All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Polypharmacy: Guidance for Prescribing

Medicines Effectiveness Summary

July 2014

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MEDICINES EFFECTIVENESS SUMMARY

Table 1 below summarises the expected effect of various commonly prescribed medicine strategies represented in terms of numbers needed to treat (NNT) per annum to achieve a desired effect. The medicines included were chosen due to the following criteria:

- Is a medicine commonly associated with admission due to ADR, or;
- Is a medicine commonly prescribed in patients with multiple co-morbidities?

Details of the trials used to compile this table are given in Appendix.

Where possible, emphasis has been given to trials that include older age groups, and where possible, meta-analysis and reviews of multiple trials from reputable sources (e.g. Cochrane Library) have been used to try and obtain the best estimates of overall effect.

In most cases the analysis demonstrates that these strategies can be very effective if given to enough people for a long enough period of time.

Limitations

It is recognised that no data in any trial or meta-analysis will ever give an exact figure for an individual patient and this table is not intended to be an accurate indicator of outcomes. It is reasonable to assume, however, that the figures give a reasonable estimate of the magnitude of effect.

It is noted that patients in medicines trials will tend on average to be younger, fitter and have less co-morbidity than those not in trials.

This is not an exhaustive list of medicines that fit the above criteria.

Table 1: Medicines Effectiveness Summary

Please note: This table is not intended to be an accurate indicator of outcome, but rather a reasonable estimate of the magnitude of effect. An update of the data is expected by autumn 2014 and this table will be revised accordingly.

Indication/medication	NNT per annum	To do what	Notes
ACE INHIBITORS			
Elevated vascular risk (normal LV function)	280	Prevent one death (all causes)	Trial ran for 5 years
Impaired LV function – mild/moderate	30	Prevent one death (all causes)	Likely **symptomatic** benefit
Chronic kidney disease (CKD)	See Notes	Increase time to dialysis, reduce cardiovascular risk	ACE inhibitors unlikely to show benefit greater than other antihypertensives unless protein: creatinine ratio (PCR) > 100; in frail adults unlikely unless severe proteinuria PCR > 500 mg/mmol due to time to show effect.
Combination therapy including ACE			
ACE + indapamide	55	Prevent one stroke	Trial ran for 5 years
Secondary prevention post myocardial infarction (MI) > 80 yrs	33	Prevent one death	
ACE + beta-blocker for impaired LV	14	Prevent one death	Likely **symptomatic** benefit
Impaired LV mild/moderate ACE + beta-blocker	15	Prevent one death	Likely **symptomatic** benefit
Impaired LV severe ACE + beta-blocker + spironolactone	7	Prevent one death	Likely **symptomatic** benefit
ASPIRIN primary prevention	Enormous	No longer recommended	
ASPIRIN post stroke/transient ischaemic attack (TIA)	100	Prevent one stroke or MI or vascular death	
DIPYRIDAMOLE in addition to ASPIRIN post stroke/TIA	100	Prevent one vascular event	BNF caution in cardiac disease
CLOPIDOGREL post stroke or TIA	Dipyridamole + aspirin	Prevent one vascular event	
WARFARIN			
Atrial fibrillation (AF) + another risk factor v ASPIRIN	40	Prevent one stroke – no difference in mortality	
HYPERTENSION			
BP > 140/190 trial predominantly systolic hypertension			
Cardiovascular morbidity and mortality > 80 yrs			
Low risk	80	Avoid one cardiovascular event	2 years for effect
High risk (diabetes, vascular disease)	32	Avoid one cardiovascular event	2 years for effect
Cerebrovascular morbidity and mortality > 80 yrs	122	Avoid one cerebrovascular event	2 years for effect
Cardiovascular morbidity and mortality > 60 yrs			
Low risk	107	Avoid one cardiovascular event	4.5 years for effect
High risk (diabetes, vascular disease)	40	Avoid one cardiovascular event	4.5 years for effect
Cerebrovascular morbidity and mortality > 60 yrs	225	Avoid one cerebrovascular event	4.5 years for effect

Medicines Effectiveness Summary (continued)

STATINS	**NNT per annum**	**To do what**	**Notes**
MI or angina	80–170	Prevent one major coronary event	No difference in mortality to 5 years
Post stroke (atorvastatin 80 v placebo)	165	Prevent one cardiovascular event	No difference in mortality to 5 years
Tight HbA1c control strategies			
Microvascular risk			
ADVANCE (HbA1c 7.3% v 6.5%)	333	Prevent one microvascular event (predominantly retinal)	Trial ran for 5 years
UKPDS (HbA1c 7.9% v 7%)	200	Prevent one microvascular event (predominantly retinal)	Trial ran for 10 years
Macrovascular risk	No difference at 10 years		
Metformin			
Overweight/obese diabetic	50	Prevent one MI or diabetes event or death	10 year follow up
Standard < 140BP in control in diabetes			
Any means	57	Prevent one stroke or major diabetes event or death	8 year follow up
Tight BP control in diabetes			
BP 120 v BP 134	500	Prevent one stroke	4 years minimum for effect
Number needed to harm for this strategy	50		
Osteoporosis (alendronate + calcium/VitD)	**Secondary prevention vertebral fractures***	**Secondary prevention hip fractures***	**Notes for osteoporosis**
70–74 years	65	430	NNT per annum to prevent further fractures
75–79 years	45	180	Potential symptomatic benefit re vertebral fractures
80–84 years	60	105	**Normally 2 years needed to see effect**
85–89 years	55	45	
90+ years	40	40	
NNTs are a guide – they do not give exact figures for individual patients. *NNT for fractures calculated for annual NNT from 5 year NNTs			

Abbreviation definitions

Number needed to treat (NNT)

- Number of patients needed to treat to avoid a single additional adverse outcome.
- Needs to refer both to what adverse outcome is avoided and over what timescale (calculated as 1/ARR).

Absolute risk reduction (ARR)

- The absolute difference in adverse outcomes between groups.

Relative risk reduction (RRR)

- The relative difference in outcomes between groups.

APPENDIX: TRIALS USED TO COMPLETE MEDICINES EFFECTIVENESS SUMMARY

Cardiac Trials

The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325(5):293-302

The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342(3):145–153

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; 353(9146):9-13

The Randomized Aldactone Evaluation Study [RALES] Investigators. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. (Pitt B; Zannad F; Remme WJ; Cody R; Castaigne A; Perez A; Palensky J; Wittes J) *N Engl J Med* 1999; 341(10):709-717

Setoguchi S; Glynn RJ; Avorn J; Mittleman MA; Levin R; Winkelmayer WC. Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. *J Am Coll Cardiol* 2008; 51(13):1247-1254

Stroke Secondary Prevention

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324(7329):71-86

PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358(9287):1033-1041

Holman RR; Paul SK; Bethel MA; Matthews DR; Neil HAW. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. *N Engl J Med* 2008; 359(15):1577-1589

Halkes PH; Gray LJ; Bath PM; Diener HC; Guiraud-Chaumeil B; Yatsu FM; Algra A. Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta-analysis by risk. *J Neurol Neurosurg Psychiatry* 2008; 79(11):1218-1223

Rashid P; Leonardi-Bee J; Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke* 2003; 34(11):2741-2748.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. *N Engl J Med* 2006; 355(6):549-559

NICE. Technology Appraisal 210: Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90). 2010

Warfarin
Mant J; Hobbs FD; Fletcher K; Roalfe A; Fitzmaurice D; Lip GY; Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; 370(9586):493-503

Hypertension
Musini VM; Tejani AM; Bassett K; Wright JM. Pharmacotherapy for hypertension in the elderly. *Cochrane Database of Syst Rev* 2009; Issue 4. Art. No.: CD000028. DOI: 10.1002/14651858.CD000028.pub2.

Statins
Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344(8934):1383-1389

LaRosa JC; He J; Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999; 282(24):2340-2346

Goldberg RB; Mellies MJ; Sacks FM; Moye LA; Howard BV; Howard WJ; Davis BR; Cole TG; Pfeffer MA; Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 1998; 98(23):2513-2519

West of Scotland Coronary Prevention Group. West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet* 1996; 348(9038):1339-1342

Colhoun HM; Betteridge DJ; Durrington PN; Hitman GA; Neil HA; Livingstone SJ; Thomason MJ; Mackness MI; Charlton-Menys V; Fuller JH; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo controlled trial. *Lancet* 2004; 364(9435):685-696

Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC; Miller ME; Byington RP; Goff DC Jr; Bigger JT; Buse JB; Cushman WC; Genuth S; Ismail-Beigi F; Grimm RH Jr; Probstfield JL; Simons-Morton DG; Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358(24):2545-2559

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo controlled trial. *Lancet* 2002; 360(9326):7-22

Diabetes
Currie CJ; Peters JR; Tynan A; Evans M; Heine RJ; Bracco OL; Zagar T; Poole CD. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010; 375 (9713): 481-489

Ray KK; Seshasai SRK; Wijesuriya S; Sivakumaran R; Nethercott S; Preiss D; Erqou S; Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; 373(9677):1765–1772

The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patient with Type 2 Diabetes. *N Engl J Med* 2008; 358:2560-2572

The ACCORD Study Group. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. 2010. *N Engl J Med* 2010; 362:1575-1585

Osteoporosis

Wells GA; Cranney A; Peterson J; Boucher M; Shea B; Robinson V; Coyle D; Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev* 2008; Issue 1. Art. No.: CD001155. DOI: 10.1002/14651858.CD001155.pub2.

Renal

The Gisen Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy [REIN study]. *Lancet* 1997; 349(9069):1857-1863

The Gisen Group. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 1998; 352(9136):1252-1256

Casas JP; Chua W; Loukogeorgakis S; Vallance P; Smeeth L; Hingorani AD; MacAllister RJ. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic reviews and meta-analysis. *Lancet* 2005; 366(9502):2026-2033

Bleeding Risk and Antiplatelet Strategies

Hansen ML; Sorensen R; Clausen MT; Fog-Petersen ML; Raunsø J; Gadsbøll N; Gislason GH; Folke F; Andersen SS; Schramm TK; Abildstrøm SZ; Poulsen HE; Køber L; Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010; 170(16):1433-1441

Aspirin in Secondary Prevention

Rodriguez LAG; Cea-Soriano L; Martin-Merino E; Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011; 343:d4094

Other

Boyd CM; Darer J; Boult C; Fried LP; Boult L; Wu AW. Clinical Practice Guidelines and Quality of Care for Older Patients with Multiple Comorbid Diseases: implications for pay for performance. *JAMA* 2005; 294(6):716-724

Guthrie B; McCowan C; Davey P; Simpson CR; Dreischulte T; Barnett K. High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice. *BMJ* 2011; 342:d3514 Source of high risk drug group information.