Practical prescribing

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Outline of presentation

- Latest evidence/advice on:
  - Antithrombotics in stroke prevention in AF
  - Reassessing “normal” blood pressure
  - CHCs - long-term cancer risks and benefits
  - HRT - long-term risks and benefits
  - Antibiotic prescribing in general practice
- Tips on cost-effective prescribing:
  - focusing on how to find and interpret cost-effectiveness information

Background and evidence-base for the presentation

- I am a GP, not an expert in therapeutics
- Most of my research is about the safe and effective use of medicines rather than on specific therapeutic topics
- I have the advantage of working with the BNF, Prescriber, MHRA and various other organisations involved in medicines use
- Nevertheless, like most GPs, I have to work hard to keep up-to-date and regularly have to look things up to check that I am doing the right thing
- This presentation gives a GP perspective based on searches for recent evidence around topics identified by the organisers and myself
- I have tried to highlight implications for practice

Where to look for evidence for best prescribing practice

- **www.bnf.org/bnf/**
- **www.library.nhs.uk/**
- **www.nelm.nhs.uk**
- **www.crd.york.ac.uk/crdweb/**
- **http://cks.library.nhs.uk/ (was PRODIGY)**
- **www.library.nhs.uk/guidelinesFinder/**
- **www.nice.org.uk/**
- Cochrane database
- Searches of Medline and other databases and reading journal articles
- Googling???

Antithrombotics in stroke prevention with AF

- Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks.
  - *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD006186. DOI: 10.1002/14651858.CD006186.pub2.
- The Birmingham AF Treatment of the Aged (BAFTA) study *Lancet* 2007; **370**:493-503
- Assessing risk of stroke:
  - JAMA 2001;285:2864-70

Background

- Non-valvular atrial fibrillation increases the risks of embolic stroke and is associated with around 16% of all ischaemic strokes
- Both oral anticoagulants and antiplatelets have been shown to be effective for stroke prevention
  - previous studies suggest that anticoagulants are more effective

Cochrane review 2007

- 8 RCTs (including 9598 patients) were identified comparing warfarin with antiplatlets (mainly aspirin)
- 90% of patients had not had a stroke previously
- Meta-analysis undertaken
- Oral anticoagulants were associated with 32% lower risk of all types of stroke compared with aspirin
- For a baseline stroke risk of 4%, warfarin will prevent 13 strokes per 1000 patients treated vs. antiplatlets (NNT 76)
- For a baseline stroke risk of 2%, warfarin will prevent around 6 strokes per 1000 patients treated vs. antiplatlets (NNT 166)

BAFTA trial 2007

- 973 patients aged 75 years or over with atrial fibrillation were randomly assigned to warfarin or aspirin
- Yearly risk of fatal or disabling stroke was 1.8% versus 3.8%
- Relative risk 0.48; absolute yearly risk reduction 2%:
  - 20 strokes prevented per 1000 patients treated per year for warfarin vs. aspirin (NNT 50)
- No difference in risks of extracranial haemorrhage

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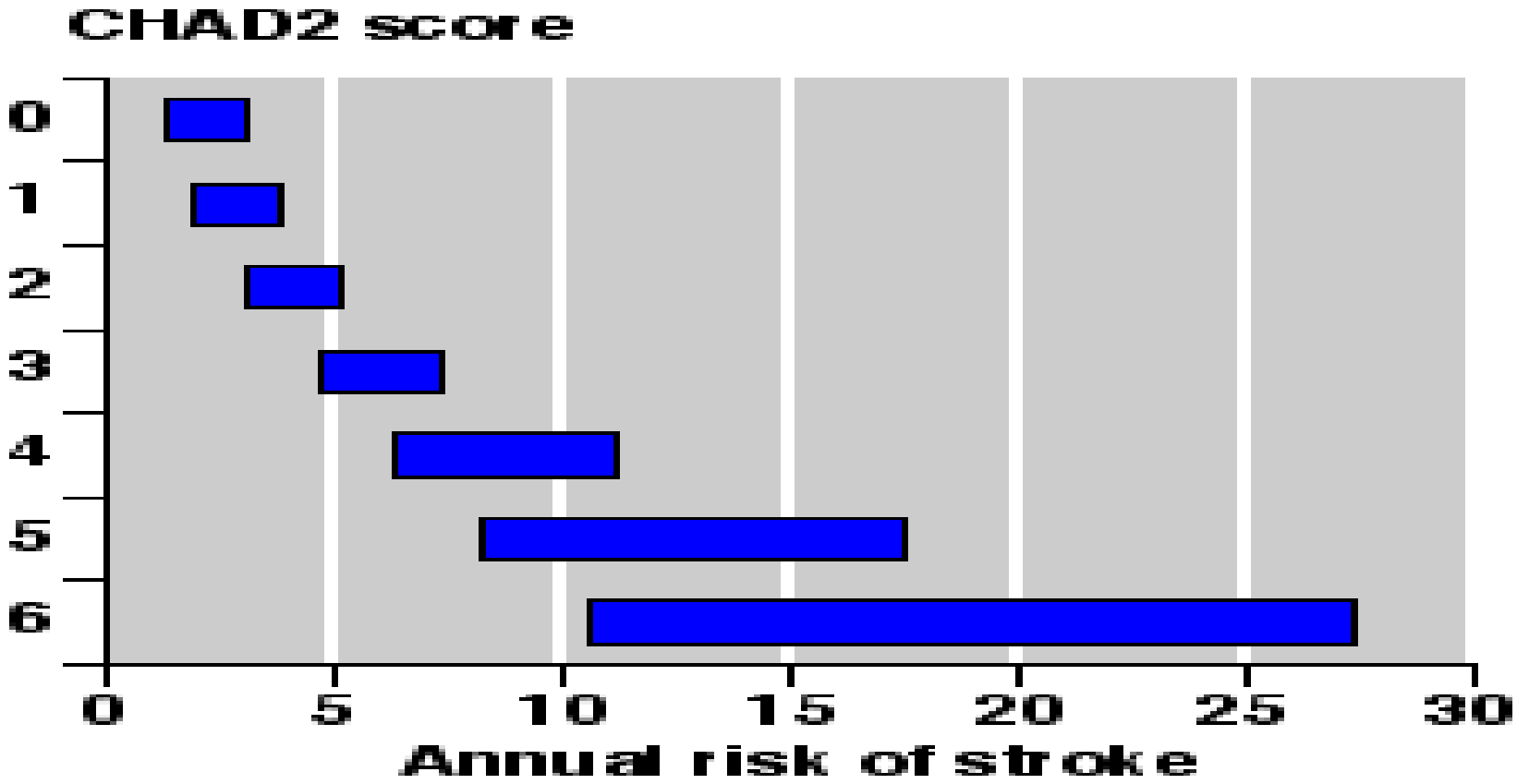
Working out risk of stroke in non-rheumatic AF (JAMA 2001;285:2864-70)

CHADS2 item	Points
Congestive heart failure	1
Hypertension	1
Age above 75 years	1
Diabetes	1
Prior cerebral ischaemia	2

Annual risk of stroke

(Graph taken from Bandolier)



What does it mean for practice?

- Evidence of relative benefits of warfarin vs. aspirin strengthened by recent Cochrane review and BAFTA study
- In patients with moderate to high risk then warfarin is indicated unless compelling reasons not to prescribe
- In younger patients with low absolute risk of stroke, aspirin may still be a reasonable choice

Reassessing “normal” blood pressure

- BMJ paper (2007;335:408-409) was a prospective cohort study of 39,000 initially healthy US women (aged >45 years) classified into four categories on baseline blood pressure and followed up for a median of 10 years

Findings

- 2.5% of women developed a major cardiovascular event
- 50% with high-normal blood pressure progressed to hypertension after 5 years
- The age-adjusted event rate for each group was:
  - 1.6 per thousand person-years for normal blood pressure
  - 2.9 per thousand person-years for high normal blood pressure (130-9/85-9)
  - 4.3 per thousand person-years for those with baseline hypertension

Implications for practice

- An accompanying BMJ editorial (2007;335:408-9) acknowledges this further evidence of the impact of blood pressure on cardiovascular events, but notes the importance of evaluating this in the context of overall cardiovascular risk
- Rather than focusing solely on BP treatment thresholds it is important to assess overall cardiovascular risk (and consider treating low normal blood pressure when there are other significant risk factors)

Combined hormonal contraception and cancer risk

- Previous studies have suggested that current users of CHCs have:
  - increased risk of cancer of the breast, cervix and liver
  - Reduced risk of cancer of the endometrium and ovaries
- Risks of breast and cervical cancer decline after stopping oral contraception:
  - returning to the level of non-users within around 10 years

RCGP Oral Contraceptive Study

- Cohort study
- Study began in 1968:
  - 1400 general practitioners recruited
    - 23,000 women who were using oral contraceptives
    - 23,000 controls
  - From the mid-1970s around ¾ of the women were flagged and followed up for subsequent cancers and deaths (in the remaining ¼ events were recorded until women became lost to follow up)

Results from recent BMJ paper

doi:10.1136/bmj.39289.649410.55

- Comparison of 744,000 women years in the "ever users" group with 339,000 years in the "never users" group showed:
  - 12% reduction in the risks of any cancer (adjusted relative risk 0.88, 95% confidence interval 0.8 to three to 0.94)
  - Statistically significant reductions in rates of cancer of the large bowel or rectum, uterine body and ovaries
  - Small and non-significant increases in risks of cancer of the lung, cervix and central nervous system or pituitary
  - No material difference in risks of breast cancer

Comments

- Important study given:
  - size (over a million women years of observation)
  - setting (relevant to UK general practice)
  - length of follow up (virtually all women now postmenopausal)
  - adjustments made for potentially important confounders (age, smoking, smoke social class, parity)
- Unknown confounders may have influenced the results
- Most of the pills used in the study contains at least 50 µg of oestrogen
- Reduced risk of uterine and ovarian cancers is consistent with other studies

What does it mean for practice?

- When counselling patients we can be reassuring about the overall long-term cancer risks from CHCs
- Lower dose CHCs may not have the same benefits although there is other evidence suggesting reduced risk of uterine and ovarian cancer
- Overall the benefits are likely to outweigh the risks for healthy women wishing to consider the CHC

HRT

- Our views on the risks and benefits of HRT have changed radically in recent years, with publication of data from randomised controlled trials contradicting the findings of earlier observational studies
- The MHRA's recent *Drug Safety Update* (Sept 2007) draws on recent evidence to give advice to prescribers and gives a table summarising risks:
  - www.mhra.gov.uk/mhra/drugsafetyupdate

Coronary heart disease

- One randomised controlled trial indicates that women on HRT more than 10 years after menopause have an increased risk of CHD
    - Womens' Health Initiative - JAMA 2007;297:1465-77
- Few RCTs have assessed newly menopausal women, but the attributable risk due to HRT is likely to be very low
- Overall message is that RCTs do **not** suggest any cardiovascular benefit from any form of HRT

Stroke

- Oestrogen-only and combined HRT increases the risk of stroke compared with placebo
  - Womens' Health Initiate:
    - Circulation 2006;113:2425-34
      - » Hazard ratio of 1.37 with oetrogen only HRT
    - JAMA 2003;289:2673-84
      - » Hazard ratio of 1.31 with combination HRT
- Increase in relative risk is not dependent on age
  - JAMA 2007;297:1465-77

Venous thromboembolism

- Increased risk of VTE with oral HRT
- Risk may be higher with combined rather than oestrogen-only HRT
- Events more likely in the first year of use
- Risk may be lower with transdermal HRT
    - Lancet 2003; 365:428-32
        - case control study where risks from oral HRT 3.5 times greater than transdermal

Endometrial cancer

- Oestrogen-only HRT greatly increases the risks of endometrial cancer
- Use of a progestogen for a least 10 days a month greatly reduces the risk
- Use of a progestogen every day eliminates the risk, but need to consider breast cancer risks as well
    - Million Women (Cohort) Study. Lancet 2005; 365:1543-51

Breast cancer

- Risk of breast cancer is increased after several years of treatment with HRT
  - e.g. with a background incidence of 10 cases per 1000 per 5 years in women aged 50-59, there will be an excess of:
    - 6 cases if HRT used > 5 years
    - 24 cases if HRT used > 10 years
- Combined HRT is associated with the highest risk
- Risk increased with duration of treatment, but returns to baseline within a few years of stopping

What does it mean for practice?

- HRT can still be used for premature menopause and the relief of vasomotor symptoms in menopause, after careful assessment and discussion of benefits and risks
- HRT should not be used for prevention of osteoporosis unless women are unable to use other effective treatments
- Use the lowest effective dose of HRT for the shortest time
- If treatment is given for more than 2-3 years make regular attempts to discontinue HRT
- When counselling women, useful information on risks is available in the BNF and charts in the Sept 2007 *Drug Safety Update* from the MHRA

Antibiotics

- GPs responsible for 80% of all antibiotic prescribing in UK and 50% considered not likely to benefit patients
- Recent studies:
  - Trends in antibiotic prescribing in general practice in the UK
    - Journal of Public Health 2004;26:268-274
  - What antibiotics do GPs use?
    - J Antimicrobial Chemotherapy 2007;60(supplement 1):i43-i47
  - Effect of antibiotic prescribing on antibiotic resistance in children
    - BMJ 2007;335:429-431
  - Containing antibiotic resistance
    - BJGP 2007;57:785-792

Trends in antibiotic use

- GPRD data derived from 108 UK general practices covering a mean of 643,000 patients between 1994 and 2000
- The authors reported:
  - age and sex standardised consultation rates for 11 different acute respiratory infections per thousand patients
  - proportions of these consultations resulting in an antibiotic prescription

Results

- Standardised consultation rates for respiratory infections declined by 35%
  - The largest reductions were for:
    - Common cold: 50% reduction
    - Laryngitis: 43% reduction
    - Sore throat: 43% reduction
- The proportion of respiratory infection consultations that resulted in an antibiotic prescription declined from 79% to 67%
  - The largest reductions were for:
    - Influenza: 52% reduction
    - URTI: 33% reduction
    - Laryngitis: 30% reduction
- Overall, antibiotic prescriptions for all acute respiratory infections declined by 45%

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What antibiotics do GPs use?

- GPRD data from 60 GPs between 1998 and 2001 were analysed
- The 20 leading indications for antibacterial prescriptions were described along with the types of antibiotics commonly used

Percentage of all antibiotic prescriptions for different indications

(% receiving a prescription for each indication)

• URTI	14%	(44%)
• LRTI	13%	(82%)
• Sore throat	11%	(64%)
• UTI	8%	(83%)
• Otitis media	8%	(62%)
• Conjunctivitis	6%	(85%)
• Vague Skin infection	4%	(31%)
• Sinusitis	4%	(85%)
• Otitis externa	3%	(75%)
• Impetigo	2%	(91%)

Types of antibiotic prescribed

• Amoxicillin	27%
• Erythromycin	9%
• Flucloxacillin	7.5%
• Trimethoprim	7.5%
• Penicillin V	7%
• Aminoglycoside	6%
• Chloramphenicol	6%
• Tetracycline	5%
• Co-amoxiclav	4%
• Cefalexin	3%

Antibiotics chosen were usually those recommended for first-line treatment

The problem of increasing antibiotic resistance

- We know that use of antibiotics increases risks of resistance in populations and individuals
- Recent BMJ paper shows that prescribing amoxicillin to a child in general practice increases bacterial resistance at two weeks
- Resistance levels subside by 12 weeks but risk of transmission of resistant strains up to this time is likely to increase antibiotic resistance in the community

A solution for containing antibiotic resistance?

- Recent BJGP observational study (with multilevel modelling) involving 240 UK general practices over 7 years showed:
  - A baseline antibiotic prescribing rate of 920 per 1000 patients per year, reducing to 659 per 1000 for practices included in year 7
  - A decrease in ampicillin resistance of 1.03% per decrease of 50 amoxicillin items per 1000 patients per year
  - A decrease in trimethoprim resistance of 1.08% per decrease of 20 trimethoprim items per 1000 patients per year

What does it mean for practice?

- We must continue to try to reduce levels of antibiotic prescribing, particularly for conditions where the benefits to individuals are minimal
- We can be encouraged in our efforts with the recent evidence that reducing antibiotic use may reduce antibiotic resistance
- "In the few cases where it is appropriate to repeat the prescription of an antibiotic within under three months, it may be sensible to choose one that has activity against beta-lactamase producing strains rather giving a further course of amoxicillin"

Top ten tips for cost-effective prescribing

1. Remember that cost effectiveness is different to cost minimisation
    - Cost effectiveness analysis compares the relative value of different clinical strategies, taking account of the costs and benefits (often expressed as costs per life year gained or QALY)
    - Cost minimisation analysis finds the least costly treatment *after* demonstration of similar effectiveness and risks

Top ten tips for cost-effective prescribing

2. Recognise that information on cost-effectiveness is often not easily available
   - Sources worth trying include:
     - **www.nice.nhs.uk**
     - **www.ncchta.org**
     - **www.crd.york.ac.uk/crdweb/**
     - **www.jr2.ox.ac.uk/bandolier/index.html**

Top ten tips for cost-effective prescribing

3. Consider thresholds for cost-effectiveness:
    - In the UK, NICE use a threshold of around £30,000 per quality adjusted life year (QALY) when recommending whether the NHS should purchase certain treatments

Top ten tips for cost-effective prescribing

4. Consider whether relevant strategies are being compared
    - We are most interested in cost-effectiveness relative to the “best” alternative
5. Ask how good the effectiveness data are?
    - Ideally need results from RCTs which is one reason why we have so little comparative cost-effectiveness information

Top ten tips for cost-effective prescribing

6. Ask how relevant the effectiveness data are:
    - Do they relate to primary care patients
    - Are they relevant to the UK
7. Consider whether the cost data seem reasonable:
    - Are there any other costs that need to be considered apart from drug costs, e.g. monitoring and follow up

Top ten tips for cost-effective prescribing

8. Ask who has funded the cost-effectiveness research
9. Whoever has funded the cost-effective research, remember that the findings can vary considerably depending on the assumptions used, especially if modelling is involved

Top ten tips for cost-effective prescribing

10. If you do not have information available from a rigorous cost effectiveness analysis, it is reasonable to take a cost minimisation approach if two treatments appear to be of similar effectiveness and safety, but with large differences in cost

Cost-effectiveness of prescribing for heart disease

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QJM 2007:100:277-289

Intervention	£/LYG
Beta-blocker post MI	502
Aspirin post MI	885
Aspirin for stable angina	1706
ACEI post MI	3398
Statins post MI	4246
Statins for 1^0 prevention 65-74 yrs	11821
Statins for 1^0 prevention 75-84 yrs	9159

Examples of cost minimisation

- Selecting the least expense drug within a drug group
  - Simvastatin vs. atorvastatin for CHD prevention
  - Tetracycline vs. minocycline for acne
- Generic prescribing vs. brand-name
  - unless advised otherwise by BNF
- Prescribe separate drugs rather than combination products
- Standard release formulations rather than modified release
  - unless advised otherwise by BNF
- Less expensive strength/formulation
  - 0.5% hydrocortisone vs. 1% hydrocortisone
  - Tablets vs. patches (where tolerated)
- Step-down treatment rather than regular treatment
- Prescribing the least expensive regime
  - e.g. simvastatin 40mg is half the cost of 2*20mg

Summary

- Increasingly we have rapid access to information to help guide our prescribing decisions
- Important to try to find time to ensure that our prescribing practice is up-to-date, while also respecting patient choices
- Important also to use the most cost-effective treatments where high quality evidence exists