# Rational Prescribing

NHS Wiltshire Clinical Commissioning Group

## How effective are the drugs we prescribe?

- With an ageing population and rising multi-morbidity, the problem of harmful polypharmacy is becoming ever more apparent
- It is well recognised that strict adherence to single condition guidelines may cause more harm than good
- A more rational approach to prescribing has been recommended in a number of national documents (see references below)
- The challenge is to select those treatments of highest benefit to an individual and think more critically about those of perhaps lower value
- Most guidelines are based on evidence from trials on middle aged patients with single conditions, but we are meant to use our clinical judgement when applying these to individuals
- This document aims to provide some at a glance information about common treatments used in primary care to help with that decision making process

## Administrative Notes

- This guidance has been developed in conjunction with Dr Julian Treadwell, Health Education South West GP Fellow for Evidence Informed Commissioning attached to Wiltshire CCG and GP at Hindon Surgery
- There is lot more valuable information in the full documents, and links are provided to full references
- All trial data shown is of statistical significance (to 95% confidence) unless otherwise stated
- For further information on interpreting clinical trial data, please see information here https://prescribing.wiltshireccg.nhs.uk/?wpdmdl=1538
- All references accessed 28/05/2015

## References:


- Polypharmacy and medicines optimisation: Making it safe and sound (The King's Fund) http://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf
- Polypharmacy: Guidance for Prescribing in Frail Adults (All Wales Medicines Strategy Group)
- http://www.awmsg.org/docs/awmsg/medman/Polypharmacy%20-%20Guidance%20for%20Prescribing%20in%20Frail%20Adults.pdf
- STOPP START Toolkit supporting Medication Review (NHS Cumbria)
- http://www.cumbria.nhs.uk/ProfessionalZone/MedicinesManagement/Guidelines/StopstartToolkit2011.pdf


# COPD

- NICE CG101 for COPD recommends prescribing inhaled corticosteroids (in combination with a LABA or LAMA) for patients with severe COPD (defined as $FEV_1$ <50 predicted) in order to reduce exacerbations and hospital admissions.
- Trials do show some effect on these outcomes but the absolute gains are very small

## Use of Combined Steroid/LABA inhalers for prevention of exacerbations

### Summary

- Data above is from a 2012 Cochrane Review. Trials were of variable duration up to 3 years.
- Other observations in the review were:
  - *Possible* benefit on mortality (NNT 42 for 3 years) but most evidence for this from one study (TORCH) and non statistically significant
  - "Moderate quality evidence…drop out rates in placebo groups…**most studies pharma funded**"
  - Data for gains in hospital admissions were *only just* statistically significant

## Use of Inhaled Steroids alone for prevention in COPD vs Placebo

### Summary

- Reduced exacerbation rate by 0.26 exacerbations per year per patient
- Tiny improvement in QOL scores (below clinical significance)
- No increase in exercise tolerance
- No reduction in bronchodilator use
- No change in mortality
- Increased risk of pneumonia 11.8% vs 7.7%

| | ICS / LABA | Placebo | Benefit/Harm |
|---|---|---|---|
| Exacerbations and Hospital Admissions | 9.3% | 11.4% | 2.1% benefit |
| Pneumonia | 6.9% | 5.5% | 1.4% harm |
| **'Net Benefit'** | | | **0.7%** |

COPD References


1. Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD003794.pub4#CD003794-sec1-0012
2. Inhaled corticosteroids for stable chronic obstructive pulmonary disease http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD002991.pub3
3. NHS Wiltshire COPD Guidance (awaiting final approval)

# Rational Prescribing

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## Hypertension

- Blood pressure lowering treatments are highly effective if hypertension is severe, but benefits diminish the milder the degree of hypertension

### Moderate and Severe Hypertension >160/100

- Effect of treatment on cardiovascular mortality and morbidity
  - 106/1000 (Treatment) vs 149/1000 (Placebo)
- 4.3% Absolute risk reduction
- NNT = 23 for 4.5 years
- Approx. 30% Relative Risk Reduction

### Summary

- Of total CV events, very roughly 60% were strokes
- Patient group >60 years, men and women
- Target BPs and BP drop achieved quite variable in the trials
- In > 80 yrs subgroup, similar benefits seen in CV mortality and morbidity, though no change in overall mortality
- Another trial on >80 yrs (HYVET) showed similar degrees of gain with a more modest target BP of 150/90

### Mild Hypertension 140/90 - 160/100

- **No statistically significant benefit** shown for treating Stage 1 Hypertension from the currently available evidence

### Summary

- Not many trials in this BP range (only approx. 8000 patients total) and low background event rates
- Reduction in stroke rate : 0.33% (Treatment) vs. 0 .66% (Placebo) over 4-5 years but *non statistically significant*
- Maybe treating Mild Hypertension over longer periods of time in higher risk groups would show clearer benefit, but no direct evidence yet (except in diabetes)
- 9% of patients withdrew from treatment due to side effects


Hypertension References

- Cochrane Review 2009 (Moderate and Severe) http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000028.pub2/abstract
- Cochrane Review 2012 (Mild) http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006742.pub2/abstract
- Hypertension in the Very Elderly Trial (HYVET) http://www.hyvet.com/pro/Results.asp


## Type 2 Diabetes

- Standard blood pressure control, statins and metformin have the most benefit in Type 2 diabetes
- Tight glucose control and tight blood pressure control have more marginal benefit

| Blood Pressure Control to < 140/90 by any means | Tight BP control SBP 120 vs 134 | Metformin | HbA1c reduction 7.3% (56 mmol/mol) vs 6.5% (47mmol/mol) (ADVANCE) | HbA1c reduction 7.9% vs 7.0% (UKPDS) |
|---|---|---|---|---|
| • NNT 57 per annum to prevent 1 MI or major diabetes event or death | • NNT 500 per annum to prevent one stroke | • NNT 50 per annum to prevent 1 MI or diabetes event or death | • NNT 333 per annum to prevent 1 microvascular event (mostly retinal) | • **NNT 200 per annum** to prevent 1 microvascular event (mostly retinal) |

### Summary

- Metformin aside, no glucose lowering drug (including insulin) has been shown to reduce macrovascular outcomes in RCTs.
- Very tight $HbA1_c$ control (<6% (42mmol/mol) vs 7-7.9%(53-63mmol/mol)) increased overall mortality by 1% and 7% had symptomatic hypoglycaemia (ACCORD)
- Tight $HbA1_c$ control (6.5% (47mmol/mol) vs. 7.3% (56mmol/mol)) did not significantly reduce macrovascular events, though did produce a 1.4% reduction in microvascular events, mainly worsening nephropathy (ADVANCE)


Diabetes References:

- NHS Scotland Polypharmacy Guidance 2012 http://www.central.knowledge.scot.nhs.uk/upload/Polypharmacy%20full%20guidance%20v2.pdf
- ACCORD Trial http://www.nhlbi.nih.gov/health-pro/resources/heart/accord-trial
- ADVANCE Trial http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2811451/

# Rational Prescribing

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## Chronic Kidney Disease

- 'Tight' blood pressure lowering and ACE inhibition in CKD is valuable only in selected patients

### Blood Pressure Targets

- **BP Target in standard CKD is in fact only <140/90**
- NICE suggest a range of SBP 120-139 because outcomes are WORSE with SBP < 120
- There is no evidence for most CKD that BP below 140/90 improves outcomes
- In selected patients there may be some gain (see next box)

### If CKD and significant proteinuria (ACR> 70) or CKD and Diabetes

- Target range is lower :
  - <130/80 (SBP range 120-129)
- **No benefit on cardiovascular outcomes or mortality shown**
- Benefit in these groups is all about **slowing progression** to end stage renal disease (ESRD) in those who have advanced, progressive CKD

### Tight BP control example outcomes

- Slows eGFR decline **5.5 vs 8.0** ml/min/1.73m$^2$ per yr
- Reduces progression to ESRD **19.6% vs 25.5%** over 3.5 yr
- Reduces doubling of creatinine **21.6% vs 26.0%** over 3.5 yr

### Summary (from evidence in full NICE Guidelines CG73)

- No clear evidence on diabetics without proteinuria (i.e. most of our T2DM patients)
- Strong evidence/big gains in Type 1 diabetics with proteinuria
- Getting blood pressure **too low** <120/80 causes striking increases in mortality and Cardiovascular Events


CKD references:

- Chronic Kidney Disease NICE Guidelines http://www.nice.org.uk/Guidance/CG73
- The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. New England Journal of Medicine. 1994; 330(13):877-884 http://www.nejm.org/doi/full/10.1056/NEJM199403313301301
- Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy (RENAAL) http://www.nejm.org/doi/full/10.1056/NEJMoa011161


### NICE Recommendations on role of ACEi / A2RAs

- Offer to patients with:
  - diabetes and an albumin creatinine ration (ACR) > 3
  - hypertension and an ACR > 30
  - ACR > 70 alone

### NICE Guidelines:

- The evidence used within the NICE CG 182 for these recommendations is quite mixed and it is hard to determine a definitive effect size for each of these recommendations

### Type I diabetes + proteinuria

- Progression to ESRD[1]
  - **26.9% vs 14.7%**
  - Placebo vs ACEi
  - over 4.5 years

### Type 2 diabetes + proteinuria + another CV risk

- Cardiovascular mortality[2]
  - **14.6 % vs. 8.4%**
  - Placebo vs ACEi
  - over 6 years

### No diabetes + proteinuria

- Doubling of Creatinine + ESRD[3]
- (many with glomerular disease)
- **45.5% vs. 23.1%**
- Placebo vs ACEi
- over 16 months

### Summary

- What's clear is that ACEIs are very valuable drugs for high risk / advanced CKD but there is no clear evidence to support their use outside of these type of groups
- ACEIs are not "good for kidneys" in general
- Remember risks associated with ACEIs including AKI


Further CKD References: (from NICE CG182)

1. EUCLID Study Group http://www.ncbi.nlm.nih.gov/pubmed/9269212
2. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial http://www.ncbi.nlm.nih.gov/pubmed/11304102
3. Ramipril in non-diabetic renal failure http://www.ncbi.nlm.nih.gov/pubmed/9291920

# Rational Prescribing

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## Osteoporosis

- Bisphosphonates do reduce fracture rates, but a relatively small proportion of these are hip fractures
- Considerable uncertainty exists around duration of treatment

### Alendronate for Primary and Secondary Prevention of Ostroporotic Fractures

- Women age range 65-80
- Alendronate vs placebo (with calcium & vit D)
- Duration up to 4 years

| Information from Cochrane Review[1] | Secondary Prevention | | Primary Prevention | |
|---|---|---|---|---|
| | Patients with T score lower than -2.0 OR Previous fragility fracture | | Patients with T score higher than 2.0 and no fracture | |
| **Type of Fracture** | **Alendronate** | **Placebo** | **Alendronate** | **Placebo** |
| Vertebral | 7.3% | 12.2% | 1.9% | 3.4% |
| Non-Vertebral | 7.2% | 9.3% | 11.3% | 13.0% |
| Hip | 0.6% | 1.3% | 0.8% | 1.5% |
| Wrist | 1.5% | 2.9% | 3.6% | 3.1% |

### Summary

- RELATIVE risk reduction (RRR) of 45-50% shown for most fracture outcomes
- ABSOLUTE risk reduction (ARR) and NNTs will depend on **baseline** fracture risk, **assuming** this same RRR applies to patients at higher risk (who have multi-factorial increases in fracture risk)
- Vertebral fractures in the trials were mainly **radiologically detected**, rather than clinically apparent
- **"Time to benefit"** was estimated at approximately 3 years
- An extension trial[1] of alendronate only showed further small reductions in vertebral fractures for treatment lasting > 5 years in women with existing vertebral fractures and/or persistently low BMD [1]
- Side effects for alendronate vs placebo the same in trials, though in a selected population


Osteoporosis References:

1. Cochrane Review 2008: Alendronate for the primary and secondary prevention of osteoporotic fractures in post menopausal women http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001155.pub2/abstract
2. Continuing bisphosphonate treatment for osteoporosis--for whom and for how long? N Engl J Med 2012;366(22):2051–3 http://www.ncbi.nlm.nih.gov/pubmed/22571169


## Calcium and Vitamin D without Bisphosphonate

- Calcium and Vitamin D achieve less than you might imagine when prescribed alone

### Primary Prevention for Community patients

- Fracture NOF reduced from **8/1000** (Placebo) to **7/1000** (Treatment) per year
- Harms: Hypercalcaemia **8/1000** excess
  GI symptoms **13/1000** excess
  Renal **2.5/1000** excess

### Primary Prevention for Elderly, institutionalised patients

- Fracture NOF reduced from **54/1000** (Placebo) to **45/1000** (Treatment) per year

### In secondary prevention

- **No benefit** was shown in this study of 5000 over 70s who previously had a fragility fracture (800iu Vit D + 1000mg Calcium)


References:

1. Cochrane Review 2013: Vitamin D and Vitamin D analogues for preventing fractures in most menopausal women and older men http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000227.pub4/abstract
2. RECORD trial. Grant et al, Lancet 2005 Mat 7 – 13 ; 365(9471) :1621-8 http://www.ncbi.nlm.nih.gov/pubmed/15885294/

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# BPH

- Many men remain on these drugs long term, they do reduce complications, but only by a few percent (see table below)

### Finasteride vs Doxazosin

- No difference in urinary retention at 4 years
- Need for surgery at 4 years : 2% Finasteride vs 4% Doxasosin
- Better urinary flow (2mls/min) with doxazosin at 1 year, but equivalent by 4 years
- Slightly lower rates ED and reduced libido with doxazosin (about half)
- Increased dizziness/ lightheadedness with doxazosin (4% vs 2.5%)

### Combination Finasteride+Doxazosin vs Doxazosin alone

- Combination reduces risk of progression (I-PSS 4 points) 4 % vs. 8% at 4 years
- Combination reduces need for surgery 1.5% vs. 4% at 4 years

| Cochrane Review 2010 [1] | 1 Year Review | | 4 Year Review | |
|---|---|---|---|---|
| | **Finasteride** | **Placebo** | **Finasteride** | **Placebo** |
| BPH Progression | | | 8.5% | 13.2% |
| Acute Retention | | | 1.9% | 4.6% |
| Need for surgery | | | 3.4% | 7.0% |
| Nocturia | | | No difference | |
| Erectile Dysfunction | 7.4% | 3.7% | 4.6% | 4.0% |
| Reduced Libido | 6.1% | 2.3% | 1.9% | 1.8% |
| Only small improvements in urinary flow rates seen – approx. 1ml/sec | | | | |


BPH References

1. Cochrane Review 2010 Finasteride for benign prostatic hyperplasia http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006015.pub3/abstract


# Antimuscarinic Drugs for Overactive Bladder

- Don't work very well and cause lots of side effects
- Perhaps only use if there is definite response

### Compared to placebo, antimuscarinic drugs result in:[1]

- 5 fewer trips to the toilet PER WEEK
- 4 fewer episodes of urinary leakage PER WEEK
- Some small gains in QOL measures
- $\frac{1}{3}$ get a dry mouth
- 41% in Placebo group improve with a further 15% with active treatment
- Gains are *statistically significant* but question of satisfactory clinical response

### Which AMD is best for OAB?[2]

- No drug shows clearly superior effectiveness
- Some variation in risk dry mouth :
  - Oxybutynin
    - -->oxybutynin SR
      - --> tolterodene
        - --> solifenacin

### Summary

- Remember hazards associated with multiple anticholinergics in the elderly: Giddiness, falls, cognitive impairment[3]
- Avoid oxybutynin in the elderly


Further references:

1. Cochrane Review 2006 Anticholinergic drugs versus placebo for overactive bladder syndrome in adults http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD003781.pub2
2. Cochrane Review 2012 Which Anticholinergic drug for overactive bladder symptoms in adults http://onlinelibrary.wiley.com/enhanced/doi/10.1002/14651858.CD005429.pub2
3. Treatment of Men with Lower Urinary Tract Symptoms and Overactive Bladder 2007 http://jama.jamanetwork.com/article.aspx?articleid=206092&resultClick=1
4. OAB Guidance Wiltshire CCG https://prescribing.wiltshireccg.nhs.uk/?wpdmdl=85