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STOPP/START criteria for potentially inappropriate medications/potential prescribing omissions in older people: uptake and clinical impact

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Abstract

Introduction: STOPP/START criteria for potentially inappropriate medications (PIMs, STOPP) and potential prescribing omissions (PPOs, START) have gained considerable interest and traction since they were first published in 2008. This review focuses on their uptake and impact in various clinical settings.

Areas covered: STOPP/START criteria, now in their third iteration, are explicit criteria designed to facilitate detection of common and clinically important PIMs and PPOs during routine medication review in any clinical setting. We examine the influence of the criteria, particularly in clinical trials that focused on their impact on clinically relevant endpoints.

Expert opinion: STOPP/START criteria are widely used in several countries within Europe and beyond for medication review and audit. As a discreet intervention, the criteria have been tested in several single-centre and two large-scale multi-centre clinical trials. The single centre trials indicate that STOPP/START criteria reduce polypharmacy, inappropriate prescribing, ADRs (adverse drug reactions), medication cost and falls. In contrast, the SENATOR and OPERAM multicentre trials did not demonstrate significant reduction in ADRs, all-cause mortality, drug-related hospital readmissions, nor any improvement in quality-of-life. Further clinical trials are required to examine whether STOPP/START criteria as an intervention can deliver significant clinical benefit in a reproducible manner in various clinical settings.

1. Introduction

Appropriate prescribing of medications is of critical importance in promoting patient safety, optimizing therapeutic outcomes, and preventing adverse drug events [1]. This is particularly true in the delivery of healthcare to older people where the interaction between multiple drugs, increasing burden of co-morbidity and the emergence of frailty creates an environment of complexity and greater therapeutic risk. Best currently available evidence indicates that 5% -10% of hospital admissions involving older adults are primarily attributable to adverse drug reactions (ADRs) [2,3]. Amongst hospitalized older adults, reported incidence of clinically significant ADRs ranges from 6.5% to 21% [4–7]. Evidence from prospective studies clearly shows that ADRs prolong hospital admissions [5] and are an important cause of avoidable mortality in hospitalized older patients [4,8].

Whilst it is acknowledged that one in ten hospital admissions in older patients is directly attributable to ADRs [9], a clear and transferrable strategy for reducing ADRs that cause hospitalization is lacking. Further hazard to older people occurs after admission to hospital, with an ADR prevalence of 16% identified in hospitalized older patients in one recent systematic review [10]. Recent meta-analyses have shown that patients experiencing suspected ADRs had significantly higher odds ratio (OR) of mortality [OR: 1.50 (95% CI: 1.21–1.86; $I^2 = 100\%$] than those patients who did not experience suspected ADRs during hospitalization [11]. Furthermore, patients having suspected ADRs also had significantly higher mean difference in hospital stay i.e. 3.98 days (95% CI: 2.91–5.05; $I^2 = 99\%$)[11].

Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) are explicit prescribing criteria, based mostly on systematic reviews, clinical trial evidence, expert opinion and consensus techniques that have been developed specifically to reduce medication-related harm in older people. The primary objective of STOPP criteria is to highlight to prescribers potentially inappropriate medications (PIMs) that place older adults at higher risk of adverse drug effects or interactions. Conversely, START criteria identify potential prescribing omissions (PPOs) i.e. medications, not yet prescribed, that are likely to be beneficial based on specific clinical characteristics of the older patient. Together, these two tools provide a comprehensive approach to medication review and optimization, particularly for older individuals who often present with multiple comorbidities and polypharmacy. They were first published in 2008 following Delphi consensus validation [12].

STOPP/START criteria are organized according to physiological systems and pharmacological classes. In addition to explicitly listing drugs to be avoided in older people, STOPP criteria indicators highlight problematic drug-drug interactions and drug disease interactions [13]. In this way, healthcare professionals can systematically assess medication regimens and identify areas that require further evaluation or modification. Similarly, START criteria provide a complementary framework for promoting appropriate prescribing in older adults. These criteria focus on medications that may be underutilized or overlooked in specific clinical situations, such as preventive therapies, disease-specific treatments, and medications for symptomatic relief [13]. By addressing PPOs, START criteria help ensure that older patients receive necessary and beneficial pharmacotherapy tailored to their individual needs.

Multiple prescribing review tools exist including Beers criteria, FORTA score, PIM-Check and others (see **Table 1**). However, STOPP/START criteria unlike other criteria have been used as an intervention in several randomized controlled clinical trials showing reductions in inappropriate medication use, adverse drug reactions, polypharmacy, and monthly medication costs [14]. Moreover, by their explicit nature, STOPP/START criteria facilitate communication and collaboration among clinicians involved in medication management, enabling a multidisciplinary approach to optimize prescribing decisions.

Medication review is a core component of comprehensive geriatric assessment (CGA)[15]. Older patients with multiple comorbidities will generally have valid indications for multiple medications. However, guideline-based prescribing may not be directly applicable to frail older people or those with significant comorbidity and clinicians should be aware that such 'real world' patients are often absent or underrepresented among clinical trial participants [16]. Furthermore, medicines prescribed for long-term risk reduction such as antihypertensives, lipid-lowering agents and certain supplements may be less relevant to older people with a limited lifespan, and their use may not reflect current patient priorities. Finally, ADRs may be challenging to recognize in older people as they often manifest as nonspecific symptoms such as fatigue, memory loss, poor appetite, constipation, and impaired balance. These symptoms, when unrecognized, may prompt the prescription of further medications, so-called prescribing cascades. Therefore, judicious review of medications, their indications, likely benefits, tolerability, and potential side effects as well as interactions with other drugs and diseases is critically important in clinically complex multimorbid older adults. Use of an explicit prescribing optimization tool, such as STOPP/START, enables a standardized approach to the formal medication review.

Initially published in 2008 [12], STOPP/START criteria were updated in 2015 [13] and, very recently, in 2023 [17]. The criteria have gained widespread recognition and application across healthcare settings globally. This article focuses on the uptake and impact of STOPP/START criteria.

2. Uptake and Validation of STOPP/START Criteria

2.1 Uptake of STOPP/START Criteria

Since the publication of the first iteration of STOPP/START criteria in 2008, the criteria have gained significant recognition and have been widely adopted for use in clinical practice, research, education and quality improvement initiatives. STOPP/START version 1 has been cited 944 times, while STOPP/START version 2 published in 2015 has already been cited 1360 times (to July 10, 2023). There have been over 1,000 published articles describing the use of STOPP/START criteria in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/?term=stopp+criteria&filter=years.2008-2023) including over 19 clinical trials and more than 100 review articles. In its 40th anniversary edition, the journal Age and Ageing listed the STOPP/START Version 2 publication among its most frequently read and cited articles since the journal's inception in 1972 [18].

STOPP/START criteria have been endorsed by various organisations including the World Health Organisation (WHO)[19], the Dutch Multidisciplinary Guidelines on Polypharmacy in Older People [20], National Institute for Clinical Excellence (NICE) [21], the British Geriatrics Society, Age UK, the UK Royal College of General Practitioners [22] and the British National Formulary [23] as a support tool to guide clinicians in making prescribing decisions in complex older patients. The criteria have also been translated into numerous languages [24–29] and have been applied in research and clinical settings across locations in Europe, Asia, Australia, North America, and South America which further emphasises their international relevance [13]. In recent years, STOPP/START criteria have been incorporated into the Comprehensive Geriatric Assessment toolkit, the international standard for best practice in older patient assessment [30].

2.2 Clinical relevance of STOPP/START Criteria

Several validation studies have been conducted worldwide to evaluate the effectiveness of STOPP/START criteria in various healthcare settings, including hospital, nursing home and primary care. In many of these studies, STOPP/START criteria were used as a measure of prescribing quality and investigators measured the prevalence of STOPP-defined PIMs and START-defined PPOs and examined their association with a range of clinical outcomes.

Moriarty et al. evaluated whether potentially inappropriate prescribing (PIP), as defined by STOPP/ START, was associated with increased healthcare utilization, functional decline and reduced quality of life (QoL) in a community-dwelling older cohort [31]. Patients prescribed one or more STOPP-defined PIMs had significantly higher rates of emergency department (ED) visits (30% higher) and general practitioner (GP) visits (15% higher) during follow up. Patients with two or more START-defined PPOs had significantly more ED visits (45% higher) and GP visits (13% higher) relative to those without PPOs. This study also demonstrated that having any START PPO had a significant association with functional decline, with a doubling of risk for those with two or more START criteria applying. Exposure to two or more START PPOs was also associated with a small but statistically significant reduction in QoL assessed using the CASP-R12 instrument.

Rodríguez Del Río et al. studied the association between PIP and the 30- and 180-day adverse event rate after discharge from a short stay unit using STOPP/START criteria [32]. The presence of ≥1 PIM after discharge was not associated with a 30-day and 180-day composite adverse event. Patients with ≥1 PIM related to a cerebrovascular or cardiovascular process were at significantly higher risk of an adverse clinical event at 30 days after discharge (adjusted odds ratio 2.1). Furthermore, those receiving ≥1 PIM related to a neuropsychiatric condition and having a concurrent risk of falls were at substantially higher risk of 30-day functional impairment (adjusted odds ratio 6.3). Finally, those with ≥ 1 PPO related to omission of cardiovascular system medication were at higher risk of 180-day hospital readmission (adjusted odds ratio 3.6).

Herawati et al. evaluated the use of STOPP/START on medication appropriateness on an adapted version of the Medication Appropriateness Index (MAI), as well as of ADR risk (GerontoNet score) and length of stay in a hospitalized older population [33]. The average adapted MAI score was significantly and substantially improved in the intervention group compared to the control group. The average (standard deviation [SD]) GerontoNet ADR risk score was significantly reduced in the intervention group compared to the control groups (3.33 (2.28) versus 5.18 (2.10)). Average (SD) hospital length of stay was also significantly reduced in the intervention group compared to the control group i.e. 7.63 (3.00) days versus 14.18 (9.97) days.

Brunetti et al. evaluated whether STOPP/START-defined PIMs and PPOs were associated with 6-month mortality and unplanned rehospitalization in hospital-discharged older patients [34]. Among 611 patients, overall PIP prevalence at discharge was 71.7% (PIMs 54.8%, PPOs 47.3%), and mortality and unplanned readmission rates were 25.0% and 30.9% respectively. Neither STOPP-defined PIMs nor START-defined PPOs were significantly associated with overall mortality, but a higher number of PIMs carried a 23% significantly higher risk of unscheduled readmission in the overall sample. In patients discharged to home as distinct from nursing care facility, the readmission rate was higher i.e. 38%.

Counter et al. used STOPP/START version 2 criteria to assess prescriptions for PIMs and PPOs in 259 older adults discharged from a general medical unit their association with hospital readmission and mortality [35]. Prescription of more than five daily long-term medications i.e. polypharmacy by

conventional definition carried a significant risk of PIMs and PPOs. They also demonstrated that presence of ≥1 PIM was significantly associated with unscheduled readmissions (odds ratio 2.43 95% CI: 1.19-4.98) and that ≥1 PPO was significantly associated with increased mortality (odds ratio 1.88, 95% CI: 1.09-3.27) compared to patients not exposed to STOPP-defined PIMs or START-defined PPOs.

Manias et al. carried out a mixed-methods, sequential explanatory study of electronic medical records of 249 patients aged 85 years and older over four time points across transitions of care [36]. The prevalence of at least 1 STOPP-defined PIM varied between 36.9% and 51.0%, while the prevalence of at least 1 START-defined PPO varied between 36.9% and 44.6% across the time points (STOPP/START version 2 criteria were applied). Poisson regression analysis showed that PIMs were significantly associated with higher probability of need for mobility aids [odds ratio 1.430 (95% CI 1.109-1.843] and the number of medications prescribed at admission [odds ratio 1.083 (95% CI 1.058-1.108)]. PPOs were significantly associated with the number of chronic comorbidities [odds ratio 1.172 (95% CI 1.073-1.280)], the number of medications prescribed at admission [odds ratio 0.989 (95% CI 0.978-0.999)], and hospital length of stay [odds ratio 1.004 (95% CI 1.002-1.006)]. This study illustrates that STOPP/START criteria readily identify PIMs and PPOs at the various points of care transition in very old patients and that the presence of these PIMs and PPOs is clinically relevant and therefore deserving of attention and correction where possible.

Sanh et al. evaluated the prevalence of PIP (PIMs and PPOs combined) to explore its impact in a pilot study of 100 older adult high-cost health care users in Ontario, Canada [37]. Eighty nine of these 100 patients had at least one instance of PIP, defined by STOPP/START version 2 criteria; 276 STOPP PIMs and 54 START PPOs were identified in these patients. Of the 271 instances of PIP identified at admission to hospital, only 38 (14%) were resolved by the time of hospital discharge. Importantly, each additional START PPO was associated with a highly significant 1.43-fold increase in the rate of future emergency department visits. Although small in scale, this pilot study indicates that STOPP/START criteria-defined PIMs and PPOs in older people who frequently access high-cost healthcare in hospital are very common and clearly linked to adverse clinical outcomes, in particular uncorrected PPOs.

In summary, several studies demonstrate that STOPP/START criteria-defined PIMs and PPOs are associated with adverse clinical outcomes including rehospitalization, prolonged length of stay and reduced QoL. Therefore, one can reasonably propose that detection and correction of STOPP/START-defined PIMs and PPOs might attenuate associated adverse clinical endpoints. This reasoning has formed the basis for a series of randomized clinical trials using STOPP/START criteria as an intervention compared to standard pharmaceutical care in multimorbid older patients with associated polypharmacy.

2.3 Clinical Trials using STOPP/START Criteria

A previous review published in 2019 described five single-centre trials as well as two large-scale multi-centre trials in which STOPP/START criteria were used as an interventional tool [38]. To date, STOPP/START criteria have been tested as an intervention in several other randomized controlled trials (RCTs). These clinical trials are summarized in Table 2. The use of STOPP/ START as an intervention in large-scale multicentre trials is summarized in the next section.

2.4 SENATOR, OPERAM and OPTIMATE trials

SENATOR (Software ENgine for the Assessment and Optimization of drug and non-drug Therapy in Older peRsons) was a randomized controlled clinical trial that evaluated a comprehensive approach to

optimizing the appropriateness of older patients' prescriptions with the core aim of avoiding ADRs in multimorbid older people presenting with acute illness to hospital [39]. The trial took place in six major medical centres in six European countries (Ireland, Scotland, Spain, Italy, Belgium and Iceland) and involved participants aged 65 or older who had at least three chronic conditions and were taking multiple long-term medications i.e. polypharmacy proportionate to multimorbidity (the median daily number of long-term medications in all trial participants was ten). The primary objective of this multi-centre trial was to determine whether providing clinical decision support systems (CDSS)-generated medication advice reports based predominantly on PIP criteria to clinicians attending hospitalized acutely ill older people with multi-morbidity could significantly reduce ADR incidence within 14 days of randomization or discharge, whichever came first. The incidence of ADRs was comparably high in both patients allocated to the control arm (usual pharmaceutical care) and those assigned to the SENATOR software intervention arm (24.5% vs. 24.8%; P = 0.88). Although SENATOR software successfully and accurately deployed STOPP/START criteria alongside major drug–drug and drug–disease interaction alerts, implementation of SENATOR prescribing advice points among attending clinicians was substantially lower than expected i.e., 15.0% on average across the six participating sites. The SENATOR trial results indicated clearly that for electronic prescribing advice aimed at prevention of ADRs in hospitalized multi-morbid older patients to be effective, a further element is required over and above provision of prescribing advice reports to attending physicians, most likely face-to-face interaction with expert physicians or pharmacists.

OPERAM (Optimising thERapy to Prevent Avoidable hospital admissions in Multimorbid older people) was a randomized controlled trial conducted in four major medical centres in four European countries (Switzerland, Netherlands, Belgium, Ireland) that examined the effectiveness of a CDSS deploying STOPP/START version 2 criteria to identify PIMs and PPOs for consideration for correction by attending hospital physicians [40]. In the conduct of the trial, there was a structured analysis of patients' drug history, treatment compliance, history of ADRs and semi-structured shared decision making with patients regarding proposed changes to their medication. In addition, there was direct face-to-face interaction between primary researchers and attending hospital physicians for the purpose of discussing proposed changes to medication based on STOPP/START recommendations as well as detailed advice reports for patients' primary care physicians to consider following discharge. Adults aged 70 years or older with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 daily drugs) were eligible for inclusion. The primary outcome was the first confirmed drug related hospital admission (DRA) after discharge following the index hospital admission occurring within 12 months of enrolment. In the intervention arm, 86.1% of participants (n=789) had potentially inappropriate prescribing, with a mean (SD) of 2.75 (2.24) STOPP/START recommendations per trial participant. Overall, 62.2% of patients in the intervention arm had ≥ 1 recommendation successfully implemented. There was no statistically significant difference in drug related hospital admissions between participants in the intervention arm compared with the control arm (21.9% vs 22.4%). Equally, none of the secondary endpoints in OPERAM was significantly improved in the intervention group compared to controls, including all-cause mortality, falls and quality of life measured by EQ-5D-5L. The OPERAM trial concluded that inappropriate prescribing was very common in older adults with multimorbidity and polypharmacy admitted to hospital and was significantly reduced through an intervention to optimise pharmacotherapy through application of STOPP/START criteria, but without any significant effect on subsequent drug related hospital readmissions, mortality, falls or QoL.

The currently enrolling OPTIMATE trial (OPTImization of Medication by Transdisciplinary Assessment of Drug Treatment in Elderly Hospitalized Patients) is another randomized controlled trial being conducted in three major medical centres in two European countries (Cork, Ireland; Waterford, Ireland; Ghent, Belgium). The purpose of the OPTIMATE trial is to evaluate whether a multi-faceted

definitive intervention designed to optimize medication in hospitalized older people with ≥3 chronic medical conditions exposed to ≥5 long-term daily medications can reduce unplanned hospital readmission and emergency department attendance compared to current usual medication management [41]. The study intervention is based on the most recent iteration of STOPP/START criteria (version 3; [17]) and aims to minimize PIMs and PPOs in a structured way using STOPP/START criteria as well as identifying and preventing serious adverse drug-drug interactions using Stockley's Drug-Drug Interaction Checker on-line tool [42]. The intervention also involves follow up with patients and GPs to enhance adherence with medication recommendations. The trial began enrolment in January 2023 and will complete in September 2024.

3. Limitations of STOPP/START criteria

STOPP/START criteria are widely used in clinical practice to identify potentially inappropriate medications in older adults. While they have proven to be valuable tools, they do have some limitations that should be considered. Firstly, the applicability of the criteria may present a limitation, particularly where patient records are not fully electronic. There is a need to consult multiple sources of medical history information to apply the criteria fully, including electronic laboratory results data as well as paper sources of information and direct contact with patients, caregivers, and healthcare professionals. Inadequate documentation in patients' clinical records of the precise rationale for prescribing or not prescribing certain medications can make the application of the criteria challenging. In the same way that Beers criteria reflect prescribing custom and practice in the USA, STOPP/START criteria are based primarily on prescribing patterns in Europe and have been validated by groups of European experts in its three iterations to date. Sceptics might argue therefore that STOPP/START criteria have limited applicability outside of Europe. However, the publication of numerous papers citing STOPP/START criteria in several countries across various continents (1,278 in PubMed on July 17 2023) has shown that this theoretical Europe-focused limitation is likely artificial and essentially unimportant.

Another possible limitation of STOPP/START is the frequency of their revision. The first version was published in 2008, followed by version 2 in 2015 and most recently version 3 in 2023. Ideally updated versions would be provided on a more regular basis to reflect the ever-changing landscape in medical and prescribing guidelines. This is the case with Beers criteria which have been updated in 3-year cycles since the remit of organized structured review and updating of the criteria was undertaken by a special committee of the American Geriatrics Society in 2012. It can be argued reasonably that STOPP/START criteria, after just 3 iterations in 15 years, should be revised and updated every 3 years, like Beers criteria in order to reflect changing evidence base and consensus relating to therapeutics in older people. Updating of explicit PIM criteria, such as Beers criteria and STOPP/START, is however both time and staff resource intensive requiring appropriate funding support to ensure that the process is carried out to a sufficient standard.

The lack of readily available software applications to facilitate integration of STOPP/START criteria with electronic health records (EHRs) is an issue that is becoming more important as STOPP/START criteria grow in number. It is noteworthy that STOPP/START version 3 with 190 criteria is 218% larger than version 1 and 67% larger than version 2. In several countries including Ireland, implementation of EHRs is slow. However, in Ireland as in many other countries, progress is being made towards a national e-prescribing programme [43]. The vision is that this will facilitate safer prescribing and dispensing of medicines through automated and better access to medicines information for prescribers and patients. Once a fully electronic prescribing and dispensing system like this has been established, it can usually

incorporate electronic clinical decision support systems (eCDSS) that could support deployment of STOPP/START criteria to enable healthcare professionals to assess patients' medications quickly and accurately and avoid PIMs and PPOs.

STOPP/START criteria are also restricted by the limited consideration of patient preferences or use of shared decision-making. In the OPERAM trial, Blum et al. showed that several recommendations cannot be implemented during hospital admission as participants wanted to discuss changes with their GP [40]. The OPTI-SCRIPT intervention led to significant reductions in the most commonly occurring PIMs nationally by incorporating tailored patient information leaflets within a multi-faceted approach [44]. The iSIMPATHY trial, which closed in March 2023 had integrated shared decision making with patients regarding their medications and is addressing the health challenges posed by polypharmacy and poor medication adherence, identified by the WHO as a priority area to focus on as a way to reduce severe, avoidable medication related harm [45]. Reflecting the centrally important need for careful dialogue between medication reviewers and patients, the OPTIMATE trial also incorporates semi-structured discussion with patients, their GPs and community pharmacists regarding the recommendations generated by application of STOPP/START version 3 criteria and Stockley's automated drug-drug interaction checking software [41].

Finally, prescribers may agree with recommendations regarding PIMs and PPOs in many situations but feel poorly equipped to adopt these changes. Incorporation of initiation and deprescribing guidelines as appendices within STOPP/START criteria may facilitate safer and more efficient medication adjustment. Similarly, future iterations of STOPP/START criteria need to incorporate indicators of PIM and PPO severity in order to assist prescribers to prioritize which particular medication adjustments are clinically more important and urgent than others.

4. Future Direction

Regarding the future direction of the STOPP/START criteria, several developments can be anticipated. The most significant of these developments is the ongoing refinement and expansion of STOPP/START. The considerable size and range of the current version of STOPP/START criteria necessitates software applications that facilitate integration with EHRs as well as eCDSS. That is, the criteria have expanded to a level where easy application of a print version is no longer user friendly. Ideally, software applications and web-based programmes amalgamated with EHRs and eCDSS would be widely and easily available to facilitate STOPP/START criteria use.

The growing and increasingly important role of pharmacogenomics in personalised medicine means that future versions of STOPP/START criteria will very likely need to include pharmacogenetic information as it becomes increasingly used in routine clinical practice. It is expected that in doing so, clinicians and medication reviewers would provide a more comprehensive, more precise and patient-specific approach to medication review [46]. Further global adoption of STOPP/START criteria by translation into more languages and application by more healthcare services will permit greater analysis of the impact of the criteria.

The results of the SENATOR and OPERAM clinical trials highlight the need for a more integrated and multifaceted approach to the detection and management of polypharmacy and inappropriate prescribing. An integrated framework involving collaboration between clinicians and patients, shared decision-making, close monitoring of medication effects and follow-up, under a clinical governance structure is likely to be required. Prescribing stewardship, practiced widely to ensure appropriate use of antimicrobials, has been proposed as a potential model that could be implemented to address the

polypharmacy crisis [47]. Polypharmacy stewardship is defined as a coordinated intervention designed to assess, monitor, improve, and measure the pharmacotherapeutic treatment of multimorbidity, considering potentially inappropriate medications, potential prescribing omissions, drug–drug and drug–disease interactions, and prescribing cascades, with the aim of aligning treatment regimens with the overall condition, prognosis, and preferences of the individual patient. STOPP/START criteria could play a key integral role in this polypharmacy stewardship method by providing some of the essential framework needed for medication review, providing education, and tracking PIMs and PPOs in older patients. It is essential to appreciate that polypharmacy stewardship model necessarily crosses care settings and is a continuous process, as medication regimens may change over time due to evolving health conditions or treatment goals. This ongoing polypharmacy stewardship reflects the chronic and ongoing nature of multimorbidity in late life. Thus, regular medication reviews and monitoring are essential to ensure that the medication regime remains optimally appropriate and effective. Overall, polypharmacy stewardship, supported by tools like STOPP/START criteria, is intended to promote patient safety, improve medication management, and enhance the quality of care for individuals taking multiple medications over an extended time period.

5. Conclusion

In conclusion, STOPP/START criteria are widely used internationally in clinical practice, research, education, and quality improvement initiatives. The success and widespread use of STOPP/START is likely explained by its organization into practical, physiological systems-based, evidence-based components which enable an intuitive approach to addressing polypharmacy in the older multimorbid patient population. As the global population of older people continues to increase, the need for accurate and comprehensive tools to guide medication management becomes increasingly important. Imminent objectives for STOPP/START include more frequent updates, digitisation, and enhanced patient involvement. Outcomes from the OPTIMATE and iSIMPATHY trials using STOPP/START will further inform its future. Overall, polypharmacy stewardship and the role of STOPP/START criteria within it will, we anticipate, shape further progress in addressing inappropriate prescribing in older people.

6. Expert Opinion

The avoidance of inappropriate prescribing in the form of PIMs and PPOs remains a fundamental imperative for all prescribers who treat older people, the majority of whom experience multimorbidity and associated polypharmacy. Polypharmacy engenders PIMs and associated ADRs and adverse drug events (ADEs) whilst PPOs engender higher rates of unscheduled hospitalization and all-cause mortality. The avoidance of PIMs and PPOs, therefore, should reduce adverse clinical outcomes for older people with multimorbidity and polypharmacy. STOPP/START criteria are designed to highlight more clinically important and common PIMs and PPOs, with the aim of prompting prescribers and medication reviewers to avoid them and make medication regimens safer and less likely to result to cause ADRs and ADEs to the patient. The recent large-scale SENATOR and OPERAM multi-centre clinical trials, in which STOPP/START version 2 criteria was the main component of the intervention, did not demonstrate significant benefit over standard pharmaceutical care in the clinically relevant endpoints of those trials. However, this does not mean that STOPP/START criteria are intrinsically incorrect or clinically irrelevant. Because implementation of STOPP/START-based medication advice was substantially suboptimal in those trials, researchers need to develop more effective, practical, and

transferrable ways of improving implementation of STOPP/START-based medication advice. This will remain a significant challenge for the future. Most experts agree that implementation of evidence-based medication advice is fundamentally sound and will remain part of the medication safety agenda for prescribers in the future. How to facilitate optimal delivery and uptake of STOPP/START criteria is a key challenge for researchers in this area.

A number of essential things need to happen in the coming 5 years to make STOPP/START criteria more relevant to clinical practice. These include digitization of the criteria on mobile hand-held devices to make them more easily applicable within electronic health records. Digitization for more easy deployment of STOPP/START criteria will require funding and investment, most likely from national governments or the European Commission i.e., the principal stakeholders in polypharmacy optimization and medication safety in older people in Europe. In addition, further clinical trials of STOPP/START as an intervention are required. However, the framework for application and implementation of STOPP/START criteria must change from the approach taken in the SENATOR and OPERAM trials. We propose a polypharmacy stewardship model in which the principles of antimicrobial stewardship in hospitalized patients being treated for infection are applied to the rapidly growing global population of people aged over 75 years with multimorbidity and polypharmacy. Since polypharmacy is the main driver of errors of inappropriate prescribing commission and omission, there is a need for specialized teams to take responsibility for polypharmacy in this high-risk population of hospitalized patients. Furthermore, there is a need for polypharmacy surveillance teams to provide specialized follow-up of these patients in the community following hospital discharge. The stewardship team should also be available for consultation with patients' primary care physicians when problems arise relating to patients' polypharmacy. In essence, if polypharmacy is inevitable in older multimorbid patients, it should be made as safe as possible and STOPP/START criteria, through careful and structured polypharmacy stewardship, will play on ongoing and important role in medication safety awareness. Furthermore, for PIM/PPO criteria to remain up to date and clinically relevant, STOPP/START criteria need to be updated more regularly than hitherto, ideally every 3 years and not less than every 5 years. How STOPP/START criteria are to be updated and validated is a matter of some debate. Clearly, this task should be the remit of expert bodies within Europe and possibly beyond, given the international interest and traction that STOPP/START criteria now hold. Experts in geriatric pharmacotherapy from several countries will be important to maintain clinical relevance and transferability of STOPP/START criteria. In our opinion, the combined collective consensus of an international panel of experts will be essential to keep the criteria evidence-based and clinically relevant. However, expertise in information and communications technology will play an increasing role in future versions of STOPP/START criteria if they are to digitized appropriately and made available through mobile computerized devices. National and international funding of this work will be important in the future to ensure ongoing high quality, clinically relevant STOPP/START criteria. To date, updating and validation of STOPP/START criteria has not received any designated funding, all work on the criteria to date being done pro bono.

The WHO Medication Without Harm initiative in 2017 was a timely and important reminder to prescribers everywhere of their professional responsibility to make medication as safe as possible for patients of all ages everywhere [48]. However, the initiative lacked detail as to how polypharmacy should be made safer in multimorbid older people, the patient group at highest risk from adverse medication (PIMs and PPOs). STOPP/START criteria in its current third iteration and in future iterations will aim to inform prescribers everywhere of potential hazards to older people with multimorbidity exposed to associated polypharmacy. As populations age globally, the imperative of making polypharmacy as safe as possible for older people will intensify. We contend that STOPP/START criteria

have a central role in the older patient safety agenda and success in that agenda will, we believe, be economically advantageous. To ignore that reality would be a major economic mistake.

Disclosure of Interest

Siobhán McGettigan discloses being a primary researcher within the OPTIMATE project. Denis O'Mahony discloses being the co-ordinator of the SENATOR project and being the co-principal investigator of the OPERAM and OPTIMATE projects.

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Table 1. Comparison of Commonly Used Prescribing Review Tools

Tool	Validation method	Population	Criteria
STOPP/START criteria [17]	Delphi consensus; 11 experts	Older people ≥65 years	STOPP: 133 criteria; START: 57 criteria; organized according to physiological system
Beers criteria [49]	Delphi consensus; 12 experts	Older people ≥65 years (except hospice and end-of-life care settings)	88 drugs/drug classes in five categories: 1. Medications considered as potentially inappropriate 2. Medications potentially inappropriate in patients with certain diseases or syndromes 3. Medications to be used with caution 4. Potentially inappropriate drug–drug interactions 5. Medications whose dosages should be adjusted based on renal function
FORTA Score [50]	Delphi consensus; 32 experts	Older people ≥65 years; or ≥60 years with ≥6 medications	267 drugs/drug classes organized into 27 categories according to diagnosis or clinical syndrome
PIM Check [51]	Delphi consensus; 40 experts	Adults in internal medicine (excluding pregnant women and inpatients with poor life expectancy or requiring palliative care)	160 statements for pathologies and drugs commonly encountered, divided into 17 medical domains and 56 pathologies
EU(7)-PIM list [52]	Delphi consensus; 27 experts	Older people ≥65 years	282 drugs from 34 drug classes
PRISCUS list [53]	Delphi consensus; 25 experts	Older people ≥65 years	83 drugs from 18 drug classes

Table 2. RCTs Using STOPP/START Criteria

Reference	Setting	Outcomes	Intervention	Results
Santolaya-Perrín et al. [54]	≥65 years ED presentations RCT 4 sites, Spain n = 666	Number of all-cause EVHAs per patient-year	Medication review using STOPP/START	Adjusted rate ratio of EVHAs: 0.808 (95% CI 0.617 to 1.059) at 3 months 0.888 (95% CI 0.696 to 1.134) at 6 months 0.954 (95% CI 0.772 to 1.179) at 12 months
Campins et al. [55]	≥70 years ≥8 drugs Community-dwelling RCT 7 sites, Spain n = 503	(i) Number of medications prescribed at 3, 6 and 12 months; (ii) treatment restart ratio (iii) primary care and emergency department consultation rate for acute conditions; (iv) hospitalization rate; (v) mortality rate; (vi) baseline, 3-month and 6-month self-reported quality of life (measured using EuroQoL-5D (vii) baseline, 3-month and 6-month treatment adherence (measured using the Morisky-Green test)	Medication review using STOPP/START criteria and the Good Palliative–Geriatric Practice algorithm	26.5% of prescriptions were rated as potentially inappropriate. 21.5% were changed Mean number of prescriptions per patient was significantly lower in the intervention group at 3- and 6-month follow-up Discontinuations, dose adjustments and substitutions were significantly higher than in the control group at 3, 6 and 12 months No differences were observed in the number of emergency visits, hospitalizations and deaths
Campins et al. [56]	≥70 years ≥8 drugs Community-dwelling	Cost-effectiveness & reduction in pharmaceutical expenditure	Medication review using STOPP/START criteria and the Good Palliative–	Decrease in DE after 12 months was significantly higher in the intervention group than in the

	RCT 7 sites, Spain n = 490		Geriatric Practice algorithm	control group (−14.3% vs.−7.7%; p=0.041) Total annual DE decreased €233.75/patient (95% confidence interval [95%CI]: 169.83-297.67) in the intervention group and €169.40/patient (95%CI: 103.37-235.43) in the control group
Parker et al. [57]	≥65 years with CKD 5 RCT 3 sites, Norway n = 180	PIMs and PPOs HRQoL Medication adherence	Medication review using STOPP/START	high prevalence of inappropriate medications in older patients with advanced CKD and reduced the number of PPOs [57]. However, there was no detectable impact of the intervention on medication adherence or HRQoL
McCarthy et al. [58] *SPPiRE study*	≥65 years ≥15 medications Cluster RCT 51 GP practices in Ireland n = 404	Number of repeat medicines Proportion of patients with any PIP	Medication review using STOPP/START	Small but significantly greater reduction of medicines in the intervention group at 6 months (IRR 0.95, 95% confidence interval [CI]: 0.899 to 0.999, p = 0.045)
Farhat et al. [59]	≥65 years with ≥1 geriatric syndrome RCT	Number and prevalence of PIPs Number of interventions and	Medication review using STOPP/START versus PIM-Check	Significant decrease in PIPs in each arm Deprescription of nervous system drugs was

	1 site, Switzerland n = 123	their acceptance rate Number of prescribed medications (at admission and discharge)		significantly higher with STOPP/START (Chi-square p = 0.025) ADL scores between home and discharge were significantly higher in the STOPP/START arm (4.42 vs 3.77; p = 0.040)
Syversen et al. [60]	≥18 years ≥4 regular drugs from minimum of 2 drug classes RCT 1 site, Norway n = 386	Mean number of PPOs and PIMs at discharge	Medication review using STOPP/START	Reduction in mean number of PPOs at discharge, compared to the control group, 1.34 vs. 1.57, respectively (mean difference 0.23, 95% CI 0.07-0.38, P = 0.005) No difference in the mean number of PIMs at discharge (1.84 vs 1.88, respectively; mean difference 0.03, 95% CI -0.18 to 0.25, P = 0.762)
Jungo et al. [61] *OPTICA trial*	≥65 years ≥5 long term medications ≥3 chronic conditions Cluster RCT 43 GP practices in Switzerland n = 323	MAI and AOU	Medication review using STRIPA (eCDSS based on STOPP/START)	37% of patients had MAI improvement between baseline and 12 months 12% (38) had an improvement in the number of prescribing omissions
Strauven et al. [62]	≥65 years	Medication appropriateness	STOPP/START and Beers criteria	Intervention had a significant

	NH residents Cluster RCT 54 NHs in Belgium n = 1804			positive effect on resolving existing PIMs and PPOs (odds ratio 1.479 [95% confidence interval 1.062-2.059, P = .021])
Boersma et al. [63]	≥70 years ≥5 medications Pre-operative assessment Cluster RCT 1 site in the Netherlands n = 124	Number of medication changes made because of PIMS and PPOs	Medication review using STRIPA (eCDSS based on STOPP/START)	Significantly more medication changes due to PPOs and PIMs made in intervention group than in control group (PPOs 26.2% vs 3.4%, odds ratio 0.04 [95% confidence interval 0.003–0.46] P < .05; PIMS 46.2% vs 15.3% odds ratio 0.14 [95% confidence interval 0.07–0.57] P < .005)
Kua et al. [64]	≥65 years ≥5 medications NH residents Cluster RCT 4 NHs in Singapore n = 295	Reduction in both fall rates (number of fallers) and fall risks	STOPP/START and Beers criteria	At 6 months, intervention did not reduce falls. Subgroup analysis showed reduced fall risk scores within the deprescribing-naïve group by 0.18 (P = .04). Intervention was associated with reduction in mortality [hazard ratio (HR) 0.16, 95% confidence interval 0.07, 0.41; P < .001] and number of hospitalized residents (HR

				0.16, 95% CI 0.10, 0.26; P < .001)

ED: emergency department, RCT: randomized controlled trial, DE: drug expenditure, EVHA: emergency visits and hospital admissions, PIM: potentially inappropriate medication, PPO: potential prescribing omission, CKD: chronic kidney disease, HRQoL: health-related quality of life, PIP: potentially inappropriate prescription, IRR: incidence rate ratio, ADL: activities of daily living, GP: general practitioner, MAI: Medication Appropriateness Index, AOU: Assessment of Underutilisation, eCDSS: electronic clinical decision support system, NH: nursing home, LTC: long term care, STRIPA: Systematic Tool to Reduce Inappropriate Prescribing Assistant