NICE clinical guideline 180: Atrial fibrillation

Prescribing and medicines optimisation issues

Andy Hutchinson
Medicines Education Technical Adviser
NICE Medicines and Prescribing Centre

Note: this is not an official NICE presentation

NICE clinical guideline 180

- Update to the guideline published in 2006 (CG36)
- New recommendations have been added for
  - a personalised package of care and information
  - referral for specialised management
  - stroke prevention
  - rate and rhythm control
  - management of acute atrial fibrillation
- This slide set can only summarise the guideline recommendations. **See the guideline for full recommendations**
- Slide content comes from the guideline unless otherwise stated

Contents

- Key medicines optimisation issues in the guideline
- Rationale for the antithrombotic recommendations in the guideline
- Key implementation issues

Contents

- **Key medicines optimisation issues in the guideline**
- Rationale for the antithrombotic recommendations in the guideline
- Key implementation issues

‘Offer’ and ‘consider’

- For **all** recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences
- NICE uses **‘offer**’ (and similar words such as ‘refer’) when it is confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective
- NICE uses **‘consider**’ when it is confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective
  - The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for a strong recommendation

Personalised package of care and information

- Offer people with atrial fibrillation a personalised package of care. Ensure that the package of care is documented and delivered, and that it covers:
  - stroke awareness and measures to prevent stroke
  - rate control
  - assessment of symptoms for rhythm control
  - who to contact for advice if needed
  - psychological support if needed
  - up-to-date and comprehensive education and information on specific issues

See the guideline for full recommendations

Rate and rhythm control - 1

- Offer rate control as the first-line strategy to people with atrial fibrillation, except in people:
  - whose atrial fibrillation has a reversible cause
  - who have heart failure thought to be primarily caused by atrial fibrillation
  - with new-onset atrial fibrillation
  - with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm
  - for whom a rhythm control strategy would be more suitable based on clinical judgement.

Rate and rhythm control - 2

- Offer either a standard beta-blocker (that is, a beta-blocker other than sotalol) or a rate-limiting calcium-channel blocker as initial monotherapy to people with atrial fibrillation who need drug treatment as part of a rate control strategy.
  - Base the choice of drug on the person's symptoms, heart rate, comorbidities and preferences when considering drug treatment.
- Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no or very little physical exercise).

Rate and rhythm control - 3

- If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy with any 2 of the following:
  - a beta-blocker
  - diltiazem
  - digoxin.
- Do not offer amiodarone for long-term rate control.

Rhythm control

- Consider pharmacological and/or electrical rhythm control for people with atrial fibrillation whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful.
- Drug therapy may include:
  - amiodarone
  - a standard beta-blocker (that is, a beta-blocker other than sotalol)
  - dronedarone (see NICE TA 197).
- **See the guideline for full recommendations**

Stroke risk assessment

- Use the CHA_2DS_2-VASc stroke risk score to assess stroke risk in people with any of the following:
  - symptomatic or asymptomatic paroxysmal, persistent or permanent atrial fibrillation
  - atrial flutter
  - a continuing risk of arrhythmia recurrence after cardioversion back to sinus rhythm

CHA_2DS_2-VASc scoring for AF stroke risk

Eur Heart J (2013) doi: 10.1093/eurheartj/eht291

Risk factor	Score
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age 75 years or greater	2
Diabetes mellitus	1
Stroke, transient ischaemic attack or thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque)	1
Age 65–74 years	1
Sex **c**ategory female	1

CHA_2DS_2-VASc score and stroke risk

Friberg L et. al. Eur Heart J 2012; 33:1500-10

CHA_2DS_2-VASc score	n	Events per 100 patients/year	
		Stroke/TIA/ peripheral emboli	Ischaemic stroke
0	5343	0.3	0.2
1	6770	1.0	0.6
2	11,240	3.3	2.5
3	17,689	5.3	3.7
4	19,091	7.8	5.5
5	14,488	11.7	8.4
6	9577	15.9	11.4
7	4465	18.4	13.1

Bleeding risk assessment

- Use the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation. Offer modification and monitoring of the following risk factors:
  - uncontrolled hypertension
  - poor control of international normalised ratio (INR) ('labile INRs')
  - concurrent medication, for example concomitant use of aspirin or a non-steroidal anti-inflammatory drug (NSAID)
  - harmful alcohol consumption.

HAS-BLED scoring for bleeding risk

Eur Heart J (2013) doi: 10.1093/eurheartj/eht291

Risk factor	Score
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Stroke	1
Bleeding	1
Labile INR	1
Elderly	1
Drugs	1
Alcohol	1

HAS-BLED score and risk of major bleeding

Friberg et al, Eur Heart J 2012; 33:1500–10

HAS-BLED score	Major bleeding events per 100 patients/ year in anticoagulant users n=48,599
0	–
1	0.7
2	1.9
3	2.4
4	3.4
5	5.7

Risks and benefits of anticoagulation

- When discussing the benefits and risks of anticoagulation, tell the person that:
  - for most people the benefit of anticoagulation outweighs the bleeding risk
  - for people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important
- Do not withhold anticoagulation solely because the person is at risk of having a fall.

Anticoagulation – 1

- **Do not offer** stroke prevention therapy to people aged under 65 years with atrial fibrillation and no risk factors other than their sex (CHA_2DS_2-VASc score of 0 for men or 1 for women).
- **Consider** anticoagulation for all men who have a CHA_2DS_2-VASc score of 1, taking bleeding risk into account.
- **Offer** anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account.
- **Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences.**

Anticoagulation – 2

- **Anticoagulation may be with apixaban, dabigatran etexilate, rivaroxaban or a vitamin K antagonist**
- Apixaban, dabigatran etexilate and rivaroxaban are each recommended as an option to be considered for preventing stroke and systemic embolism, within their marketing authorisations and the terms of the relevant technology appraisals
  - TA275 (apixaban)
  - TA249 (dabigatran etexilate)
  - TA256 (rivaroxaban)
  - **See the guideline for full recommendations**

Assessing anticoagulation control with vitamin K antagonists

- Calculate the person's time in therapeutic range (TTR) at each visit
- Reassess anticoagulation for a person with poor anticoagulation control
- When reassessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control
- If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person
- **See the guideline for full recommendations**

Antiplatelet treatment

- Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation.

Review of people with atrial fibrillation – 1

- For people who are not taking an anticoagulant, review stroke risk when they reach age 65 or if they develop any of the following at any age:
  - diabetes
  - heart failure
  - peripheral arterial disease
  - coronary heart disease
  - stroke, transient ischaemic attack or systemic thromboembolism.

Review of people with atrial fibrillation – 2

- For people who are not taking an anticoagulant because of bleeding risk or other factors, review stroke and bleeding risks annually, and ensure that all reviews and decisions are documented.
- For people who are taking an anticoagulant, review the need for anticoagulation and the quality of anticoagulation at least annually, or more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk.

Contents

- Key medicines optimisation issues in the guideline
- **Rationale for the antithrombotic recommendations in the guideline**
- Key implementation issues

Rationale for antithrombotic recommendations

Full guideline chapter 9

- Based on assessment of clinical and cost–effectiveness of anticoagulation and anti-platelet agents both alone and in combination for stroke prevention.
- As part of the economic model, a network meta-analysis was conducted to synthesize the results of the papers retrieved from the systematic review, including
  - Antiplatelet (aspirin)
  - Dual antiplatelet (aspirin plus clopidogrel)
  - Anticoagulant (warfarin, other coumarins, NOACs)
  - Control/placebo

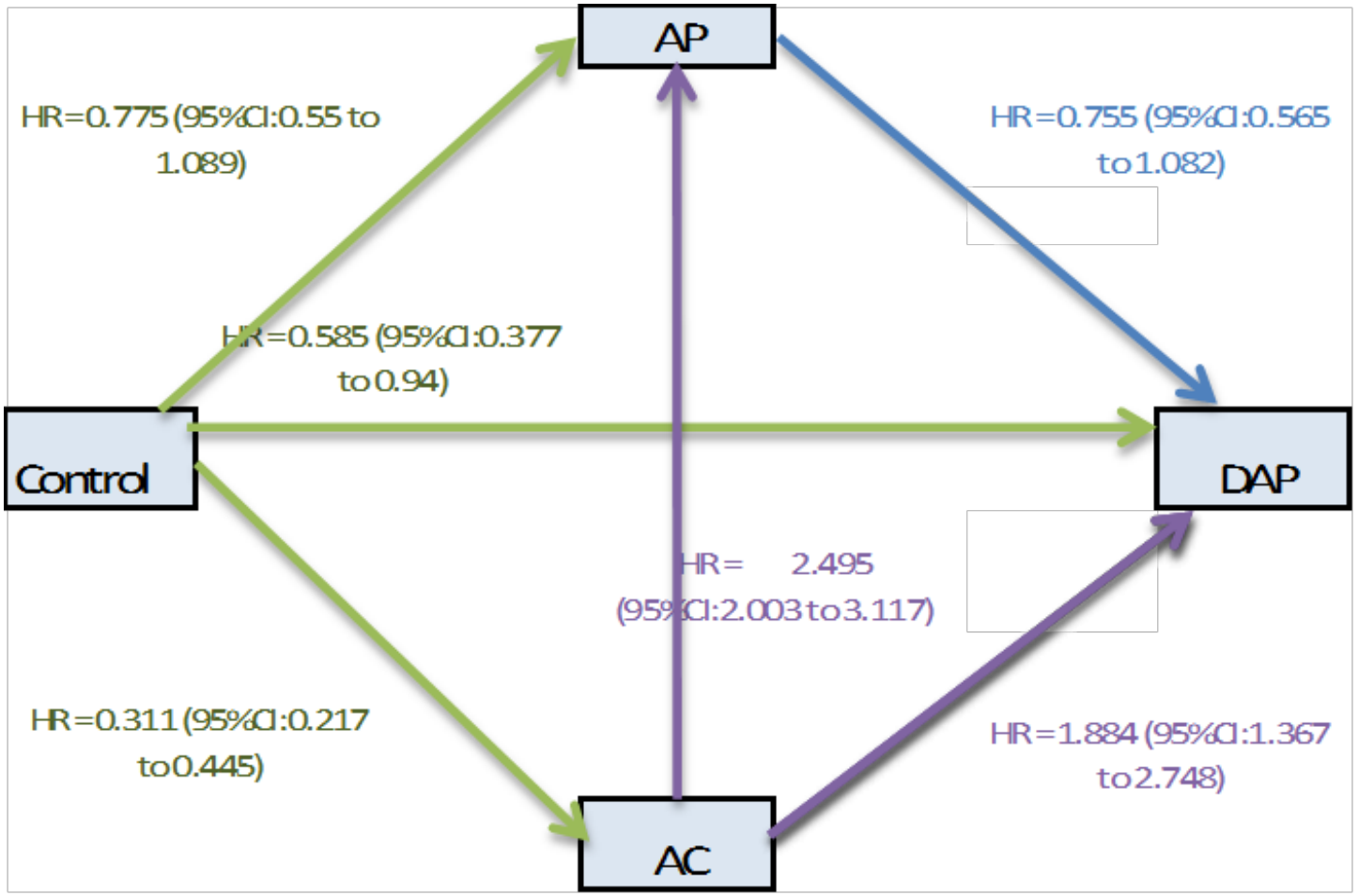
Hazard ratios compared with control

Full guideline section 9.22

Outcome	Strategy	Hazard ratio	Lower 95% CI	Upper 95% CI	Statistically significant?
All-cause mortality	Aspirin	0.847	0.709	1.012	No
	Asp+clop	0.825	0.661	1.037	No
	Anticoag	0.769	0.641	0.926	**Yes**
Ischaemic stroke	Aspirin	0.775	0.550	1.089	No
	Asp+clop	0.585	0.377	0.940	**Yes**
	Anticoag	0.311	0.217	0.445	**Yes**
Haemorrhagic stroke	Aspirin	1.876	0.617	6.521	No
	Asp+clop	2.104	0.533	9.593	No
	Anticoag	3.438	1.122	12.5	**Yes**
Major bleeding (including intracranial bleeds)	Aspirin	1.55	0.652	3.931	No
	Asp+clop	2.883	0.728	12.566	No
	Anticoag	2.721	1.214	6.623	**Yes**
Thromboembolic complications	Aspirin	0.696	0.289	1.543	No
	Asp+clop	0.834	0.271	2.714	No
	Anticoag	0.305	0.122	0.733	**Yes**

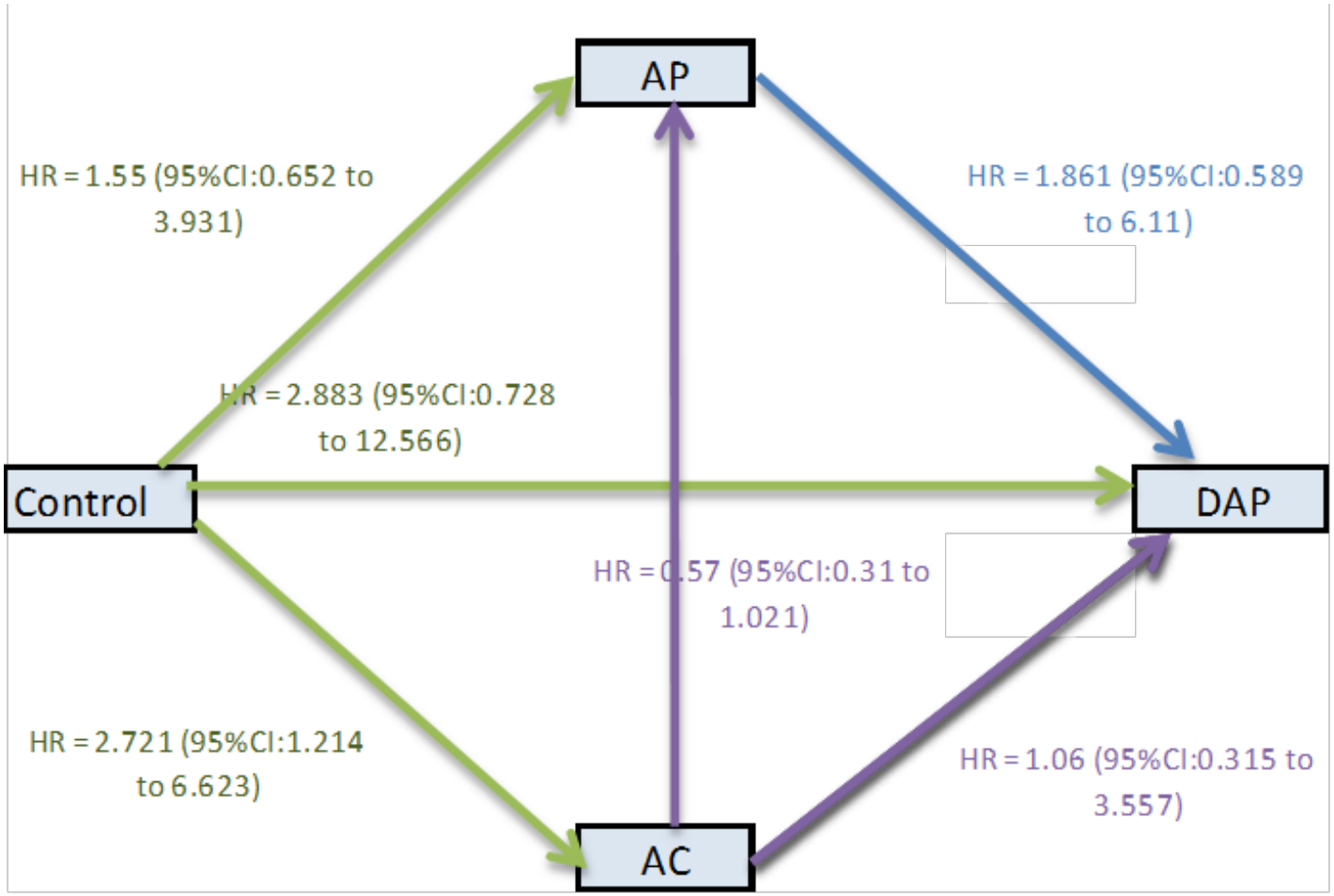
Network meta-analysis: ischaemic stroke

Full guideline appendix M.3.2.2



Network meta-analysis: major bleeding

Full guideline appendix M.3.4.2



Conclusions: antiplatelet treatment

Full guideline section 9.2.4

- No clinical benefit of aspirin in reducing mortality and systemic emboli.
- Modest benefit in reducing ischaemic stroke was partially offset by a modest harm in increased bleeding and haemorrhagic stroke.
  - heavily dependent on results from the SPAF1 study, which used 325 mg aspirin/day
- Limited benefit in offering aspirin as the benefit was not outweighed by the associated harms.
- Patients at increased stroke risk should not be offered aspirin solely for stroke prevention.

Conclusions: dual antiplatelet treatment – 1

Full guideline section 9.2.4

- Dual antiplatelet therapy reduced the risk of ischaemic stroke compared with single antiplatelet therapy, but no difference was detected in the risk for all-cause mortality, haemorrhagic stroke, or systemic emboli. Conversely, dual antiplatelet therapy increased the risk of major bleeding.
- Dual antiplatelet therapy increased the risk of ischaemic stroke and systemic emboli when compared with anticoagulant therapy. Conversely a reduced risk of haemorrhagic stroke was noted. No difference was detected on the risk of mortality or major bleeding.

Conclusions: dual antiplatelet treatment – 2

Full guideline section 9.2.4

- The guideline development group (GDG) considered making a recommendation favouring the use of dual antiplatelet therapy in patients in whom all forms of anticoagulation were contra-indicated or not tolerated.
- The GDG was concerned that the main group of patients this would apply to were those at increased bleeding risk.
- There may be some patients in whom all forms of anticoagulation might not be tolerated and amongst whom the use of dual antiplatelet therapy might be reasonable, but the GDG considered that the potential number of patients was low and that this indication did not warrant a specific recommendation.

Conclusions: anticoagulant treatment

Full guideline 9.2.4

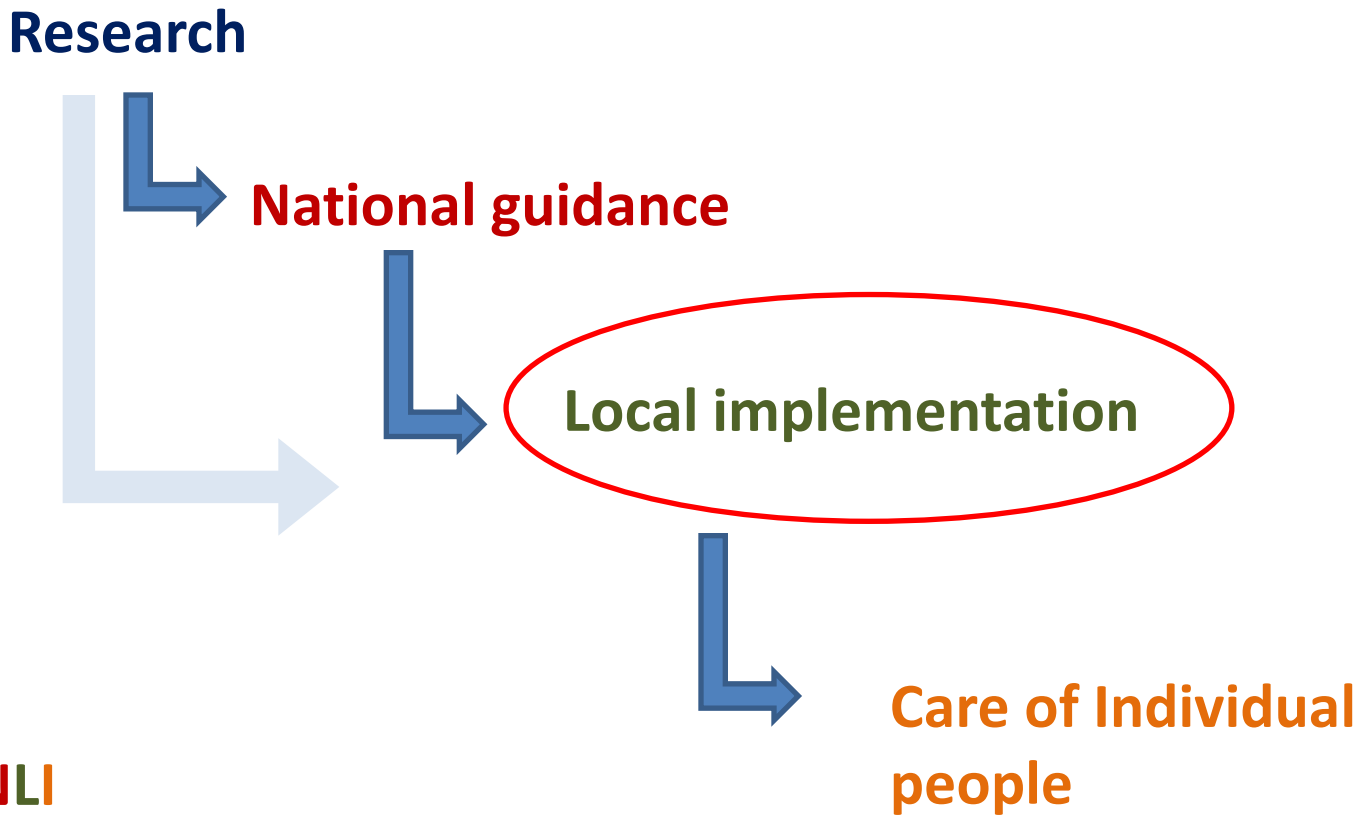
- GDG did not consider evidence relating to the comparison of specific non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin.
- GDG emphasised that following a decision to commence anticoagulation, all of the options for anticoagulation should be considered and discussed with a patient including the advantages and disadvantages of the different treatments available.
- A patient should be commenced on a particular NOAC only if they fulfil the eligibility criteria described in the TA for that particular drug.

Contents

- Key medicines optimisation issues in the guideline
- Rationale for the antithrombotic recommendations in the guideline
- **Key implementation issues**

Evidence into practice

Maskrey N, 2014: http://blogs.bmj.com/bmj/2014/08/21/neal-maskrey-tipping-the-balance-towards-individualised-care/



RNLI

Adoption of NICE technology appraisal recommendations

Developing and updating local formularies: NICE MPG1

- Include medicines with a positive NICE technology appraisal into the local formulary automatically, if relevant to the services provided by the organisation. This process should take place within 3 months. Include the medicine within the relevant care pathway(s), in line with NICE recommendations.
- If a NICE technology appraisal states 'option for treatment', adopt the medicine into the local formulary, and if necessary, identify its place in the relevant care pathway(s) provided by local organisation(s), in line with NICE recommendations.

Compliance with a NICE-approved medicine or treatment

www.nice.org.uk

Commissioners have a statutory responsibility to make funding available for a drug or treatment recommended by a NICE TA or HST within the timeframe recommended in that guidance.

Compliance is therefore achieved if a clinician and their patient think a health technology is the right treatment and it is available on the NHS, as described in the NHS Constitution, and **without any local funding or local formulary restrictions.**

For the avoidance of doubt, when NICE recommends a drug as 'an option', this is an option for the clinician and patient to consider alongside other potential treatments, not an option for commissioners or providers to not make the treatment available.

How do NOACs compare with warfarin? – 1

Ruff CT et al. Lancet 2014; 383: 955–62

- Meta-analysis of 4 pivotal studies for NOACs (n=71,683)
  - RE-LY (dabigatran etexilate)
  - ROCKET AF (rivaroxaban)
  - ARISTOTLE (apixaban)
  - ENGAGE AF–TIMI 48 (edoxaban)
- Relative risks compared with warfarin*
  - Stroke or systemic embolism 0.81 (95% CI 0.73 to 0.91) p<0.0001
  - Intracranial haemorrhage 0.48 (95% CI 0.39 to 0.59) p<0.0001
  - All-cause mortality 0.90 (95% CI 0.85 to 0.95) p=0.0003
  - Gastrointestinal bleeding 1.25 (95% CI 1.01 to 1.55) p=0.043

*dabigatran etexilate 150 mg twice a day, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, edoxaban 60 mg once daily

How do NOACs compare with warfarin? – 2

Dogliotti A et al. Sept 2013: Heart doi:10.1136/heartjnl-2013-304347

- Network meta-analysis of 20 RCTs (n=79,808)
  - Aspirin, aspirin plus clopidogrel, VKAs, apixaban, dabigatran, rivaroxaban, control/placebo
- No statistically significant differences between any NOAC and any other or VKA for key outcomes
  - prevention of stroke; ischaemic stroke or systemic embolism; mortality; major bleeding
- Authors emphasise the limitations of the evidence base:
  - 'Table 3 clearly shows the benefit of oral anticoagulants, particularly new anticoagulants as a class, but in general, we believe that none of the individual novel agents should be considered superior to another in the absence of a direct comparison.'

Possible implementation issues: NOACs

- NOACs offer advantages for some people, but not others
- Apixaban, dabigatran etexilate and rivaroxaban are each recommended as treatment options and all have a positive TA – how do you ensure all 3 are available in a way that minimises risk?
- NOACs have a higher acquisition cost than warfarin but are cost effective and have a funding directive attached to them
- Putting in hurdles to make NOACs second choice behind warfarin, or give one NOAC preference over another, is open to challenge as not complying with NICE guidance or the funding directive

The NOACs: DTB said…

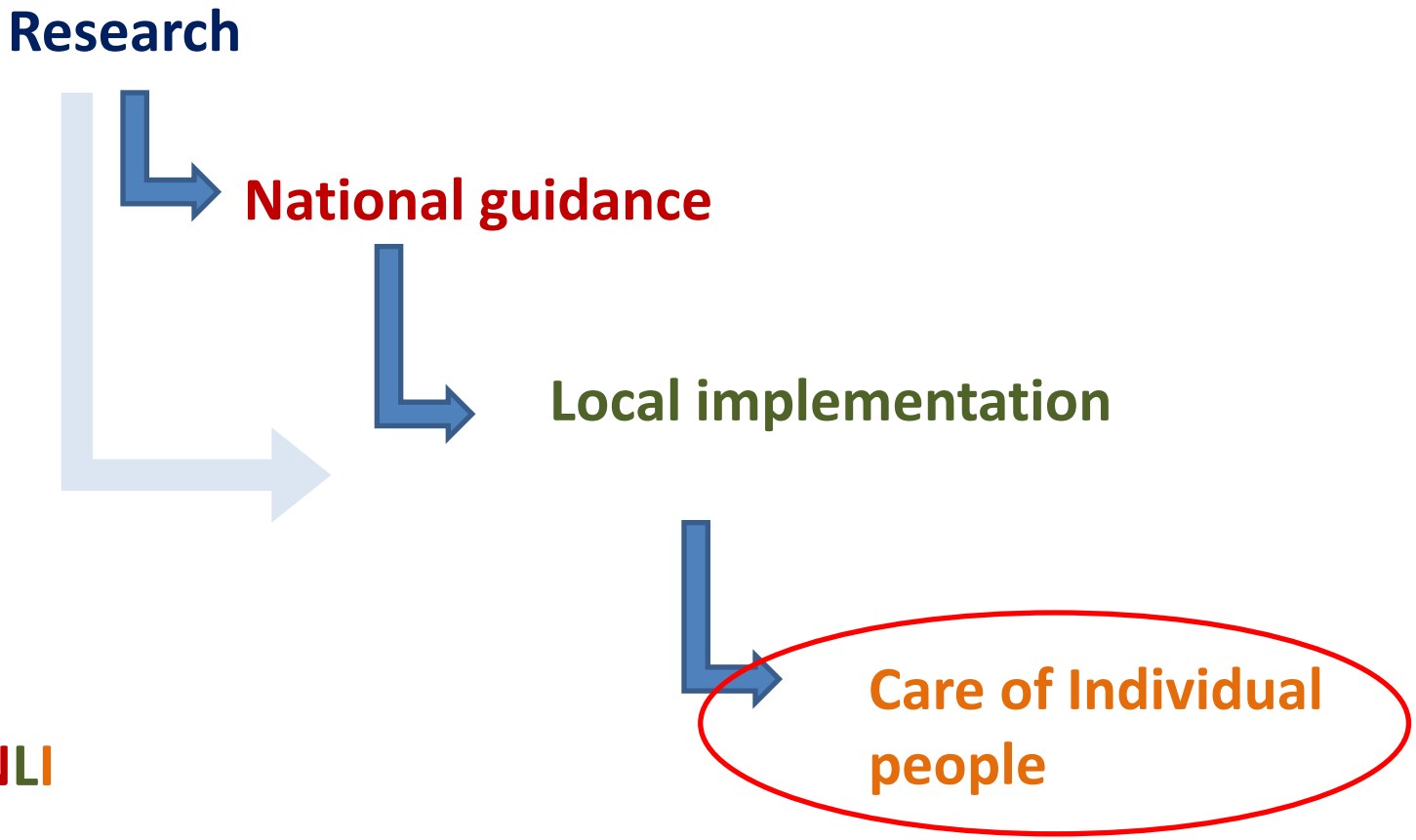
DTB (2014) 52(1): 6–9

Within their licensed indications the newer oral anticoagulants offer potential advantages for some patients. However, the cost of the newer drugs and the need to continue to provide anticoagulant monitoring services for those patients taking warfarin will present an ongoing challenge for commissioners of NHS services.

The key priority for healthcare professionals will be to ensure that patients with non-valvular atrial fibrillation are able to make an informed decision about the options for anticoagulation therapy to reduce their risk of stroke and systemic embolism.

Evidence into practice

Maskrey N, 2014: http://blogs.bmj.com/bmj/2014/08/21/neal-maskrey-tipping-the-balance-towards-individualised-care/



RNLI

Overemphasis on following algorithmic rules?

Greenhalgh T, et al. BMJ 2014;348:g3725

‘Well intentioned efforts to automate use of evidence through computerised decision support systems, structured templates, and point of care prompts can crowd out the local, individualised, and patient initiated elements of the clinical consultation…

Inexperienced clinicians may (partly through fear of litigation) engage mechanically and defensively with decision support technologies, stifling the development of a more nuanced clinical expertise that embraces accumulated practical experience, tolerance of uncertainty, and the ability to apply practical and ethical judgment in a unique case…

As the language of EBM becomes ever more embedded in medical practice, and as bureaucratic rules become the accepted way to implement ‘the best’ evidence, its requirements for evidence are quietly attenuated in favour of an emphasis on rules.’

Extracts from the NICE AF patient decision aid

NICE National Institute for Health and Care Excellence

Patient decision aid

Atrial fibrillation: medicines to help reduce your risk of a stroke – what are the options?

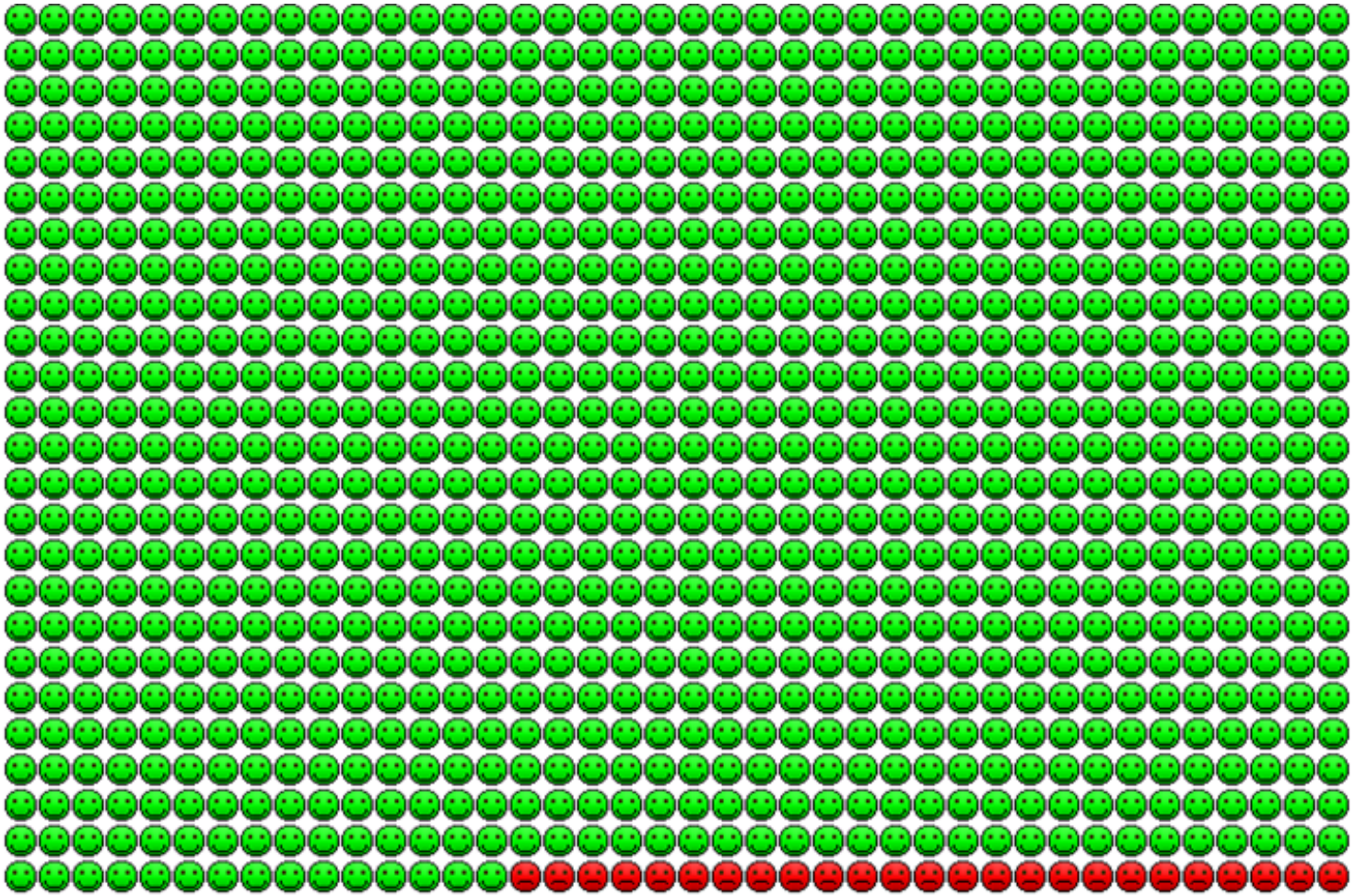
http://guidance.nice.org.uk/CG180/PatientDecisionAid/pdf/English

Published: June 2014

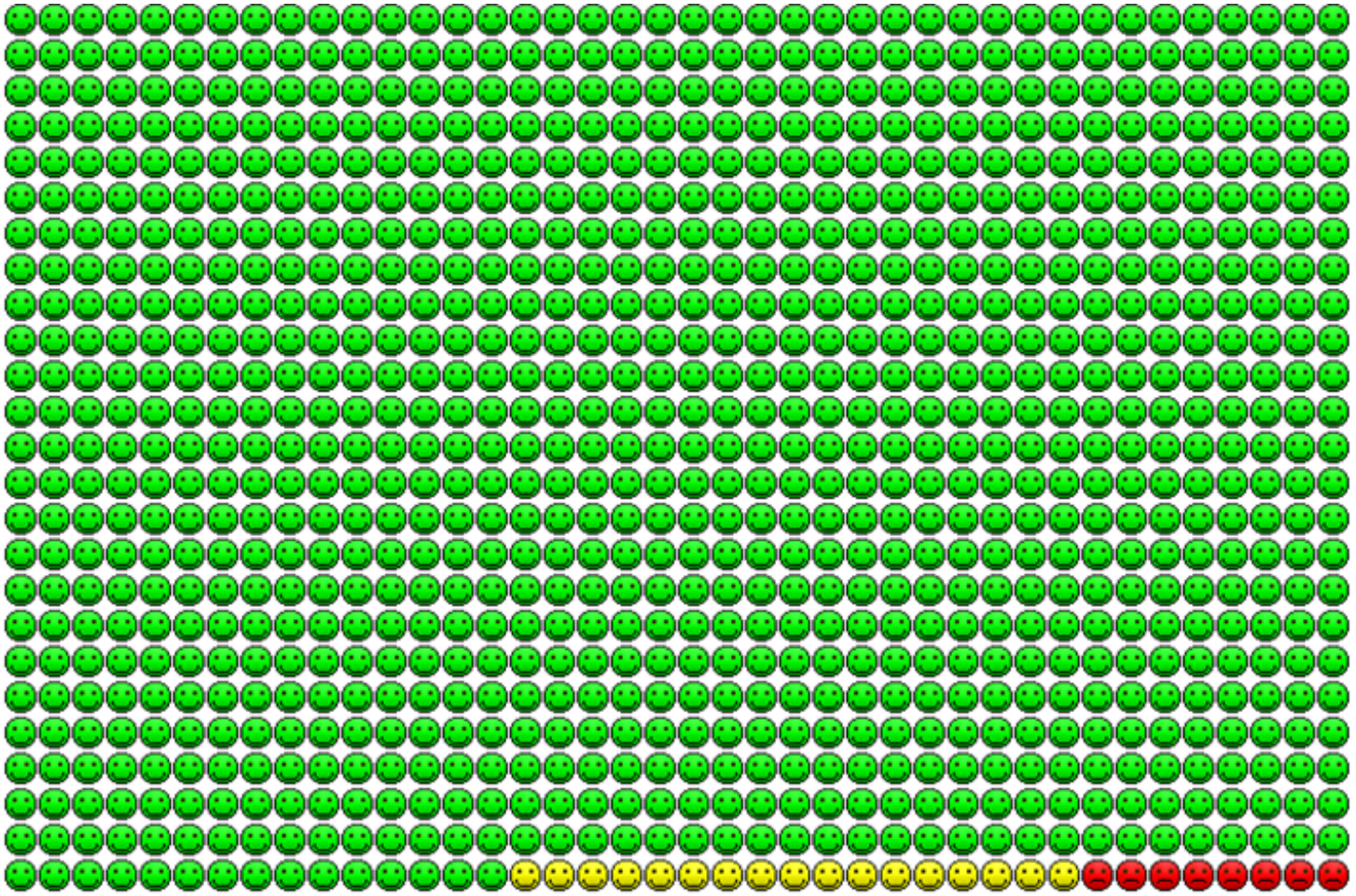
About this decision aid

This information is intended to help you reach a decision about whether to take an anticoagulant to reduce your risk of stroke, and which one to take if you decide to do so. Your decision depends on several things that this decision aid will help explain. Different people will feel that some of these things are more important to them than others, so it's important that you make a decision that is right for you personally.

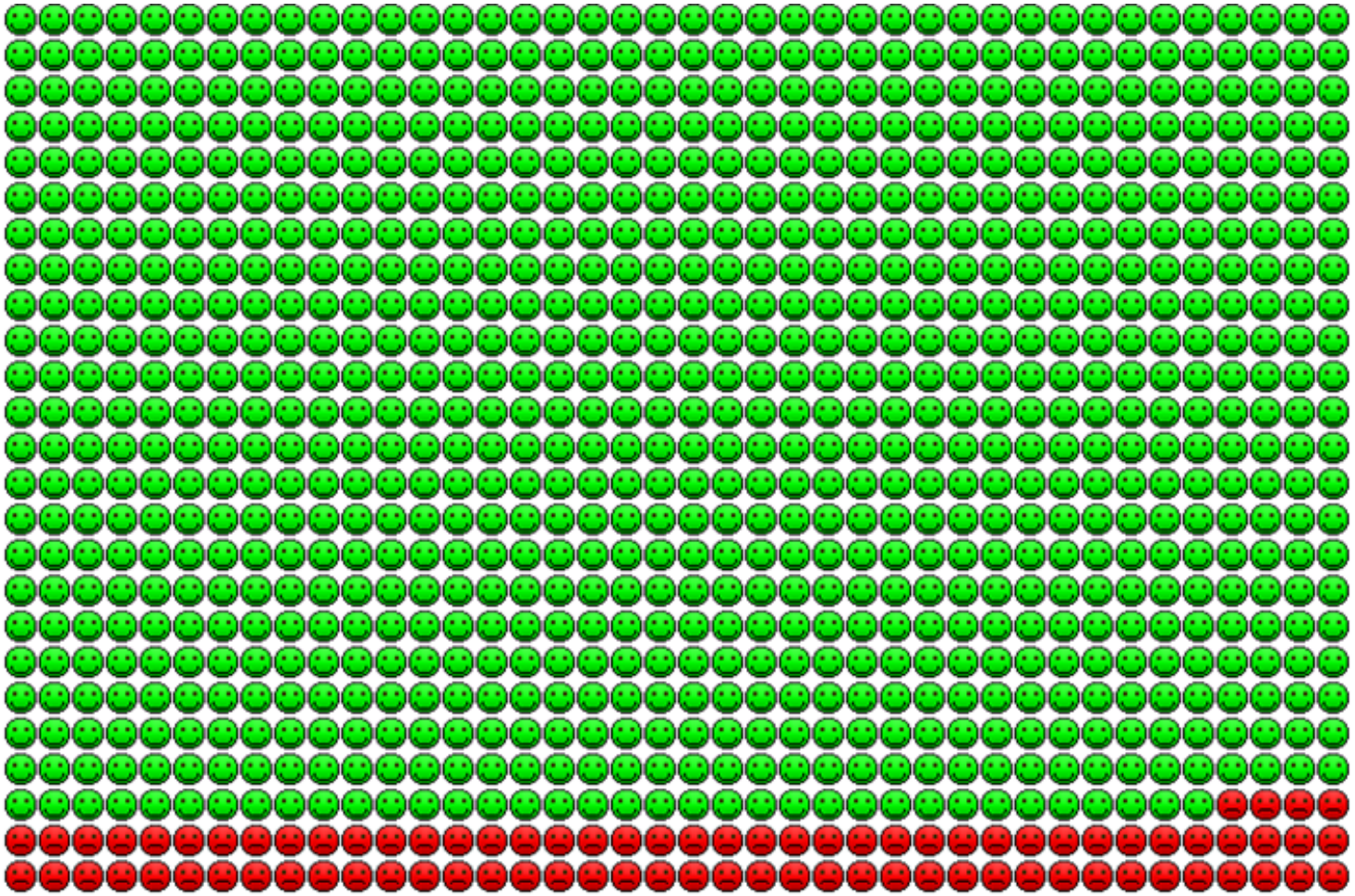
Ischaemic strokes per year
CHA_2DS_2-VASc score 2: no treatment



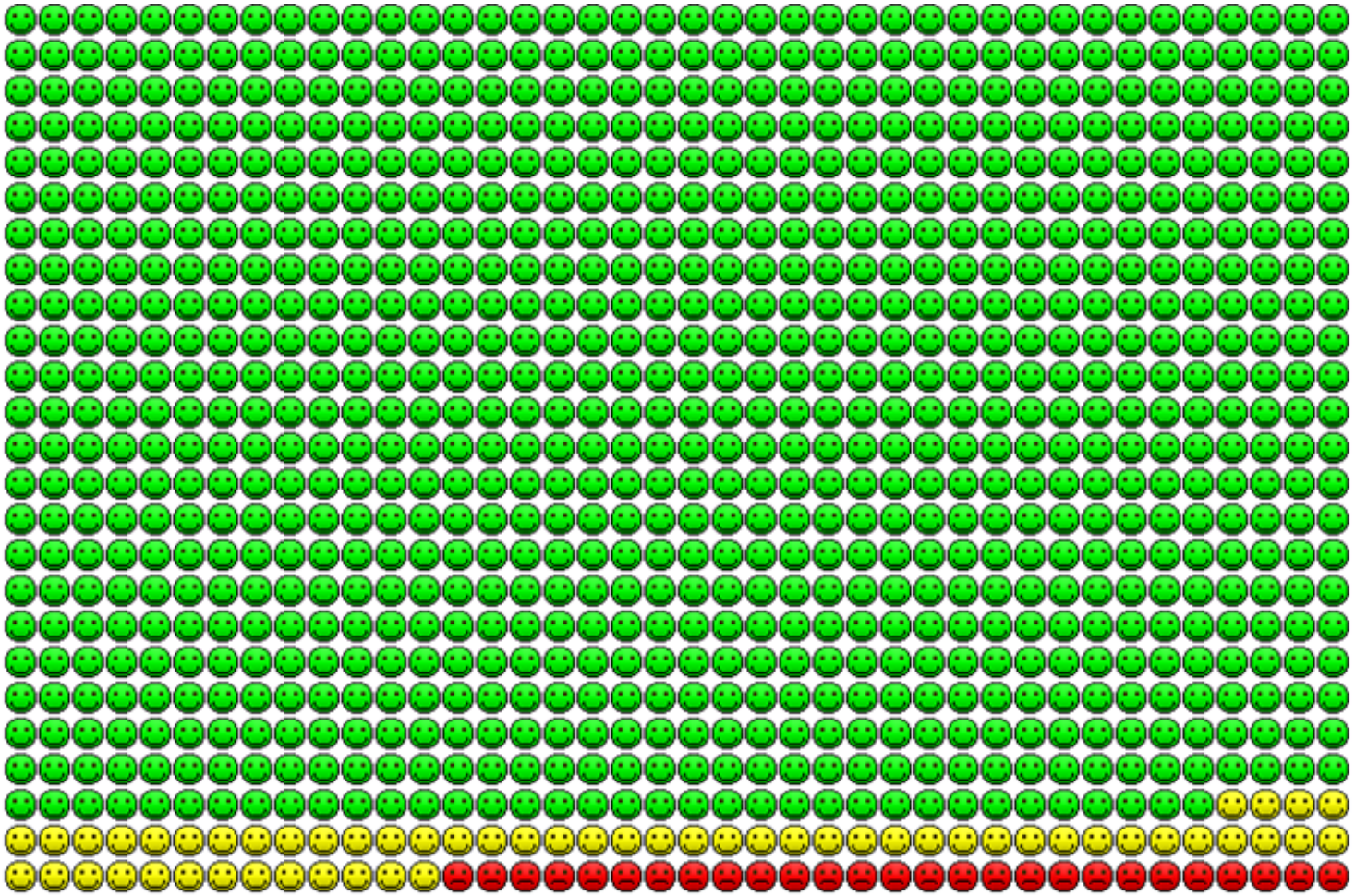
Ischaemic strokes per year
CHA_2DS_2-VASc score 2: effects of anticoagulants



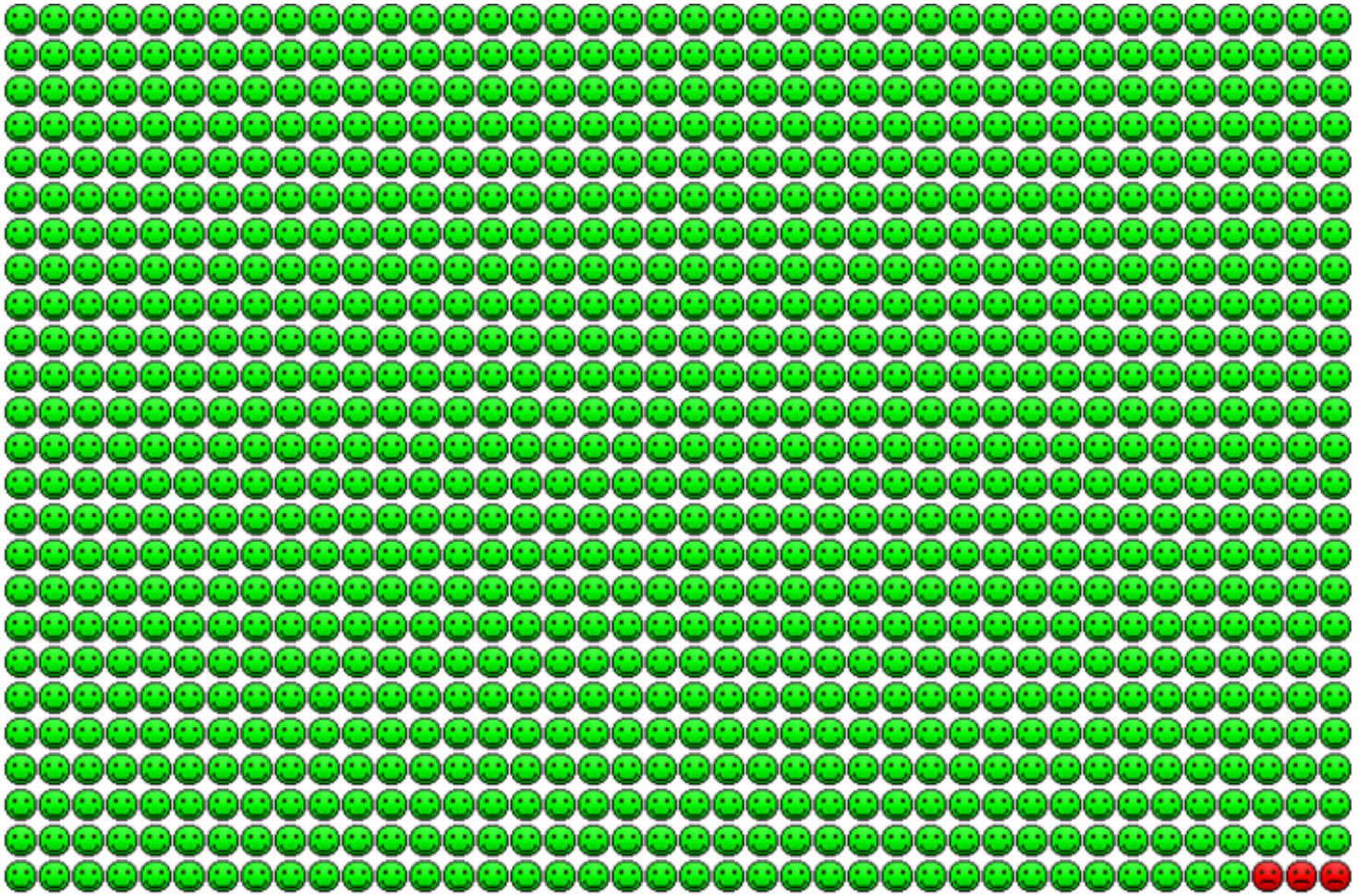
Ischaemic strokes per year
CHA_2DS_2-VASc score 5: no treatment



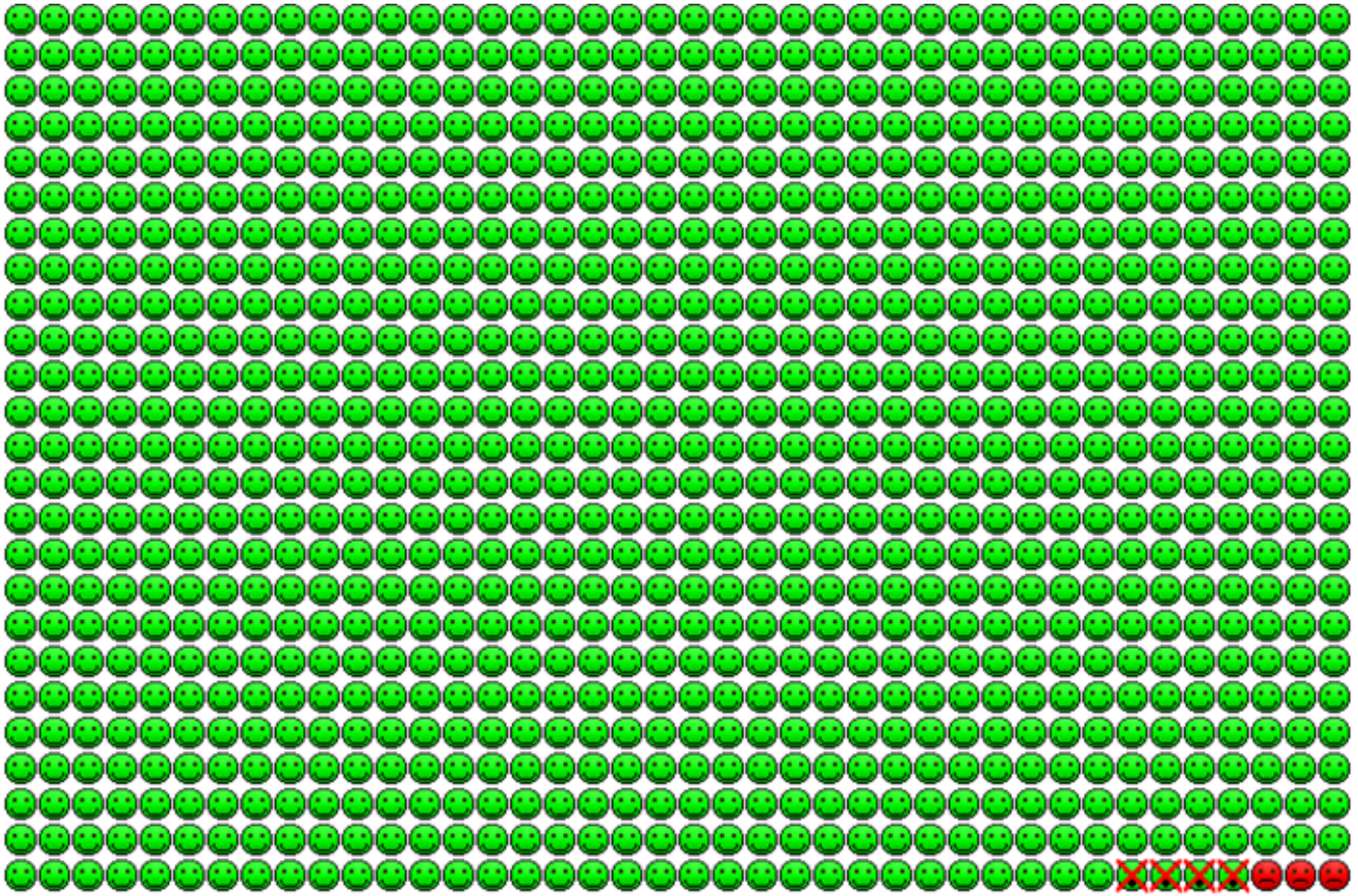
Ischaemic strokes per year
CHA_2DS_2-VASc score 5: effects of anticoagulants



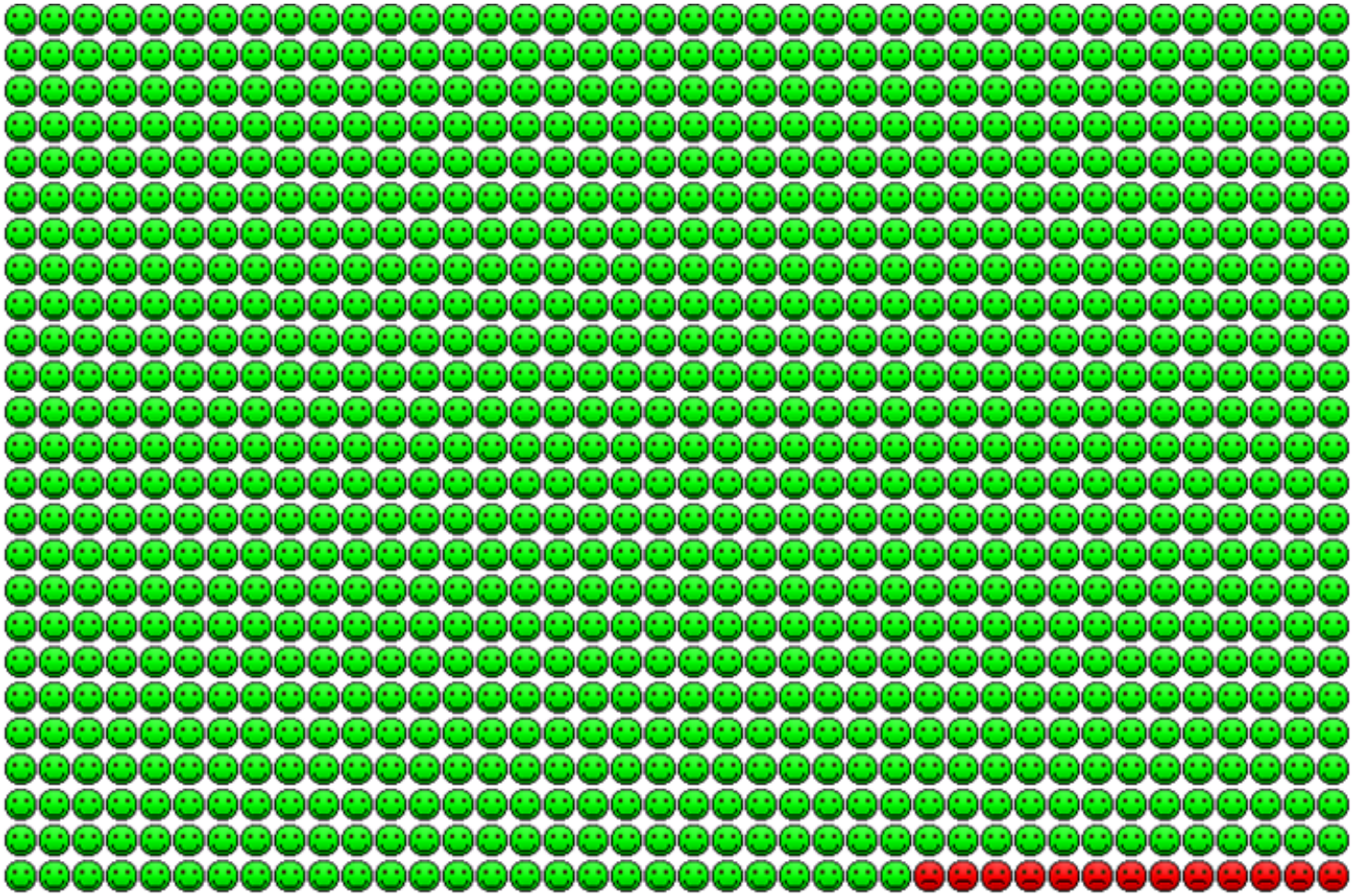
Major bleeds per year
HAS-BLED score 1: no treatment



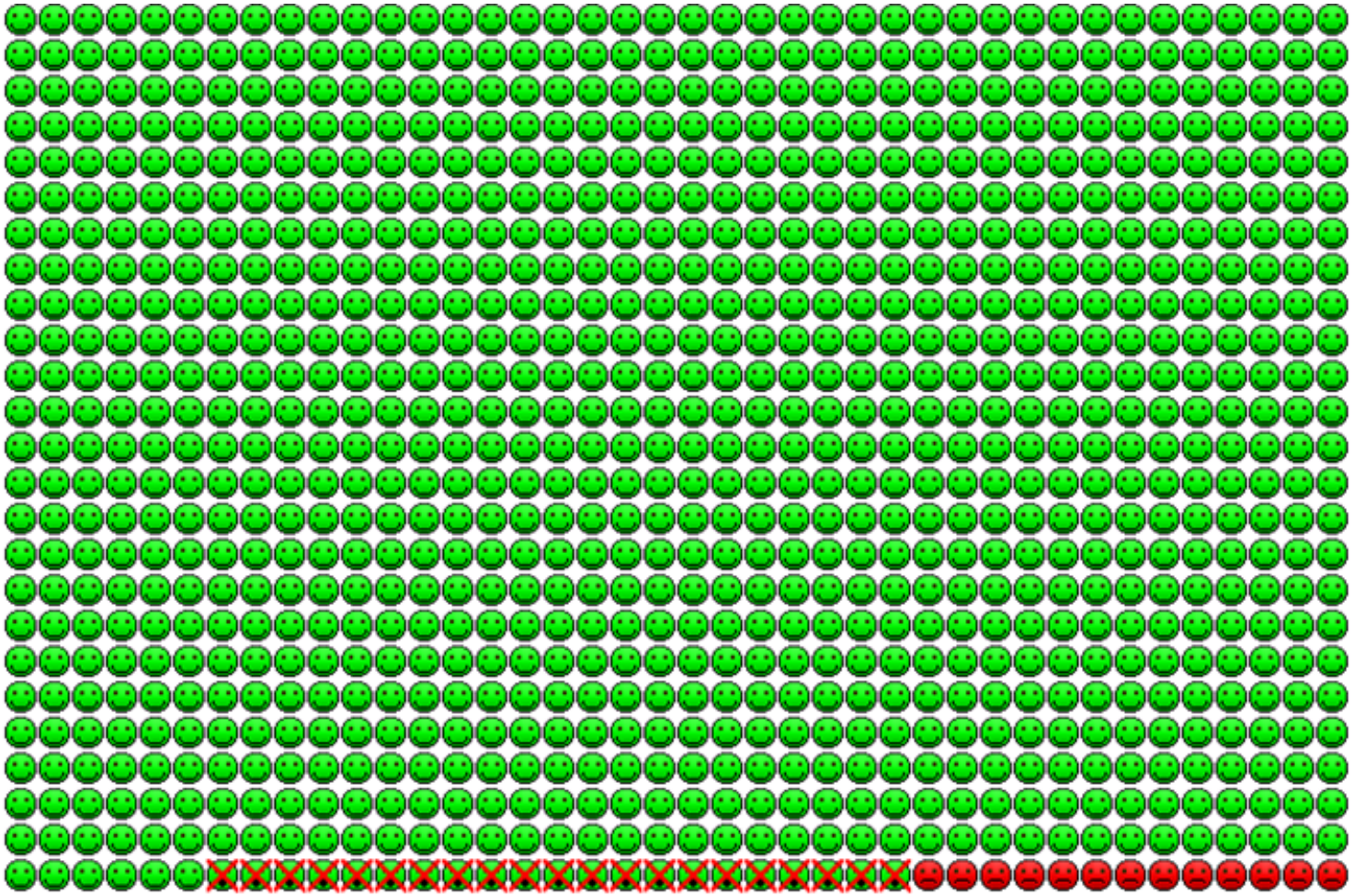
Major bleeds per year
HAS-BLED score 1: effect of anticoagulants



Major bleeds per year
HAS-BLED score 4: no treatment



Major bleeds per year
HAS-BLED score 4: effect of anticoagulants



Anticoagulation in AF: choosing an agent

Steinberg BA, Piccini JP BMJ 2014;348:g2116

The authors state that:

- Warfarin remains the preferred anticoagulant for several specific patient groups:
  - patients with concomitant valve disease
  - patients with severe renal dysfunction (eGFR<30 mL/min/1.73 m^2)
  - patients for whom the ability to readily and objectively monitor the extent of anticoagulation is paramount.
- In the remaining patients, the choice of anticoagulant can be tailored to individual needs and may include new drugs.
- **No single approach is optimal for all patients, and the subtleties of each patient's characteristics and preferences should be considered.**

Possible implementation issues: patient identification, assessment and choice

- Identifying people with AF not on treatment, or on aspirin monotherapy for stroke prophylaxis
- Assessing CHA_2DS_2-VASc and HAS-BLED scores and making patient-centred decisions
- Availability of time in therapeutic range (TTR) in local systems
- Self-monitoring and self-management of vitamin K antagonists
  - NICE diagnostics guidance expected September 2014

Atrial fibrillation: summary

- In many ways, the updated guideline is more straightforward than in the previous one
  1. Identify people with AF and risk assess
  2. Offer anticoagulation to everyone with CHA_2DS_2-VASc score ≥2*
  3. Offer rate control (consider rhythm control)
- The NOACs mean that some people can be treated who couldn't in the past, but they present an affordability challenge
- **These decisions are highly preference-sensitive, so patient-centred decisions are crucial**

**consider anticoagulants for men with CHA_2DS_2-VASc score 1, take into account bleeding risk*

Thank you for listening

Comments? Questions?