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Improving the Quality and Safety of Drug Use in Hospitalized Elderly

Assessing the Effects of Clinical Pharmacist Interventions and Identifying Patients at Risk of Drug-related Morbidity and Mortality

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Abstract

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Older people admitted to hospital are at high risk of rehospitalization and medication errors. We have demonstrated, in a randomized controlled trial, that a clinical pharmacist intervention reduces the incidence of revisits to hospital for patients aged 80 years or older admitted to an acute internal medicine ward. The aims of this thesis were to further study the effects of the intervention and to investigate possibilities of targeting the intervention by identifying predictors of treatment response or adverse health outcomes.

The effect of the pharmacist intervention on the appropriateness of prescribing was assessed, by using three validated tools. This study showed that the quality of prescribing was improved for the patients in the intervention group but not for those in the control group. However, no association between the appropriateness of prescribing at discharge and revisits to hospital was observed.

Subgroup analyses explored whether the clinical pharmacist intervention was equally effective in preventing emergency department visits in patients with few or many prescribed drugs and in those with different levels of inappropriate prescribing on admission. The intervention appeared to be most effective in patients taking fewer drugs, but the treatment effect was not altered by appropriateness of prescribing.

The most relevant risk factors for rehospitalization and mortality were identified for the same study population, and a score for risk-estimation was constructed and internally validated (the 80+ score). Seven variables were selected. Impaired renal function, pulmonary disease, malignant disease, living in a nursing home, being prescribed an opioid and being prescribed a drug for peptic ulcer or gastroesophageal reflux disease were associated with an increased risk, while being prescribed an antidepressant drug (tricyclic antidepressants not included) was linked with a lower risk. These variables made up the components of the 80+ score. Pending external validation, this score has potential to aid identification of high-risk patients.

The last study investigated the occurrence of prescription errors when patients with multi-dose dispensed (MDD) drugs were discharged from hospital. Twenty-five percent of the MDD orders contained at least one medication prescription error. Almost half of the errors were of moderate or major severity, with potential to cause increased health-care utilization.

Keywords: Adverse drug events, inappropriate prescribing, medication errors, polypharmacy, medication reconciliation, medication review, patient drug counseling, multi-dose dispensed drugs, risk-estimation, multiprofessional collaboration, prediction model, quality measure, rehospitalization

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Start where you are.
Use what you have.
Do what you can.

Arthur Ashe

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Gillespie U, Alassaad A, Hammarlund-Udenaes M, Mörlin C, Henrohn D, Bertilsson M, Melhus H. (2013) Effects of pharmacists' interventions on appropriateness of prescribing and evaluation of the instruments' (MAI, STOPP and STARTs') ability to predict hospitalization – analyses from a randomized controlled trial. *PloS One. 2013;8(5):e62401*.

II Alassaad A, Bertilsson M, Gillespie U, Sundström J, Hammarlund-Udenaes M, Melhus H. The effects of pharmacist intervention on emergency department visits in patients 80 years and older: subgroup analyses by number of prescribed drugs and appropriate prescribing. *PLoS One 2014; 9(11): e111797.*

III Alassaad A, Melhus H, Hammarlund-Udenaes M, Bertilsson M, Gillespie U, Sundström J. A tool for risk-estimation of rehospitalisation and mortality in older people. *Submitted Sept 2014*.

IV Alassaad A, Gillespie U, Bertilsson M, Melhus H, Hammarlund-Udenaes M. (2013) Prescription and transcription errors in multidose-dispensed medications on discharge from hospital: an observational and interventional study. *J Eval Clin Pract. 2013 Feb;19(1):185-91.*

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Contents

Abbreviations

ADR	Adverse drug reaction
RCT	Randomized controlled trial
ADE	Adverse drug event
MAR	Medication administration record
MDD	Multi-dose dispensing
DRP	Drug-related problem
QALY	Quality-adjusted life years
STOPP	Screening Tool of Older Persons' Prescriptions
START	Screening Tool to Alert Doctors to Right Treatment
MAI	Medication Appropriateness Index
SALAR	Swedish Association of Local Authorities and Regions
PCA	Principal components analysis
GERD	Gastroesophageal reflux disease
TCA	Tricyclic antidepressants

Introduction

Drug use in older people

Advances in medicine have resulted in increased survival and symptom relief for patients with chronic illnesses, and the numbers of fit, healthy older people are increasing. At the same time, there are increasing numbers of frail, vulnerable elderly who have multiple co-existing diagnoses and an increased need for health care. The use of medicines has become a fundamental component of the care of older people. The prescribing of drugs for patients aged 75 years and older has increased by 70% in the last 20 years, and older people living in nursing homes in Sweden are now taking an average of 8-10 prescribed medications (1). Due to physical pharmacokinetic and pharmacodynamic changes, older people are increasingly sensitive to the unwanted effects, such as adverse drug reactions (ADRs), of the drugs. There is also greater inter-individual variability in this population, which necessitates individualized treatment plans (2–4). With a growing number of older people with complex medication regimens, it is crucial that our awareness of medication-related issues is improved in order to reach a high quality of care for this population.

Clinical pharmacists involved in multidisciplinary health-care teams focus on increasing the quality and safety of drug therapy. Our research group has in a randomized controlled trial (RCT) previously demonstrated that a clinical pharmacist intervention reduces the number of revisits to hospital and drug-related readmissions (5). Additional knowledge about the intervention can be gained by assessing the impact of the different parts of the clinical pharmacist intervention. Future cost-effective interventions can be designed to include the patients at most need and who will benefit the most, by identifying risk factors of adverse health outcomes and predictors of response to the intervention.

Adverse drug events

The World Health Organization defines an ADR as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological functions”(6), i.e. harm directly caused by the drug

at normal doses. An adverse drug event (ADE) describes a broader scenario, defined as "an injury resulting from the use of a drug" (7) which includes a harm caused by the drug itself (i.e. ADRs) and also harm caused by the use of the drug (8). Inappropriate prescribing, medication errors and poor patient adherence to drug therapy are examples of suboptimal use of drugs which can cause ADEs (9). ADEs can result in drug-related morbidity and mortality, and are the main cause of up to a third of the hospital admissions in the elderly population (9–15).

Inappropriate prescribing

Inappropriate prescribing can be divided into three types: overprescribing (prescription of more drugs than are clinically needed), misprescribing (incorrect prescription of a drug that is needed), and underprescribing (failure to prescribe drugs that are clinically needed). Overprescribing often occurs when drug therapy is not adequately re-evaluated over time, with many medications continuing to be prescribed despite the patient no longer having the diagnosis for which the medication was originally intended. Misprescribing occurs when medicines that pose a significant risk of ADRs are prescribed, when there is an equally effective or more effective lower-risk alternative therapy available for the same condition. It can also occur when a drug is prescribed at a suboptimal dose, formulation or dosage interval, or when drugs with known drug-drug interactions or drug-disease interactions are prescribed. Underprescribing is sometimes associated with a phenomenom called ageism; i.e. prescribers may decide not to prescribe a drug or not to increase the dosage of a drug merely because the patient is old (16–20).

Medication errors

Medication errors are any errors in the process of prescribing/ordering, transcribing, dispensing or administering of a drug (21). Transcribing, dispensing or administering errors are all technical errors. In the prescribing/ordering process, a medication error can either occur in the decision-making process or be of a technical nature (22).

When patients are transferred between different levels of health care, unintentional discrepancies in the prescribing/ordering or transcribing process can happen. These discrepancies are highly prevalent (23–27), they are an important contributor to ADEs (25,28) and are associated with risk of re-hospitalization (29).

Non-adherence to treatment

Medication adherence can be defined as the extent to which a person follows medical advice in the use of a drug, with respect to the correct dose and dos-

age interval (30). Non-adherence to prescribed treatment occurs commonly; around one-third of older patients are estimated to be non-adherent to at least one of their drugs (31–33). Col et al. interviewed older patients admitted to hospital and found that 11% of medical admissions to hospital were due to medication non-adherence (10). In several studies, non-adherence to drug treatment was associated with increased risk of hospitalization and mortality, as well as increased costs for those with chronic diseases (34–37). Non-adherence – intentional as well as unintentional – may be the result of insufficient or inadequate information to patients about their medications, lack of understanding by the patients of their drug therapy or lack of patient access to their medications (38–40).

Polypharmacy

A high number of prescribed drugs for one individual has been associated with an increased risk of drug-drug and drug-disease interactions (1,41–43), inappropriate prescribing (44–47), medication errors (29,48) and non-compliance with treatment (10,39,49). Therefore, concomitant prescribing of a high number of drugs, or polypharmacy, is sometimes considered an indicator of inappropriate drug use. However, the principle of appropriate prescribing is not about keeping the number of drugs low: the quality of the prescribed drug treatment is more important than the actual number of drugs. Steinman et al. (44) pointed out that the issue of underprescribing is often overlooked and the underuse of medications is common in patients taking only a few medications, as well as in those taking many.

Quality of care and how to measure it

The Institute of Medicine (IOM) defines the quality of health care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (50). Further, the care should be "safe, effective, patient centered, timely, efficient and equitable" (51). Consumers, payers and regulatory agencies request evidence of the quality of care, and methods and measures for evaluating it are therefore required.

The use of quality measurement methods allows the attainment of data on the existence and magnitude of substandard quality in a certain area as well as evaluation of the effects of efforts to improve quality.

Quality measures

Quality measures help us to determine quality quantitatively (52). Quality is a multidimensional concept, and multiple indicators are required for a fair judgment (53,54). Donabedian (55) suggests that we measure the quality of health care by studying its processes, structures and outcomes. Process measures describe "what providers do", structure measures describe "how care is organized" and outcome measures describe "what happens to the patients". For example, the attendance rate of clinical pharmacists performing medication reconciliations (as described below under *"Medication reconciliation"*) at the emergency department is a measure of structure, and the number of medication discrepancies identified and corrected during the medication reconciliation is a measure of process. The readmission rate for the patients for whom medication reconciliations were conducted is a measure of outcome.

Quality measures should generate results that are meaningful, scientifically sound and interpretable (56). To be meaningful, they should measure aspects of health care that are important (e.g. those that are associated with high morbidity or mortality or that are costly), and/or those that are of financial or strategic importance to stakeholders. To be scientifically sound, they should be based on evidence-based data and they should also be validated, reliable, sensitive, and specific. Interpretability refers to the ease with which the potential user of the information can understand and apply the generated results.

Validity is the extent to which the measure accurately represent the concept that is being assessed. Reliability is the ability to generate the same results when the measure is applied repeatedly in the same population. Sensitivity is the proportion of positive responses that are correctly identified as such (sometimes referred to as "the true positive rate") and specificity is the proportion of negative responses that are correctly identified as such (or "the true negative rate").

Quality measurement methods also need to be practical and user-friendly, and data needed for assessment should be accessible. They need to keep a balance between clinical complexity (which enhances validity) and simplicity (which keeps things user-friendly). Because of the inherent tension between these aims, it can sometimes be challenging to find the balance (52–60).

Outcome assessment

Measurement of outcomes is generally considered to be the ultimate method of valuing the quality of medical care. Patients and purchasers generally place more value on outcomes than on processes (54), probably because outcomes are relatively concrete and because their validity is seldom ques-

tioned (55). However, in some situations it is more suitable to assess the quality of the processes or structures instead. For instance, the outcome may be irrelevant –as when mortality is chosen as a measure for something that does not aim to increase survival. The outcome may also be affected by factors other than medical care, and these factors then have to be controlled or adjusted for. Further, it can sometimes be a long time until some outcomes can be evaluated (55).

Process assessment

Methods of assessing processes involve evaluation of adherence to standards and guidelines. Standards are usually based on best practice, consensus among providers and/or medical evidence (52,58). The advantage of assessing processes is that this provides information about what is and what is not being done well (defined as which guidelines are followed and which are not) and consequently clearly demonstrates how quality can be improved. Also, providers are more accountable for the processes of care, and can therefore control them better than the outcomes. Hence, it is generally easier to guide improvements in the quality of health care using process measures than outcome measures. Assessing the quality of processes can also be relatively simple and less costly. On the other hand, process assessment may not be fully comprehensive and may cover only some aspects of the factors affecting outcomes.

Structure assessment

Structure measures assess the organization of the delivery of the processes of health care. The idea is that if certain settings and/or staff routines are in place, there will be a greater chance of achieving the desired outcomes. The advantages of structure assessment are that structures are concrete, and the information needed is often readily accessible. The disadvantage is that there may be a weak relationship between the structure and the processes taking place and/or between the structure and the outcomes (55).

For structure or process measures to be valid, it is essential to establish a link between the process or structure measure and the outcome measure; an improvement in a process or structure should ultimately be reflected as an improvement in an outcome. Ideally, evidence for this link should be scientifically demonstrated, but often this is not done. In these cases consensus among providers is deemed sufficient for validity (53,55,58,61).

Pharmaceutical care and clinical pharmacy practices

The aim of pharmaceutical care is to ensure that patients receive the correct medications in an appropriate dose and dosage for appropriate indications (62). Hepler (63) described pharmaceutical care as an "outcome-oriented, cooperative, systematic approach to providing drug therapy". The outcome-oriented approach indicates that the term pharmaceutical care describes not so much what the health-care provider does, but more what the patient experiences. The term cooperative is used because pharmaceutical care is conducted in a multidisciplinary setting with health-care providers working together for the benefit of the patient. As indicated by the name, pharmaceutical care is about pharmaceuticals and not about pharmacists; it should not necessitate the involvement of a pharmacist per se. However, pharmacists often play an important role in the delivery of pharmaceutical care – as providers of patient-oriented clinical pharmacy services and/or as active participants in the improvement of organizational structures through which drug therapy is provided (62,63). Patient-oriented and ward-based pharmacist practices are often referred to as clinical pharmacy. The European Society of Clinical Pharmacists (ESCP) defines clinical pharmacy as "a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational use of medicinal products and devices" (64). It is a broad definition that includes promoting of appropriate prescribing, reducing the risk of medication errors, enhancing patients' adherence to prescribed medication (through drug counseling as well as ensuring that the patient has access to current medications) and aiming for cost-effective use of medications. Examples of clinical pharmacy practices are medication reconciliation, medication reviews, medication counseling to patients and bedside dispensing of medications at discharge.

Medication reconciliation

Medication reconciliation is "the process of comparing a patient's medication orders to all of the medications that the patient has been taking" (65). This process should be undertaken at transitions in care when new drugs are ordered or existing orders rewritten (65,66). On admission to hospital, a list of the patient's current medications is compiled. Information from the patient, from the drug list at the primary care center and from the computerized hospital medical record can be used. The compiled list is compared to the patient's current medication administration record (MAR) at the hospital. On discharge, the patient's MAR is compared to the prescribed/ordered discharge medications.

Since 2012, the Swedish National Board of Health and Welfare requires health-care providers to perform a medication reconciliation – along with a brief evaluation of the appropriateness of the prescribed medications – for all

patients aged 75 years and older and with five or more medications, at every transition in care and at least once annually (67). The physician is responsible for the performance of the medication reconciliation, but the process can be carried out by a pharmacist or a nurse.

Medication review

Medication review is a systematic evaluation of an individual patient's medications, in terms of indication, effect, safety and adherence to the treament regimen. The therapeutic efficacy of each drug, any unmet therapeutic needs and the progression of the conditions being treated are evaluated. Other issues, such as adherence to drug therapy, actual and potential adverse effects, drug interactions and the patient's understanding of the condition and its treatment are also considered. The overall aim of a medication review is to optimize the prescribing of medications as well as the use of prescribed medications (68,69). A medication review should be considered as an ongoing process rather than a separate intervention. Follow-up of the effects of the medication changes is therefore an important part of the review and is necessary for a successful outcome for the individual patient.

Drug counseling to patients

During hospital admission, several changes in the patients' drug treatment are often made. The changes may be accompanied by inadequate discharge patient education and follow-up (70) and there is a high risk of ADEs to occur after hospitalization (71,72). Schnipper et al. (73) conducted a RCT in which patients in the intervention group received pharmacist counseling at discharge and a follow-up phone call a few days later. Thirty days after discharge, preventable ADEs were found in 11% of the control group patients and 1% of the intervention group patients.

Multi-dose dispensed drugs and bedside dispensing

The multi-dose dispensing (MDD) system used in Sweden is a computer-based, automated medication dispensing system. The patient receives the dose of all the medications to be taken at a specific time, packaged in a sachet labeled with the contents, patient data and the time and date the drugs should be taken. MDD is very common in Sweden, with around 180 000 users (out of a population of 9 million inhabitants) (74). The purpose of the MDD system is to enhance patient safety, particularly among outpatients taking many medications. Other potential benefits are increased patient adherence to drug therapy, saving of nurses' working time in primary health care (by facilitating medication administration), and decreased costs (by reducing waste of unused medications) (75). A recently conducted Swedish

overview concluded that the MDD system increases adherence to drug treatment regimens, but that the effect on patient safety is ambiguous (76). A few studies, mentioned in the overview, found that the prescribing of potentially inappropriate drugs was more frequent in patients enrolled in the MDD system (77,78). Other studies focused on the occurrence of medication errors in people receiving MDD. One study found that people enrolled in the MDD system had fewer discrepancies between the drug list at the primary care center and the nursing home than the people who did not have MDD drugs (79), while other studies found higher frequency of medication errors at discharge from hospital in patients with MDD drugs than in those without (23,80).

The hospital pharmacy at Uppsala University Hospital previously offered an extended distribution service to MDD patients being discharged, in order to increase medication-associated safety. As part of this service, a pharmacist visited the ward every morning to collect MDD orders for discharge patients. The orders were checked for drug-drug interactions, duplicate prescriptions and irrational dosages and doses by the pharmacist, but the medicines were not reconciled with the MAR. The packaged doses were then delivered to the patient at the ward later on the same day before discharge.

Measuring the effects of clinical pharmacist intervention

The value of adding the competence of a pharmacist to the health-care team and the role of the pharmacist in the team, have been widely discussed and studied (81–85). Many studies have focused on the quality of prescribing, showing that the intervention of a clinical pharmacist resulted in an improvement (86–90). Meta-analyses and systematic reviews of the effects of pharmacist interventions on clinical outcomes have shown discordant results. Kaboli et al. (83) determined that the addition of clinical pharmacists improved the quality, safety and efficiency of care, and Koshman et al. (84) that pharmacist care reduced the risk of hospitalizations in patients with heart failure. Conversely, Holland et al. (81) concluded that pharmacist-led medication reviews cannot be assumed to reduce hospital admissions and mortality rates in older people.

Systematic reviews of the advantages and disadvantages of medication reviews and other pharmaceutical services are often complicated by the lack of a general definition of the services and the wide variation in the interpretation of the concepts that are being compared (81,83–85,91). In some studies, the clinical pharmacist worked as a consultant and communicated with the prescriber only via written recommendations (87,92), while in other studies the pharmacist was an integrated part of the multi-professional health-care team and had direct contact with other health-care providers (5,86,90,93,94). In some studies, the pharmacist had no access to patient

medical records, and this substantially decreased their capacity to perform a thorough medication review (94–96). The studies also differed widely in the extent of interaction between the pharmacist and the patients (81).

Outcome assessment

Mortality

A number of studies have used mortality as a measure of clinical outcome, but few have shown an impact (81,83,84). This is not surprising. Mortality is multifactorial; because it can occur for a number of reasons, the causative agent behind any change in mortality is very difficult to demonstrate.

Morbidity

Morbidity is also often chosen as a measure of outcome; there are also a number of proxies for morbidity that can be and have been used. Examples are the degree of health-care utilization (in primary, secondary or tertiary care scenarios), the rate of ADEs, the severity of the illness or the perceived level of health, etc.

The underlying theory behind the utilization of health care as an outcome measure is that a readmission or a revisit to hospital reflects a change in health status. This measure has the advantage of being objective.

Drug-related problems (DRPs), or ADEs, are often used as measures for assessment of drug-related morbidity and the quality of prescribing. Because of their strong links to drug use, the presence of ADEs is often a suitable choice for measuring the effects of clinical pharmacy interventions. Methods for identifying preventable ADEs (7) and determining causality (97,98) are available for standardizing the assessment. However, these are still subjective measures which to some degree depend on the evaluator.

There are also standardized methods for grading the level of morbidity, so-called severity-of-illness scales (99) and patient-perceived level-of-health scales. An example of the latter is the SF-36, which is the most commonly used assessment of health-related quality of life (HRQoL). It is a multipurpose, short-form health survey with 36 questions which yields a profile of both physical and mental health (100). EQ-5D is another example of a scale that grades HRQoL (101).

Financial measures

All the above outcome measures are clinical, i.e. they measure the quality of care in one way or another. Some of these measures can also be translated into financial measures; the level of health-care utilization is, for instance, a measure of both clinical and financial outcomes. Other examples of financial outcome measures for pharmacist interventions are quality-adjusted life years (QALYs) (102), and the cost of a patient's prescribed drugs.

Process assessment

As pharmaceutical care involves several different processes, different measures should be chosen depending on the process to be evaluated. The rate of identified prescribing errors is often used to measure the effects of medication reconciliation on admission or at discharge (23,26,27). The effects of medication reviews are often measured in terms of the quality, or the appropriateness, of prescribing. The quality of prescribing is a multidimensional and complex phenomenon and, accordingly, evaluating and measuring it is a complicated task. A systematic approach can be used to assess the appropriateness of prescribing and several instruments have been developed for this purpose. All of them determine quality in a quantitative manner. The tools can be used prospectively as guides to appropriate prescribing or retrospectively to evaluate the quality of prescribing (45,103,104), and they can be either explicit or implicit.

Explicit instruments

Explicit tools are criterion-based and can be used as checklists. They have a drug-disease focus and consensus opinions from experts in the field or literature reviews have often been used to produce the content of these lists. These tools are generally easy to use, they are not dependent on the experience and knowledge of the user and they can be applied to large quantities of patient data. However, they are often criticized for not accounting for the presence of co-morbidities or patient preferences. Furthermore, the inclusion of some drugs/criteria on the lists is subject to controversy, the tools need continuous updating and they are not readily transferable between countries (17,20,105,106). The most well known and well studied explicit tool is the Beers criteria tool (104,107–109), which is used as a checklist for medications that should generally be avoided in older people. Other explicit tools include the Inappropriate Prescribing for Elderly People (IPET) tool (110) and the Screening Tool of Older Persons' Prescriptions (STOPP) (103,111,112). These instruments all focus on misprescribing and overprescribing, i.e. naming the drugs and the doses that should be avoided and when they should be avoided. Sets of explicit criteria that also account for underprescribing have been developed and validated: the Assessing Care of the Vulnerable Elderly (ACOVE) tool (113) and the Screening Tool to Alert doctors to Right Treatment (START) (103,112,114). The START criteria include a number of conditions and indicate which drugs should be prescribed.

Implicit instruments

Implicit tools are judgment-based and focus on the individual patient. They are more sensitive than explicit tools, but are also more time-consuming to use and require access to extensive information about the patients (medical

history, drug history, organ function, laboratory data, functional status, etc.). Further, since the results are based on informed judgment, there is always a chance that the user's knowledge and attitudes will influence the results and therefore there is a risk for reduced reliability. The Medication Appropriateness Index (MAI) (115,116) is the only available validated implicit instrument for assessing the appropriateness of prescribing.

As discussed previously, process measures need to be linked to outcome measures in order to be valid. However, the evidence that available process measures for appropriateness of prescribing are associated with clinical outcomes is equivocal and contradictory (20,117). Some studies found a positive relationship between inappropriate prescribing according to the Beers criteria and increased mortality, use of health-care services and ADEs (47,118,119), whereas others reported mixed or negative results (120,121). The prescribing of inappropriate medications, as measured with STOPP and START, is linked to serious avoidable ADEs (122) but, when tested in an RCT, an intervention aiming to reduce STOPP and START scores was not reflected in reduced mortality, falls or health-care consumption (89). Increased score in the MAI has in a few studies been associated with an increased risk of ADEs (123,124).

In this context, it should be emphasized that the tools for assessment of inappropriate prescribing have been developed through literature search, expert opinion and consensus validation. In other words, none of them are designed to prospectively reduce readmissions.

Other weaknesses of the available process measures are that they do not adjust for the patient's co-morbidities and that they do not take the patient's views and wishes into account (20,105,125). Several studies have also shown that the most commonly used measures lack agreement in what they identify as inappropriate prescribing (111,126,127). This suggests that measures of one aspect of prescribing quality may not be representative of the overall quality of a patient's prescribed drugs (126) and is a reminder that the quality of prescribing should be evaluated from multiple perspectives.

The 80+ study

In 2005 to 2006, we conducted an RCT at Uppsala University Hospital that assessed the effects of adding a clinical pharmacist to the health-care team on clinical outcomes for older patients (5). Four hundred patients, aged 80 years and older and admitted to the acute internal medicine wards were included and randomized to the intervention or control groups. Intervention consisted of a comprehensive clinical pharmacy service that was added to standard hospital care.

The main elements of the clinical pharmacist service were: medication reconciliation on admission and at discharge, a thorough medication review and patient education during the hospital admission process, communication of the treatment plan to primary care representatives at discharge, and a follow-up phone call to the patients after discharge.

For the medication reconciliation on admission, various information sources were used – including interviews with the patients, the drug lists from the primary care centers and the computerized hospital medical records. Identified discrepancies and prescription errors were recorded and reported orally to the physician who then corrected them. An interview was undertaken with all the patients (or the next of kin or caregiver), including questions about adherence to and understanding of the drug therapy, perceived problems and ADRs, and use of over-the-counter drugs.

The medication review was based on information obtained from the patient's medical records and laboratory findings, as well as information from the patient interview. Relevant DRPs were identified and the pharmacists' suggested actions were recorded and discussed in the health-care team during the daily ward rounds. Changes to drug therapy were made by the physician. The patient was monitored during the hospital stay, and was counseled about their drug therapy.

As a complement to the physician's discharge information, the pharmacist provided drug counseling to the patients at discharge. A discharge letter, summarizing all drug therapy changes made during the hospital stay as well as the rationale for the changes, therapeutic goals and monitoring needs, was written by the pharmacist. DRPs not dealt with during the hospital stay but still of importance were also listed in this letter. After approval of its content by the physician at the ward, the letter was faxed to the patient's primary care physician. For patients enrolled in the MDD system, the MDD orders were also reconciled with the MAR at discharge.

Two months after discharge, the pharmacists contacted the patient (or the next of kin or caregiver if the patient was not able to communicate coherently) by telephone. Adequate management of the medications at home was ensured, and the patient's drug list at that point of time was also recorded. We wished to measure the effect of the discharge letter, and the time chosen (two months after discharge) was considered to be long enough for the patient to have had time to visit the general practitioner after discharge but still close enough to the index admission to be relevant.

The patients were followed for 12 months after the index hospital admission and the number of revisits to hospital and deaths were recorded. The primary outcome measure was the frequency of hospital visits (emergency department visits and readmissions [in total and drug-related]) during the follow-up period; the secondary outcome measure was the cost of health care.

Of the 400 patients included in the RCT, 27 died during the index admission and five wished to be excluded (Figure 1). The remaining 368 patients were eligible for further analyses. For the intervention group, there was a 47% reduction in visits to the emergency department and a 16% reduction in total revisits to hospital versus the control group. Drug-related readmissions were reduced by 80%. The intervention was also cost-effective.

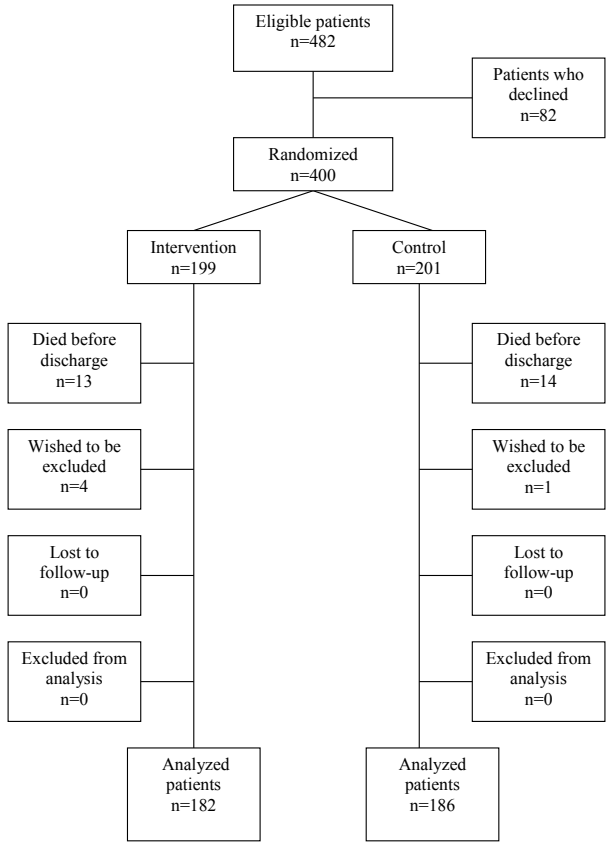

Figure 1. Patient flow diagram

Subgroup analyses

The effects of adding a clinical pharmacist service to the health-care team on process as well as outcome measures have been well studied. However, differences in the effects of clinical pharmacist intervention on clinical outcomes between different subgroups of patients have rarely been analyzed.

The main aim of a subgroup analysis is to confirm the consistency of the treatment effect or to identify differences among different categories of pa-

tients (128). If differences in effect are found, the patients who benefit from the treatment can – with good reason – be provided with it. Subgroup analysis for an intervention, such as that from a clinical pharmacist, may also provide additional understanding of the intervention itself and its focus.

Identifying areas for quality improvement

A high proportion of ADEs are avoidable, and over 50% of drug-related hospital admissions have been deemed preventable (15,129,130). Thus, it is imperative to identify stages in the medication process and/or specific groups of patients where there is a high risk of ADEs occurring, to measure the quality of the process, and, if needed, to develop appropriate preventive interventions. High-risk medication processes or groups of patients may for instance be identified from reports of medication errors or suboptimal prescribing.

A different strategy for identifying patients at high risk of an unwanted outcome is through risk-prediction models. Here, a specific outcome, e.g. readmissions to hospital, is selected and modeled and patient characteristics that are associated with a higher risk of that outcome can be determined.

Identifying high-risk areas and measuring quality of care

Medication error reports can help identifying areas with suboptimal quality. To attain data on the existence and magnitude of the problem, a quality assessment – with suitable quality measures – is needed. For example, if substandard quality in the medication discharge process is indicated, an appropriate quality measure would be the frequency of discharge errors. This measure can also be used in evaluation of the effects of efforts to improve quality.

In other situations, certain medications that are considered inappropriate or hazardous for a group of people are selected (using available evidence and the literature). The number of dispensed prescriptions of these medications can then be used as a quality measure. An example of this is the national initiative of the Swedish Association of Local Authorities and Regions (SALAR) to reduce the prescribing of certain inappropriate drugs (drugs with anticholinergic effects, long-acting benzodiazepines, tramadol and propiomazine), oral nonsteroidal anti-inflammatory drugs (NSAIDs) or neuroleptics for people aged 75 years and older. Economic reimbursement is used as incentive to reduce the prescribing (131).

It should be noted that, in both examples, process measures are used as a measure of quality. As long as a link to outcome measures has not been established, it is difficult to evaluate their clinical and financial importance to patients and society.

Identifying high-risk patients

In recent years, a substantial number of tools for predicting the risk of revisits to hospital have been suggested (132–139). One reason for the interest in these models is that they can be used to help target the delivery of transitional care interventions by identifying high-risk patients. Since these interventions are often resource-intensive, prioritization can be cost-effective. The focus on reducing readmissions can be explained by the use of unplanned 30-day readmission and mortality rates as a national quality measure for hospitals in the U.S. (140). This information is publicly reported, and hospitals with excess readmissions, have their payments from the Centers for Medicare & Medicaid Services reduced (141).

A wide range of variables have been tested for predictive ability in the prediction models, including patient sociodemographic factors, medical comorbidity data, illness severity, prior use of medical services, overall patient functional status and social determinants of health. These prediction models are also based on studies conducted in a variety of populations and settings and with different designs. Different outcome measures (e.g. all hospital admissions or only acute admissions, readmissions or emergency department visits, or mortality), different follow-up times, and different candidate variables have been included. This has resulted in a wide range of data on risk factors for rehospitalisation and mortality, but the results are difficult to compare and generalize. Besides, most models have a predictive ability that is only modestly better than chance (142,143).

The patients' prescribed medications have rarely been evaluated as potential predictors of readmission in prediction models. This is surprising, since drugs, especially in older patients, are a fundamental component of care.

Aims

The overall aim of this thesis was to study possible improvements in the quality and safety of drug use in hospitalized older people, by assessing the effects of clinical pharmacist interventions and identifying patients at risk of rehospitalization and mortality.

The specific aims were:

- To investigate the effects of pharmacist interventions on appropriateness of prescribing, assessed by STOPP, START and MAI, in older patients and to explore the relationship between these results and hospital care utilization (Paper I);

- To explore whether pharmacist intervention is equally effective in preventing subsequent emergency department visits for patients receiving few or many prescribed drugs, and in those with different levels of inappropriate prescribing (as measured with STOPP and START) on admission, and to describe the impact of the pharmacist intervention on the quality of prescribing for patients in the different subgroups (Paper II);

- To construct a score for estimating the risk of revisiting the hospital and of mortality in older people and to compare the discriminatory ability of this score with the following measures for appropriateness of prescribing: STOPP, START, MAI and the SALAR drug list (Paper III);

- To survey the frequency, type and occurrence of prescribing and transcribing errors for patients receiving MDD drugs at discharge from hospital and to assess the severity of these errors (Paper IV).

Methods

Population

Papers I, II and III were based on patient and outcome data from the previously conducted RCT (the "80+ study" (5)), in which the impact of a clinical pharmacist intervention on clinical outcomes for older patients was assessed. Data from 368 patients from this study were eligible for further analysis (Table 1). The patients were included between September 2005 and June 2006 and were followed for 12 months after the index hospital admission. The number of revisits to hospital and the number of deaths during this period were recorded.

Table 1. *Baseline characteristics 80+ population*

	Intervention Group (n=182)	**Control Group (n=186)**
Female, no (%)	105 (57.7)	111 (59.7)
Age, years, mean (SD)	86.4 (4.2)	87.1 (4.1)
Body weight, kg, mean (SD)		
Female	61.9 (13.8)	60.7 (13.0)
Male	70.6 (12.1)	72.1 (12.9)
Creatinine clearance, ml/min/1.73 m^2, mean (SD)	40.6 (19.9)	39.9 (17.1)
Sodium level, mEq/L	137.7 (4.8)	137.4 (4.7)
Potassium level, mEq/L	4.0 (0.6)	4.1 (0.7)
Daily prescription medications, mean (SD)	8.7 (4.5)	7.3 (4.4)
Social support, no (%)		
Spouse/partner	54 (29.7)	50 (26.9)
Residential home	33 (18.1)	34 (18.3)
None	95 (52.2)	102 (54.8)
Duration of admission (index), days, mean (SD)	11.9 (13.0)	10.5 (9.3)
Heart failure, no (%)	64 (35.2)	52 (28.0)
Diabetes, no (%)	48 (26.4)	39 (21.0)
Pulmonary disease, no (%)	23 (12.6)	21 (11.3)
Arrhythmia, no (%)	63 (34.6)	62 (33.3)
Malignant disease (past or present), no (%)	28 (15.4)	26 (14.0)
Coronary artery disease, no (%)	61 (33.5)	53 (28.5)
Cerebral vascular lesion (past), no (%)	38 (20.9)	19 (10.2)
Myocardial infarction (past), no (%)	45 (24.7)	42 (22.6)
Hypertension, no (%)	77 (42.3)	70 (37.6)
Dementia, no (%)	20 (11.0)	27 (14.5)

In paper IV, patients enrolled in the MDD system who were discharged from Uppsala University Hospital between February and April 2010 were studied. Patients who were discharged from any of the hospital wards (n=20) that

were using an extended pharmacist discharge service for patients receiving MDD packs, were included.

Assessment of appropriateness of prescribing (Paper I)

The effect of the pharmacists' intervention in the RCT on the quality of prescribing was retrospectively evaluated using three validated tools for measuring the appropriateness of prescribing – STOPP, START and MAI. The tools were applied to the patients' drug lists in the MAR twice: on admission and at discharge. Data from the electronic medical records were used. The assessment was blinded and was conducted by an experienced clinical pharmacist. The instructions for the instruments were followed carefully. A summed score for each tool was calculated for each patient.

The association between the tools and the clinical outcomes was also explored. For this, STOPP, START and MAI scores at discharge were used and the primary clinical outcomes were the number of readmissions and the number of total revisits to hospital during the 12-month follow-up period. The secondary outcome was the number of drug-related readmissions during the same period. In these analyses, data from the intervention and control groups were analyzed together in order to increase the power of the assessment.

STOPP and START

STOPP encompasses 65 instances of potentially inappropriate prescribing in older people, including drug-disease interactions, irrational prescribing and drugs that are known to increase risks in older people. The criteria identify Potentially Inappropriate Medications (PIMs) (103,111). START consists of 22 indicators of irrational omission of drug therapy that would be beneficial for the patient. The criteria detect Potential Prescription Omissions (PPOs) (103,114).

Each PIM and PPO generates one point, i.e. the scoring is not weighted. The sum of the STOPP and START scores for each patient is a measure of the level of inappropriate prescribing; a higher score indicating a higher level of inappropriate prescribing. The STOPP and START tools were developed to complement each other, in order to cover aspects of over-, mis- and under-prescribing. However, the creators of the instruments have not used or analyzed the combined scores.

The tools are arranged according to physiological systems for ease of use. They were developed through literature search and are based on well-established instances of potentially inappropriate prescribing for older people. The draft criteria went through a Delphi consensus process for validation, with experts in geriatric pharmacotherapy on the panel (103,112).

MAI

The MAI consists of 10 questions, or criteria, which evaluate different aspects of inappropriate prescribing: indication, effectiveness, dosage, correct and practical directions, drug-drug interactions, drug-disease interactions, no unnecessary duplications, acceptable duration of therapy and cost-effectiveness (115,116). The 10 questions are applied to every prescribed drug, and once an answer to any of the questions indicates inappropriateness, a score is assigned. The questions have weighted scores; for example, "lack of effectiveness" scores three points and a drug-drug or drug-disease interaction scores two points. The scores are then summed, either for each drug to provide a "drug score", or for each patient to provide a "patient score". A higher summed score indicates inappropriate prescribing.

The content and weighting of the MAI scores has been validated. Because it is a judgment-based tool, its inter- and intra-observer agreement have been tested in several studies, some of which showed satisfactory reliability (115,116,144), while some showed only moderate reliability and proposed potentially useful improvements (145–147). It is emphasized that the instructions accompanying the instruments should be followed carefully.

Subgroup analyses (Paper II)

The patients were divided into subgroups according to the number of prescribed drugs on admission to hospital. The prescription of <5 and ≥5 drugs was used to determine entry to the subgroups. The rationale for choosing this cut-off point was that the administration of ≥5 drugs is a common definition of polypharmacy (19). Since these subgroups were not well balanced in size, a sensitivity analysis was conducted, using the median number of drugs (≥8) as the cut-off point. The patients were also divided into subgroups based on the quality of prescribing, as measured with STOPP and START. In these analyses, the cut-off points used were based on the median scores (≥2 for STOPP and ≥1 for START), where a higher score indicated a higher level of inappropriate prescribing.

The outcome variable for both analyses was the number of revisits to the emergency department over the 12 months after the index hospital admission. This endpoint was chosen because this was the one on which the RCT pharmacist intervention had the greatest impact.

The changes in the STOPP and START scores from admission to discharge were used to describe the effects of the pharmacist intervention on the quality of prescribing for the patients in the <5 and ≥5 drugs subgroups. The number, type and acceptance rate of the pharmacists' recommendations were also used to describe the effect of the medication review. The types of

recommendations were: discontinuation of drug, initiation of drug therapy, changes to the drug/dosage/route, and medication counseling to the patient.

Development of a score for risk prediction (Paper III)

A score for estimating the risk of rehospitalization and mortality was constructed by 1) selecting the most relevant risk factors for the chosen outcome and 2) assigning a point score for each risk factor. A composite variable (combining the event of a revisit to hospital and of death during the 12-month follow-up period) was chosen as the endpoint for the analysis. The outcome variable in the regression analysis was the time to the endpoint from the day of discharge from the index admission.

Candidate patient variables were selected based on clinical judgment and the statistical properties of the variables. The clinical variables were: gender, age, renal function, level of social support and medical history (heart failure, diabetes mellitus, pulmonary disease (asthma or chronic obstructive pulmonary disease [COPD]), arrhythmia, malignant disease (past or present), coronary artery disease, cerebral vascular lesion (past), myocardial infarct (past), hypertension and dementia). The drug-disease variables were the STOPP and START criteria, and the drug variables were the patient's prescribed medications. The medications were categorized according to the ATC classification system and to similar effects and risks in older people, or according to the SALAR drug list (131).

To detect potential overlapping variables, a principal component analysis (PCA) was conducted and variables were excluded accordingly. The remaining candidate variables were subject to regression analysis. The variables extracted from the regression analysis made up the components of the new point score system for risk estimation, the 80+ score. The risk associated with each point total was calculated, and the goodness-of-fit and the discriminatory ability of the score were assessed. The score was internally validated.

The total STOPP, START and MAI scores and the total number of prescribed SALAR drugs were calculated for each patient. Their discriminatory abilities were assessed, and compared with that of the 80+ score.

The whole dataset (both intervention and control groups) was used in the development of the new score and the effect of the pharmacist intervention was not adjusted for in the regression analyses. As a sensitivity analysis, the discriminatory ability of the 80+ score was assessed for the control group only.

Survey of discharge errors in patients with MDD (Paper IV)

This study focused on technical medication errors occurring at discharge from hospital. Two pharmacy students at master degree level collected the data under the supervision of two clinical pharmacists.

The data collectors visited the wards every morning prior to the clinical pharmacist visit. For the patients who were about to be discharged with MDD drugs, the data collectors reconciled the drugs on the patients' MDD order sheets with the drug list in the MAR. Identified discrepancies were recorded as a note that was left for the clinical pharmacist. The clinical pharmacist notified the physician, and the physician had the opportunity to correct the discrepancies that were unintentional. The clinical pharmacist then sent the MDD orders to the pharmacy for dispensing. The pharmacist recorded whether the discrepancy was unintentional or not and whether the discrepancy was corrected, and this was communicated to the data collectors.

Unintentional discrepancies were classified as errors and were subject to further analysis. The errors were categorized into different types: faulty omission of drug, faulty prescribing of drug, wrong drug, wrong dose/formulation/dosage regimen, wrong dosage time and double prescribing.

A severity assessment of the errors was also conducted, using an approach similar to the method for safety assessment developed by the Veteran's Affairs group (148). The errors were classified into one of four severity categories: minor, moderate, major or catastrophic, based on the errors' potential ADEs and consequences of the errors. The severity assessment was performed by the data collectors together with two experienced clinical pharmacists, and was reviewed by an experienced physician with a specialization in internal medicine.

The associations between occurrence of errors and ward category, type of order (electronic or paper) and the patients' age, gender and number of medications were assessed. The associations between error correction and severity of errors, ward category, type of order and the patients' age, gender and number of medications were also assessed.

Statistical analyses

Paper I

To assess the effects of the pharmacist intervention, the intervention and control group patients were compared with respect to changes in STOPP,

START and MAI scores from admission to discharge. Rank analysis of covariance was used, with score at admission as a covariate.

Negative binomial models were used to analyze the relationship between the tools and the clinical outcome, with the logarithm of the time spent outside the hospital as an offset. Both unadjusted models and models adjusted for baseline covariates (age, gender, weight, social support and medical history) were developed.

Paper II

Poisson regression models were used for the subgroup analyses of the number of emergency department visits. Group (intervention or control), subgroup factor and the interaction between group and subgroup factor were used as independent variables. The logarithm of the time spent outside the hospital was used as offset. Changes in STOPP and START from admission to discharge were analyzed, using rank analysis of covariance with group (intervention or control) as a factor and scores on admission as covariate.

Paper III

A backward stepwise Cox regression elimination procedure was used to select the candidate variables with statistically significant associations with the outcome. The p-values for inclusion and exclusion were required to be less than 0.01.

The variables extracted from the regression analysis made up the components of the point score system. The point score system was developed and the risk associated with each point was calculated by following the Framingham Heart Study approach (149,150), see Paper III.

The goodness-of-fit of the 80+ score was assessed by plotting predicted vs observed risk and using the Grønnesby-Borgan test (151). The discriminatory abilities of the 80+ score, the STOPP, START and MAI scores and the SALAR drug list were assessed using C-statistics. C-statistics, which can range from 0.5 (no discrimination) to 1 (perfect discrimination), provide the ratio of the probability of predicting an event in patients with an event to that in patients without an event. The score was internally validated using an enhanced bootstrap with 1000 iterations.

Paper IV

A multiple logistic regression was performed, with occurrence of one or more medication errors as outcome. Ward category, type of order and the patients' age, gender and number of medications were included as explanatory variables. Error correction for patients with at least one medication error

was also modeled as a hierarchical multiple logistic regression, using the same explanatory variables plus the severity of errors.

Ethical considerations

Each participant in the RCT gave written informed consent and the study protocol was approved by the Uppsala Regional Ethics Committee. When the study presented in paper IV was evaluated by the Uppsala Regional Ethics Committee, no formal approval was necessary and the Committee had no objections. All patient data were de-identified and coded. Data were stored in locked cabinets and password-protected computers. None of the results can be traced back to an individual patient. Inclusion in the studies was considered to be associated with very low risk of harm.

Summary of findings

Paper I

In the first paper, the effects of the clinical pharmacist intervention on the quality of prescribing were demonstrated. The links between the process measures used for assessing the quality of prescribing – STOPP, START and MAI – and clinical outcomes were also explored.

The STOPP, START and MAI scores improved during the hospital admission for the intervention group, while the control group had higher or unchanged scores at discharge compared to admission. The change from admission to discharge differed significantly between intervention and control groups (Table 2).

***Table 2**. Effects of pharmacist intervention on quality of prescribing. Scores on admission and at discharge and change from admission*

Instrument	Intervention group (n=182)			Control group (n=186)			p-value[a]
	Admission	**Discharge**	**Change[b]**	**Admission**	**Discharge**	**Change[b]**	
STOPP[c],mean (SD)	1.4 (1.5)	0.9 (1.0)	-0.5 (1.0)	1.5 (1.5)	1.7 (1.5)	0.2 (0.7)	<0.001
START[c],mean (SD)	0.4 (0.7)	0.1 (0.3)	-0.3 (0.6)	0.4 (0.7)	0.5 (0.7)	0 (0.4)	<0.001
MAI[d], mean (SD)	8.5 (6.8)	5.0 (4.2)	-3.5 (5.1)	8.7 (7.3)	10.0 (7.3)	1.3 (3.1)	<0.001

SD, Standard deviation; a) p-values from rank analysis of covariance for the effect of group status (Intervention or Control) on change from admission, adjusted for the score on admission; b) Change from admission calculated as Score at discharge minus Score on admission; c) Number of scores per patient; d) Summed MAI score per patient

None of the scores for appropriateness of prescribing were associated with the number of readmissions or the number of total revisits to hospital. However, higher scores for MAI and STOPP were linked to a significantly higher occurrence of drug-related readmissions (Table 3).

Table 3. *Associations between STOPP, START and MAI scores and the number of total visits to hospital, number of readmissions and number of drug-related readmissions*

Model[a]	Number of total revisits to hospital RR (95% CI)	Number of readmissions RR (95% CI)	Number of drug-related readmissions RR (95% CI)
STOPP (adjusted)	1.05 (0.97-1.15), p=0.23	1.06 (0.97-1.16), p=0.20	1.34 (1.05-1.70), p<0.05
START (adjusted)	1.09 (0.90-1.32), p=0.39	1.16 (0.95-1.42), p=0.14	1.49 (0.91-2.45), p=0.11
MAI (adjusted)	1.02 (1.00-1.03), p=0.058	1.02 (1.00-1.04), p=0.060	1.09 (1.04-1.14), p<0.001

a) Negative binomial regressions. Adjusted models include age, gender, weight, social support and medical history.
RR, Rate ratio; CI, Confidence interval.

Paper II

The second paper presented results from a subgroup analysis, exploring whether the clinical pharmacist intervention was equally effective in preventing revisits to the emergency department in patients with many or few medications on admission, and in patients with high and low levels of inappropriate prescribing.

The patients receiving fewer (<5) drugs on admission benefited more from the intervention, with respect to the number of emergency department visits, than the patients receiving a higher number of drugs. The effect of intervention on the number of emergency department visits did not differ between the patients with high and low levels of inappropriate prescribing (Table 4). The sensitivity analysis confirmed our findings that the intervention was more effective for patients receiving a lower number of drugs (see Paper II).

During the hospital admission process, the START scores improved for the intervention group, across subgroups. The STOPP score improved for the intervention ≥5 drugs subgroup but was unchanged for the <5 drugs subgroup (Table 5).

***Table 4**. Effects of pharmacist intervention on emergency department (ED) visits. Subgroup analyses for the number of ED visits*

	Intervention group (n=186)				Control group (n=182)					
	Patients (n)	**Person years (n)**	**ED Visits (n)**	**Rate**	**Patients (n)**	**Person years (n)**	**ED Visits (n)**	**Rate**	**RR (95% CI)[a]**	**P-value interaction[a]**
Overall effect	182	140.9	49	0.35	186	141.0	93	0.66	0.53 (0.37-0.75)	-
Number of drugs										0.0175
<5	37	31.9	6	0.19	53	45.7	39	0.85	0.22 (0.09-0.52)	
≥5	145	109.0	43	0.39	133	95.2	54	0.57	0.70 (0.47-1.04)	
STOPP										0.9051
<2	109	86.7	31	0.36	110	85.5	59	0.69	0.52 (0.34-0.80)	
≥2	73	54.2	18	0.33	76	53.4	34	0.64	0.54 (0.31-0.96)	
START										0.2020
<1	133	102.4	43	0.42	126	95.9	70	0.73	0.58 (0.39-0.84)	
≥1	49	38.5	6	0.16	60	45.0	23	0.51	0.31 (0.12-0.75)	

a) Rate ratios, 95% confidence intervals and p-values from Poisson regression models with group, subgroup factor and their interaction as independent variables.

Table 5. *Effects of pharmacist intervention. Changes in STOPP and START scores from admission to discharge for patients receiving fewer than five drugs and five or more drugs.*

	STOPP. Change from admission[a]		
	Intervention group (n=182)	**Control group (n=186)**	**p-value[b]**
< 5 drugs (n=37+53), mean (SD)	0.1 (0.6)	0.3 (0.6)	0.0089
≥ 5 drugs (n=145+133), mean (SD)	-0.7 (1.03)	0.2 (0.8)	0.0001
All patients (n=182+186), mean (SD)	-0.5 (1.01)	0.2 (0.7)	
	START. Change from admission[a]		
	Intervention group (n=182)	**Control group (n=186)**	**p-value[b]**
< 5 drugs (n=37+53), mean (SD)	-0.4 (0.9)	0.04 (0.3)	0.0002
≥ 5 drugs (n=145+133), mean (SD)	-0.3 (0.5)	0.04 (0.4)	<0.0001
All patients (n=182+186), mean (SD)	-0.3 (0.6)	0.04 (0.4)	

SD, Standard deviation.

a) Change from admission calculated as STOPP/START Score at discharge minus STOPP/START Score on admission; b) p-values from rank analysis of covariance for the effect of group (Intervention or Control) on change from admission, adjusted for the score on admission

A recommendation was made for 65% of the patients in the <5 drugs subgroup (mean number of suggestions per patient 2.0 (SD =1.2)). The acceptance rate for these suggestions by the physician was 86%, and the most common recommendation was the initiation of new drug therapy. A recommendation was made for 90% of the patients in the ≥5 drugs subgroup (mean number of suggestions per patient 3.2 (SD=1.7)). The acceptance rate was 73%, and the most frequent recommendation was discontinuation of a current drug therapy.

Paper III

Paper III described the selection of variables associated with an increased risk of a revisit to hospital or mortality in the studied population, and the construction of a score for risk-estimation. It also assessed the discriminatory ability of the score, and compared this with the discriminatory ability of tools for measuring the appropriateness of prescribing.

Of the 78 candidate variables (14 clinical, 14 drug-disease and 50 drug variables), three were excluded after the PCA. The remaining 75 variables were entered into the Cox regression elimination model. This analysis resulted in seven statistically significant variables with an individual association with the outcome (Table 6). Impaired renal function, pulmonary disease, malignant disease (past or present), living in nursing home, being prescribed

an opioid, or being prescribed a drug for peptic ulcer or gastroesophageal reflux disease (GERD) were associated with an increased risk, while being prescribed an antidepressant drug (tricyclic antidepressants [TCAs] not included) was linked to a lower risk of the outcome.

***Table 6**. 80+ score variables associated with risk of re-entry to hospital or mortality; statistical information.*

	Regression coefficient (SE)	p-value	HR	95% CI for HR
Creatinine clearance (ml/min/1.73 m^2)	-0.012 (0.004)	0.001	0.988	0.981-0.995
Social support (living in nursing home vs living alone or with spouse)	0.481 (0.162)	0.003	1.617	1.176-2.224
Pulmonary disease[a] (vs not)	0.607 (0.177)	0.001	1.834	1.296-2.595
Malignant disease[b] (vs not)	0.506 (0.166)	0.002	1.659	1.198-2.297
Prescription of drug for peptic ulcer and GERD (vs not)	0.362 (0.135)	0.008	1.436	1.101-1.872
Prescription of opioid drug (vs not)	0.724 (0.157)	0.000	2.063	1.517-2.806
Prescription of non-TCA antidepressant drug (vs not)	-0.558 (0.170)	0.001	0.573	0.410-0.799

a) asthma or chronic obstructive pulmonary disease (COPD); b) past or present
SE=standard error, HR=hazard ratio, CI=confidence interval, GERD=gastroesophageal reflux disease, TCA=tricyclic antidepressant

These variables made up the components of the 80+ score. The point scores assigned for each category for each variable are presented in Table 7.

The point total is the sum of the scores for each patient. The estimated risk associated with each point total is shown in Table 8. A patient with a renal function of 40 ml/min, living in a nursing home and prescribed an opioid (and with "no" for the other variables), would thus have a point total of 2+1+2=5. This is translated as a risk of revisiting hospital or death of 89% during the 12 months after discharge from hospital.

***Table 7**. 80+ score variables associated with risk of re-entry to hospital or mortality; point scoring system*

***Table 8**. 80+ score variables associated with risk of re-entry to hospital or mortality; estimate of risk for each point total*

	Proportion of patients in each category	Point score
Creatinine clearance		
> 90 ml/min	0.014	0
60-89 ml/min	0.128	1
30-59 ml/min	0.552	2
< 30 ml/min	0.307	3
Social support		
Living alone or with spouse	0.818	0
Nursing home	0.182	1
Pulmonary disease[a]		
No	0.878	0
Yes	0.122	2
Malignant disease[b]		
No	0.834	0
Yes	0.166	1
Prescription of drug for peptic ulcer and GERD		
No	0.674	0
Yes	0.326	1
Prescription of opioid drug		
No	0.821	0
Yes	0.179	2
Prescription of non-TCA-antidepressant drug		
No	0.791	0
Yes	0.209	-2

Point total	Estimate of risk
-2	0.1594
-1	0.2207
0	0.3010
1	0.4021
2	0.5223
3	0.6539
4	0.7821
5	0.8879
6	0.9568
7	0.9890
8	0.9985
9	0.9999
10	>0.9999

a) asthma or chronic obstructive pulmonary disease (COPD); b) past or present
GERD=Gastroesophageal reflux disease, TCA=tricyclic antidepressants (TCA)

The Grønnesby-Borgan test indicated a good goodness-of-fit of the model (p=0.49). The 80+ score had an optimism-corrected C-statistic of 0.714. This means that a patient experiencing an event (i.e. rehospitalization or death) during the 12 months after a hospital admission has a 71% probability of being given a higher risk score than a patient not experiencing an event. The discriminatory abilities of the explicit measures for appropriateness of prescribing and for the SALAR drug list were only slightly better than chance, while MAI had a slightly higher discriminatory ability (Figure 2). When tested in the control group only, the 80+ score had a similar value (0.71) to that in the whole group.

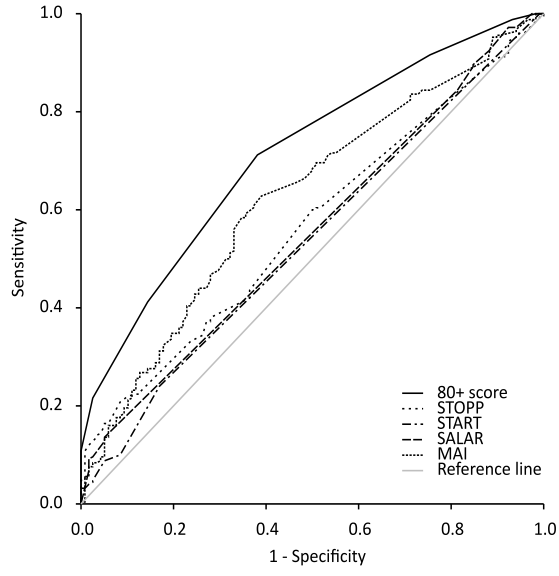

Figure 2. Area under the curve of sensitivity vs 1-specificity for rehospitalization or death. *C-statistics: 80+ score=0.72 (95% CI 0.66-0.77), 80+ score (optimism-corrected)=0.71, STOPP score=0.57 (95% CI 0.51-0.63), START score=0.54 (95% CI 0.48-0.60), SALAR drugs=0.55 (95% CI 0.49-0.62), MAI=0.63 (95% CI 0.57-0.69).*

Paper IV

The fourth study investigated the occurrence, type and severity of prescription errors on discharge from hospital for patients enrolled in an MDD system.

Of the 290 reviewed MDD orders, 72 (25%) contained at least one prescription error. There were a total of 120 discharge errors. The most common types of error were faulty omission of drug and wrong dose/frequency/formulation (44% and 31%, respectively, of the total number of errors).

Sixty-eight (57%) of the errors were considered to be of minor clinical importance and 49 (41%) of moderate importance. Three errors were assessed as being of major importance. In one case, the bisoprolol dose was halved during hospital admission but the change was not carried through to the MDD order. In another case, both bisoprolol and atenolol were present on the discharge order (bisoprolol had been substituted for atenolol during the hospital admission). In the third case, dalteparin sodium was discontinued during the hospital stay but remained on the MDD order.

The orders with at least one discharge error had a higher number of drugs compared to the orders without errors (14.6 ± 6.5 vs 13.0 ± 5.4, p=0.01). The

orders from the orthopedic wards had a higher frequency of orders with errors than the orders from other wards (orthopedics vs geriatrics odds ratio (OR) =3.97; orthopedics vs emergency medicine OR=2.91; orthopedics vs internal medicine OR=3.64; orthopedics vs surgery OR=2.97; p=0.003). There was no association between occurrence of error and type of order (electronic or paper), patient age or gender. The only factor that was linked to the proportion of error correction was the severity of errors.

Discussion

This thesis relates to how quality of care – in this case quality of drug use – in older hospitalized people can be measured and potentially improved. Questions are raised about how the effects of interventions that aim to improve quality of care can be quantified and captured. In particular, the link between process measures, often used for evaluating the effects of clinical pharmacist interventions, and clinical outcome measures is explored.

In the previously conducted RCT, the clinical pharmacist intervention reduced the number of revisits to hospital. In paper I, it was demonstrated that the intervention also improved the appropriateness of prescribing, according to the results of three tools used to measure this parameter: STOPP, START and MAI. Our next question was whether appropriateness of prescribing was linked with clinical outcome, i.e. whether low scores for STOPP, START and MAI at discharge were associated with fewer total hospital visits. The results showed that they were not.

One explanation for these results is that the tools used to measure appropriateness of prescribing only captured part of the effects of the intervention. The clinical pharmacist intervention consisted of a number of components, of which the medication review – which aimed to improve the appropriateness of prescribing – was only one. The intervention also aimed to increase patients' knowledge of and adherence to drug treatment regimens, and to reduce medication errors, and these were not accounted for by the tools used. Nor did the tools entirely capture the content of the medication review. For instance, some of the STOPP and START criteria differ from Swedish guidelines and established practice. In addition, the pharmacist medication review took co-morbidity as well as the patients' individual needs and wants into consideration, which the explicit measures do not.

With this, many of the limitations in the available measures of quantifying the processes associated with quality of prescribing are highlighted. A recent Cochrane review determined the effectiveness of interventions aiming to improve appropriateness of prescribing and their effects on clinical outcomes. The conclusion was that it is uncertain if these interventions, as assessed by tools for appropriate prescribing, resulted in clinical improvement (117).

The subgroup analysis (Paper II) showed that the effect of the pharmacist intervention on the number of emergency department visits did not differ between patients with low or high STOPP and START scores on admission.

In other words, the patients with a high level of inappropriate prescribing (as measured by these tools) did not benefit more from the intervention than the patients with low levels. Further, when the tools for appropriateness of prescribing were tested for their ability to predict the risk of rehospitalization or mortality (Paper III), it was shown that STOPP and START scores were unable to discriminate between patients at risk and those not at risk any better than chance. Thus, these results do not support the use of STOPP and START scores either in targeting clinical pharmacist interventions in a population of older patients acutely admitted to hospital, or in identification of patients with a high risk of adverse health outcomes.

The MAI had a somewhat better ability than the explicit tools for predicting the risk of rehospitalization and mortality (Paper III). This can be explained by the implicit nature of the instrument, resulting in a more individual – and hence potentially more clinically relevant – judgment of prescribing quality than is available from the explicit instruments. The strength of the MAI is its high validity, but its weakness is its moderate reliability. In addition, the MAI assessment is very time-consuming, which makes it less user-friendly.

Study I also analyzed the association between the scores and drug-related readmissions. The STOPP and MAI scores had a statistically significant positive association with drug-related readmissions. Drug-related rehospitalizations have previously been used as a clinical outcome measure for interventions aiming to improve the quality of prescribing (86,152). It seems logical to focus on drug-related readmissions when measuring the effect of these interventions. However, a disadvantage of this measure is its somewhat subjective nature, which makes it less robust. Although there are methods for identifying drug-related readmissions and assessing causality, there is a lack of a reliable procedure, and results from different studies are therefore difficult to compare.

That the subgroup of patients receiving a lower number of drugs benefited most from the clinical pharmacist intervention was somewhat surprising. Since the concomitant use of a large number of drugs is associated with an increased risk of ADEs, it is often assumed that patients receiving a larger number of drugs would benefit most from interventions aiming to improve the quality of drug use.

One plausible explanation for the results is that patients receiving a higher number of drugs supposedly have a greater co-morbidity burden, which may limit the potential effect of an intervention. The subgroup of patients who received a lower number of drugs lived in their own homes (alone or with a partner) to a higher degree than the patients receiving more drugs. Patients living in their own homes were most likely more engaged in their drug therapy, and thus more accepting of the parts of the pharmacist intervention that aimed to improve the patient knowledge and compliance to drug therapy,

than patients living in nursing homes. Arguably, these patients were also better able to communicate any drug therapy issues, which would improve the quality of the pharmacist intervention. A greater involvement of primary care nurses and/or caretakers would presumably have made the intervention more effective for the patients with more medications and a higher co-morbidity burden.

This subgroup analysis is applicable to a narrow group of patients (aged 80 years and older, admitted to an acute internal medicine ward) and to a specific, comprehensive clinical pharmacist intervention. However, the results suggest that patients with fewer drugs should not be automatically dismissed when prioritizing patients to receive interventions to improve the quality of drug use.

The 80+ score incorporated the most relevant risk factors for rehospitalization and mortality in this study population of older patients admitted to an acute internal medicine ward. The score was internally validated and had a good discriminatory ability. It has the potential to be an important tool for identifying patients at highest risk of adverse health outcomes, and an aid in targeting interventions for quality improvement.

The 80+ score is based on data from a population on whom there are strong incentives to focus: patients at high risk of hospitalization and also of mortality. The score differs from other current prediction models in that it incorporates aspects of pharmacotherapy by including drug-specific variables as candidate variables in the risk-factor selection. The use of drugs can be either positively or negatively causally related to a clinical outcome. This is particularly true for older people, who often have many co-morbidities and multiple drug use, and who also have an increased vulnerability for unwanted effects from their drugs. The use of drugs can also provide important proxies for certain conditions, diseases or circumstances.

Among the seven identified variables forming the 80+ score, three were drug-specific: being prescribed a drug for peptic ulcer and GERD or being prescribed an opioid both appeared to increase the risk, while being prescribed a non-TCA antidepressant drug lowered the risk. Drugs for peptic ulcer and GERD, as well as opioids, may be risky because of their potential to cause ADRs in older people, but they can also be indicators of high co-morbidity, multiple drug use or frailty. The prescribing of antidepressants aims to provide relief from psychological symptoms and increase the patient's general wellbeing, which supposedly has a protective effect on rehospitalization and mortality. An alternative explanation for the negative association between this variable and the outcome is that these drugs may be given more often to patients with a longer life expectancy.

The 80+ score was based on a narrowly defined population and on a limited number of patients. An external validation in another population is therefore necessary prior to a general recommendation for use.

The purpose of the MDD system is to increase patient safety, especially for patients receiving multiple medications. However, the survey conducted in Paper IV demonstrated that patients enrolled in the MDD system were exposed to discharge medication errors to the same degree as other patients. The enhanced pharmacy discharge service with bedside provision of medications increased patient safety in some ways, but did not focus on correcting the frequently occurring medication errors. A few of the identified errors were of major importance and could, if not corrected, potentially have caused a revisit to hospital.

Conclusions

- A comprehensive clinical pharmacist intervention improved the appropriateness of prescribing, as measured by STOPP, START and MAI. High STOPP and MAI scores at discharge were associated with a higher number of drug-related readmissions, but no link between the scores and the total number of revisits to hospital was found.
- The clinical pharmacist intervention appeared to be more effective in preventing future visits to the emergency department for patients who were receiving fewer drugs on admission to hospital. There was no difference in effect between the patients with higher and lower levels of inappropriate prescribing on admission. The overall quality of prescribing was improved for both the intervention subgroups (<5 and ≥5 drugs), compared to the control group.
- A score for identifying patients at highest risk of rehospitalization and mortality was developed and internally validated. The 80+ score had a good discriminatory ability for risk of the outcome. Pending external validation, the score appears to have the potential to aid the identification of high-risk patients and those requiring interventions.
- Prescribing errors frequently occur when patients enrolled in the MDD system are discharged from hospital. The majority of the identified errors were of minor clinical importance, but a few errors were of major importance with potential to cause rehospitalization.

Future perspectives

The prescribing and use of drugs, especially for older people, is a complex endeavor. It necessitates multiprofessional models that combine the knowledge and perspectives of different health-care professionals. As a relatively new member of the health-care team, the pharmacist's role in the health-care team and the value of adding a pharmacist, are under discussion. Numerous studies, using various outcomes and process measures to assess the effects of clinical pharmacist interventions, have been conducted. It is a delicate task to find suitable assessment measures: they should not only capture the effect of the intervention, they should also be able to influence, and be relevant to decision-makers. The evidence for the link between available process measures for appropriateness of prescribing and clinical outcomes is weak. In addition, there are currently no measures that fairly evaluate the effectiveness of comprehensive clinical pharmacist interventions. Therefore, the development of process measures that capture the effects of interventions and have causal links to clinical outcomes is highly warranted, and should be the focus of further studies. When measuring the quality of prescribing, it is also imperative to include the patients' views, wishes and adherence to treatment regimens, which none of the measures of today does.

General prescribing recommendations for improving the appropriateness of prescribing, such as the SALAR drug list, STOPP and START, are important in raising awareness about potential hazardous drug use in older people. However, optimization of drug therapy always needs to be based on an assessment of the individual patient. The need for, effect of and safety of each drug should be evaluated regularly, as well as the projected adherence to treatment. Therefore, even more important than to focus on avoiding specific drugs, is to develop processes and structures in the health-care system that support regular reviews of the medications. Policy makers and regulatory agencies have an important role to play in this by establishing rules and regulations. However, a work manager can be just as important, for example by allowing longer times for ward rounds.

Future efforts for increasing medication safety should, to an even greater degree, focus on the prevention of errors rather than on correcting them after they have happened. Transition between different levels of health care is a process that poses a risk for the patient; several health-care professionals are

often involved in the transition process and information has to be transferred between different systems. The transfer of correct information in this process is of major importance. Therefore, the implementation of mandatory medication reconciliations at each transition in care has to be continued. So does the implementation of provision of structured discharge drug information to the patient and the next health-care provider.

Pharmaceutical care is based on a cooperative approach and it is imperative to keep in mind that assessments of the effects of clinical pharmacist interventions are in fact evaluations of the combined multiprofessional work, and that a well functioning working relationship among health-care professionals is fundamental for a successful outcome. Ensuring the safe and effective use of drugs is the responsibility of every health-care professional involved in the medication process. The specific processes that pharmacists should be involved in should depend on the demands and needs of the patient and the setting, and where a pharmacist intervention has potential to be beneficial. The requirements differ between health-care settings, and different groups of patients have different needs and will benefit from different aspects of the intervention. For example, patients who are more engaged in their own medication therapy should be prioritized for pharmacist drug consultation, and patients enrolled in the MDD system should be prioritized for bedside distribution of drugs (since their medications are not readily available at the pharmacy). It is important to continue to develop and validate tools for identifying patients at high risk of hospital care utilization, mortality and ADEs. The design of appropriate interventions for patients who are identified as being at risk and to evaluate the effects of these interventions is at least as important. When we have information about which patients to prioritize and what to do to improve clinical outcomes, the patients at most need can be included and the resources can be used cost-effectively.

Summary in Swedish (Sammanfattning på svenska)

Läkemedel bidrar till att minska sjuklighet samt öka överlevnad, och under senare år har läkemedelsanvändningen – särskilt bland äldre människor – ökat dramatiskt. Många äldre har ett flertal diagnoser som behöver behandlas och ibland måste man även behandla läkemedelsbiverkningar med ytterligare läkemedel. En samtidig användning av 8-10 preparat per person är därför inte ovanligt. I och med att kroppen förändras med åldern, både i sin förmåga att ta hand om läkemedel och i hur den reagerar på läkemedel, ökar risken för biverkningar och skadliga effekter. Dessutom ökar risken för läkemedelsfel med ett ökat antal läkemedel. Allt detta ställer höga krav vid förskrivning av läkemedel till äldre människor. Avhandlingen handlar om hur kvalitet och säkerhet kring läkemedelsanvändning hos äldre människor dels kan mätas och dels förbättras, med fokus på klinikapotekares roll i detta arbete.

Vi har tidigare visat att när en klinikapotekare involverades i vårdteamet för äldre patienter inlagda på en medicinavdelning på Akademiska sjukhuset i Uppsala, så minskade antalet akutmottagningsbesök med 47 % och antalet totala återbesök till sjukhuset med 16 % under året efter sjukhusinläggningen. Apotekarnas insatser bestod i att kontrollera att patientens läkemedelslista på sjukhuset var korrekt och komplett, att samtala med och ge information till patienten om läkemedelsbehandlingen, att grundligt gå igenom alla patientens läkemedel och framföra eventuella förslag på förbättringar till ansvarig läkare, samt att kommunicera med läkare i primärvården om de läkemedelsförändringar som gjorts under vårdtiden. De tre första delarbetena i avhandlingen är fortsatta analyser av data från denna studie.

I det första delarbetet var kvaliteten på läkemedelsförskrivningen i fokus. Kvaliteten mättes med hjälp av ett antal metoder som bedömer grad av lämplighet i förskrivningen och omvandlar detta till en poängsumma. I studien undersöktes om förskrivningskvaliteten förändrades under vårdtiden för den grupp av patienter där en apotekare var involverad, samt om det var någon skillnad mellan denna grupp och gruppen utan apotekare. Dessutom analyserades huruvida grad av olämplig förskrivning hade ett samband med ett högre antal återbesök på sjukhus. Studien visade att kvaliteten i förskriv-

ningen ökade under vårdtiden för den patientgrupp där apotekare var med, medan den var oförändrad eller minskade för de övriga patienterna. Däremot sågs inget samband mellan att ha en ”olämplig” läkemedelsbehandling och ett ökat antal återbesök på sjukhuset. Med andra ord, effekten av apotekarinsatsen på antalet återbesök till sjukhus kan inte förklaras av att patienterna fick en högre kvalitet i läkemedelsförskrivningen mätt med de här metoderna.

I nästa delarbete analyserades huruvida olika grupper av patienter hade olika stor nytta av apotekarinsatsen när det gällde att minska antalet återbesök till akutmottagningen. Vi jämförde den patientgrupp som hade få – d.v.s. färre än fem – läkemedel vid inskrivning med den som hade många. Vi jämförde även patientgrupper med olika grad av lämplig läkemedelsförskrivning (mätt med samma metoder som ovan) vid inskrivning. Något överraskande visade det sig att apotekarinsatsen var mest effektiv för patientgruppen med få läkemedel. Det var ingen skillnad i effekt mellan de patienter som hade låg eller hög kvalitet i sin läkemedelsbehandling.

I det tredje delarbetet identifierades patientvariabler som var starkast förknippade med ett oönskat utfall. Exempel på patientvariabler som analyserades var patientens sjukdomar och ålder samt vilka läkemedel patienten använde. Som utfall valdes antal dagar från sjukhusinläggningen fram till en ny sjukhusinläggning eller död. Sju stycken variabler hade koppling till utfallet: att ha nedsatt njurfunktion, att bo på särskilt boende, att ha en lungsjukdom (astma eller kronisk obstruktiv lungsjukdom), att ha eller ha haft en malignitetsdiagnos, att vara förskriven ett läkemedel mot refluxsjukdom eller magsår, eller att vara förskriven ett opioid-läkemedel var alla förknippade med en högre risk, medan att vara förskriven ett läkemedel mot depression var förknippat med en lägre risk. Dessa sju variabler utgjorde sedan komponenterna i ett verktyg för uppskattning av risk, ”80+ score”. Nästa steg blir att testa verktyget i en annan och större grupp av patienter för att vidare undersöka dess användbarhet och prediktionsförmåga. Förhoppningen är att detta verktyg ska kunna användas i klinisk vardag för att identifiera patienter som har störst risk för återinläggning på sjukhus eller död under tiden efter sjukhusinläggningen, så att ökade insatser kan riktas mot just dessa patienter.

Det fjärde och sista delarbetet var en kartläggning över antal förskrivningsfel som skedde för patienter som blev utskrivna från Akademiska sjukhuset med dosdispenserade läkemedel. Det gjordes även en bedömning av felens typ och allvarlighetsgrad. Information om de fel som upptäcktes framfördes till ansvarig läkare, som fick chans att korrigera felen innan dosläkemedlen beställdes. För 25 % av de patienter som skrevs ut fanns minst ett förskrivningsfel. De vanligaste felen gällde läkemedel som patienten skulle ha men som inte hade blivit ordinerade vid utskrivningen, eller läkemedel som ordi-

nerades i fel dos eller doseringsform. En knapp majoritet av felen var av mindre allvarlighetsgrad. Tre fel bedömdes dock vara av stor allvarlighetsgrad, vilket innebär att om de inte hade åtgärdats hade risken för en återinläggning på sjukhus varit hög. Systemet med dosdispenserade läkemedel syftar till att öka säkerheten och följsamheten för patienter med många läkemedel. Denna kartläggning visar att förekomsten av läkemedelsfel hos dessa patienter är i nivå med den för patienter utan dosdispenserade läkemedel.

De samlade resultaten bidrar med ökad kunskap och förståelse om effekterna av att involvera klinikapotekare i vårdteamet och belyser även utmaningen i att mäta effekterna av dessa insatser. En metod för att identifiera patienter med störst risk för återbesök till sjukhus och dödlighet har också föreslagits. Dessa resultat kan i framtiden användas till att utforma åtgärder med syfte att förbättra kvaliteten och säkerheten kring läkemedelsanvändning till äldre, så att de omfattar de patienter som behöver det mest och har störst nytta av dem.

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