



Trinity College Dublin
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The University of Dublin

Development and preliminary evaluation of OPTI-3S: A deprescribing support tool for hospitalised frail older adults

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By

Ahmed AbdelMoneim Hassan Ali

Under the supervision of

Associate Professor Sheila Ryder

Adjunct Assistant Professor Niamh McMahon

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Abbreviations

ACB	Anticholinergic burden
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEIs/ARBs	Angiotensin converting enzyme inhibitors/ Angiotensin II receptor blockers
AChEIs	Acetylcholinesterase inhibitors
ACS (STEMI)	Acute coronary syndrome (ST-segment elevation myocardial infarction)
AD	Alzheimer's disease
ADA	American Diabetes Association
ADLs	Activities of daily living
ADWEs	Adverse drug withdrawal events
AF	Atrial fibrillation
AFIRE	Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease
AGS	The American Geriatric Society
AHA	American Heart Association
AKI	Acute kidney injury
AM	Anorexic malnourished
ASB	Asymptomatic bacteriuria
ASCVD	Atherosclerotic cardiovascular disease
ASPREE	Aspirin in Reducing Events in the Elderly
BBB	Blood-brain barrier
BMI	Body Mass Index
BP	Blood pressure
BPH	Benign prostatic hyperplasia

BPSD	Behavioural and psychological symptoms of dementia
BSI	Bloodstream infection
CABG	Coronary-artery bypass grafting
CAD	Coronary artery disease
CAUTIs	Catheter-associated urinary tract infections
CCBs	Calcium channel blockers
CDI	Clostridium difficile infection
CFS	Clinical Frailty Scale
CGA	Comprehensive geriatric assessment
CHA₂DS₂-VASc Score	CHA ₂ DS ₂ -VASc stands for Congestive heart failure, Hypertension, Age ≥75 (double), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74 and Sex category (female)
CKD	Chronic kidney disease
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2 (COX-2) inhibitors
CrCl	Creatinine clearance
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DAT	Dual antithrombotic therapy
DBP	Diastolic blood pressure
DCPNS	Diabetes Care Program of Nova Scotia
DM	Diabetes mellitus
DOACs	Direct-acting oral anticoagulants
DPP-4 inhibitors	Dipeptidylpeptidase-4 inhibitor
EAS	European Atherosclerosis Society
EASD	European Association for the Study of Diabetes

EAU	European Association of Urology
ED	Emergency department
eGFR	estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
FI	Faecal Incontinence
GFI	Groningen Frailty Indicator
GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
GLP-1 RA	Glucagon-like peptide-1 receptor agonists
GLP1s agonists	Glucagon-like Peptide-1 receptors agonists
GORD	Gastro-oesophageal reflux disease
H2RAs	Histamine H2-receptor antagonists
HAS-BLED	stand for Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly
HbA1c	glycosylated Hemoglobin, type A1c
HF	Heart failure
IAD	Incontinence-associated dermatitis
IADLs	Instrumental activities of daily living
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
JBDS-IP	Joint British Diabetes Societies for Inpatient Care
LDL-C	Low-density lipoprotein-cholesterol
LE	Life expectancy
LMWH	Low molecular weight heparin
LTC	Long-term care
LUTS	Lower urinary tract symptoms

MACE	Major adverse cardiovascular event
MAP	Mean arterial pressure
MCI	Mild cognitive impairment
MID-Frail	Multi-modal Intervention in Diabetes in Frailty
MMSE	Mini-Mental State Examination
NICE	National Institute for Health and Care Excellence
NMBA	Neuromuscular blocking agents
NORGEp-NH	Norwegian General Practice-Nursing Home Criteria
NPH	Neutral Protamine Hagedorn
NPO	In Latin, nil per os; means “nothing by mouth”
NPUAP/EPUAP/PPPIA	National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance
NSAIDs	Non-steroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulants
OH	Orthostatic hypotension
OPTIMISE	Optimising Treatment for Mild Systolic Hypertension in the Elderly
OTC	Over the counter
PATH	Palliative and Therapeutic Harmonization
PCI	Percutaneous Coronary Intervention
PEG	Polyethylene glycol
POCD	Postoperative cognitive decline
POD	Postoperative delirium
PONV	Postoperative nausea and vomiting
PPIs	Proton pump inhibitors
PPOs	Potential prescribing omission
PriME	Perioperative Management of Elderly Patients

RABBIT 2	Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes
RCTs	Randomised controlled trials
ROSPER	Prospective Study of Pravastatin in the Elderly at Risk
SAGE	Study Assessing Goals in the Elderly
SAS	Statin-associated symptoms
SBP	Systolic Blood Pressure
SE	Systemic embolism
SGLT2	Sodium glucose co-transporter 2 inhibitors
SHA	Toledo Study for Healthy Aging
SIPAF	Système d'Information sur la Perte d'Autonomie Fonctionnelle de la personne âgée
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SO	Sarcopenic obese
SoPPS/REC	School of Pharmacy & Pharmaceutical Sciences/ Level 1 Research Ethics Committee
SPRINT	Systolic blood PResure INtervention Trial
SSI	Sliding scale insulins
SSRIs	Selective serotonin reuptake inhibitors
STOPP/START	Screening Tool of Older Persons Prescriptions/ Screening Tool to Alert doctors to Right
STOPPFrail	Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy
SUI	Stress urinary incontinence
TCAs	Tricyclic antidepressants
TdP	Torsade de Pointes
TILDA	The Irish Longitudinal Study on Ageing
TONE	Trial of Nonpharmacologic Intervention in the Elderly

TTB	Time to benefit
UFH	Unfractionated heparin
UKMI	UK Medicines Information
UKPDS	United Kingdom Prospective Diabetes Study
USPSTF	US Preventive Services Task Force
UTIs	Urinary tract infections
UUI	Urge urinary incontinence
VADT	Veterans Affairs Diabetes Trial
VKAs	Vitamin K antagonists
VTE	Venous thromboembolism

Preliminary list statements and supporting evidence

The preliminary statements for the OPTI-3S criteria (n=109) in Chapter 3 (Section 3.3.3) were split and reworded in accordance with the comments and feedback from the experts participating in the pilot study, yielding a list of 130 statements (the “full list”) for dissemination to the Delphi method expert panel. This online supplementary file discusses the evidence underlying these statements, and its reflection in other clinical guidelines, where relevant. The OPTI-3S statements are grouped into seven physiological systems (*i.e.* cardiovascular, central nervous, endocrine, gastrointestinal, genito-urinary, skin and pressure ulcer, and musculoskeletal) and a patient-centred care setting (perioperative setting).

The evidence underpinning each statement or group of statements and concisely summarized here was derived from multiple sources, according to a hierarchy of evidence discussed in chapter 3. These included clinical practice guidelines (*e.g.* the Irish, British, European, North American, and Asian guidelines), systematic reviews or meta-analyses, controlled clinical trials, and observational study designs that summarised existing evidence on head-to-head comparisons of the effectiveness and safety of pharmacological interventions in fit or frail older adults. In addition, expert consensus-based algorithms and guides for deprescribing certain medications and medication classes in the presence of frailty were also considered. It was essential for the new OPTI-3S criteria to be evidence-based. Each statement includes a brief rationale for the recommendation provided, for the information of practitioners. Relevant references were made available to the experts in the Delphi study to draw upon if they wished, when rating statements’ suitability for the core list.

1. Cardiovascular and coagulation system

1. In patients living with severe frailty level or higher (CFS 7-9), statins for primary prevention of cardiovascular events should be discontinued (low benefit, increased risk of statin-associated adverse effects).
2. In nondiabetic patients with mild to moderate frailty (CFS 4-6) who are ≥ 75 years old, statins for primary prevention should be discontinued in those with a life expectancy of less than 3-5 years and a low cardiovascular event risk.
3. In very mildly to moderately frail older patients (CFS 4-6) with pre-existing vascular disease (coronary, cerebral, or peripheral), a trial of statin discontinuation should be

- considered if there are side effects that impair quality of life (*e.g.* myalgias, muscle weakness, cognitive function deterioration) (statins may exacerbate these symptoms).
4. In very mildly to moderately frail older patients (CFS 4-6) with pre-existing vascular disease (coronary, cerebral, or peripheral), a trial of statin discontinuation should be considered if patients have concurrent or planned treatment with azole antifungals, verapamil, diltiazem, or macrolides (clinically significant drug-drug interactions that increase exposure to statin).
 5. In older patients living with severe frailty level or higher (CFS 7-9), statins used for secondary prevention may be discontinued (limited life expectancy, increased risk of associated adverse outcomes).
 6. In all frail patients (CFS ≥ 4), the concurrent use of non-statin lipid-lowering medications with statins should be avoided (increases statin-associated adverse effects such as myopathy with ezetimibe or fibrates).
 7. In all diabetic frail patients (CFS ≥ 4) aged 85 years or older, statins for primary prevention of cardiovascular events may be discontinued if a) patients have a life expectancy of less than 3-5 years or b) statins are not well tolerated.

Most clinical practice guidelines strongly recommend initiating statin therapy for primary cardiovascular prevention based on risk assessment until the age of 75 years [1]. However, limited evidence of low quality supports the benefits for those aged 75 years or older [1]. Therefore, current guidelines provide minimal guidance on using statins for primary prevention in adults 75 years or older [1]. The National Institute for Health and Care Excellence (NICE, 2014) considered that primary prevention with atorvastatin 20 mg daily might minimise nonfatal cardiovascular events in people aged 85 years or more [2]. According to the 2018 American Heart Association/American College of Cardiology guideline (AHA/ACC), initiating moderate-intensity statin therapy may be reasonable for those over 75 years of age with a low-density lipoprotein-cholesterol (LDL-C) of 70–189 mg/dL [3]. This is consistent with the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guideline (2019), which considered initiating statins for primary prevention in high-risk older adults aged ≥ 75 years if at high risk or above [4]. Most guidelines used the cut-off age of 75 years [1]. This may be explained that most participants in controlled clinical trials had mean ages of 75 years or less [1]. Additionally, some sources depended on evidence of benefit from sub-analysis of large trials comparing those younger than 75 years and those older than 75 years [1].

Diabetes mellitus (DM) may be considered a high-risk factor for developing cardiovascular events, no matter what age is used as a cut-off [3]. Therefore, the 2018 AHA/ACC guideline considered initiating statin therapy in diabetic older adults over 75 years of age [3]. In a retrospective cohort study, 46,864 individuals aged 75 or older were stratified by DM and statin usage [5]. Statins were not associated with reduced atherosclerotic cardiovascular disease (CVD) or all-cause mortality in adults aged 75 and older without diabetes [5]. Those with diabetes mellitus who were younger than 85 years old had a slight but significant reduction in all-cause mortality and atherosclerotic cardiovascular disease [5]. This beneficial effect was significantly diminished in those aged 85 and older and completely disappeared in those aged 90 and older [5].

For secondary cardiovascular prevention, a few specific trials and numerous subgroup analyses of large trials demonstrated significant benefits of statins in reducing mortality and cardiovascular events in older adults with established cardiovascular diseases. PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) and SAGE (Study Assessing Goals in the Elderly) are the only two representative trials designed for or exclusively enrolling older adults [6-8]. In PROSPER, older adults aged 70-82 years (mean age of 75.4) were randomly assigned to receive pravastatin or a placebo [6]. Pravastatin treatment for 3.2 years reduced CHD death and fatal coronary events or coronary hospitalisations in the extended follow-up PROSPER study (total mean follow-up of 8.6 years) [6, 7]. In the SAGE trial, 893 coronary artery disease patients aged 65 to 85 years were randomised to either intensive therapy (atorvastatin 80 mg/d) or moderate-intensity therapy (pravastatin 40 mg/d) for a follow-up period of 12 months [8]. Both therapies significantly reduced the total duration of ischemia at 3 and 12 months. Compared to pravastatin, atorvastatin significantly reduced serum LDL-C levels and all-cause mortality, with nonsignificant fewer acute cardiovascular events [8].

Per the evidence mentioned earlier, the relevant NICE guideline recommended initiating statin therapy in individuals with cardiovascular disease [2]. In addition, the 2019 ESC/EAS Guidelines recommended statin therapy for older patients with atherosclerotic cardiovascular disease (ASCVD) [4]. According to the 2018 AHA/ACC guideline, it may be reasonable to initiate moderate- to high-intensity therapy in older patients aged 75 years or more with ASCVD after considering the risks of side effects, drug interactions, frailty, and patient preference [3]. Similarly, high-intensity therapy may be continued if tolerated after evaluating the potential side effects, drug interactions, frailty, and patient preference [3].

With the same level of recommendation (moderate) and level of evidence (moderate) for considering statin initiation, it is reasonable, according to the AHA/ACC guideline (2018), to discontinue statin therapy when there are factors that limit the potential benefits of statins [3]. These factors include physical or cognitive functional decline, frailty, a limited life expectancy, and multiple diseases [3]. Considering these factors, it is prudent to proceed with caution when extrapolating statins' safety and efficacy evidence in primary cardiovascular prevention to individuals aged 75 and older. Before deciding whether to initiate or continue statin therapy for primary prevention, the time to benefit and life expectancy are the most crucial factors to consider. The follow-up periods of landmark trials may be used as an estimate of the time required to experience a benefit. In PROSPER, patients were followed for 3.2 years after randomization [6]. Additionally, a survival meta-analysis suggested that statins might prevent the first major adverse cardiovascular event (MACE) in older adults aged 50 to 75 years, with a life expectancy of at least 2.5 years [9]. This 2.5-year period may exceed the life expectancy of patients with severe or very severe frailty who have limited time remaining to benefit from statin therapy.

Older adults, particularly the frail cohort, are underrepresented in randomised controlled trials. As a result, all clinical practice recommendations for the frailty cohort are based on limited or low-quality evidence, expert opinion, or formal consensus-based medication appropriateness lists. The Cholesterol Treatment Trialists' Collaboration conducted a meta-analysis of randomised trials to compare the effect of statins at different ages [10]. The findings suggested that statin therapy has significant major vascular benefits in those with pre-existing vascular diseases, regardless of age, with less direct evidence of benefits in those without pre-existing vascular disease aged 75 or older [10]. Another recent systematic review found no randomised clinical trials investigating the association between statin prescribing and MACE reduction in frail older patients [11]. According to observational cohort studies alone, statins were associated with decreased mortality when prescribed for secondary prevention in frail older adults [11]. There was a lack of evidence to draw a conclusion about statin benefits for primary prevention [11]. One randomised clinical trial suggested that discontinuing statins in palliative care patients was safe and improves their quality of life [12]. This pragmatic trial included patients with a one-month to one-year life expectancy, a recent decline in functional status, and no recent cardiovascular events who had used statins for primary or secondary prevention for at least three months [12].

The Revision Dutch Cardiovascular Disease Prevention Guideline (2019) has considered statin therapy only for frail older adults with a (recent) cardiovascular event and sufficient life expectancy to benefit, with careful consideration of adverse effects (such as myopathy) [13]. The STOPPFrail tool is a consensus-based list intended to assist clinicians in deprescribing decisions for patients living with severe irreversible frailty approaching the end of life [14]. According to the STOPPFrail v2 criteria, lipid-lowering medications (*e.g.* statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid, lomitapide, and acipimox) are potentially inappropriate [14]. Similarly, the Dalhousie Academic Detailing Service and the Palliative and Therapeutic Harmonization programme (ADS/PATH) did not support statins or other lipid-lowering medications in severely frail older adults [15]. They suggested that statins provided no benefit for primary prevention, are not necessary for secondary prevention, should not be combined with non-statin medications, may be appropriate in certain circumstances at lower doses, and may be discontinued temporarily in the event of adverse effects or drug-drug interactions [15]. Specifically, these suggestions targeted people with severe and very severe frailty (CFS scores of 7 or 8). These recommendations adhere to the Australian primary health Tasmania deprescribing guides [16]. These guides favour the deprescribing of statins in patients with a limited life expectancy, poor functional status, and suspected adverse effects [16].

8. In all frail older patients (CFS ≥ 4) who have a high risk of myopathy, high-intensity therapy (*e.g.* simvastatin > 40 mg, atorvastatin ≥ 20 , rosuvastatin ≥ 10 mg) may be potentially inappropriate.

Frail older adults are more vulnerable to statin-associated adverse effects such as myopathy [15]. The prescription appropriateness criteria for older Australians recommended against the use of high doses of high-potency statins in those at risk of statin-induced myopathy [17]. Age >70 years, diabetes, hypothyroidism, renal disease, hepatic disease, concurrent use of ciclosporin, concurrent use of fibrates, concurrent use of CYP3A4 inhibitors with all statins except pravastatin and rosuvastatin (*e.g.* diltiazem, macrolides, protease inhibitors, verapamil), severe intercurrent illness (*e.g.* infection, trauma and metabolic disorder), and daily doses ≥ 40 mg were listed among risk factors for statin myopathy [17]. According to the NICE guideline, atorvastatin 20 mg-80 mg, rosuvastatin 10 mg-40 mg, and simvastatin 80 mg are considered high-intensity statin therapy based on the percentage of (LDL) cholesterol reduction they achieve [2].

9. Setting blood pressure control goals based solely on systolic blood pressure (SBP) is insufficient. In addition to SBP targets (suggested below in statements 10 and 11), a diastolic blood pressure target (DBP) of not less than 70 mm Hg should be considered, particularly in isolated systolic hypertension.
10. In patients living with very mild to mild frailty (CFS 4-5), moderate frailty (CFS 6), and severe frailty level or higher (CFS 7-9), less intensive SBP targets of 130 -139 mm Hg, $\leq$ 150 mm Hg, and $\leq$ 160 mm Hg are appropriate, respectively.
11. More liberal SBP targets than those listed above may be acceptable in the following situations (with caution in patients on antithrombotic agents):
 - a) if the above-mentioned targets are less tolerated
 - b) in circumstances to maintain DBP not less than 70 mm Hg (*e.g.* isolated systolic hypertension), or
 - c) in the last year of life.
12. Discontinuing or omitting antihypertensive therapy solely on the basis of age (*e.g.* in patients aged 80 years or older) is a potential prescribing omission (very old patients may benefit from BP-lowering therapy if it is tolerated).
13. If SBP < 130 mm Hg, DBP < 70 mm Hg or the patient shows symptomatic orthostatic hypotension, consider the following:
 - a) For combination therapy: Deescalate to monotherapy or low-dose monotherapy,
 - b) For monotherapy: reduce the dose of the antihypertensive monotherapy or discontinue monotherapy agent in moderate frailty level or higher (CFS 6-9), and
 - c) First deprescribe non first-line therapies and antihypertensive medications that are not required for compelling indications.
14. Use of more than two antihypertensive medications is of unfavourable benefit/risk profile in the following patients (unless used for resistant hypertension or other compelling indications):
 - a) Those living with moderate frailty level or higher (CFS 6-9),
 - b) Those with moderate dementia or cognitive impairment, or
 - c) Those with a life expectancy of less than 2 years.
15. In patients with mild to moderate frailty (CFS 4-6), if the BP target is not met and the decision is taken to intensify the therapy, combination therapy is likely effective and more tolerable than titrating doses of a single-agent regimen. An exception is when

intensification of monotherapy is required for other coexisting conditions (*e.g.* ACEIs for heart failure).

Hypertension is a significant predictor of cardiovascular events, decline in cognitive and physical function, and mortality in older adults [18]. There is a constant increase in the prevalence of arterial hypertension, particularly isolated systolic hypertension, in older adults [18]. This is primarily due to physiological changes associated with ageing, such as vascular stiffness [19]. Arterial stiffening causes a rise in pulse pressure, leading to isolated systolic hypertension [19]. This elevation in systolic blood pressure (SBP) necessitates therapeutic interventions that could ultimately result in a significant decline in diastolic blood pressure (DBP) [19]. In real practice, it is challenging to keep SBP within targets without risking critically low DBP [19]. Some clinical practice guidelines have addressed this clinical dilemma. The 2018 ESC/ESH guidelines for managing arterial hypertension suggested an office DBP treatment target range of 70-79 mm Hg [20]. Nevertheless, the 2019 Dutch guideline for cardiovascular risk management supports de-intensifying antihypertensive therapy in vulnerable older adults when DBP falls below 70 mm Hg, irrespective of SBP [13].

There is inconsistency across clinical practice guidelines on targets for SBP and DBP [21]. Some clinical practice guidelines recommend therapeutic targets for SBP and DBP based on age and/or frailty status [21]. Others, however, do not modify targets and treat older or frail adults similarly to their younger counterparts [21]. The NICE guideline suggested SBP/DBP targets below 140/90 mm Hg and 150/90 mm Hg in older adults aged < 80 years and ≥ 80 years of age, respectively [22]. The guideline committee believed that frail patients may require different goals based on clinical judgement because they may not benefit from intensive targets, which may increase adverse effects [22]. Similarly, the desired SBP target by the 2018 ESC/ESH hypertension guidelines was 130-139 mm Hg for all patients aged ≥ 65 years. They advised against lowering SBP below 120 mm Hg or DBP below 80 mm Hg [20]. The 2019 Dutch guideline suggested SBP targets of < 150 mm Hg in fit older adults and of < 150 mm Hg (with the condition of careful titration) in vulnerable individuals [13]. For very old and frail adults, the 2019 Chinese guideline targeted an SBP goal of ≤ 150 mm Hg but ≥ 130 mm Hg whenever possible [23].

The limited available evidence indicates that blood pressure-lowering therapy reduces the incidence of fatal or nonfatal stroke, heart failure, and mortality in very older adults (*i.e.*, those aged more than 80 years) [24]. Therefore, the 2018 ESC/ESH guideline emphasised that older persons should not be denied or withdrawn from BP-lowering therapy based on age *per se*.

Moreover, hypertensive patients, who are not receiving therapy, should be prescribed antihypertensive medications if they can tolerate them [20]. Similarly, antihypertensive therapy may reduce the risk of developing dementia in hypertensive patients aged 80 or older (2019 Dutch guideline; low-grade evidence) [13]. Some researchers hypothesised that stratification based on the degree of frailty could improve short- and long-term outcomes when treating hypertension in older adults [18]. The evidence on the pharmacotherapy of arterial hypertension in frail patients has been systematically reviewed [25]. In randomised controlled trials, antihypertensive medications improved the quality of life, functional status, and incidence of cardiovascular events in frail older adults [25]. Nonetheless, observational studies demonstrated decreased mortality and falls in the no-treatment arms. The authors proposed an SBP target of < 150 mm Hg in patients with a gait speed of fewer than 0.8 m/s and a target of 130–139 mm Hg for patients over 80 years who are no more than mildly frail [25].

Benetos *et al.* introduced an algorithm for managing hypertension in older adults, considering the functional status and autonomy for activities of daily living (ADL) [18]. They adopted antihypertensive strategies for three distinct patient profiles based on the Clinical Frailty Scale: preserved function, loss of function/preserved ADL, and loss of function and altered ADL [18]. The "preserved function group" corresponds to CFS 1-3 and should be treated similarly to younger adults, with an SBP target range of 130–140 mm Hg. The "loss of function and altered ADL" corresponds to CFS 6-9 [18]. In this cohort of patients, keeping the SBP target below 150 mm Hg and de-intensifying hypertension treatment when the SBP falls below 130 mm Hg was recommended [18]. If antihypertensive therapy is suggested for this group, begin with a small dose and progressively increase to a maximum of three antihypertensive drugs. The in-between group, the "loss of function/preserved ADL" group, corresponds to CFS 4, and the decision for hypertension management should be individualized [18]. A recent survey of Irish and UK clinicians aimed to inform the design of hypertension treatment trials in older adults living with frailty [26]. Using different BP targets, participants tended to enrol frail individuals in therapy relaxation studies when SBP is below 130 mm Hg and to recruit patients with high cardiovascular risk in therapy intensification trials when SBP is greater than 150 mm Hg [26].

The ADS/PATH members examined the available evidence to develop a guideline for managing hypertension in frail patients with a Clinical Frailty Scale score of 7-9 [27]. SBP targets of 140 to 160 mm Hg were advised for very frail patients with a short life expectancy, with more liberal targets (160-190 mm Hg) [27]. Notably, separate recommendations for frail individuals with diabetes were not suggested [27]. This guideline recommended tapering or discontinuing

antihypertensive medications if the systolic pressure drops below 140 mm Hg unless indicated for compelling indications such as atrial fibrillation or heart failure [27]. This is consistent with the STOPPFrail v2 recommendations that recommended considering additional indications before discontinuing antihypertensive medications (such as beta-blockers for rate control in atrial fibrillation and diuretics for symptomatic heart failure) [14]. The STOPPFrail v2 suggested an SBP target range of 130–160 mm Hg and to reduce or discontinue antihypertensive medications if systolic blood pressure (SBP) persistently dropped below 130 mm Hg [14]. Similar to the decisional algorithm by Benetos *et al.*, neither the ADS/PATH guideline nor STOPPFrail v2 proposed a diastolic blood pressure (BP) target (DBP).

According to another expert consensus-based recommendations, intensive blood pressure targets of less than 140/90 mm Hg were not recommended for complex older patients with an estimated life expectancy of less than two years [28]. Experts recommended deescalating the number of antihypertensive medications in patients with symptomatic orthostatic hypotension (OH) or fall and OH to avoid multiple antihypertensive drugs [28]. In addition, experts have advised against prescribing more than three antihypertensive medications to patients with dementia, cognitive impairment, or functional limitations [28]. Similarly, the ADS/PATH guideline recommended no more than two medications for those who are very severely frail with a limited life expectancy [27]. Ouellet *et al.* investigated the longitudinal association between the number of antihypertensives and the incidence of MACE in complex older adults [29]. The findings suggested no advantages to using three antihypertensive classes over 1-2 classes in complex older adults regarding mortality and cardiovascular events [29].

A recent Cochrane review investigated the feasibility of antihypertensive medication withdrawal and its impact on mortality and cardiovascular outcomes in older adults [30]. With low certainty of the evidence, findings suggested that stopping antihypertensives did not increase the risk of stroke, cardiovascular events, or death [30]. However, several researchers have raised concerns regarding the study population and methodology, which may impact the generalizability of the findings [31]. Firstly, the selection criteria included all randomised trials in older adults who were defined as 50 years and over [31]. Consequently, a substantial proportion of younger adults could have been included in the analysis. Secondly, the wide range of confidence intervals in the odds ratios could be interpreted in favour of an increased risk of adverse outcomes following medication discontinuation rather than a decreased risk [31]. Moreover, the authors found a slight rise in blood pressure upon stopping antihypertensive medications [31]. Uncertainty

surrounds the significance of this BP increase on the outcomes of a real older cohort of study participants [31].

The Optimising Treatment for Mild Systolic Hypertension in the Elderly (OPTIMISE) study is a recent randomised, non-inferiority deprescribing trial in older adults receiving primary care in England [32]. Participants in the OPTIMISE study were older adults aged ≥ 85 years with an SBP < 150 mm Hg and receiving two or more antihypertensive medications [32]. In terms of SBP control at 12 weeks, the participants in the intervention group (discontinuation of one medication) were non-inferior to those randomised to the usual care arm (no medication change) [32]. According to the authors, more moderately and severely frail participants were enrolled in the OPTIMISE study than in the Systolic Blood Pressure Intervention Trial (SPRINT) using the same frailty assessment measure [33]. However, the study design and generalizability of the results have been criticised. First, the 12-week period is insufficient for evaluating the long-term outcomes [34]. In addition, although non-significant, the rise in systolic blood pressure in the intervention group 12 weeks after randomization may have clinical implications for long-term outcomes [34]. Moreover, the study was underpowered to assess specific safety outcomes, and there were concerning issues with unblinding and relatively frequent blood measurements in the intervention group [34]. There are also some concerns regarding the extrapolation of findings to older adults excluded from the study (such as those with poorly controlled BP, heart failure, or recent cardiovascular events) [34].

In contrast to the OPTIMISE study, the Trial of Nonpharmacologic Intervention in the Elderly (TONE) allowed three months of careful observation before deprescribing antihypertensive drugs [35]. Participants in the TONE study were 60–80 years old, had an average SBP/DBP of less than 145/85 mm Hg, and received a single antihypertensive agent or a single combination regimen [35]. Participants were initially randomised to sodium reduction and weight loss, only sodium reduction, only weight loss, or none of them for 36 months [35]. Three months after randomization, antihypertensive medication was withdrawn and then reinitiated as needed [35]. In contrast to the OPTIMIZE trial, participants in the TONE study experienced a significant rise in blood pressure (BP) and an increased risk of symptomatic adverse effects after antihypertensive therapy withdrawal [35]. Specifically, for frail patients, RETREAT-FRAIL is an ongoing randomised case-control study that was anticipated to conclude early in 2023 [36]. The investigators hypothesised that survival and mortality could be improved by gradually stepping down antihypertensive therapy in nursing home residents aged ≥ 80 years, with SBP < 130 mm Hg, and receiving more than one antihypertensive medication [36].

16. Hydralazine, nifedipine, nitroprusside and clonidine are potentially inappropriate medications in hypertensive emergencies (unfavourable adverse effects).

Severe uncontrolled hypertension can lead to a hypertensive crisis, either with end-organ dysfunction (a hypertensive emergency) or without it (urgency) [37]. In contrast to younger adults, older adults are more likely to present with a hypertensive emergency than a hypertensive urgency [37]. This may be rationalised that older adults are more likely to have a history of chronic diseases such as diabetes, chronic kidney disease, stroke, and cardiovascular disease. It is recommended to avoid abruptly lowering BP in hypertensive emergencies due to the high risk of hypoperfusion in older adults [37]. Therefore, easily titratable and reversible pharmacological options should be utilised [37]. In contrast, patients presenting with hypertensive urgencies should be administered oral short-acting agents such as ACEIs or ARBs for a less drastic reduction in blood pressure [37].

Many intravenous and oral antihypertensive agents are available to treat hypertensive crises. Older adults who receive nitroprusside are at a higher risk of complications, hypotension, and mortality [38]. Therefore, it should only be used when other alternative options are unavailable [37]. Nifedipine is a dihydropyridine calcium channel blocker that can cause a rapid and significant fall in blood pressure [37]. This increases the risk of reflex tachycardia and myocardial ischaemia in older adults [39]. Therefore, the AGS Beers criteria recommended against the use of nifedipine in older adults aged 65 years or more [39]. Clonidine is another pharmacological option, with sedative-analgesic properties and the potential to induce confusion [40]. Furthermore, abrupt withdrawal of clonidine is associated with rebound hypertension, which may discourage the use of clonidine in older adults [37]. Hydralazine is an arterial vasodilator with a broad spectrum of adverse effects, including reflex tachycardia and severe hypotension [37]. In addition, its antihypertensive effects are entirely unpredictable and may last up to 24 hours [37]. Therefore, it is advisable to avoid hydralazine in managing the hypertensive crisis in older people [37].

17. In all frail patients (CFS $\geq$ 4), the sole use of beta-blockers for hypertension (*i.e.* hypertension as a single indication) should be limited when possible (risk of orthostatic hypotension).

Although beta blockers are no longer a first-choice treatment for hypertensive patients without compelling indications, one-sixth of a sample drawn from the first wave of The Irish Longitudinal Study on Ageing received beta-blocker monotherapy for hypertension [41]. The use of beta-

blocker monotherapy for hypertension also remains prevalent in other countries, such as the United States and Korea [42]. Hypertensive patients on beta-blockers may exhibit a higher stroke risk than those on other first-line therapies, such as ACE inhibitors and thiazide diuretics [42]. Moreover, a systematic review found that beta blockers had lower efficacy in reducing cardiovascular events when compared to other antihypertensives in older adults [43]. In a multivariate analysis of TILDA data, beta blocker monotherapy was linked to a greater than twofold increase in the incidence of orthostatic hypotension and a greater than threefold increase in the odds of sustained OH and impaired blood pressure stabilisation [41]. This is consistent with the 2019 Dutch recommendations that endorsed avoiding alpha and beta blockers for the sole indication of hypertension in frail older adults due to the frequent occurrence of undesirable adverse effects such as OH [13].

18. In mildly frail older adults (CFS 4-5), caution should be taken when the antihypertensive dose is rescheduled in the evening or night-time (benefits of mitigating the daytime hypotensive symptoms may be counterbalanced by the risk of cardiovascular events and incident dementia from extreme nocturnal dipping).

In addition to SBP and DBP targets, the change in systolic blood pressure relative to daytime systolic BP is an important measure derived from 24 hour-ambulatory blood pressure monitoring [44]. It is normal for SBP to drop by more than 10% to 19% during sleep (*i.e.* normal dipping). Additionally, the following abnormal patterns can be identified: non-dipper (> 0 to 10% drop), extreme dipper (20% or more drop), or reverse dipping (0% or less drop – *i.e.* a rise) in nocturnal systolic blood pressure [44]. Several observational studies have investigated the effects of abnormal nocturnal blood pressure dipping patterns on cardiovascular and cerebrovascular outcomes, including the incidence of dementia. There is evidence that SBP dipping could be a potential therapeutic target for older patients at risk of mobility or cognitive impairment in the future [45]. A recent study suggested a U-shaped relationship between nocturnal blood pressure dipping and adverse cardiovascular outcomes [44]. Compared to normal dippers, no association was found between extreme dipping and poor cardiovascular outcomes in individuals younger than 70 years [44]. In contrast, there was a significant increase in risk among extreme dippers and reverse dippers aged 70 years or older [44].

An analysis of cross-sectional data from the Shimanami Health Promoting Program (J-SHIP study) revealed a J-shaped relationship between nocturnal blood pressure profiles and mild cognitive impairment (MCI) in older adults [46]. The findings also suggested that an abnormal

nocturnal BP profile was a strong indicator of MCI in apparently healthy community-dwelling older adults [46]. In addition, reverse dipping was identified as a risk factor for intracranial haemorrhage in a sample of older Japanese patients followed for an average of 41 months [47]. In contrast, extreme dipping was associated with hypoperfusion and silently or clinically ischaemic strokes [47]. Patients with very mild frailty have an estimated life expectancy sufficient to benefit from preventive strategies, with the goal of therapy resembling that of the general non-frail older population. Some clinicians may reschedule the hypertensive dose in the daytime or at night to mitigate the daytime symptoms of hypotension and fall. This may result in extreme dipping in nocturnal blood pressure. Considering the available and limited evidence, similar practices may deprive mildly frail patients of the consequential benefits of normal BP dipping.

19. Abrupt discontinuation of beta blockers is potentially inappropriate (due to withdrawal symptoms such as anxiety, rebound hypertension, tachycardia, worsening of heart failure symptoms, or myocardial ischaemia). Gradually tapering off beta blockers, at a rate of 25% every month over 3-4 months, is appropriate.

Most antihypertensive medications can be abruptly discontinued in many instances [48]. However, abrupt discontinuation of clonidine and beta-blockers may result in rebound hypertension and withdrawal symptoms, such as anxiety, headache, tachycardia, myocardial ischemia, and worsening heart failure symptoms [16, 49, 50]. Clonidine should be tapered slowly (over 3 to 6 weeks) to avoid physiological withdrawal reactions and rebound hypertension [49]. Australian Primary Health Tasmania deprescribing guidelines recommend gradually tapering off most antihypertensive medications, particularly beta blockers, at a rate of approximately 25% every month over 3 to 4 months [16].

20. In frail patients (CFS ≥ 4) with non-valvular atrial fibrillation (NVAf), omitting anticoagulation therapy or discontinuing anticoagulants due to frailty *per se* is a potential prescribing omission.

21. In all frail patients (CFS ≥ 4) with NVAf, apixaban 2.5 mg twice daily is an inappropriately low dose in those who lack indication for dose reduction (*i.e.* at least two of the following: Age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L)) (an increased risk of stroke and systemic embolism).

The risk of ischemic stroke in patients with atrial fibrillation increases rapidly with age [51]. Consequently, most clinical guidelines recommend anticoagulants for older adults with AF based

on their CHA₂DS₂-VASc scores unless contraindicated [52]. Frailty, dementia, and cognitive impairment are among the factors that favour not initiating or continuing anticoagulant therapy in older adults. However, such practices, with firm indications for anticoagulation, may increase the risk of ischemic stroke and mortality in AF patients [52]. In an observational study of acutely hospitalised frail older patients, half of those who were not prescribed anticoagulants for AF lacked contraindications [53]. Those who did not receive anticoagulants had a significantly higher stroke and/or bleeding rate than those who did [53]. In another retrospective cohort study, stroke and mortality were significantly increased when warfarin was discontinued after a dementia diagnosis in older adults with nonvalvular atrial fibrillation aged 65 years or more [54]. ELDERCARE-AF is a Japanese randomised controlled trial that compared 15 mg once daily edoxaban to a placebo in older people with NVAf (80 years or older) who were not candidates for full-dose oral anticoagulants [55]. Compared to the placebo, the composite stroke and systemic embolism hazard ratios in the non-frail (robust or prefrail) and frail cohorts receiving edoxaban were significant. Edoxaban did not significantly increase major bleeding compared to the placebo in either group [55].

Owing to concerns about an increased risk of bleeding, anticoagulant therapy may be denied to older adults, particularly frail patients, or their medications are underdosed. In a sub-analysis of the ORBIT-AF II Registry, individuals who received off-label direct oral anticoagulants (DOACs) had higher bleeding scores and were older than those who received the recommended dosage [56]. Compared to those on recommended dosage, underdosing DOACs was associated with an increased risk of cardiovascular hospitalisation, whereas overdosing was associated with an increased risk of mortality [56]. Underdosing direct oral anticoagulants (DOACs) did not provide additional safety benefits (*e.g.* reduced bleeding risk) in a recent retrospective chart review [57]. Inappropriate underdosing of apixaban was also associated with increased all-cause mortality after stratification by DOAC type [57]. Similarly, in another retrospective study, underdosing of apixaban was associated with an increased risk of stroke and systemic embolism in patients without a renal indication for dose reduction [58]. In patients with a renal indication for dose reduction, DOAC overdosing was associated with an increased incidence of major bleeding [58]. Another recent observational study highlighted the increased incidence of stroke, systemic embolism (SE), and major bleeding events in frail patients receiving inappropriately lower doses of DOACs [59].

22. a) In all frail patients (CFS ≥ 4), use of dabigatran and rivaroxaban should be limited when possible (increased risk of extracranial bleeding compared to vitamin K antagonists (VKAs), *e.g.* warfarin and other DOACs).
- b) Apixaban (with the most favourable benefit/risk ratio) and edoxaban are preferable alternatives to dabigatran and rivaroxaban in frail older adults.

According to the most clinical guidelines, DOACs are preferred over vitamin K antagonists (VKAs) in patients with NVAf, particularly in older adults [60, 61]. In the four pivotal randomised controlled trials of DOACs for AF management, DOACs demonstrated more favourable risk-benefit profiles than VKAs [62-65]. In the RE-LY Trial, dabigatran 150 mg twice daily was associated with significantly lower stroke and systemic embolism rates and comparable rates of major haemorrhage compared with warfarin [62]. ROCKET AF investigators found that rivaroxaban was non-inferior to warfarin in preventing stroke or systemic embolism in patients with AF, with no significant difference in the risk of major bleeding [63]. In the ENGAGE AF-TIMI 48 trial, similar stroke and systemic embolism trends were observed in edoxaban-treated patients, with a significantly lower incidence of bleeding and cardiovascular death [64]. Among all DOACs, apixaban has demonstrated superiority over warfarin in both efficacy and safety endpoints. Using apixaban was associated with lower stroke rates, systemic embolism, bleeding, and mortality in the ARISTOTLE trial [65]. In patients ≥ 75 , ≥ 80 or ≥ 85 years of age with AF, all DOACs were associated lower risks of stroke, systemic embolism and mortality when compared to warfarin in the four landmark clinical trials. However, apixaban and edoxaban were the only DOACs significantly reducing the risk of major bleeding versus warfarin [62-65].

On the basis of these four major RCTs, Grymonprez and colleagues (2020) have systematically investigated the effects of dementia, frailty, and other surrogates for frailty (such as advanced age, falling risk, polypharmacy, and multimorbidity) on the safety and effectiveness of DOACs versus VKAs [66]. DOACs had superior efficacy (*e.g.* stroke/SE and mortality) and non-inferior safety (*e.g.* major, intracranial, and gastrointestinal bleedings) when compared to VKAs in the analysis of subgroups mentioned above, with apixaban ranking first and edoxaban ranking second [66]. In a subgroup analysis of the ARISTOPHANES retrospective observational study, the use of apixaban in frail older adults was associated with a lower risk of gastrointestinal (GI) bleeding (the most prevalent major bleeding type) compared with warfarin and other DOACs [67]. However, rivaroxaban was associated with the highest bleeding risk [67]. Kim and colleagues (2021) examined the efficacy and safety of DOACs in comparison to warfarin in older adults [68]. When stratified by frailty level, apixaban was associated with lower rates of

composite endpoints of death, ischaemic stroke, or major bleeding across all frailty levels (non-frail, pre-frail, or frail patients) [68]. In contrast, dabigatran and rivaroxaban were only associated with lower rates of events in non-frail older adults [68]. This is consistent with the AGS Beers criteria (2019), which labelled both dabigatran and rivaroxaban as drugs that should be used with caution for the treatment of venous thromboembolism (VTE) or atrial fibrillation in adults aged 75 or older [39].

23. In all frail patients (CFS ≥ 4) with AF, aspirin alone or in combination with clopidogrel for stroke prevention should be avoided (no benefit regardless of stroke risk, an increased risk of bleeding).
24. In all frail patients (CFS ≥ 4) without cardiovascular disease, the use of aspirin for primary cardiovascular prevention should be avoided (aspirin significantly increases the bleeding risk in frail patients).
25. In all frail patients (CFS ≥ 4) with diabetes, antiplatelet and oral anticoagulants medications prescribed for primary prevention should be discontinued unless they are indicated by concurrent conditions (*e.g.* oral anticoagulant agents for AF) (the net benefit is counterbalanced by the bleeding risk).

Antiplatelet agents such as aspirin have been indicated for decades to prevent stroke in AF patients with low thromboembolic risk or when oral anticoagulants are contraindicated. Guidelines no longer recommend aspirin alone or in combination, regardless of the risk of stroke, for older adults with AF [69-72]. Apart from stroke prevention in AF, aspirin is commonly used in older adults to primarily prevent cardiovascular events. Findings from the TILDA Wave 3 (2014–2015) dataset revealed that 77.6% of aspirin users had no previous cardiovascular diseases [73]. The Aspirin in Reducing Events in the Elderly (ASPREE) trial casts doubt on the efficacy and safety of aspirin in primary cardiovascular prevention (as distinct from secondary prevention) in older adults aged 65 years or older [74-76]. Older adults without cardiovascular disease, dementia, or disability were randomly assigned to receive 100 mg of aspirin or a placebo for a median follow-up period of 4.7 years [74-76]. The ASPREE trial revealed that aspirin use for primary prevention resulted in higher risks of bleeding and all-cause mortality [74], did not prolong disability-free survival [75], and did not lower the risk of cardiovascular diseases in older adults compared to placebo [76]. According to AGS Beers 2019, aspirin should be used cautiously for primary prevention in adults aged 70 years or older [39].

Cardiovascular events remain one of the main macrovascular complications and causes of mortality and morbidity in diabetes mellitus [77]. Therefore, the role of antithrombotic therapy in diabetic patients for primary cardiovascular disease prevention has been the subject of several clinical practice guidelines for many years. Notably, clinical guidelines have discussed the role of only antiplatelets in diabetic patients, implying that anticoagulants have no role in diabetic patients without additional indications. In a subgroup analysis of the ASPREE trial, the impact of aspirin on all-cause mortality, cardiovascular event risk, risk of bleeding, and disability-free survival appeared to be consistent in patients with or without diabetes, with no significant p-value for interaction [74-76]. According to the 2018 American Diabetes Association (ADA) guideline, aspirin may be considered in patients (aged ≥ 50 years) with diabetes plus one additional cardiovascular risk factor and no increased risk of bleeding [78]. This is consistent with the recent update of the 2019 European Society of Cardiology guideline in collaboration with the European Association for the Study of Diabetes (EASD), which suggests aspirin use in diabetic patients who have a high or very high risk of cardiovascular disease [79].

26. a) In all NVAf frail patients (CFS ≥ 4) on DOACs who develop acute coronary syndrome (ACS), the triple therapy (an OAC plus aspirin plus a P2Y₁₂ inhibitor) should be avoided post-ACS or PCI (an increased bleeding risk).
 b) Dual antithrombotic therapy (DAT) with a DOAC plus a single antiplatelet agent (preferably apixaban and clopidogrel) is reasonable and a safer alternative to triple therapy in frail patients with recent ACS or PCI.
27. a) In all frail patients (CFS ≥ 4) with stable coronary artery disease (CAD) who develop AF, caution should be exercised on the combination use of an anticoagulant plus an antiplatelet agent (the bleeding risk outweighs the benefit).
 b) Single antithrombotic therapy consisting of only oral anticoagulants (preferably DOACs) without additional antiplatelet agents may be considered as an alternative to the combination therapy.

Atrial fibrillation, coronary artery disease, and acute coronary syndrome are frequently coexisting conditions in older persons [80]. Patients with AF who develop ACS and AF arrhythmias following percutaneous coronary intervention (PCI) represent two clinically complex situations [81]. The evidence suggests that oral anticoagulants (OAC) are preferable over single or dual antiplatelet therapy (DAPT) for preventing stroke in AF patients. DAPT is also the most effective therapy for preventing further thrombosis in patients with ACS or after myocardial revascularization [82]. However, older adults, particularly frail adults with similar

clinical scenarios, are at a high risk of bleeding from frailty *per se* or triple therapy (*i.e.* OAC plus DAPT) [83]. This encouraged the research community to hypothesise that dual therapy may resolve the dilemma [80]. Out of five relevant clinical trials, only the RE-DUAL PCI and AUGUSTUS trials were adequately powered to investigate the efficacy outcomes of OAC and antiplatelet regimens in patients with AF and PCI [80, 84, 85].

In the RE-DUAL PCI trial, patients with AF who had undergone PCI were randomised to receive either triple antithrombotic therapy (warfarin plus a P2Y12 inhibitor agent such as clopidogrel or ticagrelor plus aspirin) or dual antithrombotic therapy (110 mg or 150 mg twice daily dabigatran plus a P2Y12 inhibitor agent without aspirin) [84]. Compared to triple therapy, dual therapy demonstrated a lower bleeding risk without an increase in thromboembolic events. However, the incidence of bleeding was lower in warfarin-based triple therapy in patients aged ≥ 80 years (or ≥ 70 years of age in Japan) [84]. In the AUGUSTUS trial, AF patients with ACS or PCI were initially randomised to VKA-plus- or apixaban-plus- P2Y12 inhibitor (such as clopidogrel, ticagrelor, or prasugrel), and then each group was assigned to receive aspirin or placebo [85]. Dual therapy regimens (*i.e.* apixaban plus a P2Y12 inhibitor or VKA plus a P2Y12 inhibitor) exhibited less major bleeding or clinically significant non-major bleeding than triple-based therapy (*i.e.* apixaban plus a P2Y12 inhibitor plus aspirin or VKA plus a P2Y12 inhibitor plus aspirin) [85]. Moreover, the apixaban-based dual or triple therapy was safer than VKA-based dual or triple therapy. Compared to other regimens, the apixaban-based dual therapy (*i.e.* without aspirin) resulted in a lower incidence of bleeding, a lower incidence of hospitalization, and a non-inferior incidence rate of thrombosis [85].

Stable coronary artery disease refers to patients with stable angina, asymptomatic ischemic heart disease diagnosed by imaging or stress tests, or 1-year post-ACS stabilised by medical or revascularization interventions [86]. There is insufficient evidence on the exact antithrombotic regimens for those with CAD (one-year post-stent implementation) who develop AF [87]. The OAC-ALONE Study is an open-label, randomised trial that compared oral anticoagulant therapy alone or combined with aspirin or clopidogrel in patients with atrial fibrillation and stable CAD (beyond one year after stenting) [87]. The study was inconclusive and underpowered to establish significant non-inferiority results regarding the composite primary end point of all-cause mortality, myocardial infarction, stroke, and systemic embolism [87, 88]. The Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial is a recent study that evaluated the use of antithrombotic therapy in patients with atrial fibrillation and stable coronary artery disease [88]. It enrolled AF patients

who had undergone PCI or coronary-artery bypass grafting (CABG) more than a year prior and those with confirmed CAD who did not need revascularization [88]. Patients were randomly assigned to receive rivaroxaban monotherapy or combination therapy (rivaroxaban plus an antiplatelet) [88]. Compared to combination therapy, monotherapy established significant non-inferiority for the primary efficacy endpoints and superiority for the primary safety endpoints [88]. However, results should be carefully interpreted due to concerns regarding the open-label design, uncertainty about the choice of antiplatelet agent (aspirin versus a P2Y12 inhibitor), and low doses of rivaroxaban [89].

28. In the following patients with severe frailty level or higher (CFS 7-9) and NVAf, discontinuation of anticoagulants should be considered:

- a) Limited life expectancy of < 6 months,
- b) Evidence of noncompliance in patients with advanced dementia who get no/inadequate supervision and monitoring of medications administration from a caregiver,
- c) High bleeding risk and the inability to regularly monitoring of the patient (every 1-3 months), or
- d) Thromboembolic risk of CHA₂DS₂-VASc Score ≤ 2 (without previous stroke) and recurrent falls (despite appropriate fall preventive measures).

When deciding whether or not to deprescribe chronic medications, time to benefit is one of the most important factors to consider. It has been shown that anticoagulant therapy for atrial fibrillation has a short time to benefit [90]. An estimated life expectancy of greater than six months justifies the appropriateness of the use of anticoagulants in frail patients with AF [90]. Therefore, anticoagulation may have limited benefits in patients with severe frailty or higher with an estimated limited life expectancy of less than six months [91]. However, anticoagulants are commonly continued until shortly before death [92]. Therefore, therapeutic decisions should concentrate on how to improve the quality of life in patients with a limited life expectancy, particularly at the end of life [92].

The lack of support from caregivers significantly contributes to poor adherence in older adults. Moreover, additional age-related factors, particularly cognitive and physical function decline, may have a negative impact on adherence [93]. Compared to VKAs, DOACs have shorter half-lives, and are hardly therapeutically monitored [84]. Therefore, initiating oral anticoagulants, particularly DOACs, may require prior adherence and cognitive function assessments. There is a

potential for overmedication or suboptimal dosing of oral anticoagulants in the context of poor adherence [93]. According to a practical algorithm by Granziera *et al.* (2015), oral anticoagulant therapy may not be recommended in patients with poor adherence due to safety concerns [93]. In patients with patchy or suboptimal adherence, the algorithm advised using VKAs in preference to DOACs [93]. This is because of the availability of systematic laboratory monitoring of VKAs (*e.g.* via INR) and their long half-lives [93].

Hospitalised frail patients are at a greater risk of bleeding, and thus they are commonly denied oral anticoagulants for AF based on their high bleeding risks [94]. The HAS-BLED score is frequently used to assess potential bleeding risk from anticoagulation therapy in AF patients, with a score of ≥ 3 indicating a high bleeding risk [95]. However, older frail patients may have risk factors for bleeding that are not covered by the HAS-BLED measures [95]. Dementia, anaemia, depression, and medication use (such as anticonvulsants and antihypertensives) were significant predictors of traumatic intracranial bleeding from warfarin among older patients with AF in a retrospective cohort study [96]. In addition to bleeding assessment scores, conditions predisposing frail patients to a high bleeding risk should be considered [95]. Moreover, clinicians should be aware of modifiable risk factors (*e.g.* labile INR, medication use, hypertension), which should be identified and addressed before discontinuing anticoagulants [91, 95]. However, it may be reasonable to withhold anticoagulation therapy when frail patients continue to have a high risk of bleeding despite adequate measures [95]. Frail patients with an increased risk of bleeding may be discharged to their homes or less-staffed long-term care facilities, where they cannot receive regular monitoring services. From a safety perspective, it may be appropriate to refrain from prescribing anticoagulant therapy in these instances.

Similarly, an increased risk of falling *per se* should not be a contraindication to anticoagulant therapy in patients with atrial fibrillation [91]. However, physicians may be reluctant to prescribe anticoagulants to frail patients with a history of falls or at a high risk of falling due to fall-associated traumatic complications. In subgroup analyses of the ENGAGE AF-TIMI 48 and the ARISTOTLE trials, patients with an increased risk of falls and those with a history of falls had an increased rate of intracranial bleeding, major bleeding, and high mortality risk [97, 98]. Moreover, apixaban and edoxaban had significantly lower bleeding rates than warfarin, regardless of falling risk or history [97, 98]. According to an intriguing Markov decision model analysis, the patient's propensity to fall should not influence the decision to administer anticoagulants in older adults with AF [99]. In summary, a patient had to fall 295 times for the risk of VKAs-induced subdural hematoma to outweigh the benefits [99]. Given the greater

absolute reduction in the bleeding risk observed in the ENGAGE AF-TIMI 48 and the ARISTOTLE trials, it is anticipated that DOAC users, particularly those taking apixaban or edoxaban, need to experience more falls for the risks to outweigh the benefits [60].

When anticoagulants are initiated in older adults and frail cohorts, assessment and management of falls are of practical significance. Preventive measures may include vision assessment and correction, osteoporosis management, and cognitive function evaluation [95]. Despite preventive measures, it is reasonable to withhold anticoagulants in older adults with haemorrhagic complications from falls [95]. This may also be appropriate for patients with low CHADs/CHA₂DS₂-VASc scores and a high fall risk [100]. In a retrospective analysis, older adults with AF or atrial flutter who experienced falls in the intervention group (with anticoagulants) were compared to the control group (without anticoagulants) based on their CHA₂DS₂-VASc scores [100]. The findings suggested that anticoagulant use in patients at high risk for falls was associated with an increased mortality risk [100]. Interestingly, in patients with CHA₂DS₂-VASc scores ranging from 0 to 2, the calculated annual risk of death from a head injury caused by anticoagulation exceeded the literature-based annualised stroke risk [100]. This may imply that using anticoagulants in patients at low risk of thromboembolism and a high risk of falls may be considered inappropriate for severely frail patients.

29. a) Loop diuretics use for calcium channel blocker (CCB)-induced lower extremity oedema (after ruling out cardiogenic aetiology) is a potentially inappropriate prescribing cascade.

b) Nonpharmacological intervention (*e.g.* leg elevation, TED stockings) or switching CCB to alternative therapy (*e.g.* ACEI) may be alternatively considered.

Calcium channel blockers are widely used first-line medications for hypertension [101]. CCBs may preferably be used in older adults due to their favourable adverse event profile and the limited need for routine laboratory monitoring [101]. However, CCBs are commonly associated with peripheral oedema, particularly ankle oedema [101]. A cascade of inappropriate prescribing occurs when oedema caused by CCBs is misinterpreted as a new medical disease, and a diuretic is prescribed to relieve oedema [101]. Similar prescribing cascades are possible in older persons due to the high prevalence of hypertension and frequent prescription of CCBs. In a recent population-based cohort study, the incidence rate of this prescribing cascade in older adults with hypertension was investigated among CCBs new users versus users of other antihypertensives such as angiotensin-converting enzyme inhibitors or angiotensin II receptor

blockers [101]. The findings revealed that older adults who newly received a CCB were considerably more likely to receive a loop diuretic within 90 days than those who received other antihypertensives [101].

It is noteworthy that this prescribing cascade is not only unnecessary, but it may cause further negative downstream consequences [102]. Oedema caused by calcium channel blockers results from fluid redistribution rather than fluid overload [102]. Consequently, prescribing loop diuretics may lead to over-diuresis and hypovolemia in euvolemic patients [102]. As a result, over-diuresis and hypovolemia may place older adults at high risk for emergency department visits or hospitalisation [102]. If this prescribing cascade goes underreported or undiagnosed, a diuretic agent may be administered to offset the increased urinary frequency [102]. Moreover, additional tests, such as echocardiography, may be ordered to determine if heart failure is the primary underlying cause, raising the cost of care [102].

There are several strategies to prevent or treat CCB-related oedema [103]. In 2003, UK Medicines Information (UKMI) pharmacists for NHS healthcare professionals provided a list of alternative options and evidence summaries [103]. These options include non-pharmacological interventions, dosage adjustments, switching to a non-dihydropyridine CCB, the addition of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers, the addition of nitrate, or discontinuation of CCB [103]. They suggested that elevation of legs or graduated compression stockings may be an option in some patients with mild oedema, with the addition of an ACEI having the strongest evidence [103]. A 2017 practical approach also advised switching CCBs to ACEIs in older adults with hypertension [104]. This was justified by the additional benefits of ACEIs in preventing heart failure and avoiding the frequent side effects of CCBs, including ankle oedema [104].

30. In all frail patients (CFS ≥ 4) with heart failure with reduced ejection fraction (HFrEF), the following medications and medication classes should be avoided or discontinued (exacerbate HFrEF symptoms):

- a) NSAIDs (COX-2 Selective and non-selective inhibitors).
- b) Non-dihydropyridine calcium-channel blockers (*e.g.* verapamil or diltiazem).
- c) Inhaled anaesthesia medications (*e.g.* enflurane, desflurane, isoflurane, sevoflurane) and ketamine.
- d) Some antidiabetic medicines, specifically thiazolidinediones, saxagliptin, sitagliptin, and alogliptin.

- e) Anti-fungal medications (*e.g.* itraconazole, amphotericin B).
- f) High sodium-containing formulations of effervescent and dispersible medications (*e.g.* paracetamol effervescent tablets).

Several medications are known to exacerbate the symptoms of heart failure with a reduced ejection fraction [105]. These drugs may cause sodium and water retention or act directly on the myocardial muscles [105]. These adverse effects may be misinterpreted as signs of a new onset of congestive heart failure or worsening current heart failure, and this could result in inappropriate prescribing or intensification of heart failure therapy. The American Heart Association has released a clinically relevant list of prescription medications that may precipitate or aggravate HF [105]. The magnitude and onset of HF induction or precipitation were provided for each medication. The magnitude of the effect ranges from major effects that represent life-threatening or hospitalization-causing symptoms to minor effects that may warrant transient medication change [105]. The onset of effect was categorized into immediate, intermediate, and delayed to represent effects that manifest within one week, weeks to months, and more than a year, respectively [105].

Medications with a major magnitude and immediate onset of effects include NSAIDs, inhaled anaesthesia medications (*e.g.* enflurane, desflurane, isoflurane, sevoflurane), ketamine, thiazolidinediones and itraconazole [105]. Non-dihydropyridine calcium-channel blockers (*e.g.* verapamil or diltiazem) and dipeptidyl peptidase-4 inhibitors (*e.g.* saxagliptin or sitagliptin) were classified as medications with major effects and immediate to intermediate onsets [105]. It was emphasised, however, that this may be a class effect for all dipeptidyl peptidase-4 inhibitors [105]. In the EXAMINE study, alogliptin was associated with a nonsignificant trend toward an increased risk of hospitalisation for heart failure [106]. The American statement categorized amphotericin B as a medication with major and moderate direct myocardial toxicity effects with an immediate onset [105].

This is consistent with recommendations of the recent European Society of Cardiology position statement on inappropriate prescribing for heart failure with reduced ejection fraction [107]. However, the European statement did not establish a classification based on the onset of adverse effects. In addition, there is a slight difference in the classification of the effect magnitude between the European and American statements [107]. Moreover, the European statement considered medicinal formations of high sodium content as medications with moderate adverse effects on the exacerbation of heart failure symptoms [107]. A nested case-

control study revealed that sodium-containing effervescent, dispersible, and soluble formulations were significantly associated with an increased risk of adverse cardiovascular events compared to standard formulations of the same medication [108]. A longitudinal cross-sectional study highlighted the decreasing trend of prescribing sodium-containing medication in the UK from 2009 to 2018 [109]. However, when results were stratified by age, this change in the prescription trend was lower in patients aged 75–84 years and over 85 years compared to those aged 65–74 years [109]. According to the authors, patients with advanced age were more likely to have dysphagia, and as a result, they were more likely to be prescribed effervescent or dispersible formulations than non-sodium standard formulations [109]. Moreover, they emphasised that similar practices were less appropriate due to increased cardiovascular risks [109].

2. Central nervous system

31. In all frail patients (CFS $\geq$ 4) with dementia, cognitive impairment, or delirium, the following medications and medication classes should be avoided or discontinued (worsen cognitive functions):

- a) Benzodiazepines and non-benzodiazepine hypnotics,
- b) Tricyclic antidepressants and paroxetine,
- c) Gastrointestinal antispasmodics with anticholinergic properties (*e.g.* atropine derivatives, dicycloverine hydrochloride, propantheline bromide and hyoscine butylbromide),
- d) Anticholinergic antihistamines,
- e) Antiemetics, cough suppressants, or nasal decongestants drugs with anticholinergic properties, or
- f) Chronic opioids use.

32. In all frail patients (CFS $\geq$ 4), anticholinergic medications (*e.g.* biperiden, trihexyphenidyl, benztropine) should be avoided in the treatment of neuroleptic-associated extrapyramidal effects.

Medications with anticholinergic properties (antimuscarinic agents) are routinely prescribed for various clinical indications [110]. However, they have been deemed potentially inappropriate medications for older adults [39]. Frail patients have a compromised ability to cope with stressors like anticholinergics, rendering them more vulnerable to specific adverse effects such as falls, sedation, constipation, and blurred vision. There is also a growing concern over long-

term effects such as physical and cognitive function decline, hospitalisation, and mortality [110]. Anticholinergic medications may worsen cognitive functions in patients diagnosed with dementia, cognitive impairment, or delirium [39].

The AC-FRAIL instrument is an adapted anticholinergic burden scale (ACB) that identifies anticholinergic burden in frail older patients within the practice setting [110]. At a score of 3 or higher, ACB scores are considered clinically significant in terms of adverse outcomes [110]. This conforms to the AGS Beers criteria list of drugs with strong anticholinergic properties. These include tricyclic antidepressants (TCAs), first-generation antihistamines, gastrointestinal antispasmodic medications, urinary antimuscarinic agents, certain antiemetics (*e.g.* prochlorperazine, promethazine) and some antiparkinsonian drugs (*e.g.* biperiden, trihexyphenidyl, benztropine) [39]. AGS Beers consensus criteria (2019), based on evidence of moderate quality, strongly recommended avoiding all these potentially inappropriate medications in patients with or at high risk of delirium and patients with dementia or cognitive impairment [39].

Benzodiazepines and opioids have lower anticholinergic properties compared to the medications mentioned above [111]. Nevertheless, the depressant effects of benzodiazepines on the central nervous system predispose older patients to dizziness, falls, fractures, confusion, and cognitive impairment [39]. Due to the potential for inducing or exacerbating delirium and cognitive decline, it is prudent to avoid benzodiazepines in older adults with delirium or dementia and in patients at high risk for delirium (AGS Beers criteria 2019: strong recommendation, moderate-quality evidence) [39]. Opioids increase the risk of falls and fractures in older adults. The AGS Beers criteria strongly recommend avoiding opioids in patients with a history of falls or fractures unless patients present with acute severe pain (*e.g.* recent fractures or joint replacement) [39]. Compared to other opioids, pethidine (meperidine) poses a greater risk of neurotoxicity, including delirium [112]. Older patients may also be more susceptible to tramadol-mediated CNS adverse effects such as confusion, vertigo, and nausea [112].

33. a) In all frail patients (CFS $\geq$ 4) with impaired cognitive function or delirium, histamine H₂ antagonists (*e.g.* famotidine, cimetidine, nizatidine or ranitidine) should be avoided or discontinued (risk of confusion and delirium).
- b) When indicated, proton pump inhibitors (PPIs) may be alternatively considered at low doses for a maximum duration of 8 weeks.

An interesting modification to the recent AGS Beers criteria is the removal of H2-receptor antagonists from the “avoid” list for dementia or cognitive impairment patients [39]. However, H2-receptor antagonists remain on the "avoid" list for delirium patients (strong recommendation, low-quality evidence). The developers suggested that the adverse effects of H2-receptor antagonists on cognitive decline are supported by weak evidence [39]. In addition, according to experts, the growing concerns against the use of proton-pump inhibitors could leave dementia patients with no therapeutic options when gastric acid suppression therapy is indicated [39]. Of note, the AGS Beers criteria apply to a wide range of older populations aged 65 years or older, excluding hospice and palliative care settings [39]. However, dementia and cognitive impairment are obvious predisposing factors for delirium [113]. In real practice, dementia is typically diagnosed after delirium has been ruled out. In addition, there also exists a bidirectional association between dementia and delirium [113]. These all combined might justify the inappropriateness of using H2-receptor antagonists in older adults, particularly in frail adults and the perioperative setting.

34. Acetylcholinesterase (AChE) inhibitors prescribed for dementia should only be discontinued in patients with syncope, likely from bradycardia (otherwise, discontinuation worsens cognitive and neuropsychiatric symptoms and increases the likelihood of prescribing potentially inappropriate psychotropic medications).

Antidementia medications such as acetylcholinesterase inhibitors and the N-methyl-d-aspartate receptor antagonist (memantine) are the mainstay of treatment for dementia patients. AChE inhibitors have demonstrated positive effects in patients with Alzheimer's disease (AD) and dementia, including cognitive and functional benefits, neuropsychiatric symptoms reduction, and all-cause mortality [114-116]. However, these medications are also associated with gastrointestinal side effects and an increased risk of syncope in older adults [117]. Therefore, the AGS Beers criteria suggested avoiding AChE inhibitors in older adults with syncope caused primarily by bradycardia [39].

There is rapidly growing recognition for considering deprescribing inappropriate medications in dementia patients. There is also uncertainty surrounding the benefits of AChEIs in patients with severe dementia. However, the NICE Committee has not recommended stopping AChE inhibitor therapy based solely on disease severity [118]. According to a meta-analysis of randomised controlled trials, discontinuing AChE inhibitors significantly worsened cognitive and neuropsychiatric symptoms [119]. Moreover, a large retrospective study suggested that

antidementia medications were associated with decreased mortality in community-dwelling frail older people with dementia with no high mortality risk [120]. An analysis of a Japanese nationwide survey also revealed that antidementia medications were associated with a reduced risk of prescribing potentially inappropriate psychotropic medications [121]. Following a non-systematic search of key databases, a narrative review found limited direct evidence to inform the deprescribing of AChE inhibitors in older adults with dementia [122]. There was also a paucity of robust evidence of the impact of deprescribing AChE inhibitors on the patient-clinical centred (*e.g.* frailty and cognitive functions) and long-term outcomes in older adults with dementia [122].

35. When indicated, switch to an AChE inhibitor with a once-daily regimen (*e.g.* donepezil) (reduce pill burden with fewer symptoms of sleep disturbances).
36. When indicated, switch to an AChE inhibitor with transdermal patches forms (*e.g.* rivastigmine) (reduce pill burden with fewer adverse effects).
37. When indicated, switch to an AChE inhibitor with extended-release forms (*e.g.* galantamine) (reduce pill burden with fewer adverse effects).

AChE inhibitors are available in various dosage forms and formulations, which may result in fewer pills or side effects. There are once-daily pills for donepezil, capsules and transdermal patches for rivastigmine, and extended-release forms of galantamine. In a Cochrane review, rivastigmine transdermal patches (9.5 mg daily) were found to have fewer side effects than capsules (6 to 12 mg daily) in patients with mild to moderate Alzheimer's disease (AD) [123]. Additionally, the patches demonstrated comparable clinical efficacy [123]. In phase III, a randomised trial of mild to moderate AD patients (90% aged 65 years or older), galantamine extended-release formulations and a flexible once-daily regimen demonstrated similar clinical efficacy and safety as twice-daily galantamine [124]. In addition, a once-daily dose of donepezil may be administered in the morning as opposed to the evening to reduce sleep disturbances in certain patients [125].

38. The following medications/ medication classes should be avoided or discontinued for the treatment or prevention of dementia (inconclusive/insufficient evidence):
 - a) Antidiabetic agents, statins, and antihypertensive medications, unless indicated by concurrent conditions,
 - b) Multivitamins, vitamin B or antioxidants (*e.g.* vitamin E, selenium, vitamin C) supplements; unless indicated by deficiency,

- c) Herbal products and supplements (*e.g.* Ginkgo biloba, ginseng, omega-3 fatty acids),
- d) Piracetam,
- e) Nimodipine (except in vascular cognitive impairment),
- f) Pentoxifylline,
- g) Anti-inflammatory drugs or aspirin, or
- h) Ergot derivatives such as dihydroergocristine, and nicergoline.

Numerous additional medications may benefit patients with dementia. However, insufficient and inconclusive evidence exists for prescribing or continuing to use these medications in patients with dementia. The National Institute for Health and Care Excellence advised against prescribing antihypertensives, antidiabetics, statins, NSAIDs, or aspirin to slow the progression of dementia unless this is part of evidence synthesis as in randomised controlled trials [118]. Furthermore, the European Federation of Neurological Societies has provided a list of medications that are not recommended for treating or preventing Alzheimer's disease-related dementia. These include nootropics (such as piracetam and nicergoline), pentoxifylline and vitamin E due to a lack of evidence, and piracetam due to inconsistent evidence [126].

Herbal supplements (like Ginkgo biloba) and some ergot derivatives (like dihydroergocristine) have shown some efficacy [125]. However, their adverse effects on older adults and frail patients may limit any potential benefit. Both medications increase the risk of orthostatic hypotension and falling [112]. Moreover, herbal products are frequently involved in multiple drug-drug interactions. Other herbal supplements (*e.g.* omega-3 fatty acids) and vitamin products (such as multivitamins, vitamins B, and selenium) were not associated with improvements in cognitive functions or activities of daily living [127]. Nimodipine has also demonstrated some benefits in treating patients with vascular, mixed, or unclassified dementia [128]. When rivastigmine was investigated in patients with vascular dementia (VaD), it significantly improved most behavioural symptoms compared to nimodipine as the active control [129]. It also decreased the frequency of prescribing inappropriate medications (such as neuroleptics and benzodiazepines), but without differences in cognitive symptoms or general status [129].

39. In all frail patients (CFS ≥ 4), antipsychotic medications should be avoided for the prevention of delirium or dementia-associated behavioural and psychiatric symptoms (BPSD) (risk of cerebrovascular events, cognitive decline, and mortality).

40. a) In all frail patients (CFS ≥ 4) undergoing surgery, prophylactic use of antipsychotics for the prevention of delirium should be avoided (inconclusive evidence, deleterious adverse effects).
- b) Alternatively, perioperative administration of low-dose dexmedetomidine may reduce postoperative delirium.
41. In all frail patients (CFS ≥ 4), antipsychotic medications should only be tried for the management of BPSD or delirium after a failure of nonpharmacological therapy in patients:
- a) showing severe symptoms that are harmful to self/ others, or
- b) whose symptoms interfere with essential therapies (*e.g.* ventilation, dialysis)
42. If antipsychotics are prescribed for dementia, the following antipsychotics are potentially inappropriate:
- a) first-generation antipsychotic (except haloperidol in delirium),
- b) injectable long-acting formulations,
- c) clozapine and olanzapine in patients with syncope or at high risk (*e.g.* orthostatic hypotension, bradycardia),
- d) antipsychotics in Parkinson's disease, except for quetiapine and pimavanserin, and
- e) all use of antipsychotic medications is inappropriate in dementia with Lewy bodies due to the increased risk of specific serious sensitivity reactions
43. If antipsychotics are clinically warranted for delirium, haloperidol should not be used in patients with Parkinson's disease or Lewy-bodies dementia. Low-dose quetiapine may be considered as an alternative in Parkinson's disease.

The use of antipsychotics is strongly associated with increased risk of stroke, cognitive decline, and mortality in older patients with dementia [39]. Thus, many clinical associations do not routinely advocate for or against the use of antipsychotics in the treatment of behavioural and psychological symptoms of dementia. The AGS Beers criteria recommend avoiding the use of both first- and second-generation antipsychotics in older adults aged 65 years or more, except for patients with schizophrenia, bipolar disorder, or chemotherapy-induced vomiting and nausea [39]. The AGS Beers criteria strongly recommend (moderate quality evidence) avoiding both first- and second-generation antipsychotics for behavioural problems of dementia or delirium unless other nonpharmacological options are unavailable or ineffective and the older adult poses a substantial risk to self or others [39]. Similarly, the European Academy of Neurology (EAN) has recommended atypical antipsychotics only when all other pharmacological

options for BPSD have failed or when patients pose a significant threat to themselves or others (weak recommendation) [130].

In patients with dementia, agitation, and/or aggression, the EAN recommends risperidone or other atypical antipsychotics over haloperidol [130]. In addition, the American Psychiatric Association (APA) discourages using haloperidol as a first-line agent in dementia patients with agitation or psychosis in the absence of delirium [131]. The APA also discourages using long-acting injectable antipsychotic medications in dementia patients with agitation or psychosis unless otherwise indicated by other coexisting psychotic disorders [131]. The AGS Beers criteria have also recommended avoiding chlorpromazine, thioridazine, and olanzapine in syncope patients due to increased orthostatic hypotension risks. In addition, clozapine has been reported to have a potent anticholinergic effect, which may restrict its use in syncope patients [39]. In a systematic review of controlled trials, the authors could not make specific therapeutic recommendations for Alzheimer's disease and BPSD in frail older patients or older adults with moderate and severe functional impairments due to insufficient evidence [132].

Pharmacological options for patients with delirium include haloperidol and certain atypical antipsychotics [133]. Commonly, a low dose of haloperidol is administered initially and then titrated as needed for clinical benefit. Compared to haloperidol, atypical antipsychotics like quetiapine, olanzapine, and risperidone have demonstrated some efficacy [133]. The National Institute for Health and Care Excellence has considered short-term treatment (≤ 1 week) with haloperidol or olanzapine for the treatment of delirium in hospital or long-term care settings [134]. NICE also suggested beginning with the lowest clinical dose and titrating cautiously based on the symptoms of distressed patients [134]. In addition, using antipsychotics was discouraged in patients with Parkinson's disease or dementia with Lewy bodies [134]. On the other hand, the AGS Beers criteria recommended avoiding all antipsychotics (except for quetiapine, clozapine, and pimavanserin) in older adults with Parkinson's disease [39, 135]. Moreover, professional associations specialising in geriatric medicines have advised against using benzodiazepines or other sedative-hypnotics as the first-choice treatment for delirium in older adults [113].

As opposed to the incidence of delirium, researchers found that studies rarely report on other relevant outcomes, such as the duration of delirium, length of hospital stay, and quality of life [136]. Based on the limited evidence, a Cochrane review concluded that the use of antipsychotics failed to alleviate symptoms, lessen the severity of delirium, or reduce mortality in hospitalised non-intensive care unit (ICU) patients [136]. There was limited evidence

regarding the efficacy of pharmacological therapy in preventing delirium incidence, and it might not be associated with significant reductions in mortality rate and length of hospital stay [136]. Another Cochrane review found no difference between haloperidol and placebo for preventing delirium in adults in intensive care unit [137]. Other preventive options (such as other pharmacological, nursing, sedation, and environmental interventions) had unclear effects [137]. A third Cochrane review concluded that the current evidence does not support the use of acetylcholinesterase inhibitors, antipsychotics, or melatonin to reduce the incidence of delirium in hospitalised non-ICU patients [138]. However, strong evidence supports the role of multi-component interventions in preventing delirium [138].

Post-operative delirium (POD) is a common serious complication in older adults undergoing surgery, affecting 80% of older surgical patients [139]. POD is associated with negative short- and long-term outcomes, such as severe functional decline, institutionalisation to a higher level of care, and mortality [139]. There is insufficient evidence to argue for or against the use of antipsychotic medications to prevent POD in older surgical adults [140]. The associated adverse effects and the increased mortality risk should be carefully considered when antipsychotics are prescribed in the perioperative setting, particularly in those with pre-existing cognitive function impairment [139]. Therefore, non-pharmacological options should be considered as the mainstay of POD prevention in older adults in the perioperative setting [139, 141]. Multiple randomised clinical trials and meta-analyses have provided conclusive evidence that dexmedetomidine may reduce the incidence of POD in older adults [141-146]. However, evidence is still limited regarding the impact of dexmedetomidine on long-term outcomes [141]. Research has shown that dexmedetomidine may improve long-term outcomes and decrease POD [141-147]. These findings support the recommendations from the Chinese expert consensus on perioperative brain health in older adults, which suggests the administration of dexmedetomidine to reduce postoperative delirium [141].

44. Antipsychotic agents prescribed for behavioural and psychiatric symptoms of dementia (BPSD) should be discontinued if; a) the patient is stabilized, b) not stabilized after 3 months trial or c) when no clinically important response occurs within 4 weeks of treatment.

A Canadian clinical practice guideline recommended deprescribing antipsychotics for adults with behavioural and psychological symptoms of dementia treated for at least three months, regardless of whether symptoms were stabilised or there was no response to an adequate trial

[148]. According to the American Psychiatric Association, antipsychotic medications should be tapered and discontinued if no clinically significant response is observed after a four-week trial of an adequate dose [131]. In randomised trials, withdrawal protocols ranged from abrupt cessation to slower tapering over weeks. However, abrupt cessation of antipsychotics may result in a recurrence of behavioural symptoms or physiological withdrawal symptoms (such as nausea, vomiting, headache, anxiety, dyskinesia, insomnia, and restlessness) comparable to the conditions they were initially prescribed for [50, 149].

45. Abrupt discontinuation of atypical antipsychotic agents, used for BPSD, is potentially inappropriate due to withdrawal symptoms. Alternatively, a 25%–50% daily dose reduction every 2 weeks (or every 2 months for aripiprazole) is appropriate.

Tjia and colleagues (2015) suggested a strategy for the gradual dose reduction of chronic off-label antipsychotics used to treat behavioural and psychological symptoms of dementia [149]. These pharmacokinetic-based gradual dose reduction protocols are based on the half-lives of individual antipsychotic medications, with two stages of dosage reduction of 50% [149]. Two to four weeks were suggested as the clinically recommended time between gradual dose reductions for most antipsychotics and two months for aripiprazole [149]. Accordingly, the estimated time to complete discontinuation is 4 to 8 weeks for most antipsychotics and four months for aripiprazole [149]. On the other hand, the Canadian deprescribing guideline recommended a faster tapering approach, with a 25%–50% dose reduction every 1–2 weeks (strong recommendation, moderate quality evidence) [148]. To prevent withdrawal symptoms after discontinuing medication of the STOPPFrail list, Hanlon and colleagues (2021) suggested a 25%–50% daily dose reduction every 1-2 days (for first-generation antipsychotics), every two weeks (for second-generation antipsychotics) and every two months (for aripiprazole) [49].

46. Abrupt discontinuation of benzodiazepines and Z- hypnotic medications is potentially inappropriate due to physiological withdrawal reactions. Consider the following schedules:

Table 1: Recommended tapering regimens for benzodiazepines and Z- hypnotic medications.

Tapering schedule	Monitoring
a) 25% dose reduction every 2 weeks, with 12.5% dose reduction during the final step of tapering and/ or medication-free days.	Monitor the withdrawal symptoms closely if:

b) If available dosage forms do not permit (1) an initial 50% dose reduction with medication-free days during the end of tapering c) EMPOWER and D-PRESCRIBE trials: alternate days dosing of full pill and half pill consumption during the first part of tapering, half and quarter of dose consumption during the middle steps, and finally quarter dose consumption and medication-free days (2-week steps over 18 -22 weeks)	a) Relapsing symptoms: continue on the current dose for two weeks and resume tapering slowly b) If severe symptoms (e.g. convulsion, psychosis, high blood pressure): return to the original regimen or switch to diazepam with extremely cautious supervision.
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Withdrawal symptoms or disease recurrence are common following the cessation of benzodiazepine and z-hypnotic medications in older adults [50]. Withdrawal symptoms may include insomnia, tremors, anxiety, convulsions, psychotic reactions, irritability, tachycardia, and a rise in blood pressure [50]. Therefore, slower tapering of the daily dose is preferable to abrupt discontinuation. Several useful tapering schedules exist to guide clinicians on when and how to safely discontinue benzodiazepines in patients aged 65 years or older. The Canadian deprescribing guideline suggested a 25% reduction in dosage every two weeks [150]. If possible, a 12.5% dose reduction was suggested during the final steps of tapering with or without medication-free days [150]. If available dosage forms do not permit a 25% dose reduction, an initial 50% dose reduction was alternatively suggested, followed by medication-free days or a switch to lorazepam or diazepam in the final stages of the regimen [150]. In addition, the importance of close monitoring of withdrawal symptoms and additional nontherapeutic and behavioural interventions was emphasised. The guide recommended continuing the current dose for two weeks and then resuming the slow tapering if symptoms relapsed [150]. On the other hand, Poudel *et al.* suggested switching to long-acting benzodiazepines (e.g. diazepam) in cases of severe withdrawal symptoms and in frail patients who required supervision for adverse effects such as cognitive impairment, delirium, or falls [50].

Notably, the Canadian recommendations apply to benzodiazepines used to treat primary or secondary insomnia when potential underlying conditions are effectively controlled [150]. They also recommended continuing these medications in patients with restless leg syndrome, alcohol withdrawal, untreated anxiety, depression, or other health conditions that could be causing or aggravating insomnia [150]. These recommendations for continuation of use are consistent with the New South Wales Therapeutic Advisory Group's deprescribing guide [151]. Moreover, the

Australian guide considered BPSD as an inappropriate indication for benzodiazepines [151]. Their uses were also discouraged for insomnia for greater than two weeks. It suggested a 25%-50% daily dose reduction every 1 to 4 weeks, a slower tapering rate (12.5% dose reduction) at the end of tapering, and a faster weaning rate if adverse effects were the reason for deprescribing [151]. Alternate day dosing was also suggested if dosage forms did not permit the recommended weaning regimen [151]. In contrast to the Canadian recommendations, the Australian guideline did not recommend switching to long-acting benzodiazepines in older adults [151].

Randomised controlled trials have demonstrated the efficacy of several useful regimens for weaning older adults off benzodiazepines [152, 153]. In the EMPOWER and D-PRESCRIBE studies, a diminishing schedule of full-pill dosing, half-pill dosing, quarter-pill dosing, and no-pill consumption were followed for 21 and 18 weeks, respectively [152, 153]. During the initial tapering phase alternating days of half-pill and full-pill consumption were followed. Then, a quarter of the dose was consumed during the middle steps. Finally, a regimen of a quarter of the dose and medication-free days was implemented [152, 153].

47. Patients may experience withdrawal symptoms after abrupt discontinuation of chronic opioid use. a) Slow dose reduction (10 % -25% of the dose every week) or b) a more rapid approach (25% dose reduction every few days) may be alternatively considered.

Older adults may experience withdrawal symptoms after the abrupt discontinuation of chronic opioid use [50]. These include gastrointestinal symptoms (such as nausea, vomiting, and diarrhoea), musculoskeletal symptoms (such as myalgias, muscle aches, and cramps), insomnia, anxiety, restlessness, dysphoria, tremors, and an elevation in blood pressure [50]. According to an Australian deprescribing guide, opioid deprescribing may be considered when mental health conditions or drug-drug interactions increase the risk of opioid overdosing [151]. Slow dose reduction (by 10% to 25% of the dose each week) or a reduction schedule of 5% to 25% per month was recommended for safe weaning [151]. Alternatively, if dosage forms do not permit, it suggested an alternate-day dosing approach [151]. Poudel *et al.* suggested a more repaid tapering approach (25% dose reduction every few days) when the reasons for deprescribing include significant adverse effects or medication misuse or when frail older adults have psychiatric comorbidities [50].

3. Endocrine system

48. In all frail patients (CFS ≥ 4) with diabetes, intensive glucose control should be avoided (increased risk of severe hypoglycaemic episodes without accruing cardiovascular benefits).
49. In moderate frailty level or higher (CFS 6-9), HbA1c target up to 75 mmol/mol (9%) or blood glucose level of 6.7–11.1 mmol/L (120–200 mg/dL) for symptomatic control is reasonable (*i.e.* providing that symptomatic hyperglycaemia or hypoglycaemia are avoided).
50. In mildly frail patients (CFS 4-5) with a life expectancy of > 5 years and mild to moderate microvascular complications, an HbA1c target of 58–64 mmol/mol (7.0–8%) is appropriate, providing they are not on high-risk hypoglycaemic medications (*e.g.* insulin, long-acting sulfonylureas).

Intensive or tight glycaemic control may increase the risk of hypoglycaemia in older adults [154]. The NICE committee advocated relaxing the target HbA1c level as part of individualised care in older and frail adults with reduced life expectancy, fall risk, impaired awareness of hypoglycaemia, or significant comorbidities [154]. Sinclair *et al.* (2017) developed an evidence-based decision-support tool for older adults with frailty and diabetes [155]. This international position statement suggested an HbA1c target range of 53 to 64 mmol/mol (7 to 8%) for mild to moderately frail older adults and 59 to 69 mmol/mol (7.5 to 8.5%) for severely frail individuals [155]. It emphasised that targets in patients with mild and moderate frailty should consider their self-care management abilities and hypoglycaemia risks. In addition, the targets for older adults with moderate to severe frailty and hypoglycaemia risk were relaxed to 59–69 mmol/mol (7.5–8.5%) [155]. Multiple comorbidities may confound HbA1c measurements; therefore, a random blood glucose target range of 6.7 – 11.1 mmol/L (120–200 mg/dL) was additionally suggested [155]. Many frail patients have a history of chest and urinary infections, and polyuria usually accompanies hyperglycaemia. Therefore, statements suggested lowering the target to less than or equal to 8.5% (69 mmol/mol) to reduce infections and improve bladder control [155].

The American Diabetes Association (ADA) has incorporated multimorbidity and the severity of physical or cognitive impairments into its suggested targets [156]. The older cohort was classified as healthy, complex/intermediate, candidates for short-term rehabilitation, very complex, and at the end of life [156]. For the healthy cohort with few comorbidities and intact cognitive and physical functions, HbA1c targets of less than 7.0–7.5% (53–58 mmol/mol) have

been suggested [156]. In the complex/intermediate group, corresponding to those with multiple comorbidities, two or more instrumental ADL impairments, or mild-to-moderate cognitive impairment, a less stringent HbA1c goal of less than 8% (64 mmol/mol) was recommended [156]. However, the ADA discouraged the reliance on HbA1c in patients who are receiving short-term rehabilitation in a skilled nursing facility, very complex, and those who are approaching the end of life [153]. Short-term rehabilitation patients were advised to maintain a glucose range of 100–200 mg/dL (5.55–11.1 mmol/L) [156]. In addition, glycaemic control to avoid hypoglycaemia and hyperglycaemia was suggested for very complex patients (those who need long-term care, have end-stage illnesses, have a moderate-to-severe cognitive impairment, or have two or more ADL impairments) and patients at the end of life [156].

In addition to multimorbidity and cognitive or physical functions, the Japan Geriatrics Society has established glycaemic targets for three cohorts taking age and the hypoglycaemic risk of prescribed medications into account [157]. Patients in Category I have intact cognitive function and no ADL impairment [157]. A glycaemic HbA1c target of < 7.0%, < 7.5%, and < 8.0% was recommended for patients not taking medications with a high risk of hypoglycaemia (*e.g.* Insulin, sulfonylureas), for patients aged 65 to less than 75 years taking high-risk medicines, and for patients aged ≥ 75 years taking high-risk medications [157]. Category II corresponds to patients with mild cognitive impairment to mild dementia or with instrumental ADL impairment but no impairment in basic ADL [157]. Glycaemic HbA1c targets of 7.0% or 7.0% - < 8.5% were suggested for Category II patients without or taking medications with a high risk of hypoglycaemia, respectively [157]. Category III corresponds to patients with moderate to severe dementia, basic ADL impairment, multiple comorbidities, or functional impairments. Glycaemic HbA1c targets of 8.0% or 7.5% - < 8.5% were proposed for Category III patients without or taking medications with a high risk of hypoglycaemia, respectively [157].

A Canadian clinical practice guideline suggested glycaemic control targets stratified by the Clinical Frailty Scale for older adults [158]. An HbA1c target of less than 8% was suggested for functionally dependent patients, corresponding to mild frailty or CFS scores 4-5 [158]. In patients with frailty and/or dementia (CFS score 6-8 or moderate to severe frailty), the recommended HbA1c target was less than 8.5% [158]. However, the measurement of HbA1c was not recommended in patients at the end of life (CFS 9 or terminal illness) [158]. Moreover, recommendations emphasised on avoiding hypoglycaemia and hyperglycaemia at the end of life. Strain *et al.* (2021) have developed a guideline based on a literature review and expert options for the primary care management of diabetes in frail older adults in the United Kingdom

[159]. For moderately frail patients (defined as those with more than two comorbidities and reduced life expectancy), an HbA1c target of less than 64 mmol/mol (8.0%) was recommended [159]. In addition, an HbA1c level of less than 69 mmol/mol (8.5%) was recommended for severely frail patients (those with significant comorbidities, functional deficits, and limited independence with a markedly limited life expectancy) [159].

The 2017 Department of Veterans Affairs and Department of Defense (VA/DoD) clinical guideline uniquely considered comorbidities and estimated life expectancy in relation to the degree of microvascular complications when determining HbA1c targets for diabetic patients [160]. In the presence of no to mild microvascular complications, an HbA1c target of 7.0–8.0% was recommended for patients with a 5- to 10-year life expectancy and non-end-stage, manageable major comorbidities [160]. A higher HbA1c target of 7.5–8.5% was suggested for patients with moderate or advanced microvascular complications, a 5- to 10-year life expectancy, and non-end-stage and manageable major comorbidities [160]. Regardless of the severity of microvascular complications, an HbA1c goal of 8.0–9.0% was recommended for patients with a life expectancy of less than five years who have end-stage or management-challenging major comorbidities [160].

Notable is the VA/DoD guideline's consideration of microvascular complications as opposed to macrovascular complications [160]. Despite not including frail participants, pivotal trials such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) found that tight glycaemic control had a positive impact on microvascular outcomes in older adults [161]. However, there were no consistent benefits on macrovascular outcomes [161]. In addition, evidence suggests that diabetic patients may accrue microvascular benefits after a shorter period of tight glycaemic control than is required for macrovascular benefits [162]. The reduction in microvascular complications was profound after 6.0 to 7.5 years of intensive glycaemic control in the United Kingdom Prospective Diabetes Study (UKPDS) and after five years in the ADVANCE trial [162]. In contrast, improvements in macrovascular outcomes did not become apparent until the 10-year follow-up period following the UKPDS trial [162]. However, this longer time till macrovascular benefits may exceed the life expectancy of most frail diabetic patients [162].

51. In all hospitalized frail patients, a blood glucose level below 10 mmol/L (180 mg/dL) is appropriate for the management of inpatient hyperglycaemia while avoiding hypoglycaemia.
52. In all hospitalized frail patients (CFS ≥ 4), a blood glucose level of 15 mmol/L (270 mg/dL) may be acceptable for the management of inpatient hyperglycaemia in the context of terminal illness, multiple comorbidities or inability to monitor.

Patients with diabetes frequently experience hyperglycaemia during hospitalisation [163]. In addition, physiological stress (*e.g.* surgery), infections, and acute illness increase the risk of inpatient hyperglycaemia in frail older individuals. Specifically, the renal threshold for hyperglycaemia may be elevated in older adults [163]. As a result, osmotic symptoms from hyperglycaemia may be less apparent in older adults, and fatigue symptoms may be attributed to age-related symptoms (*e.g.* confusion and inactivity) [163]. In inpatient settings, however, the risk of hypoglycaemia is also higher among older patients. Sinclair *et al.* (2017) suggested random blood glucose levels above 6 mmol/L (108 mg/dL) and below 15 mmol/L (270 mg/dL) for the management of inpatient hyperglycaemia, providing that both hypoglycaemia and hyperglycaemia are avoided [155]. Similarly, the Joint British Diabetes Societies for Inpatient Care (JBDS-IP) has suggested less stringent targets to avoid hypoglycaemia [163]. JBDS-IP established a 6.0-12.0 mmol/L range as an acceptable target range for inpatient care of frail older adults with diabetes [163]. Higher glucose targets may be acceptable in patients with severe comorbidities, irreversible end-stage disease, or when frequent glycaemic monitoring is not feasible [164].

53. Treatment de-intensification, simplification or deprescribing (dose reduction, switching to alternative, or discontinue) may be considered in frail patients in the following circumstances:

- a) No caregiver and/or reduced self-management capacity due to cognitive or physical functions decline,
- b) Caregiver distress from regimen complexity, or
- c) Based on the patient's preference due to discomfort/ pain from frequent injections (frequent injections/day or monitoring).

54. Treatment de-intensification, simplification or deprescribing (dose reduction, switching to alternative, or discontinue) should be considered:

- a) If HbA1c drops below 53 mmol/mol (7%) in mildly frail patients,
- b) If HbA1c drops below 58 mmol/mol (7.5%) in moderate and severe frailty,

- c) If patients show symptoms consistent with severe hypoglycaemia (even if HbA1c level is within target) or in suspected hypoglycaemia, or
 - d) In patients with recurrent hypoglycaemic episodes.
55. In all frail patients (CFS $\geq$ 4) with inconsistent eating patterns, anorexia, moderate frailty level or higher, or advanced cognitive /physical impairment, medications with a high risk of hypoglycaemia such as isophane insulins, short-acting insulins, repaglinide, glibenclamide, or glimepiride should be discontinued/avoided (even if HbA1c is within target).
56. a) In all frail patients (CFS $\geq$ 4), complex or high-risk hypoglycaemic insulin regimens (*e.g.* twice daily isophane or Premix insulins) should be avoided and simplified.
- b) alternatives include reduced-dose ultra-long-acting basal insulin analogues with or without oral/injectable agents of low hypoglycaemic risk (DPP-4 inhibitors, GLP1s agonists).

The high prevalence of recurrent hypoglycaemia in older adults may be underrecognized by clinicians [165]. Hypoglycaemia is associated with adverse outcomes that may result in significant cognitive and physical dysfunctions in older adults [165]. The American Diabetes Association established a workgroup classification for hypoglycaemia types in 2005 [166]. Documented symptomatic hypoglycaemia was defined as the presence of hypoglycaemia symptoms with a plasma glucose level of $\leq$ 3.9 mmol/L (70 mg/dL) [166]. Hypoglycaemia was referred to as probable symptomatic hypoglycaemia when patients exhibit hypoglycaemia symptoms in the absence of documented plasma levels [166]. In asymptomatic hypoglycaemia, patients have no symptoms, but their plasma glucose level is below or equal to 3.9 mmol/L [166]. Of note, patients with poorly controlled diabetes for an extended period of time may experience symptomatic hypoglycaemia at glucose concentrations above the 3.9 mmol/L threshold. In such situations, the type of hypoglycaemia is referred to as relative hypoglycaemia or pseudo hypoglycaemia [166].

A Canadian deprescribing guideline recommends deprescribing antihyperglycaemic agents in older adults (aged 65 years or older) at risk for hypoglycaemia and taking one or more antihyperglycemic medications [167]. Hypoglycaemia risk may be caused by or exacerbated by advanced age, intensive glucose control, multiple comorbidities, a history of hypoglycaemia unawareness, impaired renal function, and medications associated with a high risk of hypoglycaemia (*e.g.* insulin and sulfonylurea) [167]. Inconsistent eating and drug-drug interactions were also considered potential contributors to hypoglycaemia [167]. The guideline

defined deprescribing as the abrupt discontinuation or tapering of medications, using lower doses, and substituting antihyperglycemic agents with high hypoglycaemic risk [167]. It advised decreasing the dosage of certain medications (e.g. sulfonylurea, insulins) or switching from Neutral Protamine Hagedorn (NPH) insulin or mixed insulin to detemir or glargine to reduce nocturnal hypoglycaemia [167].

Based on frailty status, Strain *et al.* (2021) suggested simple glycaemic management algorithms for antihyperglycemic agents [159]. Statements suggested simplification or de-escalation of antihyperglycemic agents in mildly frail patients whose HbA1c value falls below 53 mmol/mol (7.0%) or below 58 mmol/mol (7.5%) in moderately or severely frail patients [159]. In such cases, non-insulin medications can be de-escalated by reducing the dosage or discontinuing use [159]. For instance, the algorithms advised reducing the dosage of or discontinuing sulfonylurea or pioglitazone in moderate frailty or discontinuing all non-insulin antihypertensive medications in severe frailty and replacing them with dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors or gliptins) [159]. Insulin regimens, on the other hand, can be deescalated through either dose reduction or simplification of complex or high-risk insulin regimens [159]. According to the algorithms, this can be accomplished by reducing insulin dosage by 20% increments in frail older adults [159]. In mildly frail patients, complex regimens (such as twice-daily NPH insulins or twice-daily premix insulins) may be simplified to basal insulin analogues (with a 30% dose reduction) plus glucagon-like peptide-1 receptor agonist (GLP-1 RA) or sodium-glucose cotransporter-2 inhibitors (GLT-2i) [159]. Alternately, the algorithm suggested switching from complex/high hypoglycaemic risk regimens (such as twice-daily NPH insulins or twice-daily premix insulins) to basal insulin analogues alone with a 20% reduction in the daily dose [159]. DPP-4 inhibitors with or without basal insulin analogues were suggested for severely frail patients [159].

This coincides with the Diabetes Care Program of Nova Scotia (DCPNS) and the Palliative and Therapeutic Harmonization (PATH) Program recommendations for the management of type 2 diabetes in frail older adults [162]. According to DCPNS/PATH guidelines, NPH insulins are costly and provide no additional clinical benefits compared to long-acting insulin analogues (e.g. glargine, detemir) [162]. Consequently, the DCPNS/PATH guideline recommended simplifying insulin regimens to basal insulin only and avoiding regular and rapid-acting insulin whenever possible [162]. This recommendation took the inconsistent oral intake associated with frailty into account. When smaller postprandial glucose lowering is required, DPP-4 inhibitors may be used alone or in combination with basal insulin [155]. GLP-1 agonists also constitute a viable alternative for postprandial glucose lowering due to their low risk of hypoglycaemia and the

availability of once-weekly formulations and in combination with basal insulin [155]. However, caution should be undertaken where further weight loss might be a concern [155].

Age and frailty are two risk factors for hypoglycaemia in diabetic patients receiving treatment [165]. Therefore, therapy monitoring is a crucial aspect of caring for older adults with diabetes mellitus. Self-monitoring is particularly useful for enhancing glycaemic control and preventing severe hypoglycaemia episodes. This may be more pronounced when patients receive medications with a high risk of hypoglycaemia, such as insulin and sulfonylureas. However, this necessitates a certain level of functional and cognitive abilities, which may be compromised in older adults living with frailty. For example, moderately and severely frail older patients may have cognitive impairment or communication deficits that impede the achievement of therapeutic goals.

Caregivers and family members should be involved in the care plan for cognitively impaired or frail older adults. In addition, therapeutic guidelines for frail individuals should encourage the incorporation of patient or caregiver preferences into plans for glycaemic control. All these factors may affect older adults' adherence and compliance with anti-diabetic medications. In the presence of noncompliance issues, de-intensifying therapy, simplifying insulin regimens, or discontinuing or replacing high-risk therapies is reasonable. This may be accomplished by avoiding less stringent glycaemic control targets or substituting high-risk hypoglycaemic medications (*e.g.* DPP4 inhibitors instead of sulphonylurea). Additionally, the physical and cognitive functions should be evaluated prior to initiating insulin treatment. If additional glycaemic control is required, oral hypoglycaemic medications may be supplemented with once-daily long-acting insulin [155].

According to the UK expert consensus statement by Strain *et al.* (2021), the ultimate goals of therapy for moderate to severely frail patients should be to prevent metabolic emergencies and improve the quality of life [159]. Hypoglycaemia is associated with negative outcomes such as cognitive and physical dysfunctions in older adults [159]. Additionally, frail older adults present with hypoglycaemic symptoms such as dizziness, confusion, and visual disturbances more frequently than other alarming symptoms (*e.g.*, palpitations, sweating, tremors), and this can be misdiagnosed as cognitive dysfunction or dementia [159]. Therefore, it is reasonable to avoid new medications and discontinue these medications associated with a high risk of hypoglycaemia. These include sulfonylureas (highest with glibenclamide and glimepiride while

lowest with gliclazide), insulin (highest with short-acting and NPH insulin), and meglitinides (to a lesser extent) [39, 167].

57. a) In all frail patients ($\text{CFS} \geq 4$) in non-intensive care settings, pre-mixed or biphasic isophane insulins should be avoided as a single sliding scale regimen (risk of hypoglycaemia or glucose fluctuations).

b) Alternatives include basal-based insulins, basal-bolus regimen (in adequate oral intake), or basal-plus (in NPO or poor oral intake).

58. In all critically ill frail patients ($\text{CFS} \geq 4$), subcutaneous administration of insulin should be avoided (lack of robust supporting evidence).

Hyperglycaemia in hospitalised diabetic patients is associated with an increased risk of hospital complications, longer hospital stays, and mortality [164]. Insulin is the preferred hypoglycaemic drug for managing diabetes and hyperglycaemia in the hospital settings [164]. There are numerous insulin regimens used in ICU and non-ICU inpatient settings [164]. In the ICU, continuous insulin infusions are the most common and effective method for controlling hyperglycaemia [164]. Subcutaneous insulin has not been studied extensively in older patients for the management of hyperglycaemia in the ICU, and it should be avoided in critically ill and high-risk patients (*e.g.* hypotension or shock) [164]. In addition, basal-bolus or basal-plus insulin regimens have proven to effectively control hyperglycaemia in non-intensive care settings [164].

The basal-bolus insulin regimen comprises background insulin supplemented by rapid mealtime insulin administration. The appropriate total daily insulin dose is between 0.15 and 0.30 units/kg body weight [164]. Half of this dose is given as once daily long-acting insulin analogues (*e.g.* glargine, detemir, or degludec). The other half is given as rapid-acting insulins before meals. This plan may be flexible, but it requires careful timing of insulin administration with meals [163]. Additionally, administering multiple daily injections can be challenging for frail older patients and inexperienced staff [163]. Once-daily administration of a long-acting insulin analogue (*e.g.*, glargine, detemir, or degludec) or twice-daily administration of intermediate-acting NPH insulin may be used to administer basal insulin [168]. However, the action of NPH insulins may peak at 8-12 hours after administration. They are typically administered twice or thrice daily to patients with a more consistent diet and activity schedule [163]. Consequently, this type of premixed insulins may place older patients at high risk for hypoglycaemia, particularly during periods of illness when oral intake is compromised [163, 164].

Basal-bolus regimens, consisting of insulin detemir once daily plus insulin aspart before meals, had equivalent glycaemic control and no significant difference in hypoglycaemia frequency when compared to NPH/regular insulin twice daily in a randomised controlled trial of hospitalised patients with diabetes [169]. In a more recent randomized controlled trial, patients receiving NPH twice daily and regular insulin before meals experienced more severe hypoglycaemia than those receiving a basal-bolus regimen of glargine once daily and glulisine before meals [170]. In another study, premixed human insulin treatment (70% NPH insulin and 30% regular insulin) significantly increased the frequency of hypoglycaemia compared to basal-bolus insulin treatment (glargine once daily and glulisine before meals) in hospitalised diabetic patients (mean age 70) [164, 171]. Newer premixed insulin regimens combine insulin aspart or insulin lispro with insulin with a longer half-life in predetermined proportions. However, these newer premixed insulins are more likely to lower glucose levels than long-acting ones, resulting in a high risk of hypoglycaemia [172, 173]

Among the insulin regimens that may be utilised in inpatient settings are sliding scale insulins (SSI). However, basal-bolus insulin regimens have demonstrated better efficacy and safety when compared to SSI [174, 175]. In the RABBIT 2 trial (Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes), non-intensive care unit patients with type 2 diabetes were assigned to receive either basal-bolus insulin (glargine once daily and Insulin glulisine before meals) or a standard SSI protocol (four times per day) [174]. Treatment with a basal-bolus insulin regimen significantly improved glycaemic control, with no significant differences in the incidence of hypoglycaemia or length of hospital stay [174]. In the RABBIT-2 Surgery trial, patients who underwent general surgery and received basal-bolus as opposed to an SSI protocol had fewer hospital complications (such as wound infection, pneumonia, respiratory failure, acute renal failure, and bacteraemia) [175]. It is noteworthy that the 2019 updated AGS Beers criteria advise against the use of sole SSI regimens that do not contain basal insulins or long-acting insulins (insulin (based on evidence of moderate quality and a strong recommendation) [39].

The bolus portions of the basal-bolus regimen should be administered according to the timing and quantity of meals. However, hospitalised patients frequently have inadequate intake, which may increase the risk of hypoglycaemia in diabetic patients receiving bolus insulin [159]. In such patients, a basal-plus regimen may be considered an effective alternative option [159]. In the bolus-plus approach, the total daily insulin dose is administered primarily as basal insulin, with additional insulin dosing based on an SSI algorithm if necessary [164]. In a multicentre trial,

medical and surgical diabetic patients were randomised to receive a basal-bolus regimen (glargine once daily and glulisine before meals), a basal-plus regimen (glargine once daily and supplemental doses of glulisine according to an SSI algorithm) or sliding scale regular insulin (SSI) [176]. The findings illustrated that the basal-plus regimen produced comparable glycaemic control to the basal-bolus regimen and fewer treatment failures than SSI alone [176]. In summary, basal-bolus insulin regimens constitute a reasonable choice for controlling inpatient hyperglycaemia in older patients who are not critically ill and have adequate oral intake.

59. a) In all hospitalized frail patients ($\text{CFS} \geq 4$), switching from insulin to oral hypoglycaemic agents should be considered at discharge.

b) If insulin administration is inevitable and feasible, insulin pens should be considered.

Some older patients are discharged from the hospital with continuing insulin therapy following discharge [177]. Frail patients are at a greater risk of hypoglycaemia from medications with high alert levels, such as insulins, despite their beneficial effects on glycaemic control. Thus, any benefit may be offset by associated adverse effects [178]. Additionally, in real clinical practice, frail patients are characterised by multiple comorbidities, such as physical and cognitive impairments, which may substantially impact their adherence to hypoglycaemic medications. In a recent population-based cohort study, the risk of adverse outcomes after hospitalization was evaluated in older patients who were discharged on hypoglycaemic medications [177]. The results indicated that the incidence of 30-day mortality and the risk of hospital readmission were significantly higher among older patients discharged on insulin therapy [177]. New insulin users (those who received no insulin before hospitalisation and received one or more insulin prescriptions post-discharge) and prevalent insulin users (those who received one or more insulin prescriptions before hospitalization and post-discharge) were at the greatest risk [177]. At discharge, switching to oral medications with a low risk of hypoglycaemia should therefore be considered. Alternatives with a low risk of hypoglycaemia may be safe and effective, such as dipeptidyl peptidase-4 inhibitors alone or in combination with basal insulin (if insulin is required). Furthermore, pen devices may improve insulin therapy adherence in older adults with diabetes mellitus [179].

60. In all frail patients ($\text{CFS} \geq 4$), switching from immediate-release metformin to extended-release metformin formulations should be considered (extended-release metformin forms have less complex regimens with fewer GIT side effects).

Metformin is associated with a lower risk of hypoglycaemia, low cost, and relative tolerability compared to other hypoglycaemic drugs [155]. Therefore, it is the treatment of choice for most diabetic patients [155]. Metformin is available in immediate-release formulations and extended-release formulations. Many patients may be unable to tolerate the side effects of immediate-release metformin, especially gastrointestinal side effects like abdominal distension, flatulence, abdominal pain, diarrhoea, and dyspepsia [180]. In a systematic review and meta-analysis of randomised controlled trials, extended-release formulations of metformin demonstrated clinically comparable HbA1c benefits to immediate-release formulations, with minimal improvement in gastrointestinal intolerance [180]. In addition, extended-release formulations may play a role in enhancing treatment adherence due to their less frequent administration [181]. Therefore, long-acting and extended-release formulations of metformin may be preferably considered in frail older adults. However, weight loss and gastrointestinal side effects of metformin must be carefully monitored in all older patients with frailty [155].

61. In severely to terminally ill frail older (CFS 7-9) patients, SGLT2 inhibitors should be avoided/discontinued (increased risk of volume depletion, dehydration, incontinence, and genitourinary infections).
62. In severely to terminally ill frail patients (CFS 7-9), pioglitazone should be avoided/discontinued (risk of water retention and peripheral oedema that impair quality of life).

Several consensus-based recommendations highlighted the significance of carrying the safety of individual hypoglycaemic medications into consideration when choosing the appropriate agent for frail older patients. Due to the high risk of hypoglycaemia, the international position statement on the management of frailty in diabetes mellitus endorsed avoiding sulfonylureas and non-sulfonylurea Insulin secretagogues (*i.e.* meglitinides) in frail older adults [155]. In addition to metformin as a first-line therapy, DPP-4 inhibitors alone or in combination with basal insulin were deemed as an alternative option for lowering postprandial glucose levels in the older population [155].

In their simplification/de-escalation algorithms, Strain *et al.* (2021) recommended discontinuing sulfonylureas and pioglitazone and considering discontinuing metformin and glucagon-like peptide-1 receptor agonists (GLP-1 RA) in severely frail older adults regardless of HbA1c [159]. If the HbA1c level drops below 58 mmol/mol (7.5%) in moderately frail patients, Strain *et al.* (2021) suggested lowering the dose or ceasing sulfonylureas and pioglitazone [159]. When the

HbA1c level falls below 58 mmol/mol (7.5%) in moderately frail patients, it is also recommended to discontinue metformin in patients with reduced renal function and discontinue pioglitazone and saxagliptin if heart failure symptoms are detected or suspected [159]. In addition, these algorithms considered sodium-glucose cotransporters-2 (SGLT-2) as appropriate medications in moderate and severely frail patients with detected or suspected heart failure symptoms after carefully considering their adverse effects (*e.g.* dehydration, infection risk, fall, weight loss and hypotension) [159]. Despite the paucity of consistent evidence supporting their use in frailty, they considered discontinuing SGLT-2 only in severely frail older adults whose HbA1c level falls below 58 mmol/mol (7.5%) [159].

In a national collaborative initiative, Strain *et al.* (2018) proposed a concise statement of key diabetes management principles in the context of frailty [182]. They advised discontinuing all sulfonylureas in moderately to severely frail patients whose HbA1c falls below 58 mmol/mol (7.5%) [182]. In addition, this initiative raised concerns about using thiazolidinediones, mindful of the increased risk of heart failure [182]. Consequently, they suggested avoiding using thiazolidinediones in moderate to severely frail patients due to the possibility of adverse effects on quality of life (*e.g.* peripheral oedema reducing mobility) [182]. These statements alternatively suggested DPP-4 inhibitors and longer-acting insulins, as their safety in the targeted cohort was demonstrated [182]. SGLT2 inhibitors were also suggested to offer additional benefits to heart failure patients [182]. However, SGLT2 inhibitors have been associated with diabetes-like symptoms such as polyuria and an increased risk of urinary tract infections and candidiasis [182]. These symptoms may have a negative impact on the quality of life in patients with moderate or higher frailty, for whom the goal of therapy is to prevent further decline in quality of life [159].

63. a) In all frail patients (CFS $\geq$ 4) with anorexic-malnourished (AM) frailty, SGLT2 inhibitors and GLP1s agonists should be avoided or discontinued (risk for further weight loss).

b) Alternatives include medications with a neutral effect on weight and a low risk of hypoglycaemia, such as DPP-4.

Most discussed consensus-based guidelines and algorithms have established glycaemic goals and suggested appropriate therapeutics based on the presence (*i.e.* frail or non-frail) or the severity of frailty (*i.e.* fit, mild, moderate, or severe frailty) [183]. In a recent innovative review, Abdelhafiz *et al.* (2021) studied the metabolic profiles of frailty that may inform the use of

antihyperglycemic therapy in frail older individuals with type 2 diabetes [183]. They hypothesised that frail diabetic patients should be viewed as either sarcopenic obese (SO) or anorexic malnourished (AM) in terms of their metabolic phenotypes [183]. Patients with the AM phenotype are at an increased risk for hypoglycaemia due to their significant weight loss, decreased insulin resistance, and regressive course of diabetes [183]. De-intensification of hypoglycaemic therapy may therefore be reasonable in such patients. In contrast, sarcopenic-obese frail patients have increased insulin resistance and a progressive course of diabetes, which means they need more intensive antihyperglycemic therapy [183].

Novel hypoglycaemic treatments, such as GLP-1RAs and SGLT-2 inhibitors, are associated with weight loss [184]. In the context of the two metabolic phenotypes of frailty, SGLT-2 inhibitors and GLP-1RA have been reviewed due to their low risk of hypoglycaemia and additional benefits (such as SGLT-2 in heart failure) [184]. Abdelhafiz *et al.* (2020) suggested that these new hypoglycaemic medications should be used with caution in mild or moderate anorexic malnourished (AM) frail patients (*i.e.* mild to moderate weight loss or anorexia) and avoided in severe AM patients (*i.e.* severe anorexia or malnutrition) [184]. In contrast, authors suggested that sarcopenic obese frail patients may benefit from these medications because of their favourable metabolic profile and lower risk of adverse effects [184]. Moreover, the authors hypothesised that the beneficial extra-glycaemic impact of the new therapy might improve the metabolic profile of sarcopenic-obese frail patients [184].

4. Gastrointestinal system

64. a) In all frail patients (CFS ≥ 4), aluminium- or magnesium- containing antacids should be avoided (risk of multiple drug interactions and accumulation of aluminium or magnesium in the body).
b) When indicated, proton pump inhibitors (PPIs) may be considered with caution at low doses for a maximum duration of 8 weeks.
65. a) In all frail patients (CFS ≥ 4), slower tapering of PPIs after long-term use should be considered over abrupt discontinuation.
b) The following tapering schedules may be considered:
- 1) switching from twice-daily to once-daily or halving the daily dose for 2- 4 weeks, then stop. Patients on low doses may switch to every second-day regimen.
 - 2) An alternative: stop PPIs, then use PPIs as needed.

Gastric acid-suppressing medications such as proton pump inhibitors and histamine-2 receptor antagonists (H2RAs) have been indicated in several gastrointestinal indications. These include gastro-oesophageal reflux disease (GORD), *Helicobacter pylori* eradication, prevention and treatment of NSAID-induced ulcers, and complications of GORD (e.g. erosive oesophagitis, Barrett's oesophagus, and cancer). The use of PPIs or H2RAs is usually warranted in patients with such conditions. However, medications such as antacids can be considered in ulcer dyspepsia and in non-erosive gastro-oesophageal reflux as breakthrough medications. Despite insufficient evidence, antacids might also be used in functional (non-ulcer) dyspepsia. Other medications are usually added to antacids to relieve acid reflux (e.g. sucralfate) or flatulence (e.g. simethicone in palliative care).

Antacid preparations usually contain aluminium or magnesium compounds that may accumulate in reduced renal function [112]. Frail older adults are more likely to have age-related hepatic and renal dysfunction. As a result, there is a risk of hypermagnesemia from antacid use, with a higher risk in those with moderate to severe renal impairment [112]. Moreover, antacid use places older adults at risk of aluminium accumulation and central nervous system toxicity [112]. Therefore, the EU (7)-PIM list has recommended PPIs as possible alternatives for a maximum duration of 8 weeks [112].

Abrupt discontinuation of PPIs or H2RAs might result in rebound gastric hypersecretion or contribute to a recurrence of GORD, particularly after long-term use [49, 50]. However, evidence suggests that rebound symptoms after the abrupt stopping of H2RAs are short-term and milder than symptoms of PPI abrupt stopping [50]. A Canadian evidence-based guideline suggested that stopping PPIs could be done by either abrupt discontinuation or a tapering regimen [185]. Notably, this guideline informs the deprescribing of PPIs in patients with mild to moderate esophagitis or GORD treated for 4–8 weeks (healed or symptoms resolved) or in asymptomatic upper GI symptoms for three consecutive days without endoscopy [185]. It also applies to patients who were treated for 2–12 weeks for peptic ulcers caused by *H. pylori* or NSAIDs or to patients treated for ICU stress ulcer prophylaxis beyond the ICU [185]. Before deprescribing, the guideline outlined the ongoing indications when PPI use should be continued. They included severe esophagitis, Barrett's oesophagus, chronic NSAID use, or GI bleeding history [185].

The literature is replete with several discontinuation approaches for PPIs. The most common regimens are the step-down approach, the on-demand PPI approach, and the use of the non-PPI alternatives approach [186]. In the step-down approach, the daily dose of PPIs is decreased

either by halving the dose or deescalating from twice daily administration to once daily use for one month, then stopped in patients without rebound symptoms [49, 185, 186]. Patients on low doses may be able to switch to every other day regimen [186]. The "on-demand" approach allows patients to stop PPIs and then take them as needed or in intermittent courses [185, 186]. With low-quality evidence, the Canadian deprescribing guidelines strongly recommended these two approaches to decrease the daily PPI dose or to stop and change to PPI as needed [185]. Moreover, alternative medications have been investigated to reduce inappropriate PPI prescribing. With weak recommendation and moderate-quality evidence, the deprescribing guidelines have considered H2RAs as alternatives to PPIs [185]. In one study, patients on alginate stepped off PPI use after 12 months without any complications or deterioration of symptoms [187]. Alginate has been chosen as an attractive alternative due to poor systemic absorption [187].

66. In all frail patients (CFS ≥ 4), calcium channel blockers (CCBs), tri/tetracyclic antidepressants (TCAs), calcium- or aluminium-containing antacids, opiates, oral iron supplements, and medications with anticholinergic effects should be discontinued or switched to alternatives (may cause or worsen constipation).

67. Alternative options to constipating medications may include:

- a) SSRIs (except paroxetine) instead of TCAs,
- b) Angiotensin-converting-enzyme inhibitors (ACEIs) instead of CCBs,
- c) Proton pump inhibitors (PPIs) instead of constipating antacids, and
- d) IM/IV iron supplementation instead of oral iron supplementation.

Constipation and laxative use appear to increase with ageing [188]. The prevalence of constipation gradually increases after the age of 60 years, with the largest increase after the age of 70 years [188]. Furthermore, institutionalised older residents (where the frailty risk increases) are more likely to experience constipation than community-dwelling older adults [188]. Medication use is one of the most common causes of secondary constipation in older people [189, 190]. These medications include opiates (up to 80% of patients), medications with anticholinergic properties (*e.g.* urinary antimuscarinics, GIT antispasmodics, antihistamines), antacids (*e.g.* aluminium-, calcium-containing), antihypertensives (*e.g.* calcium channel blockers, furosemide), tricyclic antidepressants, some antipsychotics, antiepileptic drugs, anti-Parkinson's drugs (*e.g.* levodopa) and some supplements (*e.g.* iron, calcium) [190, 191]. Furthermore, the prescribing cascade may contribute to or worsen constipation in older people. For instance, urinary antimuscarinic agents used for urinary incontinence may precipitate or

worsen constipation in an older adult, contributing to faecal impaction and faecal incontinence [192]. If faecal incontinence is misdiagnosed as diarrhoea, a constipating agent may be prescribed, worsening the patient's constipation [192].

Several clinical practice guidelines and consensus-based criteria have identified these constipating medications as potentially inappropriate, with a strong recommendation to stop or modify them [112, 189]. Substituting some constipating medications and medication classes with safer alternatives may be more appropriate than prescribing laxatives. For instance, the EU 7 PIM list suggested using other antihypertensive medications such as cardioselective beta-blockers and ACE inhibitors instead of calcium channel blockers and SSRIs (except fluoxetine, paroxetine, and fluvoxamine) instead of TCAs [112]. In addition, the expert panel suggested lowering the iron dose to less than 325 mg/day or switching to intravenous iron [112]. Similarly, using PPIs rather than constipating antacids is reasonable when indicated for gastrointestinal symptoms. In people with opioid-induced constipation, the patient should use the least effective dose supplemented with prophylactic laxatives if opioids are necessary with ongoing indications [192-194]. Alternatively, naloxegol, a peripherally acting μ -receptor opioid antagonist, may be considered prophylactically [189]. Similarly, laxatives may be warranted in patients prescribed other constipating medications such as antacids (as phosphate binders), antiepileptic drugs, and antipsychotics [193].

68. In all frail patients (CFS ≥ 4) with chronic constipation, the routine use of stimulant laxatives is discouraged unless for short-term adjunctive use in refractory constipation (risk of fluid/electrolyte disturbance and worsening of bowel disfunction).
69. In all frail patients (CFS ≥ 4) with chronic constipation, phosphate- or mineral oil-containing enemas should be avoided or discontinued, unless patients have faecal impactions and inability to take oral therapy (risk of electrolyte disturbance, dehydration, and malabsorption of fat-soluble vitamins with mineral oils).

Recommendations for constipation management in older adults are similar to those in younger adults, except for some safety concerns over certain laxatives in older adults [195, 196]. There is an agreement to begin therapy with bulk-forming laxatives or/and osmotic laxatives followed by stool softeners or stimulant laxatives when needed [195, 196]. The bulk-forming laxatives should be administered with plenty of fluid intake, which makes them unsuitable for older adults, particularly those with cognitive impairment, fluid restrictions, dehydration, oesophageal strictures and dysphagia, or non-ambulatory patients [195]. In addition, the bulk-

forming laxatives are not compatible with nasogastric (NG) tubes or percutaneous endoscopic gastrostomy (PEG) tubes [191].

Stimulant laxatives and stool softeners (*e.g.* bisacodyl, senna, sodium picosulfate, docusate sodium or mineral oils) are discouraged in older adults with constipation [39, 112, 196]. Bisacodyl, sodium picosulfate, and senna are associated with adverse events such as abdominal pain, fluid and electrolyte imbalance, hypoalbuminemia, and worsening of bowel dysfunction [112]. Oral docusate sodium, a stool softener, may also exacerbate bowel dysfunction in older adults, with the potential for GIT side effects (*e.g.* cramping, nausea, diarrhoea) [112]. Furthermore, docusate has been argued to be ineffective in preventing or treating constipation in older adults [195]. However, docusate sodium demonstrated benefits over the placebo in managing constipation in three randomized controlled trials involving older adults [196, 197]. The 2019 AGS Beers criteria strongly recommend avoiding oral mineral oils due to unfavourable adverse effects, high potential for aspiration, and the availability of safer alternatives in older adults (moderate quality evidence) [39]. Because of these possible adverse effects, stimulant laxatives should be considered only after other options (*e.g.* fibres, osmotic laxatives) have been tried [196]. In consensus-based statements, participants agreed that docusate may be considered an alternative, and if the stool is soft but difficult to pass, a stimulant laxative may be considered [198].

70. In all frail patients (CFS ≥ 4), magnesium-containing osmotic laxatives should be avoided to treat chronic constipation or to reduce frequency faecal incontinence from faecal impaction (high risk of electrolyte imbalance such as hypermagnesaemia).

The effectiveness and safety of magnesium-containing osmotic laxatives (*e.g.* magnesium hydroxide and magnesium citrate) have not been conclusively studied in older adults [196]. Frail older adults usually present with reduced renal and cardiac functions. Therefore, magnesium toxicity is a major safety concern with the long-term use of these osmotic laxatives, particularly in moderate to severe renal failure [112, 196]. As in sodium phosphate enemas, osmotic laxatives may also be used rectally [191]. However, phosphate enema is associated with electrolyte, renal, cardiovascular, and neurological concerns [195]. Therefore, the use of magnesium-or phosphate-containing osmotic preparations should be discouraged in patients with renal impairment, dehydration, cardiac dysfunction, electrolyte imbalance, or diuretic users [191, 195]. Mineral oil enemas or sodium phosphate enemas may be used in refractory constipation for a short time when patients are unable to take laxatives orally [195]. However,

mineral oil enemas are preferable over sodium phosphate enemas [195]. Furthermore, in refractory faecal impactions, sodium phosphate or mineral oil enemas may be used with caution when all other options have failed [198].

71. Macrogols (or, to a lesser extent, lactulose) are preferred to other osmotic agents for treating chronic constipation or reducing faecal incontinence from faecal impaction (Macrogols and lactulose are effective, safer, and compatible with tube feeding).

Of all the laxatives, osmotic laxatives such as polyethylene glycol (macrogol) and lactulose are usually considered first-choice in managing chronic constipation in older adults [191]. Besides better efficacy and tolerability, polyethylene glycol and lactulose are compatible with tube feeding [191]. Lactulose is suitable for well-hydrated patients, while macrogols are the appropriate choice for immobile patients or those who don't drink enough fluids [191]. In a Cochrane review, the use of polyethylene glycol versus lactulose was associated with better outcomes of the frequency and consistency of stool, and the need for additional therapies [199]. However, a nonsignificant difference was found in the relief of abdominal pain in adults [199]. Therefore, polyethylene glycol is preferred over lactulose due to more effectiveness and fewer adverse effects (American Family Physician: consistent, good-quality patient-oriented evidence) [196].

72. In all frail patients ($\text{CFS} \geq 4$), the use of probiotics for the management of chronic constipation is potentially inappropriate (insufficient supporting evidence).

There is insufficient evidence to support probiotic use for chronic constipation in older patients living with frailty. In a systematic review of five RCTs, probiotics did not improve constipation in adults [196]. Two systematic reviews have highlighted the need for sufficiently powered, well-designed, and controlled clinical trials to investigate the role of probiotics in older adults [200, 201]. The first review suggested that probiotics had significantly improved constipation in older adults by 10–40% compared to placebo [200]. However, the risk of bias and the heterogeneity of the study designs and populations limited the validity of the result [200]. With similar methodological concerns, the findings from the second review suggested that probiotics may promote healthy ageing by having a moderate effect on immune functions and modifying the composition of gut microbiota in healthy older adults [201]. However, the impact of probiotics on other outcomes (*e.g.* cognitive function, digestive health, general well-being, and lipid and other biomarkers) was not inconclusive [201].

73. In all frail patients (CFS ≥ 4), diphenoxylate, opiate, atropine derivatives, or tricyclic antidepressants should be avoided for the relief of faecal incontinence associated with diarrhoea (*i.e.* with decreased rectal compliance) (have anticholinergic properties).
74. a) In all frail patients (CFS ≥ 4), loperamide should be used with caution in the management of faecal incontinence associated with diarrhoea (risk of constipation, somnolence, and GI symptoms).
- b) If used, loperamide should be considered for short-term use (preferably no longer than two days) after ruling out infection aetiology, rectal overloading, and diabetic diarrhoea.
75. In all frail patients (CFS ≥ 4) with faecal incontinence from faecal impactions (*i.e.* with increased rectal compliance), polyethylene glycol (PEG) is preferred to other laxatives for reducing the frequency of incontinence.

Faecal incontinence (FI) is a distressing and socially isolating condition in older adults, with a possible impact on mortality and dependency [202]. The prevalence of FI may approach 50% in institutionalised and long-term care older residents, where the majority are frail patients [202]. FI can be attributed to possible pathophysiologic mechanisms which are causing the incontinence [203]. FI may be caused by faecal impaction and/or increased compliance when a digital rectal exam reveals hard stool in the rectum with evidence of leakage [203]. The leading causes include medications, dementia, immobility, or muscular weakness and deconditioning [203]. In such patients, effective bowel clearance should be initiated with a combination of laxatives and enemas and then maintenance treatment with stimulant or osmotic laxatives. Frail patients usually have limited mobility, poor oral intake, and cognitive impairment. Therefore, PEG is preferable over other laxatives to reduce incontinence frequency [191].

FI may also be attributed to decreased rectal compliance, where diarrhoea and urgency are the main symptoms, with evidence of leakage [203]. Colitis, inflammatory bowel disease, surgery, or bacterial overgrowth may be the contributing causes [203]. According to the outcomes of the sixth international consultation on incontinence, loperamide may be used with caution to relieve faecal incontinence associated with loose stool and diarrhoea (after excluding infection and other causes) [202]. Although it is not considered a potentially inappropriate medication by the AGS Beers and STOPP/START criteria, loperamide is associated with abdominal pain, bloating, somnolence, and constipation [112]. It may also precipitate toxic megacolon in patients with inflammatory bowel disease or delay recovery in gastroenteritis [112]. Therefore, it is preferable to use doses not exceeding 16 mg/day for no longer than two days [112]. The NICE clinical

guidelines recommended against offering loperamide to patients with hard or infrequent stools, acute diarrhoea without a known cause, or acute episodes of ulcerative colitis [204]. The other antidiarrheal medications investigated in faecal incontinence (associated with diarrhoea) are potentially inappropriate in older adults [39, 112]. These medications include diphenoxylate, opiates, atropine derivatives, or tricyclic antidepressants. In addition to their anticholinergic properties, they may cross blood-brain barriers, precipitating unfavourable side effects [39, 112].

5. Genito-urological system

76. In all frail patients (CFS ≥ 4), pharmacological therapy for urinary incontinence should not be initiated prior to a trial of behavioural and lifestyle intervention (if possible).
77. In all frail patients (CFS ≥ 4), pharmacological therapy for urinary incontinence should not be continued in those who make no attempt to toileting with assistance or those who get agitated when toileting.

As men age, they are more likely to develop benign prostatic hyperplasia (BPH). The most common cause of lower urinary tract symptoms in older men is an enlarged prostate due to BPH [202]. LUTS may manifest as stress urinary incontinence (SUI), urge urinary incontinence (UUI), frequency/urgency, or voiding problems [202]. In older adults, BPH, LUTS and urinary incontinence can negatively impact the quality of life and increase the cost of care [202]. Evidence suggests that the association between urinary incontinence and frailty is bidirectional. UI incidence may be viewed as an early marker of the onset of frailty [202]. The benefits of pharmacological therapy in older adults with UI have been questioned due to unfavourable adverse effects [205]. A systematic review of three clinical trials involving frail older patients suggested that evidence did not support drug treatment for UUI in frail older adults [205]. Moreover, the International Continence Society has proposed a trial of behavioural and lifestyle interventions before initiating pharmacotherapy in frail older adults [202, 206]. In addition, it was stated that drug therapy might not be beneficial for those who do not attempt toileting when assisted, those who become agitated during toileting, and those with severe functional or cognitive impairments [202, 206].

78. In moderate frailty level or higher (CFS 6-9), all alpha-blockers (*e.g.* alfuzosin, doxazosin, terazosin, tamsulosin, and silodosin) used to relieve lower urinary tract

symptoms (LUTS) should be discontinued or avoided (high risk of orthostasis and hypotension).

79. In mildly frail patients (CFS 4,5) with LUTS, non-uroselective alpha-blockers (alfuzosin, doxazosin, and terazosin) should be avoided/discontinued.

80. In mildly frail patients (CFS 4,5) with LUTS, uroselective alpha-blockers (tamsulosin and silodosin) may be used with caution. If used, silodosin is preferable over tamsulosin.

For patients with moderate to severe BPH or those who prefer pharmacotherapy treatment, alpha-1 blockers may be considered [207]. The available alpha-blockers for LUTS include alfuzosin, doxazosin, terazosin, tamsulosin and silodosin. These medications increase the risk of vasodilatation, dizziness, asthenia, orthostatic blood pressure changes, syncope, falls, and arrhythmias [39, 208]. According to the AGS Beers criteria, nonselective peripheral alpha-1 blockers (*e.g.* doxazosin, prazosin, terazosin) should be avoided as antihypertensives in older patients (strong quality of evidence, strong recommendation) [39]. In addition, it was recommended that older adults with syncope likely caused by orthostatic hypotension should avoid nonselective peripheral alpha-1 blockers (high quality of evidence, weak recommendation) [39]. According to the FORTA classification system for PIMs, alfuzosin, doxazosin, and terazosin were labelled as Class D (D-on't), which refers to medications that should be avoided in older adults due to significant harms [208].

Silodosin and tamsulosin, on the other hand, are uroselective alpha -adrenergic antagonists. Both medications were FORTA-labelled as Class C (C-areful), which refers to drugs that should be avoided or omitted in the presence of adverse effects or multiple drugs [209]. Due to a lack of conclusive data regarding their efficacy and safety in older adults, they were placed in the C category of questionable efficacy or safety profiles [209]. Uroselective agents (*e.g.* tamsulosin and silodosin) demonstrated a lower risk of blood pressure changes and adverse vascular events [210]. Silodosin has a strong affinity for alpha (1A) receptors, which are more predominant in the male bladder than alpha (1B) receptors [210]. In a randomised, international clinical trial conducted in 11 European countries, silodosin was not inferior to tamsulosin in relieving both voiding and storage symptoms in patients with LUTS due to BPH [211]. Only silodosin demonstrated a significant effect on nocturia versus placebo [211]. Moreover, tamsulosin has shown a minor but significant change in blood pressure and heart rate, whereas no significant change was observed with silodosin compared with placebo [211]. However, there is a risk of hypotension, particularly with concurrent use of other antihypertensive medications [209].

81. Urinary antimuscarinic agents for LUTS should be avoided or discontinued in the following cohorts:

- a) moderate and severe frailty (CFS 6-9),
- b) if used for a long time at high dosage in cognitively intact patients, or
- c) if concurrently used (particularly oxybutynin) with other anticholinergic agents/ acetylcholinesterase inhibitors (AChEIs).

82. a) If urinary antimuscarinic medications are used, extended-release formulations have fewer side effects compared to immediate-release forms.

b) Fesoterodine is also a preferable alternative to other antimuscarinic agents due to lesser anticholinergic properties.

The efficacy and safety of urinary antimuscarinic medications may differ between older adults and their younger counterparts. Comorbidities, geriatric syndromes (*e.g.* dementia), limited life expectancy, and polypharmacy play a significant role in therapeutic decisions in older adults [206]. The available anticholinergic medications for UI and overactive bladder include oxybutynin, tolterodine, fesoterodine, solifenacin, darifenacin and trospium. Cognitive decline is the major concern regarding the use of antimuscarinic medications in frail older adults [206]. Anticholinergic drugs have been associated with an increased risk of cognitive impairment, the incidence of dementia, and a possible increase in mortality [206].

The International Consultation on Incontinence has issued recommendations for managing frail older adults with urinary incontinence. According to the fifth International Consultation on Incontinence report, there is evidence of the cognitive safety of urinary antimuscarinic agents when prescribed as single agents to cognitively intact older adults [212]. It also highlighted the increased association between the use of high dose (20 mg) prolonged-release oxybutynin tablet and the incidence of cognitive impairment, recommending the avoidance of oxybutynin at high doses, or even low doses, in patients at risk for cognitive decline [212]. Because this cognitive decline may not be apparent to patients and prescribers, other antimuscarinics were labelled with cautious use in older adults, and treatment should be initiated at the lowest effective and tolerable dose [212]. Gray *et al.* found in a prospective population-based cohort study that a higher 10-year cumulative anticholinergic medication use (*i.e.* oxybutynin 5 mg daily for more than three years) was associated with an increased risk of dementia incidence among patients without dementia at study entry [213].

Although the correlation may be weak, the sixth report cautioned against prescribing an additional anticholinergic agent in the presence of other anticholinergic agents [206]. A 2014 systematic review found a significant decline in cognitive ability with increasing anticholinergic load and a decline in physical function in anticholinergic users [214]. In addition, a 2-year longitudinal study concluded that anticholinergic medication use increased the cumulative risk of cognitive impairment and mortality [215]. Therefore, the fifth report recommended limiting the total duration of exposure to these medications, primarily when concurrently used with other anticholinergic medications [212]. This aligns with the evidence summary and the European Association of Urology (EAU) recommendations. EAU cautioned against long-term antimuscarinic treatment in older patients, particularly those at risk of, or with, cognitive dysfunction [216].

In addition to other anticholinergic medications, caution should be exercised when using antimuscarinic and acetylcholinesterase inhibitors concurrently [151, 217]. The cognitive and functional effects of concurrent use of acetylcholinesterase inhibitors and oxybutynin or tolterodine were evaluated in a prospective cohort study of residents of nursing homes (NHs) aged 65 or older [217]. The findings suggested that the concurrent use of AChEIs and bladder anticholinergics may result in a greater rate of functional decline than the use of AChEIs alone [217]. In addition, the New South Wales deprescribing guidelines considered urinary antimuscarinic medications as potentially inappropriate in patients taking multiple anticholinergic medications or those receiving or planning to receive treatment for dementia with acetylcholinesterase inhibitors [151].

Evidence suggests that once-daily, extended-release formulations of urinary antimuscarinic agents have lower rates of adverse events than immediate-release dosage forms but similar discontinuation rates [216]. Furthermore, transdermal formulations of oxybutynin demonstrated lower rates of dry mouth than oral formulations [216]. However, transdermal patches are associated with a high withdrawal rate due to skin reactions [216]. The NICE (2019) guideline did not recommend offering immediate-release oxybutynin to older women at increased risk for a sudden decline in physical or mental function [218]. In this update, the NICE committee replaced the term "frail older women" with "older women at increased risk of a sudden deterioration in physical or mental health" to refer to women with both cognitive and physical impairment [218]. In addition, the NICE committee recommended using transdermal treatment for women with overactive bladder who cannot tolerate oral medications [218].

The EURO FORTA classification system for PIMs has classified the majority of urinary antimuscarinics as Class C (C-areful) (*i.e.* with questionable efficacy/safety profiles in older adults) [208, 209]. Darifenacin, low-dose or extended-release oxybutynin, solifenacin, tolterodine, and trospium are included in "Class C." In addition, standard dose or immediate-release oxybutynin and propiverine were categorised as Class D (D-don't) drugs to avoid in older patients. Only fesoterodine was labelled as Class B (B-beneficial), which refers to medications with proven or obvious efficacy but a limited extent of effect or safety concerns in older people [208, 209]. In a randomised, double-blind, placebo-controlled study, fesoterodine significantly reduced episodes of urgency urinary incontinence in elderly individuals at risk (defined as those who are high rates of comorbidities, polypharmacy and older functional impairment) [219]. The adverse effects, including the risk of urinary retention, were comparable to those of younger populations [219]. In a pooled analysis of 10 randomised clinical trials, CNS adverse effects were infrequent and unrelated to fesoterodine dose [220]. Nonetheless, the likelihood of reporting treatment-emergent adverse events (TEAEs) increased significantly with the number of coexisting conditions or medications [220]. However, all urinary antimuscarinics, including fesoterodine, have strong anticholinergic properties, according to the recent AGS Beers criteria; however, they are not contraindicated for treating UI [39].

83. Due to recurrent/withdrawal symptoms, slower tapering of urinary antimuscarinics (*e.g.* 25% -50% dose reduction every 1-4 weeks) is preferable to abrupt discontinuation.

The abrupt discontinuation of anticholinergic medications used for urinary incontinence may be associated with withdrawal symptoms [50]. These symptoms include irritability, anxiety, insomnia, restlessness, headache, dizziness, dyskinesia, and severe symptoms (such as tachycardia and orthostatic hypotension) [50, 151]. Therefore, it may be prudent to taper urinary antimuscarinics slowly and cautiously in frail older adults [50]. The New South Wales deprescribing guideline recommends reducing the dose by 25% to 50% of the daily dose every one to four weeks, with slower tapering (*e.g.* by 12.5%) when reducing the final lowest dose [151]. Alternatively, if dosage forms are limited, alternate-day dosing may be considered [151].

84. Beta-3 adrenoceptor agonist (mirabegron) should be used to relieve neurologic overactive bladder symptoms only when there is a concern over high anticholinergic burden (risk of hypertension and urinary tract infections).

85. a) The use of urinary antimuscarinics to treat acetylcholinesterase inhibitors (AChEIs)-associated urinary incontinence is an inappropriate prescribing cascade.

b) alternatives include non-pharmacological support or mirabegron.

Mirabegron, a selective beta 3-adrenoceptor agonist, is used to relieve storage symptoms of overactive bladder [221]. The NICE committee recommended mirabegron only for patients with overactive bladder for whom antimuscarinic agents are ineffective, intolerable, or contraindicated [221]. Although mirabegron is associated with an anticholinergic adverse effect, dry mouth and constipation are relatively absent [206]. Moreover, there are concerns that mirabegron therapy may increase the risk of hypertension [206]. In a pooled analysis of studies enrolling patients aged 65 and older, hypertension, nasopharyngitis, and UTI were the three most prevalent TEAEs [222]. However, mirabegron was associated with a lower incidence of hypertension than tolterodine in a subgroup of older adults aged 75 or older [222]. According to the EUROFORA classification, mirabegron was classified as FORA C (*i.e.* a medication with questionable efficacy/safety profiles in older individuals) [208].

Mirabegron may be considered an alternative option to urinary antimuscarinic agents when a high anticholinergic burden is a concern. Patients having concurrent or planned treatment with acetylcholinesterase inhibitors for dementia are ideal examples [151]. In addition to the possibility of drug interaction, one of the most common prescribing cascades involving both medication classes may occur [223, 224]. Cholinesterase inhibitors inhibit the cholinesterase enzyme, resulting in a systemic increase in acetylcholine levels [223]. This activates muscarinic receptors in the detrusor muscle, creating forceful contractions and urging urinary incontinence. This may result in the prescription of urinary antimuscarinic medications to alleviate symptoms of urinary incontinence [223, 224]. This prescribing cascade may occur intentionally when the inciting drug-associated effect is recognised or unintentionally when antidementia drug-induced urine incontinence is interpreted as a new medical disease [223]. Given the possibility of drug-drug interactions and adverse effects of antimuscarinic medications, similar prescribing cascades should be considered inappropriate prescribing in frail patients. According to an Australian deprescribing guideline, alternatives to urinary antimuscarinics included non-pharmacological supports, changing the drug formulation, switching within the same drug class, or switching to an alternative such as mirabegron [151]. The International Consultation on Incontinence (2017) summary of evidence has highlighted the insufficient evidence regarding the efficacy, tolerability and safety of mirabegron in the frail older (Level 4 *i.e.* moderate) [202].

86. In all frail patients (CFS ≥ 4) with urinary incontinence, flavoxate or propantheline should be avoided/discontinued (uncertain effectiveness in reducing urinary leakage and anticholinergic side effects).
87. In all frail patients (CFS ≥ 4) with nocturia, desmopressin should be avoided (high risk of hyponatraemia and hypertension).

Desmopressin is associated with a high risk of hyponatremia; therefore, the AGS Beers criteria advise against its use for the treatment of nocturia or nocturnal polyuria in older adults since safer alternatives are available (moderate quality of evidence and strong recommendation) [39]. The NICE guideline also recommended avoiding desmopressin to reduce nocturia of urinary incontinence or overactive bladder in women over 65 years with cardiovascular disease or hypertension [218]. Concerning other urinary medications, the NICE committee recommended against using flavoxate, propantheline or imipramine to treat urinary incontinence or overactive bladder in women [218]. Moreover, according to the evidence summary report from the fourth international consultation on incontinence, propantheline, imipramine, and flavoxate may not be effective options [225].

88. In all frail institutionalized patients (CFS ≥ 4), the following routine use or overuse of urine analysis should be limited (may contribute to unnecessary/ inappropriate antibiotic prescribing):
- a) Urine culture or further microscopic urinalysis after a negative dipstick.
 - b) Urinalysis in response to new or change in cognitive function in non-catheterized patients without acute localized genitourinary symptoms or systemic signs and symptoms.
 - c) Urinary catheterization to obtain culture in stable patients with nonspecific symptoms.

Urinary tract infections are common in hospitalised older patients, but their diagnosis can be challenging [226]. The differential diagnosis of urinary tract infections from other conditions, such as asymptomatic bacteriuria (ASB), relies heavily on laboratory test results, the presence of symptoms, and the specificity of those symptoms [226]. However, atypical manifestations of symptoms of many conditions are common in frail older patients [226]. For instance, residential, long-term care or nursing home residents may present with non-specific signs such as confusion, function decline, poor oral intake and/or agitation [226]. A wide range of conditions besides UTI can present with similar systems. Clinicians may then attribute similar symptoms to a urinary tract infection and order additional laboratory tests (*e.g.* dipstick/urinalysis or urine culture).

Dipstick is a quick and inexpensive urinalysis method which requires requiring minimal experience. This may be the first option in places where urine culture is absent (*e.g.* emergency departments). However, dipstick tests demonstrated limited accuracy, with the potential for false negative or false positive results [226, 227]. A positive dipstick may result in unnecessary antibiotic prescriptions for patients with asymptomatic bacteriuria [226]. Therefore, a dipstick may not be a reliable method for diagnosing urinary tract infections [227].

In patients with a negative dipstick, evidence suggests that it is possible to safely avoid prescribing unnecessary antibiotics if additional testing, such as urine cultures, is omitted [226]. In addition to urine culture, microscopy urinalysis is frequently requested for faster results. In the absence of localised or systemic signs and symptoms, the microscopic urinalysis is not an accurate test due to the effect of centrifugation and intra-/inter-observer variations [228]. In addition, 50% of nursing home residents who are well may test positive for nitrite, and the proportion increases to 100% in catheterized patients [226]. Consequently, urinalysis might not be useful in this frail cohort. Urine culture (UC) is the diagnostic gold standard for UTIs when symptoms are present. Additionally, older adults may be catheterised to obtain urine samples [229]. However, the high possibility of positive results may expose older adults to risks associated with the procedure and unnecessary antibiotics in symptom-free patients [229].

Choosing Wisely Canada's practice change recommendations have highlighted that routine urine dipsticks may result in unnecessary antibiotic use for asymptomatic bacteriuria in long-term care facilities [230]. Although urine dipsticks may have some value in ruling out UTI in the presence of negative results, their poor accuracy in older adults is a major concern [230]. Choosing Wisely Canada also advises against attributing any change in health status (including behaviour) to a UTI until other potential causes (such as dehydration, constipation, skin breakdown, adverse drug reactions, and other sources of infection) have been ruled out [230]. In addition, they recommended performing a urine culture only when the minimum diagnostic criteria for a UTI accompany these health status changes [230].

89. In all hospitalised frail patients (CFS $\geq$ 4) with suspected urinary tract infections, supportive treatment (for 48 hours or until results of urine culture) is preferable to routine antibiotic prescribing in a) haemodynamically stable patients or b) febrile non-catheterized patients without upper urinary tract symptoms or other risks of sepsis.
90. In all frail patients (CFS $\geq$ 4) who are non-catheterized or intermittently catheterized, empiric antibiotic prescribing for asymptomatic bacteriuria in response to

functional/cognitive decline or delirium is potentially unnecessary (unless in high-risk patients such as perioperative patients, advanced diabetic patients, organ transplant patients, or those with progressive signs of infection).

91. In all frail patients (CFS ≥ 4) with chronic indwelling catheters, empiric antibiotic prescribing for suspected UTI is potentially unnecessary (unless the patient has one of the following: high/ > 24 hours fever, rigours/chilling, new delirium onset, haemodynamically unstable).

Some criteria have been developed to inform the initiation of antibiotic therapy for urinary tract infections in frail older adults. However, the majority poorly determined the role of nonspecific signs and symptoms in the decision to initiate antibiotic treatment in frail older adults [226]. In 2018, van Buul and colleagues specifically developed a decision tool for the empiric treatment of suspected UTI in frail patients with or without indwelling catheters [226]. The Delphi expert panel identified the UTI-specific symptoms and signs as dysuria, new urgency, new frequency, new incontinence, and visible urethral purulence [226]. In addition, the nonspecific symptoms and signs included new or worsening agitation/aggression, decreased food or fluid intake, new/worsening fatigue or weakness, nocturia, syncope, decreased urinary output, general lack of well-being, and change in mental status (no clinical suspicion of delirium) [226]. Moreover, the systemic signs and symptoms included clear-cut delirium, fever, hypotension, hypothermia, tachycardia, or rigours/shaking chills [226].

After the fourth Delphi round, participants agreed that nonspecific symptoms and signs should not be attributed to UTI and should not impact antibiotic prescribing decisions [226]. They additionally advised against prescribing antibiotic therapy based solely on nonspecific symptoms and signs, even if the urinalysis results are abnormal [226]. In the algorithm of suspected UTI without indwelling catheters, the experts agreed on the necessity of antibiotic prescribing in the following scenarios [226]:

- presence of a very bothersome UTI-specific symptom/sign plus nonspecific symptom/sign,
- presence of at least two UTI-specific symptoms/signs,
- presence of UTI-specific symptoms/signs plus new costovertebral angle pain/tenderness and/or new suprapubic pain,
- presence of new costovertebral angle pain/tenderness with systemic symptoms/signs plus nonspecific symptoms and signs.

There was consensus on the necessity of prescribing antibiotics in the abovementioned clinical situations unless urine analysis shows negative results for both nitrite and leukocyte esterase [226]. The Loeb criteria, McGeer criteria, and their modifications are the most used criteria by the clinical practice guideline to assess the quality of antibiotic prescribing in UTIs. Unlike the modified Loeb criteria and McGeer criteria, these suggested algorithms have weighted the presence of acute dysuria as similar to other UTI-related localized symptoms in non-catheterized patients [226]. The modified Loeb and McGeer criteria also considered fever among the minimum criteria for UTI diagnosis when combined with at least one specific UTI-related symptom in non-catheterised patients [230, 231]. However, the suggested algorithms of van Buul *et al.* considered fever a systematic symptom [226].

The experts also recommended prescribing empiric treatment for suspected UTI in frail older adults with an indwelling urinary catheter if no other infection source was identified and at least one of the following was present: clear-cut delirium (after ruling out urinary retention as a potential cause), fever 24 hours, or rigours/shaking chills [226]. In contrast to non-catheterized patients, these minimum criteria for UTI diagnosis and antibiotic prescription in frail older adults conform to the modified Loeb criteria [230]. However, the modified McGeer criteria considered some additional symptoms as minimum criteria for UTI in residents with an indwelling catheter [231]. These included new-onset suprapubic pain/costovertebral angle pain/tenderness, purulent discharge from around the catheter, or acute pain/swelling/tenderness of the testes, epididymis, or prostate [231]. According to Public Health England guidelines, UTI is unlikely to be considered in catheterized adults or those over 65 with acute dysuria or two or more signs/symptoms of UTI (including fever) [232]. Alternatively, Public Health England guidelines advised sending a urine culture (if possible) prior to prescribing antibiotics to older adults due to their increased resistance. In addition, screening for other causes was also recommended before treating a UTI in a patient with only fever and delirium/weakness [232].

Only symptomatic patients should be considered for empiric antibiotic therapy while awaiting urine culture results [227]. Choosing Wisely Canada has also suggested that antibiotic therapy should not be initiated unless there is a strong suspicion and until urine samples are collected (within 24 hours). Residents of long-term care facilities who are hemodynamically unstable are an exception [230]. Treating asymptomatic bacteriuria with antibiotics has been controversial for a long time. However, no clinical evidence showed that treating asymptomatic bacteriuria (ASB) is beneficial [233]. The Infectious Diseases Society of America (IDSA) recommended against screening for or treating ASB in functionally impaired older adults residing in the

community or in long-term care facilities [234]. The IDSA update also recommended further assessments rather than empiric antibiotic prescribing for bacteriuria without localised or systemic symptoms in patients with functional and/or cognitive impairment, delirium, or falls [234].

IDSA also advised against screening for or treating asymptomatic bacteriuria (ASB) in individuals with diabetes (strong recommendation, moderate-quality evidence), renal transplant recipients who had the surgery more than one month ago (strong recommendation, high-quality evidence), or nonrenal solid organ transplant (strong recommendation, moderate-quality evidence) [234]. The safety of delaying antibiotic treatment in older patients with a suspected UTI has been questioned. A recent cohort study has utilized electronic health records of older patients with community-acquired UTI in England [235]. The finding illustrated that delaying or withholding antibiotic therapy in older patients with a suspected UTI was not associated with increased bloodstream infection (BSI) [235]. However, there was an association between delaying or withholding antibiotic treatment and an increased mortality risk in the 60 days that followed, with limited evidence attributing this to urinary-source BSI [227, 235].

92. Nitrofurantoin should be used with caution in frail patients with:

- a) decreased renal function (eGFR of 30-59 ml/min),
- b) in patients with poor oral intake and/or dehydration, or
- c) if it is used for more than a week (risks of pulmonary side effects, hepatotoxicity, and neuropathy).

Nitrofurantoin is the antibiotic of choice for uncomplicated lower UTIs (such as cystitis) and UTIs without pyelonephritis [236]. If nitrofurantoin is unsuitable, trimethoprim or cephalosporins such as cefalexin are also considered first-line antibiotics [236]. The prevalence of trimethoprim resistance in *E. coli* UTIs in Ireland exceeds 30% [236]. In contrast, resistance rates to nitrofurantoin remain low in community *E. coli* UTIs, including those caused by ESBL-producing isolates [236]. This is consistent with Public Health England's reports. There were 37% trimethoprim-resistant *E. coli* and 4% nitrofurantoin-resistant *E. coli* in community urine samples [237]. 60% of *E. coli* in urine samples from long-term care facilities were resistant to trimethoprim, and 7% of *E. coli* were resistant to nitrofurantoin [237]. Therefore, empiric therapy with trimethoprim is no longer considered an effective treatment option for uncomplicated lower UTIs unless nitrofurantoin is ineffective.

Nitrofurantoin has an unfavourable risk/ benefit profile with high risks of pulmonary side effects, hepatotoxicity, and neuropathy [39, 112]. However, it is considered first-line therapy due to its lower resistance rate [236]. Patients with severe renal impairment (eGFR less than 30 mL/min) should avoid nitrofurantoin due to its low urinary tract concentration and increased risk of toxicity [236]. When benefits outweigh potential risks, it may be used with caution in patients with diminished renal function (eGFR 30 - 49 mL/min) [236]. However, renal function can deteriorate rapidly in frail older patients, particularly those who are dehydrated or with poor oral fluid intake. In such patients, nitrofurantoin should be administered with extreme caution. The AGS Beer criteria (2019) recommend avoiding nitrofurantoin in patients with eGFR less than 30 mL/min or for long-term suppression use [39]. The EU (7)-PIM list's expert panel has also recommended using nitrofurantoin for no longer than one week [112].

93. In all frail patients (CFS $\geq$ 4) with renal impairment or on ACEIs/ARBs, trimethoprim/sulfamethoxazole should be used with caution (increased risk of hyperkalaemia).

In a cohort study using UK electronic primary care records, trimethoprim was associated with higher risks of acute kidney injury and hyperkalaemia in older patients with UTIs than other antibiotics [238]. The absolute risks of acute kidney injury and hyperkalaemia were greater in populations with higher baseline risks (*e.g.* those taking renin-angiotensin system blockers and potassium-sparing diuretics) [238]. The 2019 AGS Beer criteria have recently added trimethoprim-sulfamethoxazole to the "Drugs to be Used with Caution" category due to the increased risk of hyperkalaemia in ACEI/ARB-treated patients and decreased creatinine clearance [39]. Additionally, trimethoprim has multiple drug interactions; concurrent use with certain drugs (*e.g.* phenytoin, warfarin) should be avoided in older patients [39]. The AGS Beers criteria also recommended avoiding trimethoprim-sulfamethoxazole in patients with creatinine clearance (CrCl) less than 15 mL/min and reducing the dose in patients with CrCl 15-29 mL/min [39]. Therefore, nitrofurantoin and trimethoprim may cause severe side effects in older patients, especially those who are frail, necessitating their use with caution.

94. a) In all frail patients (CFS $\geq$ 4) with lower urinary tract infection (UTI), empiric use of broad-spectrum antibiotics (*e.g.* fluoroquinolones, extended-spectrum cephalosporins, or combination of beta-lactam/ lactamase inhibitors) should be avoided (unnecessarily high risk of adverse effects and development of bacterial resistance).

b) Exceptions are when patients show severe systemic signs of infection or urosepsis or when it is guided by previous patients' cultures.

If pyelonephritis or urosepsis is suspected, antibiotics must be administered immediately [239]. Oral options include cefalexin, ciprofloxacin, trimethoprim (if urine culture demonstrates susceptibility), or a combination of beta-lactam/ lactamase inhibitors (if urine culture reveals susceptibility) [239]. Nitrofurantoin tissue concentrations are insufficient for treating systemic infections, such as pyelonephritis [239]. A parenteral antibiotic agent or combination is indicated if a patient is severely unwell or unable to take an oral antibiotic. Parenteral options include beta-lactam/ lactamase inhibitors, broad-spectrum cephalosporins, fluoroquinolones, or macrolides [239]. All catheter-associated urinary tract infections should also be treated as upper urinary tract infections [240]. However, broad-spectrum antibiotics such as fluoroquinolones and cephalosporins are associated with *Clostridium difficile* infections [240]. In a study evaluating the efficiency of β -lactams/ β -lactamase inhibitors for UTI treatment in older adults, ESBL-producing *Escherichia coli* resistant to β -lactams/ β -lactamase inhibitors were frequently reported [241]. Therefore, it may be reasonable to avoid the empiric use of such antibiotics in older adults with the lower urinary tract, where benefits are questionable, and to avoid adverse effects and increased antimicrobial resistance.

95. In patients living with severe frailty level or higher older (CFS 7-9), prophylactic use of antibiotics for recurrent UTIs should be avoided or discontinued (limited benefits after 3-6 months of use).

96. In patients with mild and moderate frailty (CFS 4-5), prophylactic use of antibiotics for recurrent UTI should be limited (unclear effects on quality of life and bacterial resistance development).

Long-term antibiotics may be prescribed to adults to prevent recurrent urinary tract infections. However, similar practices should be supported by robust evidence to justify the risk of developing antibiotic resistance in comparison to the presumed benefits [242]. One interesting modification to STOPPFrail v2 is removing the previous statement that advised against prescribing prophylactic antibiotic use to prevent recurrent urinary tract infections [14]. The authors defended their position by citing the continuous emergence of evidence regarding the role of long-term antibiotic therapy in preventing recurrent urinary tract infections [14]. However, the effects of prophylactic antibiotic use on life quality and the development of bacterial resistance are unclear [242].

Based on limited evidence, the NICE committee has reached a consensus on using antibiotic prophylaxis to prevent catheter-associated urinary tract infections (UTIs) in hospitalised patients with short-term catheters [243]. The committee did not recommend the routine use of antibiotic prophylaxis ahead of inserting short-term catheters for surgical, non-surgical, or urodynamic procedures while the catheters are in place or at catheter removal [243]. This conforms to the European Association of Urology recommendations. The EAU panel does not recommend routine antibiotic prophylaxis after catheter removal or in patients with intermittent self-catheterization [244]. Of note, continuous low-dose and post-coital antimicrobial prophylaxis demonstrated efficacy in reducing the incidence of recurrent UTIs [244]. Therefore, the EAU guideline panel suggested continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTIs when non-antimicrobial options have failed [244].

In a prespecified systematic review and meta-analysis, researchers aimed to address the uncertainty surrounding the efficacy and safety of prophylactic use of long-term antibiotics to prevent recurrent urinary tract infections in older adults [242]. However, the authors were unable to identify any studies involving men over the age of 65 [242]. Findings suggested that long-term use of antibiotics appeared to have decreased the risk of recurrence in postmenopausal women with recurrent UTIs [242]. Due to a paucity of evidence, the authors were unable to draw conclusions about other clinically relevant outcomes [242]. These clinically important outcomes included safety and benefits in older men or frail nursing home residents, the recommended duration of prophylaxis, the impact on antibiotic resistance development, and the recurrence rate after stopping prophylaxis [242].

Antibiotic prophylaxis should be prescribed for a fixed period of time. To date, there is no consistent evidence of benefits from using prophylactic antibiotics beyond 3-6 months [245]. In addition, it is advisable to review antibiotics after 3-6 months of use with the intention of stopping them [245]. Therefore, frail patients, particularly severely frail patients, may not have sufficient life expectancy to benefit from antibiotic prophylactic use for recurrent UTIs. For non-antibiotic agents, there is no consistent evidence to support or against using ascorbic acid, cranberry, cranberry with proanthocyanidin (PAC), d-mannose, lactobacillus, and methenamine hippurate for recurrent UTI to reduce recurrence rate in older adults [246].

97. In all hospitalised frail patients (CFS $\geq$ 4) with long-term catheters, antibiotic/antiseptic-impregnated catheters should be avoided (limited benefit at the expense of increasing costs, discomfort, and the development of bacteria resistance).

Indwelling urinary catheters are one of the most common causes of hospital-acquired urinary tract infections. Utilizing antiseptic-coated and antimicrobial-impregnated catheters is one way to prevent catheter-associated urinary tract infections (CAUTIs) [247]. The European Association of Urology guideline panel recommended against applying topical antiseptics or antimicrobials to the catheter, urethra, or meatus (strong rating) [244]. A systematic review of 26 trials (12,422 adult patients) found that silver alloy hydrogel-coated latex catheters (antiseptic-coated) were not associated with a statistically significant reduction in CAUTI compared to standard catheters and were costly [247]. However, nitrofurazone-impregnated catheters were associated with reduced risks of symptomatic CAUTI and bacteriuria, albeit borderline significant. Hence, this low magnitude of risk reduction may not be clinically meaningful [247]. Moreover, these catheters are more expensive and more likely to cause discomfort than standard catheters [247]. In more recent studies, nitrofurazone-infused catheters following renal transplantation and silver alloy-coated indwelling catheters in patients with spinal cord injuries showed no benefit in reducing UTI risk [248, 249].

6. Pressure ulcer

98. In all frail patients (CFS ≥ 4) with pressure injuries of grade two or higher, the routine use of topical antibiotics should be avoided (insufficient evidence and risk of microbial resistance).
99. The routine use of systemic antibiotics should be avoided for the management of pressure injuries when frail patients (CFS ≥ 4) do not have:
- a) signs of systemic infection,
 - b) high risk of severe sepsis, or
 - c) evidence of spreading infection (risks outweigh benefits).

Older adults are at an increased risk of developing pressure injuries (or ulcers), with the highest risk among frail patients [250]. This is due to diminished physiological reserves, malnutrition, inadequate hydration, skin changes associated with ageing, decreased mobility, and a high prevalence of incontinence [250]. Pressure ulcers are prevalent in acute care settings, hospice settings and geriatric care settings in Ireland, with a mean prevalence of 16% and incidence of 11% [251]. In a cross-sectional study, pressure ulcers were prevalent in 9% of 1100 older adults from twelve long-term care settings in Ireland [252].

In pressure injuries with delayed healing, the use of topical antiseptics in tissue-appropriate strengths may be considered to reduce the microbial burden or eradicate suspected or confirmed biofilm [253]. There is insufficient evidence to support the use of topical antimicrobials for pressure ulcers, and they may have limited utility and should be used only when the benefits outweigh the risks of adverse effects and microbial resistance [253, 254]. Metronidazole may be considered to control odour caused by anaerobic bacterial or fungal infections [253, 254]. A systematic review of randomised controlled trials has investigated the efficacy of topical treatments for adults with pressure ulcers of stage II or higher. It concluded that the relative effectiveness of topical and systemic antimicrobial therapies for pressure ulcers was unclear. The findings, however, favoured other comparators without antimicrobial properties [255]. In addition, the findings emphasised the need for high-quality evidence and research to determine the effects of antimicrobial treatments on pressure ulcer healing [255].

The National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance (NPUAP/EPUAP/PPPIA) recommended administering systemic antibiotics to patients with pressure injuries and clinical evidence of systemic infection [253]. However, this recommendation was not supported by a body of evidence and was listed as a “Good Practice Statement (GPS)” for clinical practice to be considered by the Guideline Governance Group [253]. Notably, frail patients may be more susceptible to severe sepsis and infection spread. Clinical signs of systemic infections include positive blood culture, cellulitis, fasciitis, osteomyelitis, systemic inflammatory response syndrome, or sepsis [254]. If signs and symptoms such as delayed healing, induration, lymphangitis, crepitus, fluctuation or discolouration of the surrounding skin, confusion/delirium and anorexia are present, a spreading infection may be suspected [253].

100. In all frail patients (CFS $\geq$ 4) with pressure injuries, the use of anabolic steroids should be avoided (inconsistent evidence, an increased risk of adverse effects such as elevation of liver enzymes).

Anabolic steroids are medications that may be used to increase muscle mass and aid in healing pressure ulcers [256]. Besides oral and injection dosage forms, anabolic steroids are also available as topical creams or gels. They may be used as alternatives or adjuvants to conventional therapy for pressure ulcers [256]. However, no high-quality evidence supports using anabolic steroids to treat pressure ulcers [256]. In addition, these medications may increase the risk of liver damage, heart attack, and stroke [256]. Another study has investigated

their efficacy in patients with spinal cord injury and stage III or IV target pressure ulcers [257]. The results indicated that oxandrolone did not improve healing or the proportion of target pressure ulcers while increasing liver enzyme levels compared to placebo [257].

101. a) In all frail patients (CFS $\geq$ 4) particularly those receiving palliative care, undertreatment of pain from pressure injuries should be avoided.
b) Topical opioids, topical anaesthetics or analgesic-impregnated dressings may be implemented to control pain before employing systemic therapy.

Pressure ulcers are painful and affect every aspect of a patient's life [258]. Patients may experience pain from PU with or without wound manipulation or a change in the patient's position [258]. Therefore, conducting a comprehensive pain assessment and administering topical and systemic medications is necessary to avoid undertreatment of pain. Non-pharmacological strategies may be considered first or as adjuvant therapy to the pain associated with pressure ulcers [254]. The NPUAP/EPUAP/PPPIA guidelines recommended using topical opioids such as diamorphine gel to control acute pressure injury pain unless it is contraindicated [259]. Analgesia, such as benzydamine 3%, may also be considered on a regular basis to treat the pain of pressure injuries [254]. Other topical options include anaesthetics like lidocaine, prilocaine cream, and ibuprofen-impregnated dressing [260].

102. In all frail patients (CFS $\geq$ 4) with faecal/urinary incontinence, preventive barrier topical products/preparations should be implemented to prevent incontinence-associated dermatitis and skin breakdown.

Urinary and faecal incontinences are highly prevalent in older adults [261]. With ageing, the skin becomes more prone to damage caused by increased moisture [261]. Consequently, incontinence increases the risk of incontinence-associated dermatitis (IAD) in older adults [261]. Incontinence and IAD are risk factors for developing pressure ulcers [262]. In such instances, barrier creams and absorbency incontinence products may protect the skin of older adults at high risk for incontinence-related pressure ulcers. However, the evidence is insufficient to recommend a primary barrier product for the older population [263]. The results of a randomised, controlled study indicated that barrier cream could protect skin from urinary incontinence by increasing stratum corneum hydration, decreasing cutaneous pH, and decreasing the incidence of erythema [261]. In addition, a multi-site, open-label, quasi-experimental study highlighted the significant cost savings of a skin care regimen that included a cleanser and a moisture barrier for preventing incontinence-related skin breakdown [264].

7. Perioperative care

103. In all frail patients ($\text{CFS} \geq 4$), anaesthetic doses greater than 50% of adult doses should be avoided (frail patients are more sensitive to anaesthesia).

The functions of organs directly affecting or affected by anaesthetic and analgesia medications generally decline with age [265]. Notably, the central nervous, cardiovascular, and pulmonary systems may have their functions diminished, influencing the responses of older adults to perioperative medications [265]. This increases the risk of induced anaesthesia/analgesia-induced postoperative delirium, volume overload, orthostatic and intraoperative hypotension, and blood loss in older adults [265]. Additionally, reduced renal functions may affect the excretion of perioperative medications and increase the risk of drug-drug interactions in the older population [265]. These changes in the pharmacokinetics and pharmacodynamics of medications render older adults more sensitive to the effects of anaesthetics [265, 266]. Therefore, it may be reasonable to reduce the dose of anaesthetic agents by 30%-50% in patients aged 70 years or older [265, 266].

This is consistent with the Perioperative Management of Elderly Patients (PriME) project's integrated care recommendations for geriatric surgical patients [267]. Dose adjustments of anaesthesia are recommended to avoid overtreatment, inadequate depth of anaesthesia, or adverse hemodynamic effects [267]. It is recommended to reduce the dose of propofol by 20% to 50% [267]. Moreover, EEG-based monitoring is required to avoid excessive anaesthesia and anaesthesia-induced postoperative delirium [267]. For halogenated anaesthetics, the minimal alveolar concentration should be calculated based on age and dosage being modulated using an anaesthesia depth monitoring system [267].

104. In all frail patients ($\text{CFS} \geq 4$), inhaled anaesthetic agents should be used with caution even with adequate intraoperative monitoring and interventions (high risk of overdosage and impairment of cerebral autoregulation).
105. If inhaled anaesthetic agents are used for anaesthesia maintenance, desflurane causes less postoperative fatigue and more rapid recovery than other inhaled agents
106. a) In all frail patients ($\text{CFS} \geq 4$), sedation with benzodiazepines (midazolam) should be avoided (high risk of delirium and cognitive decline).
- b) Non-benzodiazepine agents (*e.g.* propofol, etomidate, dexmedetomidine) may be preferred over midazolam.

107. In all frail patients (CFS ≥ 4) with compromised intravascular functions, coronary artery disease, or poor ventricular function, etomidate is preferred over other induction agents.

Recently, a multidisciplinary Chinese team published a consensus on perioperative brain health in older patients [141]. This guideline covers the perioperative management of older patients with pre-existing comorbidities (such as Alzheimer's disease, Parkinson's disease, obstructive sleep apnoea, anxiety, and depression) [141]. Moreover, it aims to improve and prevent post-operative outcomes such as cognitive decline and delirium [141]. According to the guideline, regional anaesthesia is the preferred anaesthesia technique in most pre-existing conditions unless the procedure requires general anaesthesia or the patient has severe motor deficits [141]. Moreover, propofol-based general anaesthesia is recommended over inhalation anaesthesia for improving early postoperative cognitive recovery in older patients undergoing major surgical procedures [141].

Cerebral autoregulation is a protective buffering mechanism that protects the brain from hypoperfusion and hyperperfusion [268]. Impairment of this key defence mechanism places patients at a high risk of intraoperative cerebral malperfusion, which may subsequently result in postoperative cognitive decline [268]. Several studies suggested that propofol and remifentanyl was associated with preserving cerebral autoregulation [264]. In contrast, inhaled anaesthetics may compromise intraoperative cerebral autoregulation [268]. Isoflurane and desflurane can impair cerebral autoregulation of the brain in a dose-dependent manner [269]. Sevoflurane provides the best preservation of cerebral autoregulation compared to other inhaled agents; however, it may impair autoregulation in older patients [268, 269]. Furthermore, a loading dose of dexmedetomidine may decrease cerebral blood flow (CBF) via vasoconstrictor activity [268].

Laboratory and animal data suggest that volatile anaesthetic agents can induce pathophysiological changes in the brain that may lead to Alzheimer's [270]. These alterations include amyloid-beta (A) peptide aggregation (least with desflurane), accumulation of tau protein, and neuronal apoptosis [270]. However, the causality relationship was not confirmed in humans [270]. In a less-powered study of older adults undergoing hip surgery, there was no significant difference in the incidence of delirium between desflurane and sevoflurane on postoperative days 1-3 [271]. However, patients in the desflurane group exhibited shorter hospitalisation due to a lower incidence of delirium on postoperative days 3 and 5 [271].

Two systematic reviews concluded that desflurane was associated with a faster recovery from anaesthesia in older adults than sevoflurane [272, 273]. In a review of five trials involving 300 older adults, desflurane was associated with significantly shorter times for command compliance, extubation, orientation, and recovery room discharge [272]. However, neither the time required to open the eyes nor the incidence of post-operative cognitive dysfunction (POCD) differed significantly [272]. The more recent review (six studies, 336 patients) reported significantly faster time to open eyes, time to extubation, and time to orientation, as well as significantly lower incidence of vomiting and agitation in the desflurane group [273]. In addition, there were no significant differences between the groups regarding the time of discharge from the recovery room or the incidence of hypotension and hypertension [273].

Midazolam has an anterograde amnesia effect that eliminates patients' bad memories in anaesthesia [141]. In addition, repeated doses or high doses are associated with retrograde amnesia and memory dysfunction [141]. There is consistent evidence that avoiding benzodiazepines and anticholinergics prior to surgery reduces the incidence of postoperative delirium [141]. Therefore, anticholinergics and benzodiazepines should be avoided in patients with preoperative cognitive impairment [141]. In addition, sedation with benzodiazepines such as midazolam should be avoided in mechanically ventilated patients, and non-benzodiazepine agents (*e.g.* propofol, dexmedetomidine) should be utilised instead [141, 270]. Etomidate has the advantage of having minimal hemodynamic and cardiovascular effects in older adults [141]. Therefore, it may be considered for the induction of anaesthesia in older adults with compromised cardiovascular functions [266]. However, etomidate is associated with potentially adverse effects on memory and adrenocortical functions [141]. These negative effects may discourage the use of etomidate for routine anaesthesia in older adults [141].

108. a) When neuromuscular blocking agents are likely to be administered, long-acting agents (such as vecuronium and rocuronium) should be used with caution (risk of prolonged action in frail patients).
b) Short-acting agents such as cisatracurium and atracurium are preferable alternatives, as their excretion (*i.e.* via Hofmann elimination and ester hydrolysis) is independent on renal or hepatic functions.
109. When neuromuscular blocking agents are likely to be administered, caution should be exerted on their concurrent use with perioperative cholinesterase inhibitors (ChEIs) (ChEIs may prolong the action of depolarizing neuromuscular blocking agents and reverse the action of non-depolarizing agents).

Neuromuscular blocking agents are commonly used in patients undergoing surgeries with general anaesthesia, or these require intubations [274]. There are two types of neuromuscular blocking agents: depolarizing and non-depolarizing agents [274]. The depolarizing agents, such as succinylcholine, bind to all acetylcholine receptors and act as agonists. However, non-depolarizing agents such as atracurium, cisatracurium, rocuronium, and vecuronium act as competitive antagonists [274]. Cholinesterase inhibitors, commonly prescribed for dementia, inhibit acetylcholine degradation by inhibiting acetylcholinesterase [141]. This causes an increase in acetylcholine concentrations at the neuromuscular junction, prolonging the action of depolarizing agents or being antagonised by non-depolarizing agents that act as acetylcholine receptor antagonists [141]. Cholinesterase inhibitors can reverse or reduce the neuromuscular blocking effect of non-depolarizing agents, thereby increasing the dose required to achieve satisfactory paralysis [270]. From a neuropsychiatric perspective, perioperative discontinuation of acetylcholinesterase inhibitors may worsen cognitive function [270].

Nondepolarizing neuromuscular blockers can be categorised based on their chemical structure, duration of action, and elimination routes. Short-acting agents include succinylcholine and mivacurium while intermediate-acting agents include vecuronium, rocuronium, and atracurium [270]. However, the action of mivacurium may be prolonged in older adults due to age-related changes in the activity of plasma acetylcholinesterase. Moreover, the excretion of vecuronium and rocuronium relies on end-organ elimination (*i.e.* faecal and urinary excretion) [270]. Consequently, they may have a longer duration of action in the older population, necessitating dose adjustments [270]. In contrast, atracurium and cisatracurium are primarily eliminated through spontaneous Hoffman degradation, which is independent of end-organ excretion [270]. In addition, their recovery time in older adults is also comparable to that in younger counterparts. Therefore, atracurium and cisatracurium may be preferred in older adults because dose adjustments may not be necessary [270].

110. In all frail patients (CFS ≥ 4), phenylephrine should be used with extreme caution for the management of intraoperative hypotension during general anaesthesia (high risk of decreased heart rate and bradycardia, Norepinephrine may be used in preference).

Anaesthesia agents are associated with hypotension; therefore, adequate tissue perfusion should be maintained during anaesthesia [275]. Moreover, persistent periods of hemodynamic instability are common in older adults and may result in undesirable cardiac effects [266].

Ephedrine, phenylephrine, norepinephrine, and epinephrine are commonly administered parenterally to treat perioperative hypotension [266, 275]. Ephedrine is considered the first-choice treatment for intraoperative hypotension during general anaesthesia [266, 275]. It is also effective for the management of hypotension related to spinal anaesthesia [266, 275]. Ephedrine can maintain cardiac output by increasing heart rate, whereas phenylephrine acts as a direct alpha-adrenergic agonist to decrease heart rate [266, 275]. Therefore, ephedrine is preferable to phenylephrine when treating hypotension in patients undergoing surgeries under general or spinal anaesthesia [266, 275]. Norepinephrine is a direct alpha-1 adrenergic agonist with a short duration of action [266, 275]. Thus, a continuous infusion of norepinephrine may be considered after failure of first-line medications (such as ephedrine and phenylephrine). Epinephrine, an alpha- and beta-adrenergic agonist, serves as the drug of choice for treating anaphylaxis during anaesthesia [266, 275].

111. In all frail patients (CFS ≥ 4), the routine use of perioperative opioids should be limited to absolutely necessary occasions (*e.g.* during anaesthesia induction and maintenance).

Evidence supports the association between opioid medications and increased delirium risk in medical and surgical patients [276]. Opioids may also exacerbate muscle rigidity in Parkinsonian dementia patients. Therefore, those at risk for delirium should use perioperative opioids with caution. Nonetheless, opioids are frequently combined with anaesthetic agents before surgery to prevent patients' stress response to intubation and surgical stimulation [266]. Additionally, undertreatment of patients with severe pain can itself induce delirium. A short-acting opioid such as remifentanyl, unlike other opioids, does not exhibit end-organ excretion, making it suitable for all critically ill adults. However, increased brain sensitivity and decreased clearance may necessitate a dose reduction of 50% in older patients [266]. In a randomised, controlled study of older patients undergoing major abdominal surgery, intraoperative remifentanyl did not reduce the incidence of postoperative cognitive dysfunction compared to fentanyl [277].

112. Opioid-sparing adjuvant/alternative options should be employed as alternatives to opioids when possible (*e.g.* dexmedetomidine in the maintenance of spontaneous ventilation).

The newer alpha-2-agonist (*i.e.* dexmedetomidine) demonstrated benefits in reducing the incidence of postoperative delirium and postoperative cognitive dysfunction [278, 279]. Dexmedetomidine appears to have an anaesthetic-sparing effect compared to propofol, as it

provides sedation and anxiolysis without respiratory depression [278, 279]. Dexmedetomidine is, therefore, the drug of choice for patients at high risk for respiratory complications (*e.g.* obese patients or those with a history of sleep apnoea) [278, 279]. In addition, clinical studies indicated that dexmedetomidine exhibited a pro-analgesic effect and a morphine-sparing effect in a variety of surgical procedures [278]. A recent retrospective study found that dexmedetomidine-based opioid-free anaesthesia was feasible in patients undergoing cardiac surgery, with reduced postoperative morphine consumption and improved postoperative outcomes [280]. Dexmedetomidine can therefore be used to maintain spontaneous ventilation in very older adults [281]. However, it is unsuitable for busy office-based practice due to the residual sedation upon stopping [282]. Moreover, additional caution should be exercised regarding dexmedetomidine use in older adults as they are more prone to hypotension risk from dexmedetomidine [282].

113. In all frail patients (CFS ≥ 4), clonidine use should be avoided as an adjuvant to local spinal anaesthesia (significant risk of hypotension, fainting, and sedation).

Clonidine is another alpha-2 adrenergic agonist that can be used as adjuvant therapy to local anaesthesia [283]. Unlike intrathecal opioids, clonidine is not associated with pruritus or respiratory depression [283]. Oral clonidine demonstrated a short time to the onset of local anaesthesia's sensory block and a prolonged duration of sensory and motor block [284]. However, oral clonidine was associated with an increased risk of hypotension and bradycardia [284]. In a study evaluating the efficacy and safety of intrathecal clonidine as an adjuvant to bupivacaine, clonidine increased the duration of sensory and motor block and increased the duration of analgesia [283]. Additionally, patients who received bupivacaine with a placebo (the control group) exhibited greater hemodynamic stability than those who received clonidine [283]. Most studies illustrated that the hemodynamic instability from intrathecal clonidine was dose-dependent [283].

114. In all frail patients (CFS ≥ 4), traditional postoperative analgesia regimens that are solely based on opioids or NSAIDs with or without steroids should be avoided (increased risk of pain undertreatment or adverse effects from individual medications).

115. Alternatives to traditional postoperative analgesia regimens include multimodal regimens, consisting of a combination of non-pharmacological, paracetamol, low dose (25%-50%) opioids and local/ regional anaesthesia techniques (if patients' condition and procedure permit).

116. In all frail patients (CFS $\geq$ 4), perioperative pethidine should be avoided for the management of perioperative pain (high risk of delirium).
117. In all frail patients (CFS $\geq$ 4), tramadol should be used with extreme caution for the management of perioperative pain (risk of the syndrome of inappropriate antidiuretic hormone secretion and hyponatremia)
118. In all frail patients (CFS $\geq$ 4), indometacin should be avoided for the management of perioperative pain (high risk of acute kidney injury, GI side effects, confusion, and delirium).
119. In all frail patients (CFS $\geq$ 4), ketorolac should be avoided for the management of perioperative pain (high risk of acute kidney injury and GI side effects).
120. In all frail patients (CFS $\geq$ 4), other non-steroidal anti-inflammatory drugs (NSAIDs) should be used with extreme caution for the management of perioperative pain (risk of kidney injury and GI side effects).

Inadequate or underuse of perioperative analgesics is associated with an increased risk of delirium, cardiopulmonary complications, and immobility [285]. Opioids are commonly used as perioperative analgesic agents. However, they may be associated with the incidence of postoperative delirium, particularly when used at high doses in older patients at high risk. A systematic review revealed that using meperidine (pethidine) was consistently associated with an increased risk of delirium in surgically older patients [286]. Additionally, findings did not reveal significant differences in delirium or POCD among users of other opioids like morphine, fentanyl, or hydromorphone [286]. Therefore, meperidine (pethidine) should be avoided in older surgical adults, especially those with pre-existing cognitive impairment [39, 141]. Additionally, meperidine and tramadol can cause serotonin syndrome when combined with other serotonergic medications such as monoamine oxidase inhibitors, serotonin reuptake inhibitors, tricyclic antidepressants, linezolid, and fluconazole [141]. Moreover, tramadol has been added to the list of “Drugs To Be Used With Caution” in the 2019 AGS Beers criteria due to the risk of hyponatremia or syndrome of inappropriate antidiuretic hormone secretion (evidence of moderate quality - strong recommendation) [39].

Non-steroidal anti-inflammatory drugs place older adults and vulnerable patients at an increased risk of gastrointestinal bleeding, elevation in blood pressure, and kidney injury [112]. Among all NSAIDs, indometacin has the most deleterious adverse effects and is more likely to cause adverse CNS effects than other NSAIDs [39]. The recent AGS Beers criteria recommend avoiding both indometacin and ketorolac (including parenteral forms) in older adults (evidence

of moderate quality, strong recommendation) [39]. Furthermore, caution should be exercised on the perioperative use of other NSAIDs if paracetamol fails, with the lowest effective dose for the shortest duration and concurrent gastric protection [285].

Multimodal analgesia is recommended for older adults undergoing surgeries, particularly those with impaired cognitive functions [141]. Multimodal analgesia combines various medications and medication classes such as regional anaesthesia (*e.g.* intraspinal block, peripheral nerve block, or local infiltration), opioids, paracetamol, nonsteroidal anti-inflammatory drugs, and/or dexmedetomidine [141]. Paracetamol is safe and may be considered a first-choice therapy [141]. An opioid-sparing multimodal approach may include systemic preoperative, intraoperative, and/or postoperative paracetamol with the addition of regional anaesthetic techniques such as neuraxial or peripheral nerve blockade if operations allow [266]. Multimodal analgesia may include non-pharmacological options such as postural support, pressure care, and patient warming [141]. There is consistent evidence that multimodal analgesia can reduce opioid consumption, improve pain control, and decrease the incidence of postoperative delirium [141].

121. In all frail patients (CFS ≥ 4) prepared for surgery, all over-the-counter medications and herbal and supplements products should be discontinued (risk of adverse effects from drug-drug interactions).
122. In all frail patients (CFS ≥ 4) in the perioperative setting, the following medications should be avoided/ discontinued (significant anaesthesia-drug interactions with potential for significant hypotension or arrhythmia):
 - a) ACEI/ARBs during the induction of anaesthesia.
 - b) Preoperative use of amitriptyline, clozapine, olanzapine or risperidone in the setting of general anaesthesia.
123. In all frail patients (CFS ≥ 4) in the perioperative setting, any two-agent combination of ACEI/ARBs, NSAIDs or vancomycin/aminoglycosides should be used with extreme caution (may precipitate or worsen renal impairment).
124. In all frail patients (CFS ≥ 4) in the perioperative setting, the triple combination of ACEI/ARBs, NSAIDs and diuretics should always be avoided (may precipitate or worsen renal impairment).

Polypharmacy is prevalent in older adults, which may increase the odds of adverse effects from interactions with anaesthetic medications [270]. For instance, medications used during anaesthesia may interact with medications used to treat dementia or BPSD [270]. Cholinesterase inhibitors may potentiate the actions of the depolarising neuromuscular blockers and interfere

with the action of the non-depolarizing agents. Moreover, benzodiazepines and antipsychotic medications may potentiate the neuro- and cardio-depressant effects of anaesthetic medications [270]. Polypharmacy can also interact with the actions of other chronic medications [270]. Ginkgo biloba, a dietary supplement that is available over-the-counter in many jurisdictions, may be taken by persons with cognitive impairment or dementia to promote cognitive functions [270]. It may promote bleeding in older adults receiving blood thinning medications [270]. Therefore, it is recommended to extend the medication history to include non-prescription/over-the-counter medications and herbal products [267]. An accurate and detailed medication history enables clinicians to consider appropriate perioperative adjustments to avoid potential adverse interactions [267].

Fluctuation in blood pressure is prevalent in older adults undergoing non-cardiac surgery [287]. Intraoperative hypotension is also a common side effect of general anaesthesia, which may consequently contribute to inadequate organ perfusion. In a retrospective study, the intraoperative mean arterial pressure (MAP) of less than 65 mm Hg and the use of general anaesthesia were potential predictors of increased mortality in older surgical adults [287]. However, there is no sufficient evidence to support using one blood pressure measure (*e.g.* SBP, DBP, MAP, pulse pressure) over another to predict postoperative outcomes[287]. There are concerns that angiotensin-converting enzyme inhibitors/angiotensin receptor blockers may be associated with intraoperative haemodynamic instability [288]. The Perioperative Quality Initiative-3 Workgroup has recommended withholding ACEIs/ARBs 24 hours before the surgery and restarting them after the operation as soon as earlier (within 48 hours after the operation where appropriate) [288]. In a consensus-based list of high-risk perioperative medications, it is recommended to use ACEIs/ARBs with caution during the perioperative period in older adults undergoing non-cardiac surgeries [289]. The expert panel recommended monitoring blood pressure and levels of electrolytes due to the potential for hypotension during induction of anaesthesia [289].

Levodopa may increase the risk of fluctuations in intraoperative blood pressure and arrhythmia in older adults undergoing surgery under halothane anaesthesia. The Chinese list of high-risk perioperative medications suggested stopping levodopa 12-48 hours before the operation [289]. Halothane may increase the sensitivity of the heart to catecholamines, and hence it should be avoided. Although newer inhalation anaesthesia agents are associated with less arrhythmogenic effects, there are still concerns over the related hypotension risk [290]. Perioperative psychotropic medications are associated with an increased risk of postural hypotension and

bradycardia in older adults undergoing operations under general anaesthesia [289]. These include amitriptyline, first-generation antipsychotics, clozapine, risperidone, and olanzapine. Caution should be exercised on using them after the surgery, with close monitoring of blood pressure during the operation [289]. Moreover, tricyclic antidepressants may place older surgical adults at an increased risk of arrhythmia when combined with some volatile anaesthetics or sympathomimetics such as medication for intraoperative hypotension (*e.g.* ephedrine or phenylephrine) [289].

ACE inhibitors, ARBs, diuretics, NSAIDs, aminoglycoside antibiotics and vancomycin have the potential to impair renal functions [289]. Older adults are often more susceptible to their nephrotoxic medications as they generally have a pre-existing degree of renal impairment, especially frail older people [291]. Thus, clinicians should be aware of the potential for renal impairment when these agents are used singly or in combination and should monitor renal functions carefully during the perioperative period. ACE inhibitors or ARBs with or without diuretics are associated with an increased risk of acute kidney injury (AKI) [291]. The addition of NSAIDs can significantly increase the risk of AKI [291]. The “triple whammy” is the term that refers to the concurrent use of ACEIs/ARBs, diuretics and NSAIDs [291]. The risk of acute kidney injury is highest when all three medication classes are concurrently prescribed. Therefore, it is reasonable to avoid this “triple whammy” in older adults undergoing surgery [291, 292].

125. In all frail patients (CFS $\geq$ 4), corticosteroids or scopolamine should be avoided for the prophylaxis of postoperative nausea and vomiting (PONV) (a high-risk postoperative delirium and cognitive decline).
126. In all frail patients (CFS $\geq$ 4), metoclopramide should be avoided for the treatment of PONV (high risk of extrapyramidal side effects).
127. In all frail patients (CFS $\geq$ 4), promethazine, prochlorperazine, and cyclizine should be avoided for the treatment of PONV (may precipitate or worsen delirium).
128. In all frail patients (CFS $\geq$ 4), ondansetron should be used with caution for prevention/treatment of PONV, with single IV doses not exceeding 8 mg (potential for QT prolongation and serotonin syndrome particularly with other serotonergic medications).

Postoperative nausea and vomiting (PONV) are commonly encountered during the postoperative period [293]. PONV may result in dissatisfaction, delayed discharge, and higher treatment costs [293]. Several antiemetic medications are available and have been used

successfully for years to prevent and treat PONV; however, safety concerns may restrict their use in older adults [293]. Perioperative glucocorticoids such as dexamethasone have comparable efficacy to 5-HT₃ receptor antagonists such as ondansetron [294]. Moreover, dexamethasone has an additional advantage over ondansetron due to its analgesic-sparing effect [294]. However, the AGS Beers criteria 2019 recommended avoiding oral and parenteral corticosteroids in older patients with or at high risk of delirium due to the possibility of precipitating or exacerbating delirium (moderate quality evidence-strong recommendation) [39]. These recommendations excluded inhaled or topical forms and systemic use in episodes of acute exacerbation of chronic obstructive pulmonary disease [39].

Metoclopramide, an antiemetic agent, is associated with extrapyramidal side effects [39]. The AGS Beers criteria have recommended avoiding metoclopramide in older adults and Parkinson's disease patients unless it is prescribed for gastroparesis for less than 12 weeks (moderate quality evidence-strong recommendation) [39]. Other antiemetics such as prochlorperazine, promethazine, and cyclizine have strong anticholinergic properties (*e.g.* confusion, sedation) and may worsen Parkinson's disease in older adults [39, 112]. These anticholinergic antiemetics may also increase the risk of delirium and potentiate the sedative effects of general anaesthesia [289]. Prochlorperazine may also increase the risk of QTc prolongation in older patients [112]. Moreover, the Chinese list of high-risk perioperative medications suggested using scopolamine with caution during the perioperative period due to the potential for increasing the risk of delirium and cognitive impairment [289].

Ondansetron is associated with a dose-dependent prolongation of the QT interval, with the risk increasing with a faster infusion rate and higher doses [295]. This may lead to the development of torsade de pointes (TdP), a life-threatening heart arrhythmia [295]. Therefore, caution should be exercised on using ondansetron in patients at high risk of QT interval prolongation and cardiac arrhythmias. Those include patients with electrolyte imbalance, ischaemic heart disease, congestive heart failure, bradycardia, ventricular hypertrophy, older age, or concurrent medications that lower heart rate or prolong QT interval [293, 296]. The manufacturer, in consultation with Health Canada and the Irish Medicines Board (now the Health Products Regulatory Authority), has advised that initial and subsequent doses in patients aged ≥ 75 years should not exceed 8 mg [295]. In addition, IV doses should be diluted in 50-100 millilitres of a compatible solution and should not be infused over less than 15 minutes for older patients aged 65 years or older [295, 296].

8. Musculoskeletal system

129. In severely frail patients (CFS 7) with osteoporosis and a life expectancy of less than 2 years, bisphosphonates particularly alendronate and zoledronate may be discontinued (bisphosphonates can demonstrate tail-effects (*i.e.* continued/extended benefits) for several years after discontinuation).
130. In very severely to terminally ill frail patients (CFS 8-9) with osteoporosis, bone anti-resorptive or anabolic medications such as bisphosphonates, denosumab, strontium ranelate, raloxifene and teriparatide are potentially unnecessary (unlikely to benefit patients with a limited life expectancy of less than 6 months).

The pharmacological management of osteoporosis includes sequential or combination therapy of bone-forming and antiresorptive medications [297]. These medications include bisphosphonates, denosumab, strontium ranelate, anabolic agents like teriparatide, selective oestrogen receptor modulators like raloxifene, and other sarcopenia drugs under study, such as myostatin inhibitors [297]. Oral bisphosphonates are commonly associated with upper gastrointestinal symptoms and are contraindicated in individuals with active upper gastrointestinal disease [298]. Intravenous bisphosphonates such as zoledronate or ibandronate are associated with mild self-limiting flu-like illness [298]. Denosumab is associated with high rates of severe hypocalcaemia and rebound vertebral fractures within 12 months following discontinuation [298]. The principal safety concern with raloxifene is the high risk of venous thromboembolism [298]. Mild hypercalcaemia that may require dose adjustment was reported with teriparatide [298]. In addition, teriparatide is costly and needs daily subcutaneous administration [298]. Finally, strontium ranelate should not be used in patients with cardiovascular diseases or uncontrolled hypertension [299]. Overall, the efficacy and incidence of adverse events in adults with advanced age are comparable to those reported for the general population [299]. However, specific issues, including comorbidity, polypharmacy, or estimated life expectancy, may influence the choice of therapy in older adults [299].

There has been uncertainty surrounding the long-term use of osteoporosis medications and their effectiveness [300]. A drug holiday following long-term use has been suggested in patients with low to moderate fracture risk, who are fully compliant and have a good response to therapy [300]. This has been suggested based on the extended benefits that some bone-forming and antiresorptive medications exhibit after discontinuation [300]. Evidence indicates that bisphosphonates continue to benefit patients for a number of years after being discontinued

(extended benefits or tail-effect), most evidently with alendronate and zoledronate [300]. In contrast, after discontinuing denosumab, teriparatide, and raloxifene, bone turnover returns to pre-treatment levels within a few weeks to a few months [300]. In addition, the evidence regarding strontium ranelate is limited and inconclusive [300]. In a population-based cohort study, women who had holidays from bisphosphonates for at least one year did not appear to have an increased risk of fractures compared to ongoing users [301]. However, those who had drug holidays were more likely younger than those in the control group [296].

A recent retrospective cohort study found that ceasing alendronate for more than two years was associated with a substantial increase in hip, humeral, and clinical vertebral fractures among women who were adherent to bisphosphonates for at least three years [302]. Similar results of hip and clinical vertebral fractures were observed in former risedronate users [302]. In contrast, there was no significant increase in fracture risk among former users of zoledronate or ibandronate [302]. A more recent systematic review and meta-analysis has synthesised evidence on the feasibility and outcomes of deprescribing bisphosphonates in older adults aged 60 years or older [303]. The findings suggested that bisphosphonates were successfully withdrawn after at least three years of use [303]. After discontinuation, there was no increase in the risk of any osteoporotic fractures [303]. However, discontinuers had greater risks for vertebral fractures and decreased bone mineral density [303]. Notably, anti-resorptive/bone anabolic medications for osteoporosis (such as bisphosphonates, strontium, teriparatide, and denosumab) were recognised as potentially inappropriate for older adults with irreversible frailty, according to STOPPFrail v2 criteria [14].

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