REVIEW ARTICLE

Recommendations to Prescribe in Complex Older Adults: Results of the CRIteria to Assess Appropriate Medication Use Among Elderly Complex Patients (CRIME) Project

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Abstract The occurrence of several geriatric conditions may influence the efficacy and limit the use of drugs prescribed to treat chronic conditions. Functional and cognitive impairment, geriatric syndromes (i.e. falls or malnutrition) and limited life expectancy are common features of old age, which may limit the efficacy of pharmacological treatments and question the appropriateness of treatment. However, the assessment of these geriatric conditions is rarely incorporated into clinical trials and treatment guidelines. The CRIME (CRIteria to assess appropriate Medication use among Elderly complex patients) project is aimed at producing recommendations to guide pharmacologic prescription in older complex patients with a limited life expectancy, functional and cognitive impairment, and geriatric syndromes, and providing physicians with a tool to improve the quality of prescribing, independent of setting and nationality. To achieve these aims, we performed the following: (i) Existing disease-specific guidelines on pharmacological prescription for the treatment of diabetes, hypertension, congestive heart failure, atrial fibrillation and coronary heart disease were reviewed to assess whether they include specific indications for complex patients; (ii) a literature search was performed to identify relevant articles assessing the pharmacological treatment of complex patients; (iii) A total of 19 new recommendations were developed based on the results of the literature search and expert consensus. In conclusion, the new recommendations evaluate the appropriateness of pharmacological prescription in older complex patients, translating the recommendations of clinical guidelines to patients with a limited life expectancy, functional and cognitive impairment, and geriatric syndromes. These recommendations cannot represent substitutes for careful clinical consideration and deliberation by physicians; the recommendations are not meant to replace existing clinical guidelines, but they may be used to help physicians in the prescribing process.

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1 Introduction

The aging process is characterized by a high level of complexity, which makes the care of older adults particularly challenging. Typically, older adults exhibit the co-occurrence of multiple chronic diseases (comorbidity) and conditions—such as urinary incontinence, delirium, or falls—that cannot be ascribed to a specific organ system pathology and that have multiple causes (the so-called geriatric syndromes) [1]. Both comorbidity and geriatric syndromes contribute to increase the rate of disability, mortality and poor outcomes seen in older patients (for example, institutionalization and death) [2]. This high degree of complexity is complicated by the presence of cognitive impairment, which is common in this population.

Social problems, such as lack of informal support or poor income, are also widely represented in this age group.

Consequently, physicians are facing challenging patients who present with an array of concomitant clinical conditions, whose integration and cumulative effects result in different degrees of functional deficits, cognitive deterioration, nutritional problems, and geriatric syndromes (delirium, falls, incontinence), in addition to a lack of social support and financial resources. As such, this 'modern' patient presents a degree of complexity never before considered by traditional medicine.

In particular, pharmacological treatment of this complex patient represents a challenge for the prescribing physician [3, 4]. This challenge is confirmed by the high rate of adverse drug reactions observed in this older population. In Western countries, drug-related illnesses cause 3–5 % of all hospital admissions, account for 5–10 % of in-hospital costs and are associated with a substantial increase in morbidity and mortality. The rate and severity of adverse drug reactions seem to be higher in clinically complex patients [5–8].

The occurrence of several geriatric conditions may influence the efficacy and limit the use of medications prescribed to treat chronic conditions. Functional and cognitive impairment, geriatric syndromes (i.e. falls or malnutrition) and limited life expectancy are common features of old age, which may limit the efficacy of pharmacological treatments indicated by guidelines, and raise questions about the appropriateness of treatment. Multiple underlying factors, involving chronic and acute diseases, tend to contribute to the development of these geriatric conditions. In some cases, overlap of multiple diseases, involving different organs, may result in the onset of a geriatric condition. The fact that these conditions cross organ systems and discipline-based boundaries, along with their multifactorial nature, challenges traditional ways of viewing clinical care and research. Indeed, applying the recommendation of clinical guidelines to complex elderly individuals is not straightforward since the level of evidence on which they are based (and therefore the strength) relies on randomized clinical trials (RCTs) or meta-analyses which are usually conducted on young and adult subjects, with only one disease and limited (if any) comorbidities, usually strictly related to the target disease. Patients recruited in trials take a limited number of drugs, almost all for conditions related to the specific disease studied, and for a short period of time (months or, at most, a few years). Therefore, it may be difficult to extrapolate their results to older complex people, with many comorbid conditions, who use many different drugs, are cognitively impaired and are disabled. This concept emphasizes the need for an interaction of pharmacological treatment with these geriatric conditions, which are rarely incorporated in clinical trials and treatment guidelines.

The presence of functional deficits and disability may limit the ability of patients to take medicines accurately. Functional deficits are related to a reduced ability to manage pill containers and, therefore, to the patient's reduced compliance with medication [9]. Cognitive impairment and dementia are associated with memory loss, decline in intellectual function, and impaired judgment and language, which may have obvious effects on the patient's decision-making capability. Cognitive impairment and dementia can alter the benefits and burdens, impact treatment adherence, and cause communication difficulties, including a decreased ability to report adverse effects [10, 11], Additionally, the presence of geriatric syndromes may influence the effect of pharmacological treatment. The term 'geriatric syndromes' refers to one symptom or a complex of symptoms, resulting from multiple diseases and multiple risk factors [1]. Geriatric syndromes can have a devastating effect on the quality of life of elderly patients. Specific syndromes such as falls or malnutrition have some direct implications for how intensely providers may actually manage chronic diseases. Other geriatric syndromes, such as depression, orthostatic hypotension, urinary incontinence and chronic pain are more common among elderly patients with chronic diseases and may be of great importance to the patient. The presence of these syndromes may influence the potential benefits of pharmacological treatments [3, 4]. Research studies have clearly demonstrated that drugs are frequently implicated in their pathogenesis. Finally, the estimation of life expectancy is important to understand whether a patient can benefit from a certain treatment [12].

Despite their relevance, these above-mentioned factors are rarely considered by clinical guidelines that aim to provide patients with the best quality of care. Although the clinical guidelines propose appropriate prescription for standardizing management and treating medical conditions, they seldom address the common problems encountered in geriatric care. With a few notable exceptions [13], they do not provide indications for the treatment of subjects with limited life expectancy; they tend to focus on reducing mortality rather than quality-of-life issues. Cognitive impairment is rarely discussed as a possible modifier of the treatment plan, although one in five of those patients over 80 years of age will develop a clinically detectable form of dementia. Geriatric syndromes and disability generally receive little attention, notwithstanding the fact that physicians of any specialty will see every day patients who suffer from these debilitating conditions.

2 Purpose and Methodology

Given this background, the purpose of the CRIteria to assess appropriate Medication use among Elderly complex patients (CRIME) project is to issue recommendations to assess appropriateness of pharmacological treatments indicated by clinical guidelines in older complex patients, with limited life expectancy, functional and cognitive impairment, and geriatric syndromes, giving physicians a tool to guide drug use prescribing independent of setting and nationality.

To achieve these aims, we performed the following:

1. Existing disease-specific guidelines on pharmacological prescription for the treatment of the diseases more commonly observed in the elderly were analyzed to determine if they include specific indications for complex patients with limited life expectancy, functional and cognitive impairment, and geriatric syndromes.
2. A literature search was performed to identify relevant articles that assess pharmacological treatment of five common chronic conditions (diabetes, hypertension, congestive heart failure, atrial fibrillation, and coronary heart disease) in complex patients with limited life expectancy, functional and cognitive impairment, and geriatric syndromes to integrate recommendations of disease-specific guidelines.
3. New recommendations were developed based on the data derived from the literature search and consensus.

2.1 Review of Disease-Specific Guidelines

Guidelines on the treatment of the following diseases were analyzed: diabetes, hypertension, congestive heart failure, atrial fibrillation, and coronary heart disease. These diseases were chosen because they were associated with the highest pharmacological burden and because the drugs used in their treatment most frequently cause adverse drug reactions [5–7]. Two sets of guidelines for each disease were chosen based on consensus within the CRIME research group. For each of the examined diseases, two sets of guidelines were selected based on the consensus among CRIME researchers (see Appendix 1 for a list of guidelines examined). The majority of the updated guidelines were reviewed by two independent researchers (GO and MB), who addressed the following issues: (i) Do the guidelines address treatment for older adults? (ii) Is there a discussion regarding the time required for patients to benefit from treatment in the context of life expectancy? (iii) Are specific recommendations for patients with cognitive impairment included in the guidelines? (iv) Are specific recommendations for patients with disability and functional impairment included in the guidelines? (v) Are specific recommendations for patients with geriatric syndromes included in the guidelines?

2.2 Literature Search

A literature search was performed by two independent assessors (GO and DF). For each specific disease examined, relevant studies were identified through PubMed searches of the MEDLINE database using a term to identify the disease of interest (i.e. 'diabetes') and 'treatment' and 'older adults' and each of the following terms: 'life expectancy', 'end of life', 'functional impairment', 'disability', 'cognitive impairment', 'dementia', 'geriatric syndromes', 'falls', 'incontinence', 'malnutrition'. Bibliographies of the retrieved articles were searched to identify other eligible studies. Non-English articles were not included in the search. Additional searches will be performed using the National Library of Medicine clinical trials database and the Cochrane Collaboration Library database. The search was extended through June 2012. Data from both randomized, controlled trials and observational studies were assessed to fulfill our aims. This expansion of the literature search was necessary because of the limited availability of data on complex older patients from RCTs. Articles were screened to evaluate if they were assessing the efficacy of pharmacological treatments recommended by guidelines in a sample of older adults with limited life expectancy, functional impairment or cognitive impairment, or geriatric syndromes.

2.3 New Recommendations

Based on results of the literature search, disease-specific recommendations were agreed on a consensus basis within the CRIME research group. For each recommendation, a brief description of its 'rationale' was produced. Each of these recommendations was subsequently examined by seven experts from leading Italian and international geriatric research centers, who rated, through a web-based questionnaire, the recommendations on a scale of 0–10. Experts were identified as having a predominant research focus on aging or pharmacoepidemiology (see Appendix 2 for a list of experts). Only those recommendations that received a mean score of ≥8 were selected. Figure 1 summarizes the literature search and new recommendation production process for each of the diseases of interest.

3 Results and Recommendations

The results of the review of disease-specific guidelines are presented in Table 1. All ten of the guidelines examined

Fig. 1 Literature search and new recommendation production process
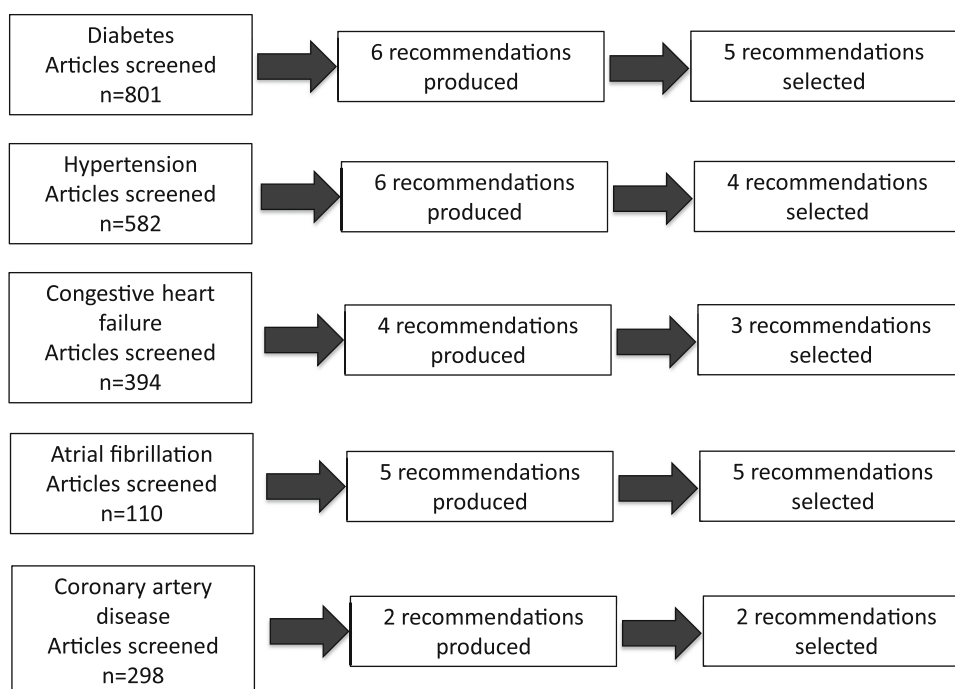
addressed the issue of pharmacological treatment in older adults. However, the common conditions that are associated with advanced aging, including limited life expectancy, functional and cognitive impairment, and geriatric syndromes, were rarely addressed.

Based on the articles identified by the literature search, a set of 23 new recommendations were produced. Overall, 19 recommendations received a mean rating of ≥8 and were selected.

3.1 Diabetes

Recommendation 1: *In patients with limited life expectancy (<5 years) or functional limitation, intensive glycemic control (HbA1c <7 %) is not recommended.*

Rationale: A glycemic goal set by current guidelines is HbA1c <7.0 %. However, many studies suggest the need for individual target, considering age and life expectancy, duration of diabetes, comorbid conditions, advanced diabetes complications, and risk of hypoglycemia unawareness [14–17].

Limited life expectancy is an important determinant of the magnitude of the expected benefit of intensive glucose control compared with moderate glucose control. It was suggested that 5 years of life expectancy is an acceptable threshold for identifying older patients who are unlikely to benefit from intensive control [18]. Finally, the presence of functional impairments and poor physical performance was shown to be an important predictor for reduced benefits from intensive glucose control [19].

Recommendation 2: *In patients with a history of falls or cognitive impairment or dementia, intensive glycemic control (HbA1c of <7 %) or use of insulin is not recommended.*

Rationale: In studies of diabetic patients, the risk of falls is higher in patients with diabetic complications (renal insufficiency, peripheral neuropathy, retinopathy) and in those using insulin with low HbA1c [20]. This could contribute to the high risk of fractures documented in diabetic patients who are treated with insulin [21]. Other studies have shown that the risk of fall is higher in diabetic women who use insulin [22, 23] and that tight glycemic control is associated with an increased risk of falling in frail older adults [24].

The presence of cognitive impairment or dementia was shown to be an important risk factor for hypoglycemia due to disorders related to eating habits or poor treatment management [25, 26]. Additionally, tight glycemic control was associated with increased risks of developing dementia in frail, diabetic, elderly patients with hypoglycemic episodes [27, 28].

Patients with cognitive impairment or dementia may have difficulties naming their medications and describing their indications; they more frequently hold health beliefs that interfere with adherence to their medical regimen, and they are more likely to have a poor understanding of their condition and its management. In addition, in patients with diabetes, presence of dementia or cognitive impairment may alter the ability of patients to fully participate in their self-care and adhere to complex treatments without special

Table 1 Results of the review of disease-specific guidelines (see Appendix 1 for reference details of the guidelines)

Society	Heart failure		Hypertension		Atrial fibrillation		Coronary artery disease		Diabetes	
	ACC/AHA	ESC	JNC7	ESH/ESC	ACC/AHA/ESC	ESC	ACCF/AHA	ESC	ADA	AGS
Guidelines addressed treatment for older adults?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time needed to treat to benefit from treatment in the context of life expectancy discussed?	Yes (specific section on end of life)	Yes (specific section on end of life)	No	No	No	No	No	No	Yes	Yes
Recommendations for patients with cognitive impairment?	No	No	Yes	Yes (need for more research is underlined)	No	No	No	No	Yes	Yes
Recommendations for patients with disability and functional impairment?	No	No	No	No	No	No	No	No	Yes	Yes
Recommendations for patients with geriatric syndromes?	Yes (syncope dizziness and hypotension)	Yes (syncope dizziness hypotension and cachexia)	Yes (postural hypotension)	Yes (postural hypotension)	No	Yes (falls)	No	No	Yes (frailty, urinary continence and pain)	Yes (urinary continence and falls)

ACC American Journal of Cardiology, *ACCF* American College of Cardiology Foundation, *ADA* American Diabetes Association, *AGS* American Geriatrics Society, *AHA* American Heart Association, *ESC* European Society of Cardiology, *ESH* European Society of Hypertension, *JNC* Joint National Committee

assistance [29, 30]. In particular, the use of insulin is common among individuals with cognitive impairment; these patients are significantly more likely not to know what to do in the event of hypoglycemia, and they tend to give more incorrect responses when asked about diabetes mellitus management than do those who are cognitively intact [31].

Recommendation 3: *In patients with a recent fall or high risk of falls or orthostatic hypotension, intensive blood pressure lowering (<130/80 mmHg) is not recommended.*

Rationale: Blood pressure goals for diabetic patients are <130/80 mmHg, so that intervention is suggested for persons in the 'pre-hypertension' group. Available antihypertensive drugs are usually safe and can be used in combination to attain the suggested therapeutic goals. However, an obvious concern in elderly diabetic patients is the possibility of autonomic dysregulation and orthostatic hypotension, which is very common in this population [32]. Orthostatic hypotension has been related to poor cardiovascular prognosis and is a common cause of falls [33]. The number of medications in use is associated with postural blood pressure changes, and some classes of drugs used to treat multiple chronic conditions (antihypertensives in particular, but also nitrates, drugs for Parkinson's disease, antipsychotics and tricyclic antidepressants) can have a causative role [34]. When patients start antihypertensive therapy, the patients' orthostatic hypotension should be routinely checked and reassessed regularly. Therefore, in patients with known autonomic dysregulation, a history of falls, or a high risk for falls, the blood pressure goals should be less stringent. This advice seems prudent, particularly if stricter control must be attained with complex drug schedules.

Recommendation 4: *Use of statins in older adults with limited life expectancy (<2 years) or advanced dementia is not recommended.*

Rationale: There is ample evidence of the usefulness of statins in secondary prevention. Withholding statins in older diabetic patients after acute coronary syndromes or with known cardiovascular disease (CVD) should not be considered good medical practice. The benefit of statin therapy has been demonstrated in primary prevention in a high-risk population without overt CVD (although significant differences exist among the studies), as outlined by recent reviews [35, 36].

However, the benefits of statin use decrease with increasing age [37]. The results of a meta-analysis [38] in patients with diabetes indicated that the benefits of statin therapy are evident and substantial after at least 2 years of therapy. Therefore, the use of statins may not lead to any beneficial effect in patients with limited life expectancy, including those with advanced dementia. A consensus statement of geriatricians indicated that the use of statins is never appropriate in patients with advanced dementia [39].

Recommendation 5: *Metformin should be avoided in malnourished (body mass index <18.5 kg/m²) older adults.*

Rationale: In overweight individuals, metformin has been associated with reductions in all-cause mortality and stroke compared with insulin or sulfonylureas [40]. These benefits seem related to the fact that metformin may cause anorexia and weight loss, and this effect is particularly relevant in older adults [41, 42]. For this reason, older patients who are frail, anorexic, or underweight may not be appropriate candidates for metformin therapy [42, 43].

3.2 Hypertension

Recommendation 1: *In patients with dementia or cognitive impairment or functional limitation, a tight blood pressure control (<140/90 mmHg) is not recommended.*

Rationale: To date, no evidence is available to demonstrate that treating older persons with blood pressure from 140 to 159 mmHg would improve morbidity or mortality. No trial in which a benefit was shown exhibited a systolic blood pressure average <140 mmHg. Although the data are strong and supportive of aggressive blood pressure reduction in older persons with a blood pressure of >160 mmHg, the probable increased risk of adverse effects and perceived lower benefits in the elderly may deter clinicians from aggressively treating hypertension in the elderly [44]. The reality of applying a tight blood pressure control to complex patients may be problematic because of limited compliance and potential medication errors, particularly in patients who have problems managing therapy (due to cognitive impairment, dementia or functional limitations) [45]. Additionally, several publications have suggested that low blood pressure levels are associated with a more rapid cognitive decline in patients with dementia [46–48].

Recommendation 2: In patients with dementia or cognitive impairment or functional limitation, use of more than three antihypertensive drugs should be avoided.

Rationale: Evidence from clinical trials is mostly derived from studies enrolling middle age patients with limited comorbidities and testing the efficacy of one to three antihypertensive agents. Scant data exist about the benefits of additional drugs [49]. Patients with dementia, cognitive impairment, or functional limitation may have difficulties in managing complex drug regimens and their adherence to treatment may be impaired [49, 50]. In particular, several studies have shown that mental health status, patient knowledge, skills in managing the illness, and participation in care affect adherence to the recommended treatments [51].

Recommendation 3: In patients with limited life expectancy (<2 years), a tight blood pressure control (<140/90 mmHg) is not recommended.

Rationale: Patients with terminal illness or end-stage non-CVD should be exempt from the use of complex drug regimens and strict blood pressure control because of different treatment priorities and goals of care, the need to prioritize a clinically dominant illness, and the expectation that the patients may not live long enough to receive the benefits of hypertension treatment [52]. Several studies have indicated that the gain in life expectancy and an event-free life expectancy related to the treatment of hypertension depend on the duration of treatment and, therefore, should be reduced in patients with a short life expectancy [53, 54].

Recommendation 4: *In case of falls associated with orthostatic hypotension (or symptomatic orthostatic hypotension), the number of antihypertensive drugs should be reduced and concomitant use of multiple antihypertensive agents should be avoided.*

Rationale: The use of antihypertensive medications is associated with an increased risk of falls [55]. This effect seems mediated by orthostatic hypotension. The concomitant use of three or more antihypertensive drugs is associated with an increased risk of orthostatic hypotension [56]. Multifactorial intervention strategies that have proven to prevent falls include a reduction in the number of hypotensive drugs in the presence of orthostatic hypotension [57]. Finally, a recent observational study showed that in hypertensive, community-dwelling, elderly patients, initiating an antihypertensive drug was associated with an immediate increased risk for hip fracture [58].

3.3 Congestive Heart Failure

Recommendation 1: *In the presence of orthostatic hypotension or falls, increasing the dosage of antihypertensive drugs is not recommended; the reduction of drug dosages should be considered.*

Rationale: Hypotension may be worsened by heart failure treatments, many of which (ACE inhibitors, β-blockers, nitrates, hydralazine) have been associated with decreased blood pressure [59, 60]. This risk for hypotension might also be increased by balance and proprioception decline, as well as the resulting bradyarrhythmias, which may be enhanced by the effects of drugs with negative chronotropic properties (β-blockers) [61]. In addition, patients with geriatric conditions, including falls, are usually excluded from clinical studies assessing the efficacy of drug treatments [62]. The dosage of these drugs should not be increased and the reduction of drug dosages might be considered to allow the continuation of treatment.

Recommendation 2: The chronic use of diuretics in asymptomatic or minimally symptomatic older adults with a history of falls and increased fracture risk is not recommended.

Rationale: Non-potassium-sparing diuretics (primarily loop diuretics) remain the cornerstone of therapy for fluid management in patients with heart failure, despite the lack of large randomized trials evaluating their safety and optimal dosing regimens in acute and chronic settings. Chronic use of diuretics in asymptomatic or minimally symptomatic heart failure patients, in the absence of signs of fluid retention, is potentially dangerous because of higher risks for hypotension, electrolyte disturbances and worsening renal function [63, 64]. Increased morbidity and mortality have been related to chronic diuretic use in heart-failure patients [65–67]. Increased risks for falls and fracture (both vertebral and hip) have been reported for patients who receive loop diuretics [68]. Diuretics increase the risk of postural and postprandial hypotension. Exposure to high doses of furosemide is associated with worsened outcomes and is broadly predictive of death and morbidity [65–67].

Recommendation 3: *Pursuit of low blood pressure targets (systolic blood pressure <130 mmHg) in older adults with dementia or cognitive impairment is not recommended.*

Rationale: There is ample evidence that low blood pressure values are associated with poor outcomes (increased mortality, higher hospitalization rate) in patients with heart failure, in the acute, post-acute, and chronic settings [69–74]. In particular, heart failure is a risk factor for cognitive decline and dementia; this association is stronger in the subgroup of patients with lower blood pressure values (systolic blood pressure <130 mmHg; diastolic blood pressure <70 mmHg) [75, 76].

3.4 Atrial Fibrillation

Recommendation 1: *In patients with non-valvular atrial fibrillation and limited life expectancy (<6 months), the use of oral anticoagulants should be avoided.*

Rationale: In the management of patients with limited life expectancy, it is important to realize that this type of patient was either excluded or underrepresented in all of the pivotal trials [77]. Expert consensus suggests to withdraw oral anticoagulants in patients with limited life expectancy [78].

Recommendation 2: *In non-valvular atrial fibrillation, the use of warfarin in the presence of malnutrition or irregular food intake is not recommended.*

Rationale: Nutritional status is a relevant issue in patients who receive warfarin. A stable anticoagulant effect of warfarin is dependent on consistent stores and intake of vitamin K. Impaired nutrition or irregular food intake are common issues in patients with limited life expectancy, and individuals with these conditions who receive warfarin are at risk for overanticoagulation [79, 80]. Additionally, warfarin pharmacokinetics are highly affected by dietary supplements, which are commonly used by malnourished patients [81].

Recommendation 3: *In non-valvular atrial fibrillation, the use of anticoagulants is not recommended in elderly patients with dementia if any of the following characteristics are present: unable to manage medications and living alone or high risk for falls.*

Rationale: There is consistent evidence that supports an association between atrial fibrillation and increased incidence of dementia, at least in patients with stroke [82]. However, dementia is clearly associated with inadequate international normalized ratio (INR) control, due to poor compliance with warfarin therapy [83–85]. The inability to manage medications, the high risk for falls, and irregular food intake are common conditions in dementia, which are associated with inadequate INR control. A consensus statement of geriatricians indicated that the use of warfarin is rarely appropriate in patients with advanced dementia [39].

Recommendation 4: *In patients with non-valvular atrial fibrillation and high risk for falls or poor physical performance, the use of anticoagulants is not recommended if the risk for stroke is low.*

Rationale: Patients at high risk for falls with atrial fibrillation are at risk for intracranial hemorrhage, especially traumatic intracranial hemorrhage [86]. Several risk scores for bleeding incorporate high risk for falls [87]. However, because of their high stroke rate, atrial fibrillation patients at risk for falls appear to benefit from anticoagulant therapy if they have multiple stroke risk factors [86, 88]. A very low risk for intracranial hemorrhage has been reported by several authors [88]. For patients at risk for falls, indication to anticoagulant therapy should be based on relative risk for stroke/transient ischemic attack (TIA), so that it is no more justified if the risk is low (i.e. CHADS2 score <2 or CHA2DS2-VASc <2) [89]. Poor physical performance is associated with an increased risk for bleeding and falls; individuals with this condition are excluded systematically from trials that assess the efficacy of warfarin in secondary prevention [90–92]. Only 8 % of the 17,046 patients screened were enrolled into the Stroke Prevention in Atrial Fibrillation Study [91]. Patients with repeated falls or unstable gait were excluded. In the European Atrial Fibrillation Trial of secondary prevention after TIA or minor stroke, 35 % of the patients were ineligible for anticoagulant therapy, with the exclusion of those with moderate-to-severe disability [92]. For this reason, in individuals with low risk for stroke and poor physical performance, use of anticoagulants should be avoided.

Recommendation 5: *In patients with known difficulties in managing therapy (i.e. cognitive impairment) and lack of assistance (i.e. caregiver), the use of drugs with a narrow therapeutic index, including digoxin and warfarin, is not recommended.*

Rationale: Patients with impaired cognition and low health literacy do not only have limitations in reading, but they may also have difficulties processing oral communication and conceptualizing risk [84, 93]. These patients have greater difficulties naming their medications and describing their indications; they more frequently hold health beliefs that interfere with adherence, and they are more likely to have a poor understanding of their condition and its management. Dementia and cognitive impairment alter the ability of patients to fully participate in their self-care and adhere to complex treatments (including the use of drugs with a narrow therapeutic index, such as digoxin or warfarin) without special assistance [29, 94].

3.5 Coronary Artery Disease

Recommendation 1: *The use of statins for secondary prevention in older adults with limited life expectancy (<2 years) or advanced dementia is not recommended.*

Rationale: There is evidence of the usefulness of statins in secondary prevention. However, existing data show a reduction in the rate of major cardiovascular events after 2 years of treatment [95]. These data, together with the evidence that the benefits of statin use decrease with increasing age [37], suggest that the use of statins may not lead to any beneficial effect in patients with limited life expectancy (<2 years), including those with advanced dementia. In this context, a consensus statement of geriatricians indicated that the use of statins is never appropriate in patients with advanced dementia [39].

Recommendation 2: *In case of orthostatic hypotension, the dosage of antihypertensive drugs should be reduced and the concomitant use of multiple antihypertensive agents should be avoided.*

Rationale: Use of antihypertensive medications is associated with an increased risk for falls [55]. This effect seems mediated by orthostatic hypotension. The concomitant use of three or more antihypertensive drugs is associated with an increased risk for orthostatic hypotension [56]. Orthostatic hypotension increases the risk for ischemic heart disease and all-cause mortality in elderly people [96, 97]. Additionally, the early administration of antihypertensive drugs had a potential pro-ischemic effect in hypotension-prone patients after a myocardial infarction [98, 99]. Multifactorial intervention strategies that have proven to prevent falls include the reduction in the dosage of hypotensive drugs in the presence of orthostatic hypotension [57].

4 Conclusions

Prescribing in complex older adults represents a challenging task, and guidelines do not always properly address the appropriateness of medication use in complex older adults. The strength of the CRIME recommendations relates to the fact that they are aimed to evaluate the appropriateness of pharmacological prescription in older complex patients, translating the recommendations of clinical guidelines to patients with limited life expectancy, functional and cognitive impairment, and geriatric syndromes. However, a relevant limitation of these recommendations is due to the fact that they addressed appropriateness of treatment of five chronic diseases and other common conditions (i.e. chronic obstructive pulmonary disease, infective diseases) were not examined. Indeed, the five selected diseases were chosen because they were associated with the highest pharmacological burden and because the drugs used in their treatment most frequently cause adverse drug reactions [5–7]. In addition, level of evidence for the proposed recommendations was not provided because most of the recommendations derived from observational studies, since clinical trials were not performed in patients with the geriatric conditions examined.

In conclusion, these recommendations could represent a tool to improve the quality of prescribing in older adults independent of setting and nationality, but the recommendations are not meant to replace existing clinical guidelines. Clinical studies are needed to test if implementation of these recommendations may result in improving quality of prescribing and reducing the risk of negative outcomes in complex older adults.

Appendix 1: List of Guidelines Examined

Heart Failure

Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW; American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009 Apr 14;53(15):e1–e90.

McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C,

Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012 Jul;33(14):1787–847.

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Appendix 2: Names and Affiliations of Experts

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Stefano Volpato	University of Ferrara	Italy
Andrea Corsonello	Italian National Research Center on Aging (INRCA)	Italy
Eva Topinkova	Prague University	Czech Republic
Mirko Petrovic	Ghent University	Belgium
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