Towards safer drug therapy and improved clinical outcomes in elderly and multimorbid patients

Marianne Lea

School of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Norway

Department of Pharmaceutical Services, Oslo Hospital Pharmacy, Hospital Pharmacies Enterprise, South Eastern Norway

Oslo 2018
To my family
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCIENTIFIC ENVIRONMENT</td>
<td>6</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>8</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>12</td>
</tr>
<tr>
<td>LIST OF PAPERS</td>
<td>14</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>15</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>16</td>
</tr>
<tr>
<td>ELDERSY AND MULTIMORBID PATIENTS</td>
<td>16</td>
</tr>
<tr>
<td>Definitions and prevalence</td>
<td>16</td>
</tr>
<tr>
<td>Safety of drugs</td>
<td>17</td>
</tr>
<tr>
<td>Provided healthcare</td>
<td>18</td>
</tr>
<tr>
<td>Treatment burden, caregiver burden and consequences for the society</td>
<td>19</td>
</tr>
<tr>
<td>ERRORS AND PATIENT HARM RELATED TO DRUGS</td>
<td>20</td>
</tr>
<tr>
<td>Drug-related problems (DRPs)</td>
<td>21</td>
</tr>
<tr>
<td>Drug-drug interactions (DDIs)</td>
<td>21</td>
</tr>
<tr>
<td>Gene-drug interactions (GDIs)</td>
<td>22</td>
</tr>
<tr>
<td>Drug-related hospitalizations (DRHs)</td>
<td>23</td>
</tr>
<tr>
<td>STRATEGIES TO IMPROVE SAFETY OF DRUG THERAPY</td>
<td>23</td>
</tr>
<tr>
<td>Clinical pharmacy and multidisciplinary care</td>
<td>23</td>
</tr>
<tr>
<td>Medicines reconciliation</td>
<td>24</td>
</tr>
<tr>
<td>Medicines review</td>
<td>24</td>
</tr>
<tr>
<td>Integrated Medicines Management (IMM)</td>
<td>25</td>
</tr>
<tr>
<td>KNOWLEDGE GAPS</td>
<td>27</td>
</tr>
<tr>
<td>AIMS</td>
<td>30</td>
</tr>
<tr>
<td>DESIGN</td>
<td>32</td>
</tr>
<tr>
<td>METHODS</td>
<td>36</td>
</tr>
<tr>
<td>OVERVIEW OF THE PAPERS AND STUDY PARTICIPANTS</td>
<td>36</td>
</tr>
<tr>
<td>STUDY SETTING</td>
<td>37</td>
</tr>
<tr>
<td>DESCRIPTION OF STUDY TEAMS</td>
<td>37</td>
</tr>
<tr>
<td>CHARACTERISTICS OF PARTICIPANTS</td>
<td>38</td>
</tr>
<tr>
<td>IDENTIFICATION AND MANAGEMENT OF DRUG-DRUG INTERACTIONS</td>
<td>38</td>
</tr>
<tr>
<td>PHARMACOGENETIC ANALYSES AND GENE-DRUG INTERACTIONS</td>
<td>39</td>
</tr>
<tr>
<td>MEDICINES RECONCILIATIONS AND REVIEWS</td>
<td>40</td>
</tr>
</tbody>
</table>
The studies presented in the three Papers included in this thesis were conducted as a cooperation between Hospital Pharmacies Enterprise South Eastern Norway, Oslo University Hospital and the University of Oslo, Norway.

**Supervisors:**

**Professor Espen Molden**, main supervisor until September 2017, then co-supervisor. Department of Pharmacology and Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Norway & Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway.

**Associate Professor Liv Mathiesen**, co-supervisor until September 2017, then main supervisor. Hospital Pharmacies Enterprise, South Eastern Norway, until July 2017. Department of Pharmacology and Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Norway, from August 2017.

**Associate Professor Morten Mowe**, co-supervisor. Internal Medicine Ward, the Medical Clinic, Oslo University Hospital, Norway & Faculty of Medicine, University of Oslo, Norway.
ACKNOWLEDGMENTS

If I have seen further than others, it is by standing upon the shoulders of giants.

Isaac Newton

I am forever grateful for this journey as a PhD-student and I want to express my gratitude to many people. First, my three eminent supervisors, Liv, Espen, and Morten, this would not have been possible without your professional expertise, supervision, and support throughout these years. All three of you have always been available when I needed you, including far beyond normal working hours. Thank you! I will always be extremely grateful for your dedication.

Liv, we have learned that we often share the same opinions. Despite this, we manage to have long conversations almost every time we speak. I have loved all our conversations and appreciated them containing both thorough research discussion as well as private matters. Thank you for prioritizing me every time I needed you to. I am very grateful for the friendship we have developed throughout these years and all along-the-way celebrations, including our evening in Shangri-La!

Espen, I would not have dared to start this PhD-journey without your support and believing in the project. Your extended experience with research has been highly valuable. Thank you for introducing me to the world of research and the world of pharmacogenetics. I am especially grateful for your thorough, high precision input during manuscript preparations and revisions.

Morten, despite your busy schedule, you have always “kept your door open” and provided quick response, e.g. by calling me from your ski vacation in the Alps or texting me from an important meeting. Thank you for always being there for me, and for all the pleasant meetings, always with coffee servings, in your office. I am extremely grateful for your believing in the project and being a door opener into the clinic.

Further, I would like to express my sincere thankfulness to:

All participants in the studies, making it possible to conduct the research.

Staff at the acute geriatric and the internal medicine ward, for the warm welcoming.
Hospital Pharmacies Enterprise, South Eastern Norway for employing me, giving me the opportunity to be a PhD-student combined with working as a clinical pharmacist, and for funding study pharmacists.

The Medical Clinic, Oslo University Hospital for the opportunity to conduct the studies, and for funding of study pharmacists.

South-Eastern Norway Regional Health Authority for the PhD grant.

Diakonhjemmet Hospital for covering the costs associated with the performance of the pharmacogenetic analyses.

The Norwegian Pharmaceutical Society and the Norwegian PhD School of Pharmacy for grants.

The Faculty of Mathematics and Natural Sciences at the University of Oslo for giving me the opportunity to conduct my PhD.

The eminent project group members from the internal medicine ward, Kristin Hestad Solheim, Anne Mette Njaastad and Kristin Thomassen, for all the productive and enjoyable project group meetings, for believing in the project and simply for being you.

Eva Skovlund, co-author of Papers II and III, for thorough expert advice in statistics and all valuable input in manuscript preparations and revisions.

Stine Eidhammer Rognan, co-author of Paper I, for eager data collection as a master student, followed by being my clinical pharmacist colleague at the Department of Pharmaceutical Services, Oslo Hospital Pharmacy, and the last year being a PhD-student colleague. I look forward to future collaboration!

Torgeir Bruun Wyller, co-author of Paper I, for the opportunity to conduct the study to the acute geriatric ward, participation in the drug-drug interaction assessment meetings and welcoming me to the geriatric research unit “loftet”.

Radojka Koristovic, co-author of Paper I, for discussions of drug-drug interactions during the inclusion period and participating in the drug-drug interaction assessment meetings.

Kristin Kvernø, co-author of Papers II and III, for the hard work you put down during the planning and patient enrolment at the internal medicine ward, for sharing your professional expertise, and for nice coffee breaks.
All my wonderful Colleagues in the Department of Pharmaceutical Services and the rest of Oslo Hospital Pharmacy. I am deeply grateful for the pleasant work environment.

Elin Trapnes, for all fruitful discussions, your enthusiasm and positivity, and for critical input on my thesis. I am honored to be your colleague in the IMM center. Thank you for contributing as a study pharmacist.

Malin Davidsson, for your continuous support during all the phases of my PhD journey, all fruitful discussions and valuable advice.

Anne Schwinghammer, Anette Engnes, Hanne Steen and Petra Foynland, for your valuable contribution as study pharmacists.

Jo Fuglestad for summarizing the Charlson Comorbidity Index scores.

PhD-student colleagues: Yvonne Lao, Karin Svensberg, Arton Baftiu, Karin Drivenes, Lisbeth Damlien Nymoen, and Niklas Nilsson, for research discussions, inspiration, and friendship. Yvonne – thank you for critical input on my thesis.

Bente Hayes, for introducing me to the hospital pharmacy world by employing me at Aker Hospital Pharmacy. Thank you for believing in the project and your constant enthusiasm, especially for clinical pharmacy.

Kirsten K. Viktil, for being an inspiration ever since I was a student, and for the pleasant meetings the recent years.

Torbjørn Heggestad, for valuable advice on readmissions in the planning of the RCT.

Dominic Anthony Hoff, for sharing your Epidata expertise.

Petter, Johanne, Hermine, and Lillebror. Petter, for being my anchor in life and my love, always being supportive and enthusiastic. Thank you for being you, for celebrating every Friday, and for our wonderful life! Johanne and Hermine, for bringing happiness, song, and laughter into my life every day. Lillebror – I can’t wait to meet you. I love you all! You are the most important to me, always.

The rest of my family for always being there for the girls, Petter and me, and especially for all help and backing during the last intensive writing period.
ABSTRACT

Increased life expectancy, a steadily improving health care and drug therapy options, lead to an ever-increasing subpopulation of elderly and multimorbid patients. The organization of healthcare services and treatment guidelines is mainly centered on single diagnoses or medical issues, and coexisting diagnoses or concurrent drug use are rarely taken into account. Elderly and multimorbid patients are also often excluded from clinical trials. As a result, a new challenge is rising, to provide safe, effective and evidence-based healthcare to these vulnerable patients. This thesis was set up as a response to this situation.

The overall aim of this thesis was to generate knowledge of how to provide safer drug therapy and achieve improved clinical outcomes in elderly and multimorbid patients. This was done by various approaches and through three studies:

- First, frequency and management of drug-drug interactions (DDIs) at hospital admission and during a hospital stay in acute geriatric patients were investigated.
- Then, the focus was turned to detecting the prevalence and risk factors of drug-related hospitalizations (DRHs) in multimorbid patients.
- Finally, the effect of tailoring drug therapy on hospital readmissions and survival in multimorbid patients was investigated.

The first study, presented in Paper I, showed that the majority of acute geriatric patients were exposed to DDIs, both at hospital admission and/or during the hospital stay. DDIs in all severity categories were revealed in 78%, and DDIs of major or moderate severity in 65% of the patients. In approximately every fifth patient, a multidisciplinary panel classified hospitalizations as “possible” related to DDIs. Around one-third of the DDIs “possible” related to hospitalization, were classified in the electronic DDI databases as being of minor relevance, reflecting that DDIs not considered being of clinical relevance on a general basis potentially could cause negative clinical outcomes in the vulnerable elderly. It seems essential that the standardized information in electronic databases are combined with skilled professional evaluations of individual risk factors.

In the second study, presented in Paper II, almost 40% of the hospitalizations of multimorbid patients were assessed as “possibly” drug-related, i.e. DRH. Adjusted analysis showed that the occurrence of three specific drug-related problem (DRP) subgroups, i.e. suspected adverse
events, adherence issues and drug monitoring DRPs, were associated with increased odds for DRHs. Receiving home nurse care was also associated with increased odds for DRHs. Patients with the highest Charlson comorbidity index score had reduced odds for DRHs, suggesting that focus should be on optimizing drug treatment in the healthiest of the multimorbid patients.

The third study, presented in Paper III, was a randomized controlled trial including 386 patients (193 in each group) in the primary analysis. Tailoring drug therapy to multimorbid patients prolonged time to readmission or death with approximately 2.5 months within 12 months, although not statistically significantly (median 116 versus 184 days, HR 0.82, 95% CI 0.64-1.04, p=0.106). A statistically significantly increased overall survival during 21-40 months follow-up was seen (HR 0.66, 95% CI 0.48-0.90, p=0.007).

The findings from these studies illustrate the great potential for improvement in providing safe drug therapy to elderly and multimorbid patients. Drug-drug interactions (DDIs) occurred frequently in acute geriatric patients both at hospital admission and during the hospital stay and were assessed as possibly causing hospitalization in every fifth patient. Drug-related hospitalizations (DRHs) occurred frequently in multimorbid patients, and three specific drug-related problem (DRP) subgroups were identified as risk factors for such hospitalizations. As DDIs, DRPs, and DRHs are generally regarded preventable, targeted actions to reduce and avoid them could be a step towards safer drug therapy and hence improved clinical outcomes in these vulnerable patients. Receiving home nurse care was also identified as a risk factor for drug-related hospitalizations in multimorbid patients, suggesting that improved quality of care and increased cooperation between different care providers also might improve clinical outcomes. Systematic, thorough and multidisciplinary tailoring of drug therapy to multimorbid patients showed promising results on clinically relevant outcomes. As a response to the increasing challenges of providing safe and evidence-based healthcare to high-risk multimorbid patients, further studies should be conducted to investigate the effect of such an intervention in a larger scale.
LIST OF PAPERS

Paper I

Paper II
Lea M, Mowe M, Mathiesen L, Kvernrod K, Skovlund E, Molden E. Prevalence and risk factors of drug-related hospitalizations in multimorbid patients admitted to an internal medicine ward. Submitted

Paper III

Paper I is reprinted by permission from Springer Nature Customer Service Centre GmbH.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>CCI</td>
<td>Charlson Comorbidity Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COS</td>
<td>Core outcome set</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report forms</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DDI</td>
<td>Drug-drug interaction</td>
</tr>
<tr>
<td>DRH</td>
<td>Drug-related hospitalization</td>
</tr>
<tr>
<td>DRP</td>
<td>Drug-related problem</td>
</tr>
<tr>
<td>DRUID</td>
<td>Drug Information Database</td>
</tr>
<tr>
<td>GDI</td>
<td>Gene-drug interaction</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IMM</td>
<td>Integrated Medicines Management</td>
</tr>
<tr>
<td>NICE</td>
<td>The National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NPR</td>
<td>Norwegian Patient Registry</td>
</tr>
<tr>
<td>OPERA</td>
<td>Oslo Pharmacist Intervention Study - Effect on Readmissions</td>
</tr>
<tr>
<td>PCNE</td>
<td>Pharmaceutical Care Network Europe</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SFINX</td>
<td>Swedish Finnish Interaction X-referencing</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Program for Social Sciences</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
INTRODUCTION

ELDERLY AND MULTIMORBID PATIENTS

Definitions and prevalence

Two groups of vulnerable adult patients are studied in this thesis: Elderly and multimorbid patients. Old age and multimorbidity are often present at the same time in an individual, but not always. Most often, an age of 65 years or older, are used to define the elderly (1). Aging is a process that follows a different course in different individuals, resulting in the elderly being a heterogeneous group (2-4). The population of the elderly is currently growing and is expected to continue to increase in the future (5-7). The World Health Organization (WHO) estimates that by 2050, one in five people will be 60 years or older, comprising in total 2 billion people worldwide (7). The increased life expectancy is a result of, among other factors, the improvements of modern medicine (6). This does not, however, for most people, lead to a longer life free from disease, but rather that we live for a longer period with disease (8). As aging is a risk factor for disease, the elderly often have a great burden of disease, also reflected in the use of a large number of drugs (5, 9, 10).

There is no consensus on the definition of multimorbidity, and different criteria both on the numbers and types of diagnoses or conditions have been used (11, 12). A frequently used definition is, however, the co-existence of two or more long-term conditions (11, 13). “Condition” is less restrictive than other terms as e.g. disease (11). Even within this definition, variations may exist, e.g. “long-term” has been defined by different time intervals, including 3, 6 or 12 months (11). Lacking consensus on the multimorbidity definition has implications for prevalence estimates and comparison of research results, but have little relevance in the clinical setting, where the main implication is the call for a special attention on how healthcare is provided (12).

Prevalence estimates of multimorbidity vary considerably due to several factors, i.e. the criteria included in the operational definition comprising the number and type of conditions included, the method used to detect multimorbidity, e.g. self-reporting or the medical record, and also on the setting, e.g. total population, primary care, or in hospitals (11, 12, 14-16). In average, the prevalence of multimorbidity is however reported to be 20-30% of the total
population, 55-98% of the elderly and 22-65% of hospitalized patients (11, 17-19). Multimorbidity is present in all age groups, and the prevalence is increasing with age (11, 15, 20, 21). The subpopulation of multimorbid patients is steadily increasing as a result of improvements in modern medicine and increased aging, combined with lifestyle factors, e.g. smoking and physical inactivity (11, 22, 23). Multimorbidity is associated with the use of multiple drugs, increased use of healthcare services and reduced life expectancy (11, 24-26).

Safety of drugs

Both age and morbidity may lead to vulnerability towards drugs. Aging causes changes in internal organs and cells, which may lead to pharmacokinetic and pharmacodynamic changes (2, 27). Pharmacokinetic changes comprise changes in the ability to metabolize drugs, e.g. reduced renal and hepatic function, as well as changes in body composition resulting in a relative increase in body fat and hence prolonged effect of lipid soluble medicines (2, 27). Pharmacodynamic changes comprise altered responses to medicines due to e.g. changes in receptor expression (2, 28). For instance are elderly especially sensitive to drugs acting on the central nervous system, e.g. opioids and sedatives (29).

In addition to pharmacokinetic and pharmacodynamic changes, age-related reduced homeostatic capacity lead to reduced ability to compensate for applied stress and drugs (2, 30). Diseases and frailty can also have significant effects on the individual’s ability to metabolize drugs (30-34). Frailty comprises an increase in the individual’s vulnerability for developing increased dependency and/or mortality when exposed to a stressor event as e.g. the introduction of a new drug or a minor infection (35, 36). Frailty is shown to increase with age (37-39), and also multimorbidity can contribute considerably to frailty (35).

Elderly and multimorbid patients are often excluded from clinical trials investigating the effect of a single drug, or comparing new treatment regimens against standard treatment (40, 41). Treatment guidelines are based on results from such studies, i.e. evidence from patients with isolated diseases, and most treatment guidelines do not include modifications for multimorbid patients (42-44). This is a paradox, considering the fact that these guidelines are commonly applied to such patients (42). Applying treatment recommendations from all relevant guidelines, one by one on every single disease a patient has, frequently result in long lists of drugs in use, as well as non-optimal drug combinations (42). Importantly, net benefits
and harms of combining all drugs recommended in disease-specific guidelines in patients with multiple medical conditions, are not known (45).

Recently, a few guidelines for the management of multimorbidity have been published (46-48). A systematic guideline review from 2018 found however that only three out of the eight included clinical practice guidelines for multimorbidity or polypharmacy reported evidence levels and grades of recommendations, possibly reflecting the lack of evidence (49).

Provided healthcare

Our healthcare system is generally built up around the treatment of single conditions, i.e. silo constructed (50). Disease-specific treatment guidelines, the medical specialties with expertise within specific organ systems, and the separate budgets and management of different care levels reflect this. As a result, patients with co-existing conditions often experience fragmented care (51).

It is increasingly common that patients address various medical specialists with their different medical issues. A survey conducted amongst pharmacy customers in Norway showed that for 70% of the customers, more than one physician had been involved in the prescription of drugs (52). Further, up to ten physicians were involved in the prescription of drugs to individual pharmacy customers (52). It may be questioned whether specialists are the ones best suited to provide care to patients with multiple medical issues and an accompanying use of numerous drugs. Recently, it was purposed in the British Medical Journal that the management of polypharmacy could be seen as a new specialty (8).

As a result of the silo construction of healthcare delivery combined with the increasing subpopulations of elderly and multimorbid patients, a new challenge is rising; to provide safe, effective and evidence-based care to these vulnerable patients. Multimorbidity is regarded as one of the greatest challenges our healthcare system is facing (13, 53-55). The World Health Organization (WHO) has referred to non-communicable diseases as an epidemic, representing 40.5 of 56.9 million (71%) of global deaths in 2016 (53, 56). Norway is one of the countries, which have committed to follow-up on the WHO’s goal of reducing avoidable mortality from non-communicable diseases with 25% by 2025 (57, 58).

WHO has developed a Global strategy and action plan on aging and health, where the vision is “a world in which everyone can live a long and healthy life” (7). The strategy addresses
five objectives, whereof two address tailored, integrated healthcare services, and both emphasizing the person-centeredness. The first refers to aligning health systems to the needs of older populations. This includes making the healthcare system better organized around older people’s needs and preferences and integrated across settings and care providers. The second concerns the development of sustainable and equitable systems for providing quality long-term, integrated, patient-centered healthcare, provided by adequately skilled providers. The goal is to maintain the best possible level of functional ability for older people (7).

In order to meet today’s patients’ needs and provide coordinated care, broad knowledge and skills are demanded, which can not be achieved by a single profession alone (59, 60). The importance of providing multidisciplinary-based and tailored care to elderly and multimorbid patients with complex medical issues is getting increased attention (7, 49, 59, 61-64). There is, however, a lack of evidence of interventions to tailor drug therapy to multimorbid patients (49).

Treatment burden, caregiver burden and consequences for the society

Increased subpopulations of elderly and multimorbid patients are followed by a burden on both patients themselves, their caregivers, and society. “Sitting on a shaky chair, not knowing whether it would collapse or stay in place” was used as a metaphor by a multimorbid participant to describe his situation, in a recent qualitative study conducted by Duguay et al. (65). Treatment burden is defined by Boyd et al. as “a patient’s perception of the aggregate weight of the actions and resources they devote to their healthcare” (66) and has received increased attention lately (67-69). Treatment burden comprises demands within various areas, including adhering to complex drug regimens, monitoring and managing symptoms at home, and financial burden (69). High treatment burden has been associated with several negative outcomes including recurrence of disease, health decline, and reduced survival and quality of life (69). The National Institute for Health and Care Excellence (NICE) guideline on multimorbidity highlights the importance of reducing the treatment burden in these patients, through tailored, patient-centered care (48).

Along with the increasing populations of elderly and multimorbid patients, follows an increasing population of caregivers, which may themselves experience various consequences of being a caregiver, including physical, emotional, social and economic (70, 71). To be a caregiver can lead to chronic stress and caregiver burden, which may lead to increased
vulnerability to disease, which again may lead to a diminished ability to provide optimal care (72, 73).

For the society, obvious consequences of the increasing subpopulations of elderly and multimorbid patients are higher demands on the healthcare sector in terms of an increasing need of both healthcare providers per se, healthcare providers with polypharmacy- and multimorbidity-expertise, as well as an ever-increasing financial burden. To prevent avoidable use of healthcare resources is obviously essential.

---

**ERRORS AND PATIENT HARM RELATED TO DRUGS**

Drugs are developed to prevent or treat disease and/or relieve symptoms. However, drugs unfortunately occasionally cause harm to the people using them. According to surveys conducted by the Norwegian Directorate of Health, drugs are one of the most frequent causes of patient harm during hospital stays, estimated to occur during approximately 2% of all hospitalizations (74). High frequencies of drug-related errors and -patient harm are also reported in other countries, e.g. 237 million errors are estimated to occur every year in England, whereof 712 are *causing* death and 1708 are *contributing* to death (75). The report from England found that errors were more frequent in elderly, or in the presence of comorbidity or the use of numerous drugs (75). In 2017, WHO launched the patient safety challenge “*Medication without harm*”, aiming to reduce severe preventable drug-related harm globally, by 50% within five years (76).

The terminology of errors and patient harm related to drugs can be confusing (77), and different concepts include:

- **Medication errors** defined by Bates et al. as “*errors occurring at any stage in the process of ordering or delivering a medication*” (78). Medication errors include the whole range of severity, from trivial errors with no clinical consequences to life-threatening errors, and are by definition obviously avoidable (78).

- **Adverse drug reaction**, defined by WHO as “*a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man*” (79).
• **Adverse drug event**, defined by WHO “any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment” (79).

In the studies included in this thesis, we have investigated drug-related problems (Paper II), drug-drug interactions (Paper I), gene-drug interactions (Paper II) and drug-related hospitalizations (Paper II), and these concepts will be introduced in this section.

**Drug-related problems (DRPs)**

Various definitions of a drug-related problem (DRP) exists. A commonly used definition is the one from Pharmaceutical Care Network Europe (PCNE), which reads “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” (80). DRP is a wide term, which can encompass both medication errors, adverse events, and adverse reactions (81). Examples of DRPs are drug-drug interactions, unnecessary drug treatment, and non-optimal dosing, and possible clinical consequences include hospitalizations, longer hospital stays, emergency department visits, increased morbidity and mortality (80, 82-86). The number of DRPs has been shown to increase with the number of drugs used by a patient, and as both elderly and multimorbid patients often use numerous drugs, they have a high risk of DRPs (82, 86, 87). Further, age and morbidity related changes make these patients more vulnerable to drugs, which also contribute to the high risk of DRPs (2, 27, 28, 33, 34, 87). DRPs are generally regarded as preventable, but to be prevented they need to be revealed and solved, e.g. by prescription changes such as choosing non-interacting drug-combinations or more optimal dosages.

**Drug-drug interactions (DDIs)**

Drug-drug interactions (DDIs) arises when a drug affects another drug’s pharmacodynamics or pharmacokinetics and may result in an altered therapeutic response (88, 89).

Pharmacokinetic DDIs comprises alterations in absorption, distribution, metabolism or excretion of a drug (89). Examples are macrolide antibiotics inhibiting the metabolism of warfarin resulting in increased INR and risk of bleeding, or proton pump inhibitors reducing gastric pH and thereby influencing the absorption and effect of other drugs (90).

Pharmacodynamic DDIs comprises two or more drugs having the same pharmacological
effects or acting at the same receptor site, resulting in an additive or decreased effect (88, 89). These DDIs can be anticipated by the drugs’ mechanism of action, and examples are combinations of several drugs that lead to excessive depression of the central nervous system, or several drugs that cause hypoglycemia (90). Pharmacodynamic DDIs are sometimes utilized to reach treatment goals, e.g. in hypertension or diabetes.

The proportion of elderly patients exposed to DDIs in different care systems is reported to be high (91-94), and this may be caused by several factors. The frequency of DDIs is shown to increase both with age, numerous conditions, and with a high number of concurrent drugs in use (92, 94-97). The use of several prescribers may introduce DDIs, as they might not be aware of each other’s involvement in the patient’s drug treatment (88, 95). Medicines discrepancies between different information sources are frequent, including omissions of the patients’ use of over-the-counter drugs and natural/herbal preparations (98-100), potentially resulting in DDIs not being revealed and solved (90).

DDIs are regarded as important contributors to increased morbidity and have been shown to account for approximately 1% of all hospitalizations and up to one in six of adverse event related hospitalizations (101, 102). Since most DDIs are predictable, they and their unfortunate consequences could be avoided (90, 101, 103).

**Gene-drug interactions (GDIs)**

Patients might respond differently to the same drug, and genetics accounts for a substantial part of this variability (104, 105). Our genes generally remain stable throughout a lifetime, unlike other factors influencing the response of drugs, e.g. organ function, comorbidities or concurrent use of drugs (104). Pharmacogenetic variability includes inherited differences in drug targets as well as drug metabolizing enzymes and –transporters mediating the effect of drugs (104). Only a single blood sample is needed to test for a genotyping panel of all genes influencing drug therapy in an individual person (104). Knowledge of the respective genotypes’ effects on pharmacokinetics or pharmacodynamics of drugs is currently expanding and can be applied to reveal gene-drug interactions (GDIs) (106, 107).

There have been great enthusiasm and expectations towards pharmacogenetics since its beginning in the 1950s, but implementation to clinical practice has been slow (106-108). Including pharmacogenetics and GDIs in “real life” research aiming to improve the safety of
drug therapy as well as patient outcomes should, therefore, be prioritized. Pharmacogenetic variability is a potential source of DRPs not previously investigated in relation to risk of hospitalizations.

**Drug-related hospitalizations (DRHs)**

Inappropriate drug use is a common cause of healthcare contact (83, 84, 86, 87). A systematic review covering various patient groups reported approximately 10% of all hospitalizations to be drug-related (84). The prevalence of drug-related hospitalizations (DRHs) is higher in the elderly, comprising around 30% of all hospitalizations (109, 110).

DRHs have both economic and clinical consequences (85, 111). Clinical consequences may include hospital-acquired infections, delirium, increased frailty, dependency, morbidity, mortality, and decreased quality of life. Advanced age and polypharmacy are main risk factors for DRHs identified in most studies (84, 112, 113). A high proportion of DRHs are preventable (84, 109, 114-118).

---

**STRATEGIES TO IMPROVE SAFETY OF DRUG THERAPY**

**Clinical pharmacy and multidisciplinary care**

Clinical pharmacy originated in the 1960s at the College of Pharmacy at the University of Michigan (119). This comprised a shift from pharmacists almost entirely focusing on the preparation and distribution of drugs, to pharmacists serving as patient-centered drug therapy experts contributing to patient safety (119, 120). Clinical pharmacy was introduced in Norwegian hospitals in the late 1970s and was a pioneer’s work (121). The European Society of Clinical Pharmacy defines clinical pharmacy as “a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices” (122). Medicines reconciliation, medicines reviews, and patient counseling are typical patient-oriented tasks included in clinical pharmacy services (120).
Clinical pharmacists working in multidisciplinary treatment teams in hospitals have been shown to detect and resolve large quantities of DRPs (120, 123, 124). The need to provide multidisciplinary care to patients with multiple diagnoses and numerous drugs in use is presently well-recognized (46, 125-128).

Medicines reconciliation

Medication errors often appear at patient transition points (98, 99, 129-132). Medicines reconciliation is a process designed to prevent these errors from occurring, thereby increasing patient safety (133). The Institute of Healthcare Improvement defines medicines reconciliation as “the process of creating the most accurate list possible of all medications a patient is taking - including drug name, dosage, frequency, and route - and comparing that list against the physician’s admission, transfer, and/or discharge orders, with the goal of providing correct medications to the patient at all transition points within the hospital” (134). Medicines reconciliation should continue at every step of transfer to a new care level, ensuring that a patient`s medicine list is always up to date (133).

A systematic review found that up to 67% of patients had minimum one medicines discrepancy at admission to hospital (99). Medicines reconciliation is still in its beginning in Norway, and the first study investigating medicines discrepancies in patients admitted to internal medicine wards was published in 2015 (98). This study identified medicines discrepancies in 80% of the patients (98), which is in line with results from studies in other countries (99, 100, 135, 136). In the Norwegian study, the majority of medicines discrepancies were evaluated to possibly harm the patient in a long-term perspective (98).

Medicines review

The Pharmaceutical Care Network Europe (PCNE) defines a medicines review as “a structured evaluation of a patient`s medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions” (137).

Further, PCNE classifies medicines reviews with regard to information sources available (137):
• Simple review based on the patient’s medicines history
• Intermediate review based on patient interview or clinical data in addition to the patient’s medicines history
• Advanced review based on both patient interview and clinical data in addition to the patient’s medicines history

All care-transitions should comprise a medicines reconciliation, but not necessarily include a medicines review. Hence, a medicines reconciliation can be regarded as the first step of, but not equal to a medicines review (137).

A recent Cochrane review found no evidence that medicines review reduced mortality or hospital readmissions (138). The authors state, however, that important effects may have been overlooked due to the short follow-up in the included studies, i.e. from 30 days to one year. High-quality studies with long follow-up, at least up to a year, in high-risk patient populations were requested.

**Integrated Medicines Management (IMM)**

In the year 2000, pharmacies in Northern Ireland were challenged by the Government to meet the changing needs of patients in terms high-quality, tailored healthcare, delivered to the individual when needed (139, 140). This resulted in the development of a systematic approach to tailor and optimize drug therapy to hospitalized patients, called Integrated Medicines Management (IMM) (139, 141). The model was established to ensure the quality and safety of drug treatment at an individual level during hospitalizations (142). IMM comprises procedures during the hospital stay at three specific steps, i.e. medicines reconciliation at admission, medicines reviews during the stay and medicines reconciliation and –information both to the patient and to the next care level, at discharge (129, 139, 141, 143-145).

Medicines management has been defined as “*encompassing the entire way that medicines are selected, procured, delivered, prescribed, administered and reviewed to optimise the contribution that medicines make to producing informed and desired outcomes of patient care*” (146). Compared to medicines review, which can be described as an on-off and time-limited event, medicines management is a continuous and longer process, including e.g. both medicines reconciliations and reviews (137). The overall goal of medicines management is to maximize health and achieve the best outcome for the individual patient through optimal use
of medicines (139, 147). *Integrated* refers to seamless, coordinated or continuous care, provided by a multidisciplinary approach and across levels of care (148).

IMM has been adapted for use in Sweden, and several studies have investigated the effect of implementing either parts of, or the complete IMM model on different efficacy measures, both in Northern Ireland and Sweden (124, 129, 139, 141, 143, 145, 149, 150). Implementing IMM medicines information at discharge has shown to reduce the frequency of medication errors significantly, i.e. 32% of patients in the intervention group had at least one medication error compared to 66% in the control group (143). Another study showed that implementing IMM medicines information at discharge reduced hospital readmissions caused by medication errors from 8.9% to 4.5% (129).

Two intervention studies on implementation of the entire IMM model showed a statistically significant decrease in the number of inappropriate drugs in the intervention group compared to the control group, measured by the Medication Appropriateness Index (149, 151).

In a randomized controlled trial (RCT) including 762 patients, providing IMM reduced the length of hospital stay from 9.8 days to 7.8 days, \( p = 0.003 \), prolonged time to readmission with 20 days and reduced the readmission frequency from 49.3% to 40.8% within 12 months, \( p = 0.027 \) (139). In another RCT including 368 patients 80 years or older, providing a similar intervention resulted in a significant reduction in all hospital visits, emergency department visits, and drug-related readmissions, as well as reduced total cost per patient (124). Mortality was either not investigated or no effect was seen, in these two RCTs (124, 139).

After a slow start, clinical pharmacy has expanded rapidly in Norwegian hospitals during the recent years (121). Today, according to a survey conducted by Hospital Pharmacies Enterprise, South Eastern Norway, approximately 160 clinical pharmacists deliver services equaling approximately 80 full-time equivalents (E. Trapnes, personal communication, November 28, 2018). This rapid expansion resulted in a need for standardization, and in 2012, IMM was chosen as the working model of all clinical pharmacists conducting patient-oriented tasks in Norwegian hospitals (152). The effect of providing tailored drug therapy by IMM in Norway has however not previously been investigated.

The Internal medicine ward at Oslo University Hospital was one of the participating wards in a multicentre study investigating medicines discrepancies at hospital admission by performing medicines reconciliation, i.e. the first step of IMM (98). After revealing that 8 out of 10 patients had medicines discrepancies at admission, a project to study the effect of
implementing IMM at the ward was started in collaboration with Oslo Hospital Pharmacy. This project has been Oslo University Hospital’s contribution to the Norwegian Patient Safety Programme (153), and is in line with the intentions in the “Coordination Reform” of the Norwegian healthcare system (154). The project was named “Oslo Pharmacist Intervention Study - Effect on Readmissions” (OPERA), and comprises the RCT described in Paper III of this thesis.

**KNOWLEDGE GAPS**

Today’s health care system is facing a great challenge in providing safe, effective and evidence-based care to the growing subpopulation of elderly and multimorbid patients. In 2017 the Institute for Healthcare Improvement and Safe & Reliable Healthcare published a white paper to provide a clearer understanding of how to achieve safe, reliable and effective health care (155). Moving to a greater proactivity is purposed as one out of six “resolutions” in patient safety work (155). Preventing avoidable harms from drugs is a proactive approach. To generate knowledge on how to provide safer drug therapy and improved clinical outcomes for patients is one way towards this goal.

The shift towards an older and more multimorbid population will naturally put an extra load on the healthcare system, which already struggles to meet today’s demand (6, 156). These patient groups are especially vulnerable to drug-related harm and the potential for improvement is assumed large. Working towards safer drug therapy for elderly and multimorbid patients is hence of obvious importance.

Knowledge of the nature of drug-drug interactions (DDIs) in elderly patients in an acute hospital setting is scarce. Such knowledge can contribute to prevent DDIs and possibly improve clinical outcomes in this vulnerable patient group.

Prevalence and risk factors for drug-related hospitalizations (DRHs) have to the best of our knowledge not been studied in multimorbid patients. Preventing hospitalizations in this resource demanding patient group, is crucial both to improve patient health, reduce avoidable stress for patients and their caregivers, reduce costs, and reduce the load on the healthcare system. Most DRHs are regarded as preventable, but to be able to effectively prevent them, adequate knowledge of risk factors is crucial.
The multimorbid patients could conceivably be a patient group which may benefit from tailoring of drug therapy due to their high risk of drug-related problems and a high degree of healthcare service utilization. The effect of tailoring drug therapy by IMM has, however, not been investigated in this high-risk patient population. Furthermore, the effect of implementing IMM in Norway has not been investigated, even if IMM is decided to be used by all clinical pharmacists conducting patient-oriented tasks at Norwegian hospitals. In studies on the efficacy of quality improvement, the context is inherently important. Documenting the effect of the IMM model in Norway, using relevant outcome measures is necessary.
The overall aim of this thesis was to generate knowledge of how to provide safer drug therapy and achieve improved clinical outcomes in elderly and multimorbid patients. Our society is experiencing an increased life expectancy, a steadily improving healthcare including drug therapy options, which lead to an ever-increasing subpopulation of these patients (6). Providing care to these vulnerable patients is a great challenge to our healthcare system, and this thesis was set up as a response to this situation.

The hospital was chosen as the study setting. By various approaches, we aimed to generate knowledge of how to provide safer drug therapy and improved clinical outcomes in the selected patient subpopulations. This was done by various approaches and through three studies. First, frequency and management of drug-drug interactions (DDIs) at hospital admission and during a hospital stay in acute geriatric patients were investigated. Then, the focus was turned to detecting the prevalence and risk factors of drug-related hospitalizations (DRHs) in multimorbid patients. Finally, the effect of tailoring drug therapy on hospital readmissions and survival in multimorbid patients was investigated. The specific aims of the three papers included in this thesis were:

**Paper I**

To investigate the severity and management of DDIs in acute geriatric patients.

**Paper II**

To investigate the prevalence and potential risk factors for DRHs in multimorbid patients admitted to an internal medicine ward.

**Paper III**

To investigate the effect of in-hospital tailoring of drug therapy to multimorbid patients, on long-term hospital readmissions and survival.
DESIGN

**Paper I**

In this study, drug-drug interactions at hospitalization and during the hospital stay were investigated by an observational approach in patients admitted to the acute geriatric ward at Oslo University Hospital, Ullevaal, Norway.

**Papers II and III**

The two studies described in papers II and III share the same research protocol (Supplement 1 of Paper III). Multimorbid patients admitted to the internal medicine ward, Oslo University Hospital, Norway, and meeting the eligibility criteria were simultaneously enrolled to both studies. Figure 1 shows the design of both studies, and Figure 2 depicts the timeline in a Gantt chart.

The study described in paper II was an observational study investigating the prevalence and risk factors of DRHs. The study described in paper III was a parallel-group randomized controlled trial investigating the effect of in-hospital tailoring of drug therapy on hospital readmissions and survival. Patients were randomly assigned, 1:1, to the intervention or control group. Intervention patients received medicines reconciliation and reviews, and information at discharge, according to the Integrated Medicines Management model, throughout the hospital stay. Control patients received standard care, which in line with normal procedures in Norwegian hospitals did not include the inclusion of clinical pharmacists in the multidisciplinary treatment team working by the IMM model. The primary endpoint was difference in time to readmission or death within 12 months after discharge. Difference in overall survival was the most important secondary endpoint.
Figure 1 The design of the two studies described in Papers II and III.
Figure 2 Gantt chart of the steps in the two studies described in papers II and III.
METHODS

OVERVIEW OF THE PAPERS AND STUDY PARTICIPANTS

All studies included patients admitted to Oslo University Hospital, Ullevaal, Norway. Table 1 shows an overview of the data collection periods and inclusion and exclusion criteria. Table 2 shows the different methods and analyses used in the three papers.

Table 1 Overview of data collection periods, inclusion- and exclusion criteria.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Data collection period</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>September 13, 2010 to January 25, 2011</td>
<td>Admitted to the acute geriatric ward</td>
<td>Terminally ill</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signed informed consent by patient or relative</td>
<td>Isolated due to severe infection</td>
</tr>
<tr>
<td>II &amp; III</td>
<td>August 30, 2014 to March 17, 2016</td>
<td>Acutely admitted to the internal medicine ward</td>
<td>Previous inclusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 18 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 4 regular drugs from ≥ 2 therapeutic classes*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norwegian personal identification number</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signed informed consent by patient or relative</td>
<td>Unable to communicate in Norwegian or English, and translator not available</td>
</tr>
</tbody>
</table>

*Anatomical Therapeutic Chemical (ATC) classification system for drugs, 1st level (157).

Table 2 Overview of the different methods and analyses used in the studies described in the three papers.

<table>
<thead>
<tr>
<th>Method/analysis</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of drug-drug interactions with electronic databases</td>
<td>x</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Pharmacogenetic analyses, assessment of gene-drug interactions</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicines reconciliations and -reviews</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Relationships between drug issues and hospitalization</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Intervention tailoring drug therapy to the individual patient</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimation of odds ratio</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Correlation analysis</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Multiple logistic regression analysis</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Time-to-event analysis</td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

*performed as a part of the medicine reviews
STUDY SETTING

During the data collection period of the study described in paper I, the acute geriatric ward comprised 20 beds organized as two parallel subunits of equal size, with random patient allocation. Since the pre-round briefings took place simultaneously, it was only feasible to include patients from one of the subunits into the study. The ward receives acutely ill elderly patients with complex somatic, cognitive, mental and social issues, and considerable multimorbidity and polypharmacy. Most patients admitted is above 65 years old and the average age is above 80. The main reason for admission is acute functional decline, i.e. loss of at least one activity of daily living for unclear reasons within the last two weeks before hospitalization (158).

The studies described in papers II and III include patients admitted to the internal medicine ward. During the data collection period, the ward comprised 24 beds, except for around 8 weeks during summer with a downscaling to 16 beds. The ward mainly receives patients suffering from multiple medical issues, in particular hematological, endocrine, infectious and/or cardiovascular. Patients are assessed and treated by physicians with expertise in internal medicine, by nursing staff, and when needed, by clinical nutrition physiologists and/or physiotherapists. Normally the ward receives clinical pharmacy service, equivalent to 12 hours per week, delivered by the Department of Pharmaceutical Services at Oslo Hospital Pharmacy. During the data collection period, these resources were instead used to deliver study pharmacists.

DESCRIPTION OF STUDY TEAMS

In the study described in paper I, two pharmacists were responsible for data collection, identifying drug-drug interactions and presenting them in multidisciplinary meetings with geriatricians and nurses. One of the pharmacists underwent practical training as a clinical pharmacist during the inclusion period, while the other had practiced as a clinical pharmacist for several years prior to the study.

During the inclusion period to the studies described in papers II and III, six experienced clinical pharmacists, all with a master degree in clinical pharmacy and standardized training in IMM, collected data, performed medicines reconciliations and -reviews and provided the intervention to tailor drug therapy.
CHARACTERISTICS OF PARTICIPANTS

Demographic variables were prospectively collected from the medical records for all patients, i.e. age, sex, the reason(s) for hospitalization, medical history, relevant laboratory results, dates for admission- and discharge. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula (159), except for obese patients (BMI > 30), where the Salazar-Corcoran formula was used (160). For patients included in the studies described in papers II and III, we also registered the following characteristics: body-mass index (BMI), living situation and assistance with drug administration before hospitalization, where the patient was discharged to and assistance with drug administration after discharge.

At the time when the data collection for the study described in Paper I was performed, medicines reconciliations were not well known or introduced neither at Oslo University Hospital nor other hospitals in Norway. Thus in this study, the drugs registered as “in use” for the included patients was solely based on drug lists in medical records during the hospital stay. Following a multicentre study investigating medicines discrepancies revealed by medicines reconciliation (98), where one of the participating wards was the internal medicine ward at Oslo University Hospital, medicines reconciliation was an obvious first step during data inclusion to the studies described in papers II and III. The drugs registered in use in these patients were hence based upon the reconciled drug list. Despite this difference due to natural progress in providing healthcare, number, type, and dosage of drugs were registered as patient characteristics in all studies included in this thesis.

An experienced senior physician collected information from the medical records (papers II and III) to calculate the Charlson Comorbidity Index (CCI) score (161). This was conducted retrospectively to the data collection.

IDENTIFICATION AND MANAGEMENT OF DRUG-DRUG INTERACTIONS

In Paper I, two Nordic electronic databases were used to identifying potential drug-drug interactions (DDIs): the Drug Information Database (DRUID, available at http://www.interaksjoner.no) and the Swedish Finnish Interaction X-referencing (SFINX, available at http://www.janusinfo.se) (162). These were applied because they were the most commonly used DDI databases in Norway at the time. The severities of DDIs identified by
the two databases were harmonized into three classifications, as shown in Table 3. In cases of inconsistency between the databases, the most severe classification was applied.

Table 3 Description of the severity classification of drug-drug interactions in Paper I.

<table>
<thead>
<tr>
<th>Severity classification in Paper I</th>
<th>Recommended management in databases</th>
<th>Classification in Drug Information Database (DRUID)</th>
<th>Classification in Swedish Finnish Interaction X-referencing (SFINX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor clinical relevance</td>
<td>No action required</td>
<td>Academic interest</td>
<td>A – Minor interaction of no clinical relevance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B – Clinical outcome of the interaction is uncertain and/or may vary</td>
</tr>
<tr>
<td>Moderate clinical relevance</td>
<td>Precaution</td>
<td>Precautions required</td>
<td>C - Clinically relevant interaction that can be handled e.g. by dose adjustments</td>
</tr>
<tr>
<td>Major clinical relevance</td>
<td>Avoidance</td>
<td>Should be avoided</td>
<td>D - Clinically relevant interaction. The combination is best avoided</td>
</tr>
</tbody>
</table>

Screening for DDIs was conducted at hospitalization and repeatedly during the hospital stay at all prescription changes. Patients were reviewed daily, Monday to Friday for changes. From the medical record, information of relevance for individual risk assessments of DDIs was retrieved, i.e. changes in laboratory results, clinical or mental state. All DDIs revealed in the databases were registered. The pharmacists made individual risk assessments of DDIs based on factors such as treatment history, laboratory measurements, and dosages. DDIs considered requiring evaluation in the multidisciplinary treatment team, were discussed in meetings with geriatricians and nurses. All actions made by the geriatricians following these discussions were recorded, comprising i) immediate prescribing changes in terms of drug withdrawal/addition, dose adjustment, or a switch to a non-interacting drug alternative, or ii) monitoring clinical signs, symptoms and/or laboratory values to determine whether future treatment adjustment was needed.

PHARMACOGENETIC ANALYSES AND GENE-DRUG INTERACTIONS

Blood samples for genotyping were collected during the patients’ hospital stay for patients included in the study presented in Paper II. The blood samples were drawn on containers with
anticoagulant (EDTA tubes), and stored in a freezer until pharmacogenetic analysis at Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway. All genotyping assays were validated and had been certified by Norwegian accreditation for routine clinical use. Due to time constraints, the pharmacogenetics analyses were conducted retrospectively, and therefore not included as a basis for the medicines reviews.

Pharmacogenetic analyses of drug-metabolizing cytochrome P450 (CYP) enzymes and the transporter mediating uptake of statins from the blood into the liver (OATP1B1) were performed. For warfarin-treated patients, \( \text{VKORC1} \) genotyping was also conducted. In order to define genotypes encoding altered (‘interacting’) phenotypes, the patients were classified into subgroups according to genotype-based interpretations. Overview of target genes variant alleles included in the genotyping panels and the respective genotype-predicted aberrant phenotypes are provided in Web-supplement 2 of Paper II.

After patient inclusion, gene-drug interactions (GDIs) were retrospectively identified by a pharmacologist and a clinical pharmacist by assessing the reconciled drug list at hospitalization against the respective patients’ genotype results. Knowledge of the respective patients’ genotypes’/phenotypes’ effects on pharmacokinetics or pharmacodynamics of drugs used by the patients were applied to define a GDI and assessments were restricted to aberrant phenotypes, as defined in Web-supplement 2 of Paper II.

MEDICINES RECONCILIATIONS AND REVIEWS

Medicines reconciliations and reviews were performed by the IMM model, with procedures translated and adapted to Norway (98, 139). Medicines reconciliations were performed through a structured interview with the patient including a checklist to discover which drugs and dosages the patient used prior to admission. The checklist is essential to reveal drugs patients tend to forget to mention and the physician forgets to ask about, e.g. use of eye-drops, inhalations, over-the-counter drugs, and specific drug types, e.g. painkillers, and also natural drugs and dietary supplements. If satisfactory information was not obtained from the patient, additional sources were used, e.g. the patient’s relatives or general practitioner. For patients not handling their own drugs prior to admission, those responsible for handling the patients’ drugs, i.e. nursing homes, district nurses or relatives, were used as the information source(s).
Thorough, structured medicines reviews were conducted for all patients at hospitalization and for intervention patients repeatedly during the entire hospital stay. These medicines reviews were advanced reviews, according to the PCNE classification (137). A list of pre-defined risk categories, shown in Table 4, were systematically addressed for each drug in each patient. In addition, an overall benefit-risk assessment was made with the main goal of tailoring drug therapy to the individual participant, giving significant weight to the patient perspective. Medicines discrepancies and DRPs, including both actual and potential problems, were identified.
Table 4 Detailed description of the risk categories that were systematically addressed for each drug in each patient during the medicines reviews, and examples of sources used by clinical pharmacists to address them.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Detailed description</th>
<th>Examples of sources</th>
</tr>
</thead>
</table>
| Drug monitoring                   | Need for therapeutic drug monitoring or laboratory monitoring, e.g. digoxin, warfarin, antiepileptic’s                          | → The Pharmacology Portal – Norwegian portal for drug and intoxicated analyses - http://www.farmakologiportalen.no/  
→ Norwegian National Centre for Epilepsy  
→ Centre for Psychopharmacology, Diakonhjemmet Hospital, Norway |
| Adverse event                     | Presence of symptoms or changes in laboratory values possibly caused by drug(s)                                                 | → Summary of Product Characteristics (SPC)  
→ UpToDate  
→ Micromedex  
→ CredibleMeds, QTDrugs List, - https://crediblemeds.org/ |
| Drug-drug interaction             | Clinically relevant drug-drug interactions                                                                                   | → The Norwegian Medicines Agency – Drug interactions checker  
→ Micromedex – Drug interactions  
→ Drugs.com – Drug interactions checker |
| Non-optimal drug therapy          | Lack of drug treatment or non-optimal drug treatment of a symptom/disease                                                     | → Therapy guidelines  
→ BMJ Best Practice  
→ UpToDate  
→ Summary of Product Characteristics (SPC) |
| Reduced organ function / contraindication | Drug or dosage of drug inappropriate due to reduced kidney function, reduced liver function, contraindications or other diseases. | → The Renal Drug Handbook - https://renaldrugdatabase.com/  
→ UpToDate  
→ Micromedex  
→ Internetmedicin - https://www.internetmedicin.se/searchresult.aspx?search=lever (reduced liver function/drugs that can harm the liver)  
→ Summary of Product Characteristics (SPC) |
| Inappropriate drugs in elderly     | Use of less favourable drugs in patients >65 years old, e.g. anticholinergics                                                  | → STOPP 2 (Screening Tool of Older Persons’ Prescriptions)  
→ Beers criteria |
| Unnecessary drug                  | Drug in use is not indicated                                                                                                 | → Therapy guidelines  
→ Summary of Product Characteristics (SPC)  
→ UpToDate |
| Course length                     | Consideration of appropriate duration of course length, e.g. duration of antibiotics                                           | → Summary of Product Characteristics (SPC)  
→ The Norwegian Directorate of Health – National guideline for the use of antibiotics in hospitals  
→ The European Committee on Antimicrobial Susceptibility Testing - EUCAST - minimum inhibitory concentrations |
| Practical problem                 | Practical challenges in drug handling, e.g. inhalation devices                                                              | → Summary of Product Characteristics (SPC)  
→ Local procedure for tablets and capsules - dividing, opening and crushing  
| Adherence issue                   | Patient does not, intentionally or unintentionally, use / take drug as agreed                                                  | → Quick guide inhalators - https://sykehusapoteket.no/Documents/Inhalasjonsmedisin%20for%20sykehusleger.pdf  
→ Videos – use of inhalators - https://www.felleskatalogen.no/medisin/bruk-av-inhalator/aerochamber |
| Other                             | E.g. prescription errors, documentation errors                                                                               | → The patient’s medical record |

42
THE INTERVENTION TO TAILOR DRUG THERAPY

The in-hospital intervention to tailor drug therapy to the individual patient was delivered to patients randomized to the intervention group in the study described in Paper III. This was a thorough intervention, and implied the inclusion of clinical pharmacist(s) in the patients’ multidisciplinary treatment team during the entire hospital stay, working in close collaboration with the patient, physicians, nursing staff and clinical nutrition physiologists and/or physiotherapists if needed. The intervention can be divided into three parts covering the patients’ hospital stay; medicines reconciliation at admission, medicines review repeatedly during the entire stay and medicines reconciliation and information at discharge. Medicines reviews were performed at admission and repeatedly as needed due to changes in either prescription, patient symptoms, clinical state, and/or laboratory values. Patients were reviewed for such changes daily, Monday to Friday, during regular daytime working hours. Identified medicines discrepancies and DRPs were consecutively discussed in the multidisciplinary treatment team. At discharge, a medicines reconciliation was conducted, followed by written and oral information tailored to the patient’s further needs of care, provided to the patient and/or next care provider. The main goals were to answer drug questions, to ensure continuous treatment, to increase adherence, and to provide the patient and/or next care provider a complete overview of all drugs. To achieve this, the pharmacists provided one or more of the tasks described in Table 5.

Table 5 Description of the tasks included in the intervention at discharge and when they should be applied.

<table>
<thead>
<tr>
<th>Task</th>
<th>When should the task be applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral information/conversation with the patient and/or relative adapted to patient needs ¹</td>
<td>If the patient and/or the relative to some extent should handle the patient’s drugs after discharge</td>
</tr>
<tr>
<td>Written information to the patient and/or relative</td>
<td>If the patient and/or the relative to some extent should handle the patient’s drugs after discharge</td>
</tr>
<tr>
<td>Written information to the next care provider ²</td>
<td>For all patients</td>
</tr>
<tr>
<td>Assistance with retrieving drugs from the pharmacy</td>
<td>If needed</td>
</tr>
<tr>
<td>Providing the patient with drugs from the hospital pending on an updated multidose delivery</td>
<td>If needed</td>
</tr>
</tbody>
</table>

¹ Sometimes regarding the entire drug list, sometimes the most important changes, sometimes regarding one specific drug. If the patient was considered to benefit from any provided information or given the opportunity to ask questions, such a targeted conversation was conducted, even if a complex conversation was not considered favorable.

² The general practitioner, nursing home, home nurse and/or multidose delivering pharmacy.
DATA ON HOSPITAL ADMISSIONS AND MORTALITY

The Norwegian Patient Registry (NPR) provided data on hospital admissions. This registry contains data on all patients who have received treatment in the secondary health care in Norway. We used data from somatic hospitals on patients included in the study described in Paper III.

Data on mortality were provided by The Norwegian Cause of Death Registry, which covers information of all deaths in Norway, as well as deaths of Norwegians who die abroad (163). Both NPR and The Norwegian Cause of Death Registry deliver information on a personally identifiable level. Hence, to be able to collect these variables, having a Norwegian personal identification number was included as an inclusion criterion in the studies described in papers II and III.

RELATIONSHIPS BETWEEN DRUG ISSUES AND HOSPITALIZATIONS

Assessments of the relationships between drug issues and hospitalizations were performed with focus on drug-drug interactions (DDIs) in Paper I and with a general approach in Paper II. In both studies, the assessments were conducted retrospectively by a panel consisting of physician(s) and pharmacist(s). The panels had not the same composition in the two studies. A comprehensive, clinical assessment was performed for each individual patient as to whether the hospitalization was ‘possibly’ or ‘unlikely’ related to drug issues. This conservative method with only two categories was applied due to the limitations of using scoring tools to grade the probability of drug issues related to hospitalizations in our heterogeneous populations, where the complexity in symptoms, disease states and treatments makes differentiation of disease-related from drug-related issues very challenging.

The main principle during the assessments was whether the conglomerate of symptoms, laboratory values and/or recorded causes of hospitalizations could possibly be explained by the patient’s drug use or lack of drug use. When these premises were absent, the hospitalizations were assessed as ‘unlikely’ related to drug issues. The assessments in both studies were made in physical meetings, where the respective panels together discussed each case thoroughly (15-20 minutes per patient) until an agreement was reached.
In the study described in Paper I, all DDIs were assessed regardless of their severity categories in the electronic databases. The overall proportion of the DDIs possibly related to hospitalizations, and the respective distribution of severity categories, was calculated.

During the assessments in the study described in Paper II, the panel consisted of researchers not involved in patient inclusion and data collection. They received prefilled case report forms (CRFs) with the following information: sex, age, brief medical history, symptoms at hospitalization, laboratory results, reconciled drug list at hospitalization, discharge diagnoses and results from the pharmacogenetic analyses. The panel was blinded to prospectively revealed drug-related problems (DRPs) and Charlson Comorbidity Index (CCI) score, to be able to include these as candidate variables in the following logistic regression analysis investigating potential risk factors for DRHs. Information beyond the CRFs was drawn from the patient records if required. The potential clinical relevance of the identified GDIs was included in the DRH assessments based on the expected consequences of the GDI. All drugs involved in ‘possible’ DRHs, and GDIs that influenced the assessments, were systematically registered.
DATA PROCESSING AND STATISTICAL CONSIDERATIONS

Data in Paper I was analysed with GraphPad prism version 5 (GraphPad Software Inc., La Jolla, CA, USA). P values < 0.05 were regarded as statistically significant. Descriptive statistics were presented as median values with ranges. The association between the number of regularly prescribed drugs at admission and the number of DDIs identified as being of major or moderate severity was analysed by Spearman’s correlation coefficient. Fisher’s exact tests were used to compare the odds for prescribing changes in relation to DDI type (pharmacokinetic versus pharmacodynamic) and DDI severity (major versus moderate). Odds ratios with 95% confidence intervals (CI) were reported.

With help from Regional Research Support, a research database for the studies described in Papers II and III was developed, using EpiData (EpiData Association, Denmark). All data was manually punched into this database. Another researcher assured the quality of the data punching by the following pre-defined protocol:

- **Critical variables** were controlled in every second participant. If errors were revealed in more than 5% of the variables, all participants should be controlled.
- **All variables** were controlled in 20 randomly selected participants, 10 of the first 200 and 10 of the last 200. If errors were revealed in more than 10% of the variables, additional 10 randomly selected participants should be controlled. If errors were revealed in more than 10% of the variables in these 10 participants, all 200 patients should be controlled. The same procedure was followed for the last 200 participants.

Following the quality assurance, all data was exported from EpiData to IBM SPSS (Statistical Program for Social Sciences) Software version 25.0 (IBM Corp. NY). The SPSS files were validated before the data was analysed. P values < 0.05 were regarded as statistically significant. Descriptive statistics were presented as median values with ranges, numbers, percentages, and proportions.

In Paper II, all patient variables and the occurrence of DRP subgroups were initially compared between patients with DRHs versus non-DRHs using the chi-square test for proportions and Mann-Whitney test for continuous variables. Variables with p values < 0.2 in the simple comparisons were then included a subsequent multiple logistic regression analysis with DRH as the dependent variable. If the association between an independent variable and DRH
appeared to be approximately linear, it was treated a continuous variable in the model. Otherwise, it was included as a categorical variable. To our knowledge, no interactions between the variables are known, hence no interaction terms were added. Backward elimination of non-significant variables was performed, and the final model was restricted to include explanatory variables with p values < 0.05. Excluded variables were reintroduced one by one in the final model to ensure that important measured variables had not been left out. Adjusted ORs with 95% CIs were reported.

A statistical analysis plan (SAP), was developed and signed by the three researchers involved in data analyses in the study described in Paper III before outcome data files were received. The analysis population was defined in the SAP, and excluded patients who died during the index hospital stay due to never being at risk for readmissions, as well as erroneously included patients. Time-to-event endpoints were analysed by the Kaplan Meier method, log-rank test, and Cox’ proportional hazards model (164). Hazard ratios (HR) are presented with 95% CIs. The proportionality assumption was checked by visual inspection of log(-log) plots. In a randomized trial, the distribution of prognostic factors is expected to be similar in the two groups, and the primary analysis is unadjusted. We have nevertheless added sensitivity analyses adjusting for variables thought to be the most important prognostic factors, i.e. age and comorbidity which are strongly related to the risk of readmissions (165-169). Continuous variable endpoints were compared between the two groups using Mann-Whitney tests.

**RANDOMIZATION AND BLINDING**

In the study described in Paper III, the patients were randomized 1:1 to the intervention or control group. The Centre for Biostatistics and Epidemiology, Oslo University Hospital, was responsible for the randomization procedure. Their staff had no contact with patients, study pharmacists or ward staff. A random number generator program and a permuted block design were used to generate the randomization sequence, which was delivered to the study pharmacists in sequentially numbered, opaque, sealed envelopes. The investigators were blinded to block size, which was randomly varied. Randomization took place following patient inclusion and baseline assessments. A study pharmacist assigned the envelope with the lowest number to the individual participant and signed the allocation before the envelope was opened.
It was neither feasible to blind participants nor study pharmacists to the allocation. It was also known by ward staff which patients belonged to the intervention group. Ward staff was, however, unable to distinguish between patients randomized to the control group and patients not participating in the trial. The staff providing outcome data were not involved in data collection or preparation of data files and were blinded to group allocation. The primary endpoint analysis was conducted on a blinded dataset, by researchers who did not see patients.

SAMPLE SIZE OF THE RANDOMIZED CONTROLLED TRIAL

The sample size calculation was based on an expected readmission frequency of 50% in 12 months (139), in line with corresponding readmission frequencies for patients discharged from the internal medicine ward (information from South-Eastern Norway Regional Health Authority). It was estimated that to detect a 15% absolute reduction in hospital readmissions with 80% power and a significance level of 5%, we would need 168 patients in each group. To compensate for any dropouts, it was decided to enroll 200 patients in each group.
ETHICAL CONSIDERATIONS

All studies were approved by the Regional Committee for Medical and Health Research Ethics (Paper I: 2010/1636/REK south-eastern, Papers II and III: 2014/704/REK south-eastern D) and the Privacy Ombudsman at Oslo University Hospital. The RCT described in Paper III was registered in ClinicalTrials.gov (NCT02336113).

Patients were enrolled following written informed consent. Obtaining informed consent could be challenging in some patients suffering from cognitive impairment or severe illness, which make them less contactable. It is important to get the most realistic picture of the clinical "real life", and it is equally important for patients lacking the capacity to consent, to be included in studies which aim to gain knowledge of how healthcare services best can be provided to them. Therefore, for patients lacking the ability to consent, written informed consent was obtained from their next of kin. An information leaflet describing all steps of the study, that participation was voluntary, and that they at any time could withdraw from the study without stating a reason, was delivered to all consenting patients or next of kins. We considered it unlikely that participation entailed any disadvantages for the participants. The blood sample to genotype the participants in the study described in Paper II was aimed to be taken as part of other blood tests, to avoid an extra needle stick. The tubes with blood for genotyping were marked with the participant’s study number and stored in a freezer in a locked room before transported by a project member to Diakonhjemmet Hospital for analyses. A biobank was established after approval from the Regional Committee for Medical and Health Research Ethics.

All patient data collected were handled confidentially, stored in a locked cabinet, and not taken out of the hospital. Data was aggregated without patient names or personal identification numbers, with a study number per patient, and the code list connecting patient identification to study number was stored in a locked cabinet separated from other data. Electronic data were stored with password-protection on the research server of Oslo University Hospital.

The basic ethics behind allocating participants to two treatments groups in a RCT, comprises clinical equipoise, i.e. that none of the treatments are regarded better than the other (170).
With respect to the RCT presented in Paper III, we considered that there was a true uncertainty regarding the effect of tailoring drug therapy to multimorbid patients, and considered it ethically acceptable to conduct the trial. Furthermore, most multimorbid patients in Norway do not receive such care. Hence the principle in the Declaration of Helsinki was fulfilled, that not participating in the trial not intentionally would affect the standard of care provided during the hospital stay (170, 171).

Planning the studies described in papers II and III, we had thorough discussions on whether it was ethically acceptable to conduct medicines reconciliations and -reviews in control patients, without discussing any medicines discrepancies or DRPs with the patient or in the multidisciplinary treatment team. We decided that, if medicines discrepancies or DRPs that could result in irreversible detrimental effects or death if not handled immediately, were revealed in control patients, the study pharmacist should discuss the case with a senior physician (the project leader), who decided whether it was necessary to intervene. To reduce bias, the pharmacist made an individual written assessment before randomization took place, whether a discussion with the senior physician was needed or not, if the patient then were allocated to the control group. In this way, control patients were given a minimum service consisting of improved drug therapy regarding their most severe DRPs, possibly preventing death or detrimental effects. By including such a discussion of the most severe DRPs in control patients as part of the study design, we could not see any ethical concerns conducting the study.
RESULTS

This chapter summarizes the main results and conclusions of the three papers, illustrates the total flow of patients in Papers II and III, and provides results from sensitivity analyses conducted in the RCT described in Paper III. Further details of the results are given in each paper.

PAPER I

The first paper reports frequency, severity and management of DDIs in acute geriatric patients at hospitalization and during a hospital stay. In total 126 patients were included, median age was 86 (range 65–101) years, the median number of regular drugs registered in use at admission was 4.5 (range 0-14), and 74 (59%) were women. The main findings were:

- The majority of patients had DDIs revealed at hospitalization and/or during the stay:
  - In total 450 DDIs in all severity categories were revealed in 98 patients (78%)
  - 245 DDIs of major or moderate severity were revealed in 80 patients (64%)
- In approximately every fifth patient (i.e. in 28 patients), the hospitalization was classified as ‘possible’ related to DDIs
- Approximately one-third of the DDIs assessed as ‘possible’ related to hospitalization, were classified as being of minor relevance in the electronic DDI databases
- Major and/or moderate DDIs were introduced in 50 patients (40%) during the hospital stay
- The geriatricians implemented risk-preventive actions for 94 of the 162 DDIs (58 %) that were presented by the pharmacists at the interdisciplinary meetings
- Increased risk of bleeding (59 cases) or excessive sedation/reduced attention (33 cases) were the most frequent types of consequences associated with the identified major/moderate DDIs

In conclusion, the study showed that acute geriatric patients frequently are exposed to DDIs, both at hospital admission and during the hospital stay. DDIs not considered to be of clinical relevance on a general basis could potentially cause hospitalizations in vulnerable elderly patients. It is therefore essential that skilled professional evaluations of individual risks are
combined with the standardized information from interaction databases, to assess and manage DDIs in an acute geriatric setting.

PAPER II

The second paper reports prevalence and risk factors associated with drug-related hospitalizations (DRHs) in multimorbid patients using minimum four regular drugs. A total of 404 participants were enrolled in the study. Median age was 79 years (range 23-96) and 216 patients were women (54%). The median number of regular drugs was 8 (range 4-19), the median number of diagnoses was 7 (range 2-17), and the median number of DRPs per patient was 13 (range 3-42). The main findings were:

- Almost 40% of the hospitalizations (155 cases) were assessed as ‘possibly’ drug-related, i.e. DRH
- Presence of three specific DRP subgroups were associated with higher odds for DRHs:
  - Presence of suspected adverse events and adherence issues was associated with around a threefold increased odds for DRHs
  - Presence of drug monitoring DRPs was associated with around a twofold increased odds for DRHs
- Home nurse assistance was associated with almost a twofold increased odds for DRHs
- Patients with the highest Charlson Comorbidity Index score had reduced odds for DRHs
- Patients receiving multidose-dispensed drugs:
  - Had significantly more DRPs compared to patients not receiving multidose
  - Represented a significantly higher proportion of patients with DRHs versus of patients with non-DRHs, i.e. 30% versus 20% (p=0.035), in univariate comparisons. In the adjusted analysis, multidose did not remain a risk factor for DRHs.
- Gene-drug-interaction (GDI):
  - Were revealed in the majority of participants, i.e. 287 patients (71%)
  - Influenced the DRH assessments in 41 of the 155 patients (27%)
In conclusion, the study showed that DRHs are prevalent in multimorbid patients. Several factors were associated with increased risk of DRHs in this patient group, with adverse event DRPs and adherence issues being most important. As DRPs generally are regarded as preventable, this suggests that a major proportion of the hospitalizations assessed as drug-related in this study could be avoided by sufficient actions to improve the quality of drug therapy in multimorbid patients.

PAPER III

Paper III reports results from a RCT investigating the effect of in-hospital tailoring of drug therapy to multimorbid patients, on long-term hospital readmissions and survival. The analysis population comprised 386 patients, 193 in each group. See the next section for total flow of patients in Papers II and III.

The median age of the analysis population in Paper III was 79 years (range 23-96), the median number of regular drugs was 8 (range 4-19) and the median number of diagnoses was 7 (range 2-17). 213 (55%) were women. The median number of DRPs revealed during baseline assessments were 13 (range 3-42). The main findings were:

- During 12 months follow-up, tailoring of drug therapy prolonged the median time to readmission or death with approximately 2.5 months compared with patients receiving standard care, although not statistically significant at the 5% level (HR 0.82, 95% CI 0.64-1.04, p=0.106). Figure 3 shows time to readmission or death in the two groups.
- Tailoring of drug therapy statistically significantly increased overall survival, HR 0.66, 95% CI 0.48-0.90, p=0.007, as shown in Figure 4.
- No differences were observed between the groups in the number of unplanned hospitalizations within 12 months or the length of stay of the first readmission
Figure 3 Time to hospital readmission or death in the intervention versus control group.

Figure 4 Overall survival in the intervention versus control group.
Participants to the studies described in papers II and III were included during the same period. The study populations hence comprise many of the same individuals. Figure 5 shows the total flow of patients. During the study period, 2174 patients were admitted to the internal medicine ward and 1769 patients (81%) were considered for inclusion.

*the same participant

**Figure 5** Flow of patients in papers II and III.
SENSITIVITY ANALYSES OF THE RCT

A set of sensitivity analyses in addition to the primary analyses of the RCT presented in Paper III were conducted. Some, but not all, are presented in the paper. Table 6 shows estimated HR with 95% CIs from all sensitivity analyses conducted, together with the results of the primary analyses.

Table 6 Results from primary analyses and sensitivity analyses of the randomized controlled trial.

<table>
<thead>
<tr>
<th>Type of analysis</th>
<th>Endpoint</th>
<th>Follow-up in months</th>
<th>Hazard ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>Time to readmission or death</td>
<td>12</td>
<td>0.82 (0.64-1.04)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Time to readmission or death, excluding 6 control patients who were intervened on due to severe drug-related problems</td>
<td>12</td>
<td>0.85 (0.68-1.06)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Time to readmission or death</td>
<td>21-40</td>
<td>0.84 (0.68-1.05)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Time to readmission, censored for death</td>
<td>12</td>
<td>0.81 (0.63-1.04)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Time to readmission, censored for death</td>
<td>21-40</td>
<td>0.85 (0.68-1.06)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Time to readmission or death, adjusted for age</td>
<td>12</td>
<td>0.83 (0.65-1.06)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Time to readmission or death, adjusted for Charlson Comorbidity Index (CCI) score</td>
<td>12</td>
<td>0.87 (0.68-1.11)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Time to readmission or death, adjusted for age and CCI score</td>
<td>12</td>
<td>0.87 (0.68-1.11)</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Overall survival</td>
<td>21-40</td>
<td>0.66 (0.48-0.90)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Overall survival, excluding 6 control patients who were intervened on due to severe drug-related problems</td>
<td>21-40</td>
<td>0.65 (0.48-0.89)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Overall survival, adjusted for age</td>
<td>21-40</td>
<td>0.69 (0.51-0.95)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Overall survival, adjusted for CCI score</td>
<td>21-40</td>
<td>0.70 (0.51-0.96)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>Overall survival, adjusted for age and CCI score</td>
<td>21-40</td>
<td>0.73 (0.54-1.01)</td>
</tr>
</tbody>
</table>

The sensitivity analyses did not influence the estimated effect of the intervention.
DISCUSSION

DISCUSSION OF MAIN FINDINGS

In this section, the main findings of the papers will be discussed. Further details are given in each paper.

**Acute geriatric patients are frequently exposed to drug-drug interactions (DDIs)**

In the study described in Paper I, DDIs of major or moderate severity were identified in more than 60% of the patients at admission and/or during the hospital stay. This prevalence is in line with other studies on DDIs in hospitalized older patients (172, 173). Shortly after Paper I was published, two studies on DDIs from acute geriatric wards in Belgium and Italy were published (174, 175). In the Belgian study, in total 240 DDIs were identified in the 50 included patients (174), compared to the 450 DDIs in 126 patients in our study. The Italian study found a prevalence of DDIs at hospital admission considerably higher than in our study, i.e. DDIs of all severity categories in 91% of patients, and DDIs of moderate to major severity in 87% of patients (175). This might be explained by their study population using a higher number of drugs, than our study population. A speculation is that their electronic database software specially developed for multimorbid elderly alerts more often than similar systems for “normal” patients, and might be an additional reason for the higher prevalence of DDIs observed in their study.

DDIs were revealed in the majority of the patients. Not only were the patients both exposed to DDIs at hospitalization and new DDIs during the hospital stay, the DDIs were also assessed as possibly causing the hospitalization in every fifth patient. This latter finding was shared by the Belgian study, were 10 of the 50 hospitalizations were attributed to an adverse drug event which could be related to one or more DDIs (174). DDIs are predictable, suggesting that conducting risk-reducing actions, both in the primary and secondary healthcare might prevent potentially severe DDIs in the elderly, and thereby reduce and avoid unfortunate clinical outcomes. Integrating DDI managing expertise, e.g. clinical pharmacists, into multidisciplinary treatment teams, is a possible approach to achieve safer drug therapy in the elderly.
Approximately one-third of DDIs assessed as ‘possible’ related to hospitalization were classified as of minor relevance in the databases. This might be explained both by organ dysfunction and age-related reduction in homeostatic capacity, which contribute to increased risk of clinically relevant DDIs in the elderly (90, 176). Our finding underpins the importance of clinical judgments in addition to the use of clinical decision support tools or databases for the detection and management of DDIs in these vulnerable patients. This is supported by the results of the Belgian study, in which clinical pharmacists were found to perform better than DDI-alerts from a clinical decision support system in both identifying and solving DDIs (174). Computerized advice will probably never be able to replace human experts in this context due to both the need of a clinical judgment, and the general challenge of healthcare providers overriding or ignoring alerts in such systems (177). This is important to keep in mind in our increasingly computerized society. Research fields outside the healthcare system have concluded that increasing complexity of computerized systems, trigger the additional need of human professional utmost expertize (178). This may be a useful reasoning to bring into healthcare.

The geriatricians made risk-reducing actions in as many as 58 % of the DDIs that were presented by the pharmacists at the multidisciplinary meetings, reflecting the close collaboration. Furthermore, this highlights the importance of dedicated healthcare providers focusing on these patients’ drug use during the hospitalization. This interpretation is reinforced by the fact that a high proportion of patients was exposed to new DDIs during their hospital stay, a finding shared by a study published shortly after Paper I (175).

**Drug-related hospitalizations are prevalent in multimorbid patients**

To the best of our knowledge, the study described in paper II is the first to characterize drug-related hospitalizations in multimorbid patients. Almost 40% of hospitalizations were assessed as *possibly* being drug-related, a frequency substantially higher than in many other patient populations (84, 115-117). Important considerations are that morbidity increases the vulnerability towards drugs (32-34) and that the included patients used a minimum of four regular drugs, which generally increases the risk of DRPs (82, 87). Avoiding DRHs, which are generally regarded as preventable, is clearly a possible approach towards improved clinical outcomes in vulnerable multimorbid patients, to the benefit of both patients and society.
Presence of three specific DRP subgroups was associated with higher odds for DRHs, namely suspected adverse events, adherence issues and drug monitoring DRPs. Other studies investigating types of DRPs most frequently associated with DRHs in various patient populations, share similar findings (84, 109, 115, 117, 118). However, our study is the first to include specific DRP subgroups together with non-drug-related factors in a multiple logistic regression analysis to investigate the impact on risk of DRHs. As DRPs are generally regarded as preventable, this suggests that targeted actions to reveal and solve suspected adverse events, adherence issues and drug monitoring DRPs, could prevent hospitalizations in multimorbid patients. This underpins the importance of a proactive approach towards safer drug therapy and the need for care personnel especially dedicated to performing this task. With the increasing subpopulation of multimorbid patients, often followed by the use of numerous drugs, this need must be expected to increase in the future.

Adherence issues were revealed as one of the most important risk factors for DRHs. Interestingly, non-adherence is one of the most widely cited consequences of treatment burden (69), and may, therefore, be expected present in multimorbid patients. Close communication between healthcare providers and patients and involving patients in drug therapy decisions is believed to be important to improve adherence (179).

The use of numerous drugs have been identified as a major risk factor for DRHs in most studies (84, 112, 113). In contrast to several other studies (109, 112, 180), we did not find that the overall number of regularly used drugs was associated with risk of DRHs. This might imply that reducing the number of drugs per se is not enough to prevent DRHs in multimorbid patients and that a closer follow-up of specific DRP subgroups, should be prioritized.

A rather provoking result was that receiving home nurse care was associated with higher odds of DRHs. In Norway, multidose is often a prerequisite for receiving home nurse care. Home nurse and multidose services are intended to improve treatment quality. However, the results from our study suggest the opposite and that the quality of provided care is a possible target for improvements. This is also shown in other studies (181-184). Improving the cooperation between different care providers (183, 185, 186) and/or a multidisciplinary home care (187-189), may be possible approaches towards improved care quality, which again may lead to improved patient outcomes.

Patients with the highest Charlson Comorbidity Index (CCI) score had reduced odds for DRHs, probably reflecting that they are hospitalized more frequently due to disease
progression rather than drug-related issues. The finding suggests that focus should be on optimizing drug treatment in the healthiest of the multimorbid patients. This is in accordance with the results of a previous Swedish study, where a pharmacist intervention was more effective in preventing emergency department visits in patients using fewer drugs (150). However, additional studies are required to evaluate the effect of interventions to prevent DRHs in multimorbid patients, including which patients that will benefit the most.

**Tailoring drug therapy can improve the prognosis of multimorbid patients**

In the RCT described in Paper III, tailoring drug therapy prolonged time to hospitalization or death by almost 2.5 months within a 12 months period, although not statistically significant on the 5% level. The sample size calculation was based on a target 15% reduction in readmissions, which may have been optimistic. However, it was not feasible to include more than 400 patients. Insufficient power may explain the non-significant result, but the 95% confidence interval is wide and compatible with a risk reduction of 36% as well as a small increase. The likelihood of a true effect of the intervention is supported by the upper limit of the CI being close to 1. Furthermore, sensitivity analyses, including adjustment for baseline characteristics, did not influence the estimated effect of the intervention. The likelihood of an effect is to some extent supported by the significantly reduced mortality.

This is, to our knowledge, the first study to investigate the effect of tailoring drug therapy on clinically relevant outcomes in multimorbid patients. Two previous RCTs on the effect of similar interventions provided to other patient populations show similar results on readmissions, i.e. a decreased readmission rate, 20 days prolonged time to readmission and a reduction in hospital visits (124, 139). The observed increase in median time to readmission or death of almost 2.5 months might, although not statistically significant, indicate that multimorbid patients are more susceptible to such an intervention.

To our knowledge, this is the first study to show an effect of tailoring drug therapy on survival. This endpoint was either not investigated (139), or no effect was seen (124), in the previous studies on similar interventions. The results of our study are in contrast to the recent Cochrane review concluding that “medication review does not seem to prevent death and hospital readmissions” (138). This might be explained by the inclusion of a high-risk patient
population and long-term follow-up in the present study, which probably contributes to the intervention’s effect on mortality. Clinical pharmacists performing the thorough intervention in close collaboration with the patient, physician and other members of the multidisciplinary treatment team are also likely to be a success criterion.

Altogether, the promising results from our study reflects a great potential for improvement in the care provided to multimorbid patients. As a response to the increasing challenges of providing safe and evidence-based healthcare to high-risk multimorbid patients, further studies should be conducted to investigate the effect of such an intervention in a larger scale.

DISCUSSION OF METHODOLOGY

Study design

In the studies described in papers I and II, we aimed to investigate the prevalence of drug-drug interactions (DDIs) and drug-related hospitalizations (DRHs) respectively. An observational approach is suitable to answer research questions regarding prevalence (164, 190).

In the study described in Paper I, we also aimed to study the management of DDIs. Study pharmacists participated in multidisciplinary team meetings, and discussed and presented possible solutions on how to manage the DDIs. All decisions made by the geriatricians during the multidisciplinary meetings were recorded. A retrospective approach was chosen in both studies described in papers I and II, to assess if DDIs and drugs in general were possibly or unlikely related to the hospitalization. In the study described in Paper II, these assessments were used to investigate risk factors for DRHs.

In the study described in Paper III, we aimed to study the effect of an intervention. A randomized controlled trial provides the best evidence on the effectiveness of interventions (164) and was hence chosen as the study design. We aimed to include patients most sensitive to an intervention tailoring drug therapy, i.e. multimorbid patients using numerous drugs. The internal medicine ward receives mainly such patients and was chosen as the preferred ward to conduct the RCT. Acute admission was chosen as an inclusion criterion, as such admissions
might be caused by DRPs, and the patient hence might be susceptible to an intervention
tailoring drug therapy.

Since there is no consensus on the definition of multimorbidity (11), studies on multimorbid
patients tend to use different definitions and inclusion criteria (191). Counting conditions or
diagnoses at hospitalization may be challenging due to lack of information in the medical
record and/or inadequate information provided by the patient, next of kin, and/or the general
practitioner. We considered it more feasible and reliable to count drugs. “Use of minimum 4
regular drugs from minimum 2 therapeutic classes” was the inclusion criterion used as a
surrogate for multimorbidity, defined as the presence of minimum two conditions (11). As
medicines discrepancies is a well-known phenomenon at hospitalization (98-100, 135), we
decided that the patient would be excluded if she/he, after a medicines reconciliation was
conducted no longer fulfilled this criterion. Our inclusion criteria resulted in a study
population with a number of diagnoses ranging from 2 to 17, according to the patients’
medical record, hence within the most common definition of multimorbidity, i.e. having two
or more conditions (11).

In the study described in Paper III, the randomization should ensure no systematic differences
in known and unknown prognostic factors between the groups, and hence that estimated
treatment effects are not biased by confounders (164). It is crucial that baseline
characteristics, especially those expected to influence the outcome, are registered, to be able
to investigate if the randomization procedure has successfully led to comparable groups (164)
and unbiased efficacy estimates. Age is a strong predictor of readmissions (165-167). Gender,
comorbidity and earlier hospital stays may also predict readmissions (168, 169, 192). These
variables were therefore important to describe as characteristics of the study population. Level
of care after hospital discharge may influence the risk of readmissions (165) but was not
feasible to register during the follow-up, which may be considered as a study limitation.
However, the p-values from a randomized study can be regarded as valid.

*Lack of medicines reconciliation*

Medicines reconciliation were not performed in the study described in Paper I, which
constitutes an important limitation. Discrepancies between medicine lists in hospitals and the
drugs actually used by the patients is a well-known phenomenon, also shown in geriatric
patients (193, 194). Medicines discrepancies revealed by medicines reconciliation often
involves omissions of both over-the-counter as well as prescription drugs (135, 193, 194), which could have led to an underestimation of DDIs in the study. However, as previously described this limitation reflects the working methods used by clinical pharmacists in Norway at the time, in which medicines reconciliation was not included.

*Classification of drug-related problems*

Prescribing drugs to the multimorbid patient without introducing DRPs seems almost impossible, especially considering the fact that potential problems are included in the DRP definition. Adherence to specific therapy guidelines might result in DRPs, i.e. ‘contraindications’ due to coexisting conditions or ‘drug-drug interactions’ with drugs the patient receives in accordance with another therapy guideline. On the other hand, non-adherence to guidelines can result in ‘non-optimal drug therapy’ DRPs. It seems like whatever action the physician takes, it might trigger a DRP. The usefulness of reporting the potential problems as a part of research results can, therefore, be discussed. On the other hand, a proactive approach with respect to drug treatment is considered important from a clinical perspective (155, 195).

Definitions and classifications of DRPs used amongst researchers differ, which is a challenge when comparing results from different studies (196). The study described in Paper II was designed from a clinical perspective and we chose to report DRPs in risk categories as they prospectively were revealed by the clinical pharmacists, to best reflect “real life”. An alternative approach would have been to categorize DRPs according to a published classification system (80, 197). As our aim was to investigate risk factors of DRHs, not to investigate prevalence estimates of DRPs, such a time-consuming translation was not prioritized.

*Logistic regression*

The aim of the multiple logistic regression analysis presented in Paper II was to investigate risk factors for DRHs. Presence of a DRH hence was the dependent variable. The assessment of DRHs was performed by two researchers and was based on their subjective clinical judgment. They were not applying a validated scale, which could be considered as a limitation. Using comprehensive, clinical and pharmacological assessments as the
methodological approach to classify DRHs was, however, a predetermined decision based on the substantial complexity in symptoms, disease states and treatments in multimorbid patients which makes differentiation of disease-related from drug-related issues very challenging.

To reduce the risk of bias, we considered whether it would be useful to draw a directed acyclic graph (198). Searching the literature we found, however, no convincing evidence that any of our variables might act as mediators and we, therefore, decided to regard them as potential confounders and include all variables with a p value of less than 0.20 in simple analyses in the subsequent multiple regression analysis. In Norway, receiving multidose dispensed drugs is sometimes considered a prerequisite for receiving home nurse care, and these two variables were expected to be highly correlated. We, therefore, pre-decided that these two variables should not both be included in the final model. During model building, it turned out that the variable “multidose dispensed drugs” in any case was eliminated during the backward elimination process.

Preventability of drug-related hospitalizations

Earlier studies have shown that a high proportion of drug-related hospitalizations (DRHs) is preventable (84, 109, 114-118). We did not consider preventability of DRHs in the study presented in Paper II. One may argue that it might have been a better approach to use preventable DRHs as the dependent variable in the multiple logistic regression analysis. An assessment of preventable DRHs would, however, have introduced another step with a certain degree of subjectivity. Our results showed that the presence of three specific DRP subgroups was significantly associated with increased risk of DRHs, adjusted for other variables. DRPs are generally regarded as preventable (199), which indicates that hospitalizations assessed as drug-related in the current study might have been avoided. The same also applies to home nurse care revealed as a risk factor of DRHs, as quality improvements of this service might prevent DRHs.

Giving a minimum service to control patients in the RCT

Planning the studies described in Papers II and III, and a future study not included in this thesis, several perspectives had to be taken into consideration. We wanted to conduct the
study with baseline assessments for *all* patients, including medicines reconciliations and reviews, in order to:

- Increase precision when estimating associations between potential risk factors and DRHs (Paper II)
- Increase precision when estimating associations between potential risk factors and readmissions and which patients benefited most from the intervention (future study)

This gave rise to an ethical discussion, further described in the Ethical Considerations section, and resulted in the decision to intervene on DRPs revealed in control patients that could result in irreversible detrimental effects or death. The drawback of this decision was the possibility of diluting a potential effect of the intervention in the RCT, by giving control patients a minimum service. In total 6 control patients were intervened on, and the sensitivity analyses without these 6 patients, did not influence the estimated effect of the intervention tailoring drug therapy, shown in Table 6.

*The intervention in the RCT*

Results from the pharmacogenetics analysis were not used during tailoring of drug therapy in the RCT presented in Paper III, which constitutes a limitation. It was unfortunately not feasible to conduct the analysis prospectively and hence utilize the genotype/phenotype results during the medicines reviews.

The intervention in the RCT is indisputable complex, and evaluating such interventions is complicated (200, 201). A key question evaluating complex interventions is how the intervention works (200). The intervention consists of various components delivered as an overall intervention. With such a design, it is not known whether the overall intervention or only parts of this are important for effect.

Another major concern studying the effect of a complex intervention is the implementation, i.e. whether one succeeds in delivering the intervention as planned (201). All study pharmacists had attended structured training and had thorough experience with both medicines reconciliation and reviews by IMM, which strengthens the study. To provide the last part of the intervention, the discharge service, all study pharmacists had to attend training in patient communication. Participating in the discharge process, was however new for the pharmacists, and one may argue that more time should have been invested in the exploring
phase to assess how this best could be done. Written procedures of all components of the intervention, piloted at the ward by the two main study pharmacists before inclusion start, strengthen the study. A further strength was the use of several study pharmacists, which made us able to study the effect of the provided intervention, instead of studying the effect of an individual pharmacist.

Endpoints in the RCT

Endpoints reported in trials studying the effect of medicines review are heterogeneous, which may lead to limitations in the validity when results are compared across studies (202-204). Recently, a core outcome set (COS) with recommended outcomes to be used in studies on medicines review in multimorbid older patients with polypharmacy, was published (205). The COS was developed during a Delphi survey, involving older patients, healthcare professionals, and researchers. The two patient-reported outcomes in the final COS were “Health-related quality of life” and “Pain relief”. Interestingly, the latter has not been reported as an outcome in earlier studies but was considered of importance for the older patients participating in the survey (205). This illustrates that patient perspectives on the importance of outcomes may differ from the perspectives of both healthcare providers and researchers. One obvious limitation of the RCT described in Paper III is not taking into account the opinions of the investigated patient population, regarding the choice of endpoints. In the Delphi survey described above, all-cause hospitalizations and deaths were not considered as essential outcomes for most of the participators, including the old patients (205). Ranking quality over quantity may not be surprising due to the old age of these patients. This might, however, be different in a multimorbid population where also younger subjects are included, as in the RCT described in Paper III. A strength of our study was that both the study protocol and the information leaflet to study participants, were presented for user representatives in the Medical Clinic of Oslo University Hospital, and adjusted after their comments. Readmissions and survival are objective measures that could be measured with a high degree of precision and were easily assessable for all included patients through national registries. These are important criteria when healthcare outcomes are chosen (206). Obtaining accurate assessments of patient-reported outcome measures through adequate response rates may be challenging (206) and favor “hard endpoints”.

67
Readmissions and overall survival were chosen as the most important endpoints when studying the effect of the intervention. Readmission frequency is widely used as a quality indicator in healthcare and as an endpoint in healthcare related research (165, 169, 207-209). The unplanned readmissions are the most relevant in this context, as these are considered avoidable and could be targeted to reduce patient burden and save costs (169, 210). Unplanned readmissions may have complex causalities, e.g. too early or poorly planned hospital discharge or lack of collaboration or misunderstandings between the primary and secondary healthcare and may also include drug-related issues. Planned readmissions may be a result of close monitoring of chronic diseases, hence may reflect high-quality care. We, therefore, chose to include only the unplanned readmissions in the endpoint.

To best exploit the information in the readmission data and achieve the highest possible power, a time-to-event analysis was conducted instead of comparing proportions readmitted within a given point of time (211). The same was done for overall survival. It was considered unlikely that tailoring of drug therapy would have an effect beyond the first readmission, hence time to the first unplanned readmission was considered to be of primary interest. As death can be regarded as a competing risk to readmissions, it was considered appropriate to use readmission or death as the primary endpoint in this time-to-event analysis.

Using readmissions as measure a for quality of care, the chosen time aspect is often as short as 30 days, to make sure the readmission is related to the care provided in the index hospitalization (165, 209, 212). The effect of an intervention aiming to improve drug therapy might manifest only after a longer period of time, hence a longer follow-up may be assumed necessary (138). We, therefore, originally planned to follow patients 12 months on both readmissions and mortality like earlier studies on similar interventions (124, 139), and to comply with the request of long follow-up on such endpoints from the authors of a Cochrane review on medicines review (138). The inclusion of patients and the retrieval of outcome data files took a longer time than planned and we, therefore, decided to extend total follow-up of all patients to December 31, 2017, corresponding to 21-40 months, to increase statistical power and further comply with the request in the Cochrane review (138). This amendment was described in the statistical analysis plan, which was finalized and signed before any outcome data files were available.

Studies investigating the effect of interventions tailoring drug therapy have not been consistent regarding the choice of drug-related and/or all-cause hospital readmissions and mortality as endpoints (124, 139, 213). Drug-related-, and not all-cause readmissions, is one
of the seven core outcomes recommended for such studies in multimorbid older patients, in a recent publication by Beuscart et al (205). The authors of a recent Danish study argue, however, that “If a patient is readmitted because of nonadherence, this will typically manifest itself as a worsening of his or her underlying disease. Unless the patient confesses to being nonadherent, the readmission is unlikely to be recognized as drug related” (213). Hence, for interventions aiming to increase adherence, an aim covered during tailoring drug therapy in the RCT described in Paper III, reporting drug-related- instead of all-cause-hospitalizations and mortality, may not be optimal. Further, it is crucial that the chosen endpoint is measurable with high precision (206). If drug-related hospitalizations or mortality is chosen as an endpoint, the necessary information must be available to be able to conduct high-quality assessments. The national registries from which data on readmissions and deaths were retrieved, only contain main diagnose and additional diagnoses registered for the readmission or death. Variations in how these diagnoses are coded may introduce bias if they are used to calculate drug-related readmissions or death (206). As a conclusion, all-cause readmissions and deaths were chosen as endpoints.

Validity

Internal validity

Internal validity implies the reliability or accuracy of the results (190, 214). In the study presented in Paper I, the reported frequencies of drug-drug interactions (DDIs) are uncertain, due to the lack of medicines reconciliation. A strength of the study is a broad and similar approach for identifying DDIs for all patients through the use of two electronic databases. The reported management of DDIs may have been biased by factors such as personal skills, the involvement of only two pharmacists, and the interpersonal and professional relations between the pharmacists and the geriatricians. Nevertheless, the findings leave little doubt that the integration of pharmacists into multidisciplinary teams could play an important role in preventing potentially severe DDIs in elderly patients.

Reported frequencies of DRHs in the study described in Paper II, may be biased due to the assessment method, as mentioned in the discussion section of this thesis. The occurrence of adherence issues, adverse event, and drug monitoring DRPs were found associated with increased risk of DRHs as in other studies on older patients, which supports the validity of the DRH assessments in the present study. Including all relevant independent variables is an
essential step in multiple logistic regression, as the omission of variables associated with the
dependent variable may represent possible sources of bias. As in all observational studies,
residual confounding can not be ruled out, but we have not been able to identify obvious
unmeasured confounders.

A well-conducted randomization procedure where investigators were not able to predict group
allocation, standardized study procedures, several trained study pharmacists, blinding on the
steps possible to blind, and the use of endpoints measurable with high precision and easily
assessable for all included patients, strengthens internal validity of the RCT presented in
Paper III.

External validity

External validity implies that the study results can be generalized to individuals beyond the
study population. High internal validity is a prerequisite for external validity (190).

We did not have permission to register characteristics of patients declining to participate,
therefore we do not know whether non-participants differs from participants. In all three studies,
the patients’ with the poorest health and/or lacking interest in drug therapy could conceivably
have declined participation to a larger degree than others. This could have caused the study
population to comprise the healthiest multimorbid patients, and that study results not can be
generalized to the multimorbid patients with the poorest health. However, broad eligibility
criteria strengthen external validity of all three studies included in this thesis. A high inclusion
rate and low dropout rate strengthen the studies presented in Papers II and III. In the study
presented in Paper I, this was not registered, which represent a limitation.

The three studies included patients from a single hospital in Norway which may challenge the
transferability to other settings. In the studies described in Papers II and III, the required use
of at least four regular drugs from different ATC groups, resulting in the inclusion of
multimorbid patients, and prospective medicines reconciliation and reviews performed by
numerous specially trained clinical pharmacists, may be considered as factors contributing to
the transferability of the findings to other clinical settings with similar patient groups. In paper
III, standard care is described thoroughly, to make assessments of the results’ relevance in
other clinical settings easier (215, 216).
CONCLUSIONS & CLINICAL IMPLICATIONS

There is no doubt that the healthcare system needs to become better fit to provide safe, effective and evidence-based care to multimorbid and elderly patients with complex drug treatments. This PhD project included three studies, which by different approaches have gained knowledge of how we can move towards safer drug therapy and improved clinical outcomes in these vulnerable patients.

Drug-drug interactions (DDIs) occurred frequently in acute geriatric patients, both at hospital admission and during the hospital stay, and possibly causing one out of five hospitalizations. Targeted work to reveal, solve and prevent DDIs, e.g. by including clinical pharmacists with DDI-expertize in multidisciplinary treatment teams, may avoid unfavorable clinical outcomes in these patients.

Drug-related hospitalizations (DRHs) were shown to be prevalent in multimorbid patients. The most important risk factors for DRHs were the presence of suspected adverse events, and adherence issues, which are generally regarded as preventable. According to Norwegian regulations, patients who use a minimum of four drugs, or/and are nursing home residents, should regularly have a medicines review conducted by their general practitioner. By detecting and solving specific DRPs in the primary healthcare, drug-related hospitalizations could be avoided and hence clinical outcomes improved.

Receiving home nurse care was identified a risk factor for DRHs in our study, underpinning the need for improved cooperation between different healthcare providers to move from fragmented to seamless care. The study also showed that pharmacogenetics may play an important role as a source to DRPs, and should be considered as a future tool to provide safer drug therapy to multimorbid patients with complex treatments.

Our results illustrate how crucial the human factor is in providing safe drug therapy to elderly and multimorbid patients. Firstly, around one-third of DDIs assessed to possibly cause hospitalizations were classified as of minor clinical relevance in the DDI databases, emphasizing that it is essential that the standardized information in electronic databases are combined with skilled professional evaluations of individual risk factors. Secondly, adherence issues were one of the most important risk factors for DRHs, emphasizing the importance of
healthcare personnel having conversations with multimorbid patients regarding their drug therapy.

Tailoring drug therapy in-hospital to multimorbid patients prolonged time to readmission or death by almost 2.5 months within 12 months, although not statistically significant. A statistically significantly increased overall survival was seen. These promising results emphasizes the large potential for improvement in the care provided to this patient group. As a response to the increasing challenges of providing safe and evidence-based healthcare to high-risk multimorbid patients, further studies should be conducted to investigate the effect of such an intervention in a larger scale.
FUTURE RESEARCH

For further research, it will be useful to conduct a health economic analysis of the RCT. The basic task of an economic evaluation is to compare the cost and consequences between two or more alternatives (217), which may be an important tool in the prioritizing and allocation of health care resources (58, 218). The cost and consequences of the alternatives could be collected in a follow-up period after hospital discharge. Direct costs may include the number of hospital admissions, outpatient visits, emergency room visits, as well as primary health care costs, e.g. general practitioner visits, home nurse and nursing home services. Data from national registries can be used for such an analysis after obtaining necessary permissions.

All knowledge useful to better prioritize limited healthcare resources are highly valuable. Data collected in the studies described in Papers II and III are planned to be used to identify patient groups within the multimorbid population with risk factors for readmission and death, and who will benefit the most from tailoring drug therapy. The inclusion of a new cohort of 100 patients from the same internal medicine ward was finalized in July 2018, based on the same eligibility criteria and randomized between the same intervention and standard care. These patients will be used to validate the results from the original sample.

The discharge process was a new arena for the clinical pharmacists providing the intervention in the RCT and was experienced to be chaotic. Through a better understanding of the patients’ journey through the discharge process, discharge transitions can be improved to further increase patient safety and clinical outcomes. We are planning a qualitative study to map the discharge process to identify factors for success and failure towards seamless and safer drug care.

Planning the RCT described in Paper III, we originally wished to extend the intervention into the primary health care after hospital discharge, as evidence tends towards this being the most effective (219, 220). This proved difficult to achieve, but during presentation and discussion of our study throughout several years, potential collaborators to make this possible, have announced their interest. Future research could, therefore, include the development of a new service in collaboration with stakeholders, followed by investigating the effect of such an extended service, as illustrated in Figure 6. This should preferably be done by a multicenter study, to be able to include a large number of patients for sufficient power, as well as increase
the generalizability of the findings. Further, as the effect of tailoring drug therapy could be anticipated to wane over time, repeated tailoring of drug therapy, e.g. during eventual readmissions, would also be an exciting approach.

**Figure 6** Proposal for a service comprising tailoring of drug therapy, extended into the primary healthcare.
REFERENCES


44. Mutasingwa DR, Ge H, Upshur RE. How applicable are clinical practice guidelines to elderly patients with comorbidities? Canadian family physician Medecin de famille canadien. 2011;57(7):e253-62.


125. Mannucci PM, Nobili A. Multimorbidity and polypharmacy in the elderly: lessons from REPOSI. Internal and emergency medicine. 2014;9(7):723-34.


169. Heggestad T. Hospital readmissions and the distribution of health care. Analyses of the Norwegian national register data. [Dissertation for the degree of philosophia doctor (PhD)].: University of Bergen, Norway; 2009.


Prevalence and risk factors of drug-related hospitalizations in multimorbid patients admitted to an internal medicine ward

Drug-related hospitalizations

Marianne Lea* (MSc), Morten Mowe (MD, PhD), Liv Mathiesen (PhD), Kristin Kvernørd (MSc), Eva Skovlund (PhD) and Espen Molden (PhD)

1 Department of Pharmaceutical Services, Oslo Hospital Pharmacy, Hospital Pharmacies Enterprise, South Eastern Norway
2 General Internal Medicine Ward, the Medical Clinic, Oslo University Hospital, Norway
3 Faculty of Medicine, University of Oslo, Norway
4 Hospital Pharmacies Enterprise, South Eastern Norway
5 Department of Pharmacology and Pharmaceutical Biosciences, School of Pharmacy, University of Oslo, Norway
6 Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
7 Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway

*Corresponding author,

Address: Department of Pharmaceutical Services, Oslo Hospital Pharmacy, Kirkeveien 166 0450 Oslo, Norway
Phone: +47-23 20 52 94
E-mail: marianne.lea@sykehusapotekene.no

Original article
Abstract

**Background:** Knowledge of risk factors for drug-related hospitalizations (DRHs) is limited.

**Objectives:** To investigate prevalence and potential risk factors of DRHs in multimorbid patients admitted to an internal medicine ward.

**Methods:** Multimorbid patients ≥ 18 years, using minimum four regular drugs from minimum two therapeutic classes, were included from the Internal Medicine ward, Oslo University Hospital, Norway, August 2014 to March 2016. Clinical pharmacists prospectively conducted medicines reconciliations and reviews to reveal drug-related problems (DRPs). Blinded for identified DRPs, an interdisciplinary group retrospectively made comprehensive, clinical assessments of each patient case to classify hospitalizations as drug-related (DRH) or non-drug-related (non-DRH). Age, sex distribution, Charlson Comorbidity Index (CCI), renal function, genotypes, body-mass index, number of drugs, proportion with homecare service, and occurrence of different DRPs, were compared separately between patients with DRHs versus non-DRHs, followed by multiple logistic regression analysis.

**Results:** Hospitalizations were classified as drug-related in 155 of the 404 included patients (38%). Metoprolol was suspected related to DRHs 39 cases (25%). Factors significantly associated with DRHs were occurrence of adverse event DRPs (adjusted odds ratio (OR) 3.3, 95% confidence interval (CI) 1.4-8.0), adherence issues (OR 2.9, 1.1-7.2), homecare service (OR 1.9, 1.1-3.5), drug monitoring DRPs (OR 1.9, 1.2-3.0), and CCI score ≥6 (OR 0.33, 0.14-0.77). Frequencies of variant genotypes did not differ between the patient groups, but in 41 patients with DRHs (26.5%), gene-drug interactions influenced the clinical assessments.

**Conclusion:** DRHs are prevalent in multimorbid patients with adverse event DRPs and adherence issues as the most important risk factors.
KEY WORDS

Multimorbidity [MeSH], Patient safety [MeSH], Internal Medicine [MeSH], Pharmacogenetics [MeSH],

Drug-related hospitalizations, Drug-related problems
Introduction

Many previous studies have investigated the occurrence of drug-related hospitalizations (DRHs) in different patient populations [1-8]. A systematic review representing various patient groups reported that around 10% of all hospitalizations are drug-related [9]. In older adults, the reported prevalence of DRHs is higher, comprising around 30% of all hospitalizations [10, 11].

Preventing hospitalizations is important both for the benefit of the patients and society. A high proportion of DRHs are preventable [1-4, 9, 10, 12], but effective prevention requires knowledge of important risk factors. The causality of DRHs may be complex and involve many predisposing factors, such as patient characteristics, disease state, living situation, and drug-related problems (DRPs) [2-4, 7, 9, 10, 13-17]. Moreover, pharmacogenetic variability is a potential source of DRPs, which has not previously been investigated in relation to risk of DRHs.

Multimorbid patients represent a group with a high risk of DRPs [18]. This is a heterogeneous patient group, but a common feature is increased health care utilisation, including frequent hospitalizations, and multiple drug treatments [19-21]. The population of multimorbid patients is growing due to a steadily improving health care and increasing life expectancy [22, 23]. These patients are often admitted to internal medicine wards due to the complex nature of their disease state. They, therefore, comprise a resource-demanding patient group, where prevention of hospitalizations is crucial to reduce social costs and improve patient health.

Several studies have previously investigated prevalence and risk factors for DRHs in various patient population, e.g. cancer patients, geriatric patients and older patients with
dementia [5, 11, 24]. Advanced age and polypharmacy are main risk factors for DRHs identified in most studies [9, 25, 26]. However, to the best of our knowledge, no studies have investigated multimorbid patients with respect to prevalence and risk factors for DRHs. The aim of the present study was therefore to investigate prevalence and potential risk factors of DRHs in multimorbid patients admitted to an internal medicine ward.
Materials and methods

Study Design and Setting

This observational study, approved by the Regional Committee for Medical and Health Research Ethics (2014/704/REK south-eastern D) and the Privacy Ombudsman, was conducted at an internal medicine ward of Oslo University hospital (Ullevaal location), Norway, from August 2014 to March 2016. The study was embedded in a randomized controlled trial, ClinicalTrials.gov Identifier: NCT02336113, using baseline data at inclusion to assess drug-related hospitalizations. Patients were considered for inclusion by clinical pharmacists Monday to Friday during regular daytime working hours until a target number 400 patients were enrolled. Eligible patients were prospectively invited and enrolled in the study following written informed consent.

Figure 1 illustrates the outline of the study with the various steps and processes performed after patient inclusion. During the inclusion period, six trained clinical pharmacists, all with a master degree in clinical pharmacy, prospectively performed medicine reviews and identified DRPs at the time of admission, based on the reconciled drug list as described below. Information about sex, age, body-mass index (BMI), living situation and home care drug assistance was also registered. In addition, blood samples were collected for biochemical measurements and pharmacogenetic analyses of drug-metabolizing cytochrome P450 (CYP) enzymes and the transporter mediating uptake of statins from the blood into the liver (OATP1B1). Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula [27], except for obese patients (BMI > 30) where the Salazar-Corcoran formula was used [28]. An experienced senior physician
retrospectively collected diagnose information from the medical records to calculate the Charlson Comorbidity Index (CCI) score of each patient [29].

**Inclusion and exclusion criteria**

Inclusion criteria were: acute admission, age $\geq 18$ years and use of at least four regular drugs from at least two Anatomical Therapeutic Chemical (ATC) groups [30] at 1st level, at admission. The latter was a surrogate for multimorbidity, defined as the presence of minimum two conditions, a commonly used definition [31]. Exclusion criteria were i) terminally ill, ii) isolated due to severe infections, or iii) unable to communicate in Norwegian or English in lack of a translator. Patients readmitted during the study period were not invited for ‘a second’ inclusion.

**Prospective medicine reconciliation and review**

A Norwegian translation of the Integrated Medicines Management (IMM) model [32], adapted to the Norwegian setting, was used as the method for the systematic medicines reconciliations and reviews. Based on the reconciled medicine list, the clinical pharmacists performed systematic medicines reviews and revealed DRPs at the time of admission. The medicine reviews only included drugs used prior to admission, and not drugs initiated during transport to or following hospital admission. The pharmacists had access to the patient’s medical history and laboratory results (up to and including admission time) when performing medicine reviews.

A DRP was defined according to the Pharmaceutical Care Network Europe (PCNE) as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” [33]. Identified DRPs during the medicine reviews were classified in the following subgroups according to the IMM procedure; ‘drug monitoring’,

**Pharmacogenetic analyses**

Blood samples drawn from the included patients were applied for pharmacogenetic analyses at Diakonhjemmet Hospital, Oslo, Norway. The analyses were conducted retrospectively due to time constraints and therefore not included as a basis for the medicine reviews. For all included patients, variant allele analyses of CYP2D6, CYP2C19, CYP2C9, CYP3A5 and SLCO1B1 (encoding OATP1B1; uptake transporter of statins into the liver) were performed. For warfarin-treated patients, VKORC1 genotyping was also conducted. Overview of target genes variant alleles included in the genotyping panels and the respective genotype-predicted aberrant phenotypes are provided in Web-supplement 2. Briefly, for CYP2D6 and CYP2C19, the most relevant polymorphic enzymes involved in drug metabolism, homozygous carriers of non-coding (null) alleles were defined as ‘poor metabolizers’ (PMs) of the respective enzymes, while heterozygous carriers of null alleles and homozygous carriers of reduced-function alleles were defined as ‘intermediate metabolizers’ (IMs). Patients carrying three or more functional CYP2D6 gene copies were classified as CYP2D6 ‘ultrarapid metabolizers’ (UMs), while patients carrying CYP2C19*17 were classified as CYP2C19 UM.
Retrospective identification of gene-drug interactions (GDIs)

Retrospectively, the authors EM and ML identified gene-drug interactions (GDIs) by assessing the reconciled drug list against the respective patients’ genotype results. Knowledge of the respective genotypes’/phenotypes’ effects on pharmacokinetics or pharmacodynamics of drugs used by the patients were applied to define a GDI and assessments were restricted to aberrant phenotypes, as defined in Web-supplement 2. The potential clinical relevance of the identified GDIs was included in the retrospective assessments of drug-related hospitalizations based on the expected consequences of the GDI.

Retrospective assessment of drug-related hospitalization (DRH)

After patient inclusion, a senior geriatrician/internal medicine physician (author MM) and a pharmacologist (author EM) made comprehensive, clinical and pharmacological assessments for each individual patient as to whether the hospitalization was possibly drug-related (classified as DRH) or unlikely to be drug-related (classified as non-DRH). This conservative method with only two categories was applied due to the limitations of using scoring tools to grade the probability of DRHs in this heterogeneous population where the complexity in symptoms, disease states and treatments makes differentiation of disease-related from drug-related issues very challenging.

Prior to the assessments, the authors MM and EM received case report forms (CRFs) prefilled by the clinical pharmacist who organized the study (author ML). The following information was included in the CRFs: sex, age, brief medical history, symptoms at hospitalization, laboratory results, reconciled drug list at hospitalization, discharge diagnoses, and results from the pharmacogenetic analyses. MM and EM were blinded to
the DRPs revealed prospectively by the study pharmacists and the CCI score. The main principle during the assessments was whether the conglomerate of symptoms, laboratory values and/or recorded causes of hospitalizations could *possibly* be explained by the patient’s drug use or lack of drug use. When these premises were absent, the hospitalizations were assessed as *unlikely* to be drug-related. The assessments were made in physical meetings, where EM and MM together discussed each case thoroughly (15-20 minutes per patient) until agreement was reached, to classify hospitalizations as *possibly* or *unlikely* drug-related. Information beyond the CRFs was drawn from the patient records if required. Drugs involved in possible DRHs, and GDIs that influenced the DRH assessments, were systematically registered.

**Statistics**

All registered patient variables, i.e. age, sex, number of prescribed drugs, living situation, assistance with drug administration, BMI, GFR, CCI score, pharmacogenetic variability and occurrence of specific DRP subgroups were initially compared between patients with DRHs versus non-DRHs using chi-square test for proportions and Mann-Whitney test for continuous variables. Variables with p values < 0.2 in the simple comparisons were included in the subsequent multiple logistic regression analysis. Backward elimination of non-significant variables was performed, and the final model was restricted to include explanatory variables with p values < 0.05. Excluded variables were reintroduced one by one in the final model to ensure that important measured variables not had been left out. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

IBM SPSS Software version 25.0 (IBM Corp. NY), was used for all statistical analyses. P values < 0.05 were defined as statistically significant.
Results

During the study period, 2174 patients were admitted to the internal medicine ward and 1769 patients (81%) were considered for inclusion. Of these, 913 patients did not meet the predefined inclusion criteria and 258 patients were not asked to participate of practical reasons. Among the remaining 598 patients, 175 (29%) declined the invitation to participate in the study (permission to register reasons for declining not obtained). After excluding patients due to i) medicines reconciliation revealed use of less than four regular drugs (n=3), ii) erroneously reinclusion (n=1), iii) withdrawal of consent (n=8), and iv) acute events preventing data collection (in-hospital death; n=3, transfer to other wards; n=3, rapid discharge; n=1), a total of 404 participants were enrolled in the study.

The median age of the included patients was 79.4 years (range 23.1-96.4) and 216 patients (54%) were females. Most patients (n=373, 92%) were living at home prior to hospitalization, and the majority (n=283, 70%) administered the drugs themselves. Median number of regular and on demand drugs in the study population was 8 (range 4-19) and 2 (range 0-11) and median number of diagnoses was 7 (range 2-17), emphasizing the multimorbidity of the study participants. The median CCI score was 3 (range 0-12).

The five most frequent reasons for hospitalization described in the medical admission journal were infections (n=72), breathlessness (n=44), heart failure exacerbation (n=37), chest pain (n=35) and general functional impairment/failure (n=27).

In the medication reviews, the study pharmacists revealed a total number of 5527 DRPs, whereof 950 (17%) as a result of completing medicine lists during medicines reconciliation. The median number of DRPs per patient was 13 (range 3-42), and 315
patients (78%) had a minimum of one detected DRP on basis of information provided in the medicines reconciliation.

After comprehensive clinical and pharmacological assessments using information about patient characteristics, disease status and history, laboratory results, reconciled medicine lists, discharge diagnoses and pharmacogenetic profiles of all included patients, authors MM and EM retrospectively classified hospitalizations as possibly drug-related in 155 patients (38%). Web-supplement 3 shows the drugs most frequently involved in the underlying causes of hospitalization in the cases assessed as DRHs. Metoprolol was the drug most frequently suspected to be related to DRHs, i.e. in as much as 39 of the cases (25%). The drug next most frequently suspected to be related to hospitalization was bumetanide (21 cases), followed by zopiclone (15 cases) and insulin or insulin analouges (13 cases).

In 287 of the patients (71%), at least one gene-drug interaction (GDI) was identified (total number of GDIs 538). One or more GDIs were found to be of relevance for the DRH assessments in 41 of the patients (26.5%). In five patients, GDIs were decisive for classifying hospitalizations as possibly drug-related. Web-supplement 4 shows frequencies of the various GDIs identified in the patient population, as well as those relevant for DRH assessments. The most frequently involved agents in GDIs were metoprolol, comprising 125 of the 538 GDIs (23%), and warfarin, comprising 60 of the 538 GDIs (11%). Proton pump inhibitors, statins and opioids were also commonly involved in GDIs, with 84, 81 and 74 identified cases.

For 9 patients the relationship between drug treatment and hospitalization was not assessed due to insufficient information in the medical record. These patients were
excluded in the further comparative analyses of patients with possibly DRHs versus unlikely DRHs, in the further text described as ‘DRHs’ (155 patients) versus ‘non-DRHs’ (240 patients).

In Table 1, patients with DRHs and non-DRHs are compared with respect to age, sex, number of prescribed drugs, living situation, assistance with drug administration, BMI, GFR, CCI score and pharmacogenetic variability. The proportion receiving multidose-dispensed drugs was the only of these variables being significantly different between the cases of DRHs versus non-DRHs in the unadjusted analysis, i.e. 30% versus 20% (p = 0.035). In addition, home nurse assistance, CCI score, BMI and number of prescribed drugs had p values < 0.2 for comparisons between DRHs and non-DRHs, and were included as candidate variables in the subsequent multiple logistic regression analysis.

Table 2 shows comparisons between patients with DRHs and non-DRHs regarding occurrence of DRPs. Patients with DRHs had significantly more DRPs in total, and significantly more of the DRP subgroups ‘drug monitoring’, ‘adverse event’, ‘other’, ‘non-optimal drug therapy’, ‘reduced organ function / contraindication’ and ‘drug-drug interaction’. ‘Adherence issues’ were also observed more frequently in patients with DRHs versus non-DRHs (p = 0.050), and included in the multiple logistic regression analysis as a DRP subgroup.

In addition to the comparisons presented in Table 1 and Table 2, it was observed that patients with multidose-dispensed drugs had significantly more DRPs in total than other patients (median number 15 (range 4-34) versus 14 (range 3-44); p = 0.038).

Table 3 shows adjusted OR with 95% CIs for the variables statistically significantly associated with DRHs, comprising occurrence of adverse event DRPs (adjusted odds ratio
(OR 3.3, 95% confidence interval (CI) 1.4-8.0), adherence issues (OR 2.9, 1.1-7.2),
homecare service (OR 1.9, 1.1-3.5), drug monitoring DRPs (OR 1.9, 1.2-3.0), and CCI score ≥6 (OR 0.33, 0.14-0.77).
Discussion

In this study on multimorbid internal medicine patients, almost 40% of hospitalizations were assessed as possibly being drug-related. To the best of our knowledge, the study is the first to characterize drug-related hospitalizations in multimorbid patients. The frequency of drug-related hospitalizations was very high, and substantially higher than in many other patient populations. Important considerations are that morbidity increases the vulnerability towards drugs [34-36] and that the included patients used a minimum of four regular drugs, which generally increases the risk of DRPs [18, 37]. The results clearly indicate the potential of managing DRPs in multimorbid patients to prevent drug-related hospitalizations (DRHs) in this population. Drug groups associated with DRHs in previous studies [10, 13, 15], e.g. beta-blockers and diuretics, were similarly frequently involved in DRHs in the present study.

Presence of three specific DRP subgroups was associated with significantly higher odds for DRHs among the included patients. Patients with suspected adverse events and adherence issues had around a threefold increased odds of DRHs, and patients with drug monitoring DRPs had nearly a twofold increased odds. Similar findings have been reported in previous studies investigating the type of DRPs most frequently associated with DRHs in various patient populations [2-4, 9, 10]. However, the present study is the first to include specific DRP subgroups together with non-drug-related factors in a multiple logistic regression analysis to investigate the impact on risk of DRHs. By adjusting for different non-drug-related factors, adherence issues and adverse events DRPs were identified as major risk factors for DRHs in this population of multimorbid internal medicine patients. According to Norwegian regulations, patients who use a
minimum of four drugs, or/and are nursing home residents, should regularly have a medicines review conducted by their general practitioner. By detecting and solving suspected adverse events, adherence issues and drug monitoring DRPs in the primary healthcare, drug-related hospitalizations could be avoided.

Patients with the highest CCI score had a significantly reduced odds for DRHs compared to the reference group with the lowest CCI scores. This probably reflects that patients with a high degree of comorbidity more frequently are hospitalized due to disease progression rather than drug-related issues. The finding suggests that focus should be on optimizing drug treatment in the healthiest of the multimorbid patients, which is in accordance with the results of a previous Swedish study, where a pharmacist intervention was more effective in preventing emergency department visits in patients using fewer drugs [38]. However, additional studies are required to evaluate which patients that will benefit the most of medication reviews to prevent DRHs.

Home nurse care was associated with increased risk of DRHs in the study population. This is a provoking result, as home nurse care and multidose drug dispensing is intended to improve the treatment quality. However, these findings provide evidence for the opposite, which has also been reported in previous studies [39-41]. One reason for the increased risk of DRHs in the multimorbid patients receiving home nurse care may be insufficient cooperation between different health care providers [42, 43]. Thus, a more seamless information transfer between different health care levels may potentially prevent DRHs.

In contrast to several other studies [10, 13, 25], we did not find that the overall number of regularly used drugs was associated with risk of DRHs. This might imply that reducing
the number of drugs in use per se not is enough to prevent DRHs in multimorbid patients
and that closer follow-up of specific DRP subgroups and care routines should be
prioritized. However, for certain types of DRPs, and in particular drug-drug interactions
(DDIs), use of multiple drugs is generally regarded a risk factor. In a recent study, we
found that DDIs were a possible cause of hospitalization in 20% of acute geriatric
patients [44]. This finding was to some extent supported by the present study, where
patients with DRHs had significantly more DDIs than others in the unadjusted analysis.
However, in the adjusted analysis, the occurrence of DDIs did not remain a risk factor for
DRHs in the multimorbid patients.

In the same way as DDIs, gene-drug interactions (GDIs) represent a potential source of
DRHs. A unique feature of the present study was that we investigated pharmacogenetic
factors related to hospitalizations. While the frequencies of genotype-predicted poor
metabolizers did not differ between patients with and without DRHs, clinically relevant
GDIs, such as a five-fold increased systemic exposure of metoprolol in CYP2D6 poor
metabolizers, were considered to influence about 25% of the hospitalizations assessed as
possibly drug-related. Thus, pharmacogenetics should be included in future studies
investigating risk factors for DRHs, but standardized guidelines or tools on how to define
clinically relevant GDIs, as for DDIs, would be necessary for the generalisability of
research findings on this topic.

We did not consider preventability of the DRHs in the study, which represents an
important limitation. However, the significantly higher frequencies of several DRP
subgroups, which generally are regarded as preventable (i.e. adverse events, adherence
issues and drug monitoring), in patients with DRHs versus non-DRHs indicates that a
major proportion of the cases assessed as DRHs could have been avoided. The same also
applies to home nurse care as a risk factor for DRHs, as quality improvements of this
service might prevent DRHs.

In multimorbid patients, symptoms and disease states at hospital admission are complex,
which may limit the suitability of objective scoring tools as a basis for assessing
relationships between drug use and hospitalizations. Thus, we decided to use a method
for individual and comprehensive assessments using complete sets of clinical and
pharmacological data to classify hospitalization as ‘possibly’ or ‘unlikely’ drug-related.
This is a time-consuming method, but enables detailed assessments of clinical
characteristics related to the admissions. On the other hand, the validity of the
methodological approach is difficult to evaluate. Occurrence of adherence issues,
adverse event, and drug monitoring DRPs were found associated with increased risk of
DRHs as in other studies on older patients, which supports the validity of the DRH
assessments in the present study. However, a standardized chart review method to
identify drug-related hospital admissions in older people was recently published [45] and
could have enabled validation of the assessments in our study.

It is likely that the findings of our study will reflect other multimorbid patient populations
using multiple drugs from different therapeutic classes. However, as for other studies
investigating DRHs, the generalisability of the findings are not necessarily transferable to
other hospitals or clinical setting. Thus, further studies on the same patient group,
preferably also including additional factors of potential importance for the risk of
hospitalization, e.g. social factors, should be conducted to compare and evaluate the
generalisability of our findings.
Conclusion

The study indicates that DRHs are prevalent in multimorbid internal medicine patients using at least four regular drugs from different therapeutic classes. Several factors were associated with risk of DRHs in these patients, with adverse event DRPs and adherence issues being most important. As DRPs are generally regarded as preventable, this suggests that a major proportion of the hospitalizations assessed as drug-related in the present study could be avoided by sufficient actions to improve the quality of drug therapy in multimorbid patients.
Conflicts of interests statement

Author ML received PhD funding from the South-Eastern Norway Regional Health Authority (grant number 12/00718). The other authors declare that they have no conflicts of interest.

Acknowledgments

The study was funded by South-Eastern Norway Regional Health Authority (PhD grant, author ML), Hospital Pharmacies Enterprise, Oslo University Hospital and Diakonhjemmet Hospital. The authors thank the study pharmacists Anne Schwinghammer, Anette Engnes, Elin Trapnes, Hanne Steen, and Petra Foynland for their valuable contribution in patient inclusion and medicines reconciliation and review, senior physician Jo Fuglestved for summarizing the CCI scores, project group members Anne Mette Njaastad, Kristin Hestad Solheim and Kristin Thomassen for valuable input on the study design, employees at the internal medicine ward for positive attitude to the study, and finally the laboratory technicians at Diakonhjemmet Hospital for performing pharmacogenetic analyses.

Author contributions

ML, MM, KK, LM, and EM designed the study. ML and KK were two main study pharmacists. ML, ES, and EM carried out the data analyses. ML and EM wrote the first draft of the manuscript. ML, MM, LM, ES, and EM contributed to interpretation of the data and revision of the manuscript. All authors approved the final version of the manuscript.
References


42. Smith SM, O'Kelly S, O'Dowd T. GPs’ and pharmacists’ experiences of managing multimorbidity: a 'Pandora's box'. *Br J Gen Pract*. 2010; 60: 285-94.


CORRESPONDANCE: Marianne Lea, Department of Pharmaceutical Services, Oslo Hospital Pharmacy, Kirkeveien 166 0450 Oslo, Norway, E-mail: marianne.lea@sykehusapotekene.no
FIGURES, TABLES, AND WEB-SUPPLEMENTS

Figure 1: Illustration of the outline of the study.

Table 1: Comparisons of characteristics in patients with drug-related hospitalizations (DRHs) versus non-drug-related hospitalizations (non-DRHs) in the study population (n=395a).

Table 2: Overview of drug-related problems (DRPs) at hospitalization, revealed by clinical pharmacists, in patients with drug-related hospitalization (DRH) versus non-drug-related hospitalizations (non-DRHs) in the study population (n=395a).

Table 3: Adjusted odds ratios (OR) with 95% confidence intervals (CI) for the characteristics related to drug-related hospitalizations estimated in multivariable logistic regression analyses.

Web-supplement 1: Detailed description of the subgroups of drug-related problems (DRPs).

Web-supplement 2: Overview of target genes variant alleles included in the genotyping panels and the respective genotype-predicted aberrant phenotypes required for gene-drug interaction (GDI) assessments.

Web-supplement 3: Overview over the number of times a drug was suspected to be related to hospitalization in 155 drug-related hospitalizations, ranked according to frequency (drugs associated 1 or 2 times are not included in the overview).

Web-supplement 4: Overview of gene-drug interactions (GDIs) identified during the retrospective reviews of the reconciled drug lists in relation to the respective patients’ genotype results. GDIs of potential relevance for assessments of drug-related hospitalizations (DRHs) were determined based on expected consequences of GDIs and information available in the medical records, including causes of hospitalization.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRHs (n=155)</th>
<th>Non-DRHs (n=240)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>79 (51)</td>
<td>135 (56)</td>
<td>0.304</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>78.4 (32.9-94.9)</td>
<td>80.3 (23.1-96.4)</td>
<td>0.666</td>
</tr>
<tr>
<td>Number of prescribed drugs, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular</td>
<td>9 (4-19)</td>
<td>8 (4-19)</td>
<td>0.107</td>
</tr>
<tr>
<td>- On demand</td>
<td>2 (0-10)</td>
<td>2 (0-11)</td>
<td>0.174</td>
</tr>
<tr>
<td>Home living before admittance, n (%)</td>
<td>146 (94)</td>
<td>218 (91)</td>
<td>0.225</td>
</tr>
<tr>
<td>Assistance with drug administration:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Nursing home, n (%)</td>
<td>9 (6)</td>
<td>22 (9)</td>
<td>0.225</td>
</tr>
<tr>
<td>- Multidose, n (%)</td>
<td>46 (30)</td>
<td>49 (20)</td>
<td>0.035</td>
</tr>
<tr>
<td>- Home nurse, n (%)</td>
<td>30 (19)</td>
<td>31 (13)</td>
<td>0.084</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, median score (range)</td>
<td>3 (0-11)</td>
<td>3 (0-11)</td>
<td>0.189</td>
</tr>
<tr>
<td>- mean score (SD)</td>
<td>2.77 (1.97)</td>
<td>3.12 (2.16)</td>
<td></td>
</tr>
<tr>
<td>Body-mass index b, median (range)</td>
<td>23.8 (14.4-48.4)</td>
<td>25.0 (13.1-43.0)</td>
<td>0.145</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min), median (range)</td>
<td>49.0 (9-182)</td>
<td>52.5 (5-235)</td>
<td>0.268</td>
</tr>
<tr>
<td>CYP2D6 poor metabolizers, n (%)</td>
<td>8 (5)</td>
<td>20 (9)</td>
<td>0.214</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizers, n (%)</td>
<td>4 (3)</td>
<td>11 (5)</td>
<td>0.289</td>
</tr>
<tr>
<td>CYP2C9 *3 carriers, n (%)</td>
<td>18 (12)</td>
<td>23 (10)</td>
<td>0.569</td>
</tr>
<tr>
<td>SLCO1B1 *5 carriers, n (%)</td>
<td>38 (25)</td>
<td>66 (29)</td>
<td>0.472</td>
</tr>
</tbody>
</table>

* Nine of the included patients were excluded from the comparison since defining hospitalizations as drug-related or not was impossible.

b Body-mass index was registered for 121/155 patients with DRHs and 175/240 patients with non-DRHs.

c Blood samples for genotyping were available for 150 patients (SLCO1B1) and 151 patients (cytochrome P450 (CYP)-enzymes) of 155 patients with DRHs and 230/240 patients with non-DRHs.
Table 2 Overview of drug-related problems (DRPs) at hospitalization, revealed by clinical pharmacists, in patients with drug-related hospitalization (DRH) versus non-drug-related hospitalizations (non-DRHs) in the study population (n=395a).

<table>
<thead>
<tr>
<th>DRPs</th>
<th>DRHs (155 patients)</th>
<th>Non-DRHs (240 patients)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Proportion of patients, n (%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>15 (4-42)</td>
<td>12 (3-30)</td>
</tr>
<tr>
<td>Subgroups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug monitoring</td>
<td>Proportion of patients</td>
<td>0.41</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>0 (0-4)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>Proportion of patients</td>
<td>0.95</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>3 (0-10)</td>
<td>2 (0-8)</td>
</tr>
<tr>
<td>Non-optimal drug therapy</td>
<td>Proportion of patients</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>4 (0-10)</td>
<td>4 (0-11)</td>
</tr>
<tr>
<td>Reduced organ function / contraindication</td>
<td>Proportion of patients</td>
<td>0.56</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>1 (0-8)</td>
<td>0 (0-7)</td>
</tr>
<tr>
<td>Adherence issue</td>
<td>Proportion of patients</td>
<td>0.80</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Drug-drug-interaction</td>
<td>Proportion of patients</td>
<td>0.76</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>2 (0-10)</td>
<td>1 (0-10)</td>
</tr>
<tr>
<td>Inappropriate drug in elderly</td>
<td>Proportion of patients</td>
<td>0.58</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>1 (0-6)</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>Unnecessary drug</td>
<td>Proportion of patients</td>
<td>0.74</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>1 (0-7)</td>
<td>1 (0-7)</td>
</tr>
<tr>
<td>Course length</td>
<td>Proportion of patients</td>
<td>0.37</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>0 (0-5)</td>
<td>0 (0-7)</td>
</tr>
<tr>
<td>Practical problem</td>
<td>Proportion of patients</td>
<td>0.14</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>0 (0-2)</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>Other</td>
<td>Proportion of patients</td>
<td>0.37</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Number per patient, median (range)</td>
<td>0 (0-4)</td>
<td>0 (0-5)</td>
</tr>
</tbody>
</table>

a Nine of the included patients were excluded from the comparison since defining hospitalizations as drug-related or not was impossible.

Drug monitoring; Need for therapeutic drug monitoring. Adverse event; Presence of symptoms or changes in laboratory values possibly caused by drug(s). Non-optimal drug therapy; Lack of drug treatment or non-optimal drug treatment of a symptom/disease. Course length; Consideration of appropriate duration of course length. Other; DRPs not applicable in other subgroups, e.g. prescription errors, documentation errors. The rest of the DRP subgroups are described in Web-supplement 1.
**Table 3** Adjusted odds ratios (OR) with 95% confidence intervals (CI) for the characteristics related to drug-related hospitalizations estimated in multivariable logistic regression analyses.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event DRPs(^a)</td>
<td>3.29 (1.36-7.99)</td>
<td>0.008</td>
</tr>
<tr>
<td>Adherence issue</td>
<td>2.86 (1.14-7.17)</td>
<td>0.025</td>
</tr>
<tr>
<td>Home nurse care</td>
<td>1.93 (1.07-3.50)</td>
<td>0.030</td>
</tr>
<tr>
<td>Drug monitoring DRPs(^a)</td>
<td>1.91 (1.21-3.00)</td>
<td>0.005</td>
</tr>
<tr>
<td>Charlson Comorbidity Index Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0-1 (ref)</td>
<td>1</td>
<td>0.033</td>
</tr>
<tr>
<td>Score 2</td>
<td>0.70 (0.38-1.29)</td>
<td>0.249</td>
</tr>
<tr>
<td>Score 3</td>
<td>1.17 (0.63-2.16)</td>
<td>0.621</td>
</tr>
<tr>
<td>Score 4</td>
<td>0.55 (0.27-1.13)</td>
<td>0.102</td>
</tr>
<tr>
<td>Score 5</td>
<td>1.21 (0.50-2.91)</td>
<td>0.670</td>
</tr>
<tr>
<td>Score ≥6</td>
<td>0.33 (0.14-0.77)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

\(^a\) drug-related problem
Clinical pharmacists, Prospective

Medicines reconciliation and review, revealing of drug related problems (DRPs):
- Drug monitoring
- Adverse event
- Drug-drug interaction
- Non-optimal drug therapy
- Reduced organ function /contraindication
- Inappropriate drug in elderly
- Unnecessary drug
- Course length
- Practical problem
- Adherence issue
- Other

Interdisciplinary group, Retrospective

Subjective, clinical and pharmacological assessments:
- Possibly drug-related hospitalization
- Unlikely drug-related hospitalization

Available:
- Medical history
- Symptoms at hospitalization
- Discharge diagnoses
- Laboratory results
- Gene-drug interactions
- Reconciled medicine list

Blinded to:
- Prospectively revealed DRPs
- Charlson Comorbidity Index Score

Figure 1 Illustration of the outline of the study.
**Web-supplement 1** Detailed description of the subgroups of drug-related problems (DRPs).

<table>
<thead>
<tr>
<th>DRP subgroup</th>
<th>Detailed description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug monitoring</td>
<td>Need for therapeutic drug monitoring</td>
</tr>
<tr>
<td>Adverse event</td>
<td>Presence of symptoms or changes in laboratory values possibly caused by drug(s)</td>
</tr>
<tr>
<td>Drug-drug interaction</td>
<td>Clinically relevant drug-drug interactions</td>
</tr>
<tr>
<td>Non-optimal drug therapy</td>
<td>Lack of drug treatment or non-optimal drug treatment of a symptom/disease</td>
</tr>
<tr>
<td>Reduced organ function / contraindication</td>
<td>Drug or dosage of drug inappropriate due to reduced kidney function, reduced liver function, contraindications or other diseases.</td>
</tr>
<tr>
<td>Inappropriate drug in elderly</td>
<td>Use of less favourable drugs in patients over 65 years old, e.g. anticholinergics</td>
</tr>
<tr>
<td>Unnecessary drug</td>
<td>Drug in use is not indicated</td>
</tr>
<tr>
<td>Course length</td>
<td>Consideration of appropriate duration of course length, e.g. duration of antibiotics</td>
</tr>
<tr>
<td>Practical problem</td>
<td>Practical challenges in drug handling, e.g. inhalation devices</td>
</tr>
<tr>
<td>Adherence issue</td>
<td>Patient do not, intentional or unintentional, use / take drug as agreed</td>
</tr>
<tr>
<td>Other</td>
<td>DRPs not applicable in other subgroups, e.g. prescription errors, documentation errors</td>
</tr>
</tbody>
</table>
Web-supplement 2 Overview of target genes variant alleles included in the genotyping panels and the respective genotype-predicted aberrant phenotypes required for gene-drug interaction (GDI) assessments.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant allele panel</th>
<th>Genotype-predicted aberrant phenotypes</th>
</tr>
</thead>
</table>
| CYP2D6 [1] | Non-coding variant alleles:  
• 2D6*3 (rs35742686)  
• 2D6*4 (rs3892097)  
• 2D6*6 (rs5030655)  
Reduced-function variant alleles:  
• 2D6*9 (rs5030656)  
• 2D6*10 (rs1065852)  
• 2D6*41 (rs29001518)  
Copy number analysis:  
• 2D6*5 (whole gene deletion)  
• multiplication of fully-functional alleles (2D6*1 or *2) | ‘Poor metabolizers’ (PMs): Homozygous carriers of non-coding alleles  
‘Intermediate metabolizers’ (IMs): Heterozygous carriers of non-coding alleles and homozygous carriers of reduced-function alleles  
‘Ultrarapid metabolizers’ (UMs): Carriers of three or more functional gene copies |
| CYP2C19 [1] | Non-coding variant alleles:  
• 2C19*2 (rs42442485)  
• 2C19*3 (rs4986893/rs5708121)  
• 2C19*4 (rs28399504)  
Gain-of-function allele:  
• CYP2C19*17 (rs12248560) | PMs: Homozygous carriers of non-coding alleles  
IMs: Heterozygous carriers of non-coding alleles  
UMs: Hetero- or homozygous carriers of the gain-of-function allele |
| CYP2C9 [1] | Reduced-function alleles:  
• 2C9*2 (rs1799853)  
• 2C9*3 (rs1057910)  
Gain-of-function allele:  
• CYP2C9*17 (rs12248560) | PMs: Homozygous carriers of CYP2C9*3  
IMs: Heterozygous carriers of CYP2C9*3 and homozygous carriers of CYP2C9*2 |
| CYP3A5 [1] | Non-coding variant allele:  
• CYP3A5*3 (rs776746) | Increased CYP3A5 metabolism: Hetero- or homozygous carriers of CYP3A5*1 |
| SLCO1B1 [2] | Reduced-function allele:  
• 521T>C/*5 (rs4149056) | Decreased OATP1B1-mediated transport, e.g. of statins: Hetero- or homozygous carriers of the reduced-function allele |
| VCORK1 [3] | Increased VCORK1-sensitivity:  
• VKORC1*2 (rs9923231) | Low-dose warfarin responders: Hetero- or homozygous carriers of VKORC1*2 |

All genotyping assays were validated and had been certified by Norwegian accreditation for routine clinical use. All variant allele analyses were performed using Taqman-based realtime PCR assays.

REFERENCES:


Web-supplement 3 Overview over the number of times a drug was suspected to be related to hospitalization in 155 drug-related hospitalizations, ranked according to frequency (drugs associated 1 or 2 times are not included in the overview).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Suspected relation with hospitalization, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>39</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>21</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>15</td>
</tr>
<tr>
<td>Insulin and insulin analogues</td>
<td>13</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>11</td>
</tr>
<tr>
<td>Furosemide</td>
<td>10</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>9</td>
</tr>
<tr>
<td>Enalapril</td>
<td>8</td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>7</td>
</tr>
<tr>
<td>Formoterol/budesonide</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
</tr>
<tr>
<td>Codeine/paracetamol</td>
<td>6</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td></td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>5</td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td></td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td></td>
</tr>
<tr>
<td>Salbutamol</td>
<td></td>
</tr>
<tr>
<td>Calcium, combinations with vitamin D and/or other drugs</td>
<td>4</td>
</tr>
<tr>
<td>Citalopram</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Nitrazepam</td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td></td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>3</td>
</tr>
<tr>
<td>Cortisone</td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>Levothyroxine sodium</td>
<td></td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td></td>
</tr>
<tr>
<td>Solifenacin</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td></td>
</tr>
</tbody>
</table>
Web-supplement 4 Overview of gene-drug interactions (GDIs) identified during the retrospective reviews of the reconciled drug lists in relation to the respective patients’ genotype results. GDIs of potential relevance for assessments of drug-related hospitalizations (DRHs) were determined based on expected consequences of GDIs and information available in the medical records, including causes of hospitalization.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Drug (*=prodrugs)</th>
<th>Total GDIs, n</th>
<th>Relevant for DRH assessments, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Losartan*</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Candesartan</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irbesartan</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Pantoprazole</td>
<td>58</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Esomeprazole</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel*</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diazepam</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escitalopram</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Metoprolol</td>
<td>125</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Codeine*</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tramadol*</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carvediolol</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fesoterodine</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorprothixene</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mianserin</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tamsulosin</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Levomepromazine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Zuclopenthixol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Donepezil</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Simvastatin</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atorvastatin</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amlodipine</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clopidogrel*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pravastatin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vardenafil</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>Buprenorphine</td>
<td>Zopiclone</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>23</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCORK</td>
<td>Warfarin</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>538</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450