Diplomarbeit

Inappropriate drug prescribing in patients with end-stage renal disease: Feasibility of the „STOPP/START“- screening tool version 2.0 in a cohort of ambulatory haemodialysis patients

eingereicht von

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Graz, 23.06.2016

Eidesstattliche Erklärung

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Graz, am 23.06.2016 *Andre Fixa eh.*

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In gratia,

Andre Fixa

Zusammenfassung

Einleitung: Die STOPP/START-Kriterien sind eine weitgehend anerkannte PIM-Liste zur Bestimmung inadäquater Medikamente bei älteren Menschen. Bis jetzt wurden die Kriterien hinsichtlich ihrer Validität noch nicht bei Dialyse-Patientinnen/-Patienten überprüft.

Ziel: Ziel der Studie war die Bestimmung von PIPs und PPOs bei Hämodialyse-Patientinnen/-Patienten mittels STOPP/START Version 2.0 und deren Anwendbarkeit bei diesem speziellen Patientenkollektiv, sowie ein Vergleich dieser PIM-Liste mit der Medikamentenbewertung einer Fachärztin für Nephrologie.

Methoden: Medikamentenlisten von 62 Dialyse-Patientinnen/Patienten (Alter ≥ 40 Jahre) wurden retrospektiv mittels STOPP/START-Kriterien analysiert. Eine Fachleitlinien- und Eminenz-basierte Bewertung derselben Medikationen wurde von einer Nephrologin durchgeführt. Die Ergebnisse beider Medikamentenbewertungen wurden verglichen und in einem strukturierten Interview erörtert.

Ergebnisse: Mittels Einsatz der STOPP-Kriterien wurden 114 PIPs bestimmt. 62 der 114 PIPs wurden laut PIM-Liste in der Analyse auch von der Nephrologin als inadäquat bewertet. 30 der übrigen 52 PIPs, die von der Fachärztin als nicht problematisch gewertet wurden, akzeptierte jene als Empfehlung zur Medikationsänderung im Interview. Die Fachärztin bewertete 25 zusätzliche Medikamente als inadäquat, welche von den STOPP-Kriterien nicht ermittelt wurden: Statine (n=15), transdermal applizierte Medikamente (n=4), andere (n=6).
Mittels START-Kriterien wurden 82 PPOs bestimmt. Die daraus resultieren Empfehlungen (Ansetzen eines Medikaments) wurden in nur 13.4% (11 Empfehlungen) im Interview angenommen. Orale Antikoagulantien (START A1, n=13) und Statine (START A5, n=20) waren die zwei größten START-Medikamentenempfehlungen, die von der Fachärztin abgelehnt wurden.

Conclusio: Die Bestimmung inadäquater Medikationen durch eine Fachärztin bei Dialyse-Patientinnen/-Patienten ist vergleichbar mit den Ergebnissen nach Screening von Medikationslisten von dialysepflichtigen Patientinnen und Patienten mittels STOPP-Kriterien. Die Annahme von START-Empfehlungen aus fachspezifisch-nephrologischer

Sicht ist sehr gering. Eigene START-Empfehlungen, die an das Patientenkollektiv „Dialyse“ angepasst werden müssen, sollten entwickelt werden.

Schlüsselwörter: Potentiell inadäquate Medikamente, Hämodialyse, STOPP/START

Abstract

Background: STOPP/START criteria are a commonly accepted screening tool to detect inappropriate prescribing in older adults. So far, the test battery has not been tested for its validity in patients undergoing chronic haemodialysis (HD).

Objective: The aim of this study was to determine PIPs/PPOs according to STOPP/START criteria, to assess applicability of corresponding recommendations in ambulatory HD patients and to compare findings with the guideline-based and eminence-based medication review performed by a nephrologist using nephrological treatment guidelines.

Methods: Retrospective cross-sectional analysis of medication regimen was performed in 62 patients aged ≥ 40 years with end-stage renal disease and undergoing regular haemodialysis (HD) using STOPP/START Version 2 criteria. A guideline-based and eminence-based medication review was separately performed by a nephrologist. Where possible, results of medication reviews of both approaches were compared and diverse results were discussed using a structured interview technique.

Results: Using the STOPP criteria 114 PIPs were identified in total. 62/114 PIPs were also detected by the nephrologist's disease-centred expert review. 30/52 STOPP recommendations, which were not detected during this expert review, were accepted by the nephrologist during the structured interview retrospectively reflecting a more patient-centred clinical approach. The specialist assessed a further 25 drugs as inadequate and ordered their use to be stopped in the study cohort: those included the use of statins (n=15), drugs with transdermal application (n=4), others (n=6).

START criteria determined 82 PPOs. The specialist's overall acceptance of introducing START recommendations was low (11 recommendations, 13.4%). The two main treatments rejected by the nephrologist were oral anticoagulant therapy (START A1, n=13) and statin therapy (START A5, n=20).

Conclusion: A specialist's assessment of a drug regimen in HD patients is comparable in process management to medication management used in STOPP approach. However, looking at medication record content and recommendations, acceptance by specialists, especially of START recommendations elaborated with the new STOPP/START criteria for HD patients, is extremely low. Therefore it may be concluded that START recommendations for HD patients need to be adapted to the needs of this patient population.

Key words: potentially inappropriate prescribing, haemodialysis (HD), STOPP/START

Table of contents

List of abbreviations

ACEI *Angiotensin Converting Enzyme Inhibitor*

ADE *Adverse Drug Event*

ADR *Adverse Drug Reaction*

AGS *American Geriatrics Society*

ARB *Angiotensin Receptor Blocker*

CKD *Chronic Kidney Disease*

DDI *Drug Drug Interaction*

DDSI *Drug Disease Interaction*

DWI *Drug Without Indication*

e.g *exempli gratia*

eGFR *estimated Glomerular Filtration Rate*

ESRD *End Stage Renal Disease*

FORTA *Fit fOR The Aged*

HD *Hemodialysis*

i.e. *id est*

IDH *Intradialytic Hypotension*

IWD *Indication Without Drug*

ME *Medication Error*

mmHg *Millimeter of Mercury*

MRP *Medication Related Problem*

NOAC *Novel Oral Anticoagulant*

PIM *Potentially Inappropriate Medication*

PIP *Potentially Inappropriate Prescription*

PPI *Proton Pump Inhibitor*

PPO *Potential Prescribing Omission*

RCT *Randomized Controlled Trial*

SD *Standard Deviation*

SSRI *Selective Serotonin Reuptake Inhibitor*

List of tables and figures

Figures:

Tables:

1 Introduction

1.1 Challenges of drug prescribing in the older population

1.1.1 Multimorbidity and polypharmacy

"Multimorbidity" is defined as the co-occurrence of at least two chronic conditions in the same person (1). Systematic reviews revealed that there is a large heterogeneity in definition, assessment and quantification of multimorbidity. A recent publication by the European General Practice Research Network listed 132 published definitions of multimorbidity, using 1631 complex descriptive criteria.(2) Similar results were obtained in a systematic review by Huntley et al. discussing data from 194 published articles (3).

By analysing 39 articles in another systematic review, Diederichs and colleagues could show that in more than half of analysed studies (59%), selection of diseases/conditions for the assessment of multimorbidity was performed without predefining criteria for selection, leading to diversity of type and quantity of selected diseases. Not surprisingly, mean number of diseases in all 39 multimorbidity indices was 18.5, ranging from 4 to 102 conditions.(4)

Multimorbidity is strongly linked to the aging process of the population. In 2008, 62% of about 31 million Medicare fee-for-service beneficiaries aged 65–74 years were multimorbide (defined as suffering from ≥ 2 chronic conditions selected out of 15 prevalent entities). Percentage of multimorbidity in people aged between 75-84 years was 75.7% and 81.5% for those aged ≥ 85 years, respectively.(5) With increasing age, the number of chronic disorders and the proportion of multimorbidity increases (5-8).

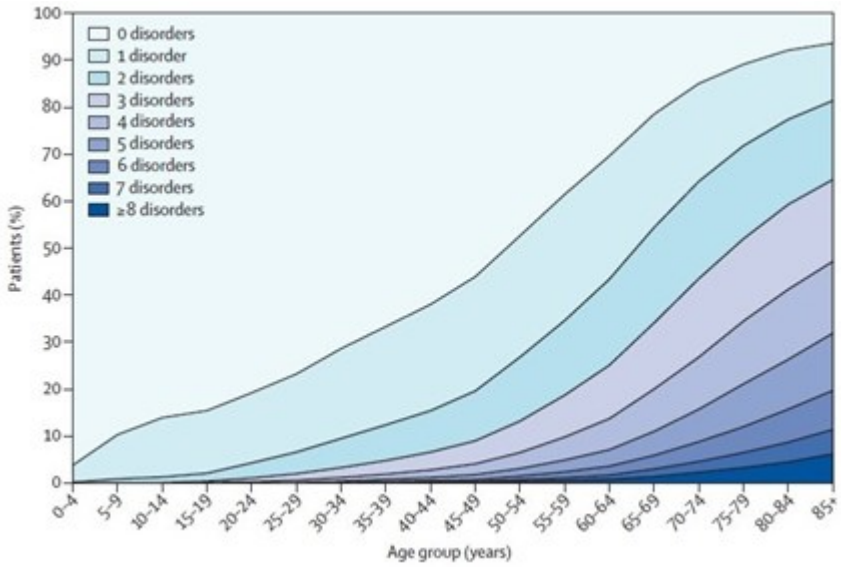

Figure 1: Number of chronic disorders by age-group (6).

Mutimorbidity is still a challenge for research and evidence-based daily clinical practice. The lack of a consistent definition is one of the major challenges in evidence-generation in research addressing topics related to multimorbidity.(9) Furthermore, older people are often underrepresented in clinical trials and there are not sufficient study results for this group of patients to be generalised into clinical routine (10-13). This is an issue that needs to be addressed in the daily work of health professionals as medical treatment is often driven by single-disease-specific guidelines, regarding medical conditions separately, not addressing a holistic therapeutic regimen for an old person's complex multimorbide condition (14). As a consequence of a disease-driven approach, guidelines don't provide explicit enough guidance recommendations for patients' comorbid conditions. Furthermore, different guidelines might also be contradictory when being applied simultaneously to multimorbide individuals.(15-17) Physicians' adherence to clinical practice guidelines therefore leads to use of multiple medications. This seems one of the major explanations why patients with multimorbidity represent "the target population" for extensive drug treatment. This phenomenon has also been reflected and critically discussed in literature. Boyd and colleagues nicely outlined the case of a 79-year-old woman suffering from five chronic conditions and examined treatment recommendations according to United States clinical practice guidelines. They were able to demonstrate in their work that a practice guideline approach would result in a drug regimen using 12 different substances with a need of 19 drug doses per day.(15) Similar results were obtained in recently published United Kingdom clinical guidelines (18). In conclusion, published data as well as clinical practice demonstrate that the number of diseases and

doctors' attitude and management skills contribute to high numbers of drugs being prescribed to patients suffering from multimorbide conditions.

Over the past two decades the management of these multiple drug regimens in multimorbide patients has become an own entity and was entitled "polypharmacy". In this context the term "polypharmacy" has simply been referred to "use of multiple drugs".(19) Research data on prevalence of polypharmacy showed that the use of multiple drugs is highly prevalent in the older population (20, 21). Fialova et al. conducted a retrospective cross-sectional study of 2707 European home care patients (mean [SD] age: 82.2 [7.2] years) in eight countries. Analysing the 7-day prevalence of drug use of residents, 51% of them were administered ≥ 6 medications and 22.2% ≥ 9 different drugs per day.(20)

Another study of nursing home residents analysed drug regimens of 4023 nursing home residents in 57 nursing homes in eight different countries and observed that polypharmacy, defined as the use of 5-9 drugs, was observed in 49.7% and excessive polypharmacy (≥ 10 drugs) occurred in 24.3% of the residents (21).

1.1.2 Pharmacological considerations

1.1.2.1 Age-related alterations in drug metabolism

Advanced age is accompanied by pharmacokinetic and pharmacodynamic changes in humans, leading to changes in metabolism of drugs in older adults. Causes for differences in pharmacokinetics are changes of individual and overall body composition (reduction of total body water and protein resulting in a relative augmentation of body fat). The relative increase of body fat leads to an extended volume of distribution of lipid soluble drugs resulting in a prolonged half-life, and a decreased volume of distribution of water soluble agents resulting in higher serum concentrations, respectively. In addition, changes in hepatic function and diminished renal capacity lead to impaired clearance of certain pharmacological substances, consecutively prolonging half-life of affected drugs. In terms of pharmacodynamics, older individuals show higher sensitivity towards specific drugs, as for example benzodiazepines.(22)

1.1.2.2 Adverse drug events

An adverse drug event (ADE) is an injury that occurs due to the use of a drug. A medication error (ME) is part of drug process management and indicates errors at any stage of medication use (from prescription to metabolism).(23)

“Potential ADEs” are defined as medication errors having the potential to cause harm, but do not necessarily lead to negative clinical outcomes. To give an example: Prescription of drug regimen, not adapted to clearance function does not intrinsically lead to toxic effects when interrelations are intercepted before delivering the drug. ADEs can be divided into preventable and non-preventable ADEs. First occur due to medication errors at any stage in the medication process, the latter due to pharmacological properties of specific drugs given at normal doses and are therefore also named adverse drug reactions (ADRs).(23) Figure 2 illustrates the relationship between the terms explained above.

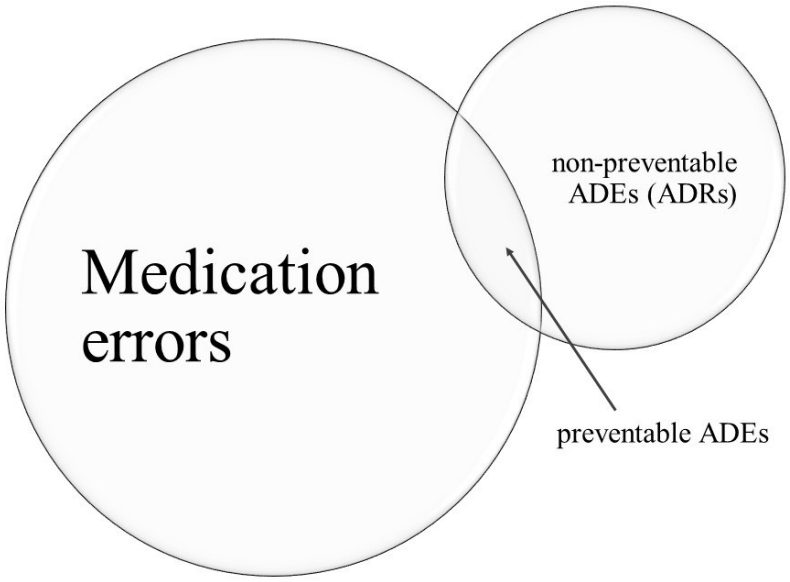

Figure 2: Relationship between medication errors and classes of ADEs (schematic illustration, size of circles do not represent any proportions). Modified from (23).

The figure outlines the background for ADEs perfectly. MEs (in prescribing, administration, monitoring) contribute to preventable ADEs. In conclusion, an unintended injury from the use of a medication taken at normal doses, is therefore called ADR (non-preventable ADEs).(23)

Pharmacological mechanisms of ADEs/ADRs are varied. These are as follows:

- Altered pharmacodynamics and pharmacokinetics lead to an altered metabolic response. Of special importance in pharmacokinetics are the decline in kidney function and an altered hepatic clearance, which is a consequence of cytochrome P450 enzyme metabolism (24).

- Drug-drug interactions (DDIs) are clinically significant changes of specific drug effects caused by pharmacokinetic or pharmacodynamic interactions when another drug is co-administered (25). For example, the combination of beta blockers and antidiabetics (risk of unrecognized hypoglycaemic episodes) or the co-administration of angiotensin-converting-enzyme inhibitors (ACEIs)/angiotensin-receptor–blockers (ARBs) and potassium-sparing diuretics (risk of hyperkalaemia) may present clinically important DDIs in poly-treated older adults (26). The risk for DDIs increases with the number of dispensed drugs and age (27, 28). Studies have reported an association between DDIs and an increased risk of ADEs (29, 30). Marengoni et al. showed that DDIs make a significant contribution to the onset of ADRs (31).
- Drug-disease interactions (DDSIs) occur when treatment of an index condition leads to an exacerbation of a co-existing disease (32). As DDIs, DDSIs are also associated with an increased risk of ADEs (30, 33).

Drug prescribing patterns as recommended by clinical practice guidelines in common diseases, lead to several DDIs and some DDSIs in the presence of multimorbidity, especially when patients suffer from chronic kidney disease (CKD) as comorbid condition (34).

1.1.3 Inappropriate prescribing in older adults

Inappropriate prescribing describes the use of medications that expose individuals to a significant risk of adverse drug-related events and where alternatives harbouring lower individual risks have been proven to be equally effective, are available. It further encompasses the more frequent and longer administration of drugs than clinically indicated, the use of multiple medications that have recognized DDIs and DDSIs and the underuse of medicines, which are clinically indicated, but not prescribed for any reason.(35)

Originally, Beers et al. described the term “potentially inappropriate medication” (PIM) as drugs being administered even though their effectiveness has not been established and/or the risk of ADEs exceeds the expected clinical benefit, especially if there is evidence of pharmacological alternatives containing lower risks of side effects (36).

Inappropriateness of drug prescription can be evaluated by considering three major domains: misprescribing (incorrect prescription), overprescribing (drugs prescribed without clear indication), underprescribing (indication for a drug is given, but it is not

administered for any reason). Accordingly, underprescribing indicates potential prescribing omissions (PPOs), whereas misprescribing and overprescribing indicate potentially inappropriate prescriptions (PIPs).(37)

All three forms of inappropriate prescribing may result in ADEs described in 1.1.2.2. In order to further address PIMs in research as well as daily clinical practice, specific screening and assessment tools have been developed across the globe with the aim to detect inappropriate prescribing patterns by using explicit (criterion-based) and implicit (judgement-based) measures. Most of the currently existing tools for assessment of medication appropriateness are explicit and focus on older people as target population.(38) Most explicit criteria specifically designed for older adults are validated by consensus of expert panels using the Delphi technique (39).

The following paragraph will only list today's most commonly used assessment tools in the field of geriatric medicine and does not represent all tools currently available.

1.1.3.1 Beers criteria

Beers criteria, first published in 1991, are the first explicit criteria dealing with the subject of inappropriate prescribing. They contain a list of 30 medications that should not be prescribed in older patients (36). Since new drugs continue to be marketed and up-coming studies continue to provide new information on safety of pre-existing drugs, criteria have been updated in 1997, 2002, 2012 and the last time in 2015 (40-43).

The 2002 version contains 48 individual drugs, which should generally be avoided in older people and 20 drugs/drug classes to be avoided in older adults suffering from specific medical conditions (41).

The 2012 American Geriatrics Society (AGS) updated Beers criteria comprise 53 drugs/medication classes, which are divided into the following three categories: drugs to be generally avoided in older adults (e.g. alpha-1 blockers as antihypertensive therapy), drugs to be avoided regarding specific diseases and syndromes (due to DDIs or drug-syndrome interactions that can exacerbate the clinical condition), and drugs to be used with caution in older adults (42).

The 2015 AGS updated version added two new areas to the classification system (DDIs and dose adjustment/drug avoidance due to impaired renal function) (43).

1.1.3.2 STOPP/START criteria

STOPP/START criteria, first published in 2008, are an explicit assessment tool with a good interrater-reliability (44, 45). Organized in physiological systems, criteria respect the

dual nature of inappropriate prescribing by including a list of PIMs/PIPs and PPOs. The 2008 criteria encompassed 65 STOPP- and 22 START criteria (45).

STOPP: Screening **T**ool of **O**lder **P**erson's **P**rescriptions → **PIM/PIP**

START: Screening **T**ool to **A**lert doctors to **R**ight **T**reatment → **PPO**

In conclusion, STOPP criteria should therefore target the domains of misprescribing and overprescribing, whereas START criteria should target underprescribing.

As a validated tool, these criteria have been used in different study settings (46). In order to reflect more complete and up-to-date sets of PIPs and PPOs, a new version of STOPP/START criteria comprising a final list of 114 criteria (80 STOPP, 34 START criteria) has recently been published (47). Criteria are assigned to different sections (labelled with letters) - structure of STOPP/START screening tool version 2.0 is briefly summarised in Table 1.

Section	STOPP description	START description
Section A	Indication of medication (3 implicit criteria)	Cardiovascular system (8 criteria)
Section B	Cardiovascular system (13 criteria)	Respiratory system (3 criteria)
Section C	Antiplatelet/anticoagulant drugs (11 criteria)	Central nervous system and eyes (6 criteria)
Section D	Central nervous system and psychotropic drugs (14 criteria)	Gastrointestinal system (2 criteria)
Section E	Renal system (6 criteria)	Musculoskeletal system (7 criteria)
Section F	Gastrointestinal system (4 criteria)	Endocrine system (1 criterion)
Section G	Respiratory system (5 criteria)	Urogenital system (3 criteria)
Section H	Musculoskeletal system (9 criteria)	Analgesics (2 criteria)
Section I	Urogenital system (2 criteria)	Vaccines (2 criteria)
Section J	Endocrine system (6 criteria)	-
Section K	Drugs that predictably increase risk of falls in older people (4 criteria)	-
Section L	Analgesic drugs (3 criteria)	-
Section N	Antimuscarinic/anticholinergic drug burden	-

Table 1: Structural organization of STOPP/START criteria version 2. Modified from (47).

1.1.3.3 German and Austrian PIM tools

There are three existing tools, which are especially representative of the German/Austrian drug market situation (48-50).

The Priscus list, published in 2010, is a German explicit tool which comprises 83 PIMs in a total of 18 drug classes. Each listed PIM is annotated with main concerns, alternative therapy options and precautions to be taken when using that drug.(48)

The FORTA list (**F**it f**OR** **T**he **A**ged) is an explicit collection of 190 medications most frequently prescribed in older patients, classified into 20 main indication groups. Each substance or group is assigned a FORTA class (A, B, C or D). These labels range from A (indispensable), B (beneficial), C (questionable) to D (avoid), depending on the state of evidence for safety, efficacy and overall age-appropriateness.(49)

An Austrian consensus panel drew up an explicit PIM list specifically adapted to the Austrian drug market. It contains 73 drugs to be avoided in older patients because of an unfavorable benefit/risk profile and/or unproven effectiveness. It also contains suggestions for therapeutic alternatives and information about unfavorable pharmacological properties of listed PIMs.(50)

1.2 How to choose the appropriate tool for determination of PIMs – Comparison of explicit criteria

Given the scope of available medications and prescribing patterns across the world, it is plausible that there might be differences in detecting PIMs when using various PIM lists for various patient groups. Over the last two decades inappropriate prescribing has come more and more into the focus of research, hence several PIM lists have been developed and validated. Nevertheless, all criteria developed show disparities in their structure, content and comprehensiveness, resulting in strengths and weaknesses of each and every tool.(38, 39, 51)

Research projects proved sparse overlap between detection profiles for PIMs. PIM prevalence and PIM profile varied substantially when applied to the same cohort of patients.(52-54) In the study conducted by Morin et al., only 5.2% of individuals were exposed to potentially inappropriate drug use as detected by all applied criteria. Furthermore, only 14% of PIMs were simultaneously detected by all sets of criteria in subjects who were exposed to potentially inappropriate drug use according to any of the criteria.(54)

Thurner et al. (unpublished data of PhD thesis) compared PIM profile of FORTA, STOPP criteria and the Priscus list by exploring three separate studies. Figure 3 shows the five most common PIMs (expressed as frequencies) according to the corresponding PIM as analysed by Thurner et al. The strongest overlap was found for pain killers and antipsychotics for FORTA and STOPP. Apart from that, few similarities were found.

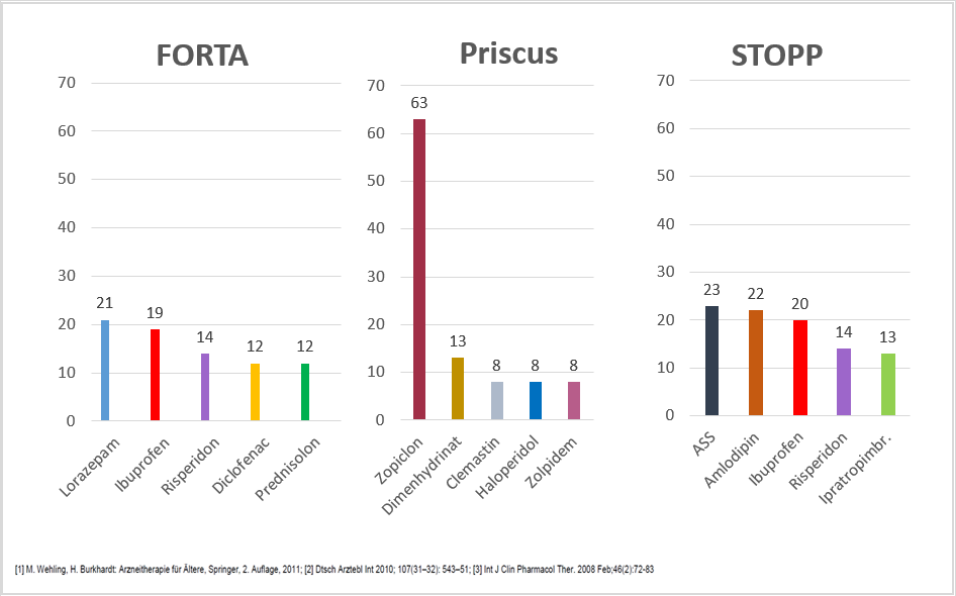

Figure 3: PIM profile according to Thurner et al. (with kind approval of Bettina Thurner)

Prevalence and PIM profile do not only occur when using different criteria in the same population, but may also be noticed due to different populations in different health care settings tested. In their multi-national survey examining home care residents among eight European countries, Fialova et al. found PIM prevalence rates ranging from 41.1% in Eastern Europe to 5.8-26.5% in Western Europe. Authors concluded that these disparities reflect differences in drug policies, care provisions, overall health conditions and socioeconomic backgrounds.(20)

Summarising the findings described above, differences on "determination level" of PIMs due to structure/comprehensiveness of criteria, country-specific drug policies and regionally available drugs, limit their practicability.

1.3 Occurrence of inappropriate prescribing

1.3.1 The patient-centred approach – a challenge of applying explicit criteria

Studies have shown that the feasibility of recommendations obtained from STOPP/START criteria is limited in specific patient populations, like the very old and frail (55, 56). A

patient-centred approach of physicians may justify non-compliance and disagreement with recommendations from explicit criteria as the STOPP/START screening tool (56). Using data of 256 outpatients aged ≥ 65 years and having more than five medications, Steinman et al. also revealed that patient-orientated expert medication review by a physician-pharmacist study team varies substantially from medication review by using explicit PIM tools (Beers criteria, Zhan criteria), finding a sparse overlap between these approaches (57).

The AGS developed guiding principles in order to address patient-centred care in older individuals suffering from multimorbidity, comprising five major domains (58):

- Patient preferences (should be incorporated in medical decision-making)
- Interpreting the evidence (evidence generation of treatment in the context of age and multimorbidity)
- Prognosis (recognize benefit, burden, risks, life expectancy)
- Clinical feasibility (consider patient adherence, complexity of therapeutic regimen)
- Optimizing therapies and care plans (strategies for choosing therapies that optimize benefit, reduce harm, and increase quality of life for older multimorbide individuals) (58)

In conclusion, the individual approach to patient care considering these five domains might be a major factor, for which recommendation of explicit criteria is not followed by specialists in daily clinical routine. Lozano-Montoya and colleagues reported and clustered reasons for rejection of STOPP/START suggestions in patients being admitted to a geriatric unit (56). Table 2 outlines information provided by the study team in their supplementary data.

Reason for rejection	Description	Example
High risk of adverse effects	Adverse effects outweigh beneficial effects of drug treatment	ACEIs in patients with severe impaired renal function
Contraindication/allergy	Patient has a record of allergy or specific medical condition	Renal impairment and metformin
Conflicting drugs/inappropriate combination of drugs	Adding a new agent which harbours the risk of serious drug-drug interactions or adverse effects when combined with other drugs in use	Adding oral anticoagulants to antiplatelet therapy- higher risk of bleeding complications
Other treatment is already used/preferred for condition/disease	Patient is already treated with another drug for the clinical condition	Diabetic patients are treated with insulin, so no metformin is added
Therapeutic prioritisation	START: drug is assigned low priority in a patient's complex, multimorbide	START: preventing fractures is of low priority in a long list of

	condition STOPP: drugs that are inappropriate for use are prescribed for a period of time assessing harms and benefits of therapy	conditions and excessive polypharmacy STOPP: benzodiazepines for treatment of sleep disturbance
Patient's refusal/poor adherence	Patient does not accept therapy, has a history of poor adherence	Patient does not accept oral anticoagulant therapy
Severe mental or physical disability	Disability changes therapy goals	Statin therapy in a patient with severe dementia
Palliative care	End-of-life status	Symptom relief in terminally ill patients

Table 2: Possible reasons for non-compliance to STOPP/START. Modified from (56).

Regarding rationales from Table 2, one can incorporate these explanations into the 5 domains proposed by the AGS. To give some examples: the category "patient's refusal" may refer to the AGS domain "patient preferences", "poor adherence" or "severe mental or physical disability" refers to the AGS domain "clinical feasibility".(56, 58)

In conclusion, there might be patient-related limitations in applicability of recommendations obtained from explicit criteria when applying them to specific patient populations. Thus, when being compared to explicit criteria, an expert making prescribing decisions based on a patient-centred level may use a different approach in identifying prescribing problems. Extrapolating these findings to other patient populations, as for example end-stage renal disease (ESRD) patients receiving maintenance dialysis, one might also expect reasons for a limited applicability of PIM tool recommendations and a different approach towards assessment of medication appropriateness from a specialist (nephrologist), based upon guideline-driven and eminence-driven considerations. These reasons might be relevant for dialysis patients on a general level, reflecting treatment needs of this patient population in its entirety, and on an individual patient-centred level, meeting the needs of the individual patient.

1.3.2 System-related influences on inappropriate prescribing

The previous chapter described the subject of discordances between explicit PIM tools and prescribers' approaches towards assessment of medication appropriateness. Patient-centred care has been discussed to be an answer to the disagreement between a prescriber's judgement and PIM tool recommendations.

However, occurrence of inappropriate prescribing is multifaceted and also encompasses other factors. Studies have addressed this issue from prescribers' perspectives. (59-61) Anderson et al. conducted a systematic review of prescribers' barriers to reduce potentially

inappropriate medications (especially referring to the domains of overprescribing and misprescribing) (59).

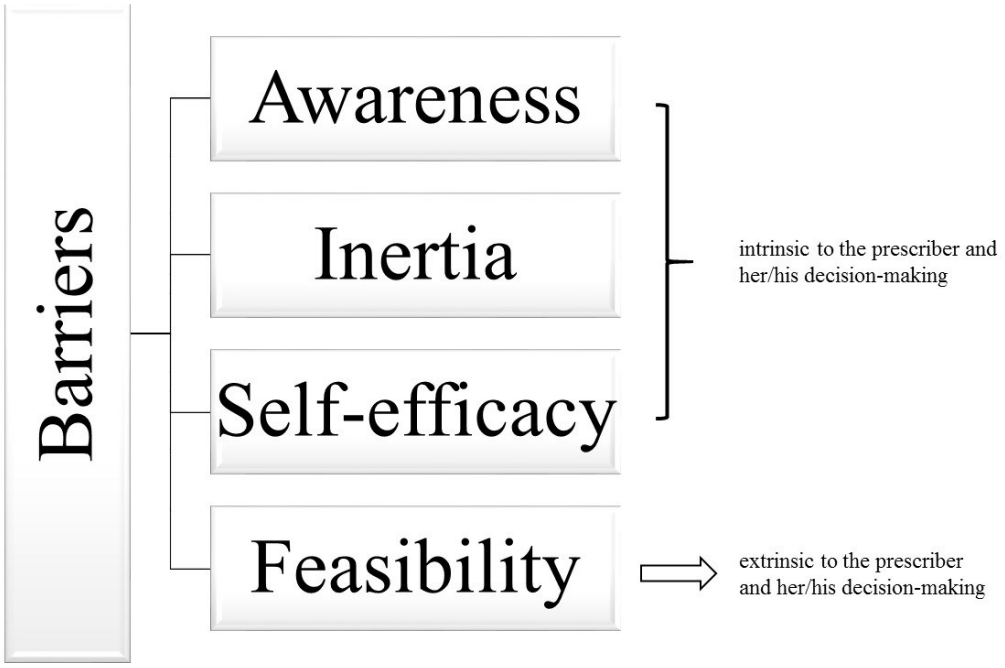

Figure 4: Prescribing barriers of minimising potentially inappropriate prescriptions (4 core themes). Modified from (59).

As Figure 4 illustrates, there are four major domains that could promote the continuation/prescribing of inappropriate prescriptions. These core factors shall be further explained according to Anderson et al. (59):

- Awareness: describes the prescriber's poor insight into appropriateness of prescribing, discrepant beliefs and practice
- Inertia: a failure to act, despite being aware of that prescribing is potentially inappropriate
    - Prescriber's beliefs/attitudes: fear of consequences when medication is withdrawn, medication works/has few side-effects, stopping is difficult/will fail
    - Prescriber's behaviour: devolve responsibility to other prescribers
- Self-efficacy: factors that influence a prescriber's belief and confidence in his or her ability to address PIM use
    - Skills/knowledge gaps: difficulties in balancing benefits and harms of therapies, recognizing ADEs, establish clear diagnoses and indications for agents
    - Information/Influencers: incomplete clinical pictures, poor communication at care interfaces, guidelines/specialists, facility routines in prescribing

- Feasibility: factors that determine ease of change, extrinsic to prescribing physician
    - Patient characteristics: refusal to change, poor acceptance of alternatives
    - Resources: time and effort, insufficient reimbursement, limited availability of effective alternatives
    - Work practice: no medication review done
    - Medical culture: respect other prescriber's autonomy and hierarchy
    - Health beliefs and culture: prescribing validates illness
    - Regulatory: quality measure driven care (59)

Another qualitative study reported four key reasons for physicians' perpetuation of inappropriate prescriptions after performing a systematic database search, which are somehow concordant with the findings above: need to meet patients' needs, feeling of being forced to prescribe, prescribers' fear, strain between own experience and guideline recommendations (60).

Underuse of indicated medications might be due to deliberate patient-centred considerations as proposed by the AGS and explained by Lozano-Montoya and colleagues (56, 58). Other not so well-considered reasons for the occurrence of underprescribing might be a prescriber's general intention to avoid polypharmacy, ageism, fear of inducing ADEs and economic issues (62).

1.4 Chronic kidney disease – medication burden and inappropriate prescribing

CKD is common in the elderly population (63). Furthermore, prevalence and number of comorbid conditions increase with decreasing estimated glomerular filtration rate (eGFR) (63, 64), as shown in Figure 5.

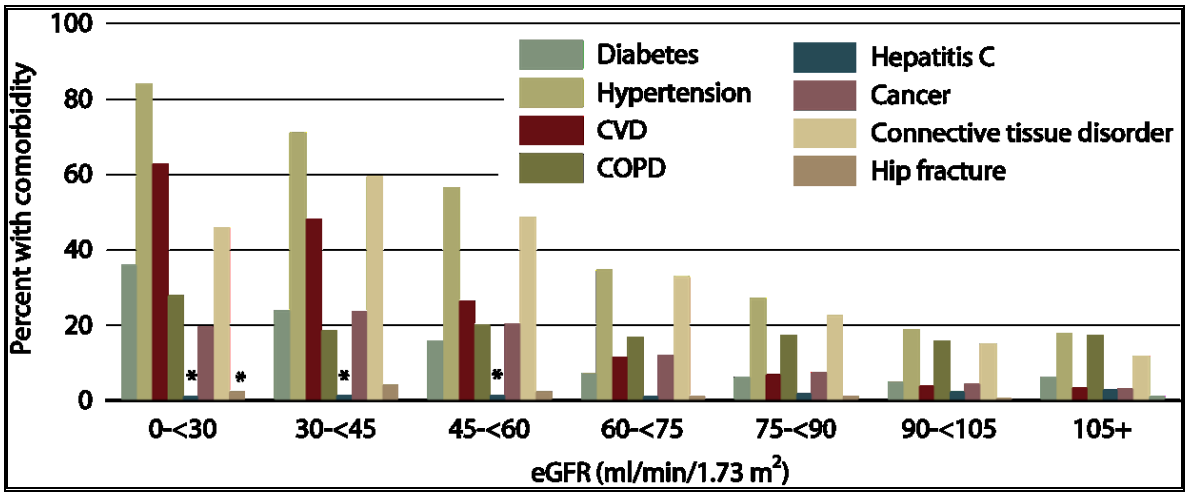

Figure 5: eGFR (creatinine formula) and the prevalence of comorbidities in the NHANES 1999–2006 population (64).

As a result of having multiple medical conditions and CKD-related complications, ESRD patients are prescribed numerous drugs. In a large cohort of ambulatory haemodialysis (HD) patients (n=10474), point-prevalence of medication prescribing patterns was assessed showing that subjects were prescribed a mean of 12.3 ± 5.0 medications.(65) Chiu et al. conducted a cross-sectional study in 233 patients on maintenance dialysis. It was shown that patients took an average number of pills of 19 per day.(66) Having such a complex medical regimen, these patients are especially prone to medication-related problems (MRPs) and non-adherence to drug therapy (67, 68).

Though studies have addressed the issue of inappropriate prescribing in patients with impaired renal function regarding dose adjustments and appropriateness of medication use in respect of renal function (69-74), as far as known only two studies have been conducted using explicit PIM criteria, whereas one study solely examined HD patients (75, 76). In a recent review on the subject of potentially inappropriate prescribing in elderly CKD patients, Gallieni et al. suggested the application of STOPP/START criteria to HD patients, since they would not only address the issue of PIPs, but would also consider PPOs.(77)

To the best of our knowledge, STOPP/START criteria have not been applied to this cohort yet.

In summary, on the one hand there might be limitations on the "determination" level of diverse tools (which PIM list is the most suitable/sensitive for a specific cluster of patients? – e.g. HD patients), on the other hand challenges limit applicability of PIM lists, e.g. STOPP/START criteria, when used in daily clinical practice. The answer to these issues could be the development of specific cohort-tailored PIM lists.

2 Aim of the study

The objectives of the current study are as follows: i) to determine PIPs and PPOs in a cohort of ambulatory HD patients at the at the dialysis ward of the Medical University of Graz according to STOPP/START criteria version 2.0 ii) to compare STOPP/START approach of medication review to medication review by a nephrologist iii) to identify possible reasons for rejection of STOPP/START prescribing recommendations when applied in a stringent manner and therefore checking the applicability/effectiveness of criteria as an interventional tool in this special clinical population iv) to develop a German language version of the STOPP/START screening tool.

Figure 6 illustrates the main study aims.

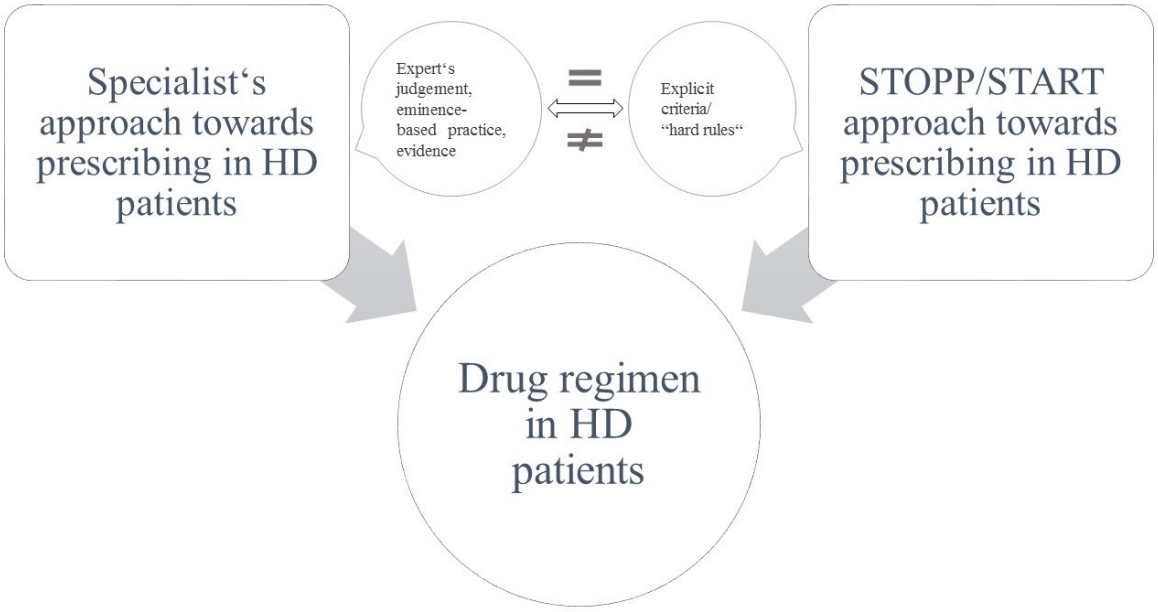

Figure 6: Study aims.

Ethical approval was granted by the local ethics committee from the Medical University of Graz (number of approval: 28-137 ex 15/16).

3 Methods

3.1 Subjects and study setting

In a retrospective cross-sectional analysis medication regimens of ambulatory HD patients who receive maintenance HD treatment at the dialysis ward of the Medical University of Graz, were screened with STOPP/START criteria version 2.0 and separately by a specialist (nephrology). Patients were included in the analysis, if they were aged ≥ 40 years, if they were in a chronic HD regimen (≥ 3 months of HD therapy) and received dialysis treatment on 13th April, 2015 (recruitment day). Drugs listed on the dialysis ward's medication lists of that date were retrospectively analysed by using the STOPP/START screening tool.

3.2 Data collection

Data from 62 eligible patients were collected for further analysis. Patients' demographic data included age, sex and number of medications prescribed. Discharge letters, medical reports and laboratory values were used as source data by the study team. Patients' medication lists and diagnoses were evaluated by hand screening electronic data records. Prescriptions were then assessed using the STOPP/START criteria 2.0. We broadened the STOPP criterion A1, originally saying "any drug prescribed without an evidence-based clinical indication" to "any drug prescribed without finding an evidence-based clinical indication/a justifying rationale in patients' medical history". We further broadened the STOPP criterion F2, adding "Proton pump inhibitors, where justifying indication is given in medical data, but re-evaluation of indication is necessary".

Only drugs used on a regular basis were included in the analysis. Medications applied during haemodialysis, preparations for topical application (except for opioids) and eye drops were excluded from analysis.

Simultaneously, a nephrologist performed a medication review. She was asked to assess medication appropriateness according to guideline-driven and eminence-driven considerations. Her findings and STOPP/START recommendations were compared and discussed in a structured feedback interview. Possible reasons for refusal of compliance with STOPP/START were further elucidated. Responses were chosen from a cluster of pre-defined reasons for non-acceptance of STOPP/START suggestions (see Tables 3 and 4). These were taken and developed from literature, combining analytic core themes from Anderson et al. and reasons for rejection of recommendations as described by Lozano-Montoya et al. (56, 59). The nephrologist could choose one or more reasons, if she could

not accept findings from STOPP/START. She was also was given the chance to provide qualitative open feedback in case predetermined rationales included in Tables 3 and 4 did not reflect the reasons for rejection of drug prescribing changes recommended by STOPP/START criteria. If findings from the specialist and the screening tool were concordant, meaning that the same drug was detected by both approaches, the specialist was asked to explain her considerations in an open feedback format (see results, 5th column in Table 8).

Analytic core themes	*Response options to STOPP*
Feasibility/patient-centred approach	Patient's refusal of change/poor acceptance of alternatives (feeling forced to prescribe to meet patient's expectations)
	Limited availability of effective alternative drugs/treatments
	STOPP recommendation deviates from current guidelines, facility routines and need to be followed (guidelines are necessary, make sense)
Self-efficacy (influencers)	STOPP recommendation deviates from current guidelines, facility routines, feeling forced to follow guideline recommendations, although being aware of inappropriate prescribing
	Respecting other professional prescriber's autonomy and medical hierarchy (involvement of specialists in treatment)
Inertia	Fear of unknown/negative consequences of change (physician: higher workload, conflict with other prescribers/health care providers, diminished credibility, patient: withdrawal syndrome, relapse of symptoms, re-occurrence of condition for which medication was prescribed)
	Devolve responsibility (continue prescriptions of other prescriber)
	Drug "works", has few side effects, is considered to be safe
	Discontinuation will fail, is futile
Prescriber's preference/patient-centred approach	Therapeutic prioritization: drug is considered to be inappropriate, but prescribed for a period of time assessing risks and benefits (e.g. benzodiazepines for insomnia)

Table 3: Response options for non-compliance to STOPP recommendations.

Analytic core themes	*Response options to START*
Feasibility/patient-centred approach	Drug is not effective in HD patients/has uncertain benefits/benefit-risk ratio (lack of evidence from medical literature, guidelines do not support evidence)
	Patient's refusal leading to poor adherence
	Severe mental disability/cognitive impairment leading to poor adherence
	Contraindication for drug
	Increased risk of a pre-calculated adverse drug event: e.g. adding an agent that harbours risk for an interaction (e.g. oral anticoagulant is added to antiplatelet agent- higher risk of bleeding)

	Therapeutic prioritization (drug is assigned low priority in patient's current clinical status)
Inertia	Avoidance of unknown (negative) consequences (ADEs, polypharmacy)
Prescriber's preference/patient centred approach	Other treatment is used for the clinical condition

Table 4: Response options for non-compliance to START recommendations.

3.3 Outcome measures

The main focus of our study was the effectiveness/applicability of STOPP/START criteria in a cohort of ambulatory HD patients. As a consequence, there was a cluster of outcome variables tested to underline our focus. Primary outcomes of the study were:

- number and type of PIPs and PPOs according to STOPP/START criteria
- number/proportion and type of accepted/non-accepted STOPP/START recommendations
- reasons for rejection of STOPP/START recommendations

Further outcomes were:

- number of inappropriate prescriptions according to the nephrologist
- number and type of overlapping inappropriate medications from both medication reviews

3.4 Statistical analysis

Data were documented and analysed in SPSS version 22 and Excel version 10. Patient characteristics and outcome variables were described using descriptive statistics. Continuous variables were expressed as mean and standard deviation or median and quartiles. Categorical variables were described as absolute or relative frequencies. Qualitative data was presented in text form.

3.5 German version of the STOPP/START screening tool

The adaptation of the STOPP/START screening tool into the German language was accomplished by using translation-back translation method similar to a way it had been done in a prior study (78). A study team member who was familiar with the original English version of STOPP/START, translated all criteria into German. After that, a graduate in English studies who was not familiar with the criteria re-translated the German version into English. The re-translated version was examined by native speakers/people with a good knowledge of English being specialists in the geriatric field (one also being an

author of the original English version), working through issues in translation process. The authorised German version was added to the appendix.

4 Results

4.1 Patient characteristics

The study cohort comprised 62 patients receiving chronic HD treatment at the dialysis ward of the Medical University of Graz. 26 patients (41.9%) were female, 36 (58.1%) were male. Mean age per patient was 63.4 years ± 11.6 (SD). Overall, 624 prescriptions were found, mean number of prescriptions per patient was 10 ± 3.4 (SD). 95.2% of the patients were prescribed at least five drugs.

variables	number	%	mean ± SD
age in years			64.4 ± 11.6
40-49	9	14.5	
50-59	14	22.6	
60-69	19	30.6	
70-79	16	25.8	
≥80	4	6.5	
sex			
female	26	41.9	
male	36	58.1	
number of drugs			10 ± 3.4
0-4	3	4.8	
≥5-9	29	46.8	
≥10	30	48.4	

Table 5: Patient demographic data

4.2 STOPP findings – potentially inappropriate prescriptions

Altogether, 114 PIPs were determined by STOPP criteria. The largest subgroup, encompassing 75 prescriptions, were drugs, for which no valid clinical indication could be found in patients' records (STOPP category A1). Implicated drug classes were as follows: proton pump inhibitors (PPIs) (n=26), antidepressants (n=13: mirtazapine [n=4], trazodone [n=4], selective serotonin reuptake inhibitors (SSRIs)[n=5]), folic acid (n=15), vitamin preparations (n=15), and miscellaneous drugs (nicorandil [n=1], tramadol [n=1],

desloratadine [n=1], fenoterole and ipratropiumbromid inhalers [n=2], salbutamol [n=1]). STOPP findings and rationales are summarized in Table 6.

STOPP recommendations	description	n (total n=114)
A1	Any drug prescribed without finding an evidence-based clinical indication/a justifying rationale in patients' medical history	75
B5	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	3
B10	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people)	6
D9	Neuroleptic antipsychotics in patients with behavioural and psychological symptoms of dementia unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke)	2
D10	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls)	5
D14	First-generation antihistamines (safer, less toxic antihistamines now widely available)	5
F2	Proton pump inhibitors for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated)/Proton pump inhibitors, where justifying indication was found in medical data, but re-evaluation of indication is necessary	9
H4	Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects)	1
K1	Benzodiazepines (sedative, may cause reduced sensorium, impair balance)	5
K4	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia)	2
L3	Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain)	1

Table 6: STOPP findings in HD patients. PIPs were assigned to only one STOPP category. For example, benzodiazepines could have been assigned to category K1, but also to category D5 (benzodiazepines for more than 4 weeks). Antipsychotics/antidepressants frequently lacked a documented clinical indication, but were assigned to other categories, possibly leading to an underestimation of PIPs in the A1 category (data not acquired).

4.3 START findings – potential prescribing omissions

START criteria determined 82 PPOs in the study cohort. The vast majority of recommended medications/PPOs pertained to drugs of the cardiovascular section (section A, n=68, 82.9%). Table 7 illustrates number and type of PPOs found in our study cohort.

START recommendation	description	n
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation	13
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease	13
A5	Statin therapy 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	20
A6	ACEIs/ARBs with systolic heart failure and/or documented coronary artery disease*	17
A7	Beta-blocker with ischaemic heart disease	3
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure	2
B1	Regular inhaled Beta-2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or chronic obstructive pulmonary disease	2
C5	SSRIs (or selective noradrenalin reuptake inhibitors or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.	1
E2	Bisphosphonates in patients taking long-term systemic corticosteroid therapy**	6
E3	Calcium*** supplement 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)	1
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout	1
H2	Laxatives in patients receiving opioids regularly	3

Table 7: START findings/PPOs (n=82). *Section A6: ARBs have been added. **Section E2: only bisphosphonates were recommended, since affected patients were administered vitamin D and calcium supplements. Section E3: only calcium supplementation (vitamin D was found on medication list).

4.4 Comparison of medication reviews

In the course of the medication review, the nephrologist identified 87 prescriptions as inappropriate. Since she assessed medication appropriateness in terms of misuse and overuse, some PIPs detected by STOPP criteria were also detected by the specialist, leading to overlaps in determination of inappropriate prescriptions. Table 8 lists proportions of detected medications within STOPP criteria findings and rationales from the nephrologist.

STOPP rationale for withdrawal	drug	number	overlap within STOPP	specialists's rationale
A1	desloratadine	1	no overlap	
	escitalopram	2	total overlap	questionable indication, adverse effects
	fenoterole and ipratropiumbromid inhaler	2	no overlap	
	folic acid	15	no overlap	
	mirtazapine	4	total overlap	questionable indication, adverse effects
	nicorandil	1	no overlap	
	salbutamol	1	no overlap	
	sertralin	3	total overlap	questionable indication, adverse effects
	tramadol	1	total overlap	no ideal choice in HD patients
	trazodone	4	total overlap	questionable indication, adverse effects
	vitamin preparations	15	no overlap	
	proton pump inhibitors	26	25/26	questionable indication
B10	moxonidine	5	no overlap	
	rilmenidine	1	no overlap	
B5	amiodarone	3	no overlap	
D9	quetiapine	1	total overlap	
D9	risperidone	1	total overlap	questionable indication, adverse effects
D10	prothipendyl	3	total overlap	questionable indication, adverse effects
D10	risperidone	2	1/2	questionable indication, adverse effects
D14	dimetindene	3	total overlap	questionable indication, adverse effects
	hydroxyzine	2	no overlap	
F2	proton pump inhibitors	9	8/9	questionable indication
H4	aprednislone	1	no overlap	

K1	clobazam	1	no overlap	
	lorazepam	2	1/2	adverse effects
	nitrazepam	1	total overlap	adverse effects
	triazolam	1	total overlap	adverse effects
K4	zolpidem	2	total overlap	adverse effects
L3	oxycodone	1	total overlap	polytoxicomanic patient

Table 8: Comparison of medication reviews: overlapping PIPs and specialist's rationales for withdrawal.

Of the 87 determined inappropriate prescriptions, 62 were concordant with PIPs as determined by STOPP criteria. The remaining 25 prescriptions identified as problematic by the specialist, but not by STOPP criteria and are described in Table 9.

Four agents (three of them being opioid analgesics, one dopamine agonist) were deemed inappropriate due to transdermal delivery. All statin prescriptions were identified as inappropriate.

drug	number	rationale
fentanyl	1	transdermal delivery
buprenorphin	2	transdermal delivery
dexibuprofen	1	risk of bleeding
duloxetine	1	drug interactions
paracodine	1	risk of breathing depression
prophyphenazon, dihydroergotamine (combination of drugs)	1	vasoconstrictive qualities
rotigotine	1	transdermal delivery
statin	15	no benefit in HD patients
trazodone	1	dosage too high
zolmitriptan	1	polytoxicomaniac patient, vasoconstrictive qualities

Table 9: PIPs solely detected by the specialist (n=25).

4.5 Applicability of STOPP recommendations

STOPP criteria identified 114 prescriptions as problematic. 62 of these PIPs were also identified as problematic by the nephrologist. The remaining 52 PIPs, which were not detected by the specialist, were provided as recommendations and subsequently discussed

with the nephrologist. 30 (57.7%) of these recommendations were accepted by the specialist. Feedback and rationales were obtained for the rejected suggestions.
These are presented in Table 10.

STOPP recommendation	drug	number of recommendations	number of accepted recommendations	rationale for non-acceptance
A1	folic acid	15	15	
	proton pump inhibitor	1	0	Respecting other prescriber's autonomy and medical hierarchy when specialists are involved
	fenoterol and ipratropriumbromide inhaler	2	2	
	vitamin preparations	15	0	Dietary supplementation, beneficial for patient's nutritional status, medication does not harm
	desloratadine	1	1	
	nicorandil	1	1	
	salbutamol	1	1	
B5	amiodarone	3	0	Respecting other prescriber's autonomy and medical hierarchy when specialists are involved
B10	moxonidine, rilmenidine	6	6	
F2	proton pump inhibitor	1	1	
H4	aprednislone	1	1	
K1 (both in the same patient)	lorazepam	1	0	Respecting other prescriber's autonomy and medical hierarchy when specialists are involved, therapeutic prioritization
	clobazam	1	0	Respecting other prescriber's autonomy and medical hierarchy when specialists are involved, therapeutic prioritization
D10	risperidone	1	0	Fear of unknown/negative consequences of change, therapeutic prioritization
D14	hydroxyzine	2	2	

Table 10: STOPP recommendations and acceptance.

More than half of the A1 recommendations were accepted by the specialist. B5 recommendations (n=3) were not accepted. Both K1 PIPs occurred in the same patient and were rejected. Figure 7 charts the above described findings graphically.

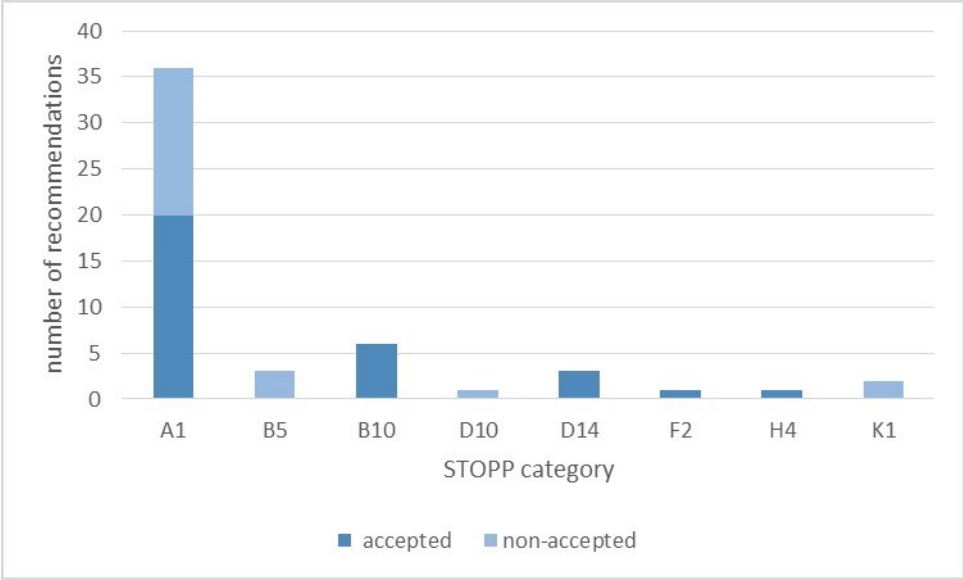

Figure 7: proportion of non-accepted recommendations per STOPP category.

If "vitamin preparations" had not been considered (since they were considered as rather harmless over-the-counter products by the specialist) in the analysis, acceptance rate of STOPP recommendations would have been 81.1% (30 of 37).

4.6 Applicability of START recommendations

Of the 82 START recommendations, only 11 (13.4%) were accepted by the nephrologist. For four recommendations (1 A3, 2 A6, 1 A7) feedback was not possible as the nephrologist rejected detailed analysis due to the retrospective design and inconsistent documentation. The remaining 67 (81.7%) START suggestions were rejected and reasons for non-acceptance were provided by the nephrologist. Table 11 shows details of all START recommendations and corresponding acceptance rate.

START recommendation	description	n	accepted cases (n)	accepted cases (%)
A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation	13	0	0
A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease	13	3	23.1

A5	Statin therapy 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	20	0	0
A6	Angiotensin Converting Enzyme (ACE)/Angiotensin-II-antagonists with systolic heart failure and/or documented coronary artery disease*	17	4	23.5
A7	Beta-blocker with ischaemic heart disease	3	0	
A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure	2	0	0
B1	Regular inhaled Beta-2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or chronic obstructive pulmonary disease	2	2	100
C5	SSRIs (or selective noradrenalin reuptake inhibitor or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.	1	0	0
E2	Bisphosphonates in patients taking long-term systemic corticosteroid therapy**	6	0	0
E3	Calcium*** supplement 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)	1	0	0
E6	Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout	1	0	0
H2	Laxatives in patients receiving opioids regularly	3	2	66.7

Table 11: START recommendations in HD patients. Each detected criterion is shortly described and numerical data of acceptance is provided. *Section A6: ARBs have been added. **Section E2: only bisphosphonates were recommended, since affected patients were administered vitamin D and calcium supplements. Section E3: only calcium supplementation (vitamin D was found on medication list).

As shown in Table 11, acceptance of recommendations in the cardiovascular section, which represents the largest section of PPOs, is outstandingly low. For example, acceptance rate of initiating oral anticoagulant therapy (suggested in 13 cases) and statin therapy (suggested in 20 cases) was 0%. The overall acceptance rate of recommendations from the cardiovascular system was 10.3%. Figure 8 illustrates the distribution of all non-accepted START recommendations.

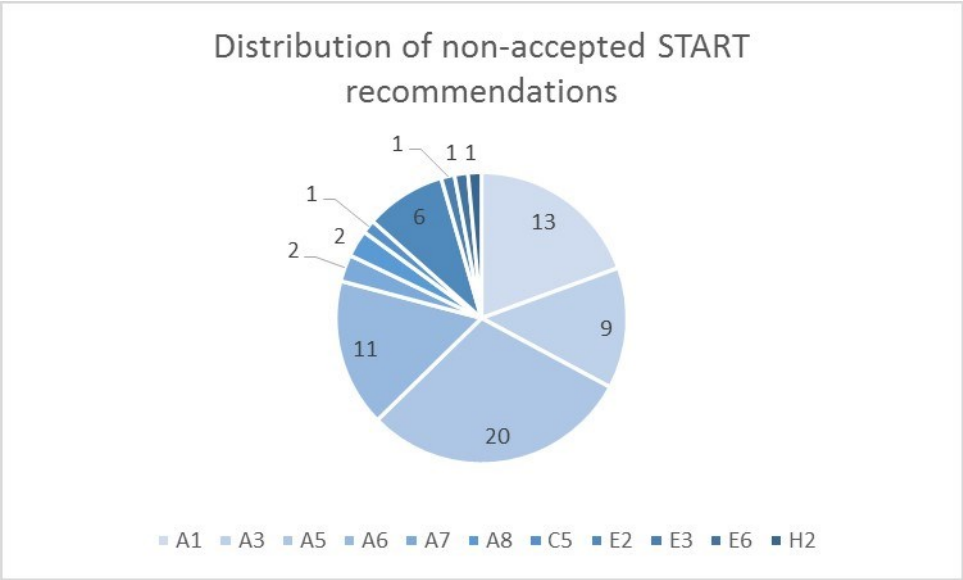

Figure 8: Distribution of rejected recommendations expressed in total numbers (total number=67). The cardiovascular section starts with A1 (n=13) in the right upper area of the chart and goes clockwise to H2.

For each rejected START recommendation, the nephrologist named at least one reason for rejection. The following table lists START categories and numerical data of reasons for non-acceptance. Non-acceptance of recommendations was justified by the specialist. Table 12 lists all START categories and shows particular reasons for non-acceptance of recommendations.

category	total number of given reasons	rationales (further explanation in bracelets)	n	relative frequency among rejected recommendations (%)
A1	42	Drug is not effective in HD patients/has uncertain benefits/benefit-risk ratio (lack of evidence from medical literature, guidelines do not support evidence)	13	100
		Increased risk of a pre-calculated adverse drug event (i.e. bleeding complications, calciphylaxis)	13	100
		Other treatment is used for the clinical condition (i.e. hemodialysis- heparin solution, low-molecular-weight heparin at interval days)	12	92.3
		Contraindication for drug (calciphylaxis)	1	7.7
		Therapeutic prioritization (drug is assigned low priority in patient's current clinical status)	2	15.4
		Setting INR* is assumed to be problematic	1	7.7
A3	15	Patient's refusal leading to poor adherence	1	11.1
		Increased risk of a pre-calculated adverse drug event (bleeding complication)	5	55.6
		Therapeutic prioritization (drug is assigned low priority in patient's current clinical status)	3	33.3

		Other treatment is used for the clinical condition	5	55.6
		Involvement of other specialists in the prescribing decision-making process (angiologist, cardiologist)	1	11.1
A5	32	Drug is not effective in HD patients/has uncertain benefits/benefit-risk ratio (lack of evidence from medical literature, guidelines do not support evidence)	20	100
		Therapeutic prioritization (drug is assigned low priority in patient's current clinical status)	4	20
		Inappropriate in geriatric patients	7	35
		Patient's refusal leading to poor adherence	1	5
A6	13	Patient's refusal leading to poor adherence	2	18.2
		Increased risk of a pre-calculated adverse drug event (hypotension, falls, syncope, intradialytic hypotension and related complications as vascular access thrombosis	9	81.8
		Therapeutic prioritization (drug is assigned low priority in patient's current clinical status)	2	18.2
A7	2	Increased risk of a pre-calculated adverse drug event (hypotension, falls, syncope, intradialytic hypotension and related complications as vascular access thrombosis)	2	100
A8	2	Increased risk of a pre-calculated adverse drug event (hypotension, falls, syncope, intradialytic hypotension and related complications as vascular access thrombosis)	2	100
C5	1	Specialist should be involved, devolve responsibility	1	100
E2	6	Contraindication for drug	6	100
E3	1	Inappropriate due to possible overload	1	100
E6	1	Inappropriate	1	100
H2	1	Therapy is not considered necessary	1	100

Table 12: Qualitative feedback for non-acceptance in detail. Reasons are clustered by START category. Relative frequencies of reasons among rejected recommendations are described. *INR: International Normalized Ratio.

The frequency distribution of clustered reasons and implicated START categories is illustrated in Figure 9.

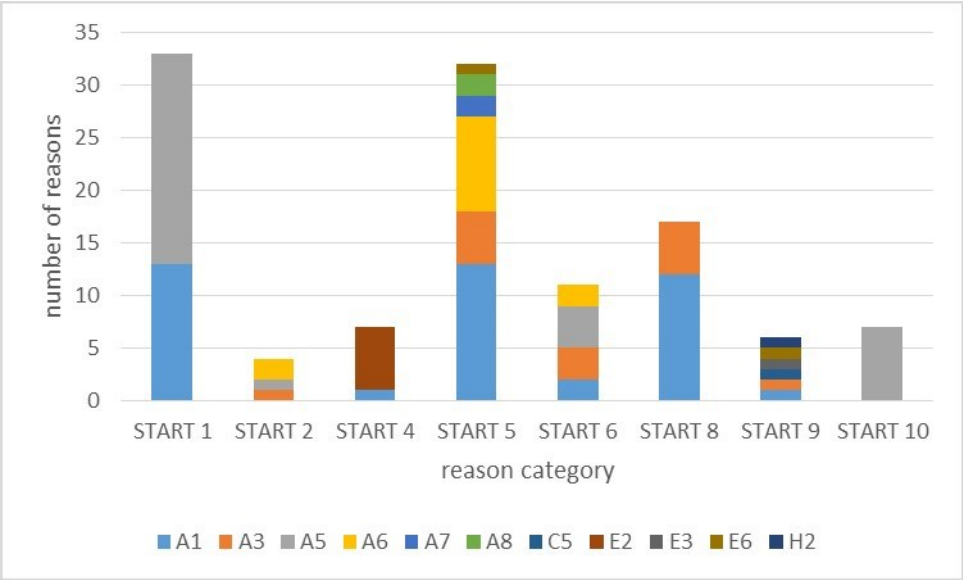

Figure 9: Distribution of obtained START reasons. Y-axis lists coded forms of reasons described in table 9. START 1: Drug is not effective in HD patients. START 2: Patient's refusal leading to poor adherence. START 4: Contraindication for drug. START 5: Increased risk of calculated ADE. START 6: therapeutic prioritization. START 8: Other treatment is used for the condition. START 9: Other reasons (described in table 11). START 10: Inappropriate in geriatric patients.

Two reasons, that were not included in our findings above but mentioned during the feedback discussion, should be added. Concerning START A1, the specialist said that novel oral anticoagulants (NOACs) were contraindicated in HD patients (our focus was on vitamin K antagonists). When talking about antiplatelet therapy, she mentioned platelet dysfunction in HD patients as a considerable reason for omitting antiplatelet therapy.

5 Discussion

5.1 PIPs/Drugs without indication

Our study revealed that 75 (65.8%) of 114 detected PIPs were allocated to missing clinical indications in patients' medical records, making up 12% of all prescriptions. Drug classes for missing indications were PPIs (n=26), antidepressants (n=13), folic acid (n=15) and vitamin preparations (n=15). Some antipsychotic drugs also contributed to this STOPP category, but since drugs were only assigned to one category, they were not included in STOPP A1, and therefore possibly leading to an underestimation of medications without justifying clinical indication. To the best of our knowledge, no studies on determination of inappropriate prescribing in HD patients explicitly using the STOPP/START screening tool have been conducted yet.

However, previous studies have addressed the issue of overprescribing in HD patients. Otto et al. (unfinished PhD thesis, unpublished data) evaluated drug prescriptions in renal replacement therapy patients (92 % HD, 8 % peritoneal dialysis) treated in two dialysis units (the dialysis unit of the Medical University of Graz and a private dialysis centre) in Graz, finding similar results compared to our study. They included 116 patients ≥ 65 years old in the analysis. 310 (20%) out of 1548 found prescriptions were labelled as "unnecessary therapy", which was annotated when patients' medical data (encompassing diagnoses, diagnostic findings, laboratory parameters) did not justify the treatment noted (data on implicated drug classes were not provided).

Manley et al. conducted a pooled analysis of MRPs in 395 ambulatory HD patients. Of 1593 detected MRPs, 14.9% accounted for "drugs without indication" (DWI: a patient is administered a drug for which no clinically valid reason can be found) (68).

In our study, the largest drug class being possibly overprescribed were PPIs. Overuse of PPIs has been described in HD patients before. Strid et al. conducted a study analysing acid suppressive therapy use (PPIs and H2-blockers) in 293 dialysis patients in comparison to hospitalized patients and patients with another chronic disease (i.e. chronic lung disease, rheumatic disease): generally, 119 dialysis subjects received acid suppressive therapy. 93% of all subjects (encompassing control groups) received PPIs, 7% received H2-blockers. Authors reported a significantly higher use of antacids in chronic renal failure subjects compared to hospitalized patients and individuals with chronic lung disease, but not with

rheumatic disease (this was explained due to use of non-steroidal anti-inflammatory drugs in this cohort). Furthermore, more than 70% of dialysis patients used antacids for ≥ 8 weeks and the majority of these drugs was prescribed without having an adequate indication, e.g. for non-specific symptoms like dyspepsia, abdominal pain or no reason to be found.(79) These findings from literature imply that there is a need of future studies addressing reasons for overuse in patients receiving chronic HD therapy.

5.2 PPOs - Indication without drug

We detected 82 PPOs, most of them belonging to the cardiovascular system.

Underuse of indicated drugs has been shown to be a problem in ambulatory HD patients. According to the study conducted by Manley et al., 16.9% of 1593 found MRPs were "indications without drug" (IWDs: patient has a valid indication for a drug, but does not receive it - referring to PPOs) (68). Furthermore, a study conducted by Ong and colleagues showed that IWDs were even the most common events related to MRPs in HD patients on hospital admission (80).

5.3 Comparison of medication reviews

62 of 114 detected STOPP PIPs as identified by the study team were also identified as inappropriate by the specialist. 33 of 35 PPIs labelled STOPP A1 were also selected because of questionable indication. Moreover, strong agreement was observed for antidepressants, antipsychotic agents, benzodiazepines and hypnotic Z-drugs. These findings might imply that clinicians, although not explicitly using PIM tools in clinical routine, are aware of specific risk drugs due to clinical experience and eminence. However, this assumption has to be regarded with caution, as it can not be seen as representative for all nephrologists.

The specialist further rated 25 prescriptions as inappropriate that were not identified by STOPP criteria approach. Of special interest is the fact that she selected all prescribed statins (n=15, will be discussed in the START section of discussion) and medications with transdermal delivery (n=4, opioid analgesics, rotigotine). Again, such findings have to be interpreted with caution, since only one doctor assessed medication appropriateness. This does not necessarily reflect the prevailing specialist opinion. To give an example why caution is indicated: One pharmacokinetic study on transdermally delivered rotigotine (inappropriate according to the nephrologist) showed similar pharmacokinetic profiles in healthy subjects and in individuals with renal impairment (81).

Nonetheless, these results might indicate that there are inappropriate prescriptions which cannot be detected by explicit PIM tools such as STOPP criteria in special patient populations (as in our example individuals receiving chronic HD treatment). Perhaps STOPP criteria need to be broadened and adapted to the needs of HD patients.

5.4 Applicability of STOPP recommendations in HD patients

Acceptance of residual given STOPP recommendations was overall good (30/52 STOPP recommendations [57.7%] or 81.1% if we had excluded vitamin preparations). Although being small in number, an important reason for non-acceptance was involvement of other specialists in the prescribing process (STOPP B5: amiodarone, STOPP K1: benzodiazepines).

In such cases, referring to the work of Anderson et al. (see Figure 4 in the introduction), PIM tools might only increase "awareness" (one of the analytic core themes proposed by Anderson and colleagues) of prescribers towards inappropriate prescribing, but might not lead to actual changes in drug regimens as recommended by criteria (59). This proofs that in daily clinical practice barriers of applicability of PIM tool recommendations go beyond patient-centred considerations and researchers should also put the focus on system-related issues.

5.5 Applicability of START recommendations in HD patients

Although START criteria detected 82 PPOs, the specialist's acceptance of corresponding prescribing recommendations was outstandingly low (13.4%). In the structured interview, the specialist named various reasons for non-acceptance of START recommendations. Many of them mirrored patient-centred considerations, reflecting the special clinical situation of the HD patients in general.

Oral anticoagulant therapy of atrial fibrillation was refused by the specialist in all cases. Main reasons were a lack of evidence in effectiveness, unclear benefit-risk ratio and risk of an ADE.

Observational studies on safety and effectiveness of warfarin therapy with atrial fibrillation showed conflicting results: a recent meta-analysis of 11 observational studies comprising all together 25407 patients comparing warfarin use to non-warfarin treatment, revealed that anticoagulation with warfarin was not associated with lower risks of ischemic stroke but harboured a 27% higher risk of bleeding. Authors could not find any prospective RCT investigating the benefit-risk ratio of warfarin.(82)

In addition to this uncertain net benefit regarding thromboembolic prophylaxis and bleeding complications, use of warfarin can be a predisposing factor for calciphylaxis (83, 84). Not surprisingly, a recent survey of Canadian nephrologists revealed that there is a great uncertainty among physicians regarding literature on this medical issue and showed that the majority of participating nephrologists would advocate RCTs and integrate their results in clinical practice (85).

This lack of evidence is also apparent with NOACs. Major randomized-controlled trials (RCTs) comparing NOACs with warfarin explicitly excluded patients with severe renal impairment, limiting the transferability of study results to patients on haemodialysis (86, 87). According to a study by Chan et al., 5.9% of 29977 dialysis patients with atrial fibrillation were started on dabigatran or rivaroxaban over the 4-year study period, although these agents were not approved for people with ESRD. The same study also revealed that the use of these NOACs was associated with higher risk of major bleedings (defined as a haemorrhagic event resulting in hospitalization or death) and haemorrhagic death when compared to warfarin.(88)

Bleeding risk was also a major concern of antiplatelet therapy in our study. This concern goes along with findings of a recent Cochrane systematic review that found an increased risk of bleeding in CKD patients under antiplatelet therapy, though the absolute risk of myocardial infarction was found to be reduced in this cohort (89).

Like oral anticoagulant therapy, initiation of statin therapy was also rejected by the nephrologist in all recommended cases. Rationales given were lack of effectiveness in HD patients and inappropriateness in geriatric patients. In a systematic review, Hou et al. demonstrated that the beneficial effects of statin therapy in patients with CKD get attenuated as kidney function declines: in CKD stage 5, the number needed to treat to prevent one cardiovascular event is 46, whereas it is 36 in stage 4 and 24 in stage 2-3 (90). Furthermore, a recently published Cochrane systematic review revealed that statin therapy has little or no beneficial effect on cardiovascular outcomes in patients receiving dialysis treatment, whereas statements on adverse events remained uncertain (91). A recent project, aiming to develop guiding principles for prescribing in older complex adults, advised against using statins as secondary prevention in patients with limited life expectancy (less than two years) or advanced dementia due to decreasing benefits with increasing age and a delayed onset of effects in cardiovascular prevention (92).

The most common reasons for rejection of START recommendations given by the specialist in terms of ACEIs/ARBs and beta-blockers were the risk of ADEs. According to

the nephrologist, affected patients would be at risk of having low blood pressure, intradialytic hypotension (IDH) and postural hypotension after dialysis and at dialysis intervals. The European Best Practice Guidelines defined IDH as a decrease in systolic blood pressure by 20 mmHg or a decrease in mean arterial pressure by 10 mmHg proposed with associated clinical events and the need of a nursing intervention (93). It has been shown that IDH is associated with increased risks of vascular access thrombosis and cardiovascular morbidity and mortality (94, 95). Patients with predialysis systolic blood pressure < 100 mmHg are at risk of developing IDH (96). Therefore, omission of antihypertensive agents might be a reasonable decision. It might further be justified to prevent hypotension-related ADEs, since blood pressure lowering drugs might increase the risk of complications like falls (97).

In terms of evidence, recent meta-analyses showed an overall benefit of antihypertensive therapy on cardiovascular outcomes and mortality in HD patients. Included studies were substantially heterogenic in their inclusion criteria and used different antihypertensive treatment strategies.(98, 99) When it comes to ACEIs/ARBs, research findings provide conflicting evidence: a systematic review of RCTs revealed that ACEIs and ARBs do not significantly lower the risk of cardiovascular events when compared to controls (100). Also, observational studies obtained conflicting results and have to be interpreted with caution due to non-randomized study designs allowing for potential confounding (101-103).

A RCT investigating effects of carvedilol (a combined alpha- and beta-blocker) in dialysis patients with dilated cardiomyopathy showed a significantly reduced mortality and morbidity in the intervention group (104). Observational studies also have shown beneficial effects of beta-blocker use in dialysis, but again they have to be interpreted with caution due to limitations of the observational study design (105-107).

START criteria have been developed to aid physicians in detecting evidence-based omitted medications in older adults (108). In patient-centred care of multimorbide patients it is important to consider evidence of treatment strategies that are chosen to be given to patients (58). Evidence generation in CKD/ESRD might therefore generally be an obstacle to this approach, since this population is underrepresented in RCTs, especially in those investigating cardiovascular disease outcomes (109-111).

Patients receiving chronic HD treatment are unique in terms of pathophysiology. Though a high cardiovascular disease burden is observed in this patient population, traditional risk

factors, which are treatment targets for secondary prevention in the general population, cannot fully explain pathology and progression of these medical conditions, leading to the assumption that cardiovascular drugs might not be as effective as in the general population.(112) Furthermore, as we observed during the interview, the complex nature of HD patients (pathophysiology, dialysis-related complications) might predispose them to ADEs (bleeding risk due to anticoagulants/antiplatelet therapy, IDH due to antihypertensive management) when applying START recommendations or might also present a contraindication for specific drugs (i.e. NOACs, bisphosphonates).

Besides HD patient-related factors, our study also found other determinants influencing the specialist's decisions. Patient's refusal/poor adherence was present in four cases, where the specialist was certain about individual patient preferences. In addition, therapeutic prioritization was chosen frequently, assigning recommended drugs low priority in their current complex clinical status. Treatment with a SSRI for anxiety, as recommended in one case, was rejected, since involvement of a specialist should be considered.

5.6 Comparison to existing literature

As mentioned before, this is the first attempt to describe PIPs/PPOs and applicability of STOPP/START criteria in HD patients. However, previous studies have examined the clinical importance and applicability of these criteria in the very old (≥ 80 years) population (56, 113).

In the study conducted by Dalleur and colleagues, a multidisciplinary geriatric team rated clinical importance of 143 PIM tool recommendations (STOPP/START criteria, Beers criteria) in 50 patients. Experts agreed that 40 (28%) recommendations were non-applicable and clustered rationales for rejection into two categories: 25 cases were rated as non-applicable due to patient-related factors (e.g. patient preferences, allergies, DDIs), 15 cases were rated as non-applicable because experts questioned content validity of criteria (e.g. START-PPO "Warfarin in the presence of chronic atrial fibrillation" in patients with low stroke risk).(113)

Lozano-Montoya et al. observed physicians' compliance with STOPP/START recommendations in a geriatric unit in Spain (criteria are routinely applied in clinical practice at hospital admission). Researchers analysed whether recommendations had been followed by geriatricians at hospital discharge. In 346 subjects 284 PIPs and 397 PPOs were detected at hospital admission. At discharge, STOPP recommendations were not

followed in 37 cases (13.0% of PIPs), and START recommendations were rejected in 265 cases (66.5% of recommendations), showing an overall high proportion in non-compliance with START suggestions. Authors concluded, that reasons for non-compliance to START recommendations might be intention to avoid polypharmacy, conflicting evidence, a minor preventative role in older people and end-of life treatment strategies.(56)

In our study cohort about two thirds of the patients were aged < 70 years, only 6.5% were ≥ 80 years. The fact that the acceptance of START recommendations is outstandingly smaller in our HD cohort might emphasize the exceptional clinical position of ESRD patients, attenuating the influence of advanced age on applicability of criteria in this specific patient population.

6 Strengths and limitations

Our study is a pilot project on the applicability of STOPP/START criteria in a very special patient cohort. We used the current version 2.0 of the STOPP/START screening tool. The structured feedback interview allowed us to collect information on barriers of feasibility of criteria on different levels of clinical practice (physician level, individual patient level, HD population level).

However, our study has some shortcomings. It was a retrospective study design and we only interviewed one specialist working at one single dialysis ward, not being representative for a general specialist opinion on inappropriate prescriptions in HD patients.

7 Conclusion and further implications for research

The scope of this diploma thesis and the structured interview with the specialist allowed a reflection on theoretical data obtained by applying STOPP/START criteria in the light of clinical practice.

A specialist's approach towards drug regimen in HD patients is partially comparable to recommendations included in the STOPP criteria approach. Reasons for rejection of STOPP recommendations are not only patient-related but also influenced by involvement of other specialists being part of the prescribing process. In these cases, STOPP criteria can only increase awareness of PIMs. Additional drugs have been rated as problematic by the specialist. Therefore, development of HD patient-tailored STOPP criteria should be discussed in future.

START acceptance by specialists in HD care is extremely low and recommendations in their current form are not applicable due to HD patient-specific characteristics. Distinctive START recommendations adapted to this patient population need to be developed on evidence basis also reflecting the specialists' views. Further prospectively designed studies, which address patient-related, physician-related and system-related obstacles in feasibility of recommendations, are needed in this patient population.

Finally, our findings generate the hypothesis that cohort-tailored PIM tools have to be developed in order to address the special needs of specific patient clusters.

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Appendix

Screening Tool of Older Persons' Prescriptions (STOPP) version 2.0

Die folgenden Medikamentenverschreibungen sind für Personen über 65 Jahre potentiell ungeeignet.

A. Indikation der Medikation

1. Jegliches Medikament, welches ohne eine evidenz-basierte klinische Indikation verschrieben wird.
2. Jegliches Medikament, welches über eine empfohlene Dauer hinaus verschrieben wird, für welches aber eine Behandlungsdauer genau festgelegt ist.
3. Jegliche Doppelverschreibungen von Medikamenten der gleichen Gruppe- z.B. zwei gleichzeitig verschriebene NSARs, SSRIs, Schleifendiuretika, ACE-Hemmer, Antikoagulantien (die Optimierung der Monotherapie innerhalb einer einzelnen Medikamentengruppe sollte gegenüber der Verschreibung eines neuen, zusätzlichen Wirkstoffs vorrangig betrachtet werden).

B. Kardiovaskuläres System

1. Digoxin bei Herzinsuffizienz bei normaler systolischer Ventrikelfunktion (keine klare Evidenz eines Nutzens).
2. Verapamil oder Diltiazem bei Herzinsuffizienz NYHA-Klasse III oder IV (kann eine Herzinsuffizienz verschlimmern).
3. Betablocker in Kombination mit Verapamil oder Diltiazem (Risiko eines AV-Blocks).
4. Betablocker bei Bradykardie (< 50/min), AV-Block 2. Grades Typ II oder komplettem AV-Block (Risiko eines kompletten AV-Blocks, Asystolie).
5. Amiodaron als „first-line" antiarrhythmische Therapie bei supraventrikulären Tachyarrhythmien (höheres Risiko an Nebenwirkungen als Betablocker, Digoxin, Verapamil und Diltiazem).
6. Schleifendiuretika als „first-line" Therapie der Hypertonie (sicherere, effektivere Alternativen stehen zur Verfügung).
7. Schleifendiuretika bei „Dependent"- Knöchelödemen ohne klinischen, laborchemischen, sowie radiologischen Nachweis einer Herz-, Leber- oder Niereninsuffizienz oder eines nephrotischen Syndroms (Beinelevation und/oder Kompressionsstrümpfe sind für gewöhnlich geeigneter).

8. Thiazid-Diuretika bei aktueller erheblicher Hypokaliämie (z.B. Serum-K+ < 3.0 mmol/l),
Hyponatriämie (z.B. Serum-Na+ < 130 mmol/l), Hyperkalziämie (zB. korrigiertes Serum-Ca2+ > 2.65 mmol/l) oder bei positiver Gicht-Anamnese (Einnahme von Thiazid-Diuretika kann zu Hypokaliämie, Hyponatriämie, Hyperkalziämie und Gicht führen).
9. Einsatz von Schleifendiuretika zur Behandlung einer Hypertonie bei gleichzeitig bestehender Harninkontinenz (kann eine Inkontinenz exazerbieren).
10. Einsatz zentral wirksamer Antihypertensiva (z.B. Methyldopa, Clonidin, Moxonidin, Rilmenidin, Guanfacin), sofern keine klar erwiesene Intoleranz oder eine insuffiziente Wirksamkeit anderer Wirkstoffklassen der Antihypertensiva besteht (zentral wirksame Antihypertensiva werden von älteren Menschen generell schlechter toleriert als von jungen).
11. Einsatz von ACE-Hemmern oder Angiotensin-Rezeptorblockern bei Patientinnen/Patienten mit Hyperkaliämie.
12. Aldosteron-Antagonisten (z.B. Spironolacton, Epleron) bei gleichzeitiger Einnahme von Kalium-sparenden Medikamenten (z.B. ACE-Hemmer, Angiotensin-Rezeptorblocker, Amilorid, Triamteren) ohne Überwachung des Serum-Kalium-Spiegels (Risiko einer bedrohlichen Hyperkaliämie z.B. > 6.0 mmol/l – Serum-Kalium sollte regelmäßig kontrolliert werden, d.h. zumindest alle 6 Monate).
13. Phosphodiesterase-5-Inhibitoren (z.B. Sildenafil, Tadalafil, Vardenafil) bei schwerer Herzinsuffizienz gekennzeichnet durch eine Hypotonie (z.B. systolischer Blutdruck < 90 mmHg) oder bei gleichzeitiger Nitrat-Therapie einer Angina pectoris (Risiko kardiovaskulärer Synkopen).

C. Thrombozytenaggregationshemmer/Antikoagulantien

1. Langfristige Aspirin-Einnahme in Dosierungen von mehr als 160 mg/Tag (erhöhtes Blutungsrisiko, keine Evidenz einer erhöhten Wirksamkeit).
2. Aspirin bei einer Anamnese von peptischen Ulzera ohne begleitende PPIs (Risiko wiederkehrender peptischer Ulzera).
3. Aspirin, Clopidogrel, Dipyridamol, Vitamin-K-Antagonisten, direkte Thrombininhibitoren oder Faktor Xa-Inhibitoren bei gleichzeitig bestehendem erheblichen Blutungsrisiko z.B. unkontrollierte schwere Hypertonie, Blutungsdiathese, rezente non-triviale spontane Blutungen (hohes Blutungsrisiko).

4. Aspirin und Clopidogrel als Sekundärprophylaxe bei Schlaganfall, sofern der Patientin/dem Patient kein(e) koronarer/koronaren Stent(s) in den letzten 12 Monaten implantiert worden ist (sind) oder sie/er zur gleichen Zeit unter akutem Koronarsyndrom leidet oder eine hochgradige symptomatische Karotisstenose aufweist (keine Evidenz eines zusätzlichen Nutzens bei Dualtherapie verglichen mit der Monotherapie).
5. Aspirin in Kombination mit Vitamin-K-Antagonisten, direkten Thrombininhibitoren oder Faktor Xa-Inhibitoren bei Patientinnen/Patienten mit chronischer Vorhofflimmerarrhythmie (keine Evidenz eines zusätzlichen Nutzens durch Aspirin).
6. Thrombozytenaggregationshemmer und Vitamin-K-Antagonisten, direkte Thrombininhibitoren oder Faktor Xa-Inhibitoren bei Patientinnen/Patienten mit stabiler koronarer Herzkrankheit, zerebrovaskulärer Erkrankung oder peripherer arterieller Verschlusskrankheit (kein Nachweis eines zusätzlichen Nutzens bei Dualtherapie).
7. Ticlopidin unter jeglichen Umständen (Clopidogrel und Prasugrel haben ähnliche Wirksamkeit, sind besser belegt und haben weniger Nebenwirkungen).
8. Vitamin-K-Antagonisten, direkte Thrombininhibitoren oder Faktor Xa-Inhibitoren bei erstmalig aufgetretener tiefer Beinvenenthrombose ohne fortbestehende prädisponierende Risikofaktoren (z.B. Thrombophilie) für > 6 Monate (kein nachweislicher Nutzen).
9. Vitamin-K-Antagonisten, direkte Thrombininhibitoren oder Faktor Xa-Inhibitoren bei ertsmalig aufgetretener Pulmonalarterienembolie ohne fortbestehende prädisponierende Risikofaktoren (z.B. Thrombophilie) für > 12 Monate (kein nachweislicher Nutzen).
10. Kombination von NSARs mit Vitamin-K-Antagonisten, direkten Thrombininhibitoren oder Faktor Xa-Inhibitoren (Risiko erheblicher Blutungen im Gastrointestinaltrakt).
11. NSARs bei gleichzeitiger Einnahme von Thrombozytenaggregationshemmern ohne PPI-Prophylaxe (erhöhtes Risiko peptischer Ulzera).

D. Zentralnervensystem und psychotrope Substanzen

1. Trizyklische Antidepressiva (TZAs/TCAs) bei Demenz, Engwinkelglaukom, kardialen Erregungsleitungsstörungen, Prostatismus oder früherem Harnverhalt in der Anamnese (Risiko einer Verschlechterung dieser Zustände).
2. Beginn mit Trizyklischen Antidepressiva (TZAs) als „first-line“ antidepressive Therapie (höheres Risiko unerwünschter Arzneimittelnebenwirkungen als beim Einsatz von SSRIs oder SNRIs).
3. Neuroleptika mit mäßigen bis ausgeprägten antimuskarinischen/anticholinergen Auswirkungen (Chlorpromazin, Clozapin, Flupenthixol, Fluphenzin, Pipothiazin,

Promazin, Zuclopenthixol) bei Prostatismus oder früherem Harnverhalt in der Anamnese (hohes Risiko eines Harnverhalts).

4. Selektive Serotonin-Wiederaufnahme-Hemmer (SSRIs) bei gleichzeitig bestehender oder rezenter erheblicher Hyponatriämie z.B. Serum-Na+ < 130 mmol/l (Risiko der Exazerbation oder Entwicklung einer Hyponatriämie).

5. Benzodiazepine ≥ 4 Wochen (keine Indikation für eine längere Behandlung, Risiko einer verlängerten Sedierung, einer Verwirrung, von Gleichgewichtsstörungen, Stürzen, und Verkehrsunfällen: alle Benzodiazepine sollten ausschleichend abgesetzt werden, falls länger als 4 Wochen eingenommen, da hier bei abruptem Absetzen ein Benzodiazepin-Entzugssyndrom entstehen kann).

6. Antipsychotika (andere als Quetiapin und Clozapin) bei Patientinnen/Patienten mit Parkinsonismus oder Lewy Body Demenz (Risiko schwerer extrapyramidaler Symptome).

7. Anticholinergika/Antimuskarinika zur Behandlung extrapyramidaler Nebenwirkungen von Neuroleptika (Risiko einer anticholinerg-toxischen Wirkung).

8. Anticholinergika/Antimuskarinika bei PatientInnen mit Delir oder Demenz (Risiko einer Exazerbation der kognitiven Beeinträchtigung).

9. Neuroleptika/Antipsychotika bei Patientinnen/Patienten mit BPSD (behavioural and psychological symptoms of dementia), sofern die Symptome nicht schwerwiegend sind und andere nicht-pharmakologische Therapien nicht versagt haben (erhöhtes Risiko für Schlaganfälle).

10. Neuroleptika als Schlafmittel, sofern die Schlafstörung nicht aufgrund einer Demenz oder Psychose auftritt (Risiko von Verwirrungszuständen, einer Hypotonie, von extrapyramidalen Nebenwirkungen und Stürzen).

11. Acetylcholinesterase-Inhibitoren bei bekannter Vorgeschichte einer persistierenden Bradykardie (< 60 Schläge/min), eines AV-Blocks, wiederkehrender unerklärlicher Synkopen oder bei gleichzeitiger Einnahme von Medikamenten, die die Herzfrequenz senken wie z.B. Betablocker, Digoxin, Diltiazem, Verapamil (Risiko einer Erregungs- bzw. Reizleitungsstörung, Synkope und Verletzung).

12. Phenothiazine als „first-line“ Therapie, da sicherere und wirksamere Alternativen existieren (Phenothiazine wirken sedierend, haben erhebliche anti-muskarinische Nebenwirkungen bei älteren Menschen; ausgenommen Prochlorperazin bei Übelkeit/Erbrechen/Schwindel, Chlorpromazin zur Linderung von persistierendem Schluckauf und Levomepromazin als Antiemetikum im palliativen Setting).

13. Levodopa oder Dopaminagonisten bei benignem essentiellen Tremor (keine Evidenz der Wirksamkeit).
14. Antihistaminika der 1. Generation (sicherere, weniger toxische Antihistaminika sind heutzutage weitgehend verfügbar).

E. Renales System

Die folgenden Medikamente sind potentiell ungeeignet bei älteren Menschen mit akutem Nierenversagen oder chronischer Niereninsuffizienz mit einer Nierenfunktion unterhalb bestimmter Level der eGFR (in Bezug auf die Zusammenfassung des Produktmerkmaldatenblattes und lokaler Arzneimittellisten-Richtlinien).

1. Digoxin in einer Langzeitdosierung mit > 125 µg/Tag falls eGFR < 30 ml/min/1.73 m2 (Risiko einer Digoxin- Toxizität falls die Plasmaspiegel nicht gemessen werden).
2. Direkte Thrombininhibitoren (zB. Dabigatran) falls eGFR < 30 ml/min/1.73m2 (Blutungsrisiko).
3. Faktor-Xa-Hemmer (zB. Rivaroxaban, Apixaban) falls eGFR < 15 ml/min/1.73m2 (Blutungsrisiko).
4.NSARs falls eGFR < 50 ml/min/1.73m2 (Risiko einer Verschlechterung der Nierenfunktion).
5. Colchicin falls eGFR < 10 ml/min/1.73m2 (Risiko einer Colchicin-Toxizität).
6. Metformin falls eGFR < 30 ml/min/1.73m2 (Risiko einer Laktazidose).

F. Gastrointestinales System

1. Prochlorperazin oder Metoclopramid bei Parkinsonismus (Risiko einer Exazerbation der Parkinson-Symptomatik).
2. PPIs bei unkomplizierten peptischen Ulzera oder erosiver Ösophagitis unter voller therapeutischer Dosis für > 8 Wochen (Dosisreduktion oder eine frühere Absetzung der Medikation ist indiziert).
3. Medikamente, die Obstipationen verursachen können (z.B. antimuskarinische/anticholinerge Medikamente, Eisen per os, Opioide, Verapamil, Aluminium-Antazida), bei Patientinnen/Patienten mit chronischer Obstipation, wenn andere nicht-obstipierende Wirkstoffe verfügbar sind (Risiko einer Exazerbation der Obstipation).

4. Orales natürliches Eisen in Dosierungen > 200 mg/Tag (z.B. Eisenfumarat > 600 mg/Tag, Eisensulfat > 600 mg/Tag, Eisenglukonat > 1800 mg/Tag; keine Evidenz einer gesteigerten Eisenabsorption über diesen Dosierungen).

G. Respiratorisches System

1. Theophyllin als Monotherapie bei COPD (sicherere, wirksamere Alternativen verfügbar; Risiko von Nebenwirkungen aufgrund geringer therapeutischer Breite).
2. Systemische Gabe von Kortikosteroiden anstelle von inhalativen Kortikosteroiden bei der Erhaltungstherapie einer mäßigen bis schweren COPD (unnötige Belastung mit den Langzeitnebenwirkungen einer systemischen Kortikosteroidtherapie, effektive Inhalationstherapien sind verfügbar).
3. Antimuskarinische Bronchodilatatoren (z.B. Ipratropium, Tiotropium) bei Engwinkelglaukomen (kann ein Glaukom akut verschlimmern) oder obstruktiven Harnabflussstörungen (kann Harnverhalt verursachen).
4. Nicht-selektive Betablocker (egal ob oral oder topisch zur Glaukombehandlung) bei behandlungsdürftigem Asthma in der Anamnese (Risiko verstärkter Bronchospasmen).
5. Benzodiazepine bei akuter oder chronischer respiratorischer Insuffizienz z.B. $pO2 < 8.0$ kPa +/- $pCO2 > 6.5$ kPa (Risiko einer Exazerbation der respiratorischen Insuffizienz).

H. Muskuloskeletales System

1. Nicht steroidale Antirheumatika mit Ausnahme COX-2 selektiver Wirkstoffe, wenn sich in der Vorgeschichte peptische Ulzera oder gastrointestinale Blutungen erheben lassen und wenn keine PPIs oder H2-Antagonisten als Begleitmedikation verabreicht werden (Risiko eines Ulkus-Rezidivs).
2. NSARs bei schweren Hypertonie (Risiko einer Exazerbation) oder einer schweren Herzinsuffizienz (Risiko einer Exazerbation).
3. Langfristige Einnahme von NSAR (> 3 Monate) für die Symptomlinderung der Osteoarthritis, wenn Paracetamol nicht versucht wurde (Paracetamol ist vorzuziehen und für gewöhnlich gleich effektiv in der Schmerzlinderung).
4. Langfristige Einnahme von Kortikosteroiden (> 3 Monate) als Monotherapie bei rheumatoider Arthritis (Risiko systemischer Kortikosteroidnebenwirkungen).
5.Kortikosteroide (mit Ausnahme periodischer intraartikulärer Injektionen bei monoartikulärem Schmerz) bei Osteoarthritis (Risiko systemischer Kortikosteroidnebenwirkungen).

6. Langfristige Einnahme von NSARs oder Colchicin (> 3 Monate) in der chronischen Behandlung von Gicht, wenn keine Kontraindikationen für Xanthinoxidase-Inhibitoren (z.B. Allopurinol, Febuxostat) bestehen (Xanthinoxidase-Inhibitoren sind die 1.Wahl in der prophylaktischen Therapie der Gicht).
7. COX-2 selektive NSARs bei gleichzeitig bestehender kardiovaskulärer Erkrankung (erhöhtes Herzinfarkt-und Schlaganfallrisiko).
8. NSARs und gleichzeitige Kortikosteroidtherapie ohne PPI-Prophylaxe (erhöhtes Risiko peptischer Ulzera).
9. Orale Bisphosphonate bei Patientnnen/Patienten mit gegenwärtiger oder rezenter Anamnese einer Erkrankung des oberen Gastrointestinalrakts wie Dysphagie, Ösophagitis, Gastritis, Duodenitis, Geschwüre, Blutungen des oberen Gastrointestinaltrakts (Risiko eines Rezidivs/einer Exazerbation einer Ösophagitis, ösophagealer Ulzera oder ösophagealer Strikturen).

I. Urogenitales System

1. Antimuskarinische Medikamente bei Demenz oder chronischer kognitiver Beeinträchtigung (Risiko gesteigerter Verwirrtheit, Agitation) oder bei Engwinkelglaukomen (Risiko einer akuten Exazerbation) oder bei chronischem Prostatismus (Risiko eines Harnverhalts).
2. Selektive alpha-1-Blocker bei symptomatischer orthostatischer Hypotonie oder bei Miktionssynkope (Risiko rezidivierender Synkopen).

J. Endokrines System

1. Sulfonylharnstoffe mit langer Wirkdauer (z.B. Glibenclamid, Chlorpropamid, Glimepirid) bei Diabetes mellitus Typ 2 (Risiko einer prolongierten Hypoglykämie).
2. Thiazolidindione (z.B. Rosiglitazon, Pioglitazon) bei Patientinnen/Patienten mit Herzinsuffizienz (Risiko einer Exazerbation der Herzinsuffizienz).
3. Betablocker bei Diabetes mellitus mit häufigen hypoglykämischen Episoden (Risiko einer Unterdrückung der hypoglykämischen Symptome).
4. Östrogene bei Brustkrebs oder venösen Thrombembolien in der Anamnese (erhöhtes Risiko eines Rezidivs).
5. Orale Östrogene ohne Progesteron bei Patientinnen mit gesundem/intaktem Uterus (Risiko eines Endometrium-Karzinoms).

6. Androgene (männliche Geschlechtshormone) in Abwesenheit eines primären oder sekundären Hypogonadismus (Risiko einer androgen-toxischen Wirkung; kein nachgewiesener Nutzen außerhalb der Indikationsstellung „Hypogonadismus“).

K. Medikamente, die das Sturzrisiko bei älteren Menschen vorhersehbar erhöhen

1. Benzodiazepine (sedierend, können eine reduzierte Wahrnehmung verursachen, beeinträchtigen das Gleichgewicht).
2. Neuroleptika (können die Ganggeschicklichkeit beeinträchtigen und Parkinsonismus verursachen).
3. Vasodilatatorische Medikamente (z.B. alpha-1-Rezeptorblocker, Kalziumkanalblocker, langwirksame Nitrate, ACE-Inhibitoren, Angiotensin-1-Rezeptorblocker) bei persistierender orthostatischer Hypotonie, wie z.B. ein rezidivierender Fall des systolischen Blutdrucks ≥ 20 mmHg (Risiko einer Synkope, Sturzgrisiko).
4. „Z-Drugs“ z.B. Zopoclon, Zolpidem, Zaleplon (können langwierige tageszeitliche Sedierung und Ataxie verursachen).

L. Analgetische Medikamente

1. Anwendung oraler oder transdermaler starker Opioide (Morphin, Oxycodon, Fentanyl, Buprenoprhin, Diamorphin, Methadon, Tramadol, Pethidin, Pentazocin) als „first-line“ Therapie bei mildem Schmerz (WHO-Stufenplan nicht eingehalten).
2. Regelmäßiger Einsatz von Opioiden (im Unterschied zur Gabe bei Bedarf = prn „pro re nata“) ohne Laxantien als Begleitmedikation (Risiko einer schweren Obstipation).
3. Langwirksame Opioide ohne kurzwirksame Opioide für den akuten Durchbruchsschmerz (Risiko des Bestehenbleibens schwerer Schmerzzustände).

N. Antimuskarinische/Anticholinerge Medikamentenbelastung

Gleichzeitige Anwendung zweier oder mehrerer Medikamente mit antimuskarinischen/anticholinergen Eigenschaften (z.B. Spasmolytika für die Harnblase oder den Darm, trizyklische Antidepressiva, Antihistaminika der 1. Generation) (Risiko einer erhöhten antimuskarinerg-/anticholinerg-toxischen Wirkung).

Screening Tool to Alert to Right Treatment (START) version 2.0

Sofern der gesundheitliche Zustand eines älteren Menschen nicht schon absehbar in die terminale Lebensphase übergeht und daher eher palliative Strategien in der

Pharmakotherapie anzustreben sind, sollten die folgenden medikamentösen Therapien in Erwägung gezogen werden, falls sie ohne validen klinischen Grund unterlassen worden sind. Es wird davon ausgegangen, dass die verschreibende Ärztin/der verschreibende Arzt all die spezifischen Kontraindikationen der einzelnen Medikamente beachtet, bevor jene älteren Patientinnen/Patienten empfohlen werden.

A. Kardiovaskuläres System

1. Vitamin-K-Antagonisten oder direkte Thrombininhibitoren oder Faktor Xa-Hemmer bei bestehender chronischer Vorhofflimmerarrhythmie.
2. Aspirin (75 mg – 160 mg einmal täglich) bei bestehender chronischer Vorhofflimmerarrhythmie, wenn Vitamin-K-Antagonisten, direkte Thrombininhibitoren oder Faktor Xa-Hemmer kontraindiziert sind.
3. Thrombozytenaggregationshemmer (Aspirin, Clopidogrel, Prasugrel, Ticagrelor) bei dokumentierter Vorgeschichte einer koronaren, zerebralen oder peripheren vaskulären Erkrankung.
4. Antihypertensive Therapie, wenn der der systolische Blutdruck konsequent >160 mmHg ist und/oder der diastolische Blutdruck konsequent > 90 mmHg ist; bei Diabetikerinnen/Diabetikern: wenn der systolische Blutdruck > 140 mmHg und/oder der diastolische Blutdruck > 90 mmHg ist.
5. Therapie mit Statinen bei dokumentierter Vorgeschichte einer koronaren, zerebralen oder peripheren vaskulären Erkrankung, wenn der Patientenstatus nicht „end-of-life“ ist oder er älter als 85 Jahre ist.
6. ACE-Hemmer bei systolischer Herzinsuffizienz und/oder bekannter koronarer Herzerkrankung.
7. Betablocker bei ischämischer Herzerkrankung.
8. Angemessene Betablocker-Therapie (Bisoprolol, Nebivolol, Metoprolol, Carvedilol) bei stabiler systolischer Herzinsuffizienz.

B. Respiratorisches System

1. Regelmäßig inhalierte Beta-2-Agonisten oder antimuskarinische Bronchodilatatoren (z.B. Ipratropium, Tiotropium) bei mildem bis mäßigem Asthma oder COPD.
2. Regelmäßig inhalierte Kortikosteroide bei mäßigem bis schwerem Asthma oder COPD, wenn die FEV1 < 50% des prognostizierten Wertes und wiederholte Exazerbationen eine Behandlung mit oralen Kortikosteroiden erforderlich machen.

3. Kontinuierliche Sauerstofftherapie zuhause bei bekannter chronischer Hypoxämie (z.B. pO2 < 8.0 kPa oder 60 mmHg oder SaO2 < 89%).

C. Zentralnervensystem und Augen

1. L-DOPA oder Dopaminagonisten bei idiopathischem Parkinson-Syndrom mit funktioneller Beeinträchtigung und resultierender Behinderung.
2. Nicht-TZA-Antidepressiva in Gegenwart persistierender Symptome einer Major-Depression.
3. Acetylcholinesterasehemmer (z.B. Donepezil, Rivastigmin, Galantamin) bei milder bis moderater Alzheimer Demenz oder Lewy Body Demenz (Rivastigmin).
4. Topische Prostaglandine, Prostamide oder Betablocker für das primäre Offenwinkelglaukom.
5. SSRIs (oder SNRIs/Pregabalin falls SSRIs kontraindiziert) bei persistierenden schweren Angstzuständen, die ein unabhängiges, selbstständiges Leben und Arbeiten beeinträchtigen.
6. Dopaminagonisten (Ropinorol, Pramipexol, Rotigotin) beim Restless-Legs-Syndrom, wenn erst einmal ein Eisenmangel und ein schweres Nierenversagen ausgeschlossen worden sind.

D. Gastrointestinales System

1. PPIs bei schwerer gastroösophagealer Refluxerkrankung oder einer peptischen Striktur, bei welcher eine Dilatation erforderlich wäre.
2. Supplementation von Ballaststoffen (z.B. Kleie, Flohsamen, Methylcellulose, Sterkuliengewächse) bei Divertikulose mit Obstipationsproblemen in der Anamnese.

E. Muskuloskeletales System

1. DMARDs („disease-modifying anti-rheumatic drugs“) bei aktiver, einschränkender rheumatoider Arthritis.
2. Bisphosphonate und Vitamin D und Kalzium bei Patientinnen/Patienten, die eine langfristige systemische Kortikosteroidtherapie erhalten.
3. Vitamin D- und Kalzium-Substitution bei Patientinnen/Patienten mit bekannter Osteoporose und/oder vorherigen Bagatellfrakturen und/oder Knochendichtemessung T-Wert größer als 2.5 an mehreren Stellen.

4. Anti-resorptive oder anabolische Knochentherapie (z.B. Bisphosphonate, Strontiumranelat, Teriparatid, Denosumab) bei Patientinnen/Patienten mit nachgewiesener Osteoporose, wenn keine pharmakologischen und klinischen Kontraindikationen bestehen (Knochendichte T-Wert ≥ 2.5 an mehreren Stellen) und/oder eine Vorgeschichte an Bagatellfrakturen besteht.
5. Vitamin D-Substitution bei älteren Menschen, die ans Haus gefesselt sind oder mehre Stürze erlitten haben oder osteopenisch sind (Knochendichtemessung T-Wert > 1.0 aber < 2.5 an mehreren Stellen).
6. Xanthinoxidase-Inhibitoren (z.B. Allopurinol, Febuxostat) bei rezidivierenden Gichtepisoden in der Anamnese.
7. Folsäure-Substitution bei Patientinnen/Patienten, die Methotrexat einnehmen.

F. Endokrines System

1. ACE-Hemmer oder Angiotensin-Rezeptorblocker (falls ACE-Hemmer nicht toleriert werden) bei Diabetes mit Nachweis einer renalen Beteiligung, d.h. Proteinurie oder Mikroalbuminurie (>30 mg/24 Stunden) am Harnstreifentest mit oder ohne laborchemischen Nachweis einer Beeinträchtigung der renalen Serum-Parameter.

G. Urogenitales System

1. Alpha-1-Rezeptorblocker bei symptomatischem Prostatismus, wenn eine Prostataresektion nicht als notwendig erachtet wird.
2. 5-Alpha-Reduktase-Inhibitoren bei symptomatischem Prostatismus, wenn eine Prostataresektion nicht als notwendig erachtet wird.
3. Topische vaginale Östrogenanwendung oder Östrogenpessare bei symptomatischer atrophischer Vaginitis.

H. Analgetika

1. Hochpotente Opioide bei moderaten bis schweren Schmerzen, wenn Paracetamol, NSARs oder niedrigpotente Opioide für das Ausmaß des Schmerzes unangemessen sind oder die Wirkung nicht ausreichend ist.
2. Laxantien bei PatientInnen mit regelmäßiger Opioideinnahme.

I. Impfstoffe

1. Jährliche saisonale trivalente Infuenza-Impfung.

2. Pneumokokken-Impfung zumindest einmal ab dem Alter von 65 Jahren gemäß den jeweiligen nationalen Leitlinien.