NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

UNIVERSITY OF
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# Developing clinical guidelines

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Dec 2015

CEBM

# Key objectives of this session

- Understand the key stages of guideline development
- Use GRADE to assess the quality of evidence
- Learn how to develop a recommendation using the available evidence

# What is a guideline?

- Systematically developed document designed to help healthcare providers and patients decide on appropriate healthcare for specific circumstances

- Enable individuals with diverse backgrounds to come to an agreement about healthcare and devise a quality framework, against which such care can be measured

- Assists policy makers with making informed decisions about useful frameworks for assessing healthcare costs

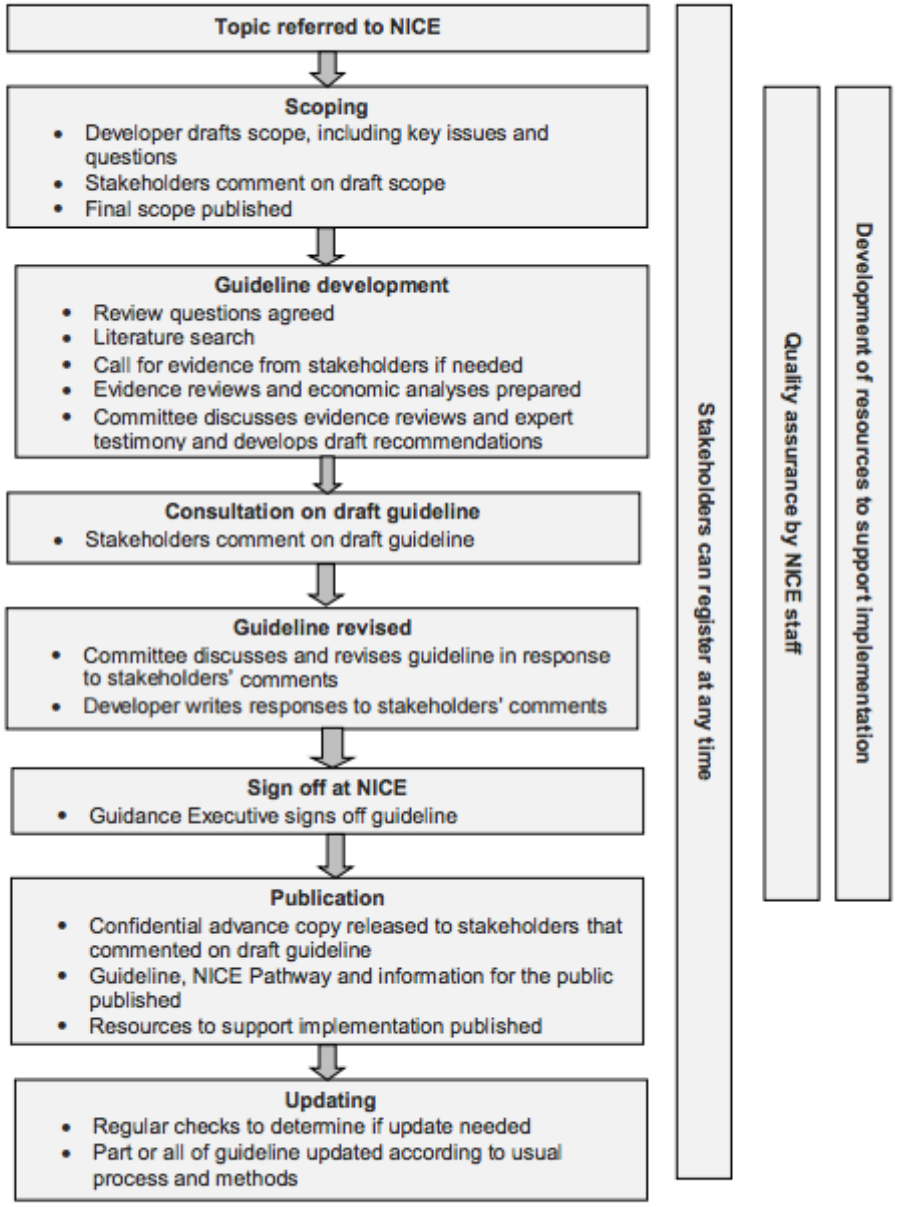
http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/whatareclinguide.pdf

# What are the key steps in developing a guideline?

NICE National Institute for Health and Care Excellence

## Summary of key stages of NICE guideline development

**Figure 1.1 Stages of guideline development**



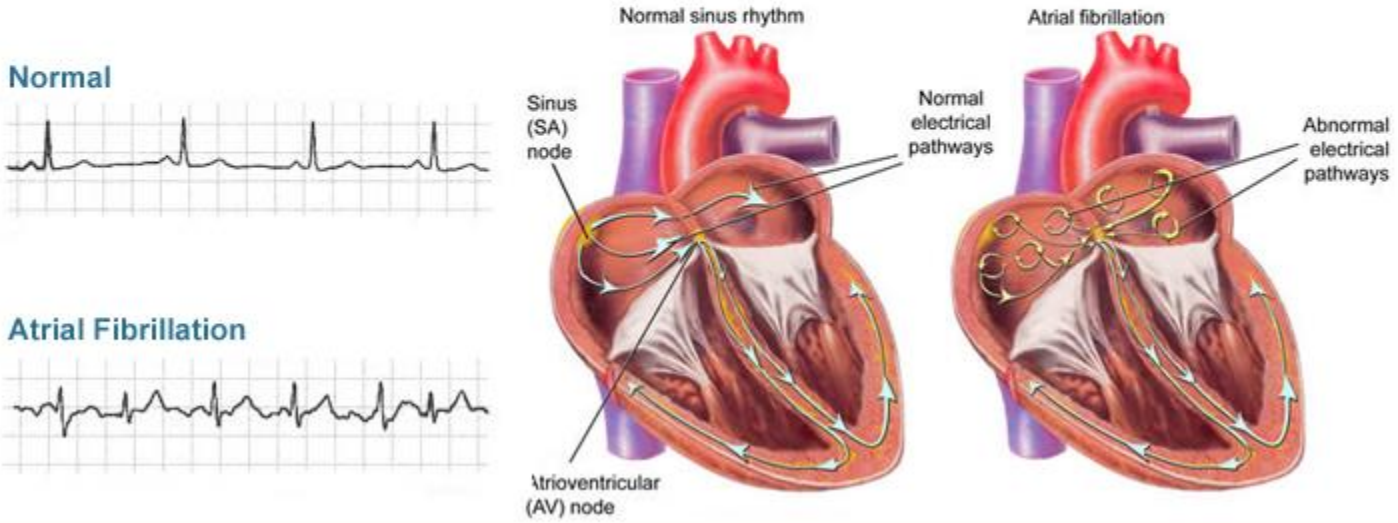



https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf

# 1. Topic identification

- What is the optimal way to manage atrial fibrillation?

***People with Afib are at a greater chance of a stroke (about 2 to 7 times the regular population), and Afib is the leading cause of stroke.***



Developing/updating local guidelines

# 2. Scope review – carried out by the developer

- defines the population(s) and setting(s) that will and will not be covered
- describes what the guideline will consider
- identifies the key issues and lists the key questions that will be considered
- describes the economic perspective(s) to be used.

# Carrying out the scope - sources

- identify related NICE guidance
- Related guidance websites e.g. NHS England, Public Health, Royal Colleges
- Policy and legislation: e.g. www.gov, Regulatory e.g. GMC
- Evidence reviews: e.g. Cochrane, HTA, The Campbell Collaboration
- Information on current practice: e.g. Audit Commission, Care Quality Commission
- Statistics: Health and Social Care Information Centre
- User experience: Websites/databases of people's experiences of health and social care

Local?

https://www.nice.org.uk/article/pmg21/chapter/Appendix-F-Sources-for-scoping

**Box 2.1 Factors to consider when identifying and prioritising key issues for inclusion in the draft scope**

| |
|---|
| **Uncertainty or disagreement on best practice** |
| Is there variation in current care provision and practice? |
| Is there variation in the level of integration of care and support for people using services or accessing care? |
| Is there evidence suggesting that common practice may not be best practice? |
| Is there debate in the literature? |
| **Potential to improve outcomes or make better use of resources** |
| How many people are affected and in which age groups or sectors of the population? |
| What is the potential for improved outcomes at acceptable cost? |
| What is the potential for reducing ineffective care? |
| What is the potential to provide care in a more efficient way (for example, through organisation of services to integrate care and support, or telecare)? |
| Are there issues about the staffing required to provide safe and efficient care? |
| Are there safety concerns that need addressing? |
| What is the potential for achieving cost savings with acceptable outcomes? |
| **Potential for avoiding unlawful discrimination, advancing equality and reducing health inequalities** |
| Are there any health inequalities or impacts on equality? |
| Are there any specific access issues (for example, by population, geographical location or group sharing a protected characteristic)? |
| Are exclusions (for example, populations, interventions or settings, or groups sharing a protected characteristic) justified? |
| Have all relevant mental health issues been considered, including where topics focus on physical health problems? |
| Are there any specific issues for people with a learning disability? |
| Do inequalities in prevalence, access, outcomes or quality of care for any groups (particularly those sharing protected characteristics) need to be addressed by the scope? |
| In the cases of any group of disabled people, might there be a need to consider reasonable adjustments when making recommendations? |
| **Likelihood that the guideline could contribute to change** |
| Is a new review of the evidence or an economic evaluation likely to reduce existing uncertainties? |
| How does the guideline fit with existing legal frameworks, statutory and professional guidance or government policies, and what is its anticipated impact? |
| What is the potential for achieving consensus within the Committee and in the wider stakeholder community? |
| **Other important factors** |
| Will the guideline update or incorporate any recommendations in other published NICE guidance? |
| Will the guideline take into account other NICE guidance (for example, technology appraisal guidance)? |
| How does the topic relate to existing NICE Pathways? |
| Where is it proposed that the topic will fit into NICE Pathways? |

# What does a scope look like?

# checking the population and selected key issues with stakeholders

- Who are the key stake holders?

# 3. Decision-making Committees (GDC)

- draws on its expertise to develop recommendations in the areas defined by the guideline scope
- Specifically:
  - may refine and agree the review questions
  - may advise on developing the review protocol and alternative analyses
  - considers the evidence
  - develops the recommendations
  - considers factors that may help or hinder implementation (‘levers and barriers’)
- Therefore the Committee needs to be multidisciplinary…

# Factors to consider for committee members

- MDT
  - specialists and generalists, and/or academics
  - Service users
- Conflicts of interest
- Training needs of your committee
- How often will you meet
- How will you record your meetings

# 4. Developing review questions and planning the evidence review

- Turn key issues in scope into review questions
  - How many?
  - How much time do you have?
  - Are they focused?
- Scope of review questions:
  - interventions that work
  - mechanisms of action likely to explain behavior or effects of proposed change
  - views and experiences of people using services of affected by guidance
  - practitioners' or providers' views, experiences and working practices (including any factors hindering the implementation of the intervention and factors supporting implementation)
  - costs and resource use
  - potential for an intervention to do harm or have unintended consequences

# Developing focused questions and key outcomes from scope…

***3.2 Current practice***

a) The aim of treatment for AF is to prevent complications, in particular stroke, and to alleviate symptoms.

b) AF is confirmed by an electrocardiogram (ECG), and an echocardiogram may also be performed.

c) Drug treatments for AF include anticoagulants to reduce the risk of stroke and antiarrhythmics to restore the normal heart rhythm or to slow the heart rate.

**4.3.1 Key clinical issues that will be covered**

a) Risk stratification for:

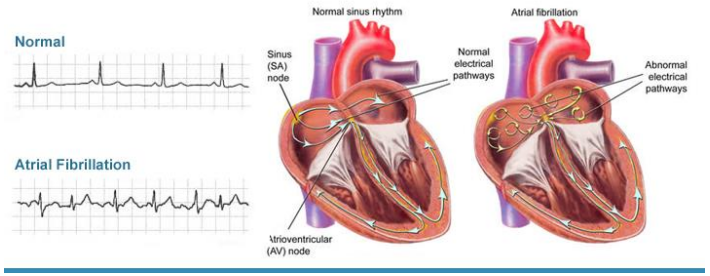
- stroke or thromboembolic events
- bleeding.

b) Prevention of stroke using:

- antithrombotic therapy
- left atrial appendage occlusion*.

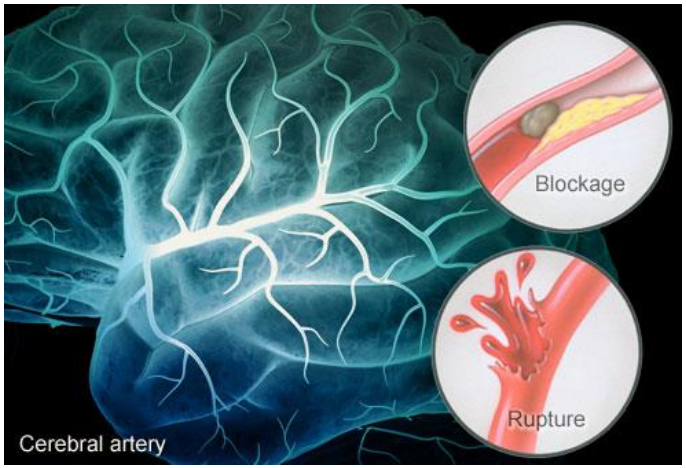
https://www.nice.org.uk/guidance/cg180/resources/atrial-fibrillation-update-draft-scope2

***People with Afib are at a greater chance of a stroke (about 2 to 7 times the regular population), and Afib is the leading cause of stroke.***




Antiplatelet

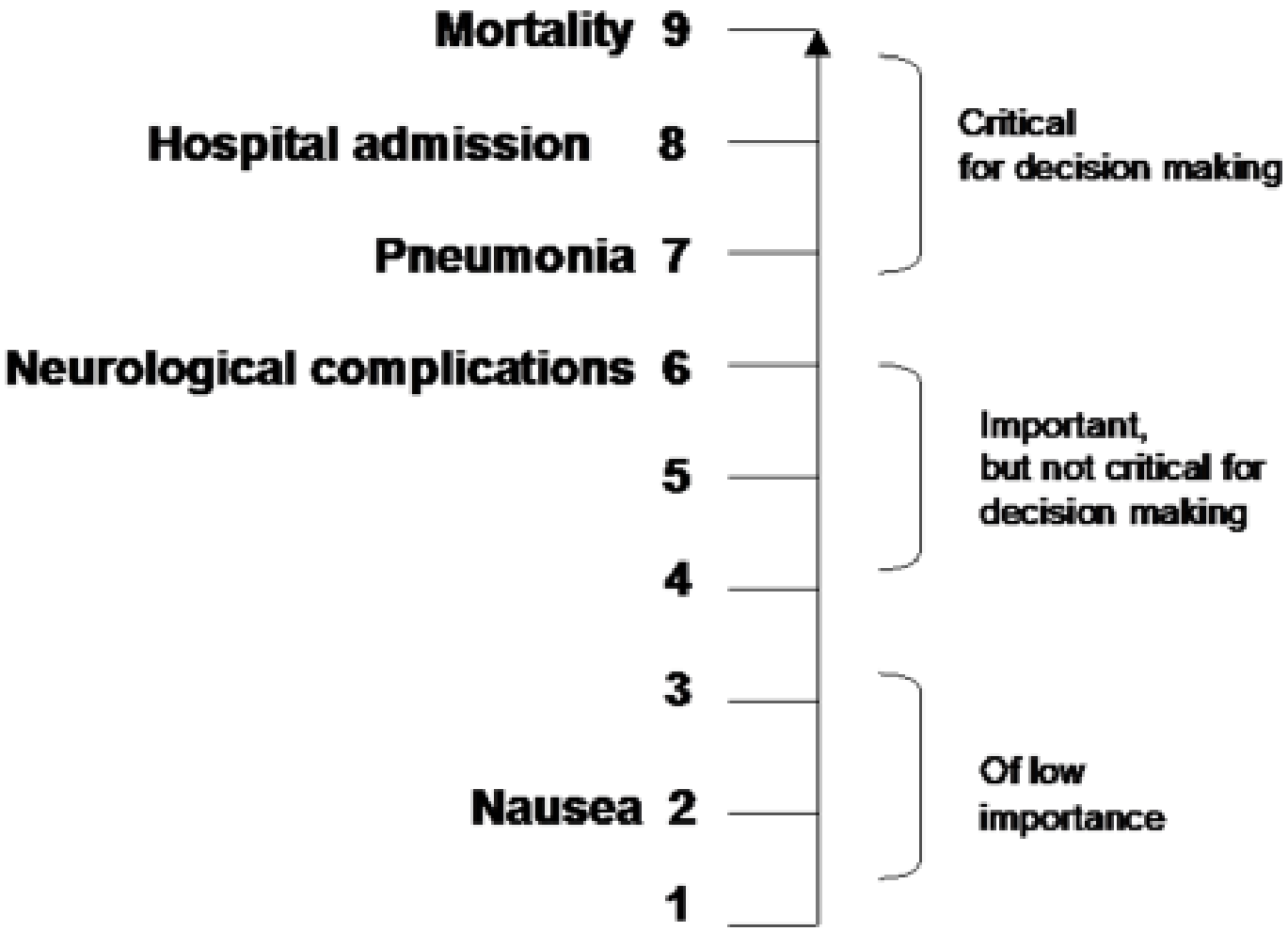

Anticoagulant


PICO?

Key outcomes

# Prioritising outcomes



# Sources of evidence

- Scientific evidence
  - explicit, transparent and replicable
  - evidence reviews or meta-analyses of quantitative studies, qualitative, cost-effective, individual studies or theoretical models
- Colloquial evidence
  - can complement scientific evidence or provide missing information on context
  - expert testimony
  - members of the Committee
  - reference group of people using services
  - registered stakeholders
- Other sources of evidence
  - reports, audits, and standard operating procedures

# 5. Identifying the evidence: literature searching and evidence submission

- Systematic literature searches should be
  - Thorough
  - Transparent
  - Reproducible
- Develop search protocol
- Sources
  - Databases, websites, others
  - Stakeholders evidence
- Key terms

# 6. Reviewing research evidence

- identifying and selecting relevant evidence
- extracting and synthesizing the results
- assessing quality
- interpreting the results
- deriving evidence statements.

# Assessing the quality of evidence

- Quality assessment by outcome - the GRADE approach to assessing and rating quality

# Presenting and summarizing evidence

- summary of the evidence, including the ‘summary of findings’ section from the GRADE profile
- evidence statements
- full GRADE profiles or links to the profiles in an appendix (if GRADE has been used)
- evidence tables

**Table 27: Clinical evidence profile: Anticoagulant versus antiplatelet**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Oral anticoagulant | Antiplatelet | Relative (95% CI) | Absolute | | |
| **Haemorrhagic stroke (fatal and non-fatal)**[85, 86,103,127,181,190,195,264,303,355,368,442,447] | | | | | | | | | | | | |
| 13 | randomised trials | serious[a] | no serious inconsistency | no serious indirectness | serious[b] | none | 47/5274 (0.89%) | 25/5653 (0.43%) | RR 1.6 (1 to 2.56) | 3 more per 1000 (from 0 more to 7 more) | LOW | CRITICAL |
| **Ischaemic strokes (fatal and non-fatal)**[85, 86,103,127,181,190,195,264,303,355,368,442,447] | | | | | | | | | | | | |
| 13 | randomised trials | serious[a] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 131/5889 (2.2%) | 281/5591 (5.0%) | RR 0.45 (0.37 to 0.55) | 28 fewer per 1000 (from 22 fewer to 32 fewer) | MODERATE | CRITICAL |
| **All-cause mortality**[103,127,181,190,195,264,303,368,447 86] | | | | | | | | | | | | |
| 11 | randomised trials | serious[a] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 345/5329 (6.5%) | 377/4987 (7.9%) | RR 0.89 (0.78- 1.03) | 9 fewer per 1000 (from 17 fewer to 2 more) | MODERATE | CRITICAL |
| **All-cause mortality - Hazard ratio**[127,195] | | | | | | | | | | | | |
| 2 | randomised trials | serious[a] | no serious inconsistency | no serious indirectness | serious[c] | none | 123/2938 (4.2%) | 157/2930 | HR 0.77 (0.61 to | 16 fewer per 1000 (from 1 fewer to 27 | LOW | CRITICAL |





| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (7.2%) | 0.98) | fewer) | | |
| **Major bleeding**[103,127,181,190,195,264,303,354,355,368,442,447 86] | | | | | | | | | | | | |
| 12 | randomised trials | serious[a] | no serious inconsistency | no serious indirectness | serious[b] | none | 122/5884 (2.1%) | 86/5546 (1.6%) | RR 1.35 (1.03 to 1.76) | 6 more per 1000 (from 0 more to 12 more) | LOW | IMPORTANT |
| **Systemic (non-CNS) emboli**[86,103,127,181,190,195,264,303,354,355,447] | | | | | | | | | | | | |
| 11 | randomised trials | serious[a] | no serious inconsistency | no serious indirectness | serious[c] | none | 15/5628 (0.27%) | 25/5284 (0.39%) | RR 0.54 (0.29 to 0.99) | 2 fewer per 1000 (from 0 fewer to 3 fewer) | LOW | IMPORTANT |

*a. Majority of the evidence, the studies were randomised and allocation concealment was performed. In most of the evidence patients were not blinded, however it is difficult to blind warfarin treatment and the outcome is unbiased.*
*b. Confidence interval crossed one MID (1.25)*
*c. Confidence interval crossed one MID (0.75)*

# Cost effectiveness?

**Table 32: Economic evidence profile: Antithrombotic therapy**

| Study | Applicability | Limitations | Other comments | Incremental cost (£) | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Jowett 2011[217] UK | Directly applicable (a) | Potentially serious limitations (b) | Within trial (BAFTA) analysis comparing<br>1. Warfarin<br>2. Aspirin<br>In a population older than 75. | - 166 (95% CI:-452 to 89) | 0.020 (95% CI:-0.070 to 0.111) | Warfarin dominates aspirin being less costly and more effective | Inspection of results on the cost-effectiveness plane suggests there is a high degree of uncertainty in the results, with Warfarin most likely to be the most cost-effective option (% NR)<br>For age groups 75-79 years old, warfarin is the dominant strategy. In age groups 80-84 years old warfarin has a cost per QALY of £14556. In age groups of 85 years plus warfarin with a cost per QALY of £6917. |
| Kansal 2012 [224] UK | Directly applicable (c) | Potentially serious limitations (d) | Markov model comparing<br>**Intervention 1:**<br>No antithrombotic therapy<br>~~**Intervention 2:**~~<br>~~High dose dabigatran 150 mg twice daily (which switched to a dose of 110mg after 80 years of age in age adjusted dosing)~~<br>**Intervention 3:**<br>Dose adjusted 5mg warfarin ((64% time in therapeutic range)<br>**Intervention 4:**<br>Aspirin monotherapy (162.5mg) | **Total costs (mean per patient):**<br>Intvn 1: 20475<br>~~Intvn 2: 19645~~<br>~~(drug costs 35%; stroke follow up costs 47%; 18% acute event management)~~<br>Intvn 4: 18561<br>Intvn 3: 18474<br>(drug and INR costs 17%; stroke follow up costs 61%; 22% acute event management) | **QALYs (mean per patient):**<br>Intvn 1: 7.12<br>~~Intvn 2: 8.06~~<br>Intvn 4: 7.59<br>Intvn 3: 7.82 | Warfarin dominates aspirin and no treatment being less costly and more effective | Detailed results of the sensitivity analyses were not given for the comparators for this review question. Incomplete incremental results not reported for subgroup analysis (age over and under 80 years) for comparators of interest. |
| Shah 2012 [401] USA | Partially applicable (e) | Potentially serious limitations (f) | **Intervention 1:**<br>No antithrombotic | **Total costs (mean per patient):** | **QALYs (mean per patient):** | Warfarin dominates dual antiplatelet | Inspection of graphics for three way sensitivity analysis suggests that for patients with: |

# Evidence statements

**Anticoagulant versus antiplatelet therapy**

Evidence showed that, compared to antiplatelets, anticoagulants reduce:

- All-cause mortality (eleven studies, N= 10316),
- Ischaemic stroke (thirteen studies, N= 11482)

Low quality evidence showed that, compared to antiplatelets, anticoagulants may reduce:

- all-cause mortality, as calculated as time to event (two studies, N=5868)
- haemorrhagic stroke (thirteen studies, N=11542)
- major bleeding (thirteen studies, N= 11430)
- systemic embolic (eleven studies, N= 10912)

What would you recommend in your draft guideline?

# 7. Consultant and review guideline

- Who will you consult with?

# Guideline development group

**Anticoagulant versus antiplatelet monotherapy:**

The GDG agreed that for people at increased risk of stroke anticoagulants compared to single antiplatelet therapy:

- decreased the risk of all-cause mortality and ischaemic stroke
- moderately decreased the risk of systemic emboli
- however, in contrast, anticoagulants had a moderately harmful effect by increasing the risk of haemorrhagic stroke and major bleeding compared with antiplatelet therapy.

The GDG agreed that anticoagulants were more clinically beneficial than antiplatelets and should be clearly recommended as first line therapy for patients at increased stroke risk.

# 8. Making recommendations from the evidence

- using a range of scientific evidence and other evidence
- Committee must use its judgement to decide what the evidence means in context
- Summarise relative value placed on:
  - Outcomes
  - benefits and harms
  - resource use
  - overall quality of the evidence
  - other considerations of the Committee

# Strength of recommendation

- the evidence is high quality and the desirable effects clearly outweigh the undesirable effects
- there is a close or uncertain balance
- The GRADE system offers two grades of recommendations:
- “strong” and “weak”

**Factors that affect the strength of a recommendation**

| Factor | Examples of strong recommendations | Examples of weak recommendations |
|---|---|---|
| Quality of evidence | Many high quality randomised trials have shown the benefit of inhaled steroids in asthma | Only case series have examined the utility of pleurodesis in pneumothorax |
| Uncertainty about the balance between desirable and undesirable effects | Aspirin in myocardial infarction reduces mortality with minimal toxicity, inconvenience, and cost | Warfarin in low risk patients with atrial fibrillation results in small stroke reduction but increased bleeding risk and substantial inconvenience |
| Uncertainty or variability in values and preferences | Young patients with lymphoma will invariably place a higher value on the life prolonging effects of chemotherapy than on treatment toxicity | Older patients with lymphoma may not place a higher value on the life prolonging effects of chemotherapy than on treatment toxicity |
| Uncertainty about whether the intervention represents a wise use of resources | The low cost of aspirin as prophylaxis against stroke in patients with transient ischemic attacks | The high cost of clopidogrel and of combination dipyridamole and aspirin as prophylaxis against stroke in patients with transient ischaemic attacks |

http://www.gradeworkinggroup.org/publications/GRADE-1_BMJ2008.pdf

# Strength of recommendation

- NICE has chosen not to do this, but to reflect the strength in the wording of the recommendation
- Strong recommendation
  - ‘offer’ ‘measure’, ‘advise’, ‘commission’ or ‘refer’
- Weaker recommendation
  - ‘consider’

**Box 9.3 Examples of recommendations made with 3 different levels of certainty**

**Recommendations for activities or interventions that must or must not be used**

- Ultra-rapid detoxification under general anaesthesia or heavy sedation (where the airway needs to be supported) must not be used. This is because of the risk of serious adverse events, including death.
- Patient group directions must be authorised only by an appropriate authorising body in line with legislation.

**Recommendations for activities or interventions that should or should not be used**

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.
- Offer a trial of supervised pelvic floor muscle training of at least 3 months' duration as first-line treatment to women with stress or mixed urinary incontinence.
- If a smoker's attempt to quit is unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months, unless special circumstances have hampered the person's initial attempt to stop smoking, when it may be reasonable to try again sooner.
- Record the person's blood pressure every 6 months.

**Recommendations for activities or interventions that could be used**

- Consider combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.
- Consider collaborating with other organisations and sharing existing educational materials to ensure a comprehensive approach.

### 9.2.4 Recommendations and link to evidence

| | |
|---|---|
| Recommendations | 11. Do not offer stroke prevention therapy to people aged under 65 years with atrial fibrillation and no risk factors other than their sex (that is, very low risk of stroke equating to a $CHA_2DS_2$-VASc score of 0 for men or 1 for women). [new 2014]<br><br>12. Consider anticoagulation for men with a $CHA_2DS_2$-VASc score of 1. Take the bleeding risk into account. [new 2014]<br><br>13. Offer anticoagulation to people with a $CHA_2DS_2$-VASc score of 2 or above, taking bleeding risk into account. [new 2014]<br><br>14. Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences. [new 2014]<br><br>15. Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation. [new 2014] |

# 9. Sending your draft guideline for review/consultation

- Who will you send to?
- How will you deal with comments?

# 10. Implementing guideline

- How will you help users take up the guidance?
- implémentation consultants support local organisations

# 11. Maintaining guidance

- How often will you update?
- How much resource will you have?

# Summary

- Guidelines can take months-years to develop
- Adequate time taken in the steps to formulate
- Specific areas to consider:
  - Scope of guidance
  - Key stakeholders
  - Key questions
  - Evidence review
  - Rating the quality of evidence
  - Strength of recommendation and wording in guidance
  - Implementation of guidance

Thank you