

## **STOPP-START version 2**

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O'Mahony D, O'Sullivan D, Byrne S et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2.

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[Appendix 1 STOPP criteria references; page 2](#)

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# Supplementary Data

## Appendix 1: STOPP Criteria References

### Section A: Drug indication criteria

**A1. Any drug prescribed without an evidence-based clinical indication.**

No references (self-evident)

**A2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.**

No references (self-evident)

**A3. Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).**

A3. (i): Olsson J, Bergman A, Carlsten A, Oké T, Bernsten C, Schmidt IK, Fastbom J. Quality of drug prescribing in elderly people in nursing homes and special care units for dementia: a cross-sectional computerized pharmacy register analysis. *Clin Drug Investig* 2010; 30(5): 289-300. PubMed PMID: 20384385.

A3. (ii): Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Ann Pharmacother* 2009; 43(1): 36-44. PubMed PMID: 19126828.

A3. (iii): Laurier C, Moride Y, Kennedy WA. Health survey data on potentially inappropriate geriatric drug use. *Ann Pharmacother* 2002; 36(3): 404-9. PubMed PMID: 11895051.

### Section B: Cardiovascular System criteria

**B1. Digoxin for heart failure with preserved systolic ventricular function (no clear evidence of benefit)**

B1 (i). Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119(14): 1977-2016. PubMed PMID: 19324967.

B1 (ii): Cheng JW, Nayar M. A review of heart failure management in the elderly population. *Am J Geriatr Pharmacother* 2009; 7(5): 233-49. Review. PubMed PMID: 19948300.

**B2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).**

B2 (i): Amabile CM, Spencer AP. Keeping your patient with heart failure safe: a review of potentially dangerous medications. *Arch Intern Med* 2004; 164(7): 709-20. Review. PubMed PMID:15078640.

B2 (ii): Opie LH, Yusuf S, Kübler W. Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: a critical analysis based on 100 studies. *Prog Cardiovasc Dis* 2000; 43(2): 171-96. Review. PubMed PMID:11014332.

**B3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).**

B3 (i): Lee DW, Cohan B. Refractory cardiogenic shock and complete heart block after verapamil SR and metoprolol treatment. A case report. *Angiology* 1995; 46(6): 517-9. Review. PubMed PMID: 7785794.

B3 (ii): Edoute Y, Nagachandran P, Svirski B, Ben-Ami H. Cardiovascular adverse drug reaction associated with combined beta-adrenergic and calcium entry-blocking agents. *J Cardiovasc Pharmacol* 2000; 35(4): 556-9. PubMed PMID: 10774785.

**B4. Beta blocker with symptomatic bradycardia (< 50/min), type II heart block or complete heart block (risk of profound hypotension, asystole).**

B4. British National Formulary, No. 61, March 2011, p97.

**B5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)**

B5 (i): Lafuente-Lafuente C, Mouly S, Longás-Tejero MA, Mahé I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. *Arch Intern Med* 2006; 166(7):719-28. Review. PubMed PMID: 16606807.

B5 (ii): Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2009; 30(10):1245-53. Review. PubMed PMID: 19336434.

**B6. Loop diuretic as first-line treatment for hypertension (lack of outcome data for this indication; safer, more effective alternatives available).**

B6 (i): Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. J Clin Hypertens (Greenwich) 2011; 13(9): 639-43. Review. PubMed PMID: 21896142.

B6 (ii). Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM; BHS guidelines working party, for the British Hypertension Society. British Hypertension Society guidelines for hypertension management 2004(BHS-IV): summary. BMJ 2004; 328(7440):634-40. Erratum in: BMJ 2004; 328(7445):926. PubMed PMID: 15016698.

**B7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).**

B7 (i): Wehling M. Morbus diureticus in the elderly: epidemic overuse of a widely applied group of drugs. J Am Med Dir Assoc 2013; 14(6): 437-42. Review. PubMed PMID: 23510827.

B7 (ii). Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part I: mechanisms of action, pharmacological effects and clinical indications of diuretic compounds. Expert Opin Drug Saf 2010; 9(2):243-57. Review. PubMed PMID: 20095917.

**B8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K<sup>+</sup> < 3.0 mmol/l), hyponatraemia (i.e. serum Na<sup>+</sup> < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic)**

B8 (i).Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. J Clin Hypertens (Greenwich) 2011; 13(9):639-43. Review. PubMed PMID: 21896142.

B8 (ii). Gurwitz JH, Kalish SC, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J. Thiazide diuretics and the initiation of anti-gout therapy. J ClinEpidemiol1997; 50(8): 953-9. PubMed PMID: 9291881.

**B9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).**

B9 (i). Ekundayo OJ. The association between overactive bladder and diuretic use in the elderly. Curr Urol Rep 2009; 10(6):434-40. Review. PubMed PMID: 19863854.

B9 (ii) Ekundayo OJ, Markland A, Lefante C, Sui X, Goode PS, Allman RM, Ali M, Wahle C, Thornton PL, Ahmed A. Association of diuretic use and overactive bladder syndrome in older adults: a propensity score analysis. Arch Gerontol Geriatr2009; 49(1):64-8. PubMed PMID: 18752858.

B9 (iii) Finkelstein MM. Medical conditions, medications, and urinary incontinence. Analysis of a population-based survey. Can Fam Physician 2002; 48:96-101.PubMed PMID: 11852617.

**B10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives**

**(centrally-active antihypertensives are generally less well tolerated by older people than younger people)**

B10 (i). Potter JF. Hypertension. In: Brocklehurst's Textbook of Geriatric Medicine & Gerontology, 6<sup>th</sup> edition, Churchill Livingstone, 2003, p403.

B10 (ii). Khindri S, Jackson S. Hypertension. In: Prescribing for Elderly Patients, S. Jackson, P. Jansen, A. Mangoni, eds., Wiley-Blackwell, Chichester, UK, 2009, pp97-98.

**B11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.**

B11 (i) Izzo JL Jr, Weir MR. Angiotensin-converting enzyme inhibitors. J Clin Hypertens (Greenwich) 2011; 13(9):667-75. Review. PubMed PMID: 21896148.

B11 (ii) Desai AS, Swedberg K, McMurray JJ, Granger CB, Yusuf S, Young JB, Dunlap ME, Solomon SD, Hainer JW, Olofsson B, Michelson EL, Pfeffer MA; CHARM Program Investigators. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. J Am Coll Cardiol 2007 Nov 13;50(20):1959-66. PubMed PMID: 17996561.

B11(iii): Reardon LC, Macpherson DS. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med 1998; 158(1):26-32. PubMed PMID: 9437375.

**B12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).**

B12 (i): Bauersachs J, Fraccarollo D. Aldosterone antagonism in addition to angiotensin-converting enzyme inhibitors in heart failure. Minerva Cardioangiol 2003; 51(2):155-64. Review. PubMed PMID: 12783071.

B12 (ii): Poggio R, Grancelli HO, Miriuka SG. Understanding the risk of hyperkalaemia in heart failure: role of aldosterone antagonism. Postgrad Med J 2010; 86 (1013):136-42. Review. PubMed PMID: 20237007.

B12 (iii): Wrenger E, Müller R, Moesenthin M, Welte T, Frölich JC, Neumann KH. Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. BMJ 2003; 327(7407):147-9. PubMed PMID: 12869459.

B12 (iv) Marcy TR, Ripley TL. Aldosterone antagonists in the treatment of heart failure. Am J Health Syst Pharm 2006; 63(1): 49-58. PubMed PMID: 16373465.

B12 (v): Tang WH, Parameswaran AC, Maroo AP, Francis GS. Aldosterone receptor antagonists in the medical management of chronic heart failure. Mayo Clin Proc 2005; 80(12): 1623-30. Review. PubMed PMID: 16342656.

**B13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent daily nitrate therapy for angina (risk of cardiovascular collapse)**

B13 (i): British National Formulary, No. 61, March 2011, p516.

B13(ii): Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G. Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003; 42 (10): 1855-60. PubMed PMID: 14642699.

## **Section C: Coagulation System criteria**

**C1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).**

C1 (i). Dalen JE. Aspirin to prevent heart attack and stroke: what's the right dose? *Am J Med* 2006; 119(3):198-202. Review. PubMed PMID: 16490462.

C1 (ii). Fisher M, Knappertz V. The dose of aspirin for the prevention of cardiovascular and cerebrovascular events. *Curr Med Res Opin* 2006; 22(7):1239-48. Review. PubMed PMID: 16892516.

**C2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).**

C2 (i). Yeomans ND. Reducing the risk of gastroduodenal ulcers with a fixed combination of esomeprazole and low-dose acetyl salicylic acid. *Expert Rev Gastroenterol Hepatol* 2011; 5(4):447-55. Review. PubMed PMID: 21780891.

C2 (ii): Burness CB, Scott LJ. Acetylsalicylic acid/esomeprazole fixed-dose combination. *Drugs Aging* 2012; 29(3):233-42. Review. PubMed PMID: 22372726.

C2 (iii): Lanas A. Gastrointestinal bleeding associated with low-dose aspirin use: relevance and management in clinical practice. *Expert Opin Drug Saf* 2011; 10(1):45-54. Review. PubMed PMID: 20645883.

**C3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).**

C3 (i): Lip GY. Implications of the CHA(2)DS(2)-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation. *Am J Med.* 2011; 124(2):111-4. PubMed PMID: 20887966.

C3 (ii): Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; 138(5):1093-100. PubMed PMID: 20299623.

**C4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high**

**grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy)**

C4 (i): Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364(9431):331-7. PubMed PMID: 15276392.

C4 (ii): Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006; 354(16):1706-17. PubMed PMID: 16531616.

C4 (iii): Usman MH, Notaro LA, Nagarakanti R, Brahini E, Dessain S, Gracely E, Ezekowitz MD. Combination antiplatelet therapy for secondary stroke prevention: enhanced efficacy or double trouble? *Am J Cardiol* 2009;103(8):1107-12. Review. PubMed PMID: 19361598.

C4 (iv): Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2011;(1):CD005158. Review. PubMed PMID: 21249668.

C4 (v): Fares RR, Lansing LS, Gallati CA, Mousa SA. Antiplatelet therapy with clopidogrel and aspirin in vascular diseases: clinical evidence for and against the combination. *Expert Opin Pharmacother* 2008; 9(3): 377-86. Review. PubMed PMID: 18220489.

**C5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation without a clear indication for aspirin (no added benefit from aspirin)**

C5 (i): Flaker GC, Gruber M, Connolly SJ, Goldman S, Chaparro S, Vahanian A, Halinen MO, Horrow J, Halperin JL; SPORTIF Investigators. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J* 2006; 152(5):967-73. PubMed PMID: 17070169.

C5 (ii): Larson RJ, Fisher ES. Should aspirin be continued in patients started on warfarin? *J Gen Intern Med* 2004; 19(8):879-86. Review. PubMed Central PMCID: PMC1492499.

**C6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease without a clear indication for anticoagulant therapy (no added benefit from dual therapy).**

C6 (i): Holmes DR Jr, Kereiakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. Combining antiplatelet and anticoagulant therapies. *J Am Coll Cardiol* 2009; 54(2):95-109. Review. PubMed PMID: 19573725.

C6 (ii): Rubboli A, Halperin JL, Airaksinen KE, Buerke M, Eeckhout E, Freedman SB, Gershlick AH, Schlitt A, Tse HF, Verheugt FW, Lip GY. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation. *Ann Med* 2008; 40(6):428-36. Review. PubMed PMID: 18608125.

**C7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).**

C7 (i): Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke* 2011; 42(1):227-76. PubMed PMID: 20966421.

C7 (ii): Porto I, Giubilato S, De Maria GL, Biasucci LM, Crea F. Platelet P2Y<sub>12</sub> receptor inhibition by thienopyridines: status and future. *Expert Opin Investig Drugs* 2009; 18(9):1317-32. Review. PubMed PMID: 19678800.

**C8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors for > 6 months, (no proven added benefit).**

C8 (i): Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, Nony P, Sanson C, Boissel JP; Investigators of the "Durée Optimale du Traitement AntiVitamines K" (DOTAVK) Study. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; 103(20): 2453-60. PubMed PMID: 11369685.

C8 (ii): Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl): e419S-94S. PubMed PMID: 22315268.

**C9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors for > 12 months (no proven added benefit).**

C9 (i): Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl): e419S-94S. PubMed PMID: 22315268; PubMed Central PMCID: PMC3278049.

**C10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of gastrointestinal bleeding).**



C10 (i): Knijff-Dutmer EA, Van der Palen J, Schut G, Van de Laar MA. The influence of cyclo-oxygenase specificity of non-steroidal anti-inflammatory drugs on bleeding complications in concomitant coumarine users. QJM 2003; 96(7):513-20. PubMed PMID: 12881594.

C10 (ii): Peng S, Duggan A. Gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. Expert Opin Drug Saf 2005; 4(2):157-69. Review. PubMed PMID: 15794710.

### **C11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)**

C11 (i): Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009; 104(3):728-38. PubMed PMID: 19240698.

C11 (ii): Nardulli G, Lanas A. [Risk of gastrointestinal bleeding with aspirin and platelet antiaggregants]. Gastroenterol Hepatol 2009; 32(1):36-43. Review. Spanish. PubMed PMID: 19174098.

C11 (iii): Zullo A, Hassan C, Campo SM, Morini S. Bleeding peptic ulcer in the elderly-risk factors and prevention strategies. Drugs Aging 2007; 24(10): 815-28. Review. PubMed PMID: 17896831.

## **Section D: Central Nervous System criteria**

### **D1. Tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).**

D1 (i): Tricyclic and related antidepressant drugs. British National Formulary, No. 61, BMJ Group & Pharmaceutical Press, March 2011, p233.

D1 (ii): Mintzer J, Burns A. Anticholinergic side-effects of drugs in elderly people. J R Soc Med 2000; 93 (9):457-62. Review. PubMed PMID: 11089480.

D1 (iii): Verhamme KM, Sturkenboom MC, Stricker BH, Bosch R. Drug-induced urinary retention: incidence, management and prevention. Drug Saf 2008; 31(5):373-88. Review. PubMed PMID: 18422378.

D1 (iv): Vieweg WV, Wood MA, Fernandez A, Beatty-Brooks M, Hasnain M, Pandurangi AK. Proarrhythmic risk with antipsychotic and antidepressant drugs: implications in the elderly. Drugs Aging 2009; 26(12): 997-1012. Review. PubMed PMID: 19929028.

D1 (v): Tripathi RC, Tripathi BJ, Haggerty C. Drug-induced glaucomas: mechanism and management. Drug Saf 2003; 26(11): 749-67. Review. PubMed PMID: 12908846.

### **D2. Initiation of tricyclic antidepressants as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).**

D2 (i): Emslie G, Judge R. Tricyclic antidepressants and selective serotonin reuptake inhibitors: use during pregnancy, in children/adolescents and in the elderly. *Acta Psychiatr Scand Suppl.* 2000; 403: 26-34. Review. PubMed PMID: 11019932.

D2 (ii) Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. *Cochrane Database Syst Rev* 2006 Jan 25; (1):CD003491. Review. PubMed PMID: 16437456.

**D3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).**

D3 (i): Verhamme KM, Sturkenboom MC, Stricker BH, Bosch R. Drug-induced urinary retention: incidence, management and prevention. *Drug Saf* 2008; 31(5):373-88. Review. PubMed PMID: 18422378.

**D4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na<sup>+</sup> < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).**

D4 (i): Jacob S, Spinler SA. Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother* 2006; 40(9):1618-22. Review. PubMed PMID: 16896026.

D4 (ii): Draper B, Berman K. Tolerability of selective serotonin reuptake inhibitors: issues relevant to the elderly. *Drugs Aging* 2008; 25(6): 501-19. Review. PubMed PMID: 18540689.

**D5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).**

D5 (i): Madhusoodanan S, Bogunovic OJ. Safety of benzodiazepines in the geriatric population. *Expert Opin Drug Saf* 2004; 3(5): 485-93. Review. PubMed PMID:15335303.

D5 (ii): Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005; 331(7526): 1169. Review. PubMed PMID: 16284208.

D5 (iii): Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs* 2004; 18(1):37-48. PubMed PMID: 14731058.

**D6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms)**

D6 (i): Mena MA, de Yébenes JG. Drug-induced parkinsonism. *Expert Opin Drug Saf* 2006; 5(6):759-71. Review. PubMed PMID: 17044803.

D6(ii): Eng ML, Welty TE. Management of hallucinations and psychosis in Parkinson's disease. *Am J Geriatr Pharmacother* 2010; 8(4):316-30. Review. PubMed PMID:20869621.

**D7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),**

D7 (i): Heinik J. Effects of trihexyphenidyl on MMSE and CAMCOG scores of medicated elderly patients with schizophrenia. *Int Psychogeriatr* 1998; 10(1): 103-8. PubMed PMID: 9629529.

D7 (ii): Drimer T, Shahal B, Barak Y. Effects of discontinuation of long-term anticholinergic treatment in elderly schizophrenia patients. *Int ClinPsychopharmacol* 2004; 19(1):27-9. PubMed PMID: 15101567.

**D8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).**

D8 (i): Pagoria D, O'Connor RC, Guralnick ML. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. *Curr Urol Rep* 2011; 12 (5): 351-7. Review. PubMed PMID: 21607875.

D8 (ii): Gerretsen P, Pollock BG. Drugs with anticholinergic properties: a current perspective on use and safety. *Expert Opin Drug Saf* 2011; 10(5): 751-65. Review. PubMed PMID: 21635190.

**D9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other treatments have failed (increased risk of stroke).**

D9 (i): Sacchetti E, Turrina C, Valsecchi P. Cerebrovascular accidents in elderly people treated with antipsychotic drugs: a systematic review. *Drug Saf* 2010; 33(4): 273-88. Review. PubMed PMID: 20297860.

D9 (ii): Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: a literature review of evidence. *Am J Alzheimers Dis Other Demen* 2011; 26(1): 10-28. Review. PubMed PMID: 21282274.

D9 (iii): Chahine LM, Acar D, Chemali Z. The elderly safety imperative and antipsychotic usage. *Harvard Rev Psychiatr* 2010; 18:3 158-172. PubMed PMID: 20415632.

**D10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).**

D10 (i): British National Formulary, no. 61, March 2011, pp 216 -227.

D10 (ii): RD McEvoy, KS Nyfort-Hansen. Sleep disorders in the elderly: the pros and cons of prescribing. In: *Prescribing for Elderly Patients*, eds. S. Jackson, P. Jansen, A. Mangoni. Wiley-Blackwell 2009, pp 45-52.

D10 (iii): Alexopoulos GS, Streim J, Carpenter D, Docherty JP. Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients. Using antipsychotic agents in older patients. *J Clin Psychiatry* 2004; 65 Suppl 2:5-99; discussion 100-102; quiz 103-4. Review. PubMed PMID: 14994733.

**D11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).**

D11 (i): Salarbaks AM, Boomkamp-Snoeren CM, van Puijenbroek E, Jansen PA, van Marum RJ. [Cardiac effects of cholinesterase inhibitors: a reason for restraint?]. *Tijdschr Gerontol Geriatr* 2009; 40(2):79-84. PubMed PMID: 19472574.

D11 (ii): Fisher A.A. and Davis M.W. Prolonged QT interval, syncope, and delirium with galantamine *Ann Pharmacother* 2008 42; 2: 278-283. PubMed PMID: 18182475.

D11 (iii): Suleyman T., Tevfik P., Abdulkadir G. and Ozlem S. Complete atrioventricular block and ventricular tachyarrhythmia associated with donepezil. *Emerg Med J* 2006; 23(8): 641-2. PubMed PMID: 16858101.

D11 (iv): Bordier P., Lanusse S., Garrigue S., Reynard C., Robert F., Gencel L. and Lafitte A. Causes of syncope in patients with Alzheimer's disease treated with donepezil. *Drugs Aging* 2005; 22(8): 687-694. PubMed PMID: 16060718.

**D12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).**

D12 (i): Chahine L.M., Acar D., Chemali Z. The elderly safety imperative and antipsychotic usage. *Harvard Review of Psychiatry* 2010; 18(3): 158-72. PubMed PMID: 20415632.

D12 (ii): Love R.C. The differential pharmacology of atypical antipsychotics: Impact on patients with comorbid conditions. *Consult Pharm* 2006; 21; SUPPL. B: 11-18.

**D13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)**

D13 (i): Zesiewicz TA, Elble RJ, Louis ED, Gronseth GS, Ondo WG, Dewey RB Jr, Okun MS, Sullivan KL, Weiner WJ. Evidence-based guideline update- treatment of essential tremor-report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology* 2011; 77(19):1752-5. Review. PubMed PMID: 22013182.

D13 (ii): Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. *Lancet Neurol* 2011; 10(2): 148-61. Review. PubMed PMID:21256454.

**D14. First-generation antihistamines (safer, less toxic antihistamines now widely available).**

D14 (i): Hansen J, Klimek L, Hörmann K. Pharmacological management of allergic rhinitis in the elderly-safety issues with oral antihistamines. *Drugs Aging* 2005; 22(4): 289-96. Review. PubMed PMID: 15839718.

D14 (ii): Slavin RG. Special considerations in treatment of allergic rhinitis in the elderly: role of intranasal corticosteroids. *Allergy Asthma Proc* 2010; 31(3): 179-84. Review. PubMed PMID: 20615319.

**Section E. Renal System criteria.**

**E1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m<sup>2</sup> (risk of digoxin toxicity if plasma levels not measured).**

E1 (i): Ahmed A. Digoxin and reduction in mortality and hospitalization in geriatric heart failure: importance of low doses and low serum concentrations. *J Gerontol A Biol Sci Med Sci.* 2007; 62(3): 323-9. PubMed PMID: 17389731.

E1 (ii): Podrazik PM, Schwartz JB. Cardiovascular pharmacology of aging. *Cardiol Clin* 1999; 17(1): 17-34. Review. PubMed PMID: 10093763.

**E2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m<sup>2</sup> (risk of bleeding)**

E2(i): Hariharan S, Madabushi R. Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment. *J ClinPharmacol* 2012; 52(1 Suppl):119S-25S. PubMed PMID: 21956605.

E2(ii): Samama MM. Use of low-molecular-weight heparins and new anticoagulants in elderly patients with renal impairment. *Drugs Aging* 2011; 28(3): 177-93. PubMed PMID: 21329400.

**E3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m<sup>2</sup> (risk of bleeding)**

E3(i): Kubitzka D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, Lufft V, Wand DD, Philipp T, Bruck H. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol* 2010; 70(5): 703-12. PubMed PMID: 21039764.

E3(ii): Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011; 32(19): 2387-94. PubMed PMID: 21873708.

**E4. NSAID's if eGFR < 50 ml/min/1.73m<sup>2</sup> (risk of deterioration in renal function).**

E4(i): Harirforoosh S, Jamali F. Renal adverse effects of non-steroidal anti-inflammatory drugs. *Expert Opin Drug Saf* 2009; 8(6): 669-81. Review. PubMed PMID: 19832117.

E4(ii): Cheng HF, Harris RC. Renal effects of non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors. *Curr Pharm Des* 2005; 11(14): 1795-804. Review. PubMed PMID: 15892676.

#### **E5. Colchicine if eGFR < 10 ml/min/1.73m<sup>2</sup> (risk of colchicine toxicity).**

E5(i): Hoskison KT, Wortmann RL. Management of gout in older adults: barriers to optimal control. *Drugs Aging* 2007; 24(1): 21-36. Review. PubMed PMID: 17233545.

E5(ii): Hanlon JT, Aspinall SL, Semla TP, Weisbord SD, Fried LF, Good CB, Fine MJ, Stone RA, Pugh MJ, Rossi MI, Handler SM. Consensus guidelines for oral dosing of primarily renally cleared medications in older adults. *J Am Geriatr Soc* 2009; 57(2):335-40. Erratum in: *J Am Geriatr Soc* 2009; 57(11): 2179. Dosage error in article text. PubMed PMID: 19170784.

#### **E6. Metformin if eGFR < 30 ml/min/1.73m<sup>2</sup> (risk of lactic acidosis).**

E6(i): Germino FW. Non-insulin treatment of type 2 diabetes mellitus in geriatric patients: a review. *Clin Ther* 2011; 33(12): 1868-82. Review. PubMed PMID: 22136979.

E6(ii): Lalau JD. Lactic acidosis induced by metformin: Incidence, management and prevention. *Drug Safety* 2010; 33(9): 727-40. PubMed PMID: 20701406.

### **Section F: Gastrointestinal System criteria.**

#### **F1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).**

F1 (i): Stephen PJ, Williamson J. Drug-induced parkinsonism in the elderly. *Lancet* 1984; 2(8411): 1082-3. PubMed PMID: 6150149.

F1 (ii): Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. *Arch Intern Med* 1993; 153(12): 1469-75. PubMed PMID: 8512437.

F1 (iii): Pasricha PJ, Pehlivanov N, Sugumar A, Jankovic J. Drug Insight: from disturbed motility to disordered movement - a review of the clinical benefits and medicolegal risks of metoclopramide. *Nat Clin Pract Gastroenterol Hepatol* 2006; 3(3): 138-48. Review. PubMed PMID: 16511548.

#### **F2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).**

F2 (i): British National Formulary vol. 61 (March, 2011), section 1.3.5. Proton pump inhibitors, pp 54-57.

F2 (ii): NICE guideline 2000/022 (last updated 14 July 2008). [www.nice.org.uk](http://www.nice.org.uk).

**F3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are appropriate (risk of exacerbation of constipation).**

F3 (i): Meek PD, Evang SD, Tadrous M, Roux-Lirange D, Triller DM, Gumustop B. Overactive bladder drugs and constipation: a meta-analysis of randomized, placebo-controlled trials. *Dig Dis Sci* 2011; 56(1): 7-18. Review. PubMed PMID: 20596778.

F3 (ii): Müller-Lissner S. General geriatrics and gastroenterology: constipation and faecal incontinence. *Best Pract Res Clin Gastroenterol* 2002; 16(1): 115-33. Review. PubMed PMID: 11977932.

F3 (iii): Harari D, Gurwitz JH, Avorn J, Choodnovskiy I, Minaker KL. Correlates of regular laxative use by frail elderly persons. *Am J Med* 1995; 99(5): 513-8. PubMed PMID: 7485209.

F4 (iv): Opie LH. Choosing the correct drug for the individual hypertensive patient. *Drugs* 1992; 44 Suppl 1: 147-55. Review. PubMed PMID: 1283579.

**F4. Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate > 1800 mg/day; no evidence of enhanced iron absorption above these doses).**

F4 (i): Rimon E, Kagansky N, Kagansky M, Mechnick L, Mashiah T, Namir M, Levy S. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005; 118(10): 1142-7. PubMed PMID: 16194646.

F4 (ii): British National Formulary vol. 61 (March, 2011), section 9.1.1.1. Iron deficiency anaemia, pp 576-7.

## **Section G. Respiratory System criteria.**

**G1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).**

G1(i): Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J; Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176(6): 532-55. Review. PubMed PMID: 17507545.

G1(ii): Ramsdell J. Use of theophylline in the treatment of COPD. *Chest* 1995; 107(5 Suppl): 206S-209S. Review. PubMed PMID: 7743828.

**G2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).**

G2(i): Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J; Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176(6): 532-55. Review. PubMed PMID: 17507545.

G2(ii): Wood-Baker R, Walters J, Walters EH. Systemic corticosteroids in chronic obstructive pulmonary disease: an overview of Cochrane systematic reviews. *Respir Med* 2007; 101(3): 371-7. Review. PubMed PMID: 16962307.

**G3. Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).**

G3(i): Gupta P, O'Mahony MS. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: recommendations for prescribing. *Drugs Aging* 2008; 25(5): 415-43. Review. PubMed PMID: 18447405.

G3(ii): Oba Y, Zaza T, Thameem DM. Safety, tolerability and risk benefit analysis of tiotropium in COPD. *Int J Chron Obstruct Pulmon Dis* 2008; 3(4): 575-84. Review. PubMed PMID: 19281075.

**G4. Benzodiazepines with acute or chronic respiratory failure i.e.  $pO_2 < 8.0 \text{ kPa} \pm pCO_2 > 6.5 \text{ kPa}$  (risk of exacerbation of respiratory failure).**

G4 (i): Model DG, Berry DJ. Effects of chlordiazepoxide in respiratory failure due to chronic bronchitis. *Lancet* 1974; 2(7885): 869-70. PubMed PMID: 4137638.

G4 (ii): Hak E, Bont J, Hoes AW, Verheij TJ. Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. *Fam Pract* 2005; 22(4): 375-80. PubMed PMID: 15805127.

**Section H: Musculoskeletal System criteria.**

**H1. Non-COX-2 selective non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).**

H1 (i): Blandizzi C, Tuccori M, Colucci R, Gori G, Fornai M, Antonioli L, Ghisu N, Del Tacca M. Clinical efficacy of esomeprazole in the prevention and healing of gastrointestinal toxicity associated with NSAIDs in elderly patients. *Drugs Aging* 2008; 25(3): 197-208. Review. PubMed PMID: 18331072.



H1 (ii): Lanas A, Ferrandez A. Inappropriate prevention of NSAID-induced gastrointestinal events among long-term users in the elderly. *Drugs Aging* 2007; 24(2):121-31. Review. PubMed PMID: 17313200.

H1(iii): Alaa Rostom, Catherine Dube, George A Wells, Peter Tugwell, Vivian Welch, Emilie Jolicoeur, Jessie McGowan, Angel Lanas. Prevention of NSAID-induced gastroduodenal ulcers. Editorial Group: [Cochrane Upper Gastrointestinal and Pancreatic Diseases Group](#) Published Online: 20 Jan 2010. DOI: 10.1002/14651858.CD002296.

## **H2. NSAID with established hypertension (risk of exacerbation of hypertension) or heart failure (risk of exacerbation of heart failure).**

H2(i): White WB. Defining the problem of treating the patient with hypertension and arthritis pain. *Am J Med.* 2009; 122(5 Suppl): S3-9. Review. PubMed PMID: 19393824.

H2(ii): Park KE, Qin Y, Bavry AA. Nonsteroidal anti-inflammatory drugs and their effects in the elderly. *Aging Health* 2012; 8(2): 167-177.

## **H3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief)**

H3(i): Nikles CJ, Yelland M, Del Mar C, Wilkinson D. The role of paracetamol in chronic pain: an evidence-based approach. *Am J Ther* 2005; 12(1): 80-91. Review. PubMed PMID: 15662295.

H3(ii): Seed SM, Dunican KC, Lynch AM. Osteoarthritis: a review of treatment options. *Geriatrics* 2009; 64(10): 20-9. Review. PubMed PMID: 20726384.

H3(iii): Jawad AS. Analgesics and osteoarthritis: are treatment guidelines reflected in clinical practice? *Am J Ther* 2005; 12(1): 98-103. Review. PubMed PMID: 15662297.

## **H4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects).**

H4(i): Onishi S, Iwamoto M, Minota S. Management of elderly-onset rheumatoid arthritis. *J Clin Immunol* 2010; 33(1): 1-7. PubMed PMID: 20190503.

H4(ii): American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002; 46(2): 28-46. PubMed PMID: 11840435.

H4(iii): Soubrier M, Mathieu S, Payet S, Dubost JJ, Ristori JM. Elderly-onset rheumatoid arthritis. *Joint Bone Spine* 2010; 77(4): 290-6. Review. PubMed PMID: 20554241.

## **H5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).**

H5(i): British National Formulary volume 61, March 2011, pp 443-4.

H5 (ii): Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum 2000; 43(9): 1905-15. PubMed PMID: 11014340.

**H6. Long-term NSAID or colchicine for prevention of relapses of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).**

H6(i): De Leonardis F, Govoni M, Colina M, Bruschi M, Trotta F. Elderly-onset gout: a review. Rheumatol Int 2007; 28(1): 1-6. Review. PubMed PMID: 17653719.

H6(ii): Hoskison KT, Wortmann RL. Management of gout in older adults: barriers to optimal control. Drugs Aging 2007; 24(1): 21-36. Review. PubMed PMID: 17233545.

**H7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)**

H7 (i): Pilotto A, Sancarlo D, Addante F, Scarcelli C, Franceschi M. Non-steroidal anti-inflammatory drug use in the elderly. Surg Oncol 2010; 19(3): 167-72. Review. PubMed PMID: 20022240.

H7 (ii): Strand V. Are COX-2 inhibitors preferable to non-selective non-steroidal anti-inflammatory drugs in patients with risk of cardiovascular events taking low-dose aspirin? Lancet 2007; 370(9605): 2138-51. Review. PubMed PMID: 18156036.

**H8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)**

H8 (i): Peng S, Duggan A. Gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. Expert Opin Drug Saf 2005; 4(2): 157-69. Review. PubMed PMID: 15794710.

H8 (ii): Zullo A, Hassan C, Campo SM, Morini S. Bleeding peptic ulcer in the elderly: risk factors and prevention strategies. Drugs Aging 2007; 24(10): 815-28. Review. PubMed PMID: 17896831.

H8 (iii): Scheiman JM. NSAID-induced peptic ulcer disease: a critical review of pathogenesis and management. Dig Dis 1994; 12(4): 210-22. Review. PubMed PMID: 7851000.

**H9. Oral bisphosphonates in patients with a history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)**

H9(i): Pazianas M, Abrahamsen B. Safety of bisphosphonates. Bone 2011; 49(1): 103-10. Review. PubMed PMID: 21236370.

H9(ii): Civitelli R, Napoli N, Armamento-Villareal R. Use of intravenous bisphosphonates in osteoporosis. *Curr Osteoporos Rep* 2007; 5(1): 8-13. PubMed PMID: 17320022.

H9(iii): Gaudio A, Morabito N. Pharmacological management of severe postmenopausal osteoporosis. *Drugs Aging* 2005; 22(5): 405-17. Review. PubMed PMID: 15903353.

## **Section I: Urogenital System criteria.**

### **I1. Antimuscarinic drugs for overactive bladder syndrome with concurrent dementia or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).**

I1 (i): Pagoria D, O'Connor RC, Guralnick ML. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. *Curr Urol Rep* 2011; 12(5): 351-7. Review. PubMed PMID: 21607875.

I1 (ii): Kay GG, Abou-Donia MB, Messer WS Jr, Murphy DG, Tsao JW, Ouslander JG. Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients. *J Am Geriatr Soc* 2005; 53(12): 2195-201. Review. PubMed PMID: 16398909.

### **I2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)**

I2 (i): Lowe FC. Role of the newer alpha<sub>1</sub>-adrenergic-receptor antagonists in the treatment of benign prostatic hyperplasia-related lower urinary tract symptoms. *Clin Ther* 2004; 26(11): 1701-13. Review. PubMed PMID: 15639685.

I2 (ii): British National Formulary vol. 61, March 2011: p 506.

## **Section J: Endocrine System criteria.**

### **J1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).**

J1(i): Graal MB, Wolffenbuttel BH. The use of sulphonylureas in the elderly. *Drugs Aging* 1999; 15(6): 471-81. Review. PubMed PMID: 10641958.

J1(ii): Langtry HD, Balfour JA. Glimepiride. A review of its use in the management of type 2 diabetes mellitus. *Drugs* 1998; 55(4): 563-84. Review. PubMed PMID: 9561345.

### **J2. Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with documented heart failure (risk of exacerbation of heart failure)**

J2(i): Germino FW. Noninsulin treatment of type 2 diabetes mellitus in geriatric patients: a review. *Clin Ther* 2011; 33(12): 1868-82. Review. PubMed PMID: 22136979.

J2(ii): Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007; 370(9593): 1129-36. Review. PubMed PMID: 17905165.

**J3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).**

J3(i): Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: causes and strategies for prevention. *Drugs Aging* 2004; 21(8): 511-30. Review. PubMed PMID: 15182216.

J3 (ii): British National Formulary vol. 61, March 2011: p 98.

**J4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).**

J4(i): Calle EE, Feigelson HS, Hildebrand JS, Teras LR, Thun MJ, Rodriguez C. Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. *Cancer* 2009; 115(5): 936-45. Erratum in: *Cancer* 2009; 115(7): 1587. PubMed PMID: 19156895.

J4(ii): Diergaarde B, Potter JD, Jupe ER, Manjeshwar S, Shimasaki CD, Pugh TW, Defreese DC, Gramling BA, Evans I, White E. Polymorphisms in genes involved in sex hormone metabolism, estrogen plus progestin hormone therapy use, and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008; 17(7): 1751-9. PubMed PMID: 18628428.

**J5. Oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).**

J5(i): Dick SE, DeWitt DE, Anawalt BD. Postmenopausal hormone replacement therapy and major clinical outcomes: a focus on cardiovascular disease, osteoporosis, dementia, and breast and endometrial neoplasia. *Am J Manag Care* 2002; 8(1): 95-104. Review. PubMed PMID: 11814176.

J5(ii): Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev* 2012 Aug 15;8:CD000402. doi: 10.1002/14651858.CD000402.pub4. Review. PubMed PMID: 22895916.

J5(iii): Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2012 Jul 11;7:CD004143. doi: 10.1002/14651858.CD004143.pub4. Review. PubMed PMID: 22786488

**J6. Androgens in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of hypogonadism indication).**

J6(i): Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; 95(6): 2536-59. Review. PubMed PMID: 20525905.

J6(ii): Kazi M, Geraci SA, Koch CA. Considerations for the diagnosis and treatment of testosterone deficiency in elderly men. *Am J Med* 2007; 120(10): 835-40. Review. PubMed PMID: 17904450.

## **Section K: Drugs that predictably increase the risk of falls in older people.**

### **K1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).**

K1(i): Huang AR, Mallet L, Rochefort CM, Egualé T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs Aging* 2012; 29(5): 359-76. Review. PubMed PMID: 22550966.

K1(ii): Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, Marra CA. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009; 169(21): 1952-60. Review. Erratum in: *Arch Intern Med* 2010 Mar 8;170(5):477. PubMed PMID: 19933955.

### **K2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).**

K2(i): Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. *Drugs Aging* 2012; 29(1): 15-30. Review. PubMed PMID: 22191720.

K2(ii): Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, Marra CA. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009; 169(21): 1952-60. Review. Erratum in: *Arch Intern Med* 2010; 170(5): 477. PubMed PMID: 19933955.

### **K3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers, diazoxide, minoxidil, hydralazine) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure $\geq$ 20mmHg (risk of syncope, falls).**

K3(i): Aronow WS. Treating hypertension in older adults: safety considerations. *Drug Saf* 2009; 32(2): 111-8. PMID: 19236118

K3(ii): Verhaeverbeke I, Mets T. Drug-induced orthostatic hypotension in the elderly: avoiding its onset. *Drug Saf* 1997; 17(2): 105-18. Review. PubMed PMID: 9285201.

### **K4. Hypnotic Z-drugs (e.g. zopiclone, zolpidem, zaleplon) (may cause protracted daytime sedation, ataxia).**

K4(i): Mets MA, Volkerts ER, Olivier B, Verster JC. Effect of hypnotic drugs on body balance and standing steadiness. *Sleep Med Rev* 2010; 14(4): 259-67. PubMed PMID: 20171127.

K4(ii): Shuto H, Imakyure O, Matsumoto J, Egawa T, Jiang Y, Hirakawa M, Kataoka Y, Yanagawa T. Medication use as a risk factor for inpatient falls in an acute care hospital: a case-crossover study. *Br J Clin Pharmacol* 2010; 69(5): 535-42. PubMed PMID: 20573090.

## **Section L: Analgesic Drugs.**

**L1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).**

L1(i): World Health Organization (WHO). Cancer pain relief. With a guide to opioid availability, 2nd ed. Geneva 1996: WHO. ISBN 92-4-154482-1.

L1(ii): Scoping Document for WHO Guidelines for the pharmacological treatment of persisting pain in adults with medical illnesses, Geneva 2012, GRC-08-04-0052A, p 9.

[http://www.who.int/medicines/areas/quality\\_safety/Scoping\\_WHO\\_GLs\\_PersistPainAdults\\_webversion.pdf](http://www.who.int/medicines/areas/quality_safety/Scoping_WHO_GLs_PersistPainAdults_webversion.pdf); accessed Dec 28, 2012.

**L2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).**

L2(i): Forman WB. Opioid analgesic drugs in the elderly. Clin Geriatr Med 1996; 12(3): 489-500. Review. PubMed PMID: 8853941

L2(ii): Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004; 112(3): 372-80. PubMed PMID: 15561393.

**L3. Long-acting opioids without short-acting opioids for break-through pain (risk of non-control of severe pain)**

L3(i): Johnson AG, Seideman P, Day RO. Adverse drug interactions with nonsteroidal anti-inflammatory drugs (NSAIDs). Recognition, management and avoidance. Drug Saf 1993; 8(2): 99-127. Review. PubMed PMID: 8452660.

L3(ii): Zullo A, Hassan C, Campo SM, Morini S. Bleeding peptic ulcer in the elderly: risk factors and prevention strategies. Drugs Aging 2007; 24(10): 815-28. Review. PubMed PMID: 17896831.

L3(iii): Peng S, Duggan A. Gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. Expert Opin Drug Saf 2005; 4(2): 157-69. Review. PubMed PMID: 15794710.

L3(iv): Peura DA. Prevention of nonsteroidal anti-inflammatory drug-associated gastrointestinal symptoms and ulcer complications. Am J Med 2004; 117 Suppl 5A: 63S-71S. Review. PubMed PMID: 15478855.

## **Section M: Antimuscarinic/anticholinergic drug burden.**

**M1: Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity)**

M1(j): Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging* 1993; 3(4): 335-48. Review. PubMed PMID: 8369593.

M1(ii): Gerretsen P, Pollock BG. Drugs with anticholinergic properties: a current perspective on use and safety. *Expert Opin Drug Saf* 2011; 10(5): 751-65. Review. PubMed PMID: 21635190.

M1(iii): Karimi S, Dharia SP, Flora DS, Slattum PW. Anticholinergic burden: clinical implications for seniors and strategies for clinicians. *Consult Pharm* 2012; 27(8): 564-82. Review. PubMed PMID: 22910177.

## Appendix 2: START Criteria References

### Section A: Cardiovascular System criteria.

#### **A1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.**

A1 (i): Hughes M, Lip GY; Guideline Development Group, National Clinical Guideline for Management of Atrial Fibrillation in Primary and Secondary Care, National Institute for Health and Clinical Excellence. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008; 99(2): 295-304. Review. PubMed PMID: 18278178.

A1 (ii): Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation* 2012; 126(20): 2381-91. Review. PubMed PMID: 23071159.

A1 (iii): Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. *Ann Intern Med* 2007; 146(12): 857-67. PubMed PMID: 17577005.

A1 (iv): Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD001927. DOI: 10.1002/14651858.CD001927.pub2.

#### **A2. Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.**

A2 (i): 1: Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011; 8(10): 602-6. PubMed PMID: 21788962.

A2 (ii): Cairns JA, Connolly S, McMurry S, Stephenson M, Talajic M; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol* 2011; 27(1): 74-90. PubMed PMID: 21329865.

A2 (iii): Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, Petersen P. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 2004; 110(16): 2287-92. PubMed PMID: 15477396.

A2 (iv): Ezekowitz MD, Levine JA. Preventing stroke in patients with atrial fibrillation. *JAMA* 1999; 281(19): 1830-5. PubMed PMID: 10340371.

#### **A3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.**

A3 (i): Zuckerman IH, Yin X, Rattinger GB, Gottlieb SS, Simoni-Wastila L, Pierce SA, Huang TY, Shenolikar R, Stuart B. Effect of exposure to evidence-based pharmacotherapy on outcomes after



acute myocardial infarction in older adults. *J Am Geriatr Soc* 2012; 60(10): 1854-61. PubMed PMID: 23003000.

A3 (ii): Alonso-Coello P, Bellmunt S, McGorrian C, Anand SS, Guzman R, Criqui MH, Akl EA, Olav Vandvik P, Lansberg MG, Guyatt GH, Spencer FA; American College of Chest Physicians. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2Suppl): e669S-90S. PubMed PMID: 22315275.

A3 (iii): Fleg JL, Aronow WS, Frishman WH. Cardiovascular drug therapy in the elderly: benefits and challenges. *Nat Rev Cardiol* 2011; 8(1): 13-28. Review. PubMed PMID: 20978470.

A3 (iv): Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg FA, Alonso-Coello P, Akl EA, Lansberg MG, Guyatt GH, Spencer FA; American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2Suppl): e637S-68S. Erratum in: *Chest* 2012; 141(4): 1129. Dosage error in article text. PubMed PMID: 22315274.

**A4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently > 90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.**

A4 (i): Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM; BHS guidelines working party, for the British Hypertension Society. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004; 328(7440):634-40. Erratum in: *BMJ* 2004; 328(7445): 926. PubMed PMID: 15016698.

A4 (ii): Papademetriou V, Farsang C, Elmfeldt D, Hofman A, Lithell H, Olofsson B, Skoog I, Trenkwalder P, Zanchetti A; Study on Cognition and Prognosis in the Elderly study group. Stroke prevention with the angiotensin II type 1-receptor blocker candesartan in elderly patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (SCOPE). *J Am Coll Cardiol* 2004; 44(6): 1175-80. PubMed PMID: 15364316.

A4 (iii): Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, Staessen JA, Gueyffier F. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *J Hypertens* 2010; 28(7): 1366-72. PubMed PMID: 20574244.

**A5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.**

A5 (i): Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, Eyawo O, Guyatt G, Berwanger O, Briel M. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM* 2011; 104(2): 109-24. Review. PubMed PMID: 20934984.

A5 (ii): Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, de Craen AJ, Knopp RH, Nakamura H, Ridker P, van Domburg R, Deckers JW. The benefits of statins in people without

established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* 2009; 338: b2376. Review. PubMed PMID: 19567909.

A5 (iii): Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol* 2009; 8(5): 453-63. Review. PubMed PMID:19375663.

#### **A6. Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.**

A6 (i): Fleg JL, Aronow WS, Frishman WH. Cardiovascular drug therapy in the elderly: benefits and challenges. *Nat Rev Cardiol* 2011; 8(1):13-28. Review. PubMed PMID: 20978470.

A6 (ii): Arif SA, Mergenhagen KA, Del Carpio RO, Ho C. Treatment of systolic heartfailure in the elderly: an evidence-based review. *Ann Pharmacother* 2010; 44(10): 1604-14. Review. PubMed PMID: 20841514.

A6 (iii): Lahoud R, Howe M, Krishnan SM, Zacharias S, Jackson EA. Effect of use of combination evidence-based medical therapy after acute coronary syndromes on long-term outcomes. *Am J Cardiol* 2012; 109(2): 159-64. PubMed PMID: 22011560.

A6 (iv): Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006; 368(9535): 581-8. Review. PubMed PMID: 16905022.

A6 (v): Danchin N, Cucherat M, Thuillez C, Durand E, Kadri Z, Steg PG. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: an overview of long-term randomized controlled trials. *Arch Intern Med* 2006; 166(7): 787-96. PubMed PMID: 16606817.

A6 (vi): McAlister FA; Renin Angiotension System Modulator Meta-Analysis Investigators. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are beneficial in normotensive atherosclerotic patients: a collaborative meta-analysis of randomized trials. *Eur Heart J* 2012; 33(4): 505-14. PubMed PMID: 22041554.

#### **A7. Beta-blocker with ischaemic heart disease.**

A7 (i): Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV, Gibbons RJ, Alpert JS, Antman EM, Hiratzka LF, Fuster V, Faxon DP, Gregoratos G, Jacobs AK, Smith SC Jr; American College of Cardiology; American Heart Association Task Force on Practice Guidelines. Committee on the Management of Patients With Chronic Stable Angina. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina - summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation* 2003 ; 107(1): 149-58. PubMed PMID: 12515758.

A7 (ii): Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: a critical review of the evidence. *J Am Coll Cardiol* 2007; 50(7): 563-72. Review. PubMed PMID: 17692739.

A7 (iii): Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007 ; 297(2): 177-86. PubMed PMID: 17213401.

A7 (iv): Everly MJ, Heaton PC, Cluxton RJ Jr. Beta-blocker underuse in secondary prevention of myocardial infarction. *Ann Pharmacother* 2004; 38(2): 286-93. Review. PubMed PMID: 14742768.

#### **A8. Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.**

A8 (i): Ambrosio G, Flather MD, Böhm M, Cohen-Solal A, Murrone A, Mascagni F, Spinucci G, Conti MG, van Veldhuisen DJ, Tavazzi L, Coats AJ.  $\beta$ -blockade with nebivolol for prevention of acute ischaemic events in elderly patients with heart failure. *Heart* 2011; 97(3): 209-14. PubMed PMID: 21138861.

A8 (ii): Lipsic E, van Veldhuisen DJ. Nebivolol in chronic heart failure: current evidence and future perspectives. *Expert Opin Pharmacother* 2010; 11(6): 983-92. Review. PubMed PMID: 20307222.

A8 (iii): Tangeman HJ, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. *Ann Pharmacother* 2003; 37(5): 701-10. Review. PubMed PMID:12708950.

### **Section B: Respiratory System criteria.**

#### **B1. Regular inhaled beta 2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.**

B1(i): Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001; 46(8): 798-825. Review. PubMed PMID: 11463370.

B1(ii): Keating GM. Tiotropium bromide inhalation powder: a review of its use in the management of chronic obstructive pulmonary disease. *Drugs* 2012; 72(2):273-300. Review. PubMed PMID: 22217233.

B1(iii): Yohannes AM, Hardy CC. Treatment of chronic obstructive pulmonary disease in older patients: a practical guide. *Drugs Aging* 2003; 20(3): 209-28. Review. PubMed PMID: 12578401.

B1(iv): McCrory DC, Brown CD. Anticholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease Editorial Group: Cochrane Airways Group Published Online: 8 OCT 2008. Assessed as up-to-date: 3 OCT 2005 DOI: 10.1002/14651858.CD003900

**B2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.**

B2(i): Spencer S, Evans DJ, Karner C, Cates CJ. Inhaled corticosteroids versus long-acting beta 2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2011 Oct 5;(10):CD007033. doi: 10.1002/14651858.CD007033.pub2. Review. Update in: *Cochrane Database Syst Rev* 2011; (12):CD007033. PubMed PMID: 21975759.

B2(ii): Gaebel K, McIvor RA, Xie F, Blackhouse G, Robertson D, Assasi N, Hernandez P, Goeree R. Triple therapy for the management of COPD: a review. *COPD* 2011; 8(3): 206-43. Review. PubMed PMID: 21513437.

B2(iii): Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ. Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2003; 58(11): 937-41. PubMed PMID: 14586043.

**B3. Home continuous oxygen with documented chronic hypoxaemia (i.e. pO<sub>2</sub> < 8.0 kPa or 60 mmHg or SaO<sub>2</sub> < 89%).**

B3(i): Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005 Oct 19; (4):CD001744. Review. PubMed PMID: 16235285.

B3(ii): Weitzenblum E, Chaouat A, Kessler R. [Long-term oxygen therapy for chronic respiratory failure. Rationale, indications, modalities]. *Rev Pneumol Clin* 2002; 58(4 Pt 1): 195-212. Review. French. PubMed PMID: 12407284.

**Section C: Central Nervous System & Ophthalmic Criteria.**

**C1. L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.**

C1(i): Marjama-Lyons JM, Koller WC. Parkinson's disease. Update in diagnosis and symptom management. *Geriatrics* 2001; 56(8): 24-5, 29-30, 33-5. Review. PubMed PMID: 11505857.

C1(ii): Danisi F. Parkinson's disease. Therapeutic strategies to improve patient function and quality of life. *Geriatrics* 2002; 57(3): 46-50; quiz 52. Review. PubMed PMID: 11899548.

**C2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.**

C2(i): Lebowitz BD, Pearson JL, Schneider LS, Reynolds CF 3rd, Alexopoulos GS, Bruce ML, Conwell Y, Katz IR, Meyers BS, Morrison MF, Mossey J, Niederehe G, Parmelee P. Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA* 1997; 278(14): 1186-90. Review. PubMed PMID: 9326481.

C2(ii): Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. *Cochrane Database Syst Rev.* 2006 Jan 25;(1):CD003491. Review. PubMed PMID: 16437456.

**C3. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild or moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).**

C3(i): Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, Booker L, Oremus M. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med* 2008; 148(5): 379-97. Review. PubMed PMID: 18316756.

C3(ii): Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006 Jan 25;(1):CD005593. Review. PubMed PMID: 16437532.

C3(iii): Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database Syst Rev* 2012 Mar 14;3:CD006504. doi: 10.1002/14651858.CD006504.pub2. Review. PubMed PMID: 22419314.

**C4. Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.**

C4 (i): Cheng JW, Li Y, Wei RL. Systematic review of intraocular pressure-lowering effects of adjunctive medications added to latanoprost. *Ophthalmic Res* 2009; 42(2): 99-105. Review. PubMed PMID:19546601.

C4 (ii): Aptel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandin analogs: a meta-analysis of randomized controlled clinical trials. *J Glaucom* 2008; 17(8): 667-73. PubMed PMID: 19092464.

C5 (iii): Cheng JW, Cheng SW, Gao LD, Lu GC, Wei RL. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: a systematic review and meta-analysis. *PLoS One* 2012; 7(9): e45079. Review. PubMed PMID: 23028770.

**C5. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.**

C5 (i): Ballenger JC. Remission rates in patients with anxiety disorders treated with paroxetine. *J Clin Psychiatry* 2004; 65(12):1696-707. PubMed PMID: 15641876.

C5 (ii): Allgulander C, Hartford J, Russell J, Ball S, Erickson J, Raskin J, Rynn M. Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin* 2007; 23(6): 1245-52. PubMed PMID: 17559726.

C5 (iii): Rickels K, Rynn M, Iyengar M, Duff D. Remission of generalized anxiety disorder: a review of the paroxetine clinical trials database. *J Clin Psychiatry* 2006; 67(1): 41-7. PubMed PMID: 16426087.

C5 (iv): National Institute for Health and Clinical Excellence. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. Clinical Guideline 113. 2011. <http://guidance.nice.org.uk/CG113> (accessed 22 September, 2012).

**C6. Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.**

C6 (i): Zintzaras E, Kitsios GD, Papathanasiou AA, Konitsiotis S, Miligkos M, Rodopoulou P, Hadjigeorgiou GM. Randomized trials of dopamine agonists in restless legs syndrome: a systematic review, quality assessment, and meta-analysis. *Clin Ther* 2010; 32(2): 221-37. Review. PubMed PMID: 20206780.

C6 (ii): Hansen RA, Song L, Moore CG, Gilsenan AW, Kim MM, Calloway MO, Murray MD. Effect of ropinirole on sleep outcomes in patients with restless legs syndrome: meta-analysis of pooled individual patient data from randomized controlled trials. *Pharmacotherapy* 2009; 29(3): 255-62. PubMed PMID: 19249945.

C6 (iii): Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. *Cochrane Database Syst Rev.* 2011 Mar 16;(3):CD006009. doi: 10.1002/14651858.CD006009.pub2. Review. PubMed PMID: 21412893.

**Section D: Gastrointestinal System criteria.**

**D1. Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.**

D1 (i): Hungin AP, Raghunath A. Managing gastro-oesophageal reflux disease in the older patient. *Digestion* 2004; 69 Suppl 1: 17-24. Review. PubMed PMID: 15001831.

D1 (ii): Pilotto A, Franceschi M, Paris F. Recent advances in the treatment of GERD in the elderly: focus on proton pump inhibitors. *Int J Clin Pract* 2005; 59(10): 1204-9. Review. PubMed PMID: 16178989.

D1 (iii): Metz DC. Managing gastroesophageal reflux disease for the lifetime of the patient: evaluating the long-term options. *Am J Med* 2004; 117, Suppl 5A :49S-55S. PubMed PMID: 15478853.

**D2. Fibre supplement (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.**

D2(i): Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. A prospective study of diet and the risk of symptomatic diverticular disease in men. *Am J Clin Nutr* 1994; 60(5): 757-64. PubMed PMID: 7942584.

D2(ii): Ünlü C, Daniels L, Vrouwenraets BC, Boermeester MA. A systematic review of high-fibre dietary therapy in diverticular disease. *Int J Colorectal Dis* 2012; 27(4): 419-27. Review. PubMed PMID: 21922199.

D2(iii): Rocco A, Compare D, Caruso F, Nardone G. Treatment options for uncomplicated diverticular disease of the colon. *J Clin Gastroenterol* 2009; 43(9): 803-8. Review. PubMed PMID: 19652620.

## **Section E: Musculoskeletal System criteria.**

### **E1. Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.**

E1(i): Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Suarez Almazor M, Bridges SL Jr, Chatham WW, Hochberg M, MacLean C, Mikuls T, Moreland LW, O'Dell J, Turkiewicz AM, Furst DE; American College of Rheumatology. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008; 59(6): 762-84. PubMed PMID: 18512708.

E1(ii): Köller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. *Rheumatology (Oxford)* 2009; 48(12): 1575-80. PubMed PMID: 19812228.

E1(iii): Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. *Ann Rheum Dis* 2006; 65(3): 379-84. PubMed PMID: 16150792.

### **E2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.**

E2(i): Homik J, Suarez-Almazor ME, Shea B, Cranney A, Wells G, Tugwell P. Calcium and vitamin D for corticosteroid-induced osteoporosis. *Cochrane Database Syst Rev* 2000; (2): CD000952. Review. PubMed PMID: 10796394.

E2(ii): Homik J, Cranney A, Shea B, Tugwell P, Wells G, Adachi R, Suarez-Almazor M. Bisphosphonates for steroid induced osteoporosis. *Cochrane Database Syst Rev* 2000; (2): CD001347. Review. PubMed PMID: 10796432.

E2(iii): Iwamoto J, Takeda T, Sato Y. Effects of antifracture drugs in postmenopausal, male and glucocorticoid-induced osteoporosis--usefulness of alendronate and risedronate. *Expert Opin Pharmacother* 2007; 8(16): 2743-56. Review. PubMed PMID: 17956196.

### **E3. Vitamin D supplement in patients with known osteoporosis and previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).**

E3(i): Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2009 Apr 15; (2): CD000227. doi: 10.1002/14651858.CD000227.pub3. Review. PubMed PMID: 19370554.

E3(ii): Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, Flicker L, Wark J, Jackson RD, Cauley JA, Meyer HE, Pfeifer M, Sanders KM, Stähelin HB, Theiler R, Dawson-Hughes B. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med* 2012; 367(1):40-9. Erratum in: *N Engl J Med*. 2012 Aug 2; 367(5):481. Orav, Endel J [corrected to Orav, Endel J]. PubMed PMID: 22762317.

**E4. Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores  $\rightarrow$  2.5 in multiple sites) and/or previous history of fragility fracture(s).**

E4(i): 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 Jan 23; (1): CD001155. doi: 10.1002/14651858.CD001155.pub2. Review. PubMed PMID: 18253985.

E4(ii): O'Donnell S, Cranney A, Wells GA, Adachi JD, Reginster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database Syst Rev* 2006 Oct 18; (4): CD005326. Review. PubMed PMID: 17054253.

E4 (iii): Nakamura T, Tsujimoto M, Hamaya E, Sowa H, Chen P. Consistency of fracture risk reduction in Japanese and Caucasian osteoporosis patients treated with teriparatide: a meta-analysis. *J Bone Miner Metab* 2012; 30(3): 321-5. PubMed PMID: 21938382.

E4(iv): von Keyserlingk C, Hopkins R, Anastasilakis A, Toulis K, Goeree R, Tarride JE, Xie F. Clinical efficacy and safety of denosumab in postmenopausal women with low bone mineral density and osteoporosis: a meta-analysis. *Semin Arthritis Rheum* 2011; 41(2):178-86. PubMed PMID: 21616520.

**E5. Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is  $>$  -1.0 but  $<$  -2.5 in multiple sites).**

E5(i): Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, Kerse N. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev* 2012 Dec 12; 12: CD005465. doi:10.1002/14651858.CD005465.pub3. Review. PubMed PMID: 23235623.

E5(ii): Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R; US Preventive Services Task Force. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2010; 153(12): 815-25. Review. PubMed PMID: 21173416.

E5(iii): Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. *J Am Geriatr Soc* 2010; 58(7): 1299-310. Review. PubMed PMID: 20579169.

**E6. Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.**

E6(i): Fravel MA, Ernst ME. Management of gout in the older adult. *Am J Geriatr Pharmacother* 2011; 9(5): 271-85. Review. PubMed PMID: 21849262.

E6(ii): Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, Gerster J, Jacobs J, Leeb B, Lioté F, McCarthy G, Netter P, Nuki G, Perez-Ruiz F, Pignone A, Pimentão J, Punzi L, Roddy E, Uhlig T, Zimmermann-Gòrska I; EULAR Standing Committee for International Clinical Studies Including



Therapeutics. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis*. 2006; 65(10): 1312-24. Review. PubMed PMID: 16707532.

E6(iii): Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev*. 2012 Nov 14;11:CD008653. doi:10.1002/14651858.CD008653.pub2. Review. PubMed PMID: 23152264.

#### **E7. Folic acid supplement in patients taking methotexate.**

E7(i): Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, Bombardier C, Carmona L, van der Heijde D, Bijlsma JW, Boumpas DT, Canhao H, Edwards CJ, Hamuryudan V, Kvien TK, Leeb BF, Martín-Mola EM, Mielants H, Müller-Ladner U, Murphy G, Østergaard M, Pereira IA, Ramos-Remus C, Valentini G, Zochling J, Dougados M. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; 68(7): 1086-93. PubMed PMID: 19033291.

E7(ii): Ortiz Z, Shea B, Suarez Almazor M, Moher D, Wells G, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 2000; (2):CD000951. Review. PubMed PMID: 10796393.

### **Section F: Endocrine System criteria.**

#### **F1. ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. overt dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.**

F1(i): Lv J, Perkovic V, Foote CV, Craig ME, Craig JC, Strippoli GF. Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database Syst Rev* 2012 Dec 12;12:CD004136. doi: 10.1002/14651858.CD004136.pub3. Review. PubMed PMID:23235603.

F1(ii): Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev* 2006 Oct 18;(4):CD006257. Review. PubMed PMID: 17054288.

F1(iii): Blacklock CL, Hirst JA, Taylor KS, Stevens RJ, Roberts NW, Farmer AJ. Evidence for a dose effect of renin-angiotensin system inhibition on progression of microalbuminuria in Type 2 diabetes: a meta-analysis. *Diabet Med* 2011; 28(10): 1182-7. PubMed PMID: 21627686.

### **Section G: Urogenital System criteria.**

#### **G1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.**

G1(i): Lowe FC. Role of the newer alpha<sub>1</sub>-adrenergic-receptor antagonists in the treatment of benign prostatic hyperplasia-related lower urinary tract symptoms. *Clin Ther* 2004; 26(11): 1701-13. Review. PubMed PMID: 15639685.

G1(ii): Schwinn DA, Roehrborn CG. Alpha<sub>1</sub>-adrenoceptor subtypes and lower urinary tracsymptoms. *Int J Urol* 2008; 15(3):193-9. Review. PubMed PMID: 18304211

G1(iii): Dunn CJ, Matheson A, Faulds DM. Tamsulosin: a review of its pharmacology and therapeutic efficacy in the management of lower urinary tract symptoms. *Drugs Aging* 2002; 19(2):135-61. Review. PubMed PMID: 11950378.

## **G2. 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.**

G2(i): Tacklind J, Fink HA, Macdonald R, Rutks I, Wilt TJ. Finasteride for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2010 Oct 6;(10): CD006015. doi: 10.1002/14651858.CD006015.pub3. Review. PubMed PMID: 20927745.

G2(ii): O'Leary MP, Roehrborn CG, Black L. Dutasteride significantly improves quality of life measures in patients with enlarged prostate. *Prostate Cancer Prostatic Dis* 2008; 11(2):129-33. PubMed PMID: 17592479.

G2(iii): Roehrborn CG. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. *BJU Int* 2008; 101 Suppl 3: 17-21. Review. PubMed PMID: 18307681.

## **G3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.**

G3 (i): Lynch C. Vaginal estrogen therapy for the treatment of atrophic vaginitis. *J Womens Health (Larchmt)* 2009; 18(10): 1595-606. Review. PubMed PMID: 19788364.

G3 (ii): Bachmann G, Bouchard C, Hoppe D, Ranganath R, Altomare C, Vieweg A, Graepel J, Helzner E. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. *Menopause* 2009; 16(4): 719-27. PubMed PMID: 19436223.

G3 (iii): Mainini G, Scaffa C, Rotondi M, Messalli EM, Quirino L, Ragucci A. Local estrogen replacement therapy in postmenopausal atrophic vaginitis: efficacy and safety of low dose 17beta-estradiol vaginal tablets. *Clin Exp Obstet Gynecol* 2005; 32(2): 111-3. PubMed PMID: 16108394.

## **Section H: Analgesics criteria.**

### **H1. High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.**

H1(i): Papaleontiou M, Henderson CR Jr, Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, Reid MC. Outcomes associated with opioid use in the treatment of chronic non-cancer pain in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2010; 58(7): 1353-69. Review. PubMed PMID: 20533971.

H1(ii): van Ojik AL, Jansen PA, Brouwers JR, van Roon EN. Treatment of chronic pain in older people: evidence-based choice of strong-acting opioids. *Drugs Aging* 2012; 29(8): 615-25. Review. PubMed PMID: 22765848.

## **H2. Laxatives in patients receiving opioids regularly.**

H2(i): Cook SF, Lanza L, Zhou X, Sweeney CT, Goss D, Hollis K, Mangel AW, Fehnel SE. Gastrointestinal side effects in chronic opioid users: results from a population-based survey. *Aliment Pharmacol Ther* 2008; 27(12): 1224-32. PubMed PMID: 18363893.

H2(ii): Chodosh J, Ferrell BA, Shekelle PG, Wenger NS. Quality indicators for pain management in vulnerable elders. *Ann Intern Med* 2001; 135(8 Pt 2): 731-5. PubMed PMID: 11601956.

## **Section I: Vaccines criteria.**

### **I1: Seasonal trivalent influenza vaccine annually.**

I1 (i): Lam S, Jodlowski TZ. Vaccines for older adults. *Consult Pharm* 2009; 24(5): 380-91. Review. PubMed PMID: 19555147.

I1 (ii): Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med* 2007; 357(14): 1373-81. PubMed PMID: 17914038.

I1 (iii): Michel JP, Chidiac C, Grubeck-Loebenstien B, Johnson RW, Lambert PH, Maggi S, Moulias R, Nicholson K, Werner H. Advocating vaccination of adults aged 60 years and older in Western Europe: statement by the Joint Vaccine Working Group of the European Union Geriatric Medicine Society and the International Association of Gerontology and Geriatrics-European Region. *Rejuvenation Res* 2009; 12(2): 127-35. PubMed PMID: 19415978.

### **I2: Pneumococcal vaccine at least once after age 65, according to national guidelines.**

I2 (i): Fedson DS, Liss C. Precise answers to the wrong question: prospective clinical trials and the meta-analyses of pneumococcal vaccine in elderly and high-risk adults. *Vaccine* 2004; 22(8): 927-46. PubMed PMID: 15161070.

I2 (ii): Vila-Córcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodríguez T, Llor C; EVAN Study Group. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. *Clin Infect Dis* 2006; 43(7): 860-8. PubMed PMID: 16941367.

I2 (iii): Vila-Corcoles A, Ochoa-Gondar O. Preventing pneumococcal disease in the elderly: recent advances in vaccines and implications for clinical practice. *Drugs Aging* 2013; 30(5): 263-76. Review. PubMed PMID: 23420119.

## **Appendix 3: Screening Tool of Older Persons' Prescriptions (STOPP) version 2**

The following prescriptions are potentially inappropriate to use in patients aged 65 years and older.

### **Section A: Indication of medication**

1. Any drug prescribed without an evidence-based clinical indication.
2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
3. Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).

### **Section B: Cardiovascular System**

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)
2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).
4. Beta blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).
5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)
6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).
7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K<sup>+</sup> < 3.0 mmol/l), hyponatraemia (i.e. serum Na<sup>+</sup> < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic)

9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people)
11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.
12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e.  $> 6.0$  mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).
13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP  $< 90$  mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse)

### **Section C: Antiplatelet/Anticoagulant Drugs**

1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).
2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer ).
3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).
4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy)
5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)
6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy).

7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).
8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).
9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).
10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).
11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)

#### **Section D: Central Nervous System and Psychotropic Drugs**

1. TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).
2. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).
3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).
4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na<sup>+</sup> < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).
5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).
6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms)

7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),
8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).
10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).
11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).
12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care ).
13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)
14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

**Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)**

1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m<sup>2</sup> (risk of digoxin toxicity if plasma levels not measured).
2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m<sup>2</sup> (risk of bleeding)
3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m<sup>2</sup> (risk of bleeding)
4. NSAID's if eGFR < 50 ml/min/1.73m<sup>2</sup> (risk of deterioration in renal function).
5. Colchicine if eGFR < 10 ml/min/1.73m<sup>2</sup> (risk of colchicine toxicity)
6. Metformin if eGFR < 30 ml/min/1.73m<sup>2</sup> (risk of lactic acidosis).

## **Section F: Gastrointestinal System**

1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).
2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).
3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).
4. Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate > 1800 mg/day; no evidence of enhanced iron absorption above these doses).

## **Section G: Respiratory System**

1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).
3. Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).
4. Benzodiazepines with acute or chronic respiratory failure i.e.  $pO_2 < 8.0 \text{ kPa} \pm pCO_2 > 6.5 \text{ kPa}$  (risk of exacerbation of respiratory failure).

## **Section H: Musculoskeletal System**

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).
2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).



3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief)
4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects).
5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).
6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).
7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)
8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)
9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)

### **Section I: Urogenital System**

1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).
2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)

### **Section J. Endocrine System**

1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
2. Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure)

3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).
4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).
5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).
6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

### **Section K: Drugs that predictably increase the risk of falls in older people**

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).
2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).
3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers, ) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure  $\geq 20\text{mmHg}$  (risk of syncope, falls).
4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

### **Section L: Analgesic Drugs**

1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).
2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).
3. Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain)

### **Section N: Antimuscarinic/Anticholinergic Drug Burden**

Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity)

## **Appendix: 4: Screening Tool to Alert to Right Treatment (START), version 2**

Unless an elderly patient's clinical status is end-of-life and therefore requiring a more palliative focus of pharmacotherapy, the following drug therapies should be considered where omitted for no valid clinical reason(s). It is assumed that the prescriber observes all the specific contraindications to these drug therapies prior to recommending them to older patients.

### **Section A: Cardiovascular System**

1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
2. Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.
4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.
5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.
6. Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.
7. Beta-blocker with ischaemic heart disease.
8. Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.

### **Section B: Respiratory System**

1. Regular inhaled  $\beta_2$  agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.

2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
3. Home continuous oxygen with documented chronic hypoxaemia (i.e. pO<sub>2</sub> < 8.0 kPa or 60 mmHg or SaO<sub>2</sub> < 89%)

### **Section C: Central Nervous System& Eyes**

1. L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.
2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.
3. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).
4. Topical prostaglandin, prostamide or beta-blocker for primary open-angle glaucoma.
5. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.
6. Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.

### **Section D: Gastrointestinal System**

1. Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.
2. Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.

### **Section E: Musculoskeletal System**

1. Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.
2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.
3. Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).

4. Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores  $\rightarrow$  2.5 in multiple sites) and/or previous history of fragility fracture(s).
5. Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is  $> -1.0$  but  $< -2.5$  in multiple sites).
6. Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.
7. Folic acid supplement in patients taking methotexate.

### **Section F: Endocrine System**

1. ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria ( $>30\text{mg}/24$  hours) with or without serum biochemical renal impairment.

### **Section G: Urogenital System**

1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.
2. 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.
3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.

### **Section H: Analgesics**

1. High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.
2. Laxatives in patients receiving opioids regularly.

### **Section I: Vaccines**

1. Seasonal trivalent influenza vaccine annually
2. Pneumococcal vaccine at least once after age 65 according to national guidelines

