espe*
  risk (i.e. CHADS2 score ≥3) may benefit from anti-thrombotic therapy, s
- Recent major extracranial bleed within the last 6 months where the ca
  decision for oral anti-thrombotic therapy should be deferred.
- Recent documented peptic ulcer (PU) within last 3 months– *decision f*
  deferred until treatment for PU completed. In all cases with history PU
- Recent history recurrent iatrogenic falls in patient at higher bleeding ris
  A patient at higher bleeding risk is assessed by having 3 or more of the f
  - *age > 65 years*
  - *previous history bleed or predisposition to bleeding (e.g. diverticulitis)*
  - *uncontrolled hypertension*
  - *severe renal impairment (i.e. serum creatinine > 200umol/L,* GFR < 30
  - *acute hepatic impairment (e.g. bilirubin > 2xULN + LFTS > 3x ULN), c*
  - *low platelet count < 80 x 10^9/L or a thrombocytopenia or anaemia of*
  - *on concomitant drugs associated with an increased bleeding risk e.g.*
    or other immune-suppressant agents.

  N.B. ***A risk of falls is not a contraindication to initiating oral anticoagulat***
  of 5% (CHADS2 score 2-3) would need to fall 295 times for fall risk to outweigh
- Dementia or marked cognitive impairment with poor medicines complia
- Chronic alcohol abuse – especially if associated with binge drinking.

N.B. Poor compliance with any oral anticoagulant agent will reduce benefits but

Anticoagulants for prevention of stroke and systemic embolism in NVAF
Drug use and dosing based on renal function estimation
(CrCl - creatinine clearance ml/min)

CrCl >50 ml/min	**Any Anticoagulant** - no dose adjustment needed.
CrCl 30-49 ml/min	**Apixaban** 5mg bd or 2.5mg bd if have 2 of: age ≥ 80 yrs, body weight ≤ 60 kg, serum creatinine ≥ 133 micromol/l **Dabigatran** 110mg bd if 80 years and over or high risk of bleeding (HAS-BLED ≥3) or on verapamil or amiodarone; otherwise 150mg bd. **Rivaroxaban** 15mg od. **Warfarin** INR dependant dose adjustment.
CrCl 15-29 ml/min	**Apixaban** 2.5mg bd **Dabigatran** contraindicated. **Rivaroxaban** 15mg od but caution - plasma concentrations significantly increased (average 1.6 fold) which may increase bleeding risk. **Warfarin** INR dependant dose adjustment under expert advice and review.
CrCl <15 ml/min	No anticoagulant use recommended in general use, take expert advice

Female ≥60kg* creatinine clearance ml/min (NB do not use if weight lower than 60kg – see below)

age / serum creatinine	40	45	50	55	60	65	70	75	80	85	90	95	100
50	120	114	108	102	96	90	84	78	72	66	60	54	48
60	100	95	90	85	80	75	70	65	60	55	50	45	40
70	86	81	77	73	69	64	60	56	51	47	43	39	34
80	75	71	68	64	60	56	53	49	45	41	38	34	30
90	67	63	60	57	53	50	47	43	40	37	33	30	27
100	60	57	54	51	48	45	42	39	36	33	30	27	24
110	55	52	49	46	44	41	38	35	33	30	27	25	22
120	50	48	45	43	40	38	35	33	30	28	25	23	20
130	46	44	42	39	37	35	32	30	28	25	23	21	18
140	43	41	39	36	34	32	30	28	26	24	21	19	17
150	40	38	36	34	32	30	28	26	24	22	20	18	16
160	38	36	34	32	30	28	26	24	23	21	19	17	15
170	35	34	32	30	28	26	25	23	21	19	18	16	14
180	33	32	30	28	27	25	23	22	20	18	17	15	13
190	32	30	28	27	25	24	22	21	19	17	16	14	13
200	30	29	27	26	24	23	21	20	18	17	15	14	12

Male ≥70kg* creatinine clearance ml/min (NB do not use if weight lower than 70kg – see below)

age / serum creatinine	40	45	50	55	60	65	70	75	80	85	90	95	100
50	168	160	151	143	134	126	118	109	101	92	84	76	67
60	140	133	126	119	112	105	98	91	84	77	70	63	56
70	120	114	108	102	96	90	84	78	72	66	60	54	48
80	105	100	95	89	84	79	74	68	63	58	53	47	42
90	93	89	84	79	75	70	65	61	56	51	47	42	37
100	84	80	76	71	67	63	59	55	50	46	42	38	34
110	76	73	69	65	61	57	53	50	46	42	38	34	31
120	70	67	63	60	56	53	49	46	42	39	35	32	28
130	65	61	58	55	52	48	45	42	39	36	32	29	26
140	60	57	54	51	48	45	42	39	36	33	30	27	24
150	56	53	50	48	45	42	39	36	34	31	28	25	22
160	53	50	47	45	42	39	37	34	32	29	26	24	21
170	49	47	44	42	40	37	35	32	30	27	25	22	20
180	47	44	42	40	37	35	33	30	28	26	23	21	19
190	44	42	40	38	35	33	31	29	27	24	22	20	18
200	42	40	38	36	34	32	29	27	25	23	21	19	17

Absolute creatinine clearance CrCl (Cockcroft & Gault) should be used for dosing decisions, not normalised eGFR especially for older patients and for drugs with narrow therapeutic index.

The tables should not be used for patients in acute renal impairment, who are dehydrated or if under the stated weights when CrCl should be calculated individually (manually or on e.g. SystmOne>clinical tools>renal calculations).

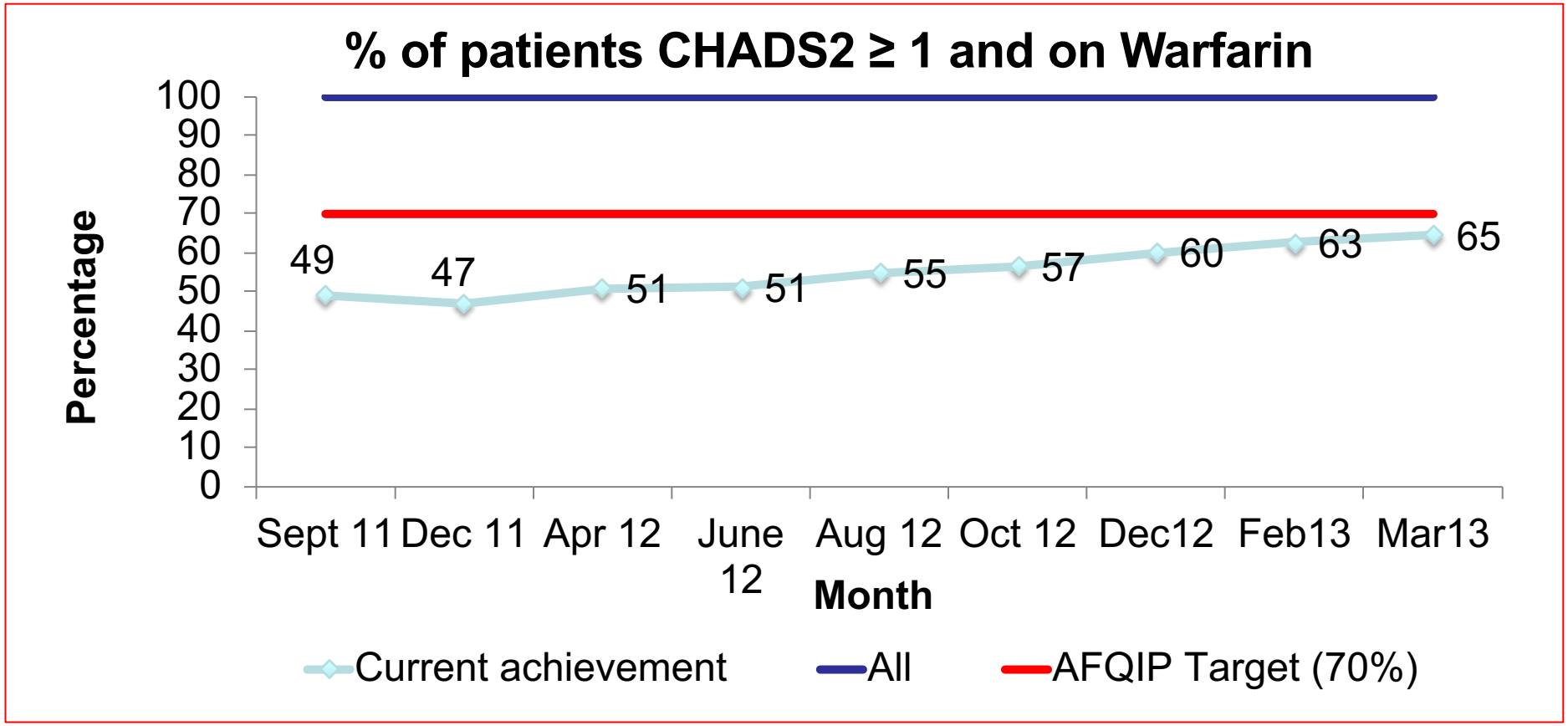
$$CrCl = \frac{[140 - age(yrs)] \times \text{ideal body weight or actual if less (kg)}}{\text{Serum creatinine (micromol/L)}} \times 1.2 \text{ for males}$$

*average ideal body weight

Prescribing Support Services

Su Wood Prescribing Support Services for Primary Care
Anticoagulant dosing based on renal function estimation December 2012

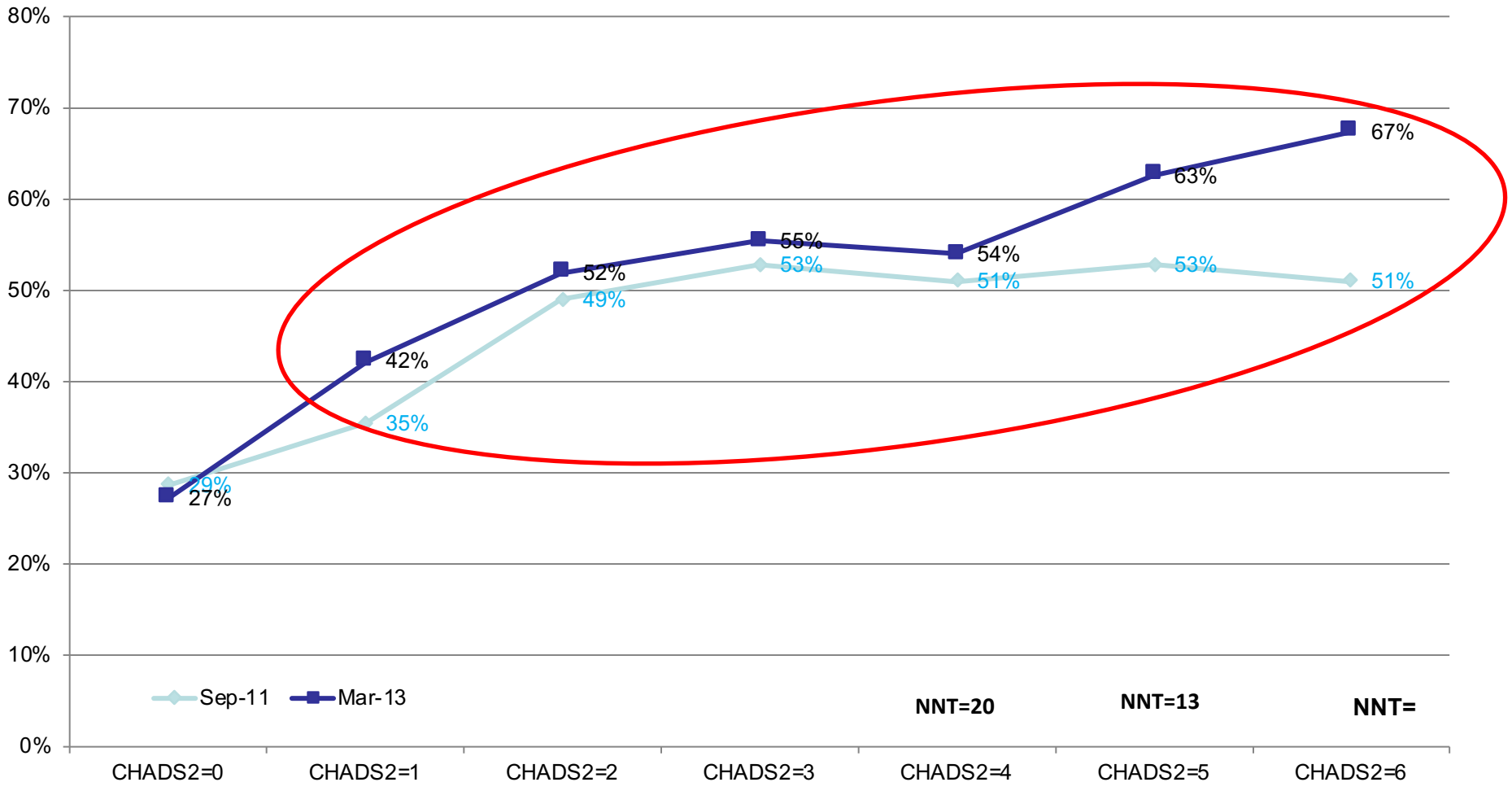
AF QIP achievements



65% of patients with CHADS2 ≥1 on Warfarin

6% absolute improvement

AFQIP Improvement by CHADS2



National Clinical Guideline Centre

Document information (draft for consultation)

Atrial Fibrillation

Atrial fibrillation: the management of atrial fibrillation

Clinical guideline

Methods, evidence and recommendations

January 2014

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians | The Royal College of Surgeons of England | Royal College of General Practitioners | Royal College of Nursing | NICE accredited

Atrial Fibrillation-Stroke risk: CHA_2DS_2VASc

CHA_2DS_2VASc risk criteria	Score
Cardiac failure	1
Hypertension	1
Age >75 yrs	2
Diabetes mellitus	1
Stroke or TIA (previous history)	2
Vascular disease (IHD, PAD)	1
Age 65-74 yrs	1
Sex Category	1

AF Bleeding Risk: HASBLED

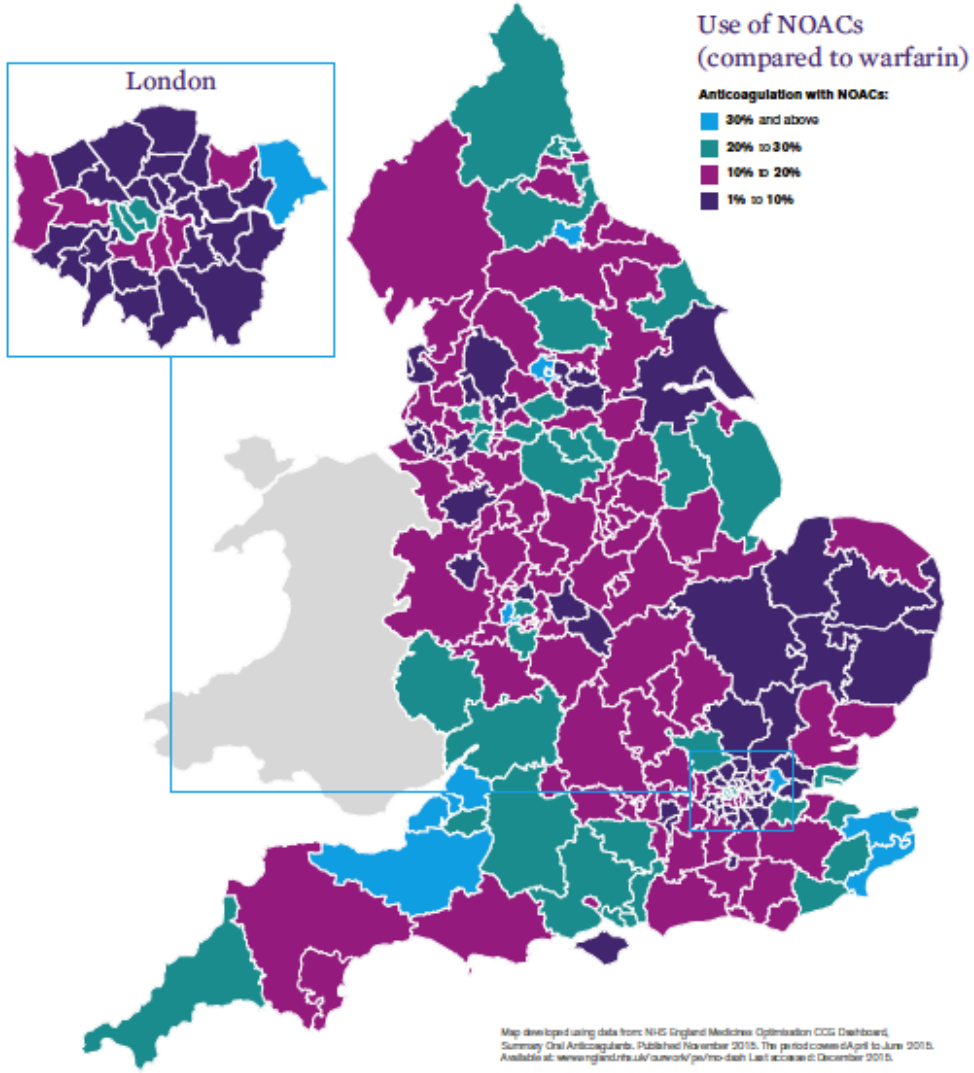
HAS-BLED risk criteria	Points awarded
Hypertension (i.e. Uncontrolled BP)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. age >65 years, frail condition)	1
Drugs or alcohol (1 point each)	1 or 2
	Maximum 9 points

DOAC Technology Appraisals

	Primary prevention of VTE in adults undergoing elective hip and knee replacement	Prevention of stroke of systemic embolisation in patients with non-valvular AF	Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults	ACS with elevated cardiac biomarkers, co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine
Dabigatran[1-3]	✓ Technology Appraisals (TA157) Sep 2008	✓Technology Appraisals (TA249) Mar 2012	✓Technology Appraisals (TA327) Dec 2014	✗
Rivaroxaban[4-7]	✓Technology Appraisals (TA170) Apr 2009	✓Technology Appraisals (TA256) May 2012	✓Technology Appraisals (TA261) Jul 2012	✓Technology Appraisals (TA335) March 2015
Apixaban[8-10]	✓Technology Appraisals (TA245) Jan 2012	✓Technology Appraisals (TA275) Feb 2013	✓Technology Appraisals (TA341) Jun 2015	✗
Edoxaban[11.12]	✗	✓Technology Appraisals (TA355) Sept 2015	✓Technology Appraisals (TA354) Sept 2015	✗

1. NICE. TA157. Available at: https://www.nice.org.uk/guidance/ta335. Accessed: May 2017; 2. NICE. TA249 Available at: https://www.nice.org.uk/guidance/ta249. Accessed: May 2017; 3. NICE. TA327 Available at: https://www.nice.org.uk/guidance/ta327. Accessed: May 2017; 4. NICE. TA170 Available at: https://www.nice.org.uk/guidance/ta170. Accessed: May 2017; 5. NICE. T256. Available at: https://www.nice.org.uk/guidance/ta256. Accessed: May 2017; 6. NICE. TA261 Available at: https://www.nice.org.uk/guidance/ta261. Accessed: May 2017; 7. NICE. TA335 Available at: https://www.nice.org.uk/guidance/ta335. Accessed: May 2017; 8. NICE. TA245 Available at: https://www.nice.org.uk/guidance/ta245. Accessed: May 2017; 9. NICE. TA275 Available at: https://www.nice.org.uk/guidance/ta275. Accessed: May 2017; 10. NICE. TA341 Available at: https://www.nice.org.uk/guidance/ta341. Accessed: May 2017; 11. NICE. TA355 Available at: https://www.nice.org.uk/guidance/ta355. Accessed: May 2017; 12. NICE. TA354 Available at: https://www.nice.org.uk/guidance/ta354. Accessed: May 2017.

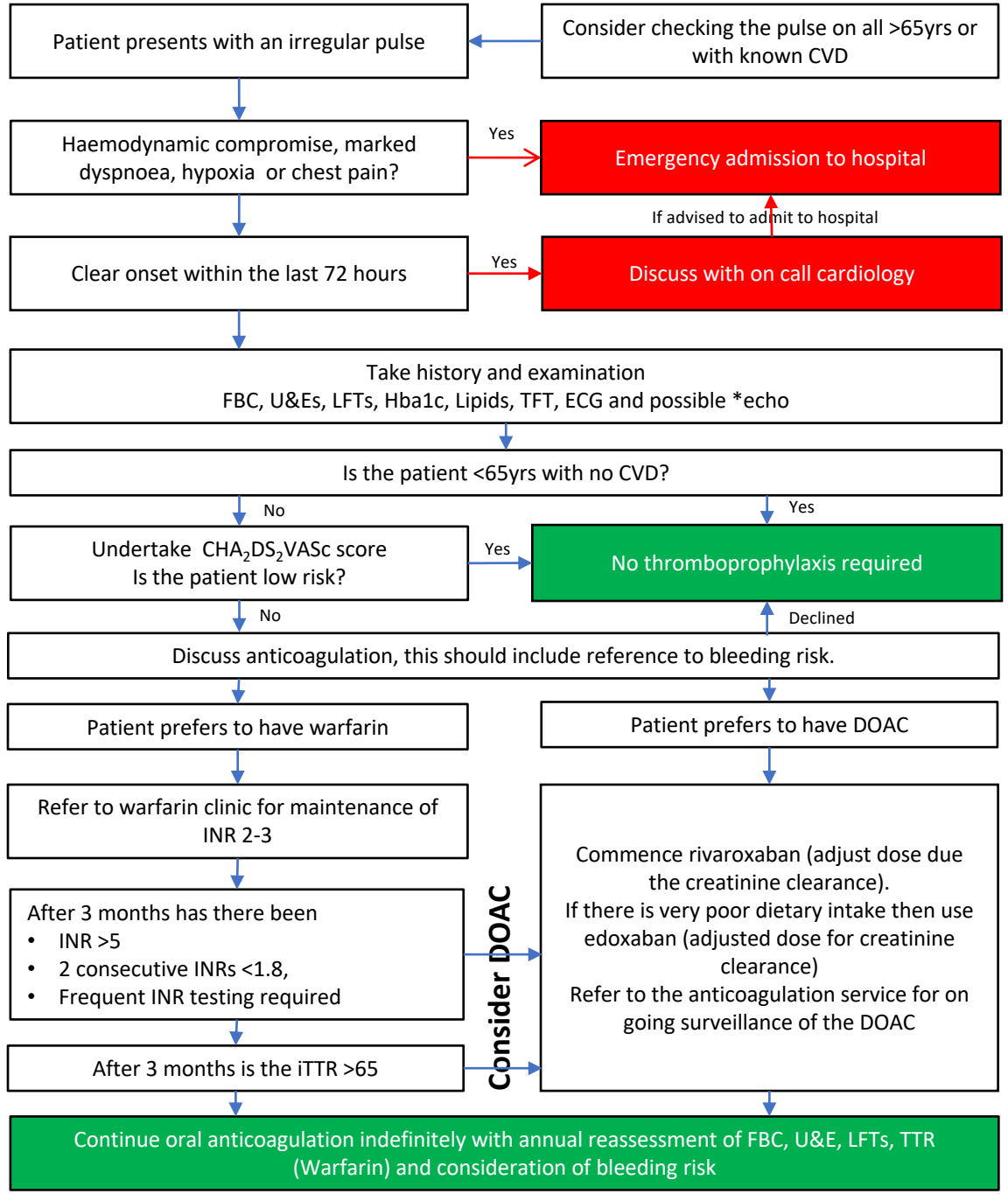
Use of Novel Oral Anticoagulants (NOACs) across Clinical Commissioning Groups (CCGs) in England



NOAC uptake is symptomatic of local variations in AF management and the need to provide all patients high quality anticoagulation.

"Hold it, I wonder if I might try the warfarin again?"

Guide to the Management of AF: Detection and stroke consideration



Bleeding Risk
Bleeding risk can be calculated using the HASBLED score
HASBLED score should not be used to preclude anticoagulation
Modifiable risk factors should be adjusted:
-Reduce blood pressure
-Reduce alcohol intake
-Review medication

***Echocardiogram consideration**
The default option should be to undertake an echocardiogram however if due to the clinical setting the echo will not change management then it should not be undertaken

Contraindications to oral anticoagulation

Absolute Contraindications
- Known large oesophageal varices.
- Significant thrombocytopenia (platelet count < 50 x 10^9/L)
- Within 72 hours of major surgery with risk of severe bleeding - defer & reassess risk postoperatively.
- Previously documented hypersensitivity to either the drug or excipients.
- Acute clinically significant bleed - defer & re-assess stroke versus bleeding risk within 3 months.
- Decompensated liver disease or deranged baseline clotting screen (INR>1.5)
- Pregnancy or within 48 hours post partum

Relative Contraindications
- Previous history intracranial haemorrhage:-seek the opinion of a stroke specialist.
- Recent major extracranial bleed within the last 6 months where the cause has not been identified or treated –decision for oral anti-thrombotic therapy should be deferred.
- Recent documented peptic ulcer within last 3 months – decision for oral anti-thrombotic therapy should be deferred until treatment for PU completed & given PPI cover whilst on anti-thrombotic agent.
- Recent history recurrent iatrogenic falls in patient at higher bleeding risk.
    - **N.B. A risk of falls is not a contraindication to initiating oral anticoagulation.**
- Dementia or marked cognitive impairment with poor medicines compliance & no access to carer support.
- Chronic alcohol abuse – especially if associated with binge drinking.

PIONEER

AF-PCI

Study objective: To assess the safety of two rivaroxaban treatment strategies compared with the current standard of care in patients with paroxysmal, persistent or permanent NVAF undergoing PCI with stent placement

PIONEER AF-PCI
Rationale for Dual and Triple Therapy Arms

Study group 1

12 months

Rivaroxaban 15 mg OD plus $P2Y_{12}$

The WOEST study showed oral anticoagulation in combination with clopidogrel was associated with significantly lower bleeding than triple therapy with no increase in thrombotic events[1]

This strategy has not yet been tested in a large study

Study group 2

1, 6 or 12 months: Rivaroxaban 2.5 mg BID plus ASA plus $P2Y_{12}$

→

Up to 12 months: Rivaroxaban 15 mg OD plus ASA

Where US guidelines recommend triple therapy with a VKA,[2,3] recent European guidelines suggest that a NOAC may be used in triple and dual therapy after PCI[4,5]

Study group 3

1, 6 or 12 months: VKA plus ASA plus $P2Y_{12}$

→

Up to 12 months: VKA plus ASA

Triple therapy with a VKA plus DAPT followed by dual therapy with VKA plus ASA is the standard of care for patients with AF and ACS, as recommended by US guidelines[2,3]

1. Dewilde WJ *et al*, *Lancet* 2013;381:1107–1115; 2. Amsterdam EA *et al*, *Circulation* 2014;130:e344–e426;
3. O'Gara PT *et al*, *J Am Coll Cardiol* 2013;61:e78–e140; 4. Kirchhof P *et al*, *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw210;
5. Heidbuchel H *et al*, *Europace* 2015;17:1467–1507

Rivaroxaban is the First NOAC to Provide Data From a Dedicated RCT in AF-PCI

Design: An open-label, randomized, controlled phase IIIb safety study

Population: patients with paroxysmal, persistent or permanent NVAF undergoing PCI (with stent placement)

N=2,124

Decision for DAPT duration: 1, 6 or 12 months

1:1:1

R

Rivaroxaban 15 mg OD* plus single antiplatelet‡

Rivaroxaban 2.5 mg BID plus DAPT§ → Rivaroxaban 15 mg OD* plus low-dose ASA

VKA (INR 2.0–3.0) plus DAPT§ → VKA plus low-dose ASA

DAPT duration (1, 6 or 12 months)

End of treatment (12 months)

DAPT
1 m: 15%
6 m: 35%
12 m: 50%

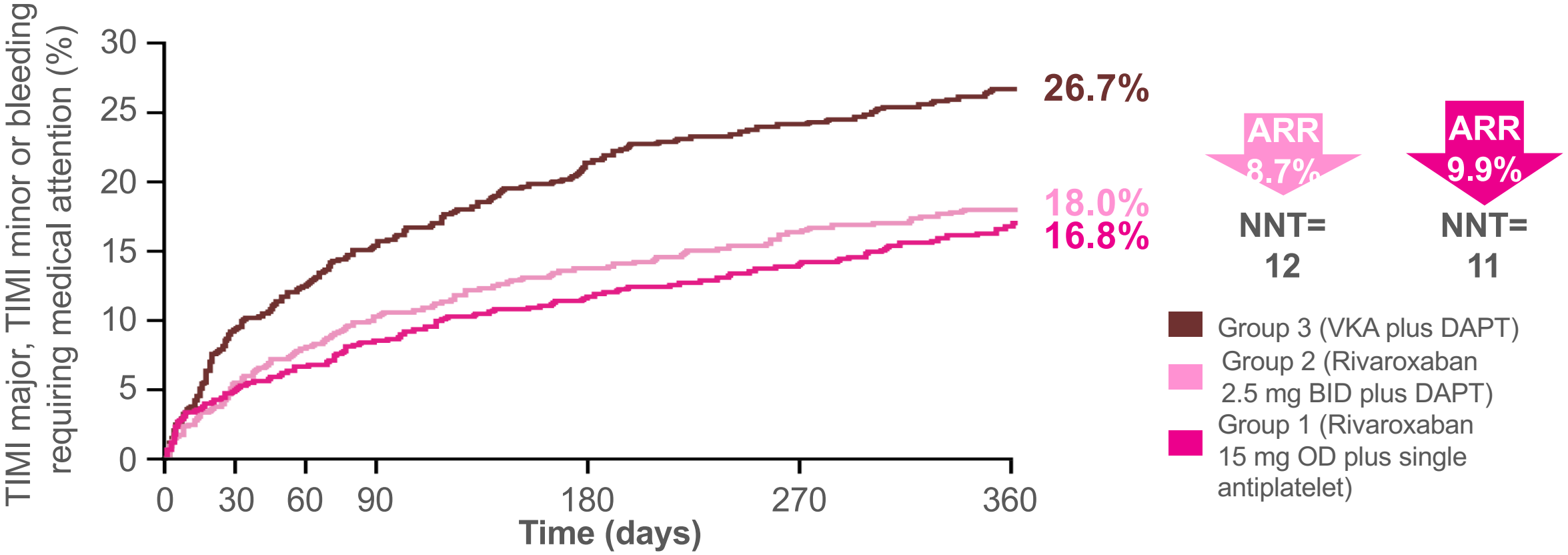
DAPT
1 m: 16%
6 m: 35%
12 m: 49%

*CrCl 30-50 ml/min: 10 mg OD; ‡clopidogrel (75 mg daily) [alternative use of prasugrel or ticagrelor allowed, but capped at 15%]; §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) [alternative use of prasugrel or ticagrelor allowed, but capped at 15%]

1. Janssen Scientific Affairs, LLC. 2016. https://clinicaltrials.gov/ct2/show/NCT01830543 [accessed 10 Oct 2016];
2. Gibson CM *et al*, *Am Heart J* 2015;169:472–478e5; 3. Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Both Rivaroxaban Strategies Were Associated With A Significantly Improved Safety Profile

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); *p*<0.001
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); *p*<0.001



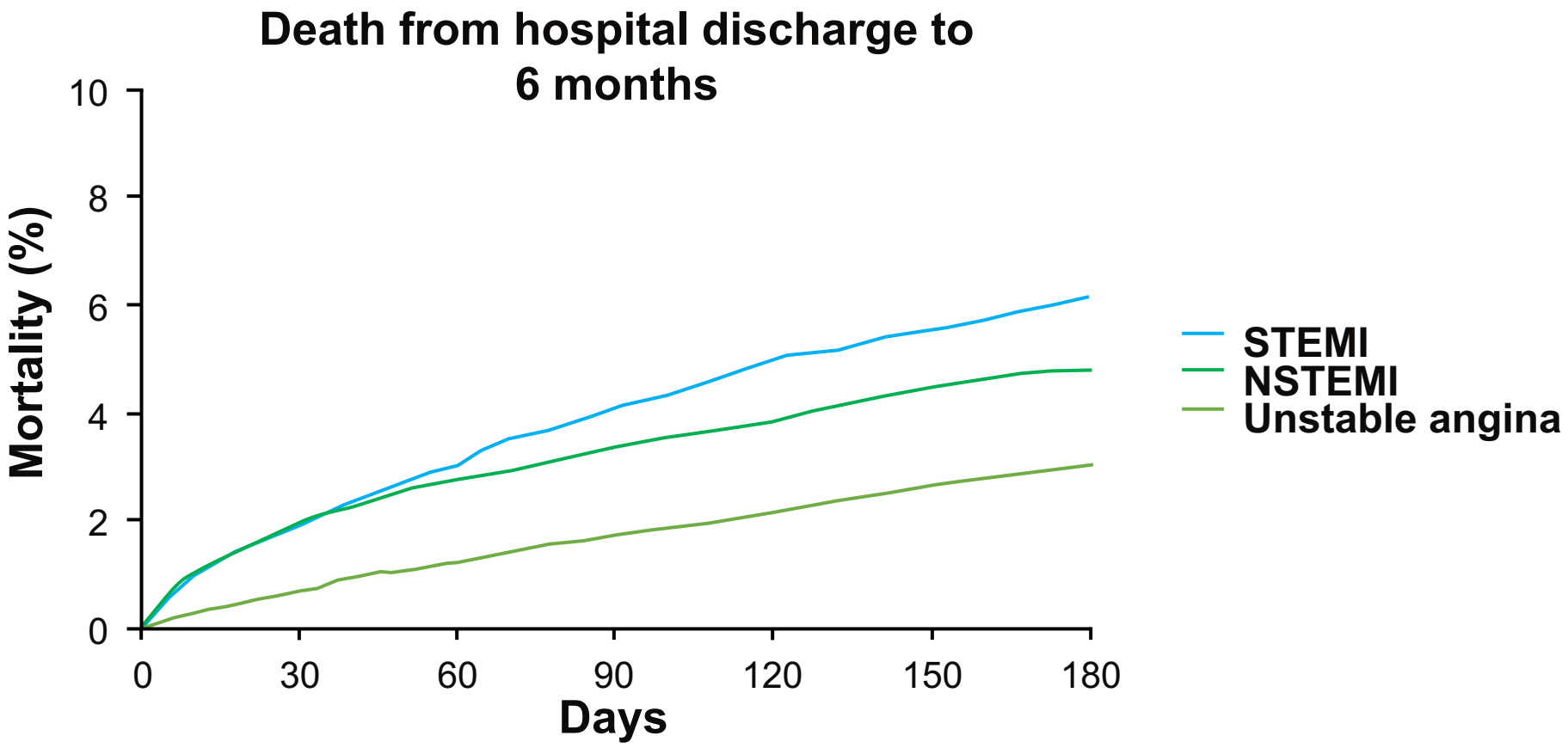
Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594]

PIONEER AF-PCI
Conclusions

- Administration of either rivaroxaban 15 mg OD plus a single antiplatelet for 1 year, or rivaroxaban 2.5 mg BID plus 1, 6 or 12 months of DAPT reduced the risk of clinically significant bleeding compared with a standard VKA plus DAPT strategy
- Although the study was not powered to detect differences in efficacy endpoints, both rivaroxaban strategies demonstrated similar efficacy compared with a standard VKA plus DAPT strategy
- Both rivaroxaban strategies showed a reduced risk of recurrent hospitalization compared with the VKA strategy.

Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Mortality rate after hospital discharge for ACS remains high



ATLAS 2

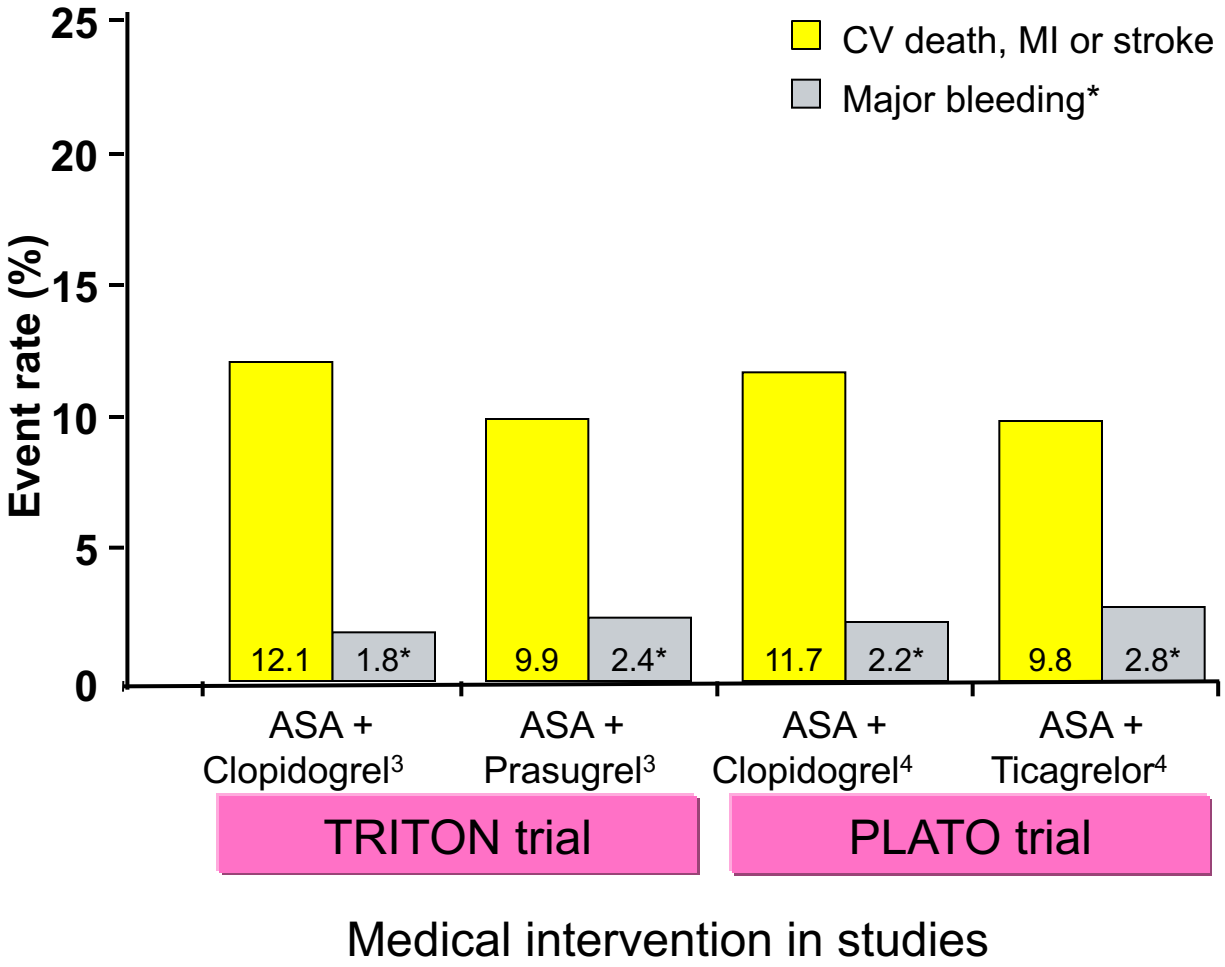
ACS TIMI 51

ATLAS 2

ACS TIMI 51

- Xarelto 2.5mg, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

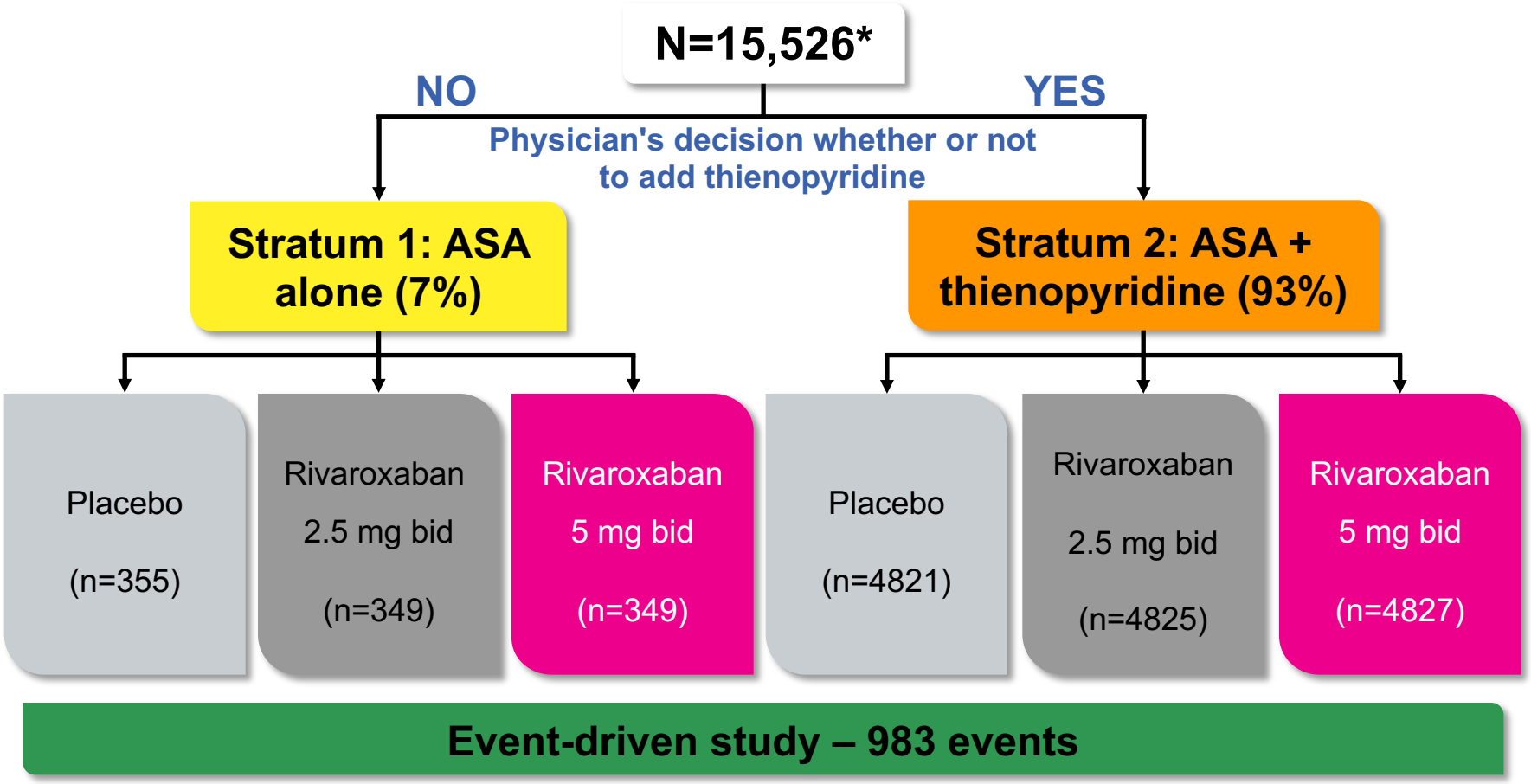
Event rate of CV death, MI or stroke at 12 months post event remains ~10%



3. Wiviott *et al*. *N Engl J Med* 2007; 357:2001–2015
4. Wallentin et al. N Eng J Med 2009; 361: 1045–1054

Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81–106
Antithrombotic Trialists' Collaboration. *BMJ* 2002; 324:71–86

ATLAS ACS 2 TIMI 51: a randomized, double-blind, event-driven phase III trial in patients hospitalized with ACS



Patients with prior stroke were excluded from the study.

*184 patients were excluded from the efficacy analyses prior to unblinding because of trial misconduct at three sites.

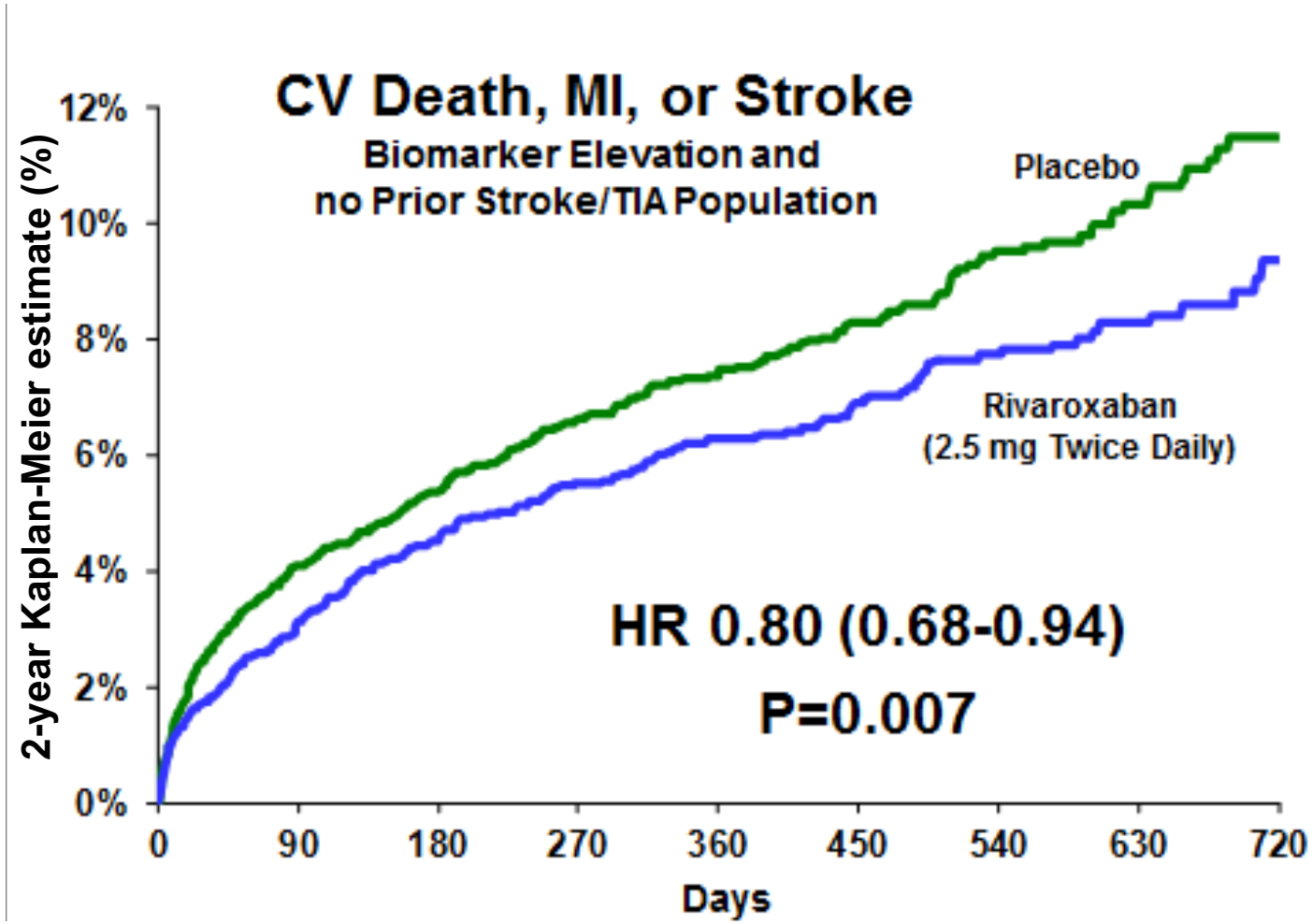
1. Gibson *et al. Am Heart J* 2011;161:815–21.e6; 2. Mega *et al. N Engl J Med* 2012;366:9–19.

ATLAS ACS 2 TIMI 51: Study endpoints

- **Primary efficacy endpoint:** composite of cardiovascular death, MI or stroke (ischaemic, haemorrhagic or uncertain)
- **Secondary efficacy endpoint:** composite of all-cause death, MI or stroke
- **Main safety endpoint:** incidence of major bleeding not associated with CABG surgery (assessed according to the TIMI bleeding definition)
- Other safety endpoints:
  - Other bleeding events classified according to the TIMI, GUSTO and rivaroxaban programme scales
  - Adverse events
  - Clinical laboratory tests
  - Liver safety assessments

Gibson CM *et al. Am Heart J* 2011;161:815–821

Xarelto 2.5mg bd reduces Cardiovascular death, MI or stroke among patients with elevated biomarkers and no prior stroke or TIA



Mega *et al. European Heart Journal* (2014) 35 (Abstract Supplement), 992

Summary

- Among patients with a recent ACS with cardiac biomarker elevation and no prior stroke or TIA, rivaroxaban 2.5 mg twice daily as compared with placebo:
  - Reduces CV death, MI, or stroke
  - Reduces CV death and all-cause death
  - Increases non-CABG TIMI major bleeding, without an increase in fatal bleeding

NAVIGATE ESUS

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

Robert Swaminat

BACKGROUND

Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a high rate of recurrence. Anticoagulant treatment with rivaroxaban, an oral factor Xa inhibitor, may result

CONCLUSIONS

Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Development; NAVIGATE ESUS ClinicalTrials.gov number, NCT02313909.)

stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding.

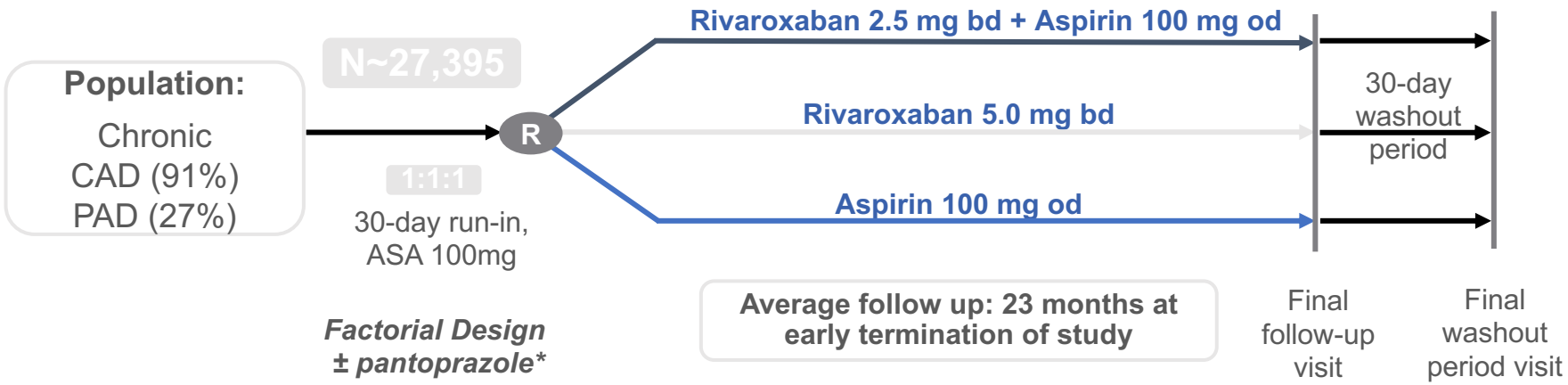
kumar

AVIGATE

COMPASS

A Dual Pathway Strategy Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

Objective: To determine the efficacy and safety profile of rivaroxaban plus aspirin, rivaroxaban alone or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Factorial Design
± pantoprazole*

Average follow up: 23 months at early termination of study

** pantoprazole arms ongoing*

The independent DSMB recommended early study termination due to clear and consistent benefit in the rivaroxaban treatment arms

COMPASS

1. Eikelboom JW *et al. New Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

A Dual Pathway Strategy Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

- Primary study objectives
  - To determine whether rivaroxaban 2.5 mg bd + ASA 100 mg od or rivaroxaban 5 mg bd alone reduces the risk of a composite of MI, stroke and CV death compared with ASA 100 mg od in patients with CAD or PAD

- Secondary study objectives
  - To determine, in patients with CAD or PAD, whether rivaroxaban 2.5 mg bd + ASA 100 mg od or rivaroxaban 5 mg bd alone versus ASA 100 mg od:
    - Reduces risk of composite of major thrombotic events: (1) coronary heart disease, MI, ischaemic stroke, acute limb ischaemia; (2) CV death, MI, ischaemic stroke, acute limb ischaemia
    - Reduces the risk of mortality

Bosch J *et al*. *Can Journal of Cardiology* 33 (2017) 1027-1035; Eikelboom JW *et al. New Engl J Med* 2017;

Inclusion and Exclusion Criteria Ensure That Patients Are Chronic CAD and PAD Patients

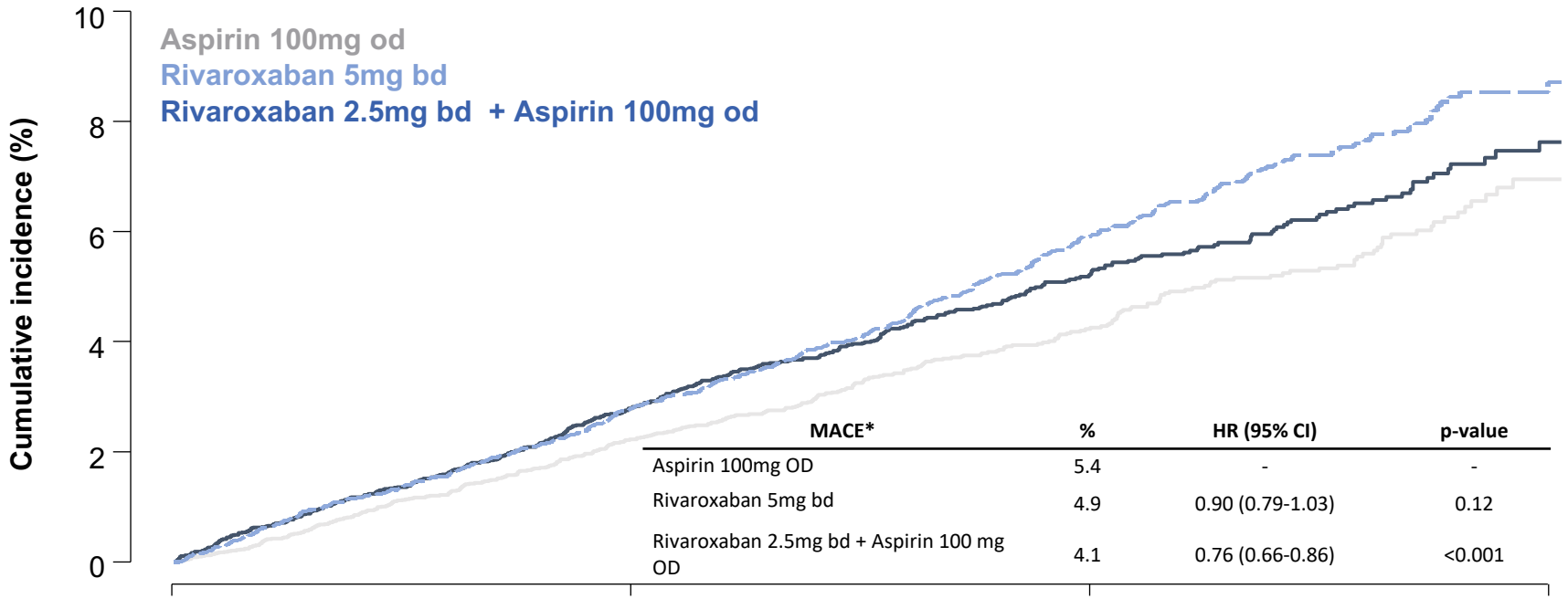
Key inclusion criteria*	Key exclusion criteria‡

• PAD
• CAD with ≥1 of:
  • Age ≥65 years
  • Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
  • Current smoker
  • Diabetes mellitus
  • Renal dysfunction (eGFR<60 ml/min)
  • Heart failure
  • Non-lacunar ischaemic stroke ≥1 month ago
	• Stroke ≤1 month or any haemorrhagic or lacunar stroke
	• Severe HF with known ejection fraction <30% or NYHA class III or IV symptoms
	• **Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy**
	• eGFR <15 ml/min

#Including but not limited to; ‡any other exclusion criteria in conjunction with the local Product Information and any other contraindication listed in the local labelling for rivaroxaban or the comparator have to be considered

Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035

Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5mg bd + Aspirin Reduced Stroke, CV Death and MI



MACE*	%	HR (95% CI)	p-value
Aspirin 100mg OD	5.4	-	-
Rivaroxaban 5mg bd	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5mg bd + Aspirin 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

Number at risk	0	1	2	3
Aspirin 100mg od	9126	7808	3860	669
Riva 5mg bd	9117	7824	3862	670
Riva 2.5mg bd + Aspirin 100mg od	9152	7904	3912	658

*Rates as at mean follow up of 23 month

Eikelboom JW *et al. New Engl J Med* 2017;DOI: 10.1056/NEJMoa1709118

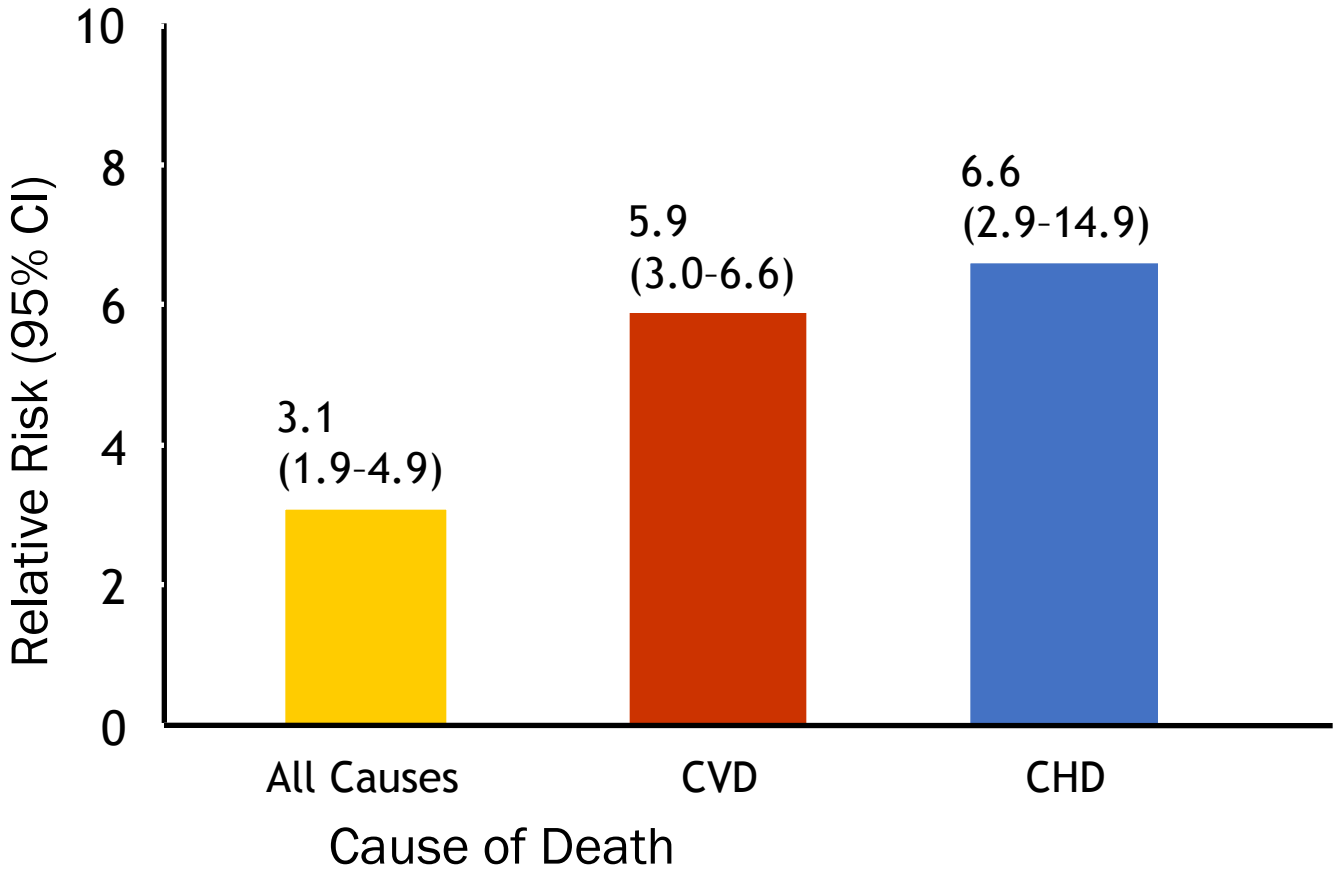
Rivaroxaban led to Significant Reduction in the Primary Efficacy Outcome in Patients with Chronic CAD or PAD

Dual pathway inhibition with rivaroxaban vascular dose 2.5mg bd and aspirin 100mg OD, versus aspirin alone:

- Significantly reduced the combined risk of stroke, CV death and MI by 24%
- Demonstrated 42% reduction in stroke and 22% reduction in CV death
- Resulted in an increase in major bleeding rates (of 70%) compared to aspirin alone, with no significant increase in intracranial, critical organ or fatal bleeding
- Showed an improvement in net clinical benefit of 20% and 18% nominal reduction in all-cause mortality

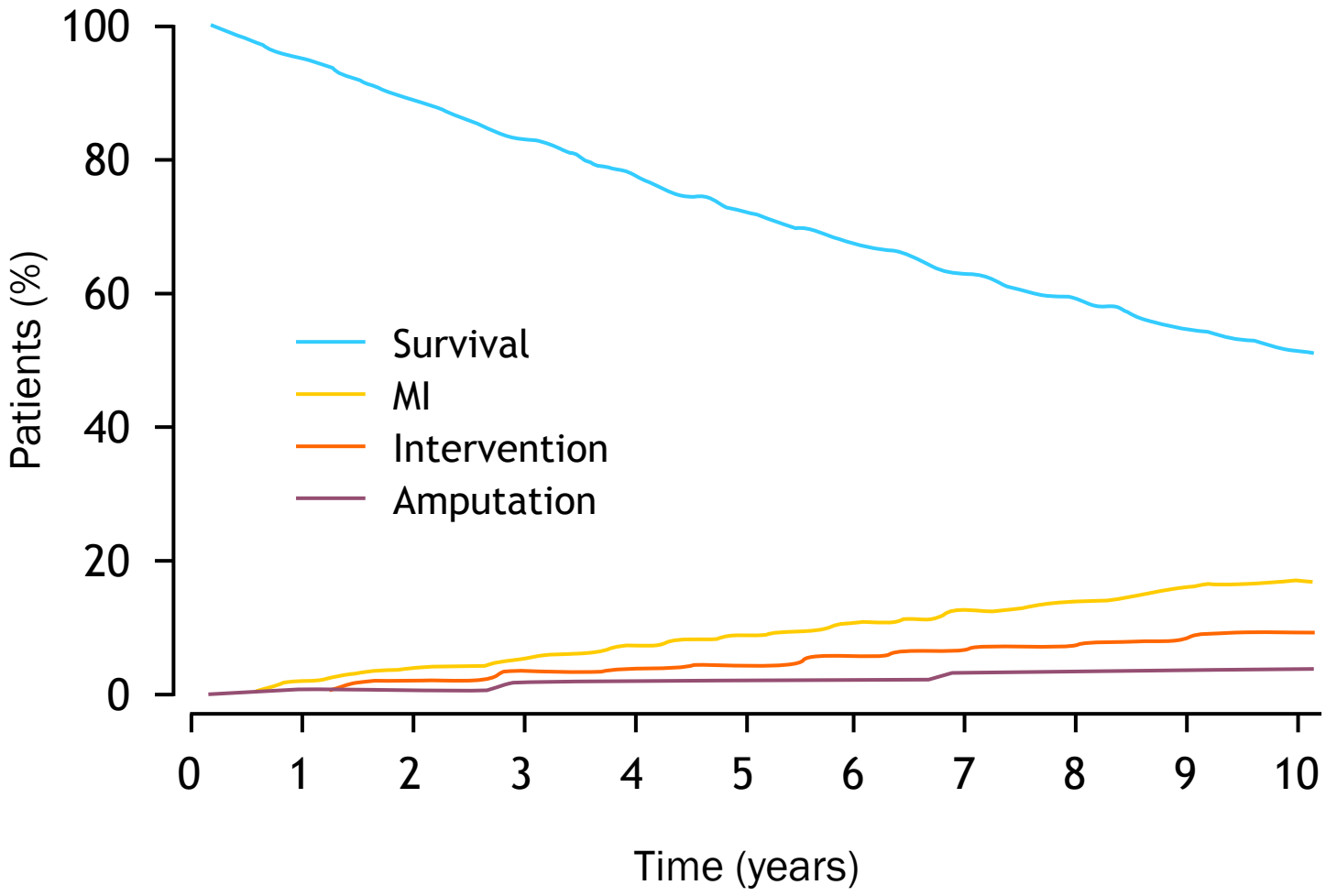
1. Eikelboom JW *et al. New Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

Claudication-Survival



Criqui MH et al. N Engl J Med. 1992;326:381-386.

Claudication-10 year natural history survival



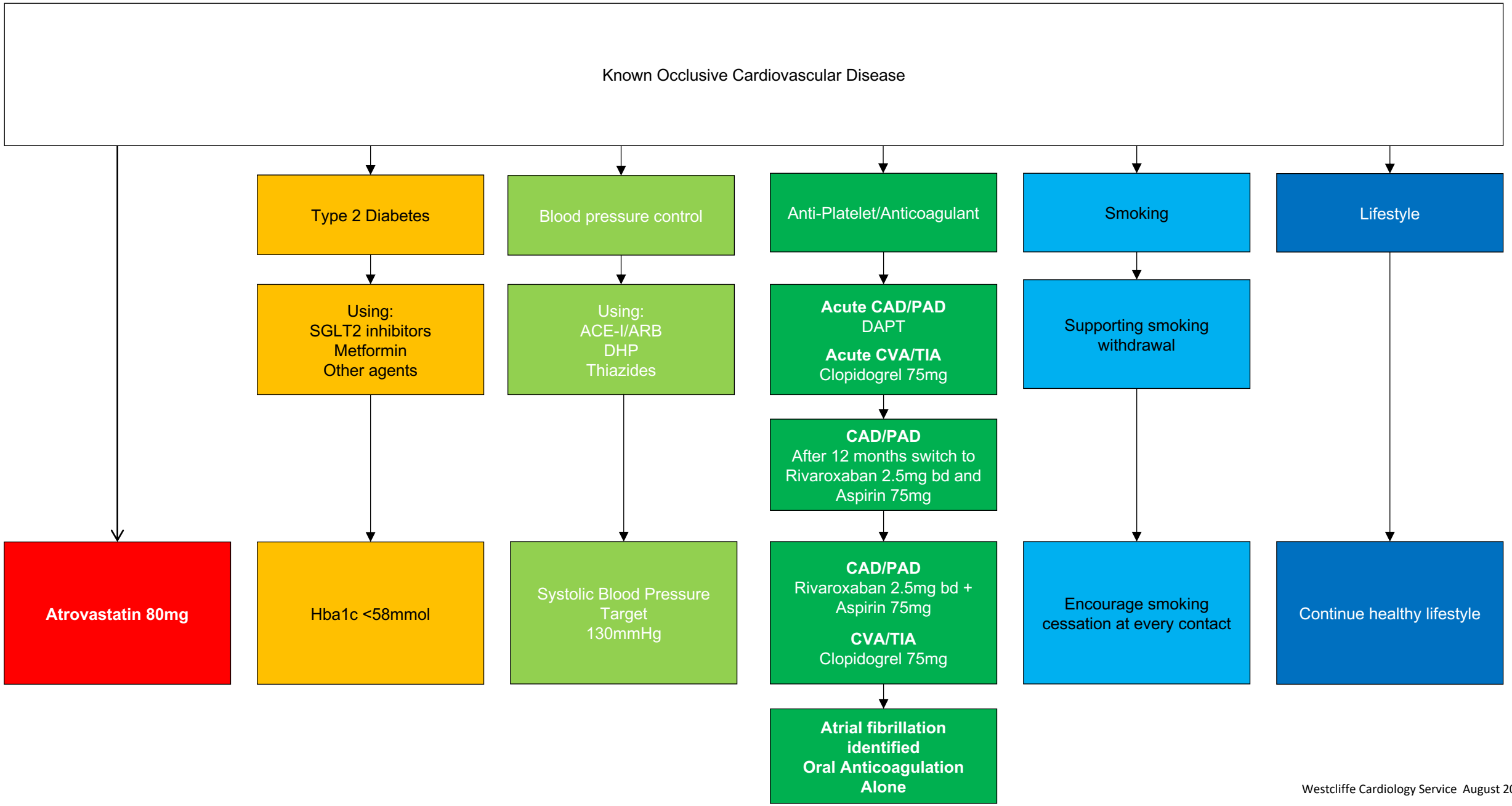
Ouriel K. Lancet. 2001;358;1257-1264.

COMPASS:-Affinity Care Implications

Intervention		Percentage
Antiplatelet agent		90.3
At time of event Aspirin with	Ticagrelor	50.60
	Clopidogerl*	32.10
	Prasagrel	1.23
	Monotherapy	12.35
	Anticoagulation**	3.72
Beta-Blocker		89.59
Statin		89.96
	Ezetimibe	
	Fibrate	
ACE-I/ARB		89.96
Combination of therapies		
Antiplatelet agent and Beta-blocker (BB)		76.69
Antiplatelet agent, BB and Statin		72.64
Antiplatelet agent, BB, Statin, ACEI/ARB		70.61
Antiplatelet agent and Statin		77.03
Antiplatelet agent, statin and ACE-I/ARB		74.32
Other Indices		
Smokers		19.70
Systolic blood pressure< 131mmHg		61.15
Systolic blood pressure< 141mmHg (QOF target)		76.35

Across just the PAD/CAD population this is 1.7% of the population

Occlusive Vascular Disease Vascular Protection



Westcliffe Cardiology Service August 2018

Thank you for your attention

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