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Evaluation of clarity of the STOPP/START criteria for clinical applicability in prescribing for older people

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ABSTRACT

Objectives: Safe and effective drug prescribing for older people is challenging. Studies continue to report a high prevalence of inappropriate prescribing in older people. Clear formulation of recommendations in clinical guidelines is crucial for successful implementation. The aim of this study was to evaluate the clarity of the STOPP/START criteria for clinical applicability in drug prescribing for older people.

Methods: For each of the 114 STOPP/START criteria version 2, elements describing the action (*what/how to do*), condition (*when to do*) and explanation (*why to do*) were identified. Next, the clarity ratings of these three elements were determined using tools provided by the Appraisal of Guidelines for Research & Evaluation (AGREE) consortium. The elements of each recommendation were rated independently on a 7-point Likert scale by a panel of two appraisers and discussed with a third appraiser in case ratings differed >1 point.

Clarity ratings were determined per element and categorized into high (>67.7%), moderate (33.3-67.7%) and low (<33.3%). Recommendations with lowest and highest clarity ratings were analysed to identify factors that positively or negatively affected clarity most. Additionally, the nature of the conditions was further classified into five descriptive components: disease, sign, symptom, laboratory finding and medication.

Results: STOPP recommendations had an average clarity rating of 65%, 60% and 67% for actions, conditions and explanations respectively. The average clarity rating in START recommendations was 60% and 57% for actions and conditions respectively. Since no statements were present to substantiate the prescription of potential omissions, no clarity ratings could be assessed for explanations of the 34 START criteria.

Conclusions: Our results show that the clarity of the STOPP/START criteria can be improved. For future development of explicit drug optimization tools, such as STOPP/START, our findings provide directions to assure clarity of drug recommendations and therefore enhance clinical applicability.

Strengths

- To the best of our knowledge, this is the first study that explores the clarity of STOPP/START criteria.
- Clarity ratings were scored independently by appraisers who were experienced in applying STOPP/START-criteria in clinical practice
- By evaluating the '*what'*, '*when'* and '*why'* of recommendations, element-specific strategies were formulated to improve their clarity

Limitations

- No validated tool exists to rate clarity of singular clinical recommendations
- The scoring process is partly subjective, however consensus ratings show high inter-rater agreement

INTRODUCTION

Clinical practice guidelines (CPG) are instruments intended to provide guidance to healthcare professionals in patient care. Translation of healthcare knowledge, evidence and experience into clear recommendations for patient care is, however, challenging. Studies in the USA and the Netherlands suggest that about 30–40% of patients do not receive care according to current scientific evidence as represented in guidelines. A clear description of the desired performance has been associated with better compliance with guideline recommendations.[1,2]

Recommendations about safe and effective pharmacotherapy are an important part of CPGs. However, it is often unclear whether recommendations also apply to older people.[3-5] A complicating factor is that older people experience more concurrent illnesses, while CPGs often focus on best treatment of a single disease. Ambiguity among prescribers about pharmacotherapy in older people results in inappropriate prescribing, which causes adverse drug reactions, drug-related hospitalizations, decreased quality of life and even death.[6,7]

To fill in a lack of clear statements in CPGs about (in)appropriate prescribing in multimorbid older people, several explicit screening tools have been developed.[8,9] The most widely used are the Beers criteria[10] and the Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria.[11] CPG recommendations are rarely specified in precise behavioural terms such as *what, how, when,* and *why* to stop or start a drug, while explicit screening tools are designed to make clear statements and therefore ease clinical implementation.[2] However, studies continue to report a high prevalence of inappropriate prescribing in older people.[12-14] This suggests there is still an incomplete implementation.

Although STOPP/START criteria have shown good inter-rater reliability in studies involving physicians and (hospital)pharmacists working in geriatric units, data on how physicians less familiar with medication optimization would interpret STOPP/START criteria are lacking.[15,16] The question then arises whether the recommended actions are formulated clear enough to guide prescribers less experienced with treating geriatric patients.

In this study, the clarity of STOPP/START criteria for clinical applicability will be evaluated.

METHODS

STOPP/START criteria

The STOPP/START criteria were first published in 2008 and have been updated in 2015 to STOPP/START version 2.[17] STOPP/START is a product of two Delphi rounds by 19 experts from 13 European countries.

For this study, the supplementary data of the corrigendum of the STOPP/START criteria version 2 as published in November 2017 were used.[18] STOPP/START version 2 consists of a list of 80 Potentially Inappropriate Medications (PIMs, STOPP criteria) and 34 Potential Prescribing Omissions (PPOs, START criteria).

Clarity assessment

The AGREE II Instrument and GUIDE-M were used to develop a framework to assess the clarity of language used in STOPP/START. AGREE II Instrument is an internationally validated tool to rate the quality of CPGs, developed by the Appraisal of Guidelines for Research & Evaluation (AGREE) Consortium.[19] In addition to the AGREE II Instrument, AGREE developed a Guideline Implementability Decision Excellence Model (GUIDE-M).[20] This model identifies '*communicating content'* as a core tactic for CPG implementability. Obviously, language is an important domain of this tactic. The language subdomain promotes a clear, simple, and persuasive message.

The relevant part of the AGREE II Instrument ('clarity of presentation', domain 4, item 15) states that recommendations should be 'specific and unambiguous', which is defined as *'a concrete and precise description of which option is appropriate for which situation and for what population group'*. In line with this statement and the corresponding section of the AGREE II Instrument, three elements were identified that influence the clarity of recommendations:

- **Action:** description of the recommended action - i.e. *what* to do and *how* to act?
- **Condition:** identification of the relevant target population and statements about patients or conditions for whom the recommendations would apply or not apply – i.e. *when*?
- **Explanation:** identification of the intent or purpose of the recommended action – i.e. *why*?

In order to quantify the clarity of STOPP/START criteria, the three elements of each recommendation were rated independently on a 7-point Likert scale by a panel of two appraisers, consisting of a geriatric resident (CH) and a hospital pharmacist resident (BS), both experienced with the application of STOPP/START criteria in daily practice. The clarity for each of these three elements was rated from the perspective of a 'junior' physician or pharmacist with a basic level of knowledge (≤ 5 years of clinical post-graduate experience). The appraisers were trained with a rating guidance, developed and approved by senior clinicians (TE/EP/IW/WK) prior to

rating the elements independently. In case ratings differed more than 1 point, a senior hospital pharmacist/clinical pharmacologist (IW) or a senior geriatrician/clinical pharmacologist (WK) was consulted as a third appraiser until consensus was reached.

Descriptive components of conditions

In addition to the calculation of clarity ratings for the action, condition and explanation, the nature of the conditions was further explored. The condition identifies the target population and is the most heterogeneous element. By stratifying the conditions into descriptive components, the nature of the components in relation to their clarity could be assessed. These components could lead to different strategies to optimize 'specific and unambiguous' wording in describing conditions.

The conditions were subdivided into five components that were considered essential for identification of the target population: *disease, sign, symptom, laboratory finding* and *medication*. Definitions of four components were based on the ontology as described by Scheuermann et al.[21] *Signs* are defined as bodily features observed in a physical examination including measurements like blood pressure, while *symptoms* are bodily features experienced by a patient, like parkinsonism. Since optimization of polypharmacy is the main focus of the STOPP/START, the target population can also be described by (co-)*medication*. *Medication* is not defined by Scheuermann et al. Therefore, medication was added as a fifth component using the commonly accepted definition as *'a drug used to diagnose, cure, treat, or prevent disease.'*

Data analysis

Clarity ratings for each of the three elements (action, condition, explanation) were calculated as a percentage of the obtained scores given by appraiser 1 and 2 divided by the maximum score.

$$Clarity\ rating(\%) = \frac{obtained\ score(sum\ of\ 2\ appraisers) - minimum\ possible\ score(2)}{maximum\ possible\ score(14) - minimum\ possible\ score(2)}$$

This calculation method is in accordance with the approach provided by AGREE II instrument. The scores of appraisers 1 and 2 were both replaced by the consensus score in case a third appraiser was consulted. After scoring the elements, clarity ratings were categorized into low (<33.3%), moderate (33.3% - 67.7%) and high (>67.7%).

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research .

RESULTS

The elements 'action' and 'condition' in STOPP and START recommendations were rated on their clarity, resulting in 80 and 34 scores per element, respectively. The element 'explanation' was present in all but three (A1, A2, B11) STOPP recommendations, resulting in 77 scores. None of the START criteria contained an explanation to substantiate the prescription of potential omissions. Therefore, Likert scores for explanations were only assessed in STOPP recommendations.

The agreement among the two appraisers for Likert scores was high and ranged from 76.3% (STOPP – condition) to 91.3% (STOPP – action). 44 out of 305 (14.4%) scores were replaced after consensus meetings with a third appraiser. Replacements did not alter average Likert scores per element with more than 0.2 points compared to the average scores prior to consensus.

Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively. (*figure 1*)

In 80 STOPP and 34 START recommendations, 35 actions were categorized as high (30.7%), 65 as moderate (57.0%) and 14 as low (12.3%). 38 (33.3%), 67 (58.8%) and 9 (7.9%) conditions had a high, moderate or low clarity rating, respectively. In 77 STOPP criteria, 41 (53,2%) explanations were categorized as high, 35 (45.5%) as moderate and 1 (1.3%) as low.

13 STOPP criteria (C1, C2, C4, C7, D6, D12, D13, E5, E6, F1, G1, H1, H9) had high clarity ratings for all three elements. 4 START criteria (B3, G3, I1, I2) had high clarity ratings for both action and condition. Detailed information of clarity ratings per element for all individual STOPP/START-criteria can be found in *Supplementary data S1*.

Recommendations with the lowest and highest clarity ratings per element were analysed in more detail to identify factors that either positively or negatively affected 'specific and ambiguous' language most. These findings for actions, conditions and explanations with illustrative examples for STOPP and START recommendations are presented in *table 1*.

Table 1. *Main barriers and facilitators that affected clarity of the elements action, condition and explanation of STOPP/START recommendations.*

Barriers	**Example** [a] (clarity rating, %)
ACTION	
Lack of explicit drug (class)	STOPP D7/8. **Anticholinergics / antimuscarinics** (17%)
➢ 'e.g.' is inconclusive	STOPP B10. Centrally-acting antihypertensives (**e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine**) (33%)
➢ Use of adjectives that need further investigation to allow use	STOPP D14. **First-generation** antihistamines (17%) START H1. **High potency** opioids (17%)
Lack of drug deprescribing schedules while considered necessary	STOPP K2. **Neuroleptic drugs** (17%)
Starting dose and target dose not mentioned	START C2. **Angiotensin Converting Enzyme (ACE) inhibitor** with systolic heart failure (67%)
Lack of directions how and what to monitor after starting a drug	SART E1. **Disease-modifying anti-rheumatic drug** (DMARD) (25%)
CONDITION	
General - Patient population for whom recommendations would not apply was not (clearly / unambiguously) defined	
➢ In patients with a strong indication for a potentially inappropriate drug, it may be harmful to stop it	STOPP B5. **as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias** (33%)
➢ In patients with potential omissions, warnings for important contra indications are lacking / not clearly defined	START A2. **where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated** (33%)
Medication – see also *action*	
➢ Ambiguous adjectives were used	STOPP D2. as **first-line antidepressant treatment** (33%)
➢ Description of drug therapy (substance / dosage) not specific enough	START E7. in patients taking **methotrexate** (33%)
Disease - Clinical interpretation of 'disease state' for defining population needed	STOPP D1. with **dementia**, narrow angle glaucoma, **cardiac conduction abnormalities**, prostatism, or **prior history of urinary retention** (33%) START A5**.** with a documented **history of coronary, cerebral or peripheral vascular disease** (33%)
Sign - Measurement or scores were not described unambiguously	STOPP H2. with **severe hypertension** or **severe heart failure** (33%) START E1. with **active**, **disabling rheumatoid disease** (42%)
Symptom - Symptoms were not described unambiguously	STOPP K-section. Not clear whether the occurrence of **'falls'** - as mentioned only in the title of section K - is a condition or used to address the risk of falls. In case 'falls' is a condition, the frequency of 'falls' is not specified. (0%) STOPP D10. unless **sleep disorder** is due to (33%) START C2. with **persistent major depressive symptoms** (33%)
Laboratory finding - Parameters lack clear cut-off levels with reference ranges	START C6. once **iron deficiency** and **severe renal failure** have been excluded (33%)

EXPLANATION	
Risk of continuing therapy not clearly described: explanation does not cover clinical relevance of benefit / harm balance (specific adverse drug reactions, toxicity).	STOPP D7. **(risk of anticholinergic toxicity)** (17%) START N/A
Facilitators	**Example** [a] (clarity rating, %)
ACTION	
Drugs were specified on individual drug level and -if necessary- route / dosage was specified	STOPP C7. **Ticlopidine** (100%) START A2. **Aspirin (75 mg – 160 mg once daily)** (92%)
CONDITION	
Medication – see also *action* Specific description of drug therapy (substance / dosage) to clearly identify the target population (i.e. patients using a certain drug regimen).	STOPP B3. in combination with **verapamil** or **diltiazem** (92%) START I2. **at least once after age 65 according to national guidelines** (83%)
Disease - Diseases clearly described so that the target population could be easily identified	STOPP H9. in patients **with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding** (92%) START C4. for **primary open-angle glaucoma**. (100%)
Signs - Signs clearly described as scores or measurements and therefore unambiguous	START B3. with documented chronic hypoxaemia **(i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)** (92%)
Symptom - Symptoms clearly and unambiguous described	STOPP F1. with **Parkinsonism** (92%)
Laboratory findings - Clear cut-off levels with reference ranges present	STOPP E6. if **eGFR < 30 ml/min/1.73m2** (100%)
EXPLANATION	
Risk of discontinuing clearly described	STOPP D5. (**no indication for longer treatment**; **risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly**). (100%) START N/A

[a]*The examples shown are selected from elements with low and moderate (≤67.7%) clarity ratings for barriers and from high (>67.7%) clarity ratings for facilitators to substantiate the main findings. An overview of all clarity ratings can be found in the Supplementary data S1.*

The results of stratifying the element 'condition' into the five descriptive components medication, disease, sign, symptom and laboratory finding are shown per STOPP/START recommendation in *figure 2*. The clarity rating per condition is displayed by the addition of a colouring scale. Clarity ratings were scored on the level of condition as an element and not on the level of descriptive components. Therefore, components that together form the condition of one recommendation share the same colouring for their clarity.

In 33 (41%) STOPP criteria and 17 (50%) START criteria, the condition consisted of more than one component. No strong association was found between the clarity of conditions and the nature of the descriptive components, as the clarity ratings of the condition section varied regardless of the nature of the component. However, laboratory findings used to identify the target population were discovered to have the highest clarity rating compared with other descriptive components in STOPP recommendations; 9 out of 13 laboratory-based conditions had a high clarity rating (>67.7%).

DISCUSSION

Main findings

Only 13 out of 80 STOPP and 4 out of 34 START criteria had a high clarity rating for the three elements action, condition and explanation. To improve clarity of recommendations, element-specific strategies can be formulated (*table 1*).

Actions were considered unclear in case recommendations included non-explicitly specified drug classes (e.g. 'anticholinergics'). To improve clear description of the action (*what and how*) we advise to maximally specify drugs at an individual substance level. The addition of how to start or stop a drug (immediately versus gradually including monitoring guidelines and deprescribing schedules) were considered necessary in some actions to further improve clarity.

The definition of the condition (*the when*) had the lowest average clarity rating in both START and STOPP. Low clarity ratings for conditions were a result of insufficient distinctiveness in the identification of patients for whom recommendations apply and for whom it does not. Conditions were described by medication, diseases, signs, symptoms and laboratory findings. To increase the clarity of the conditions, laboratory findings and signs have the highest potential to be optimized by adding statements about clear cut-off levels (for example 'potassium > 5.0 mmol/L' instead of 'hyperkalaemia') and measurements ('systolic blood pressure >140 mmHg for two consecutive measures' instead of 'hypertension'). In case medication use defines the condition, the same improvements as suggested for actions apply. However, it was also found that in some cases even a description on a drug substance level was not specific enough. For instance, folic acid for patients on methotrexate therapy (START E7) only applies to patients using a low dose, weekly methotrexate schedule and not for patients on high dose methotrexate. In such cases, a more detailed description of a drug dosage, route or indication was deemed necessary. Conditions described by diseases - like 'heart failure' - might seem clear at first

glance but can often be further specified (systolic vs. diastolic) to avoid ambiguity. Adherence to terminology of internationally used dictionaries to describe diseases, such as International Classification of Primary Care (ICPC) and International Classification of Diseases (ICD), could be a solution.

Furthermore, no explanations were present for START criteria to substantiate *why* a potential omitted drug should be initiated. Even though the reason to start a drug might seem obvious in most cases, the risk-benefit balance should always be addressed to assist a physician's decision-making process whether or not to expose their patient to a drug treatment.

Other remarks

STOPP/START criteria provide best evidence-based practices for the over- and undertreatment of single conditions. It should be noted that STOPP/START criteria sometimes contradict each other. For example, in case a patient has a clear indication for a beta blocker to treat ischaemic heart disease (START A7), this is contradicted if a patient is already using verapamil or diltiazem (STOPP B3). This requires clinical consideration and could be a challenge for physicians less experienced in polypharmacy. Merging such recommendations could increase implementation and prevent potential patient harm by overlooking relevant contra-indications.

Besides making the *what*, *how*, *when* and *why* as clear as possible, guideline developers should ask themselves whether recommendations are tailored for its intended end-users (i.e. the *who*). Explicit screening tools to detect inappropriate prescribing in older people such as Beers criteria and STOPP/START, are likely to be developed to reach all healthcare professionals concerned with drug prescribing to significantly reduce under- and overprescribing. Clinicians with high affinity and expertise in geriatric medicine may not need explicit treatment recommendation to provide best patient care. However, STOPP/START criteria also contain recommendations that are best applied by physicians with a certain expertise, such as to start an 'acetylcholinesterase inhibitor for mild-moderate Alzheimer's dementia or Lewy Body dementia (START C3)'. In such cases, the focus for general physicians should probably be recognition and detection, rather than to start a drug treatment. An explicit action could be to refer such patients to a geriatrician or neurologist, thus separating the trigger for potential undertreatment from the actual prescriber.

Strengths and limitations

To the best of our knowledge, this is the first study that explores the clarity of STOPP/START criteria. By systematically reviewing the clarity of the given action, condition and explanation, we identified facilitators (high clarity) and barriers (low clarity) that may be used to improve the content on a language level. As a result, element-specific strategies can be extracted to improve items requiring refinement. Although no previous studies have reviewed the clarity of recommendations of explicit drug screening tools, comparable research has been conducted concerning clarity of monitoring instructions in CPGs and drug labels. Their conclusions to improve ambiguous instructions concerning the monitoring of laboratory values are in line with

our suggestions to add clear statements about the what, why, when and how of recommendations.[22,23]

Clarity ratings were scored by appraisers who were experienced in applying STOPP/START-criteria in clinical practice, as they contributed to a large multicentre, randomized controlled trial that evaluated the impact of a STOPP/START-based medication review in older people with polypharmacy. We believe that these experiences allowed clear identification of difficulties prescribers not familiar with STOPP/START may encounter. Although the scoring process remains partly subjective, the consensus ratings show high inter-rater agreement. Differences (>1 point) were discussed with a third appraiser and consensus was reached for all items. Therefore, the final clarity ratings were considered accurate.

Tools that have been developed to review the quality of entire CPGs underline the importance of clear and unambiguous recommendations[24], but no validated tool exists to rate singular clinical recommendations. As clarity of presentation is both part of the AGREE II Instrument and described by GUIDE-M, we used tools from the AGREE Consortium to develop a review method. Moreover, the AGREE II Instrument is internationally formally endorsed for guideline assessment and provides a Likert-scale that allowed us to quantify clarity.

One concern of further specifying recommendations might be that they 'replace' important clinical considerations made by physicians. However, guideline recommendations are never meant to fully substitute clinical judgement to treat individual patients. This is why the explanation of a recommendation – next to the action and condition sections – is important for facilitating translation to an individual patient level.

A lack of strong evidence to support the recommended actions could impede formulating clear explanations. For example, clear statements on numbers needed to treat (NNT) or numbers needed to harm (NNH) might be difficult to extract from currently available evidence. In such cases, the addition of the strength of recommendations and supporting evidence could further direct clinicians. This is also endorsed by internationally renowned CPG quality assessment tools from AGREE and GRADE.[25]

Furthermore, our study only highlights barriers that could be optimized to prevent unintentional deviations from STOPP/START due to unclear language. Apart from the clarity of presentation, many other factors attribute to clinical implementation of evidence-based recommendations.[26]

Implications

To clarify the action, condition and explanation sections of a recommendation, a more detailed statement is often required. This may directly affect choices on how to present recommendations without giving up formulating a short, simple message. Next to improvements in 'language', also the presentation style or 'format' of a guideline could have a high impact on applicability. In a time where almost all evidence-based knowledge is electronically requested, a dynamic, electronical format could be used to integrate information that will improve clarity of

presentation without making recommendations too extensive. Integrating clinical rules within electronic healthcare systems – with an option to request more detailed information - could contribute to a continuing learning cycle as part of (but without slowing down) the usual care process. For example, a drug class (stop benzodiazepines) may be provided with a hyperlink including information on drug substance levels (ATC5-codes) and a deprescribing tool, accessible upon request. Once a prescriber has become familiar with all the details of a certain recommendation, such information is no longer required. However, converting recommendations into effective software assistance starts with a clear message of the initial statements.[27,28] Another advance to present clear recommendations in an electronic, dynamic format, is that content could be easily modified based on updates in evidence, country specific guidelines, available drugs and local expertise. Collaboration of guideline developers with experts in medical informatics for considering content formatting could therefore be of great value to facilitate future implementation of recommendations in clinical practice.

Conclusion

In conclusion, for future development of recommendations on drug prescribing in older people, our findings provide direction to assure the clarity of recommendations. We see possibilities to transform STOPP/START from a tool to *detect* inappropriate prescribing to a guideline that provides clear statements on how to *act* after detection. The use of specific and unambiguous language in CPG recommendations is likely to aid physicians to prescribe the right drug to the right patient at the right time.

CONTRIBUTORS

Authorship eligibility is based on the four ICMJE authorship criteria. All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: BS, CH, WK, EP, TE, IW. Data acquisition: BS, CH, WK, IW. Analysis and/or interpretation of data: BS, CH, WK, EP, TE, IW. Drafting the manuscript: BS. Revising the manuscript critically for important intellectual content: BS, CH, WK, EP, TE, IW. We have not received substantial contributions from non-authors.

COMPETING INTERESTS

None declared.

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DATA SHARING

All data relevant to the study are included in the article or uploaded as supplementary information.

PATIENT CONSENT FOR PUBLICATION

Not required.

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FIGURE LEGENDS

Fig. 1 *Distribution of clarity ratings for STOPP and START recommendations per element. Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively.*

Fig. 2 *Clarity ratings of conditions for STOPP and START criteria related to five descriptive components*

APPENDICES

Supplementary Dataset S1. *Clarity ratings per element for 80 STOPP and 34 START recommendations*

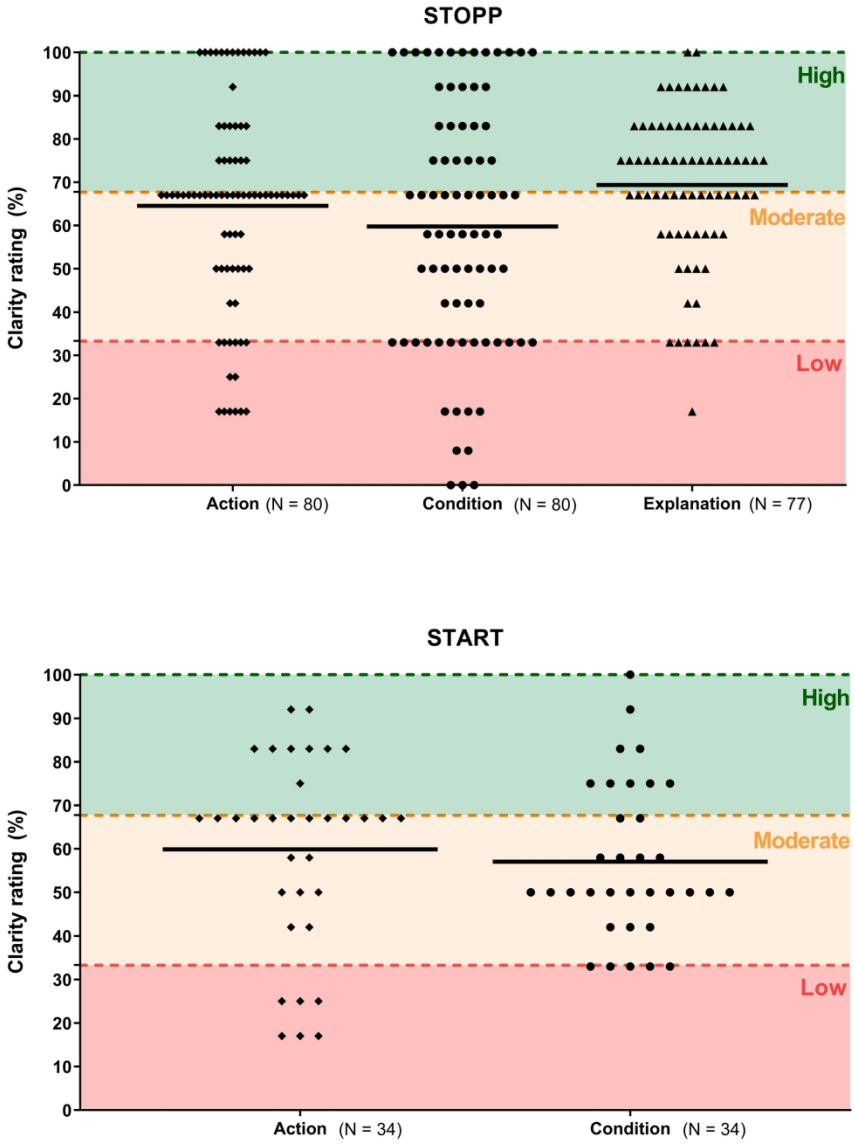

Fig. 1 Distribution of clarity ratings for STOPP and START recommendations per element. Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively.

195x247mm (300 x 300 DPI)

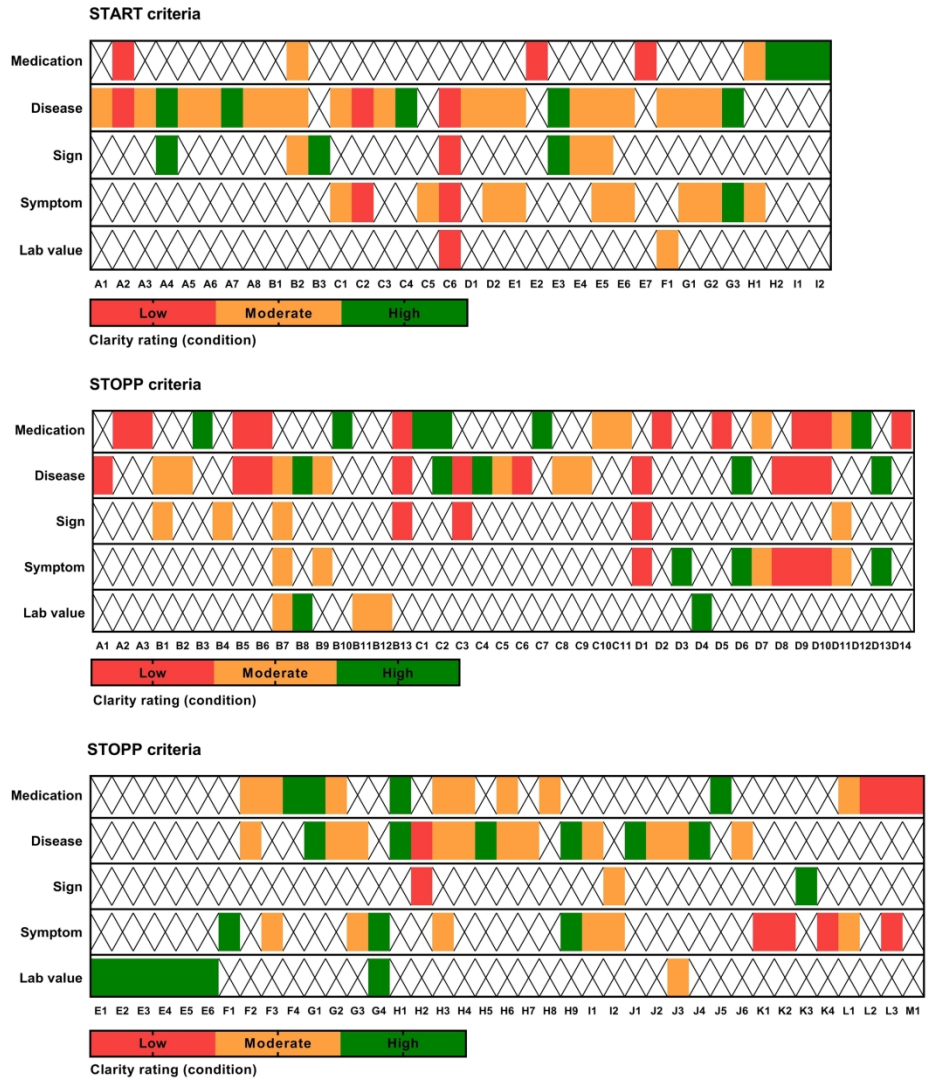

Fig. 2 Clarity ratings of conditions for STOPP and START criteria related to five descriptive components.

215x243mm (300 x 300 DPI)

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Any drug	100%	prescribed without an evidence-based clinical indication.	8%		N/A
A2	Any drug	100%	prescribed beyond the recommended duration, where treatment duration is well defined	8%		N/A
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%	*[users with...duplicate drug class prescription]*	17%	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B						
B1	Digoxin	100%	for heart failure with normal systolic ventricular function	58%	(no clear evidence of benefit).	58%
B2	Verapamil or diltiazem	100%	with NYHA Class III or IV heart failure	58%	(may worsen heart failure).	75%
B3	Beta-blocker	67%	in combination with verapamil or diltiazem	92%	(risk of heart block).	75%
B4	Beta blocker	67%	with bradycardia (< 50/min) , type II heart block or complete heart block	42%	(risk of profound hypotension, asystole).	75%
B5	Amiodarone	100%	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B6	Loop diuretic	67%	as first-line treatment for hypertension	33%	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
B7	Loop diuretic	67%	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	58%	(leg elevation and /or compression hosiery usually more appropriate)	75%
B8	Thiazide diuretic	67%	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	75%	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
B9	Loop diuretic	67%	for treatment of hypertension with concurrent urinary incontinence	67%	(may exacerbate incontinence).	58%
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	75%	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%	in patients with hyperkalaemia.	50%		N/A
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%	without monitoring of serum potassium	67%	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina	33%	(risk of cardiovascular collapse).	67%
C						
C1	Long-term aspirin at doses greater than 160mg per day	83%		92%	(increased risk of bleeding, no evidence for increased efficacy).	75%
C2	Aspirin	92%	with a past history of peptic ulcer disease without concomitant PPI	100%	(risk of recurrent peptic ulcer).	83%
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	33%	(high risk of bleeding)..	58%
C4	Aspirin plus clopidogrel	100%	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	83%	(no evidence of added benefit over clopidogrel monotherapy) .	83%

C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%	in patients with chronic atrial fibrillation	67%	(no added benefit from aspirin).	83%
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in patients with stable coronary, cerebrovascular or peripheral arterial disease	33%	(no added benefit from dual therapy).	67%
C7	Ticlopidine	100%	in any circumstances	100%	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,	67%	(no proven added benefit).	83%
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	67%	(no proven added benefit).	83%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in combination	67%	(risk of gastrointestinal bleeding).	67%
C11	NSAID	67%	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%	(increased risk of peptic ulcer disease)	67%
D						
D1	Tricyclic Antidepressants (TCAs)	67%	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%	(risk of worsening these conditions).	50%
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%	as first-line antidepressant treatment	33%	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%	with a history of prostatism or previous urinary retention	75%	(high risk of urinary retention).	92%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/L	75%	(risk of exacerbating or precipitating hyponatraemia).	92%
D5	Benzodiazepines	67%	for ≥ 4 weeks	33%	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%	in those with parkinsonism or Lewy Body Disease	100%	(risk of severe extra-pyramidal symptoms)	83%
D7	Anticholinergics/antimuscarinics	17%	to treat extra-pyramidal side-effects of neuroleptic medications	50%	(risk of anticholinergic toxicity),	50%
D8	Anticholinergics/antimuscarinics	17%	in patients with Delirium or dementia	33%	(risk of exacerbation of cognitive impairment).	75%
D9	Neuroleptic antipsychotic	25%	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	33%	(increased risk of stroke).	33%
D10	Neuroleptics	33%	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
D11	Acetylcholinesterase inhibitors	67%	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	50%	(risk of cardiac conduction failure, syncope and injury).	92%

D12	Phenothiazines	75%	as first-line treatment,	83%	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
D13	Levodopa or dopamine agonists	83%	for benign essential tremor	100%	(no evidence of efficacy)	83%
D14	First-generation antihistamines	17%	*[users of…first-generation antihistamines]*	33%	(safer, less toxic antihistamines now widely available).	75%
E						
E1	Digoxin at a long-term dose greater than 125µg/day	100%	if eGFR < 30 ml/min/1.73m2	83%	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%	if eGFR < 30 ml/min/1.73m2	100%	(risk of bleeding)	67%
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%	if eGFR < 15 ml/min/1.73m2	100%	(risk of bleeding)	67%
E4	NSAID's	42%	if eGFR < 50 ml/min/1.73m2	100%	(risk of deterioration in renal function).	75%
E5	Colchicine	100%	if eGFR < 10 ml/min/1.73m2	100%	(risk of colchicine toxicity).	83%
E6	Metformin	100%	if eGFR < 30 ml/min/1.73m2	100%	(risk of lactic acidosis).	83%
F						
F1	Prochlorperazine or metoclopramide	100%	with Parkinsonism	92%	(risk of exacerbating Parkinsonian symptoms).	92%
F2	PPI	58%	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%	(dose reduction or earlier discontinuation indicated).	33%
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%	in patients with chronic constipation where non-constipating alternatives are available	67%	(risk of exacerbation of constipation).	100%
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day;	50%		100%	(no evidence of enhanced iron absorption above these doses).	75%
G						
G1	Theophylline	100%	as monotherapy for COPD	75%	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
G2	Systemic corticosteroids	75%	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%	with a history of narrow angle glaucoma or bladder outflow obstruction	42%	(may cause urinary retention).	50%
G4	Benzodiazepines	67%	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%	(risk of exacerbation of respiratory failure).	67%
H						
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	100%	(risk of peptic ulcer relapse).	75%
H2	NSAID	67%	with severe hypertension or severe heart failure	33%	(risk of exacerbation of hypertension/heart failure)	67%
H3	Long-term use of NSAID (>3 months)	75%	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%	(simple analgesics preferable and usually as effective for pain relief)	42%
H4	Long-term corticosteroids (>3 months)	83%	as monotherapy for rheumatoid arthrtitis	67%	(risk of systemic corticosteroid side-effects).	58%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%	for osteoarthritis	100%	(risk of systemic corticosteroid side-effects).	58%
H6	Long-term NSAID or colchicine (>3 months)	67%	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat	50%	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
H7	COX-2 selective NSAIDs	83%	with concurrent cardiovascular disease	42%	(increased risk of myocardial infarction and stroke).	75%
H8	NSAID	58%	with concurrent corticosteroids without PPI prophylaxis	58%	(increased risk of peptic ulcer disease).	75%

H9	Oral bisphosphonates	75%	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	92%	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
I						
I1	Antimuscarinic drugs	17%	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%	(risk of increased confusion, agitation / risk of urinary retention).	67%
I2	Selective alpha-1 selective alpha blockers	67%	in those with symptomatic orthostatic hypotension or micturition syncope	50%	(risk of precipitating recurrent syncope).	75%
J						
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%	with type 2 diabetes mellitus	75%	(risk of prolonged hypoglycaemia).	75%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%	in patients with heart failure	58%	(risk of exacerbation of heart failure).	67%
J3	Beta-blockers	67%	in diabetes mellitus with frequent hypoglycaemic episodes	50%	(risk of suppressing hypoglycaemic symptoms).	83%
J4	Oestrogens	67%	with a history of breast cancer or venous thromboembolism	83%	(increased risk of recurrence).	67%
J5	Oral oestrogens	83%	without progestogen in patients with intact uterus	100%	(risk of endometrial cancer).	67%
J6	Androgens (male sex hormones)	67%	in the absence of primary or secondary hypogonadism	58%	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
K						
K1	Benzodiazepines	67%	*[falls]*	0%	(sedative, may cause reduced sensorium, impair balance).	58%
K2	Neuroleptic drugs	17%	*[falls]*	0%	(may cause gait dyspraxia, Parkinsonism).	58%
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	83%	(risk of syncope, falls).	75%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%	*[falls]*	0%	(may cause protracted daytime sedation, ataxia).	58%
L						
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%	as first line therapy for mild pain	50%	(WHO analgesic ladder not observed).	33%
L2	Use of regular (as distinct from PRN) opioids	67%	without concomitant laxative	17%	(risk of severe constipation).	83%
L3	Long-acting opioids	17%	without short-acting opioids for break-through pain	17%	(risk of non-control of severe pain)	67%
M						
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%	*[users with…concomitant use of two or more drugs with antimuscarinic/anticholinergic properties]*	17%	(risk of increased antimuscarinic/anticholinergic toxicity)	17%

STOPP	Action	Clarity rate
n=80		
D7	Anticholinergics/antimuscarinics	17%
D8	Anticholinergics/antimuscarinics	17%
D14	First-generation antihistamines	17%
I1	Antimuscarinic drugs	17%
K2	Neuroleptic drugs	17%
L3	Long-acting opioids	17%
D9	Neuroleptic antipsychotic	25%
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%
D10	Neuroleptics	33%
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%
E4	NSAID's	42%
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day;	50%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%

F2	PPI	58%
H8	NSAID	58%
B3	Beta-blocker	67%
B4	Beta blocker	67%
B6	Loop diuretic	67%
B7	Loop diuretic	67%
B8	Thiazide diuretic	67%
B9	Loop diuretic	67%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C11	NSAID	67%
D1	Tricyclic Antidepressants (TCAs)	67%
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%
D5	Benzodiazepines	67%
D11	Acetylcholinesterase inhibitors	67%
G4	Benzodiazepines	67%
H2	NSAID	67%
H6	Long-term NSAID or colchicine (>3 months)	67%
I2	Selective alpha-1 selective alpha blockers	67%
J3	Beta-blockers	67%
J4	Oestrogens	67%
J6	Androgens (male sex hormones)	67%
K1	Benzodiazepines	67%
L2	Use of regular (as distinct from PRN) opioids	67%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%
D12	Phenothiazines	75%
G2	Systemic corticosteroids	75%
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%
H3	Long-term use of NSAID (>3 months)	75%
H9	Oral bisphosphonates	75%
C1	Long-term aspirin at doses greater than 160mg per day	83%
D13	Levodopa or dopamine agonists	83%
H4	Long-term corticosteroids (>3 months)	83%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%
H7	COX-2 selective NSAIDs	83%
J5	Oral oestrogens	83%
C2	Aspirin	92%

A1	Any drug	100%
A2	Any drug	100%
B1	Digoxin	100%
B2	Verapamil or diltiazem	100%
B5	Amiodarone	100%
C4	Aspirin plus clopidogrel	100%
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%
C7	Ticlopidine	100%
E1	Digoxin at a long-term dose greater than 125µg/day	100%
E5	Colchicine	100%
E6	Metformin	100%
F1	Prochlorperazine or metoclopramide	100%
G1	Theophylline	100%

STOPP	Condition	Clarity rate
n=80		
K1	*[falls]*	0%
K2	*[falls]*	0%
K4	*[falls]*	0%
A1	prescribed without an evidence-based clinical indication.	8%
A2	prescribed beyond the recommended duration, where treatment duration is well defined	8%
A3	*[users with...duplicate drug class prescription]*	17%
L2	without concomitant laxative	17%
L3	without short-acting opioids for break-through pain	17%
M1	*[users with…concomitant use of two or more drugs with antimuscarinic/anticholinergic properties]*	17%
B5	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%
B6	as first-line treatment for hypertension	33%
B13	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina	33%
C3	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	33%
C6	in patients with stable coronary, cerebrovascular or peripheral arterial disease	33%
D1	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%
D2	as first-line antidepressant treatment	33%
D5	for ≥ 4 weeks	33%
D8	in patients with delirium or dementia	33%
D9	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	33%
D10	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%
D14	*[users of…first-generation antihistamines]*	33%
H2	with severe hypertension or severe heart failure	33%
B4	with bradycardia (< 50/min) , type II heart block or complete heart block	42%
G3	with a history of narrow angle glaucoma or bladder outflow obstruction	42%
H7	with concurrent cardiovascular disease	42%
I1	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%
B11	in patients with hyperkalaemia.	50%
D7	to treat extra-pyramidal side-effects of neuroleptic medications	50%

D11	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	50%
F2	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%
H6	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat	50%
I2	in those with symptomatic orthostatic hypotension or micturition syncope	50%
J3	in diabetes mellitus with frequent hypoglycaemic episodes	50%
L1	as first line therapy for mild pain	50%
B1	for heart failure with normal systolic ventricular function	58%
B2	with NYHA Class III or IV heart failure	58%
B7	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	58%
H3	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%
H8	with concurrent corticosteroids without PPI prophylaxis	58%
J2	in patients with heart failure	58%
J6	in the absence of primary or secondary hypogonadism	58%
B9	for treatment of hypertension with concurrent urinary incontinence	67%
B12	without monitoring of serum potassium	67%
C5	in patients with chronic atrial fibrillation	67%
C8	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,	67%
C9	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	67%
C10	in combination	67%
C11	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%
F3	in patients with chronic constipation where non-constipating alternatives are available	67%
G2	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%
H4	as monotherapy for rheumatoid arthrtitis	67%
B8	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	75%
B10	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	75%
D3	with a history of prostatism or previous urinary retention	75%
D4	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l	75%
G1	as monotherapy for COPD	75%
J1	with type 2 diabetes mellitus	75%

C4	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	83%
D12	as first-line treatment,	83%
E1	if eGFR < 30 ml/min/1.73m2	83%
J4	with a history of breast cancer or venous thromboembolism	83%
K3	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	83%
B3	in combination with verapamil or diltiazem	92%
C1	[Long-term aspirin at doses greater than 160mg per day]	92%
F1	with Parkinsonism	92%
G4	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%
H9	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	92%
C2	with a past history of peptic ulcer disease without concomitant PPI	100%
C7	in any circumstances	100%
D6	in those with parkinsonism or Lewy Body Disease	100%
D13	for benign essential tremor	100%
E2	if eGFR < 30 ml/min/1.73m2	100%
E3	if eGFR < 15 ml/min/1.73m2	100%
E4	if eGFR < 50 ml/min/1.73m2	100%
E5	if eGFR < 10 ml/min/1.73m2	100%
E6	if eGFR < 30 ml/min/1.73m2	100%
F4	*[Oral elemental iron doses greater than 200 mg daily]*	100%
H1	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	100%
H5	for osteoarthritis	100%
J5	without progestogen in patients with intact uterus	100%

STOPP	Explanation	Clarity rating
n=77		
M1	(risk of increased antimuscarinic/anticholinergic toxicity)	17%
A3	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B6	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
D9	(increased risk of stroke).	33%
F2	(dose reduction or earlier discontinuation indicated).	33%
H6	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
L1	(WHO analgesic ladder not observed).	33%
D2	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
H3	(simple analgesics preferable and usually as effective for pain relief)	42%
B10	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
D1	(risk of worsening these conditions).	50%
D7	(risk of anticholinergic toxicity),	50%
G3	(may cause urinary retention).	50%
B1	(no clear evidence of benefit).	58%
B9	(may exacerbate incontinence).	58%
C3	(high risk of bleeding)..	58%
H4	(risk of systemic corticosteroid side-effects).	58%
H5	(risk of systemic corticosteroid side-effects).	58%
K1	(sedative, may cause reduced sensorium, impair balance).	58%
K2	(may cause gait dyspraxia, Parkinsonism).	58%
K4	(may cause protracted daytime sedation, ataxia).	58%
B13	(risk of cardiovascular collapse).	67%
C6	(no added benefit from dual therapy).	67%
C10	(risk of gastrointestinal bleeding).	67%
C11	(increased risk of peptic ulcer disease)	67%
D10	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
E1	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	(risk of bleeding)	67%
E3	(risk of bleeding)	67%
G4	(risk of exacerbation of respiratory failure).	67%
H2	(risk of exacerbation of hypertension/heart failure)	67%
I1	(risk of increased confusion, agitation / risk of urinary retention).	67%
J2	(risk of exacerbation of heart failure).	67%
J4	(increased risk of recurrence).	67%
J5	(risk of endometrial cancer).	67%

L3	(risk of non-control of severe pain)	67%
B2	(may worsen heart failure).	75%
B3	(risk of heart block).	75%
B4	(risk of profound hypotension, asystole).	75%
B7	(leg elevation and /or compression hosiery usually more appropriate)	75%
C1	(increased risk of bleeding, no evidence for increased efficacy).	75%
D8	(risk of exacerbation of cognitive impairment).	75%
D14	(safer, less toxic antihistamines now widely available).	75%
E4	(risk of deterioration in renal function).	75%
F4	(no evidence of enhanced iron absorption above these doses).	75%
G1	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
G2	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
H1	(risk of peptic ulcer relapse).	75%
H7	(increased risk of myocardial infarction and stroke).	75%
H8	(increased risk of peptic ulcer disease).	75%
I2	(risk of precipitating recurrent syncope).	75%
J1	(risk of prolonged hypoglycaemia).	75%
K3	(risk of syncope, falls).	75%
B5	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B8	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
C2	(risk of recurrent peptic ulcer).	83%
C4	(no evidence of added benefit over clopidogrel monotherapy) .	83%
C5	(no added benefit from aspirin).	83%
C8	(no proven added benefit).	83%
C9	(no proven added benefit).	83%
D6	(risk of severe extra-pyramidal symptoms)	83%
D13	(no evidence of efficacy)	83%
E5	(risk of colchicine toxicity).	83%
E6	(risk of lactic acidosis).	83%
H9	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
J3	(risk of suppressing hypoglycaemic symptoms).	83%
L2	(risk of severe constipation).	83%
B12	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
C7	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
D3	(high risk of urinary retention).	92%
D4	(risk of exacerbating or precipitating hyponatraemia).	92%
D11	(risk of cardiac conduction failure, syncope and injury).	92%

D12	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
F1	(risk of exacerbating Parkinsonian symptoms).	92%
J6	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
D5	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
F3	(risk of exacerbation of constipation).	100%

START	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%	in the presence of chronic atrial fibrillation.	50%		N/A
A2	Aspirin (75 mg – 160 mg once daily)	92%	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%		N/A
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%	with a documented history of coronary, cerebral or peripheral vascular disease.	58%		N/A
A4	Antihypertensive therapy	25%	where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%		N/A
A5	Statin therapy	67%	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%		N/A
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%	with systolic heart failure and/or documented coronary artery disease.	58%		N/A
A7	Beta-blocker	67%	with ischaemic heart disease.	75%		N/A
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%	with stable systolic heart failure.	67%		N/A
B						
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%	for mild to moderate asthma or COPD.	50%		N/A
B2	Regular inhaled corticosteroid	58%	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%		N/A
B3	Home continuous oxygen	83%	with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	92%		N/A
C						
C1	L-DOPA or a dopamine agonist	67%	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%		N/A
C2	Non-TCA antidepressant drug	25%	in the presence of persistent major depressive symptoms.	33%		N/A
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%		N/A
C4	Topical prostaglandin, prostamide or beta-blocker	67%	for primary open-angle glaucoma.	100%		N/A
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%	for persistent severe anxiety that interferes with independent functioning.	50%		N/A
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%		N/A
D						
D1	Proton Pump Inhibitor	67%	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%		N/A
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%	for diverticulosis with a history of constipation.	58%		N/A
E						
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%	with active, disabling rheumatoid disease.	42%		N/A
E2	Bisphosphonates and vitamin D and calcium	67%	in patients taking long-term systemic corticosteroid therapy.	33%		N/A

E3	Vitamin D and calcium supplement	17%	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%		N/A
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%		N/A
E5	Vitamin D supplement	42%	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%		N/A
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%	with a history of recurrent episodes of gout.	50%		N/A
E7	Folic acid supplement	92%	in patients taking methotexate.	33%		N/A
F						
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%		N/A
G						
G1	Alpha-1 receptor blocker	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G2	5-alpha reductase inhibitor	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%	for symptomatic atrophic vaginitis	75%		N/A
H						
H1	High-potency opioids	17%	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%		N/A
H2	Laxatives	17%	in patients receiving opioids regularly.	75%		N/A
I						
I1	Seasonal trivalent influenza vaccine	83%	annually	83%		N/A
I2	Pneumococcal vaccine	83%	at least once after age 65 according to national guidelines	83%		N/A

START	Action	Clarity rating
n=34		
E3	Vitamin D and calcium supplement	17%
H1	High-potency opioids	17%
H2	Laxatives	17%
A4	Antihypertensive therapy	25%
C2	Non-TCA antidepressant drug	25%
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%
E5	Vitamin D supplement	42%
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%
B2	Regular inhaled corticosteroid	58%
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%
A5	Statin therapy	67%
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%
A7	Beta-blocker	67%
C1	L-DOPA or a dopamine agonist	67%
C4	Topical prostaglandin, prostamide or beta-blocker	67%
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%
D1	Proton Pump Inhibitor	67%
E2	Bisphosphonates and vitamin D and calcium	67%
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%
G1	Alpha-1 receptor blocker	67%
G2	5-alpha reductase inhibitor	67%
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%
B3	Home continuous oxygen	83%
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%
I1	Seasonal trivalent influenza vaccine	83%
I2	Pneumococcal vaccine	83%
A2	Aspirin (75 mg – 160 mg once daily)	92%
E7	Folic acid supplement	92%

START	Condition	Clarity rate
n=34		
A2	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%
C2	in the presence of persistent major depressive symptoms.	33%
C6	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%
E2	in patients taking long-term systemic corticosteroid therapy.	33%
E7	in patients taking methotexate.	33%
A5	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%
C3	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%
E1	with active, disabling rheumatoid disease.	42%
A1	in the presence of chronic atrial fibrillation.	50%
B1	for mild to moderate asthma or COPD.	50%
B2	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%
C1	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%
C5	for persistent severe anxiety that interferes with independent functioning.	50%
D1	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%
E5	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%
E6	with a history of recurrent episodes of gout.	50%
G1	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
G2	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
H1	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%
A3	with a documented history of coronary, cerebral or peripheral vascular disease.	58%
A6	with systolic heart failure and/or documented coronary artery disease.	58%
D2	for diverticulosis with a history of constipation.	58%

E4	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%
A8	with stable systolic heart failure.	67%
F1	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%
A4	where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%
A7	with ischaemic heart disease.	75%
E3	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%
G3	for symptomatic atrophic vaginitis	75%
H2	in patients receiving opioids regularly.	75%
I1	annually	83%
I2	at least once after age 65 according to national guidelines	83%
B3	with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	92%
C4	for primary open-angle glaucoma.	100%

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Evaluation of clarity of the STOPP/START criteria for clinical applicability in prescribing for older people: a quality appraisal study

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ABSTRACT

Objectives: Appropriate prescribing in older people continues to be challenging. Studies still report a high prevalence of inappropriate prescribing in older people. To reduce the problem of under- and overprescribing in this population, explicit drug optimization tools have been developed. The aim of this study was to evaluate the clinical applicability in daily patient care of the STOPP/START criteria, an explicit screening tool for potentially inappropriate prescribing in older people, by assessing clarity.

Design: Quality appraisal study

Methods: For each of the 114 STOPP/START criteria version 2, elements describing the action (*what/how to do*), condition (*when to do*) and explanation (*why to do*) were identified. Next, the clarity of these three elements were quantified on a 7-point Likert scale using tools provided by the Appraisal of Guidelines for Research & Evaluation (AGREE) consortium.

Primary and secondary outcomes: The primary outcome measure was the clarity rating per element, categorized into high (>67.7%), moderate (33.3-67.7%) or low (<33.3%). Secondary, factors that positively or negatively affected clarity most were identified. Additionally, the nature of the conditions were further classified into five descriptive components: disease, sign, symptom, laboratory finding and medication.

Results: STOPP recommendations had an average clarity rating of 65%, 60% and 67% for actions, conditions and explanations respectively. The average clarity rating in START recommendations was 60% and 57% for actions and conditions respectively. There were no statements present to substantiate the prescription of potential omissions for the 34 START criteria.

Conclusions: Our results show that the clarity of the STOPP/START criteria can be improved. For future development of explicit drug optimization tools, such as STOPP/START, our findings identified facilitators (high clarity) and barriers (low clarity) that can be used to improve the clarity of drug recommendations on a language level and therefore enhance clinical applicability.

Strengths and limitations of this study

- To the best of our knowledge, this is the first study that explores the clarity of STOPP/START criteria
- Clarity ratings were scored independently by appraisers who were experienced in applying STOPP/START-criteria in clinical practice
- By evaluating the '*what'*, '*when'* and '*why'* of recommendations, element-specific strategies were formulated to improve their clarity
- The scoring process remains partly subjective, however consensus ratings show high inter-rater agreement

INTRODUCTION

Clinical practice guidelines (CPG) are instruments intended to provide guidance to healthcare professionals in patient care. Translation of healthcare knowledge, evidence and experience into clear recommendations for patient care is, however, challenging. Studies in the USA and the Netherlands suggest that about 30–40% of patients do not receive care according to current scientific evidence as represented in guidelines. A clear description of the desired performance has been associated with better compliance with guideline recommendations.[1,2]

Recommendations about safe and effective pharmacotherapy are an important part of CPGs. However, it is often unclear whether recommendations also apply to older people.[3-5] A complicating factor is that older people experience more concurrent illnesses, while CPGs often focus on best treatment of a single disease. Ambiguity among prescribers about pharmacotherapy in older people results in inappropriate prescribing, which causes adverse drug reactions, drug-related hospitalizations, decreased quality of life and even death.[6,7]

To fill in a lack of clear statements in CPGs about (in)appropriate prescribing in older people with multimorbidity, several explicit screening tools have been developed.[8,9] The most widely used are the Beers criteria[10] and the Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria.[11] CPG recommendations are rarely specified in precise behavioural terms such as *what, how, when,* and *why* to stop or start a drug, while explicit screening tools are designed to make clear statements and therefore ease clinical implementation.[2] However, studies continue to report a high prevalence of inappropriate prescribing in older people.[12-14] This suggests there is still an incomplete implementation.

Although STOPP/START criteria have shown good inter-rater reliability in studies involving physicians and (hospital)pharmacists working in geriatric units, data on how physicians less familiar with medication optimization would interpret STOPP/START criteria are lacking.[15,16] The question then arises whether the recommended actions are formulated clearly enough to guide prescribers less experienced with treating geriatric patients.

The aim of this study was to evaluate for clinical applicability in daily patient care the STOPP/START criteria by assessing the clarity of the different criteria with the purpose of improving future clinical guideline recommendations for prescribing in older people.

METHODS

STOPP/START criteria

The STOPP/START criteria were first published in 2008 and have been updated in 2015 to STOPP/START version 2.[17] STOPP/START is a product of two Delphi rounds by 19 experts from 13 European countries.

For this study, the supplementary data of the corrigendum of the STOPP/START criteria version 2 as published in November 2017 were used.[18] STOPP/START version 2 consists of a list of 80 Potentially Inappropriate Medications (PIMs, STOPP criteria) and 34 Potential Prescribing Omissions (PPOs, START criteria).

Clarity assessment

The AGREE II Instrument and GUIDE-M were used to develop a framework to assess the clarity of language used in STOPP/START. AGREE II Instrument is an internationally validated tool to rate the quality of CPGs, developed by the Appraisal of Guidelines for Research & Evaluation (AGREE) Consortium.[19] In addition to the AGREE II Instrument, AGREE developed a Guideline Implementability Decision Excellence Model (GUIDE-M).[20] This model identifies '*communicating content'* as a core tactic for CPG implementability. Obviously, language is an important domain of this tactic. The language subdomain promotes a clear, simple, and persuasive message.

The relevant part of the AGREE II Instrument ('clarity of presentation', domain 4, item 15) states that recommendations should be 'specific and unambiguous', which is defined as *'a concrete and precise description of which option is appropriate for which situation and for what population group'*. In line with this statement and the corresponding section of the AGREE II Instrument, three elements were identified that influence the clarity of recommendations:

- **Action:** description of the recommended action - i.e. *what* to do and *how* to act?
- **Condition:** identification of the relevant target population and statements about patients or conditions for whom the recommendations would apply or not apply – i.e. *when*?
- **Explanation:** identification of the intent or purpose of the recommended action – i.e. *why*?

In order to quantify the clarity of STOPP/START criteria, the three elements of each recommendation were rated independently on a 7-point Likert scale by a panel of two appraisers, consisting of a geriatric resident (CH) and a hospital pharmacist resident (BS), both experienced with the application of STOPP/START criteria in daily practice. The clarity for each of these three elements was rated from the perspective of a 'junior' physician or pharmacist with a basic level of knowledge (≤ 5 years of clinical post-graduate experience). The appraisers were trained with a rating guidance, developed and approved by senior clinicians (TE/EP/IW/WK) prior to

rating the elements independently. If ratings differed more than 1 point, a senior hospital pharmacist/clinical pharmacologist (IW) or a senior geriatrician/clinical pharmacologist (WK) was consulted as a third appraiser until consensus was reached.

Descriptive components of conditions

In addition to the calculation of clarity ratings for the action, condition and explanation, the nature of the conditions was further explored. The condition identifies the target population and is the most heterogeneous element. By stratifying the conditions into descriptive components, the nature of the components in relation to their clarity could be assessed. These components could lead to different strategies to optimize 'specific and unambiguous' wording in describing conditions.

The conditions were subdivided into five components that were considered essential for identification of the target population: *disease, sign, symptom, laboratory finding* and *medication*. Definitions of four components were based on the ontology as described by Scheuermann et al.[21] *Signs* are defined as bodily features observed in a physical examination including measurements like blood pressure, while *symptoms* are bodily features experienced by a patient, like parkinsonism. Since optimization of polypharmacy is the main focus of the STOPP/START, the target population can also be described by (co-)*medication*. *Medication* is not defined by Scheuermann et al. Therefore, medication was added as a fifth component using the definition for medicinal products by the European Medicines Agency (EMA) as *'a substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action'*.[22]

Data analysis

Clarity ratings for each of the three elements (action, condition, explanation) were calculated as a percentage of the obtained scores given by appraiser 1 and 2 divided by the maximum score.

$$Clarity\ rating(\%) = \frac{obtained\ score\ (sum\ of\ 2\ appraisers) - minimum\ possible\ score\ (2)}{maximum\ possible\ score\ (14) - minimum\ possible\ score\ (2)}$$

This calculation method is in accordance with the approach provided by AGREE II instrument. The scores of appraisers 1 and 2 were both replaced by the consensus score when a third appraiser was consulted. After scoring the elements, clarity ratings were categorized into low (<33.3%), moderate (33.3% - 67.7%) and high (>67.7%).

Patient and public involvement

Since this is an appraisal study of clinical guideline recommendations intended to be used by clinicians, this research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or

interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Ethics approval

Ethics approval was not required for this appraisal study as no human or animal data was involved.

RESULTS

The elements 'action' and 'condition' in STOPP and START recommendations were rated on their clarity, resulting in 80 and 34 scores per element, respectively. The element 'explanation' was present in all but three (A1, A2, B11) STOPP recommendations, resulting in 77 scores. None of the START criteria contained an explanation to substantiate the prescription of potential omissions. Therefore, Likert scores for explanations were only assessed in STOPP recommendations.

The agreement among the two appraisers for Likert scores was high and ranged from 76.3% (STOPP – condition) to 91.3% (STOPP – action). 44 out of 305 (14.4%) scores were replaced after consensus meetings with a third appraiser. Replacements did not alter average Likert scores per element with more than 0.2 points compared to the average scores prior to consensus.

Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively. (*figure 1*)

In 80 STOPP and 34 START recommendations, 35 actions were categorized as high (30.7%), 65 as moderate (57.0%) and 14 as low (12.3%). 38 (33.3%), 67 (58.8%) and 9 (7.9%) conditions had a high, moderate or low clarity rating, respectively. In 77 STOPP criteria, 41 (53,2%) explanations were categorized as high, 35 (45.5%) as moderate and 1 (1.3%) as low.

13 STOPP criteria (C1, C2, C4, C7, D6, D12, D13, E5, E6, F1, G1, H1, H9) had high clarity ratings for all three elements. 4 START criteria (B3, G3, I1, I2) had high clarity ratings for both action and condition. Detailed information of clarity ratings per element for all individual STOPP/START-criteria can be found in *Supplementary data S1*.

Elements with high (>67.7%) and moderate or low (≤67.7%) clarity ratings were analysed in more detail to identify factors that either positively or negatively affected 'specific and ambiguous' language most. These findings for actions, conditions and explanations with illustrative examples for STOPP and START recommendations are presented in *table 1*.

Table 1. *Main barriers and facilitators that affected clarity of the elements action, condition and explanation of STOPP/START recommendations.*

Barriers	**Example** [a] (clarity rating, %)
ACTION	
Lack of explicit drug (class)	STOPP D7/8. **Anticholinergics / antimuscarinics** (17%)
➢ 'e.g.' is inconclusive	STOPP B10. Centrally-acting antihypertensives (**e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine**) (33%)
➢ Use of adjectives that need further investigation to allow use	STOPP D14. **First-generation** antihistamines (17%) START H1. **High potency** opioids (17%)
Lack of drug deprescribing schedules while considered necessary	STOPP K2. **Neuroleptic drugs** (17%)
Starting dose and target dose not mentioned	START C2. **Angiotensin Converting Enzyme (ACE) inhibitor** with systolic heart failure (67%)
Lack of directions how and what to monitor after starting a drug	SART E1. **Disease-modifying anti-rheumatic drug** (DMARD) (25%)
CONDITION	
General - Patient population for whom recommendations would not apply was not (clearly / unambiguously) defined	
➢ In patients with a strong indication for a potentially inappropriate drug, it may be harmful to stop it	STOPP B5. **as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias** (33%)
➢ In patients with potential omissions, warnings for important contra indications are lacking / not clearly defined	START A2. **where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated** (33%)
Medication – see also *action*	
➢ Ambiguous adjectives were used ➢ Description of drug therapy (substance / dosage) not specific enough	STOPP D2. **as first-line antidepressant treatment** (33%) START E7. in patients taking **methotrexate** (33%)
Disease - Clinical interpretation of 'disease state' for defining population needed	STOPP D1. with **dementia**, narrow angle glaucoma, **cardiac conduction abnormalities**, prostatism, or **prior history of urinary retention** (33%) START A5**.** with a documented **history of coronary, cerebral or peripheral vascular disease** (33%)
Sign - Measurement or scores were not described unambiguously	STOPP H2. with **severe hypertension** or **severe heart failure** (33%) START E1. with **active**, **disabling rheumatoid disease** (42%)
Symptom - Symptoms were not described unambiguously	STOPP K-section. Not clear whether the occurrence of **'falls'** - as mentioned only in the title of section K - is a condition or used to address the risk of falls. If 'falls' is considered a condition, the frequency of 'falls' is not specified. (0%) STOPP D10. unless **sleep disorder** is due to (33%) START C2. with **persistent major depressive symptoms** (33%)

Laboratory finding - Parameters lack clear cut-off levels with reference ranges	START C6. once **iron deficiency** and **severe renal failure** have been excluded (33%)
EXPLANATION	
Risk of continuing therapy not clearly described: explanation does not cover clinical relevance of benefit / harm balance (specific adverse drug reactions, toxicity).	STOPP D7. **(risk of anticholinergic toxicity)** (17%) START N/A
Facilitators	**Example** [a] (clarity rating, %)
ACTION	
Drugs were specified on individual drug level and -if necessary- route / dosage was specified	STOPP C7. **Ticlopidine** (100%) START A2. **Aspirin (75 mg – 160 mg once daily)** (92%)
CONDITION	
Medication – see also *action* Specific description of drug therapy (substance / dosage) to clearly identify the target population (i.e. patients using a certain drug regimen).	STOPP B3. in combination with **verapamil** or **diltiazem** (92%) START I2. **at least once after age 65 according to national guidelines** (83%)
Disease - Diseases clearly described so that the target population could be easily identified	STOPP H9. in patients **with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding** (92%) START C4. for **primary open-angle glaucoma**. (100%)
Signs - Signs clearly described as scores or measurements and therefore unambiguous	START B3. with documented chronic hypoxaemia **(i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)** (92%)
Symptom - Symptoms clearly and unambiguous described	STOPP F1. with **Parkinsonism** (92%)
Laboratory findings - Clear cut-off levels with reference ranges present	STOPP E6. if **eGFR < 30 ml/min/1.73m2** (100%)
EXPLANATION	
Risk of discontinuing clearly described	STOPP D5. (**no indication for longer treatment**; **risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly**). (100%) START N/A

[a] *The examples shown are selected from elements with low and moderate (≤67.7%) clarity ratings for barriers and from high (>67.7%) clarity ratings for facilitators to substantiate the main findings. An overview of all clarity ratings can be found in the Supplementary data S1.*

The results of stratifying the element 'condition' into the five descriptive components medication, disease, sign, symptom and laboratory finding are shown per STOPP/START recommendation in *figure 2*. The clarity rating per condition is displayed by the addition of a colouring scale. Clarity ratings were scored on the level of condition as an element and not on the level of descriptive components. Therefore, components that together form the condition of one recommendation share the same colouring for their clarity.

In 33 (41%) STOPP criteria and 17 (50%) START criteria, the condition consisted of more than one component. No strong association was found between the clarity of conditions and the nature of the descriptive components, as the clarity ratings of the condition section varied regardless of the nature of the component. However, laboratory findings used to identify the target population were discovered to have the highest clarity rating compared with other descriptive components in STOPP recommendations; 9 out of 13 laboratory-based conditions had a high clarity rating (>67.7%).

DISCUSSION

Main findings

Only 13 out of 80 STOPP and 4 out of 34 START criteria had a high clarity rating for the three elements action, condition and explanation. To improve clarity of recommendations, element-specific strategies can be formulated (*table 1*).

Actions were considered unclear if recommendations included non-explicitly specified drug classes (e.g. 'anticholinergics'). To improve clear description of the action (*what and how*) we advise to specify drugs at an individual substance level. The addition of how to start or stop a drug (immediately versus gradually including monitoring guidelines and deprescribing schedules), route of administration and dosage were considered necessary in some actions to further improve clarity.

The definition of the condition (*the when*) had the lowest average clarity rating in both START and STOPP. Low clarity ratings for conditions were a result of insufficient distinctiveness in the identification of patients for whom recommendations apply and for whom it does not. Conditions were described by medication, diseases, signs, symptoms and laboratory findings. To increase the clarity of the conditions, laboratory findings and signs have the highest potential to be optimized by adding statements about clear cut-off levels (for example 'potassium >5.0 mmol/L' instead of 'hyperkalaemia') and measurements ('HAS-BLED score >2' instead of 'significant bleeding risk'). For conditions defined by medication use, the same improvements as suggested for actions apply. Again, in some cases even a description on a drug substance level was not specific enough. For instance, folic acid for patients on methotrexate therapy (START E7) only applies to patients using a low dose, weekly methotrexate schedule and not for patients on high dose methotrexate. In such cases, a more detailed description of a drug dosage, route or indication was deemed necessary. Conditions described by diseases - like 'heart failure' - might

seem clear at first glance but often need further specification (systolic vs. diastolic or reduced vs. preserved ejection fraction) to avoid ambiguity, as international guidelines of cardiologists too distinguish between these subtypes of heart failure, which affects treatment recommendations. Adherence to terminology of internationally used dictionaries to describe diseases, such as International Classification of Primary Care (ICPC) and International Classification of Diseases (ICD), could be a solution.

Furthermore, no explanations were present for START criteria to substantiate *why* a potential omitted drug should be initiated. Even though the reason to start a drug might seem obvious in most cases, the risk-benefit balance should always be addressed to assist a physician's decision-making process whether or not to expose their patient to a drug treatment.

Other remarks

STOPP/START criteria provide best evidence-based practices for the over- and undertreatment of single conditions. It should be noted that STOPP/START criteria sometimes contradict each other. For example, if a patient has a clear indication for a beta blocker to treat ischaemic heart disease (START A7), this is contradicted if a patient is already using verapamil or diltiazem (STOPP B3). Merging such recommendations could increase implementation and prevent potential patient harm by overlooking relevant contra-indications.

Besides making the *what*, *how*, *when* and *why* as clear as possible, guideline developers should ask themselves whether recommendations are tailored for its intended end-users (i.e. the *who*). Explicit screening tools to detect inappropriate prescribing in older people such as Beers criteria and STOPP/START, are likely to be developed to reach all professionals concerned with prescribing, as all prescribers take part into the problem of under- and overprescribing in older people. . Clinicians with high affinity and expertise in geriatric medicine may not need explicit treatment recommendation to provide best patient care, whereas clinicians - such as surgical specialists - who treat older people but may be less experienced with appropriate prescribing in older people probably require more clear guidance. Clear recommendations are therefore important to reach all prescribers, because the success of STOPP/START criteria as an intervention depends on its integration and implementation in clinical practice.[23] Some recommendations may be best applied by physicians with a certain expertise, such as to start an 'acetylcholinesterase inhibitor for mild-moderate Alzheimer's dementia or Lewy Body dementia (START C3)'. In such cases, the focus for all clinicians should probably be the recognition and detection of a potential omission, rather than to actually start a drug treatment. An explicit action could be to refer such patients to a geriatrician or neurologist, thus separating the trigger for potential undertreatment from the actual prescriber.

Strengths and limitations

To the best of our knowledge, this is the first study that explores the clarity of STOPP/START criteria. By systematically reviewing the clarity of the given action, condition and explanation, we identified facilitators (high clarity) and barriers (low clarity) that may be used to improve the content on a language level. As a result, element-specific strategies can be extracted to improve items requiring refinement. Although no previous studies have reviewed the clarity of singular recommendations of explicit drug screening tools, comparable research has been conducted concerning clarity of monitoring instructions in CPGs and drug labels. Their conclusions to improve ambiguous instructions concerning the monitoring of laboratory values are in line with our suggestions to add clear statements about the what, why, when and how of recommendations.[24,25]

Furthermore, there have been studies carried out to refine the methodology of developing deprescribing guidelines to facilitate the deprescribing process.[26,27] A good example are the tools provided by the Bruyère Research Institute, based on their research about developing deprescribing guidelines. The Bruyère research group has published evidence-based clinical practice guidelines (for instance how to deprescribe benzodiazepines), accompanied by clear algorithms including well-described populations for which patients the recommendation does not apply, a list of available drugs and dosage, monitoring recommendations and tapering regimes, thereby complementing the clarity some STOPP-recommendations are lacking.[28]

Tools that have been developed to review the quality of entire CPGs underline the importance of clear and unambiguous recommendations[29], but no validated tool exists to rate singular clinical recommendations. As clarity of presentation is both part of the AGREE II Instrument and described by GUIDE-M, we used tools from the AGREE Consortium to develop a review method. Moreover, the AGREE II Instrument is internationally formally endorsed for guideline assessment and provides a Likert-scale that allowed us to quantify clarity.

Clarity ratings were scored by appraisers who were experienced in applying STOPP/START-criteria in clinical practice, as they contributed to a large multicentre, randomized controlled trial that evaluated the impact of a STOPP/START-based medication review in older people with polypharmacy. We believe that these experiences allowed clear identification of difficulties prescribers not familiar with STOPP/START may encounter. Although the scoring process remains partly subjective, the consensus ratings show high inter-rater agreement. Differences (>1 point) were discussed with a third appraiser and consensus was reached for all items. Therefore, the final clarity ratings were considered accurate.

One concern of further specifying recommendations might be that they ‘replace’ important clinical considerations made by physicians. However, guideline recommendations are never meant to fully substitute clinical judgement to treat individual patients. This is why the

explanation of a recommendation – next to the action and condition sections – is important for facilitating translation to an individual patient level.

A lack of strong evidence to support the recommended actions could impede formulating clear explanations. For example, clear statements on numbers needed to treat (NNT) or numbers needed to harm (NNH) might be difficult to extract from currently available evidence. In such cases, the addition of the strength of recommendations and supporting evidence could further direct clinicians. This is also endorsed by internationally renowned CPG quality assessment tools from AGREE and GRADE.[30]

Furthermore, our study only highlights barriers that could be optimized to prevent unintentional deviations from STOPP/START due to unclear language. Apart from the clarity of presentation, many other factors attribute to clinical implementation of evidence-based recommendations. [27,31]

Implications

To clarify the action, condition and explanation sections of a recommendation, a more detailed statement is often required. This may directly affect choices on how to present recommendations without giving up formulating a short, simple message. Next to improvements in 'language', also the presentation style or 'format' of a guideline could have a high impact on applicability. In a time where almost all evidence-based knowledge is electronically requested, a dynamic, electronical format could be used to integrate information that will improve clarity of presentation without making recommendations too extensive. Integrating clinical rules within electronic healthcare systems – with an option to request more detailed information - could contribute to a continuing learning cycle as part of (but without slowing down) the usual care process. For example, a drug class (stop benzodiazepines) may be provided with a hyperlink including information on drug substance levels (ATC5-codes) and a deprescribing tool, accessible upon request. Once a prescriber has become familiar with all the details of a certain recommendation, such information is no longer required. However, converting recommendations into effective software assistance starts with a clear message of the initial statements.

To make the current version of STOPP/START criteria suitable for software engines, multiple multidisciplinary expert rounds turned out to be necessary to reach consensus on how to interpret ambiguous wordings.[32] For instance, due to different lists of anticholinergic drugs in current literature, expert opinion is needed to translate this drug class to clinically relevant, individual drugs with high anticholinergic burden. Furthermore, it was found that some recommendations, such as to 'stop any drug beyond the recommended duration (STOPP A3)' were too vague to convert into an algorithm. Selecting specific recommendations concerning potentially inappropriate long-term use of medication, such as long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (STOPP H4) or continuing bisphosphonates >5 years without evaluating efficacy (not a criterion), will probably result in a better uptake among

clinicians and can be easily integrated in clinical decision support systems. Consequently, a lack of clear statements may impede software implementation.[32,33]

Another advance to present clear recommendations in an electronic, dynamic format, is that content could be easily modified based on updates in evidence, country specific guidelines, available drugs and local expertise. Collaboration of guideline developers with experts in medical informatics for considering content formatting could therefore be of great value to facilitate future implementation of recommendations in clinical practice.

Conclusion

In conclusion, for future development of recommendations on drug prescribing in older people, our findings provide direction to assure the clarity of recommendations. We see possibilities to transform STOPP/START from a tool to *detect* inappropriate prescribing to a guideline that provides clear statements on how to *act* after detection. The use of specific and unambiguous language in CPG recommendations is likely to aid physicians to prescribe the right drug to the right patient at the right time.

CONTRIBUTORS

Authorship eligibility is based on the four ICMJE authorship criteria. All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: BS, CH, WK, EP, TE, IW. Data acquisition: BS, CH, WK, IW. Analysis and/or interpretation of data: BS, CH, WK, EP, TE, IW. Drafting the manuscript: BS. Revising the manuscript critically for important intellectual content: BS, CH, WK, EP, TE, IW. We have not received substantial contributions from non-authors.

COMPETING INTERESTS

None declared.

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DATA SHARING

All data relevant to the study are included in the article or uploaded as supplementary information.

PATIENT CONSENT FOR PUBLICATION

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FIGURE LEGENDS

Fig. 1 *Distribution of clarity ratings for STOPP and START recommendations per element. Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively.*

Fig. 2 *Clarity ratings of conditions for STOPP and START criteria related to five descriptive components*

APPENDICES

Supplementary Dataset S1. *Clarity ratings per element for 80 STOPP and 34 START recommendations*

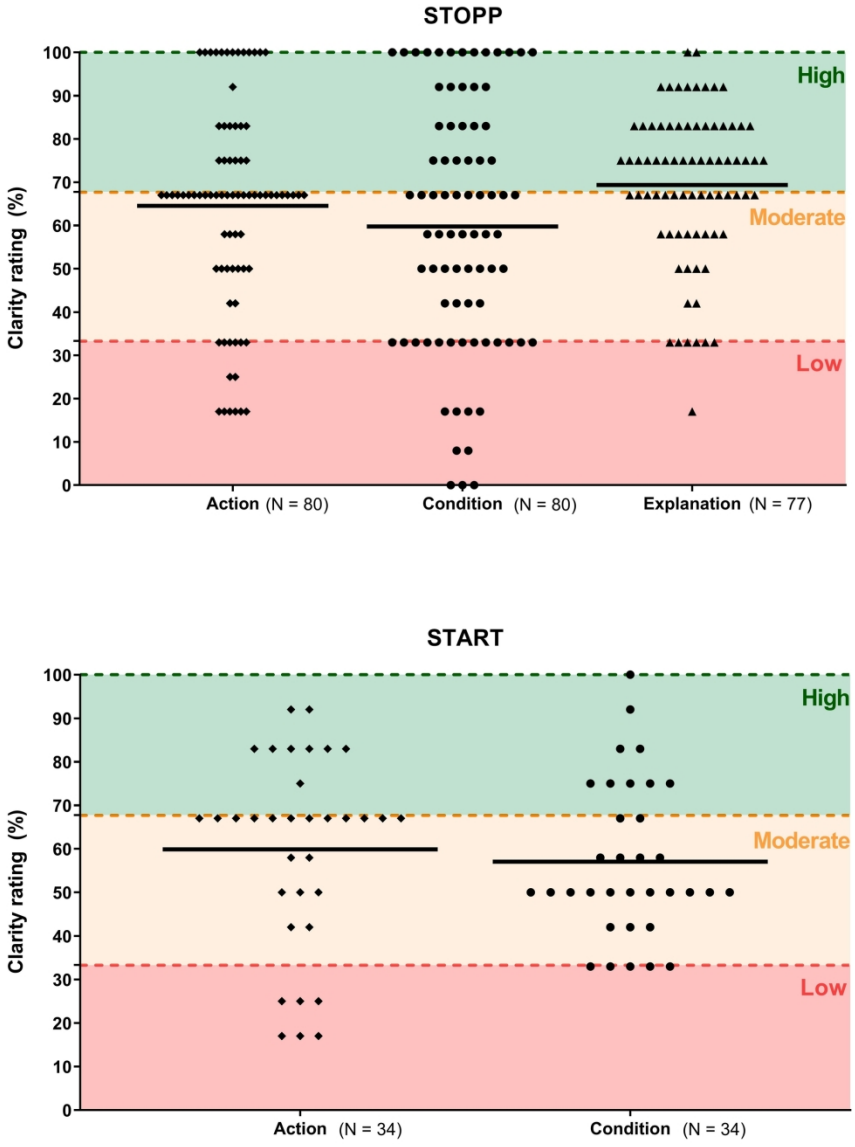

Fig. 1 Distribution of clarity ratings for STOPP and START recommendations per element. Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively.

195x247mm (300 x 300 DPI)

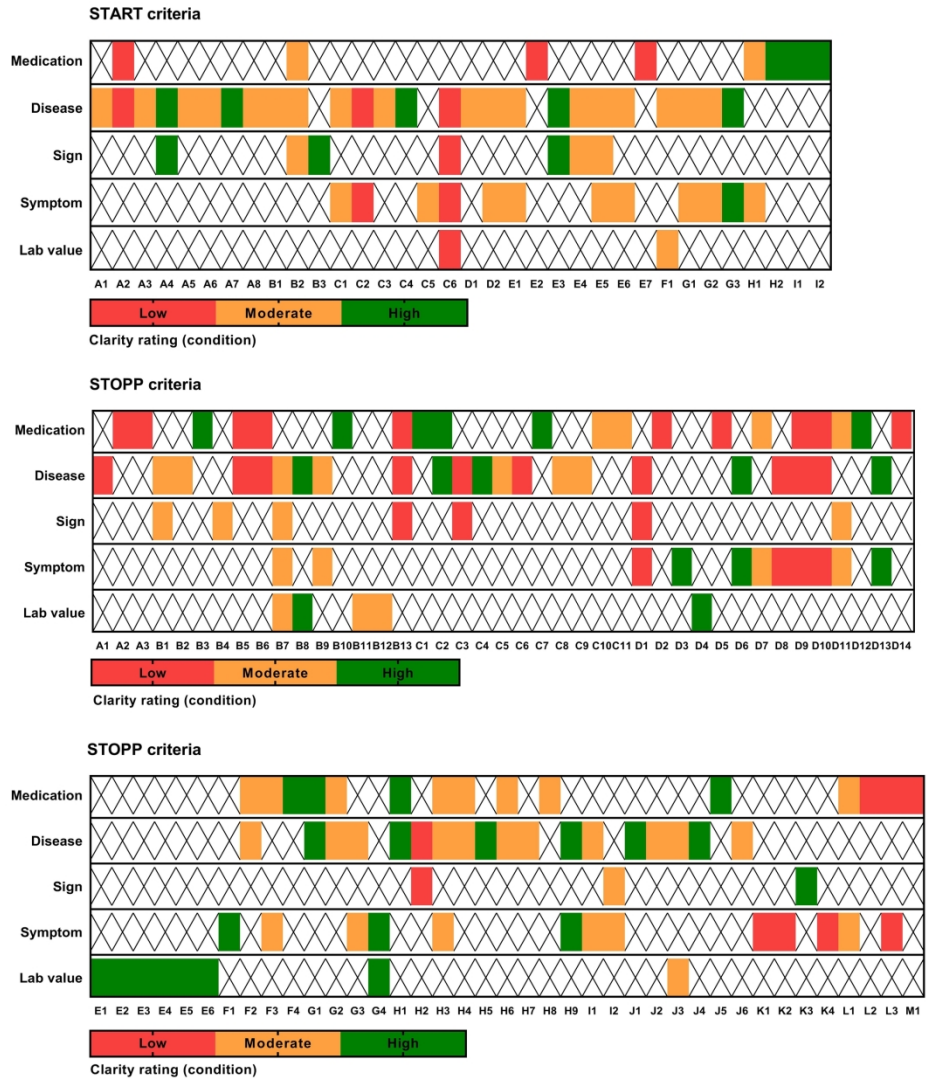

Fig. 2 Clarity ratings of conditions for STOPP and START criteria related to five descriptive components.

215x243mm (300 x 300 DPI)

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Any drug	100%	prescribed without an evidence-based clinical indication.	8%		N/A
A2	Any drug	100%	prescribed beyond the recommended duration, where treatment duration is well defined	8%		N/A
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%	*[users with...duplicate drug class prescription]*	17%	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B						
B1	Digoxin	100%	for heart failure with normal systolic ventricular function	58%	(no clear evidence of benefit).	58%
B2	Verapamil or diltiazem	100%	with NYHA Class III or IV heart failure	58%	(may worsen heart failure).	75%
B3	Beta-blocker	67%	in combination with verapamil or diltiazem	92%	(risk of heart block).	75%
B4	Beta blocker	67%	with bradycardia (< 50/min) , type II heart block or complete heart block	42%	(risk of profound hypotension, asystole).	75%
B5	Amiodarone	100%	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B6	Loop diuretic	67%	as first-line treatment for hypertension	33%	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
B7	Loop diuretic	67%	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	58%	(leg elevation and /or compression hosiery usually more appropriate)	75%
B8	Thiazide diuretic	67%	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	75%	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
B9	Loop diuretic	67%	for treatment of hypertension with concurrent urinary incontinence	67%	(may exacerbate incontinence).	58%
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	75%	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%	in patients with hyperkalaemia.	50%		N/A
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%	without monitoring of serum potassium	67%	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina	33%	(risk of cardiovascular collapse).	67%
C						
C1	Long-term aspirin at doses greater than 160mg per day	83%		92%	(increased risk of bleeding, no evidence for increased efficacy).	75%
C2	Aspirin	92%	with a past history of peptic ulcer disease without concomitant PPI	100%	(risk of recurrent peptic ulcer).	83%
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	33%	(high risk of bleeding)..	58%
C4	Aspirin plus clopidogrel	100%	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	83%	(no evidence of added benefit over clopidogrel monotherapy) .	83%

C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%	in patients with chronic atrial fibrillation	67%	(no added benefit from aspirin).	83%
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in patients with stable coronary, cerebrovascular or peripheral arterial disease	33%	(no added benefit from dual therapy).	67%
C7	Ticlopidine	100%	in any circumstances	100%	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,	67%	(no proven added benefit).	83%
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	67%	(no proven added benefit).	83%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in combination	67%	(risk of gastrointestinal bleeding).	67%
C11	NSAID	67%	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%	(increased risk of peptic ulcer disease)	67%
D						
D1	Tricyclic Antidepressants (TCAs)	67%	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%	(risk of worsening these conditions).	50%
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%	as first-line antidepressant treatment	33%	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%	with a history of prostatism or previous urinary retention	75%	(high risk of urinary retention).	92%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/L	75%	(risk of exacerbating or precipitating hyponatraemia).	92%
D5	Benzodiazepines	67%	for ≥ 4 weeks	33%	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%	in those with parkinsonism or Lewy Body Disease	100%	(risk of severe extra-pyramidal symptoms)	83%
D7	Anticholinergics/antimuscarinics	17%	to treat extra-pyramidal side-effects of neuroleptic medications	50%	(risk of anticholinergic toxicity),	50%
D8	Anticholinergics/antimuscarinics	17%	in patients with Delirium or dementia	33%	(risk of exacerbation of cognitive impairment).	75%
D9	Neuroleptic antipsychotic	25%	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	33%	(increased risk of stroke).	33%
D10	Neuroleptics	33%	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
D11	Acetylcholinesterase inhibitors	67%	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	50%	(risk of cardiac conduction failure, syncope and injury).	92%

D12	Phenothiazines	75%	as first-line treatment,	83%	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
D13	Levodopa or dopamine agonists	83%	for benign essential tremor	100%	(no evidence of efficacy)	83%
D14	First-generation antihistamines	17%	*[users of…first-generation antihistamines]*	33%	(safer, less toxic antihistamines now widely available).	75%
E						
E1	Digoxin at a long-term dose greater than 125µg/day	100%	if eGFR < 30 ml/min/1.73m2	83%	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%	if eGFR < 30 ml/min/1.73m2	100%	(risk of bleeding)	67%
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%	if eGFR < 15 ml/min/1.73m2	100%	(risk of bleeding)	67%
E4	NSAID's	42%	if eGFR < 50 ml/min/1.73m2	100%	(risk of deterioration in renal function).	75%
E5	Colchicine	100%	if eGFR < 10 ml/min/1.73m2	100%	(risk of colchicine toxicity).	83%
E6	Metformin	100%	if eGFR < 30 ml/min/1.73m2	100%	(risk of lactic acidosis).	83%
F						
F1	Prochlorperazine or metoclopramide	100%	with Parkinsonism	92%	(risk of exacerbating Parkinsonian symptoms).	92%
F2	PPI	58%	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%	(dose reduction or earlier discontinuation indicated).	33%
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%	in patients with chronic constipation where non-constipating alternatives are available	67%	(risk of exacerbation of constipation).	100%
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day;	50%		100%	(no evidence of enhanced iron absorption above these doses).	75%
G						
G1	Theophylline	100%	as monotherapy for COPD	75%	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
G2	Systemic corticosteroids	75%	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%	with a history of narrow angle glaucoma or bladder outflow obstruction	42%	(may cause urinary retention).	50%
G4	Benzodiazepines	67%	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%	(risk of exacerbation of respiratory failure).	67%
H						
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	100%	(risk of peptic ulcer relapse).	75%
H2	NSAID	67%	with severe hypertension or severe heart failure	33%	(risk of exacerbation of hypertension/heart failure)	67%
H3	Long-term use of NSAID (>3 months)	75%	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%	(simple analgesics preferable and usually as effective for pain relief)	42%
H4	Long-term corticosteroids (>3 months)	83%	as monotherapy for rheumatoid arthrtitis	67%	(risk of systemic corticosteroid side-effects).	58%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%	for osteoarthritis	100%	(risk of systemic corticosteroid side-effects).	58%
H6	Long-term NSAID or colchicine (>3 months)	67%	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat	50%	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
H7	COX-2 selective NSAIDs	83%	with concurrent cardiovascular disease	42%	(increased risk of myocardial infarction and stroke).	75%
H8	NSAID	58%	with concurrent corticosteroids without PPI prophylaxis	58%	(increased risk of peptic ulcer disease).	75%

H9	Oral bisphosphonates	75%	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	92%	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
I						
I1	Antimuscarinic drugs	17%	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%	(risk of increased confusion, agitation / risk of urinary retention).	67%
I2	Selective alpha-1 selective alpha blockers	67%	in those with symptomatic orthostatic hypotension or micturition syncope	50%	(risk of precipitating recurrent syncope).	75%
J						
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%	with type 2 diabetes mellitus	75%	(risk of prolonged hypoglycaemia).	75%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%	in patients with heart failure	58%	(risk of exacerbation of heart failure).	67%
J3	Beta-blockers	67%	in diabetes mellitus with frequent hypoglycaemic episodes	50%	(risk of suppressing hypoglycaemic symptoms).	83%
J4	Oestrogens	67%	with a history of breast cancer or venous thromboembolism	83%	(increased risk of recurrence).	67%
J5	Oral oestrogens	83%	without progestogen in patients with intact uterus	100%	(risk of endometrial cancer).	67%
J6	Androgens (male sex hormones)	67%	in the absence of primary or secondary hypogonadism	58%	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
K						
K1	Benzodiazepines	67%	*[falls]*	0%	(sedative, may cause reduced sensorium, impair balance).	58%
K2	Neuroleptic drugs	17%	*[falls]*	0%	(may cause gait dyspraxia, Parkinsonism).	58%
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	83%	(risk of syncope, falls).	75%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%	*[falls]*	0%	(may cause protracted daytime sedation, ataxia).	58%
L						
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%	as first line therapy for mild pain	50%	(WHO analgesic ladder not observed).	33%
L2	Use of regular (as distinct from PRN) opioids	67%	without concomitant laxative	17%	(risk of severe constipation).	83%
L3	Long-acting opioids	17%	without short-acting opioids for break-through pain	17%	(risk of non-control of severe pain)	67%
M						
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%	*[users with…concomitant use of two or more drugs with antimuscarinic/anticholinergic properties]*	17%	(risk of increased antimuscarinic/anticholinergic toxicity)	17%

STOPP	Action	Clarity rate
n=80		
D7	Anticholinergics/antimuscarinics	17%
D8	Anticholinergics/antimuscarinics	17%
D14	First-generation antihistamines	17%
I1	Antimuscarinic drugs	17%
K2	Neuroleptic drugs	17%
L3	Long-acting opioids	17%
D9	Neuroleptic antipsychotic	25%
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%
D10	Neuroleptics	33%
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%
E4	NSAID's	42%
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day;	50%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%

F2	PPI	58%
H8	NSAID	58%
B3	Beta-blocker	67%
B4	Beta blocker	67%
B6	Loop diuretic	67%
B7	Loop diuretic	67%
B8	Thiazide diuretic	67%
B9	Loop diuretic	67%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C11	NSAID	67%
D1	Tricyclic Antidepressants (TCAs)	67%
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%
D5	Benzodiazepines	67%
D11	Acetylcholinesterase inhibitors	67%
G4	Benzodiazepines	67%
H2	NSAID	67%
H6	Long-term NSAID or colchicine (>3 months)	67%
I2	Selective alpha-1 selective alpha blockers	67%
J3	Beta-blockers	67%
J4	Oestrogens	67%
J6	Androgens (male sex hormones)	67%
K1	Benzodiazepines	67%
L2	Use of regular (as distinct from PRN) opioids	67%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%
D12	Phenothiazines	75%
G2	Systemic corticosteroids	75%
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%
H3	Long-term use of NSAID (>3 months)	75%
H9	Oral bisphosphonates	75%
C1	Long-term aspirin at doses greater than 160mg per day	83%
D13	Levodopa or dopamine agonists	83%
H4	Long-term corticosteroids (>3 months)	83%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%
H7	COX-2 selective NSAIDs	83%
J5	Oral oestrogens	83%
C2	Aspirin	92%

A1	Any drug	100%
A2	Any drug	100%
B1	Digoxin	100%
B2	Verapamil or diltiazem	100%
B5	Amiodarone	100%
C4	Aspirin plus clopidogrel	100%
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%
C7	Ticlopidine	100%
E1	Digoxin at a long-term dose greater than 125µg/day	100%
E5	Colchicine	100%
E6	Metformin	100%
F1	Prochlorperazine or metoclopramide	100%
G1	Theophylline	100%

STOPP	Condition	Clarity rate
n=80		
K1	*[falls]*	0%
K2	*[falls]*	0%
K4	*[falls]*	0%
A1	prescribed without an evidence-based clinical indication.	8%
A2	prescribed beyond the recommended duration, where treatment duration is well defined	8%
A3	*[users with...duplicate drug class prescription]*	17%
L2	without concomitant laxative	17%
L3	without short-acting opioids for break-through pain	17%
M1	*[users with…concomitant use of two or more drugs with antimuscarinic/anticholinergic properties]*	17%
B5	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%
B6	as first-line treatment for hypertension	33%
B13	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina	33%
C3	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	33%
C6	in patients with stable coronary, cerebrovascular or peripheral arterial disease	33%
D1	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%
D2	as first-line antidepressant treatment	33%
D5	for ≥ 4 weeks	33%
D8	in patients with delirium or dementia	33%
D9	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	33%
D10	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%
D14	*[users of…first-generation antihistamines]*	33%
H2	with severe hypertension or severe heart failure	33%
B4	with bradycardia (< 50/min) , type II heart block or complete heart block	42%
G3	with a history of narrow angle glaucoma or bladder outflow obstruction	42%
H7	with concurrent cardiovascular disease	42%
I1	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%
B11	in patients with hyperkalaemia.	50%
D7	to treat extra-pyramidal side-effects of neuroleptic medications	50%

D11	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	50%
F2	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%
H6	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat	50%
I2	in those with symptomatic orthostatic hypotension or micturition syncope	50%
J3	in diabetes mellitus with frequent hypoglycaemic episodes	50%
L1	as first line therapy for mild pain	50%
B1	for heart failure with normal systolic ventricular function	58%
B2	with NYHA Class III or IV heart failure	58%
B7	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	58%
H3	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%
H8	with concurrent corticosteroids without PPI prophylaxis	58%
J2	in patients with heart failure	58%
J6	in the absence of primary or secondary hypogonadism	58%
B9	for treatment of hypertension with concurrent urinary incontinence	67%
B12	without monitoring of serum potassium	67%
C5	in patients with chronic atrial fibrillation	67%
C8	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,	67%
C9	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	67%
C10	in combination	67%
C11	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%
F3	in patients with chronic constipation where non-constipating alternatives are available	67%
G2	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%
H4	as monotherapy for rheumatoid arthrtitis	67%
B8	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	75%
B10	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	75%
D3	with a history of prostatism or previous urinary retention	75%
D4	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l	75%
G1	as monotherapy for COPD	75%
J1	with type 2 diabetes mellitus	75%

C4	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	83%
D12	as first-line treatment,	83%
E1	if eGFR < 30 ml/min/1.73m2	83%
J4	with a history of breast cancer or venous thromboembolism	83%
K3	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	83%
B3	in combination with verapamil or diltiazem	92%
C1	[Long-term aspirin at doses greater than 160mg per day]	92%
F1	with Parkinsonism	92%
G4	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%
H9	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	92%
C2	with a past history of peptic ulcer disease without concomitant PPI	100%
C7	in any circumstances	100%
D6	in those with parkinsonism or Lewy Body Disease	100%
D13	for benign essential tremor	100%
E2	if eGFR < 30 ml/min/1.73m2	100%
E3	if eGFR < 15 ml/min/1.73m2	100%
E4	if eGFR < 50 ml/min/1.73m2	100%
E5	if eGFR < 10 ml/min/1.73m2	100%
E6	if eGFR < 30 ml/min/1.73m2	100%
F4	*[Oral elemental iron doses greater than 200 mg daily]*	100%
H1	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	100%
H5	for osteoarthritis	100%
J5	without progestogen in patients with intact uterus	100%

STOPP	Explanation	Clarity rating
n=77		
M1	(risk of increased antimuscarinic/anticholinergic toxicity)	17%
A3	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B6	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
D9	(increased risk of stroke).	33%
F2	(dose reduction or earlier discontinuation indicated).	33%
H6	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
L1	(WHO analgesic ladder not observed).	33%
D2	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
H3	(simple analgesics preferable and usually as effective for pain relief)	42%
B10	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
D1	(risk of worsening these conditions).	50%
D7	(risk of anticholinergic toxicity),	50%
G3	(may cause urinary retention).	50%
B1	(no clear evidence of benefit).	58%
B9	(may exacerbate incontinence).	58%
C3	(high risk of bleeding)..	58%
H4	(risk of systemic corticosteroid side-effects).	58%
H5	(risk of systemic corticosteroid side-effects).	58%
K1	(sedative, may cause reduced sensorium, impair balance).	58%
K2	(may cause gait dyspraxia, Parkinsonism).	58%
K4	(may cause protracted daytime sedation, ataxia).	58%
B13	(risk of cardiovascular collapse).	67%
C6	(no added benefit from dual therapy).	67%
C10	(risk of gastrointestinal bleeding).	67%
C11	(increased risk of peptic ulcer disease)	67%
D10	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
E1	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	(risk of bleeding)	67%
E3	(risk of bleeding)	67%
G4	(risk of exacerbation of respiratory failure).	67%
H2	(risk of exacerbation of hypertension/heart failure)	67%
I1	(risk of increased confusion, agitation / risk of urinary retention).	67%
J2	(risk of exacerbation of heart failure).	67%
J4	(increased risk of recurrence).	67%
J5	(risk of endometrial cancer).	67%

L3	(risk of non-control of severe pain)	67%
B2	(may worsen heart failure).	75%
B3	(risk of heart block).	75%
B4	(risk of profound hypotension, asystole).	75%
B7	(leg elevation and /or compression hosiery usually more appropriate)	75%
C1	(increased risk of bleeding, no evidence for increased efficacy).	75%
D8	(risk of exacerbation of cognitive impairment).	75%
D14	(safer, less toxic antihistamines now widely available).	75%
E4	(risk of deterioration in renal function).	75%
F4	(no evidence of enhanced iron absorption above these doses).	75%
G1	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
G2	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
H1	(risk of peptic ulcer relapse).	75%
H7	(increased risk of myocardial infarction and stroke).	75%
H8	(increased risk of peptic ulcer disease).	75%
I2	(risk of precipitating recurrent syncope).	75%
J1	(risk of prolonged hypoglycaemia).	75%
K3	(risk of syncope, falls).	75%
B5	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B8	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
C2	(risk of recurrent peptic ulcer).	83%
C4	(no evidence of added benefit over clopidogrel monotherapy) .	83%
C5	(no added benefit from aspirin).	83%
C8	(no proven added benefit).	83%
C9	(no proven added benefit).	83%
D6	(risk of severe extra-pyramidal symptoms)	83%
D13	(no evidence of efficacy)	83%
E5	(risk of colchicine toxicity).	83%
E6	(risk of lactic acidosis).	83%
H9	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
J3	(risk of suppressing hypoglycaemic symptoms).	83%
L2	(risk of severe constipation).	83%
B12	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
C7	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
D3	(high risk of urinary retention).	92%
D4	(risk of exacerbating or precipitating hyponatraemia).	92%
D11	(risk of cardiac conduction failure, syncope and injury).	92%

D12	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
F1	(risk of exacerbating Parkinsonian symptoms).	92%
J6	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
D5	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
F3	(risk of exacerbation of constipation).	100%

START	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%	in the presence of chronic atrial fibrillation.	50%		N/A
A2	Aspirin (75 mg – 160 mg once daily)	92%	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%		N/A
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%	with a documented history of coronary, cerebral or peripheral vascular disease.	58%		N/A
A4	Antihypertensive therapy	25%	where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%		N/A
A5	Statin therapy	67%	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%		N/A
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%	with systolic heart failure and/or documented coronary artery disease.	58%		N/A
A7	Beta-blocker	67%	with ischaemic heart disease.	75%		N/A
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%	with stable systolic heart failure.	67%		N/A
B						
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%	for mild to moderate asthma or COPD.	50%		N/A
B2	Regular inhaled corticosteroid	58%	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%		N/A
B3	Home continuous oxygen	83%	with documented chronic hypoxaemia (i.e. pO_2 < 8.0 kPa or 60 mmHg or SaO_2 < 89%)	92%		N/A
C						
C1	L-DOPA or a dopamine agonist	67%	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%		N/A
C2	Non-TCA antidepressant drug	25%	in the presence of persistent major depressive symptoms.	33%		N/A
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%		N/A
C4	Topical prostaglandin, prostamide or beta-blocker	67%	for primary open-angle glaucoma.	100%		N/A
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%	for persistent severe anxiety that interferes with independent functioning.	50%		N/A
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%		N/A
D						
D1	Proton Pump Inhibitor	67%	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%		N/A
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%	for diverticulosis with a history of constipation.	58%		N/A
E						
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%	with active, disabling rheumatoid disease.	42%		N/A
E2	Bisphosphonates and vitamin D and calcium	67%	in patients taking long-term systemic corticosteroid therapy.	33%		N/A

E3	Vitamin D and calcium supplement	17%	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%		N/A
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%		N/A
E5	Vitamin D supplement	42%	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%		N/A
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%	with a history of recurrent episodes of gout.	50%		N/A
E7	Folic acid supplement	92%	in patients taking methotexate.	33%		N/A
F						
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%		N/A
G						
G1	Alpha-1 receptor blocker	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G2	5-alpha reductase inhibitor	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%	for symptomatic atrophic vaginitis	75%		N/A
H						
H1	High-potency opioids	17%	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%		N/A
H2	Laxatives	17%	in patients receiving opioids regularly.	75%		N/A
I						
I1	Seasonal trivalent influenza vaccine	83%	annually	83%		N/A
I2	Pneumococcal vaccine	83%	at least once after age 65 according to national guidelines	83%		N/A

START	Action	Clarity rating
n=34		
E3	Vitamin D and calcium supplement	17%
H1	High-potency opioids	17%
H2	Laxatives	17%
A4	Antihypertensive therapy	25%
C2	Non-TCA antidepressant drug	25%
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%
E5	Vitamin D supplement	42%
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%
B2	Regular inhaled corticosteroid	58%
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%
A5	Statin therapy	67%
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%
A7	Beta-blocker	67%
C1	L-DOPA or a dopamine agonist	67%
C4	Topical prostaglandin, prostamide or beta-blocker	67%
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%
D1	Proton Pump Inhibitor	67%
E2	Bisphosphonates and vitamin D and calcium	67%
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%
G1	Alpha-1 receptor blocker	67%
G2	5-alpha reductase inhibitor	67%
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%
B3	Home continuous oxygen	83%
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%
I1	Seasonal trivalent influenza vaccine	83%
I2	Pneumococcal vaccine	83%
A2	Aspirin (75 mg – 160 mg once daily)	92%
E7	Folic acid supplement	92%

START	Condition	Clarity rate
n=34		
A2	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%
C2	in the presence of persistent major depressive symptoms.	33%
C6	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%
E2	in patients taking long-term systemic corticosteroid therapy.	33%
E7	in patients taking methotexate.	33%
A5	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%
C3	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%
E1	with active, disabling rheumatoid disease.	42%
A1	in the presence of chronic atrial fibrillation.	50%
B1	for mild to moderate asthma or COPD.	50%
B2	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%
C1	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%
C5	for persistent severe anxiety that interferes with independent functioning.	50%
D1	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%
E5	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%
E6	with a history of recurrent episodes of gout.	50%
G1	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
G2	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
H1	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%
A3	with a documented history of coronary, cerebral or peripheral vascular disease.	58%
A6	with systolic heart failure and/or documented coronary artery disease.	58%
D2	for diverticulosis with a history of constipation.	58%

E4	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%
A8	with stable systolic heart failure.	67%
F1	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%
A4	where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%
A7	with ischaemic heart disease.	75%
E3	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%
G3	for symptomatic atrophic vaginitis	75%
H2	in patients receiving opioids regularly.	75%
I1	annually	83%
I2	at least once after age 65 according to national guidelines	83%
B3	with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	92%
C4	for primary open-angle glaucoma.	100%

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Evaluation of clarity of the STOPP/START criteria for clinical applicability in prescribing for older people: a quality appraisal study

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ABSTRACT

Objectives: Appropriate prescribing in older people continues to be challenging. Studies still report a high prevalence of inappropriate prescribing in older people. To reduce the problem of under- and overprescribing in this population, explicit drug optimization tools like STOPP/START have been developed. The aim of this study was to evaluate the clinical applicability of STOPP/START criteria in daily patient care by assessing the clarity of singular criteria.

Design: Quality appraisal study

Methods: For each of the 114 STOPP/START criteria version 2, elements describing the action (*what/how to do*), condition (*when to do*) and explanation (*why to do*) were identified. Next, the clarity of these three elements were quantified on a 7-point Likert scale using tools provided by the Appraisal of Guidelines for Research & Evaluation (AGREE) Consortium.

Primary and secondary outcomes: The primary outcome measure was the clarity rating per element, categorized into high (>67.7%), moderate (33.3-67.7%) or low (<33.3%). Secondary, factors that positively or negatively affected clarity most were identified. Additionally, the nature of the conditions were further classified into five descriptive components: disease, sign, symptom, laboratory finding and medication.

Results: STOPP recommendations had an average clarity rating of 65%, 60% and 67% for actions, conditions and explanations, respectively. The average clarity rating in START recommendations was 60% and 57% for actions and conditions, respectively. There were no statements present to substantiate the prescription of potential omissions for the 34 START criteria.

Conclusions: Our results show that the clarity of the STOPP/START criteria can be improved. For future development of explicit drug optimization tools, such as STOPP/START, our findings identified facilitators (high clarity) and barriers (low clarity) that can be used to improve the clarity of clinical practice guidelines (CPGs) on a language level and therefore enhance clinical applicability.

Strengths and limitations of this study

- To the best of our knowledge, this is the first study that explores the clarity of STOPP/START criteria
- Clarity ratings were scored independently by appraisers who were experienced in applying STOPP/START-criteria in clinical practice
- The scoring process remains partly subjective, however consensus ratings show high inter-rater agreement
- By evaluating the '*what'*, '*when'* and '*why'* of recommendations, element-specific strategies were formulated to improve their clarity

INTRODUCTION

Clinical practice guidelines (CPGs) are instruments intended to provide guidance to healthcare professionals in patient care. Translation of healthcare knowledge, evidence and experience into clear recommendations for patient care, however, is challenging. Studies in the USA and the Netherlands suggest that about 30–40% of patients do not receive care according to evidence based guidelines. A clear description of the desired behaviour has been associated with better compliance with guideline recommendations.[1,2]

Recommendations about safe and effective pharmacotherapy are an important part of CPGs. However, it is often unclear whether recommendations also apply to older people.[3-5] A complicating factor is that older people experience more concomitant morbidities, while CPGs often focus on best treatment for a single disease. Ambiguity among prescribers about pharmacotherapy in older people results in inappropriate prescribing, which causes adverse drug reactions, drug-related hospitalizations, decreased quality of life and even death.[6,7]

Due to the lack of clear statements in CPGs about (in)appropriate prescribing in older people with multimorbidity, several explicit screening tools have been developed.[8,9] The most widely used are the Beers criteria[10] and the Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria.[11] CPG recommendations are rarely specified in precise behavioural terms such as *what, how, when,* and *why* to stop or start a drug, while explicit screening tools are designed to make clear statements and therefore ease clinical implementation.[2] However, studies continue to report a high prevalence of inappropriate prescribing in older people.[12-14] This suggests implementation can still be improved.

Although STOPP/START criteria have shown good inter-rater reliability in studies involving physicians and (hospital)pharmacists working in geriatric units, data on how physicians less familiar with medication optimization would interpret STOPP/START criteria are lacking.[15,16] The question then arises whether the recommended actions are formulated clearly enough to guide prescribers less experienced in geriatric patient care.

The aim of this study was to evaluate the clinical applicability of STOPP/START criteria in daily patient care by assessing the clarity of singular criteria with the purpose of improving future clinical guideline recommendations for appropriate prescribing in older people.

METHODS

STOPP/START criteria

The STOPP/START criteria were first published in 2008 and have been updated in 2015 to STOPP/START version 2.[17] STOPP/START is a product of two Delphi rounds by 19 experts from 13 European countries.

For this study, the supplementary data of the corrigendum of the STOPP/START criteria version 2 as published in November 2017 were used.[18] STOPP/START version 2 consists of a list of 80 Potentially Inappropriate Medications (PIMs, STOPP criteria) and 34 Potential Prescribing Omissions (PPOs, START criteria).

Clarity assessment

The AGREE II Instrument and GUIDE-M were used to develop a framework to assess the clarity of language used in STOPP/START. AGREE II Instrument is an internationally validated tool to rate the quality of CPGs, developed by the Appraisal of Guidelines for Research & Evaluation (AGREE) Consortium.[19] In addition to the AGREE II Instrument, AGREE developed a Guideline Implementability Decision Excellence Model (GUIDE-M).[20] This model identifies *'communicating content'* as a core tactic for CPG implementability. Obviously, language is an important domain of this tactic. The language subdomain promotes a clear, simple, and persuasive message.

The relevant part of the AGREE II Instrument ('clarity of presentation', domain 4, item 15) states that recommendations should be 'specific and unambiguous', which is defined as *'a concrete and precise description of which option is appropriate for which situation and for what population group'*. In line with this statement and the corresponding section of the AGREE II Instrument, three elements were identified that influence the clarity of recommendations:

- **Action:** description of the recommended action - i.e. *what* to do and *how* to act?
- **Condition:** identification of the relevant target population and statements about patients or conditions for whom the recommendations would apply or not apply – i.e. *when*?
- **Explanation:** identification of the intent or purpose of the recommended action – i.e. *why*?

In order to quantify the clarity of STOPP/START criteria, the three elements of each recommendation were rated independently on a 7-point Likert scale by a panel of two appraisers, consisting of a geriatric resident (CH) and a hospital pharmacist resident (BS), both experienced with the application of STOPP/START criteria in daily practice. The clarity for each of these three elements was rated from the perspective of a 'junior' physician or pharmacist with a basic level of knowledge (≤ 5 years of clinical post-graduate experience). The appraisers were trained with a rating guidance, developed and approved by senior clinicians (TE/EP/IW/WK) prior to

rating the elements independently. If ratings differed more than 1 point, a senior hospital pharmacist/clinical pharmacologist (IW) or a senior geriatrician/clinical pharmacologist (WK) was consulted as a third appraiser until consensus was reached.

Descriptive components of conditions

In addition to the calculation of clarity ratings for the action, condition and explanation, the nature of the conditions was further explored. The condition identifies the target population and is the most heterogeneous element. By stratifying the conditions into descriptive components, the nature of the components in relation to their clarity could be assessed. These components could lead to different strategies to optimize 'specific and unambiguous' wording in describing conditions.

The conditions were subdivided into five components that were considered essential for identification of the target population: *disease, sign, symptom, laboratory finding* and *medication*. Definitions of four components were based on the ontology as described by Scheuermann et al.[21] *Signs* are defined as bodily features observed in a physical examination including measurements (e.g. blood pressure), while *symptoms* are bodily features experienced by a patient (e.g. parkinsonism). Since optimization of polypharmacy is the main focus of the STOPP/START, the target population can also be described by (co-)*medication*. *Medication* is not defined by Scheuermann et al. Therefore, medication was added as a fifth component using the definition for medicinal products by the European Medicines Agency (EMA) as *'a substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action'*.[22]

Data analysis

Clarity ratings for each of the three elements (action, condition, explanation) were calculated as a percentage of the obtained scores given by appraiser 1 and 2 divided by the maximum score.

$$Clarity\ rating\ (\%) = \frac{obtained\ score\ (sum\ of\ 2\ appraisers) - minimum\ possible\ score\ (2)}{maximum\ possible\ score\ (14) - minimum\ possible\ score\ (2)}$$

This calculation method is in accordance with the approach provided by AGREE II Instrument. The scores of appraisers 1 and 2 were both replaced by the consensus score when a third appraiser was consulted. After scoring the elements, clarity ratings were categorized into low (<33.3%), moderate (33.3% - 67.7%) and high (>67.7%).

Patient and public involvement

Since this is an appraisal study of clinical guideline recommendations intended to be used by clinicians, this research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or

interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Ethics approval

Ethics approval was not required for this appraisal study since no humans or animals were involved.

RESULTS

The elements 'action' and 'condition' in STOPP and START recommendations were rated on their clarity, resulting in 80 and 34 scores per element, respectively. The element 'explanation' was present in all but three (A1, A2, B11) STOPP recommendations, resulting in 77 scores. None of the START criteria contained an explanation to substantiate the prescription of potential omissions. Therefore, Likert scores for explanations were only assessed in STOPP recommendations.

The agreement among the two appraisers for Likert scores was high and ranged from 76.3% (STOPP – condition) to 91.3% (STOPP – action). 44 out of 305 (14.4%) scores were replaced after consensus meetings with a third appraiser. Replacements did not alter average Likert scores per element with more than 0.2 points compared to the average scores prior to consensus.

Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively (*Figure 1*).

In 80 STOPP and 34 START recommendations, the clarity ratings of 35 actions were categorized as high (30.7%), 65 as moderate (57.0%) and 14 as low (12.3%). 38 (33.3%), 67 (58.8%) and 9 (7.9%) conditions had a high, moderate or low clarity rating, respectively. In 77 STOPP criteria, the clarity ratings of 41 (53,2%) explanations were categorized as high, 35 (45.5%) as moderate and 1 (1.3%) as low.

13 STOPP criteria (C1, C2, C4, C7, D6, D12, D13, E5, E6, F1, G1, H1, H9) had high clarity ratings for all three elements. 4 START criteria (B3, G3, I1, I2) had high clarity ratings for both action and condition. Detailed information of clarity ratings per element for all individual STOPP/START-criteria can be found in *Supplementary data S1*.

Elements with high (>67.7%) and moderate or low (≤67.7%) clarity ratings were analysed in more detail to identify factors that either positively or negatively affected 'specific and unambiguous' language most. These findings for actions, conditions and explanations with illustrative examples for STOPP and START recommendations are presented in *Table 1*.

Table 1. *Main barriers and facilitators that affected clarity of the elements action, condition and explanation of STOPP/START recommendations.*

Barriers	**Example** [a] (clarity rating, %)
ACTION	
Lack of explicit drug (class)	STOPP D7/8. **Anticholinergics / antimuscarinics** (17%)
➢ 'e.g.' represents a non-limitative list and is therefore inconclusive	STOPP B10. Centrally-acting antihypertensives (**e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine**) (33%)
➢ Use of adjectives that need further investigation to allow use	STOPP D14. **First-generation** antihistamines (17%) START H1. **High potency** opioids (17%)
Lack of drug deprescribing schedules while considered necessary	STOPP K2. **Neuroleptic drugs** (17%)
Starting dose and target dose not mentioned	START C2. **Angiotensin Converting Enzyme (ACE) inhibitor** with systolic heart failure (67%)
Lack of directions how and what to monitor after starting a drug	START E1. **Disease-modifying anti-rheumatic drug** (DMARD) (25%)
CONDITION	
General - Patient population for whom recommendations would not apply was not (clearly / unambiguously) defined	
➢ In patients with a strong indication for a potentially inappropriate drug, it may be harmful to stop it	STOPP B5. **as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias** (33%)
➢ In patients with potential omissions, warnings for important contra indications are lacking / not clearly defined	START A2. **where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated** (33%)
Medication – see also *action*	
➢ Ambiguous adjectives were used ➢ Description of drug therapy (substance / dosage) not specific enough	STOPP D2. **as first-line antidepressant treatment** (33%) START E7. in patients taking **methotrexate** (33%)
Disease - Clinical interpretation of 'disease (state)' for defining population needed	STOPP D1. with **dementia**, narrow angle glaucoma, **cardiac conduction abnormalities**, prostatism, or **prior history of urinary retention** (33%) START A5**.** with a documented **history of coronary, cerebral or peripheral vascular disease** (33%)
Sign - Measurement or scores were not described unambiguously	STOPP H2. with **severe hypertension** or **severe heart failure** (33%) START E1. with **active**, **disabling rheumatoid disease** (42%)
Symptom - Symptoms were not described unambiguously	STOPP K-section. Not clear whether the occurrence of **'falls'** - as mentioned only in the title of section K - is a prerequisite for the applicability of the recommendation or only used to address the increased risk of falls. If 'falls' is considered a condition, the frequency of 'falls' is not specified. (0%) STOPP D10. unless **sleep disorder** is due to (33%) START C2. with **persistent major depressive symptoms** (33%)

Laboratory finding - Parameters lack clear cut-off levels with reference ranges	START C6. once **iron deficiency** and **severe renal failure** have been excluded (33%)
EXPLANATION	
Risk of continuing therapy not clearly described: explanation does not cover clinical relevance of benefit / harm balance (specific adverse drug reactions, toxicity).	STOPP D7. **(risk of anticholinergic toxicity)** (17%) START N/A
Facilitators	**Example** [a] (clarity rating, %)
ACTION	
Drugs were specified on individual drug level and -if necessary- route / dosage was specified	STOPP C7. **Ticlopidine** (100%) START A2. **Aspirin (75 mg – 160 mg once daily)** (92%)
CONDITION	
Medication – see also *action* Specific description of drug therapy (substance / dosage) to clearly identify the target population (i.e. patients using a certain drug regimen).	STOPP B3. in combination with **verapamil** or **diltiazem** (92%) START I2. **at least once after age 65 according to national guidelines** (83%)
Disease - Diseases clearly described, the target population could be easily identified	STOPP H9. in patients **with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding** (92%) START C4. for **primary open-angle glaucoma**. (100%)
Signs - Signs clearly described as scores or measurements and therefore unambiguous	START B3. with documented chronic hypoxaemia **(i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)** (92%)
Symptom - Symptoms clearly and unambiguous described	STOPP F1. with **Parkinsonism** (92%)
Laboratory findings - Clear cut-off levels with reference ranges present	STOPP E6. if **eGFR < 30 ml/min/1.73m2** (100%)
EXPLANATION	
Risk of discontinuing clearly described	STOPP D5. (**no indication for longer treatment**; **risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly**). (100%) START N/A

[a] *The examples shown are selected from elements with low and moderate (≤67.7%) clarity ratings for barriers and from high (>67.7%) clarity ratings for facilitators to substantiate the main findings. An overview of all clarity ratings can be found in the Supplementary data S1.*

The results of stratifying the element 'condition' into the five descriptive components medication, disease, sign, symptom and laboratory finding are shown per STOPP/START recommendation in *Figure 2*. Clarity ratings were scored on the level of condition as an element and not on the sublevel of the five descriptive components. Therefore, all components of one condition share the same colouring for their clarity.

In 33 (41%) STOPP criteria and 17 (50%) START criteria, the condition consisted of more than one component. No strong association was found between the clarity of conditions and the nature of the descriptive components, as the clarity ratings of the condition section varied regardless of the nature of the component. However, laboratory findings used to identify the target population were discovered to have the highest clarity rating compared to other descriptive components in STOPP recommendations; 9 out of 13 laboratory-based conditions had a high clarity rating (>67.7%).

DISCUSSION

Main findings

In this study, we evaluated the clinical applicability of STOPP/START criteria in daily patient care by assessing the clarity of singular criteria. We found that 13 out of 80 STOPP and 4 out of 34 START criteria had a high clarity rating for the three elements action, condition and explanation. To improve clarity of recommendations, element-specific strategies can be formulated (*Table 1*).

Actions were considered unclear if recommendations included non-explicitly specified drug classes (e.g. 'anticholinergics'). To improve clear description of the action (*what and how*) we advise to specify drugs at an individual substance level. The addition of how to start or stop a drug (immediately versus gradually, including monitoring guidelines and deprescribing schedules), route of administration and dosage were considered necessary for some actions to further improve clarity.

The definition of the condition (*the when*) had the lowest average clarity rating in both START and STOPP. Low clarity ratings for conditions resulted from insufficient distinctiveness in the identification of patients for whom recommendations do or do not apply. Conditions were described by medication, diseases, signs, symptoms and laboratory findings. To increase the clarity of the conditions, laboratory findings and signs have the highest potential to be optimized by adding statements about clear cut-off levels (e.g. 'potassium >5.0 mmol/L' instead of 'hyperkalaemia') and measurements (e.g. 'systolic blood pressure >160 mmHg' instead of 'uncontrolled severe hypertension'). For conditions defined by medication use, the same improvements as suggested for actions apply. In some cases even a description on a drug substance level was not specific enough. For instance, folic acid for patients on methotrexate therapy (START E7) only applies to patients using a low dose, weekly methotrexate schedule and not for patients on high dose methotrexate. In such cases, a more detailed description of a

drug dosage, route or indication was deemed necessary. Conditions described by diseases - like 'heart failure' - might seem clear at first, but often need further specification (reduced vs. preserved ejection fraction) to avoid ambiguity. Moreover, international cardiology guidelines distinguish between these subtypes of heart failure, subsequently affecting treatment recommendations. Adherence to terminology of internationally used dictionaries to describe diseases, such as International Classification of Primary Care (ICPC) and International Classification of Diseases (ICD), could be a solution.

Furthermore, no explanations were present for START criteria to substantiate *why* a potential omitted drug should be initiated. Even though the reason to start a drug might seem obvious in most cases, the risk-benefit balance should always be addressed to assist a physician's decision-making process whether or not to expose a patient to additional drug therapies.

Other remarks

STOPP/START criteria provide best evidence-based practices for the over- and undertreatment of single conditions. However, it should be noted that STOPP/START criteria provide conflicting recommendations. For example, if a patient has a clear indication for a beta blocker to treat ischaemic heart disease (START A7), this is contradicted if a patient is already using verapamil or diltiazem (STOPP B3). Merging such recommendations could increase implementation and prevent potential patient harm by overlooking relevant contra-indications.

Besides making the *what*, *how*, *when* and *why* as clear as possible, guideline developers should consider whether recommendations are tailored for its intended end-users (i.e. the *who*). Explicit screening tools to detect inappropriate prescribing in older people such as Beers criteria and STOPP/START, are likely to be developed to reach all professionals involved in prescribing, as all prescribers encounter the problem of under- and overprescribing in older people. Clinicians with high affinity for geriatric medicine may not need explicit treatment recommendation to provide best patient care, whereas some clinicians - such as e.g. surgical specialists - who treat older people but may be less experienced with (in)appropriate prescribing in older people, probably require more clear guidance. Clear recommendations are therefore important to reach all prescribers, because the success of STOPP/START criteria as an intervention depends on its integration and implementation in clinical practice.[23] Some recommendations may be best applied by physicians with a certain expertise, such as to start an 'acetylcholinesterase inhibitor for mild-moderate Alzheimer's dementia or Lewy Body dementia (START C3)'. In such cases, the focus for all clinicians should probably be the recognition and detection of a potential omission, rather than to actually start drug treatment. An explicit action could be to refer such patients to a geriatrician or neurologist, thus separating the trigger for potential undertreatment from the actual prescriber.

Strengths and limitations

To the best of our knowledge, this is the first study that explores the clarity of STOPP/START criteria. By systematically reviewing the clarity of the given action, condition and explanation, we identified facilitators (high clarity) and barriers (low clarity) that may be used to improve the content on a language level. As a result, element-specific strategies can be extracted to improve items requiring refinement. Although no previous studies have reviewed the clarity of singular recommendations of explicit drug screening tools, comparable research has been conducted concerning clarity of monitoring instructions in CPGs and drug labels. Their conclusions to improve ambiguous instructions concerning the monitoring of laboratory values are in line with our suggestions to add clear statements about the *what*, *why*, *when* and *how* of recommendations.[24,25]

Moreover, studies to refine the methodology of developing deprescribing guidelines to facilitate the deprescribing process were conducted.[26,27] A good example are the tools provided by the Bruyère Research Institute, based on their research about developing deprescribing guidelines. The Bruyère research group has published evidence-based clinical practice guidelines (for instance how to deprescribe benzodiazepines), accompanied by clear algorithms including well-described populations (including for which patients the recommendation does not apply), a list of available drugs and dosages, monitoring recommendations and tapering regimes, thereby complementing the clarity some STOPP-recommendations are lacking.[28]

Tools that have been developed to review the quality of entire CPGs underline the importance of clear and unambiguous recommendations[29], but no validated tool exists to rate singular clinical recommendations. As clarity of presentation is both part of the AGREE II Instrument and described by GUIDE-M, we used tools from the AGREE Consortium to develop a review method. Moreover, the AGREE II Instrument is internationally formally endorsed for guideline assessment and provides a Likert scale that allowed us to quantify clarity.

Clarity ratings were scored by appraisers who are experienced in applying STOPP/START criteria in clinical practice, as they contributed to a large multicentre, randomized controlled trial that evaluated the impact of a STOPP/START-based medication review in older people with polypharmacy. We believe that these experiences allowed clear identification of difficulties prescribers not familiar with STOPP/START may encounter. Although the scoring process remains partly subjective, the consensus ratings show high inter-rater agreement. Differences (>1 point) were discussed with a third appraiser and consensus was reached for all items. Therefore, the final clarity ratings were considered reliable.

One concern of further specifying recommendations might be that they ‘replace’ important clinical considerations made by physicians. However, guideline recommendations are never meant to fully substitute clinical judgement to treat individual patients. This is why the explanation of a recommendation – next to the action and condition sections – is important for facilitating translation to an individual patient level.

A lack of strong evidence to support the recommended actions could impede formulating clear explanations. For example, clear statements on numbers needed to treat (NNT) or numbers needed to harm (NNH) might be difficult to extract from currently available evidence. In such cases, the addition of the strength of recommendations and supporting evidence could further direct clinicians. This is also endorsed by internationally renowned CPG quality assessment tools from AGREE and GRADE.[30]

Furthermore, our study only highlights barriers that could be optimized to prevent unintentional deviations from STOPP/START due to unclear language. Apart from the clarity of presentation, many other factors attribute to clinical implementation of evidence-based recommendations. [27,31]

Implications

To clarify the action, condition and explanation sections of a recommendation, a more detailed statement is often required. This may directly affect choices regarding the presentation of recommendations. In addition to improvements in 'language', the presentation style or 'format' of a guideline could have a high impact on applicability as well. In a time where almost all evidence-based knowledge is electronically requested, a dynamic, electronical format could be used to integrate information that will improve clarity of presentation without making recommendations too extensive. Integrating clinical rules within electronic healthcare systems – with an option to request more detailed information - could contribute to a continuing learning cycle as part of (but without slowing down) the usual care process. For example, a drug class (stop benzodiazepines) may be provided with a hyperlink including information on drug substance levels (ATC5-codes) and a deprescribing tool, accessible upon request. Once a prescriber has become familiar with all the details of a certain recommendation, such information is no longer required. However, converting recommendations into effective software assistance starts with a clear message of the initial statements.

To make the current version of STOPP/START criteria suitable for software engines, multiple multidisciplinary expert rounds turned out to be necessary to reach consensus on how to interpret ambiguous wordings.[32] For instance, due to different lists of anticholinergic drugs in current literature, expert opinion is needed to translate this drug class to clinically relevant, individual drugs with high anticholinergic burden. Furthermore, it was found that some recommendations, such as to 'stop any drug beyond the recommended duration (STOPP A3)' were too general or unspecific to convert into an algorithm. Selecting specific recommendations concerning potentially inappropriate long-term use of medication, such as long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (STOPP H4) or continuing bisphosphonates >5 years without evaluating efficacy (not a criterion), will probably result in a better uptake among clinicians and can be easily integrated into clinical decision support systems. Consequently, the lack of clear statements may impede software implementation.[32,33]

Another advance to present clear recommendations in an electronic, dynamic format, is that content could be easily modified based on updates in evidence, country specific guidelines, available drugs and local expertise. Collaboration of guideline developers with experts in medical informatics for considering content formatting could therefore be of great value to facilitate future implementation of recommendations in clinical practice.

Conclusion

In conclusion, for future development of clinical practice guidelines (CPGs), our findings provide direction to assure the clarity of recommendations. We believe in the opportunity to transform STOPP/START from a tool to *detect* inappropriate prescribing to a guideline that provides clear statements on how to *act* after detection. The use of specific and unambiguous language in CPG recommendations is likely to assist physicians in prescribing the right drug to the right patient at the right time.

CONTRIBUTORS

Authorship eligibility is based on the four ICMJE authorship criteria. All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: BS, CH, WK, EP, TE, IW. Data acquisition: BS, CH, WK, IW. Analysis and/or interpretation of data: BS, CH, WK, EP, TE, IW. Drafting the manuscript: BS. Revising the manuscript critically for important intellectual content: BS, CH, WK, EP, TE, IW. We have not received substantial contributions from non-authors.

COMPETING INTERESTS

None declared.

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DATA SHARING

All data relevant to the study are included in the article or uploaded as supplementary information.

PATIENT CONSENT FOR PUBLICATION

Not required.

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FIGURE LEGENDS

Figure 1. *Distribution of clarity ratings for STOPP and START recommendations per element. Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively.*

Figure 2. *Clarity ratings of conditions for STOPP and START criteria related to five descriptive components. Green, orange and red colours correspond with high (>67.7%), moderate (33.3-67.7%) or low (<33.3%) clarity ratings of conditions.*

APPENDICES

Supplementary Dataset S1. *Clarity ratings per element for 80 STOPP and 34 START recommendations*

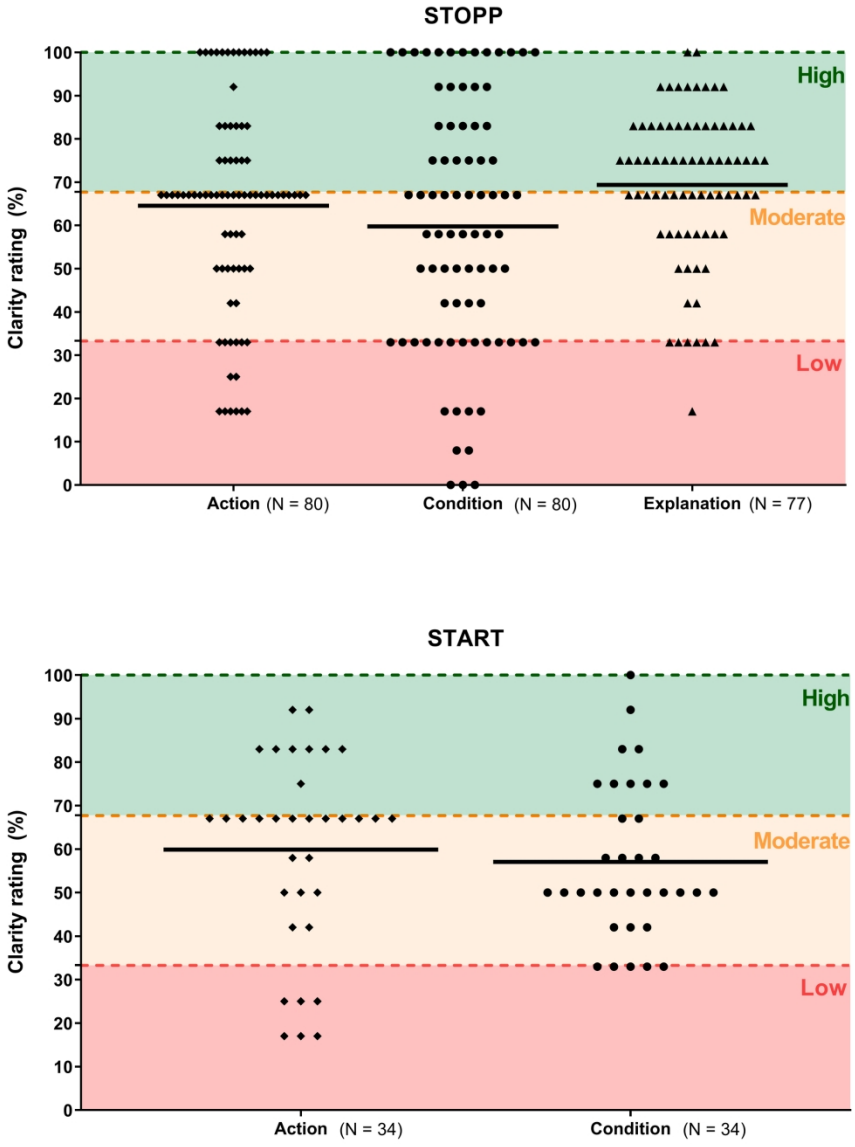

Fig 1. Distribution of clarity ratings for STOPP and START recommendations per element. Average clarity ratings for STOPP recommendations were 65%, 60% and 67% for actions, conditions and explanations, respectively. Average clarity ratings for START recommendations were 60% and 57% for actions and conditions, respectively.

195x247mm (300 x 300 DPI)

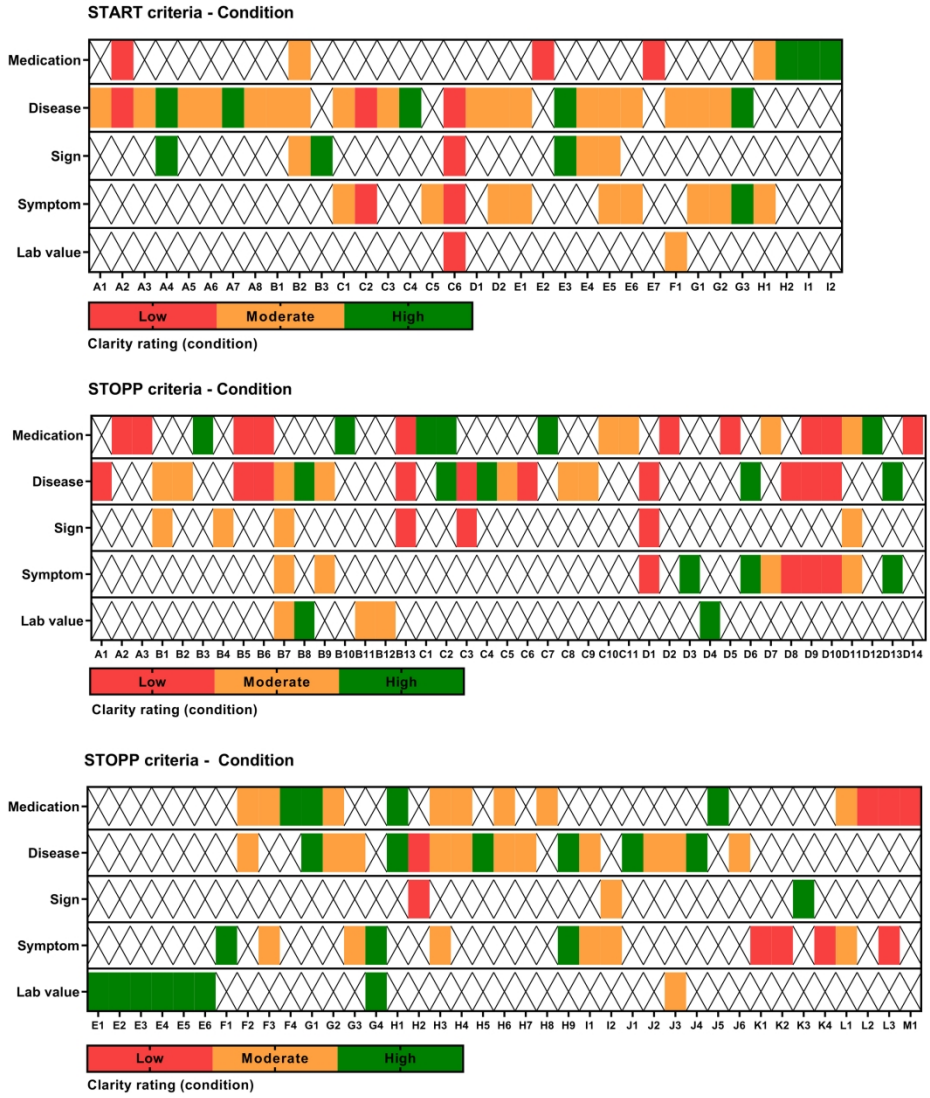

Figure 2. Clarity ratings of conditions for STOPP and START criteria related to five descriptive components. Green, orange and red colours correspond with high (>67.7%), moderate (33.3-67.7%) or low (<33.3%) clarity ratings of conditions.

211x243mm (300 x 300 DPI)

STOPP	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Any drug	100%	prescribed without an evidence-based clinical indication.	8%		N/A
A2	Any drug	100%	prescribed beyond the recommended duration, where treatment duration is well defined	8%		N/A
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%	*[users with...duplicate drug class prescription]*	17%	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B						
B1	Digoxin	100%	for heart failure with normal systolic ventricular function	58%	(no clear evidence of benefit).	58%
B2	Verapamil or diltiazem	100%	with NYHA Class III or IV heart failure	58%	(may worsen heart failure).	75%
B3	Beta-blocker	67%	in combination with verapamil or diltiazem	92%	(risk of heart block).	75%
B4	Beta blocker	67%	with bradycardia (< 50/min) , type II heart block or complete heart block	42%	(risk of profound hypotension, asystole).	75%
B5	Amiodarone	100%	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B6	Loop diuretic	67%	as first-line treatment for hypertension	33%	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
B7	Loop diuretic	67%	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	58%	(leg elevation and /or compression hosiery usually more appropriate)	75%
B8	Thiazide diuretic	67%	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	75%	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
B9	Loop diuretic	67%	for treatment of hypertension with concurrent urinary incontinence	67%	(may exacerbate incontinence).	58%
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	75%	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%	in patients with hyperkalaemia.	50%		N/A
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%	without monitoring of serum potassium	67%	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina	33%	(risk of cardiovascular collapse).	67%
C						
C1	Long-term aspirin at doses greater than 160mg per day	83%		92%	(increased risk of bleeding, no evidence for increased efficacy).	75%
C2	Aspirin	92%	with a past history of peptic ulcer disease without concomitant PPI	100%	(risk of recurrent peptic ulcer).	83%
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	33%	(high risk of bleeding)..	58%
C4	Aspirin plus clopidogrel	100%	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	83%	(no evidence of added benefit over clopidogrel monotherapy) .	83%

C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%	in patients with chronic atrial fibrillation	67%	(no added benefit from aspirin).	83%
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in patients with stable coronary, cerebrovascular or peripheral arterial disease	33%	(no added benefit from dual therapy).	67%
C7	Ticlopidine	100%	in any circumstances	100%	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,	67%	(no proven added benefit).	83%
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	67%	(no proven added benefit).	83%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%	in combination	67%	(risk of gastrointestinal bleeding).	67%
C11	NSAID	67%	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%	(increased risk of peptic ulcer disease)	67%
D						
D1	Tricyclic Antidepressants (TCAs)	67%	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%	(risk of worsening these conditions).	50%
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%	as first-line antidepressant treatment	33%	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%	with a history of prostatism or previous urinary retention	75%	(high risk of urinary retention).	92%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/L	75%	(risk of exacerbating or precipitating hyponatraemia).	92%
D5	Benzodiazepines	67%	for ≥ 4 weeks	33%	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%	in those with parkinsonism or Lewy Body Disease	100%	(risk of severe extra-pyramidal symptoms)	83%
D7	Anticholinergics/antimuscarinics	17%	to treat extra-pyramidal side-effects of neuroleptic medications	50%	(risk of anticholinergic toxicity),	50%
D8	Anticholinergics/antimuscarinics	17%	in patients with Delirium or dementia	33%	(risk of exacerbation of cognitive impairment).	75%
D9	Neuroleptic antipsychotic	25%	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	33%	(increased risk of stroke).	33%
D10	Neuroleptics	33%	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
D11	Acetylcholinesterase inhibitors	67%	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	50%	(risk of cardiac conduction failure, syncope and injury).	92%

D12	Phenothiazines	75%	as first-line treatment,	83%	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
D13	Levodopa or dopamine agonists	83%	for benign essential tremor	100%	(no evidence of efficacy)	83%
D14	First-generation antihistamines	17%	*[users of…first-generation antihistamines]*	33%	(safer, less toxic antihistamines now widely available).	75%
E						
E1	Digoxin at a long-term dose greater than 125µg/day	100%	if eGFR < 30 ml/min/1.73m2	83%	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%	if eGFR < 30 ml/min/1.73m2	100%	(risk of bleeding)	67%
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%	if eGFR < 15 ml/min/1.73m2	100%	(risk of bleeding)	67%
E4	NSAID's	42%	if eGFR < 50 ml/min/1.73m2	100%	(risk of deterioration in renal function).	75%
E5	Colchicine	100%	if eGFR < 10 ml/min/1.73m2	100%	(risk of colchicine toxicity).	83%
E6	Metformin	100%	if eGFR < 30 ml/min/1.73m2	100%	(risk of lactic acidosis).	83%
F						
F1	Prochlorperazine or metoclopramide	100%	with Parkinsonism	92%	(risk of exacerbating Parkinsonian symptoms).	92%
F2	PPI	58%	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%	(dose reduction or earlier discontinuation indicated).	33%
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%	in patients with chronic constipation where non-constipating alternatives are available	67%	(risk of exacerbation of constipation).	100%
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day;	50%		100%	(no evidence of enhanced iron absorption above these doses).	75%
G						
G1	Theophylline	100%	as monotherapy for COPD	75%	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
G2	Systemic corticosteroids	75%	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%	with a history of narrow angle glaucoma or bladder outflow obstruction	42%	(may cause urinary retention).	50%
G4	Benzodiazepines	67%	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%	(risk of exacerbation of respiratory failure).	67%
H						
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	100%	(risk of peptic ulcer relapse).	75%
H2	NSAID	67%	with severe hypertension or severe heart failure	33%	(risk of exacerbation of hypertension/heart failure)	67%
H3	Long-term use of NSAID (>3 months)	75%	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%	(simple analgesics preferable and usually as effective for pain relief)	42%
H4	Long-term corticosteroids (>3 months)	83%	as monotherapy for rheumatoid arthrtitis	67%	(risk of systemic corticosteroid side-effects).	58%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%	for osteoarthritis	100%	(risk of systemic corticosteroid side-effects).	58%
H6	Long-term NSAID or colchicine (>3 months)	67%	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat	50%	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
H7	COX-2 selective NSAIDs	83%	with concurrent cardiovascular disease	42%	(increased risk of myocardial infarction and stroke).	75%
H8	NSAID	58%	with concurrent corticosteroids without PPI prophylaxis	58%	(increased risk of peptic ulcer disease).	75%

H9	Oral bisphosphonates	75%	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	92%	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
I						
I1	Antimuscarinic drugs	17%	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%	(risk of increased confusion, agitation / risk of urinary retention).	67%
I2	Selective alpha-1 selective alpha blockers	67%	in those with symptomatic orthostatic hypotension or micturition syncope	50%	(risk of precipitating recurrent syncope).	75%
J						
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%	with type 2 diabetes mellitus	75%	(risk of prolonged hypoglycaemia).	75%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%	in patients with heart failure	58%	(risk of exacerbation of heart failure).	67%
J3	Beta-blockers	67%	in diabetes mellitus with frequent hypoglycaemic episodes	50%	(risk of suppressing hypoglycaemic symptoms).	83%
J4	Oestrogens	67%	with a history of breast cancer or venous thromboembolism	83%	(increased risk of recurrence).	67%
J5	Oral oestrogens	83%	without progestogen in patients with intact uterus	100%	(risk of endometrial cancer).	67%
J6	Androgens (male sex hormones)	67%	in the absence of primary or secondary hypogonadism	58%	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
K						
K1	Benzodiazepines	67%	*[falls]*	0%	(sedative, may cause reduced sensorium, impair balance).	58%
K2	Neuroleptic drugs	17%	*[falls]*	0%	(may cause gait dyspraxia, Parkinsonism).	58%
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	83%	(risk of syncope, falls).	75%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%	*[falls]*	0%	(may cause protracted daytime sedation, ataxia).	58%
L						
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%	as first line therapy for mild pain	50%	(WHO analgesic ladder not observed).	33%
L2	Use of regular (as distinct from PRN) opioids	67%	without concomitant laxative	17%	(risk of severe constipation).	83%
L3	Long-acting opioids	17%	without short-acting opioids for break-through pain	17%	(risk of non-control of severe pain)	67%
M						
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%	*[users with…concomitant use of two or more drugs with antimuscarinic/anticholinergic properties]*	17%	(risk of increased antimuscarinic/anticholinergic toxicity)	17%

STOPP	Action	Clarity rate
n=80		
D7	Anticholinergics/antimuscarinics	17%
D8	Anticholinergics/antimuscarinics	17%
D14	First-generation antihistamines	17%
I1	Antimuscarinic drugs	17%
K2	Neuroleptic drugs	17%
L3	Long-acting opioids	17%
D9	Neuroleptic antipsychotic	25%
M1	Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines)	25%
A3	Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants	33%
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine),	33%
D3	Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol)	33%
D10	Neuroleptics	33%
F3	Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids)	33%
K3	Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,)	33%
E4	NSAID's	42%
L1	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine)	42%
B12	Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene)	50%
B13	Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)	50%
F4	Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day;	50%
G3	Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium)	50%
J1	Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride)	50%
J2	Thiazolidenediones (e.g. rosiglitazone, pioglitazone)	50%
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon	50%
E2	Direct thrombin inhibitors (e.g. dabigatran)	58%
E3	Factor Xa inhibitors (e.g. rivaroxaban, apixaban)	58%

F2	PPI	58%
H8	NSAID	58%
B3	Beta-blocker	67%
B4	Beta blocker	67%
B6	Loop diuretic	67%
B7	Loop diuretic	67%
B8	Thiazide diuretic	67%
B9	Loop diuretic	67%
B11	ACE inhibitors or Angiotensin Receptor Blockers	67%
C3	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors	67%
C6	Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C8	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C9	Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C10	NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	67%
C11	NSAID	67%
D1	Tricyclic Antidepressants (TCAs)	67%
D2	Initiation of Tricyclic Antidepressants (TCAs)	67%
D4	Selective serotonin re-uptake inhibitors (SSRI's)	67%
D5	Benzodiazepines	67%
D11	Acetylcholinesterase inhibitors	67%
G4	Benzodiazepines	67%
H2	NSAID	67%
H6	Long-term NSAID or colchicine (>3 months)	67%
I2	Selective alpha-1 selective alpha blockers	67%
J3	Beta-blockers	67%
J4	Oestrogens	67%
J6	Androgens (male sex hormones)	67%
K1	Benzodiazepines	67%
L2	Use of regular (as distinct from PRN) opioids	67%
D6	Antipsychotics (i.e. other than quetiapine or clozapine)	75%
D12	Phenothiazines	75%
G2	Systemic corticosteroids	75%
H1	Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents	75%
H3	Long-term use of NSAID (>3 months)	75%
H9	Oral bisphosphonates	75%
C1	Long-term aspirin at doses greater than 160mg per day	83%
D13	Levodopa or dopamine agonists	83%
H4	Long-term corticosteroids (>3 months)	83%
H5	Corticosteroids (other than periodic intra-articular injections for mono-articular pain)	83%
H7	COX-2 selective NSAIDs	83%
J5	Oral oestrogens	83%
C2	Aspirin	92%

A1	Any drug	100%
A2	Any drug	100%
B1	Digoxin	100%
B2	Verapamil or diltiazem	100%
B5	Amiodarone	100%
C4	Aspirin plus clopidogrel	100%
C5	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors	100%
C7	Ticlopidine	100%
E1	Digoxin at a long-term dose greater than 125µg/day	100%
E5	Colchicine	100%
E6	Metformin	100%
F1	Prochlorperazine or metoclopramide	100%
G1	Theophylline	100%

STOPP	Condition	Clarity rate
n=80		
K1	*[falls]*	0%
K2	*[falls]*	0%
K4	*[falls]*	0%
A1	prescribed without an evidence-based clinical indication.	8%
A2	prescribed beyond the recommended duration, where treatment duration is well defined	8%
A3	*[users with...duplicate drug class prescription]*	17%
L2	without concomitant laxative	17%
L3	without short-acting opioids for break-through pain	17%
M1	*[users with…concomitant use of two or more drugs with antimuscarinic/anticholinergic properties]*	17%
B5	as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	33%
B6	as first-line treatment for hypertension	33%
B13	in severe heart failure characterised by hypotension i.e. systolic BP < 90 mmHg, or concurrent nitrate therapy for angina	33%
C3	with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	33%
C6	in patients with stable coronary, cerebrovascular or peripheral arterial disease	33%
D1	with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	33%
D2	as first-line antidepressant treatment	33%
D5	for ≥ 4 weeks	33%
D8	in patients with delirium or dementia	33%
D9	in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed	33%
D10	as hypnotics, unless sleep disorder is due to psychosis or dementia	33%
D14	*[users of…first-generation antihistamines]*	33%
H2	with severe hypertension or severe heart failure	33%
B4	with bradycardia (< 50/min) , type II heart block or complete heart block	42%
G3	with a history of narrow angle glaucoma or bladder outflow obstruction	42%
H7	with concurrent cardiovascular disease	42%
I1	with dementia, or chronic cognitive impairment or narrow-angle glaucoma or chronic prostatism	42%
B11	in patients with hyperkalaemia.	50%
D7	to treat extra-pyramidal side-effects of neuroleptic medications	50%

D11	with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil	50%
F2	for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	50%
H6	for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor e.g. allopurinol, febuxostat	50%
I2	in those with symptomatic orthostatic hypotension or micturition syncope	50%
J3	in diabetes mellitus with frequent hypoglycaemic episodes	50%
L1	as first line therapy for mild pain	50%
B1	for heart failure with normal systolic ventricular function	58%
B2	with NYHA Class III or IV heart failure	58%
B7	for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	58%
H3	for symptom relief of osteoarthritis pain where paracetamol has not been tried	58%
H8	with concurrent corticosteroids without PPI prophylaxis	58%
J2	in patients with heart failure	58%
J6	in the absence of primary or secondary hypogonadism	58%
B9	for treatment of hypertension with concurrent urinary incontinence	67%
B12	without monitoring of serum potassium	67%
C5	in patients with chronic atrial fibrillation	67%
C8	for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months,	67%
C9	for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months	67%
C10	in combination	67%
C11	with concurrent antiplatelet agent(s) without PPI prophylaxis	67%
F3	in patients with chronic constipation where non-constipating alternatives are available	67%
G2	instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	67%
H4	as monotherapy for rheumatoid arthrtitis	67%
B8	with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout	75%
B10	unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives	75%
D3	with a history of prostatism or previous urinary retention	75%
D4	with current or recent significant hyponatraemia i.e. serum Na+ < 130 mmol/l	75%
G1	as monotherapy for COPD	75%
J1	with type 2 diabetes mellitus	75%

C4	as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	83%
D12	as first-line treatment,	83%
E1	if eGFR < 30 ml/min/1.73m2	83%
J4	with a history of breast cancer or venous thromboembolism	83%
K3	with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg	83%
B3	in combination with verapamil or diltiazem	92%
C1	[Long-term aspirin at doses greater than 160mg per day]	92%
F1	with Parkinsonism	92%
G4	with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa	92%
H9	in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	92%
C2	with a past history of peptic ulcer disease without concomitant PPI	100%
C7	in any circumstances	100%
D6	in those with parkinsonism or Lewy Body Disease	100%
D13	for benign essential tremor	100%
E2	if eGFR < 30 ml/min/1.73m2	100%
E3	if eGFR < 15 ml/min/1.73m2	100%
E4	if eGFR < 50 ml/min/1.73m2	100%
E5	if eGFR < 10 ml/min/1.73m2	100%
E6	if eGFR < 30 ml/min/1.73m2	100%
F4	*[Oral elemental iron doses greater than 200 mg daily]*	100%
H1	with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist	100%
H5	for osteoarthritis	100%
J5	without progestogen in patients with intact uterus	100%

STOPP	Explanation	Clarity rating
n=77		
M1	(risk of increased antimuscarinic/anticholinergic toxicity)	17%
A3	(optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).	33%
B6	(lack of outcome data for this indication; safer, more effective alternatives available).	33%
D9	(increased risk of stroke).	33%
F2	(dose reduction or earlier discontinuation indicated).	33%
H6	(xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	33%
L1	(WHO analgesic ladder not observed).	33%
D2	(higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	42%
H3	(simple analgesics preferable and usually as effective for pain relief)	42%
B10	(centrally-active antihypertensives are generally less well tolerated by older people than younger people).	50%
D1	(risk of worsening these conditions).	50%
D7	(risk of anticholinergic toxicity),	50%
G3	(may cause urinary retention).	50%
B1	(no clear evidence of benefit).	58%
B9	(may exacerbate incontinence).	58%
C3	(high risk of bleeding)..	58%
H4	(risk of systemic corticosteroid side-effects).	58%
H5	(risk of systemic corticosteroid side-effects).	58%
K1	(sedative, may cause reduced sensorium, impair balance).	58%
K2	(may cause gait dyspraxia, Parkinsonism).	58%
K4	(may cause protracted daytime sedation, ataxia).	58%
B13	(risk of cardiovascular collapse).	67%
C6	(no added benefit from dual therapy).	67%
C10	(risk of gastrointestinal bleeding).	67%
C11	(increased risk of peptic ulcer disease)	67%
D10	(risk of confusion, hypotension, extra-pyramidal side effects, falls).	67%
E1	(risk of digoxin toxicity if plasma levels not measured).	67%
E2	(risk of bleeding)	67%
E3	(risk of bleeding)	67%
G4	(risk of exacerbation of respiratory failure).	67%
H2	(risk of exacerbation of hypertension/heart failure)	67%
I1	(risk of increased confusion, agitation / risk of urinary retention).	67%
J2	(risk of exacerbation of heart failure).	67%
J4	(increased risk of recurrence).	67%
J5	(risk of endometrial cancer).	67%

L3	(risk of non-control of severe pain)	67%
B2	(may worsen heart failure).	75%
B3	(risk of heart block).	75%
B4	(risk of profound hypotension, asystole).	75%
B7	(leg elevation and /or compression hosiery usually more appropriate)	75%
C1	(increased risk of bleeding, no evidence for increased efficacy).	75%
D8	(risk of exacerbation of cognitive impairment).	75%
D14	(safer, less toxic antihistamines now widely available).	75%
E4	(risk of deterioration in renal function).	75%
F4	(no evidence of enhanced iron absorption above these doses).	75%
G1	(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	75%
G2	(unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).	75%
H1	(risk of peptic ulcer relapse).	75%
H7	(increased risk of myocardial infarction and stroke).	75%
H8	(increased risk of peptic ulcer disease).	75%
I2	(risk of precipitating recurrent syncope).	75%
J1	(risk of prolonged hypoglycaemia).	75%
K3	(risk of syncope, falls).	75%
B5	(higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	83%
B8	(hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).	83%
C2	(risk of recurrent peptic ulcer).	83%
C4	(no evidence of added benefit over clopidogrel monotherapy) .	83%
C5	(no added benefit from aspirin).	83%
C8	(no proven added benefit).	83%
C9	(no proven added benefit).	83%
D6	(risk of severe extra-pyramidal symptoms)	83%
D13	(no evidence of efficacy)	83%
E5	(risk of colchicine toxicity).	83%
E6	(risk of lactic acidosis).	83%
H9	(risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)	83%
J3	(risk of suppressing hypoglycaemic symptoms).	83%
L2	(risk of severe constipation).	83%
B12	(risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months).	92%
C7	(clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects)..	92%
D3	(high risk of urinary retention).	92%
D4	(risk of exacerbating or precipitating hyponatraemia).	92%
D11	(risk of cardiac conduction failure, syncope and injury).	92%

D12	since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).	92%
F1	(risk of exacerbating Parkinsonian symptoms).	92%
J6	(risk of androgen toxicity; no proven benefit outside of hypogonadism indication).	92%
D5	(no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for > 2 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	100%
F3	(risk of exacerbation of constipation).	100%

START	Action	Clarity rating	Condition	Clarity rating	Explanation	Clarity rating
A						
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%	in the presence of chronic atrial fibrillation.	50%		N/A
A2	Aspirin (75 mg – 160 mg once daily)	92%	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%		N/A
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%	with a documented history of coronary, cerebral or peripheral vascular disease.	58%		N/A
A4	Antihypertensive therapy	25%	where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%		N/A
A5	Statin therapy	67%	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%		N/A
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%	with systolic heart failure and/or documented coronary artery disease.	58%		N/A
A7	Beta-blocker	67%	with ischaemic heart disease.	75%		N/A
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%	with stable systolic heart failure.	67%		N/A
B						
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%	for mild to moderate asthma or COPD.	50%		N/A
B2	Regular inhaled corticosteroid	58%	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%		N/A
B3	Home continuous oxygen	83%	with documented chronic hypoxaemia (i.e. pO_2 < 8.0 kPa or 60 mmHg or SaO_2 < 89%)	92%		N/A
C						
C1	L-DOPA or a dopamine agonist	67%	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%		N/A
C2	Non-TCA antidepressant drug	25%	in the presence of persistent major depressive symptoms.	33%		N/A
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%		N/A
C4	Topical prostaglandin, prostamide or beta-blocker	67%	for primary open-angle glaucoma.	100%		N/A
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%	for persistent severe anxiety that interferes with independent functioning.	50%		N/A
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%		N/A
D						
D1	Proton Pump Inhibitor	67%	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%		N/A
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%	for diverticulosis with a history of constipation.	58%		N/A
E						
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%	with active, disabling rheumatoid disease.	42%		N/A
E2	Bisphosphonates and vitamin D and calcium	67%	in patients taking long-term systemic corticosteroid therapy.	33%		N/A

E3	Vitamin D and calcium supplement	17%	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%		N/A
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%		N/A
E5	Vitamin D supplement	42%	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%		N/A
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%	with a history of recurrent episodes of gout.	50%		N/A
E7	Folic acid supplement	92%	in patients taking methotexate.	33%		N/A
F						
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%		N/A
G						
G1	Alpha-1 receptor blocker	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G2	5-alpha reductase inhibitor	67%	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%		N/A
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%	for symptomatic atrophic vaginitis	75%		N/A
H						
H1	High-potency opioids	17%	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%		N/A
H2	Laxatives	17%	in patients receiving opioids regularly.	75%		N/A
I						
I1	Seasonal trivalent influenza vaccine	83%	annually	83%		N/A
I2	Pneumococcal vaccine	83%	at least once after age 65 according to national guidelines	83%		N/A

START	Action	Clarity rating
n=34		
E3	Vitamin D and calcium supplement	17%
H1	High-potency opioids	17%
H2	Laxatives	17%
A4	Antihypertensive therapy	25%
C2	Non-TCA antidepressant drug	25%
E1	Disease-modifying anti-rheumatic drug (DMARD)	25%
E4	Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab)	42%
E5	Vitamin D supplement	42%
C3	Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine)	50%
D2	Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia)	50%
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat)	50%
B1	Regular inhaled B2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium)	58%
B2	Regular inhaled corticosteroid	58%
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors	67%
A5	Statin therapy	67%
A6	Angiotensin Converting Enzyme (ACE) inhibitor	67%
A7	Beta-blocker	67%
C1	L-DOPA or a dopamine agonist	67%
C4	Topical prostaglandin, prostamide or beta-blocker	67%
C5	Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated)	67%
D1	Proton Pump Inhibitor	67%
E2	Bisphosphonates and vitamin D and calcium	67%
F1	ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor)	67%
G1	Alpha-1 receptor blocker	67%
G2	5-alpha reductase inhibitor	67%
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor)	75%
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol)	83%
B3	Home continuous oxygen	83%
C6	Dopamine agonist (ropinirole or pramipexole or rotigotine)	83%
G3	Topical vaginal oestrogen or vaginal oestrogen pessary	83%
I1	Seasonal trivalent influenza vaccine	83%
I2	Pneumococcal vaccine	83%
A2	Aspirin (75 mg – 160 mg once daily)	92%
E7	Folic acid supplement	92%

START	Condition	Clarity rate
n=34		
A2	in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.	33%
C2	in the presence of persistent major depressive symptoms.	33%
C6	for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.	33%
E2	in patients taking long-term systemic corticosteroid therapy.	33%
E7	in patients taking methotexate.	33%
A5	with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	42%
C3	for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).	42%
E1	with active, disabling rheumatoid disease.	42%
A1	in the presence of chronic atrial fibrillation.	50%
B1	for mild to moderate asthma or COPD.	50%
B2	for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.	50%
C1	in idiopathic Parkinson's disease with functional impairment and resultant disability.	50%
C5	for persistent severe anxiety that interferes with independent functioning.	50%
D1	with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.	50%
E5	in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	50%
E6	with a history of recurrent episodes of gout.	50%
G1	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
G2	with symptomatic prostatism, where prostatectomy is not considered necessary.	50%
H1	in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.	50%
A3	with a documented history of coronary, cerebral or peripheral vascular disease.	58%
A6	with systolic heart failure and/or documented coronary artery disease.	58%
D2	for diverticulosis with a history of constipation.	58%

E4	in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores -> 2.5 in multiple sites) and/or previous history of fragility fracture(s).	58%
A8	with stable systolic heart failure.	67%
F1	in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	67%
A4	where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.	75%
A7	with ischaemic heart disease.	75%
E3	in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites.	75%
G3	for symptomatic atrophic vaginitis	75%
H2	in patients receiving opioids regularly.	75%
I1	annually	83%
I2	at least once after age 65 according to national guidelines	83%
B3	with documented chronic hypoxaemia (i.e. pO2 < 8.0 kPa or 60 mmHg or SaO2 < 89%)	92%
C4	for primary open-angle glaucoma.	100%