APPENDIX 1. Managing Medications In Patients With Reduced Creatinine Clearance

Drug Class	Dose Adjustment based on eGFR (BNF advice)[41]
Antibiotics	
Cephalosporins Macrolides: • clarithromycin • azithromycin • erythromycin Penicillins • amoxicillin Flouroquinolones • ciprofloxacin Trimethaprim Nitrofurantoin	• many require dose adjustment • Use ½ dose if eGFR<30 • use with caution if eGFR <10 • max dose 1.5g daily in severe renal impairment • reduce dose in severe impaiment • adjust dose if eGFR<60 • adjust dose if eGFR <30 • contraindicated if eGFR <60
Cardiovascular	
Furosemide Spironolactone ACE inhibitors Beta-Blockers: • atenolol, bisoprolol , sotalol, nadolol labetolol, propanolol • metoprololl	• no contraindications in renal impairment; higher doses may be needed to induce desired response • monitor K+, avoid if rapid deterioration/severe impairment • adjust dose if eGFR <60 for may; Even if eGFR <60 is normal, check within first few weeks of ACE-i initiation and while on medication, as eGFR may fall. Stop if falls by>20% • adjust dose if eGFR dec • no dose adjustment
Diabetes	
Metformin Glibenclamide Glicazide	• reduce if eGFR<45, avoid eGFR<30 • Use with care mild-moderate impairment • contraindicated in severe renal impairment (eGFR < 30)
Osteoporosis	
Bisphosphonates • risedronate • aledronate	 • not recommended with eGFR < 30 • avoid if eGFR<35
Pain Management	
Morphine NSAID Gabapentin Pregabalin	• avoid or adjust dose in renal impairment • use with caution+adjust dose/avoid in renal impairment. Monitor U+E • adjust dose if eGFR < 60 • adjust dose for eGFR < 60
GI Meds	
Proton pump inhibitors H2 blockers	• no dose adjustment • adjust dose if eGFR < 50

How to Make Dosing Adjustments

Loading Doses: Adjustments are not usually required in patients with reduced eGFR.

Maintenance Doses: Adjustments can be made by reducing the dose, lengthening the dosing interval or both.

- Dose reduction involves reducing each dose while maintaining the usual dosing interval. This strategy maintains a more constant drug concentration but poses a higher risk of toxicity if the dosing interval is not sufficient for elimination of the drug.
- Lengthening the dose interval maintains normal doses but increases the dosing interval to allow time for drug elimination before a subsequent dose. This approach poses a lower risk of toxicity but a higher risk of subtherapeutic drug concentrations, particularly toward the end of the dosing interval.

Guidelines for dosing recommendations are typically divided into categories based on eGFR, although it is important to further individualise regimens according to patient response and serum drug concentration. The critical point for avoiding these drugs is often considered to be eGFR < 30, although there are different thresholds for different medications. However, if there is no effective alternate drug, these drugs can and should be used when needed, even in patients with severely compromised renal function. They will require dose adjustment and/or extra monitoring, and consultation may be advised. http://www.patient.co.uk/doctor/Drug-Prescribing-in-Renal-Impairment.htm is a useful link on this.[42]

See BNF for advice on using Cockcroft and Gault formula to calculate creatinine clearance for patients with renal impairment requiring toxic drugs.41

Adapted from: **1)** Munar M, Singh H. Drug Dosing Adjustments in Patients with Chronic Kidney Disease. Am Fam Physician 2007; May 15;75(10):1487-1496.; **2)** Lacey CF, Armstrong LL, Goldman MP, Lance LL. Drug Information Handbook, 20th Edition. Hudson, Ohio, Lexi-Comp, Inc.; 2011. http://webstore.lexi.com/Store/Pharmacology-Books/Drug-Information-Handbook ; **3)** Williams CM. Using Medications Appropriately in Older Adults. AFP 2002;66(10):1917-24; **4)** Luisi AF et al. In: Gallo JJ, Reichel W, eds. Reichel's Care of the Elderly: clinical aspects of aging, 5th ed. Philadelphia: Williams & Wilkins, 1999:59-87; **5)** Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician. 2008 Sep 15;78(6):743-50.
Websites Accessed June 2012.

APPENDIX 2. Some Medications That Interact With Warfarin

Increases Risk of Bleeding	• Antibiotics: Use caution with *all* antibiotics, especially metronidazole, macrolides, fluoroquinolones • Antifungals: Fluconazole, miconazole • Antidepressants: SSRIs • Antiplatelets: Aspirin, clopidogrel • Amiodarone • Anti-inflammatory agents: Use caution with *all* anti-inflammatory agents, especially COX-2 inhibitors • Alternative remedies: Ginkgo biloba, dong quai, fenugreek, chamomile
Decreases Risk of Bleeding	• Rifampin • St John's Wort

PRACTICE TIP

When starting any medication that interacts with warfarin, it is important to ensure that INR will be checked within 2-3 days of starting the new medication. Remember to tell people about the fact that Cranberry juice can enhance the effect of warfarin.

Note: The above is not a complete list. For a more detailed discussion, refer to:

- Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med 2005; 165:1095-106.
- Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, natural substances, and foods. J Clin Pharmacol 2005;45:127-32
- British National Formulary

Source: Juurlink DN, Drug interactions with warfarin: what clinicians need to know. *CMAJ* 2000; 177(4):369-371.

APPENDIX 3. Screening Tool Of Older People's Potentially Inappropriate Prescriptions (STOPP)

The following are potentially inappropriate in persons > 65 years old.

Cardiovascular System

Digoxin at a long-term dose > 0.125 mg/day with impaired renal function (eGFR < 50ml/min) *(↑risk of toxicity)*
Loop diuretic: For dependent ankle oedema only i.e., no clinical signs of heart failure *(no evidence of efficacy, use compression hosiery)*
Thiazide diuretic with a history of gout *(may exacerbate gout)*
Non-cardioselective beta-blocker with COPD *(risk of bronchospasm)*
Beta-blocker in combination with verapamil *(risk of symptomatic heart block)*
Diltiazem or verapamil with NYHA Class III or IV heart failure *(may worsen heart failure)*
Calcium channel blockers with chronic constipation *(may worsen constipation)*
Combining aspirin and warfarin without H2 antagonist (except cimetidine due to interaction with warfarin) or PPI *(high risk of gastrointestinal bleeding)*
Dipyridamole as monotherapy for cardiovascular 2° prevention *(no evidence of efficacy)*
Aspirin: With a history of peptic ulcer disease without H2 antagonist or PPI *(risk of bleeding)*; At a dose > 150 mg day *(↑ bleeding risk, no evidence for ↑ efficacy)*; With no history of coronary, cerebral or peripheral vascular symptoms or occlusive arterial event *(not indicated)*; To treat dizziness not clearly attributable to cerebrovascular disease *(not indicated)*
Warfarin: For first, uncomplicated deep venous thrombosis > 6 months duration or first uncomplicated pulmonary embolus > 12 months duration *(no proven added benefit)*
Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder *(high risk of bleeding)*

Central Nervous System and Psychotropic Drugs

Tricyclic antidepressants: With dementia *(risk of worsening cognitive impairment)*; With glaucoma *(likely to worsen glaucoma)*; With cardiac conductive abnormalities *(proarrhythmic effects)*; With constipation *(likely to worsen constipation)*; With opiates or calcium channel blockers *(risk of severe constipation)*; With prostatism or history of prior urinary retention *(risk of urinary retention)*
Long-term (> 1 month), benzodiazepines e.g., diazepam *(risk of prolonged sedation, confusion, impaired balance, falls)*
Long-term neuroleptics as long-term hypnotics *(risk of confusion, hypotension, extra-pyramidal side effects, falls)*
Long-term neuroleptics in those with parkinsonism *(likely to worsen extra-pyramidal symptoms)*
Phenothiazines in patients with epilepsy *(may lower seizure threshold)*
Anticholinergics to treat extrapyramidal side effects of neuroleptics *(risk of anticholinergic toxicity)*
SSRIs with history of clinically significant hyponatremia *(non-iatrogenic hyponatremia < 130 mmol/l for 2 months)*
Prolonged use (> 1 week) of first generation antihistamines e.g., chlorpheniramine, cyclizine, promethazine *(risk of sedation and anti-cholinergic side effects)*

Gastrointestinal System

Diphenoxylate, loperamide or codeine phosphate: • For treatment of diarrhea of unknown cause *(risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in IBD, may delay recovery in unrecognized gastroenteritis)* • For treatment of severe infective gastroenteritis i.e., bloody diarrhea, high fever or severe systemic toxicity *(risk of exacerbation or protraction of infection)*
Prochlorperazine or metoclopramide with Parkinsonism *(risk of exacerbating Parkinsonism)*
PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks *(earlier discontinuation or dose reduction for maintenance/ prophylactic treatment of peptic ulcer disease, oesophagitis or GORD indicated)*
Anticholinergic antispasmodic drugs with chronic constipation *(may worsen constipation)*

Respiratory System

Theophylline as monotherapy for COPD *(safer, more effective alternative, risk of adverse effects due to narrow therapeutic index)*
Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD *(unnecessary exposure to long-term side-effects of systemic steroids)*
Nebulised ipratropium with glaucoma *(may worsen glaucoma)*

APPENDIX 3. (STOPP, continued)

Musculoskeletal System

NSAIDs: With history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent H2 antagonist, PPI or misoprostol *(risk of peptic ulcer relapse)* With moderate (160/100–179/109 mmHg) to severe (≥ 180/110 mmHg) hypertension *(may worsen hypertension)*; With heart failure: (*may worsen heart failure)* With long-term use (> 3 months) for relief of mild joint pain in osteoarthritis *(simple analgesics preferable and usually as effective for pain relief)* With warfarin *(risk of gastrointestinal bleeding)*; With chronic renal failure** *(risk of deterioration in renal function)*
Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthritis or osteoarthritis *(risk of major systemic corticosteroid side-effects)*
Long-term NSAID or colchicines for chronic treatment of gout where there is no contraindication to allopurinol *(allopurinol first choice prophylactic drug in gout but NB reduce dose if eGFR reduced)*

**Estimated GFR 20-50 mL/min.

Urogenital System

Bladder antimuscarinic drugs: oxybutinin, toleridine: With dementia *(risk of increased confusion, agitation)*; With chronic glaucoma *(risk of acute exacerbation of glaucoma)*; With chronic constipation *(risk of worsening constipation)*; With chronic prostatism *(risk of urinary retention)*
Alpha-blockers: In males with frequent incontinence i.e., ≥ one episode of incontinence daily *(risk of urinary frequency and worsening of incontinence)*; With long-term urinary catheter in situ > 2 months *(drug not indicated)*

Endocrine System

Glibenclamide with type 2 diabetes *(risk of prolonged hypoglycemia)*
Beta-blockers with diabetes and frequent hypoglycemic episodes ≥ 1 episode per month *(risk of masking hypoglycemic symptoms)*
Oestrogens: With a history of breast cancer or venous thromboembolism *(↑ risk of recurrence)*; Without progestogen in patients with intact uterus *(risk of endometrial cancer)*

Drugs that adversely affect those prone to falls (≥ 1 fall in past three months)

Benzodiazepines *(sedative, may cause reduced consciousness/awareness, impair balance)*
Neuroleptic drugs *(may cause gait dyspraxia, Parkinsonism)*
First generation antihistamines *(sedative, may impair consciousness/awareness)*
Vasodilator drugs known to cause hypotension in those with persistent postural hypotension i.e., recurrent > 20 mmHg drop in systolic blood pressure *(risk of syncope, falls)*
Long-term opiates in those with recurrent falls *(risk of drowsiness, postural hypotension, vertigo)*

Analgesic Drugs

Use of long-term powerful opiates e.g. morphine or fentanyl as first line therapy for mild-moderate pain *(WHO analgesic ladder not observed)*
Regular opiates for > 2 weeks in those with chronic constipation without concurrent use of laxatives *(risk of severe constipation)*
Long-term opiates in those with dementia unless indicted for palliative care or management of moderate/severe chronic pain syndrome *(risk of exacerbation of cognitive impairment)*

Duplicate Drug Class

Any duplicate drug class prescription e.g., two concurrent opiates, NSAIDs, SSRIs, loop diuretics, ACE inhibitors *(optimization of monotherapy within a single drug class should be observed prior to considering a new class of drug)* • This excludes duplicate prescribing of inhaled beta 2 agonists (long and short acting) for asthma or COPD, and opiates for management of breakthrough pain.

Reprinted from: O'Mahony D, Gallagher P, Ryan C, Byrne S, Hamilton H, Barry P et al. STOPP & START criteria: A new approach to detecting potentially inappropriate prescribing in old age. European Geriatric Medicine 2010;1:45-51 with permission from Elsevier.

APPENDIX 4. Screening Tool To Alert Doctors To Right (e.g., Appropriate) Indicated Treatments (START)

These medications should be considered for people ≥ 65 years of age with the following conditions, where no contraindication to prescription exists.

Cardiovascular System

- Warfarin in the presence of chronic atrial fibrillation
- A NICE summary (June 2014) suggested that aspirin should not be used as monotherapy in AF to prevent stroke
- Aspirin with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm
- Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg
- Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy > 5 years
- ACE inhibitor for chronic heart failure
- ACE inhibitor following acute MI
- Beta blocker with chronic stable angina

Respiratory System

- Regular inhaled beta 2 agonist or anticholinegric agent for mild to moderate asthma or COPD
- Home continuous oxygen with documented chronic type 1 respiratory failure (pO_2 < 8.0 kPa, PCO_2 < 6.5 kPa) or type 2 respiratory failure (pO_2 < 8.0 kPa, PCO_2 > 6.5 kPa).

SI units: Hypoxemic (type 1) respiratory failure pO_2 < 60 mmHg; Hypercapnic (type 2) respiratory failure PCO_2 > 50 mmHg.

Central Nervous System

- L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability
- Antidepressant drug in the presence of moderate to severe depressive symptoms lasting at least three months

Gastrointestinal System

- PPI with severe gastroesophageal acid reflux disease or peptic stricture requiring dilatation
- Fibre supplement for chronic, symptomatic diverticular disease with constipation

Musculoskeletal System

- Disease-modifying antirheumatic drug (DMARD) with active moderate to severe rheumatoid disease lasting > 12 weeks
- Bisphosphonates in patients taking maintenance oral corticosteroid therapy
- Calcium and vitamin D supplement in patients with known osteoporosis (radiological evidence or previous fragility fracture or acquired dorsal kyphosis)

Endocrine System

- Metformin with type 2 diabetes ± metabolic syndrome (in the absence of renal impairment*)
- ACE inhibitor or ARB in diabetes with nephropathy
- Antiplatelet therapy in diabetes if one or more coexisting major cardiovascular risk factor present (hypertension, hypercholesterolemia, smoking history)
- Statin therapy in diabetes if one or more coexisting major cardiovascular risk factor present.

Reprinted from: Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment): an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 2007; 36(6):632-638 with permission of Oxford University Press.