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DRUG USE IN THE ELDERLY – ARE QUANTITY AND QUALITY COMPATIBLE

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To the memory of

Johann Elsässer
** 1888 in Ukraine, Russian Empire*
† 1928 in Ukraine, Soviet Union

and

Albertina Davidsson
** 1886 in Racksund, Lapland*
† 1971 in Stockholm

Education is the only thing that no one can take away from you (J.E.)

Abstract English

The increasing number of elderly, and the increasing drug use among the elderly, emphasizes the need to continuously monitor drug utilization in this group. The scarcity of randomized controlled trials including elderly people give population-based, observational studies an important role as source of information on drug use and drug-related problems. The aim of this thesis was to explore drug consumption patterns and quality in people aged ≥ 75 years within the Kungsholmen Project, a population-based, longitudinal study 1987-2001. Cross-sectional data from the urban cohort in Kungsholmen, Stockholm and cross-sectional and longitudinal data from the rural cohort in Nordanstig, Hälsingland were used.

Over 90% of the participants used drugs, with a mean of five drugs per person 1999-2001. The pattern was consistent with morbidity patterns in old age. The most common drug classes were cardiovascular drugs, nervous system drugs, and drugs for the alimentary tract and metabolism. Polypharmacy was common, especially among the oldest old. Drug use increased over time, and the utilization patterns were fairly stable regarding drugs for chronic diseases, as opposed to a larger turnover of users of drugs for mainly temporary conditions. Regional differences in the drug use patterns among the oldest old were found. 'Vasodilators in cardiac disease' with an odds ratio 95% confidence interval [OR (95% CI)] of 2.51 (1.46-4.30), and high ceiling diuretics 2.62 (1.77-3.90) were used more often, and 'Antithrombotic agents' less often 0.43 (0.29-0.65) in the rural area compared to the urban area.

ACE-inhibitors were used by only one fourth of the participants with heart failure (HF) diagnosis in Nordanstig. Crude data suggested an even lower utilization of ACE-inhibitors by demented or cognitively impaired participants with HF, but after adjustment for covariates the significance disappeared. However, advanced age was associated with lower use with an OR (95% CI) of 0.11 (0.01-0.95) for being a user if aged ≥90 compared with 75-79 years, and there was also lower use by those living in institutions compared to community-living: 0.28 (0.09-0.91). Other quality issues were fairly frequent use of calcium channel blockers with negative inotropic effects, and of NSAIDs, practices not recommended in patients with HF.

Inappropriate drug use (IDU), as defined by consensus-based criteria, was an increasingly common phenomenon over time with some intra-individual variability. At baseline in Nordanstig approximately one fifth of the participants used at least one inappropriate drug regiment. IDU increased with number of used drugs. An association was found between being a user of at least one inappropriate drug and at least one hospitalization during three years of follow-up in community residing participants in Nordanstig, OR (95% CI): 2.75 (1.66-4.55).

Conclusions: In this study drug use was extensive, and both drugs for chronic diseases and temporary symptoms were common. Some regional differences were found in prescribing behaviours. Inappropriate drug regiments were also common, increasingly so with number of used drugs. There was an association between IDU and hospitalization in community residing participants, suggesting negative health outcomes of IDU. However, despite the high drug utilization there may also have been under-use of modern HF medications. There is potential to improve drug therapy in elderly people.

Key words: population-based, cross-sectional, longitudinal, aged, aged 80 and over, drug utilization, cardiovascular agents, angiotensin-converting enzyme inhibitors, inappropriate drug use, heart failure, dementia, hospitalization, mortality, Sweden.

Sammanfattning Svenska

Det ökande antalet äldre och den ökande läkemedelsanvändningen bland äldre understryker behovet av kontinuerlig läkemedelsbevakning i denna grupp. Bristen på randomiserade kontrollerade studier med äldre deltagare gör populationsbaserade observationsstudier viktiga som källa för kunskap om användningsmönster och läkemedelsproblem. Syftet med denna avhandling var att undersöka mönster och kvalitet i läkemedelsanvändningen bland deltagarna ≥ 75 år i Kungsholmsprojektet, en populationsbaserad, longitudinell studie 1987-2001. Tvärsnittsdata från storstadsdelen på Kungsholmen, Stockholm, och tvärsnitts- samt uppföljningsdata från glesbygdsdelen i Nordanstig, Hälsingland användes.

Över 90 % av deltagarna använde läkemedel, med i genomsnitt fem läkemedel per person 1999-2001. Användningsmönstret var förenligt med sjuklighetsmönster i hög ålder. Mest använda var läkemedel för hjärta och kärl, nervsystemet samt mag-tarmkanal och metabolism. Polyfarmaci var vanligt särskilt hos de allra äldsta. Läkemedelsanvändningen ökade över tid. Användningen av läkemedel för kroniska sjukdomar var tämligen stabil, till skillnad från läkemedel för huvudsakligen tillfälliga besvär, där omsättningen var högre. Det fanns också regionala skillnader mellan de allra äldsta. Glesbygdsborna var oftare användare av ’kärlvidgande medel för hjärtsjukdomar’ med en oddskvot (95 % konfidensintervall) [OR (95%CI)] på 2,51 (1,46-4,30) och ’loop-diuretika’ 2,62 (1,77-3,90) och mer sällan användare av ’antikoagulantia’ 0,43 (0,29-0,65) jämfört med storstadsborna.

ACE-hämmare användes enbart av en fjärdedel av deltagarna med hjärtsviktsdiagnos (HF) i Nordanstig. Rådata visade en ännu lägre användning av ACE-hämmare hos personer med demens eller kognitiv störning, men sambandet upphörde efter kontroll för andra faktorer. Däremot hade ålder och boende samband med användning av ACE-hämmare. Personer ≥ 90 år var mer sällan användare jämfört med gruppen 75-79 år: OR (95 % CI) 0,11 (0,01-0,95). Likaså var de personer, som bodde på servicehus eller sjukhem mer sällan användare än de i ordinärt boende: 0,28 (0,09-0,91). Andra kvalitetsproblem var användning av kalcium-antagonister med negativ inotrop effekt samt NSAID, något som är olämpligt vid HF.

Olämplig läkemedelsanvändning, definierat utifrån konsensusbaserade kriterier, ökade över tid, med viss variabilitet i användningen på individnivå. Vid baslinjeundersökningen i Nordanstig hade ca 1/5 av deltagarna minst en olämplig läkemedelsregim. Användning av olämpliga preparat ökade med antal använda läkemedel och ett samband fanns mellan att vara användare av minst ett olämpligt läkemedel och minst en akutinläggning på sjukhus under tre års uppföljning av äldre i ordinärt boende i Nordanstig: OR (95% CI): 2,75 (1,66-4,55).

Slutsatser: Läkemedelsanvändningen var hög och läkemedel både för kroniska sjukdomar och övergående symptom var vanliga. Det fanns vissa regionala skillnader i läkemedels-användning, vilket tyder på förekomst regionala behandlingstraditioner. Olämplig läkemedelsbehandling var också vanlig och ökade med antalet använda läkemedel. Det fanns ett samband mellan olämplig läkemedelsbehandling och sjukhusinläggning vilket kan tyda på negativa hälsoeffekter. Emellertid kan det också, trots den höga läkemedelsanvändningen, ha förelegat underanvändning av moderna hjärtsviktspreparat. Det finns således utrymme för att förbättra läkemedelsbehandlingen av äldre personer.

List of original papers

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

I. Klarin I, Fastbom J, Wimo A. A population-based study of drug use in the very old living in a rural district of Sweden, with focus on cardiovascular drug consumption. Comparison with an urban cohort. *Pharmacoepidemiology and Drug Safety* 2003; 12 (8): 669-678.

II. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalization and mortality. A population-based study of the very old. *Drugs & Aging* 2005; 22 (1): 69-82.

III. Klarin I, Fastbom J, Wimo A. The Use of Angiotensin-Converting Enzyme Inhibitors and Other Drugs with Cardiovascular Effects by Non-demented and Demented Elderly with a Clinical Diagnosis of Heart Failure. A Population-Based Study of the Very Old. *European Journal of Clinical Pharmacology.* In press.

IV. Klarin I, Fastbom J, Wimo A. The continuity of drug use in very old people. A longitudinal, population-based study of variations in overall and potentially inappropriate drug use. Manuscript.

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Abbreviations

ACEI	Angiotensin-Converting Enzyme Inhibitor
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
ARB	Angiotensin II antagonist (Angiotensin II receptor blocker)
ATC	Anatomical Therapeutic and Chemical classification
BP	Blood Pressure
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cerebrovascular Disease
DDD	Defined Daily Dose
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition – Revised
DUR	Drug Utilization Review
FASS	Farmaceutiska Specialiteter i Sverige
HF	Heart Failure
IDU	Inappropriate Drug Use
K5	Kungsholmen phase V investigation (third follow-up)
MMSE	Mini-Mental State Examination
N84+	Nordanstig baseline investigation, participants 84 years and older
NSAID	Non-Steroid Anti-Inflammatory Drug
OR	Odds Ratio
RCT	Randomized Controlled Trial
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
WHO	World Health Organization

ATC-groups

A	Alimentary tract and metabolism
B	Blood and blood forming organs
B01	Antithrombotic agents
B01AC06	Acetylsalicylic acid (aspirin), low dose
C	Cardiovascular system
C01	Cardiac therapy
C01A	Cardiac glycosides
C01D	Vasodilators used in cardiac diseases
C03	Diuretics
C03C	High-ceiling (loop-) diuretics
C03D	Potassium-sparing agents
C07	Beta blocking agents
C08	Calcium channel blockers
C09	Agents acting on the renin-angiotensin system
G	Genito urinary system and sex hormones
H	Systemic hormonal preparations, excl. sex hormones
M	Musculo-skeletal system
N	Nervous system
R	Respiratory system
S	Sensory organs

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Introduction

Ageing and health

The worldwide demographic transition is characterized by decreasing fertility and mortality rates with continuously growing elderly populations. The developed countries have experienced this for decades, and it is now also evident for the developing countries, where both the absolute and relative numbers of elderly persons are increasing rapidly, with 80 years and older as the fastest growing age group. In 1950, people 80 years and older constituted 1% of the population in the developed countries and 0.3% in the developing countries. In 2000 the corresponding figures were 3.1% and 0.7%, and the projections for 2050 are 9.4% and 3.6%, respectively. In absolute numbers, the world population 80 years and older is expected to increase from 70 million people in 2000 to almost 400 million people in 2050, with seven out of ten living in the developing countries [1].

In Sweden the ageing of the population became prominent in the second half of the 20th century. In 1950 the age group 80 years and older constituted 1.5% of the population, and the proportion increased to 5% in 2000, and it is projected to be 9.7% in 2050. In the middle of the 20th century the life expectancy at birth was 70 years for men and 73 years for women compared to presently 78 years and 82 years, respectively [1].

Ageing is characterized by molecular changes, loss of functional units i.e., cells and tissues, and reduction in function of the remaining structures. This leads to an increased vulnerability and decreased ability to maintain homeostasis. The inter-individual physiological differences increase, and there are often indefinite transitional phases or overlapping stages between normal ageing and many age related diseases [2].

The occurrence of most chronic, or potentially life threatening, and disabling diseases increases with increasing age. Among others, hypertension, heart disease, stroke, chronic obstructive pulmonary disease (COPD), cancer, diabetes mellitus, osteoporosis, incontinence, depression, dementia, and some infectious diseases are common health threats in advanced

age [3-5]. The prevalence of multimorbidity, referring to co-occurrence of several medical conditions within an individual, is also increasing with increasing age [6].

According to the Swedish Public Health Report in 2005, seven to eight out of ten persons, aged 65-79 years old, and eight to nine out of ten persons aged 80 years and older, report chronic disease or disability. An increase of the prevalence was described for the younger group of men and for the older group of women between 1988/89 and 2002/03. One example of the disabling problems occurring in old age is that 27% of men and 34% of women among persons 80 years and older reported severe pain [5].

Drugs and ageing

Drug utilization

Considering the high and increasing prevalence of chronic diseases and symptoms in advanced ages, and that the most commonly used treatment option is pharmaceutical drugs, it is not surprising that drug utilization is high in elderly populations. An increasing utilization of drugs with increasing age is reported both nationally and internationally, with some diverging results for the extremely old [7-11]. In Sweden the age group 75 years and older constitutes 9% of the population but receives approximately one fourth of all prescriptions [12].

A number of studies regarding drug utilization in different settings in Western countries have shown similar patterns of drug utilization among elderly people (ages 60 years and older). It has been consistently reported that the most frequently used drug types are drugs for cardiovascular diseases, drugs acting on the nervous system (analgesics and psycholeptics), and drugs for the gastrointestinal system, including vitamins. Most studies have also reported a higher drug utilization in women compared to men [8, 9, 11, 13-15].

Pharmacological changes in old age

Ageing affects all organs and processes to a varying degree and leads to changes in both *pharmacokinetics*, i.e., how the organism handles pharmaceuticals, and *pharmacodynamics*, i.e., how pharmaceuticals affect the organism.

Pharmacokinetics [16-18]

Generally, *absorption* of drugs is marginally affected by ageing. Most drugs are absorbed from the gastrointestinal tract by diffusion, a mechanism not affected by ageing. However, carrier-mediated transport mechanisms can be reduced, leading to lower absorption of, e.g., calcium, iron, and vitamin B12. The *first-pass metabolism* in the liver is affected by ageing, leading to higher serum levels of active drugs that are subject to extensive first-pass metabolism, e.g., propranolol, and lower levels of pro-drugs that need activation by first-pass metabolism, e.g., enalapril.

No substantial reduction of plasma proteins related to ageing has been reported, although albumin can be reduced in acute illness and malnutrition. The possible alterations of *protein binding* seem to have limited clinical relevance. However, changes in body composition with declining lean body mass, especially muscles, and reduction in total body water leading to an increased proportion of body fat, are of extreme importance for *drug distribution.* Water-soluble drugs have a smaller distribution volume with increasing age, leading to higher serum concentrations. This is especially crucial for water-soluble drugs with narrow therapeutic index, e.g., gentamicin, digoxin, and lithium. Lipid-soluble drugs have an increased distribution volume with increasing age, leading to prolonged half-life, e.g., diazepam and verapamil.

There may be a considerable reduction of drug clearance with increasing age. The metabolism in the liver can be affected by decreasing liver size, liver blood flow, and hepatic enzyme capacity. Several studies have shown a reduction in clearance of drugs metabolized by "phase-1" pathways (Cytochrome P-450 enzymes) in the liver, but individual differences are large. In general, "phase-2" metabolism (conjugation) is not affected by ageing. Probably the most important pharmacokinetic change in old age is the reduction of renal excretion. Starting approximately at the age of forty, there is a yearly reduction of glomerular filtration with about 1 ml/minute, leading to a substantial reduction of renal function during ageing. This affects the clearance of a large number of drugs, including diuretics, digoxin, non-steroid antiinflammatory drugs (NSAIDs), some antibiotics, and water-soluble beta-blockers. The significance of this depends on how toxic the individual drug is. A complicating factor is that the routine laboratory measurement of renal function (serum creatinine) is of limited value in the very old, as they have a reduced muscle mass (the main source of creatinine).

Pharmacodynamics [17-19]

Pharmacodynamic changes occur at several levels and can vary between drugs from the same class. Therefore, generalizations are difficult to make. There may be a reduction of homeostatic mechanisms, e.g., impairment of the baro-reflex leads to an increased risk of postural hypotension in response to blood pressure (BP) lowering agents, which may lead to syncope and falls. Reduced beta-receptor function leads to reduced effect of both salbutamol (beta-receptor agonist) and propranolol (beta-receptor antagonist). Other important changes are the increased vulnerability to the effects of NSAIDs on the gastric mucosa, which increases the risk of ulcers and bleeding, and increased sensitivity to warfarin, leading to a greater inhibition of coagulation factors in elderly people.

The aged central nervous system is particularly vulnerable. Neuronal loss and decreased dopamine and acetylcholine activity increases the risk of extra pyramidal symptoms in neuroleptic treatment and adverse effects such as delirium when treated with drugs with anticholinergic effects, respectively. Elderly persons are also markedly more sensitive to opioids, anxiolytics, and sedatives/hypnotics such as benzodiazepines, especially the long acting compounds.

In summary, due to age-related changes, a careful attitude must be taken when prescribing drugs to elderly patients. Cautious selection of preparations, assessment of renal and other physiological functions, individual dose adjustment – most often dose reduction, and regular evaluation of drug effects are some of the precautions that need to be implemented in geriatric clinical practice.

Potentially inappropriate drug use and adverse drug reactions

Considering the numerous problems related to drug prescribing in elderly people, it is not surprising that potentially inappropriate drug use (IDU) is common. The phenomenon is extensively described in the literature and the prevalence of IDU according to explicit criteria has been reported to be between 3% and 48% (Table 1). Several studies have also explored possible risk factors for IDU, and the most consistently described association is with total number of drugs [20-22]. However, few researchers have addressed IDU in Swedish elderly persons. Studies have included investigations into psychotropic drug prescribing in nursing

Table 1. Prevalence (%) of potentially inappropriate drug use (IDU) in elderly persons in different settings in USA and Europe according to criteria published by Beers 1991 and 1997 [23, 24]

Reference (1st author, year)	Country	Setting	Design, Data source	Age	Criteria from	IDU %
Beers 1992 [25]	USA	Nursing home	Cohort †, P,	≥ 65	1991	40
Stuck 1994 [26]	USA	Community	Cross-sectional, I	≥ 75	1991*	14
Willcox 1994 [27]	USA	Community	Cross-sectional, I	≥ 65	1991*	24
Spore 1997 [28]	USA	Board and Care Facilities	Cross-sectional, I	≥ 65	1991*	24
Chin 1999 [29]	USA	Emergency department	Cohort †, I	≥ 65	1997*	11
Fick 1999 [30]	USA	Medicare managed care	Cross-sectional, A	≥ 65	1997*	24
Golden 1999 [31]	USA	Medicaid NHE, Community	Cross-sectional, P	≥ 60	1997*	40
Hanlon 2000 [32]	USA	Community	Cohort, I	≥ 68	1997	27 / 23
Piecoro 2000 [33]	USA	Medicaid population, all: Community Nursing home	Cross-sectional, A	≥ 65	1997*	27 24 33
Meredith 2001 [34]	USA	Medicare, Visiting nurse service	Cross-sectional, I	≥ 65	1997*	17
Zhan 2001 [35]	USA	Community	Cross-sectional, I P	≥ 65	1997*	21
Sloane 2002 [36]	USA	Residential Care	Cross-sectional, I R	≥ 65	1997*	16
Stuart 2003 [37]	USA	Medicare, Community	Cohort (open), I	≥ 65	1997*	25 / 21
Fu 2004 [38]	USA	Community	Cohort †, I	≥ 65	1997*	13
Perri 2005 [39]	USA	Nursing home	Cohort †, R	> 65	1997	47
Rigler 2005 [40]	USA	Medicaid Ambulatory NHE, Community Nursing home	Cross-sectional, A	≥ 60	1997*	21 48 38
Pitkala 2002 [41]	Finland	Community	Cross-sectional, M	≥ 75	1997*	13
Heininger-Rothbucher 2003 [42]	Austria	Emergency department	Cross-sectional, R	≥ 60	1997*	12
Onder 2003 [43]	Italy	Hospital wards	Cross-sectional, I R	≥ 65	1997*	15
Ay 2005 [44]	Turkey (Istanbul)	Community	Cross-sectional, I	≥ 70	1997*	10
Fialova 2005 [45]	*Europe: 8 countries*: Czech republic Denmark Finland Iceland Italy Netherlands Norway UK	Home care patients	Cohort †, I	≥ 65	1997*	*10* 16 3 17 6 14 9 10 6
v d Hooft 2005 [46]	Netherlands	Population-based	Cohort (open), PC	≥ 65	1997*	17 / 19

*Based on criteria published by Beers 1991 [23] or 1997 [24], but modified according to available data and setting. **†** Cohort study, cross-sectional prevalence data at baseline. **IDU=** Inappropriate drug use. **NHE=** Nursing-home eligible persons. **UK=** United Kingdom.
Drug data source: **A=**administrative claims data base, **I=**interview, **P=**pharmacy, **PC=**primary care data base, **R=**medical record, **M=**mailed questionnaire.

homes [47], drug use in nursing home residents with epilepsy or Parkinson's disease [48], drug-review in nursing homes [49], and assessment of IDU in a population-based study stratified by absence or presence of dementia [21].

Several tools to assess the appropriateness of medication have been described and used. Implicit methods are based on review of individual medications by experts in geriatric pharmacology, without given criteria. These methods have low inter-rater reliability, making comparisons between raters and comparative studies difficult [50].

Explicit methods are based on defined criteria. The advantages of explicit criteria are that they are objective with a high inter-rater reliability, and the disadvantages are that they are rigid and do not take individual clinical situations into account. Drug Utilization Evaluation/ Medication Utilization Evaluation uses explicit criteria and measures indications, critical process indicators, as well as complications and outcomes. The method is typically used in institutional settings, and is time consuming. The inter-rater reliability is questionable regarding complications and outcomes, as clinical judgment is needed to assess these domains [50].

Drug Utilization Review (DUR) programs have a long history, mainly in the USA [51]. Today the programs are typically computerized systems; using consensus based explicit criteria in large administrative databases, checking each prescription not only for type of drug, but also for dose, duration of therapy, and interactions. The aim is to reduce inappropriate prescribing. DUR has been used to study Medicaid populations and in other cohort studies [52-54].

Several sets of explicit consensus-based criteria have been developed since the first set for nursing home residents was published in 1991 [23]. The original criteria were further developed to be applicable for community residing elderly people [24] and have been recently updated [55]. These criteria, referred to as 'Beers criteria', are widely used, both in the proposed and modified versions. Other researchers have used consensus techniques to identify risky prescribing practices [56, 57], and criteria developed in the USA have been partly validated for use in the United Kingdom [58]. As mentioned above the inter-rater reliability is better for explicit methods than for implicit methods, but a limitation is that complex entire medication regimens cannot be evaluated.

Tools combining implicit and explicit methods have also been developed and evaluated, but generally they are complex and time-consuming, and thus difficult to implement in regular clinical practice [50].

IDU is an important and avoidable cause of adverse drug reactions (ADRs) [59]. There are two main types of ADRs. Type A reactions are caused by the pharmacological effects of the drug. They are dose-dependent and considered to be largely preventable, while Type B reactions are bizarre and unpredictable. Type A reactions are the most common type, accounting for about 80% of all ADRs [60].

ADRs are frequent, potentially dangerous, and common causes of hospital admission [61], and elderly persons are over represented in many ADR studies [62]. Although age in itself probably is not an important risk factor for ADRs, age-related changes in pharmacokinetics and pharmacodynamics may enhance the pharmacological effect of a drug and thus increase the risk of an ADR. Also, elderly people on average use a larger number of medications (polypharmacy) and thus are more exposed to drug-drug interactions. There is a close, possibly even an exponential, relationship between number of drugs and the likelihood of ADRs [63, 64].

ADRs in elderly patients can also be misinterpreted as a new disease, in the worst case leading to a new and unnecessary drug treatment, a phenomenon known as “the prescribing cascade” [65]. Thus, a good rule when assessing an elderly patient is to always consider the possibility of an ADR when a patient on drug treatment presents a new symptom.

Under-representation in clinical trials and under-use of drugs

Another quality issue is the low and restricted representation of elderly persons, if any, in many clinical trials of new drugs. Although elderly people constitute the majority with, e.g., heart failure (HF) they are under-represented in the major HF clinical trials [66]. Another example is the increasing use of antidepressants among elderly people, with the introduction of new drug classes with better ADR profiles, while principles for treatment of depression are based on clinical trials where elderly people are under-represented [67]. This exemplifies the common practice to try out new treatments in other groups than the main target population,

and also stresses the importance of observational pharmacoepidemiological studies monitoring utilization patterns and outcomes in the elderly.

In contrast to the rapid introduction of new antidepressants among elderly people, the utilization of, e.g., antithrombotic therapy in chronic atrial fibrillation [68] and angiotensin-converting enzyme inhibitors (ACEIs) in HF [69] has been low in elderly patient groups. This slow introduction may be appropriate considering the lack of clinical trials, but may also have lead to under-treatment of elderly patients.

Cardiovascular disease and heart failure

Although the risk of acquiring or dying from cardiovascular disease has decreased in Sweden during the period 1987-2002, the prevalence is still high in the elderly age groups, and there are large regional differences within Sweden [5, 70]. The decrease in cardiovascular mortality is presently the most important reason for the increasing average length of life, but it is still the most common cause of death in Swedish persons aged 75 years and older [71].

HF is a clinical syndrome caused by an underlying disease. Although the incidence and prevalence vary in different studies depending on differences in diagnostic criteria and procedures [72], all studies agree on an increase of incidence with age [73-75], as well as of prevalence, with an often cited prevalence of 10% in the ages 80 years and older [74]. The most common causes of HF in elderly people do not differ from younger people, and are hypertension and ischemic heart disease [75]. However, the presentation of HF can be atypical in elderly persons. For example, the classical symptom of exertional dyspnoea might be attributed to normal ageing, which would lead to a change in lifestyle [76] rather than to a visit to a physician, causing a delay in the diagnosis.

There are differences in the ‘mechanics’ of HF between younger and older patients. Abnormalities can be seen in both the contraction phase (systole) and the filling phase (diastole) of the cardiac pump cycle. With increasing age diastolic HF becomes increasingly common and constitutes up to 50% of HF cases in patients aged 70 years and older [76, 77]. This may be due to the fact that disorders associated with diastolic dysfunction increases with increasing age, e.g., hypertension, coronary heart disease, diabetes, chronic renal disease, and atrial fibrillation [76]. The differential diagnosis between systolic and diastolic HF is

clinically relevant due to different therapeutic indications. So far there is limited evidence on efficacious pharmacological treatment of diastolic dysfunction [75, 78].

HF is an extremely serious disease with a prognosis equal to or worse than most cancers - with the exception of lung cancer - and is worse with increasing age [79]. However, the prognosis improved between 1993 and 2003 [80], possibly because treatment of HF with modern drugs has been widely implemented at the population level. In addition, HF has a considerable impact on society, as this disease is the most common diagnosis at discharge from internal medicine clinics in Sweden [81], and the cost constitutes 1-2% of the healthcare budget in developed countries [82].

Dementia

Dementia is a clinical syndrome composed of a memory deficit and impairment in at least one other cognitive domain, severe enough to affect social daily life, occupational life, or relationships with others. This impairment is not due to depression or delirium [83]. There are several possible underlying diseases that may lead to dementia, with e.g., Alzheimer's disease responsible for more than 50% of all dementia cases, and cerebrovascular disease (CVD) responsible for 15-20% of the cases [84]. Dementia is common in old age with a prevalence of about 6% in ages 65 years and older [85]. The incidence increases exponentially with age [84].

Dementia is not only a tragic event for the affected individuals and their families, but also a major cause of costs for the health and social care systems in industrialized countries [86]. As there is no cure for dementia, there is substantial interest in risk factors and prevention possibilities. Lately, vascular factors have been discussed not only in relation to vascular dementia but also in relation to Alzheimer's disease [87]. HF has been found to be a risk factor at least for vascular dementia, with low cerebral perfusion as one possible mechanism [88]. In addition, the role of the angiotensin I converting enzyme and ACEIs has been discussed in relation to cognitive decline, with results suggesting a protective effect of ACEI treatment [89, 90].

Aims

General aims

The overall aim of this thesis was to describe drug use in very old people with focus on cardiovascular drugs, covering both quantitative and qualitative aspects, and to explore possible negative outcomes of IDU.

Specific aims

Study I

To describe drug use in the general population, with focus on cardiovascular drugs and regional differences.

Study II

To study the association between IDU and acute hospitalization and mortality during three years of follow-up.

Study III

To investigate the pharmacological treatment patterns in non-demented and demented persons with a HF diagnosis as a continuation of **Study I**, where a lower use of ACEIs was detected in cognitively impaired persons.

Study IV

To describe drug use patterns and continuity of drug use over time at the population and individual level, under the hypothesis of continuous use of inappropriate drugs as suggested by **Study II**.

Figure 1. Evolution of the thesis study populations in the Kungsholmen Project

Kungsholmen parish
2368 inhabitants
≥75 years Oct 1987

Non-participants = 558
Died 181
Refused 291
Moved/not reached 86

Study I
418 participants from Kungsholmen phase V and 918 from Nordanstig baseline
Study II
785 participants from Nordanstig baseline
Study III
265 from Nordanstig baseline
Study IV
561 participants from Nordanstig baseline and follow-up

Baseline
Phase I & II
1987-89

1810 participants

Dropouts = 711
Died 427
Refused 256
Moved 22
Not reached 6

1st follow-up
Phase III
1991-93

1099 participants

Dropouts= 419
Died 363
Refused 48
Moved 8

2nd follow-up
Phase IV
1994-96

680 participants

Dropouts= 259
Died 218
Refused 39
Moved 2

Nordanstig municipality
1168 inhabitants
≥ 75 years Sept 1995

Non-participants= 249
Died 147
Refused 74
Moved 1
Not investigated 8
Not known 19

3rd follow-up
Phase V
1997-98

421 participants

Dropouts= 156
Died 126
Refused 26
Moved 4

919 participants

Dropouts = 340
Died 292
Refused 27
Moved 9
Not investigated 1
Not known 11

Baseline
1995-98

4th follow-up
Phase VI
1999-2000

265 participants

579 participants

Follow-up
1999-2001

Methods

The study participants

All data used in this thesis were obtained from the Kungsholmen Project, a longitudinal, population-based, cohort study on ageing and dementia (Figure 1). The project consists of two major cohorts. The urban part of the study was initiated in October 1987, when all inhabitants 75 years of age or older in the Kungsholmen parish in central Stockholm, Sweden, were invited to participate. A rural study was initiated in September 1995 in the municipality of Nordanstig, a coastal district in Hälsingland, 350 km north of Stockholm. All inhabitants 75 years and older at that time point were invited to participate. Both community residing and institutionalized persons were included in both cohorts [91, 92]. The populations in Kungsholmen and Nordanstig were identified through the Swedish registration of inhabitants system, where age, sex, and area of residence are available.

The non-participants at the baseline examination (phase I-II) in the Kungsholmen population due to refusal or moving from the area did not differ in age or sex from the participants, but those who did not participate due to death were older and more often men [93]. For corresponding data for the Nordanstig population, see Results.

Study I participants

All participants from Kungsholmen phase V (K5) (third follow-up) (n=418) and all participants from Nordanstig baseline (n=918) investigation with drug data were included. The participants in Nordanstig of the same age group as Kungsholmen participants (84 years and older) (n=335) were included in the comparison with the K5 participants.

Study II participants

All participants from Nordanstig baseline investigation with complete data on drug use, selected covariates, and outcome variables were included (n=785).

Study III participants

All participants from Nordanstig baseline investigation with HF diagnosis and use of at least one drug from the Anatomical, Therapeutic, and Chemical classification (ATC) group 'Cardiovascular system' were included (n=265).

Study IV participants

All participants with information on drug use from both Nordanstig baseline and follow-up investigations were included (n=561).

Data collection and classification

In the urban study, a two-step baseline investigation (phase I and II) and four follow-up investigations (phase III-VI) were conducted approximately every three years. In the rural part of the study, one baseline investigation and one follow-up was conducted (Figure 1). The following description of the Kungsholmen Project will only include information relevant for this thesis. For further details of the study design, the reader is referred to the publications of Fratiglioni et al [91, 93, 94].

At baseline examination and follow-ups, the participants in the Kungsholmen Project underwent an extensive medical, functional, psychological, and social investigation following structured protocols. This included blood testing, a medical interview including drug use data, and medical examination by physicians, as well as an extensive interview including medical and psychosocial history, and assessment of activities of daily living (ADL), performed by research nurses**.** The medical history was most detailed on diseases associated with dementia or with symptoms similar to dementia, e.g., due to neurological, cardiovascular, endocrine, and psychiatric diseases. Trained psychologists also examined the participants (a sample at baseline) with a neuropsychological test battery. In addition, an interview was performed with a next-of-kin or another person close to the participant.

The Nordanstig participants were investigated by nurses and physicians using basically the same protocols as in the Kungsholmen Project. However, the drug data were obtained by physicians in Kungsholmen and by research nurses in Nordanstig. In addition, no psychologist was available in Nordanstig, restricting the psychological testing to basic tests

administered by the nurses. Interviews with next-of-kin or another close person were performed. The examinations and interviews took place at the research centre (Kungsholmen), healthcare centre (Nordanstig), or in the participant's home, including institutions.

Basic demographic data

Age was categorized into four groups for Nordanstig baseline and follow-up and into two groups in the comparisons between Kungsholmen and the participants in Nordanstig aged 84 years and older (N84+). Sex was entered as a covariate in the statistical models if the analyses were not stratified by sex. Data on housing were obtained from the nurse interview. The data were categorized as living in (i) a one-family house (rural participants only), (ii) an apartment (owned or rented), (iii) sheltered housing (service home, home for the elderly, group living for the demented), and (iv) nursing home. As the criteria for admittance to sheltered housing or nursing homes are decided regionally, we did not differentiate between them in the comparisons between Nordanstig and Kungsholmen. The housing variable was dichotomized as (i) independent or community residing (house or apartment) and (ii) dependent or institutionalized (sheltered housing or nursing home).

Drug use

Drug use data collected during K5 **(Study I)**, Nordanstig baseline **(Study I-IV)** and Nordanstig follow-up **(Study III-IV)** were used in this thesis. Data on drug use were obtained from the participant interview. The participant was asked to give information on brand name, administration form, dose, and frequency, for both prescription drugs and over-the-counter drugs taken regularly at the time of the interview or as needed at any time during the preceding month. The participant was also asked to bring drug containers, prescriptions, medication lists, including over-the counter medications if visiting the research centre, and to show them when the data were collected at a home visit. If the participant was unable to give information, it was obtained from a relative, caregiver, medical staff, or from prescription lists for those residing in institutions. 'Drug use' was defined as the use of drugs on a regular basis at the time of the interview and 'as needed' at any time during the preceding month, if no other explanation was given.

Persons with knowledge of pharmacology (pharmacist or physician) entered or revised the entry of collected drug data into the database. Custom made computer programs were used, allowing automatic classification according to the ATC-system and selected criteria for IDU (see below). The author checked the data entries in K5, and Nordanstig baseline and follow-up.

Drugs were classified according to the ATC-system, recommended by the World Health Organization (WHO). The ATC-system was originally developed by the Norwegian Medicinal Depot, (based on the European Pharmaceutical Market Research Association classification system), as well as the concept "Defined Daily Dose (DDD)" (not used in the analyses). Both were developed to facilitate drug utilization studies, especially international comparisons, and should not be regarded as recommendation for use, or confer of status (i.e., efficacy) on a substance [95, 96].

The ATC-system classifies drugs using five levels. The drugs are first divided into 14 main groups based on anatomy, then further subdivided by therapeutic/pharmacological characteristics (second and third level). The fourth level is a therapeutic/ pharmacological/chemical subgroup and the fifth level is the active chemical substance [95].

Example:

1st level	C	Cardiovascular system
2nd level	C03	Diuretics
3rd level	C03C	High-ceiling diuretics
4th level	C03CA	Sulfonamides
5th level	C03CA01	Furosemide

The drug data in the study were classified using 13 main classes out of 14. Group V (various, containing, e.g., allergens, diagnostic agents, nutrients, and X-ray contrast media) was excluded. Alternative medicines were recorded only in the Nordanstig study and were not possible to classify using the ATC-system.

There is no consensus on how to define polypharmacy. One possibility is to simply count the number of used drugs. Many use a cut-off point between three and five drugs per individual. However, with modern therapy many persons will quickly reach these cut-off levels, but still have pharmacological treatment of good quality. An alternative definition of polypharmacy is the use of more medications than are clinically indicated [53], which means that use of only one drug could be "polypharmacy". However this definition calls for a clinical review, which is beyond the scope of this thesis. Therefore, in this thesis polypharmacy is defined as use of five drugs or more, without a quality judgment.

Potentially inappropriate drug use

To classify potentially IDU for **Study II**, selected consensus-based criteria from several sources published in the international literature were used [24, 56, 57]. The criteria were selected based on (i) if the substance was available in Sweden at the time of data collection, (ii) if adequate information, i.e., of contraindicating diseases, was available in the data set, and (iii) if the potentially inappropriate regimen was considered to be of 'high severity' (according to the Beers criteria). These criteria were supplemented with (iv) additional drugs with prominent anticholinergic effects, (v) additional long acting benzodiazepines (regular use), (vi) unnecessary or potentially harmful drug duplication within the same therapeutic subgroup, or regular use of three or more psychotropic drugs, and (vii) potentially severe drug-drug interactions. A detailed list is available in the enclosed reprint of **Study II.** In this study the independent variable was classified as being a user of at least one inappropriate drug according to the criteria above or being a non-user.

To classify potentially IDU for **Study IV**, selected criteria from the recommendations published in 2003 by the Swedish National Board of Health and Welfare were used [97]. The criteria were selected if no other information than drug consumption data was needed, and included (i) drugs with prominent anticholinergic effects, (ii) long acting benzodiazepines, (iii) unnecessary or potentially harmful drug duplication within the same therapeutic subgroup, (iv) use of three or more psychotropic drugs, and (v) potentially severe drug-drug interactions. A custom made Swedish software (Monitor, developed by Johan Fastbom M.D., Ph.D.), designed for drug quality reviews, was used for this classification. A detailed list of included drugs is available in the enclosed manuscript of **Study IV**.

Drug-drug interactions are common, although not all are serious. The process of identifying potentially serious interactions needs more detailed description. The potential interactions were identified using the system developed by Sjöqvist, which is based on more than 1900 references from the international literature, continually revised, and published on a yearly basis in the Swedish drug compendium 'FASS' [98]. FASS is distributed to all Swedish physicians, and widely used for reference when prescribing drugs. In brief, the Sjöqvist system identifies four levels of clinical relevance (A-D) and four levels of evidence (1-4):

Clinical Relevance:

A. Probably none
B. Not yet assessed
C. Can modify the pharmacological effects, or cause ADRs, but can be controlled by individual dosing and/or measuring of plasma concentration of the drug. The drug combination may require dose adjustment
D. May have serious clinical consequences, like serious ADRs, suppressed effect or is difficult to control with dose adjustment. The drug combination should be avoided

Evidence:

1. Incomplete case reports, in vitro studies, or presumed possible drug interaction on evidence from similar drugs
2. Well documented case reports
3. Studies on healthy volunteers or pilot studies in patients
4. Controlled studies in relevant patient groups

The most serious and best-documented interactions (D3, D4) were included in the criteria above.

Heart failure

The study protocols did not include a specific diagnostic procedure for HF, but data on patient history, including hospital care and cause of stay, and specified questions for clinical signs of HF (e.g., leg oedema and rales) at the physicians' examination were recorded. The physicians' clinical diagnoses, based on the participant's medical history, physical findings at the medical

examination, and medical records if available, were used for classification if HF was present or not. HF diagnosis was used in **Studies I-III.**

Data on chest X-rays were not registered and electrocardiograms were not performed in the K5 or Nordanstig baseline examinations. Moreover, no records on echocardiography were available, but even if it had been performed, routine echocardiography is not necessarily helpful for a HF diagnosis, as the question of diastolic dysfunction is not always addressed. Diastolic HF (with normal left ventricular systolic function) is reported to approach 50% of the HF prevalence in ages >70 [76, 77], with a prevalence of up to 73% in women over 90 years of age [99].

Cognitive impairment and dementia

As part of the diagnostic process for dementia, a validated instrument, the Mini-Mental State Examination (MMSE) was used. The MMSE includes measures of orientation, immediate and delayed word recall, attention, ability to name and follow verbal and written commands, write a sentence spontaneously, and figure-copying. The maximum score is 30 [100]. In **Study I** a score of 0-23 was considered as indicative of cognitive impairment [101].

Dementia diagnosis in Nordanstig baseline was used in **Studies II and III** and was based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, third edition–revised (DSM-III-R) (Table 2) [83]. The patient history, findings at the medical examination, and cognitive testing, as well as information from the next-of-kin interview in a three-step diagnostic procedure were used as follows: Two independent clinicians diagnosed clinically definite dementia (fulfilling DSM-III-R criteria), questionable dementia (evident memory impairment but dysfunction of a second cognitive ability questionable) or no dementia using the study protocols. In case of agreement, the diagnosis was accepted and in case of disagreement the case was re-examined and a final diagnosis was made by a third independent expert.

Health related variables and other relevant diseases and disorders

Basic ADLs, smoking [102] and Body Mass Index (BMI) measured as weight in kg/(height in meters)^2 [103, 104] have been shown to predict mortality in elderly people. Katz ADL index [105] was dichotomized into independent or dependent in at least one item of six (bathing,

dressing, toileting, transferring, continence, and feeding). Smoking was dichotomized into being a current smoker or not. BMI was used with a cut-off where <20 kg/m^2 was considered as low. These variables were used in **Study II.**

Table 2. DSM-III-R* criteria for dementia (abbreviated)

1 Demonstrable evidence of impairment in short- and long-term memory

2 At least one of the following:
   (a) Impairment in abstract thinking
   (b) Impaired judgment
   (c) Other disturbances of higher cortical function, as aphasia, apraxia, agnosia and "constructional difficulty"
   (d) Personality change, i.e., alteration or accentuation of premorbid traits

3 The disturbance in 1 and 2 significantly interferes with work or usual social activities or relationships with others

4 Not occurring exclusively during the course of Delirium

5 Either a) or b):
   a) There is evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
   b) In the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., Major Depression accounting for cognitive impairment

*American Psychiatric Association (1987): Diagnostic and Statistical Manual of Mental Disorders, third edition – revised [83]

We used data from the physician protocol for a history of diseases or disorders relevant for the studies. Patient history and/or signs at the clinical examination were used, including: hypertension; heart disease i.e., in addition to HF, angina pectoris, myocardial infarction, and atrial fibrillation; CVD, i.e., stroke, and transient ischemic attacks; diabetes mellitus; thyroid disease i.e., earlier goiter surgery, goiter present, earlier treatment for thyreotoxicosis, other thyroid diseases; COPD; connective tissue disease; tumours; and psychiatric disease, e.g., depression or manic-depressive disorder, schizophrenia, paranoia, neurosis including asthenia, anamnesis of dementia, and personality disturbances.

In **Study I** all of the above mentioned diseases and disorders, except COPD, connective tissue disease, and tumours were used. For **Study II**, a comorbidity score based on the validated Charlson Comorbidity Index [106-108] was constructed, using data on HF, CVD, dementia, COPD, connective tissue disease, diabetes, tumours, and renal disease. **Study III** used data on diseases related to HF and treatment of HF: diabetes mellitus, hypertension, low BP, myocardial infarction, atrial fibrillation, stroke, and renal dysfunction.

Data on arterial BP (systolic Korotkoff Phase I and diastolic Korotkoff phase V) were obtained at the medical examination (measured once with a standardized mercury sphygmomanometer, with the patient sitting). Systolic BP >160 mmHg and diastolic BP >95 mmHg was considered as high in **Study I**. Systolic BP < 110 mmHg was considered as low in **Study III.**

We also used serum thyroid stimulating hormone level to detect hypothyroidism, and glycosylated haemoglobin as a marker for diabetes mellitus (routine laboratory analyses) as additional information used in **Study I.** The laboratory's reference values were used for classification. Renal function was measured with an estimation of creatinine clearance as a proxy for glomerular filtration, using the Cockcroft-Gault formula based on serum creatinine, body weight, age, and sex [109]. An estimated creatinine clearance <25 ml/minute was used as a proxy for chronic moderate or severe renal disease in the comorbidity index in **Study II**, and in **Study III** estimated creatinine clearance was introduced as a dichotomous variable with a cut-off level at < 55 ml/minute.

Dependent variables

In **Study I** the dependent variable was defined as being a user of drugs or a non-user from the different main ATC-groups and cardiovascular drug subgroups.

In **Study II** the dependent variable was defined as at least one acute hospitalization or no hospitalization, and mortality, during three years of follow-up after drug data collection in Nordanstig baseline investigation. Information concerning whether participants had been admitted to hospital was obtained from the Gävleborg county computerized inpatient register, and date of death from the community authorities of Nordanstig.

In **Study III** the dependent variable was defined as being a user or a non-user of an ACEI.

Statistical analyses

Data were analyzed with SPSS® software [110]. Background population characteristics were presented with descriptive statistics in each study.

Study I: Mean and median number of drugs with 95% confidence intervals (CI) were calculated for different participant subgroups and comparisons were also made with non-parametric tests (Kruskal-Wallis and Mann-Witney tests). Differences in disease prevalence and some crude drug consumption data (ACEI and polypharmacy) between the rural participants (N84+) and the urban K5 participants were investigated with chi-square tests. Comparisons of use of the main ATC-groups and subgroups of cardiovascular drugs between K5 and N84+ were performed, adjusting for sociodemographic and relevant medical covariates in logistic regressions models. Logistic regression models were also used to further analyze factors related to use of cardiovascular drugs in all Nordanstig baseline participants.

Study II: Prevalence of IDU with 95% CI was calculated for participant subgroups. In the first step of analysis, cross tabulations or regression models were calculated for IDU and each considered covariate and outcome (hospitalization or death). The covariates were then entered simultaneously and together with the independent variable IDU into logistic regression models for hospital admissions and proportional hazard models (Cox regression) for mortality as outcome. As a final step, logistic regressions, and proportional hazard models, stratified for the housing variable were performed.

Study III: Prevalence of diseases and drug use related to HF by dementia status were analyzed with chi-square tests, and these covariates were then entered into a logistic regression model together, where dementia status was the independent variable and being a user of an ACEI the dependent variable.

Study IV: Drug use data were analyzed with descriptive statistics and chi-square tests. Skewed, dependent longitudinal data were analyzed with Wilcoxon matched-pairs signed-rank test. Differences in drug use prevalence over time was analyzed with the McNemar test for repeated measurements of dichotomous variables.

Ethical issues

Careful ethical consideration is necessary when approaching a large number of people, based on their advanced age and area of residence, to ask them to be part of a longitudinal study. As the persons invited in to the Kungsholmen Project were part of the general population, as opposed to, e.g., healthy volunteers, the possibility that a fair proportion of them could be frail and/or be cognitively impaired needed to be addressed.

Each potential participant was contacted with a multi-step procedure. First a letter was sent explaining the outline, purpose, and importance of the study, that participation was voluntary, and that if entering the study they could discontinue at any time. Then the potential participant was contacted via telephone for an answer concerning whether or not they were available. Informed consent to participate, including an interview with a next-of-kin or other close person named by the participant, and access to medical records, was given in writing. However, if the person was severely cognitively impaired, a proxy (usually a close family member) was asked for consent. In these cases special attention was given to the participants' reactions during the investigation, which was stopped if signs of discomfort were noted.

Although treatment of disease was not a part of the project, participants were referred to medical care if a pathological result was found in, e.g., in a laboratory test. Also, in the Kungsholmen area, where the project has been going on for a long time, and where a large number of results have been published, the participants have been given feed-back of the results both at seminars and in writing, e.g., a special issue of the journal 'Äldre i centrum' (Elderly in Focus) [111].

All phases of the Kungsholmen Project have been approved by Ethics Committees, for this thesis as stated below:

Studies I, III & IV:	Karolinska Institutet	Dnr 94:122
	Karolinska Institutet	Dnr 97:413
	Umeå University	Dnr 94-100

Study II:	Karolinska Institutet	Dnr 94:122
	Umeå University	Dnr 94-100

Main results

The study populations

At baseline 1987-89, 1810 (76.4%) of the invited 2368 inhabitants in Kungsholmen parish participated in the project. (For description of the non-participants at baseline, see 'Methods – Study Populations'). At the third follow-up (1997-98) of the Kungsholmen Project (K5), the participants were 84 years and older. Out of the original 1810 participants at baseline, 421 (23.3%) still participated. The 1389 dropouts were older than the participants in phase V and a larger proportion of men dropped out compared to women. See also Figure 1.

At baseline 1995-98, 919 (78.7%) of the 1168 inhabitants in the Nordanstig municipality participated. The non-participants differed from the participants in that those who died were older, and those who refused or did not participate for other reasons were younger. More women refused to participate, and a larger proportion of men had died. See also Figure 1. The dropouts between baseline and follow-up, including those with missing drug data at follow-up, were older but there was no difference in gender distribution.

Basic demographic characteristics at Nordanstig baseline and K5 are presented in Table 3. The majority of participants were women and living independently. At the time of Nordanstig follow-up the participants were 78 years or older, and the mean age was 84.4 years (SD 4.2 years). Only 7 % of the participants in Nordanstig baseline (5 % of N84+) compared to 55% in K5 had additional education after elementary school.

There were no significant differences in prevalence of cardiovascular diseases between N84+ and K5, with the exception that hypertension was diagnosed more often in Kungsholmen. However, the prevalence of hypertension diagnosis *or* high BP (systolic > 160 mmHg or diastolic >95 mmHg) did not differ (data presented in **Study I**).

Drug use

Data on drug use were available for 418 of the 421 participants in K5. In Nordanstig baseline investigation, 918 out of 919 participants had drug use data, of which 335 were 84 years and

Table 3. Participant characteristics at baseline: Nordanstig, all; Nordanstig, 84 years and older (84+); and Kungsholmen phase V (K5).

	Nordanstig, all			**Nordanstig, 84+**		**Kungsholmen V**	
Mean age (SD)	82.3	(4.7)		87.4	(3.1)	89.1	(3.5)
	n	**%**		**n**	**%**	**n**	**%**
Total	918			335		418	
Age (y) at interview							
75-79	307	33.4					
80-84	347	37.8					
85-89	183	19.9	84-89	254	75.8	256	61.2
90 -	81	8.8	90 -	81	24.2	162	38.8
Gender							
Male	378	41.2		126	37.6	73	17.5
Female	540	58.8		209	62.4	345	82.5
Housing							
House	425	46.3		107	31.9	0	0.0
Apartment	317	34.5		133	39.7	294	70.3
Sheltered*	143	15.6		82	24.5	77	18.4
Nursing home	33	3.6		13	3.9	47	11.2

* Sheltered housing (service home, home for the elderly, group living for the demented)

SD= standard deviation

older. At follow-up in Nordanstig, 562 of the 579 participants had drug use data, and 561 had drug data at both time points.

The drug information was collected at home visits for the vast majority of participants in Nordanstig baseline and follow-up investigation. A visit to the participant's residence including institutions was considered as "at home". About one third of the K5 participants were examined at the research centre.

Studies I and IV: Overall drug use

More than 90% of all participants used at least one drug at K5, Nordanstig baseline and follow-up. The three most commonly used drug classes were drugs from ATC-groups C

Table 4. Users (%) of drugs, regular and/or as needed, according to ATC-group. Main ATC-classes with at least 10% users within at least one study population are shown. Additional levels of interest are shown for drugs used in cardiovascular diseases

ATC-group		N1	N2	N84+	K5
n		918	562	335	418
Total	User of drugs, regular and as needed	91.4	93.6	93.1	93.3
A	Alimentary tract and metabolism	42.7	46.6	49.0	54.1
B	Blood and blood forming organs	29.6	39.0	33.1	49.0
B01	Antithrombotic agents	19.5	27.7	20.3	34.7
C	Cardiovascular system	66.2	71.0	72.8	61.0
C01	Cardiac therapy	34.3	34.3	40.3	32.8
C01A	Cardiac glycosides	16.2	15.8	23.6	21.3
C01D	Vasodilators used in cardiac diseases	23.4	24.6	25.1	16.5
C03	Diuretics	46.2	50.9	53.7	42.8
C03C	High-ceiling (loop-) diuretics	39.1	43.4	46.6	33.0
C03D	Potassium-sparing agents	11.7	11.6	15.2	13.9
C07	Beta blocking agents	14.7	18.5	10.4	11.2
C08	Calcium channel blockers	11.5	10.9	9.6	12.0
C09	Agents acting on the renin-angiotensin system	11.3	15.3	9.0	10.3
G	Genito urinary system and sex hormones	11.3	15.5	11.9	17.7
H	Systemic hormonal preparations, excl. sex hormones	9.9	11.2	7.8	16.7
M	Musculo-skeletal system	16.4	15.8	14.6	13.6
N	Nervous system	53.5	57.1	61.2	58.1
R	Respiratory system	14.4	15.7	14.9	13.4

N1 = Nordanstig baseline, N2= Nordanstig follow-up, N84+ = Nordanstig baseline, 84 years and older, K5 = Kungsholmen phase V (84 years and older).

(Cardiovascular system), N (Nervous system), and A (Alimentary tract and metabolism). Further, the high utilization of ATC-group B (Blood and blood forming organs) was due, to a large extent, to the use of antithrombotics, a treatment for some cardiovascular diseases (Table 4).

The comparison between Nordanstig baseline and follow-up investigations showed that a significantly increased proportion of men used a drug from the main ATC-groups ‘Blood and blood forming organs’, ‘Cardiovascular system’, ‘Genito urinary system’, ‘Musculo-skeletal

Table 5. Prevalences (%) of drug use in Nordanstig participants with drug data at baseline (N1) and follow-up (N2) by sex

	Men	n=223		Women	n=338	
User at:	N1	N2	p-value*	N1	N2	p-value*
ATC-group						
At least one drug	**85.7**	**91.0**	**0.029**	**92.3**	**95.3**	**0.041**
A Alimentary tract and metabolism	34.5	40.8	0.065	40.5	50.3	0.001
B Blood and blood forming organs	31.4	40.4	0.005	21.6	37.9	<0.001
B01AC06 Acetylsalicylic acid (aspirin), low dose	21.5	27.4	0.035	11.2	20.7	<0.001
C Cardiovascular system	59.2	66.4	0.009	65.1	74.0	<0.001
C01A Cardiac glycosides	12.6	15.2	0.263	12.4	16.3	0.002
C01D Vasodilators used in Cardiac disease (nitrates)	26.0	29.1	0.210	17.2	21.6	0.017
C03C High-ceiling diuretics	26.5	34.1	0.002	39.6	49.4	<0.001
C03D Potassium-sparing agents	7.6	8.1	1.000	12.4	13.9	0.424
C07 Beta blocking agents	15.7	16.1	1.000	17.5	20.1	0.150
C08 Calcium channel blockers	13.9	13.0	0.774	11.8	9.5	0.134
C09 Agents acting on the renin-angiotensin system	10.8	13.9	0.118	11.8	16.3	0.008
G Genito urinary system and sex hormones	3.6	9.0	0.008	15.4	19.8	0.024
H Systemic hormonal drugs, excl. sex hormones	5.8	8.1	0.125	11.2	13.3	0.118
M Musculo-skeletal system	9.4	17.9	0.001	19.5	14.5	0.024
N Nervous system	38.1	44.8	0.082	52.7	65.1	<0.001
R Respiratory system	11.7	16.6	0.043	13.6	15.1	0.487
S Sensory organs	4.0	5.8	0.344	5.9	10.9	0.002

* Difference in prevalence between baseline and follow-up analyzed with the McNemar test for repeated measures of dichotomous variables

system', and 'Respiratory system' at follow-up, whereas a significantly increased proportion of women at follow-up used a drug from main ATC-groups 'Alimentary tract and metabolism', 'Blood and blood forming organs', 'Cardiovascular system', 'Genito urinary

system', 'Nervous system', and 'Sensory organs'. The most prominent increase of a subgroup was a three-fold increase in use in men and almost three-fold increase in women of antidepressants of the selective serotonin reuptake inhibitor (SSRI) type (N06AB). The only decrease at follow-up was registered for use of 'Musculo-skeletal system' drugs in women (Table 5).

The mean total number of drugs used at Nordanstig baseline was 4.5 (n=918) compared to 5.1 at follow-up (n=562). When comparing those who participated at both baseline and follow-up and had drug data at both times (n=561) the corresponding results were 3.9 and 5.1 ($p<0.001$). Women (n=338) used more drugs compared to men (n=223) with a mean number of 4.2 at baseline compared to 3.4 ($p=0.001$) and 5.5 at follow up compared to 4.5 ($p<0.001$). The sums of used drugs by the study participants for ATC-groups with minimum 10% users at one of the Nordanstig data collections are shown in Figure 2.

The Nordanstig baseline investigation (n=918) also showed an increasing trend of drug use with increasing age, with use of approximately one drug more by the oldest age group. The difference was significant between the youngest age group 75-79 years and each of the other age groups. In addition, there was an increasing number of drugs with increasing dependency measured according to housing type. Nursing home residents on average used 8.8 drugs per person.

Polypharmacy was common, with use of up to 19 drugs in one individual. Especially high use of five drugs or more was found in the oldest-old people: half of the participants from K5, and 46% of the N84+ participants used five drugs or more. It was also common at the Nordanstig follow-up investigation when 56% of the women and 44% of the men were users. However, there was no difference in the mean number of drugs used between the participants from K5 and N84+ .

Regional differences were further studied: After adjustment in logistic regression models for sex, age group, education, housing, place of data collection (home or research centre), and relevant medical conditions for each ATC-group, the comparison between N84+ and K5 participants showed no difference in the utilization of most of the main ATC-groups with more than 10% users. However, the Odds Ratio (OR) (95% CI) for being a user of drugs from ATC-group B was 0.60 (0.39-0.93), indicating a lower use in Nordanstig, and was

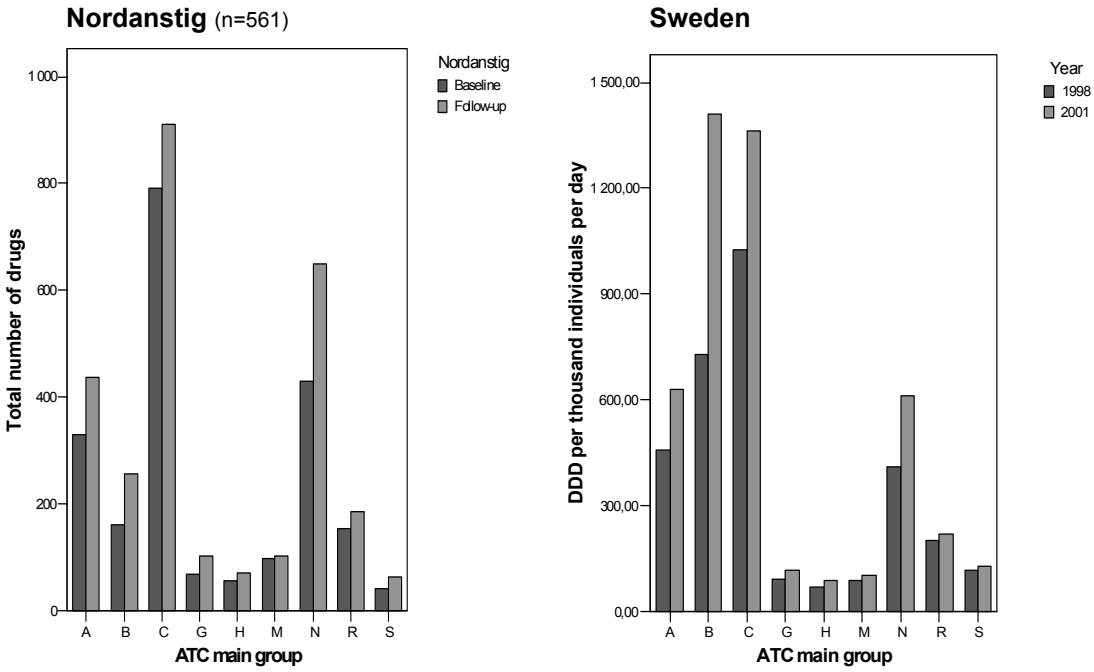

Figure 2.
Left:
Total number (accumulated from all participants) of used drugs in main ATC- groups with at least 10% users at Nordanstig baseline or follow-up investigation.

Right: Number of sold Defined Daily Doses (DDD) of prescribed drugs in the same main ATC-groups per 1000 individuals 75 years and older, per day, in Sweden 1998 and 2001

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Courtesy Karolina Antonov, Pharm. D , The National Corporation of Swedish Pharmacies for access to national figures.

2.95 (1.69-5.15) for ATC-group C, indicating a higher use in Nordanstig compared to Kungsholmen.

Studies I, III, and IV: Cardiovascular drug use

Further analyses of the above mentioned differences in utilization of ATC-groups B and C between the oldest people in Nordanstig and K5 included adjustment in logistic regression models for age group, sex, housing, MMSE score, and relevant medical conditions. These showed that the higher use of ATC-group C in Nordanstig was mainly explained by higher use of 'Vasodilators in cardiac disease' (mainly nitrates) with an OR (95% CI) of 2.51 (1.46-4.30) and high ceiling diuretics 2.62 (1.77-3.90), while the lower utilization of

ATC-group B in Nordanstig was explained by lower use of 'Antithrombotic agents' (mainly aspirin) with an OR (95% CI) of 0.43 (0.29-0.65). There was no significant regional difference in the utilization of 'Agents acting on the renin-angiotensin system'[1] but the proportion of persons with HF who used ACEIs was low in both areas; 18% in Nordanstig and 21% in Kungsholmen.

Cardiovascular drug use was also further analyzed in all the 918 Nordanstig baseline participants. Logistic regression models were performed for the second level of ATC-groups with at least 10% users among the participants, adjusting drug utilization data for age, sex, education, housing, MMSE score, and the diseases that could be an indication for use of each drug class. The most important explanatory variables were the different cardiovascular diseases. However, men had a lower OR (95% CI) of 0.64 (0.46-0.91) for being a user of diuretics than women, and persons living in sheltered housing or nursing homes were more often users of the group 'cardiac therapy' (including, among others, the drugs digoxin and nitrates) with an OR (95% CI) of 2.69 (1.55-4.67), and diuretics 2.11 (1.26–3.53) compared to community residing participants. Persons with a MMSE score <24 were users of beta-blockers to a lesser extent OR (95% CI): 0.50 (0.28-0.87) as well as 'agents acting on the renin-angiotensin system' OR (95% CI) 0.44 (0.24-0.80) than the participants with a MMSE score $\geq$ 24.

Based on the finding that only 24% of the participants with HF in the total Nordanstig baseline investigation used ACEIs, and the possible under-use by persons with cognitive impairment, the drug utilization patterns in relation to dementia, with focus on ACEIs, was explored in 265 persons with a clinical diagnosis of HF at baseline who were using at least one drug from the main ATC-group C. In this study group, 25.7% used ACEI at baseline and among 136 participants for whom follow-up data were available, 28.7% used ACEI at baseline and 29.4% at follow-up. Compared to the non-demented, the demented participants used significantly less 'agents acting on the renin-angiotensin system' with a prevalence of 13.3 % in demented persons.

[1] ACEIs are used interchangeably with 'Agents acting on the renin-angiotensin system' in the result section, as there were very few users of the other drug class in ATC-group C09, namely Angiotensin II antagonists (ARBs): 1 user in Kungsholmen phase V, in Nordanstig 3 at baseline and 5 at follow-up, and no users in Study III.

ACEI use was thereafter analyzed in a logistic regression model with dementia status at baseline as the independent variable, and age group, sex, housing (community residing versus sheltered housing or nursing home), medical conditions (hypertension, systolic BP <110 mmHg, atrial fibrillation, diabetes mellitus, estimated creatinine clearance <55ml/minute, and history of myocardial infarction or stroke) as covariates. The significant difference in ACEI use between the non-demented and demented participants in the descriptive analysis disappeared. The OR (95% CI) for being a user of an ACEI was 0.66 (0.22-1.97) for participants with questionable dementia, and 0.70 (0.25-1.93) for those with dementia compared to the non-demented participants. In this analysis, the oldest age group 90 years and older and participants living in an institution had a significantly lower OR (95% CI) for being a user of an ACEI: 0.11 (0.01-0.95) and 0.28 (0.09-0.91) respectively, while participants with atrial fibrillation had a higher OR (95% CI): 2.36 (1.17-4.76). Low creatinine clearance was not associated with non-use of ACEIs, but with lower doses.

Furthermore, in the HF patients 16% used beta-blockers (C07), 82% of the 'calcium channel blocker' users (C08) used preparations with negative inotropic effects on the heart muscle, 51% of the cardiac glycoside users (C01A) had atrial fibrillation, and one tenth of the participants used NSAIDs (M01A).

Finally, exploring cardiovascular drug use in all of the Nordanstig participants who had drug use data at both investigations (561 persons) there was a significantly increased proportion of both men and women using low dose aspirin, high ceiling diuretics (mainly furosemide), and for women also cardiac glycosides (mainly digoxin), nitrates, and ACEIs between baseline and follow-up (Table 5 and Figure 3).

Study IV: Continuity of drug use

The most common longitudinal pattern of drug use was that the majority of users of a drug/drug class at baseline were also users at follow-up, and the increase (although not always statistically significant) was due to new users. However, for some drug classes the turnover of users was especially high. In men the subgroups ' drugs for treatment of peptic ulcer' and most subgroups from the ATC main group N, including drugs for pain, had a high turnover, whereas in women the corresponding findings were a high turnover of subgroups 'laxatives' and several subgroups of drugs for treatment of pain.

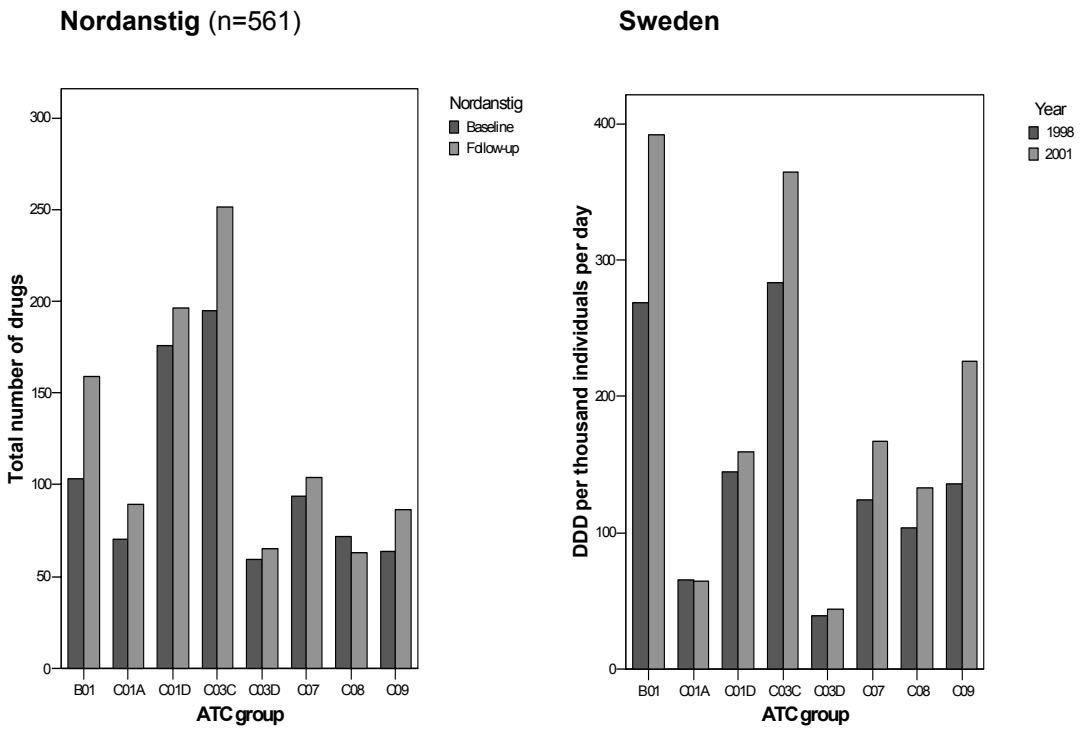

Figure 3.
Left: Total number (accumulated from all participants) of used drugs in ATC subgroups B01, C01A, C01D, C03C, C03D, C07, C08, C09 (antithrombotics and cardiovascular drugs) at Nordanstig baseline or follow-up investigation.

Right: Number of sold Defined Daily Doses (DDD) of prescribed drugs in the same ATC-groups per 1000 individuals 75 years and older, per day, in Sweden 1998 and 2001.

Courtesy Karolina Antonov, Pharm. D., The National Corporation of Swedish Pharmacies for access to national figures.

Studies II and IV: Potentially inappropriate drug use

Potential IDU was classified somewhat differently in **Studies II** and **IV**. The prevalence of at least one inappropriate drug for both classifications in Nordanstig baseline participants with drug data are shown in Table 6. Almost one-fifth of the participants used at least one potentially inappropriate drug with either classification. The use increased with number of diseases and number of drugs, and almost half of the participants residing in nursing homes had at least one inappropriate medication. The differences in IDU prevalence according to **Study II** compared to **Study IV** criteria were small.

Further analyses with logistic regression were performed, with IDU (being a user of at least one drug according to **Study II** criteria or a non-user) as the independent variable, and at least

Table 6. Users of at least one potentially inappropriate drug (%) by participant characteristics in Nordanstig baseline participants (n=918)

		Study II criteria ‡		Study IV criteria ‡	
	n	%	(95% CI)	%	(95% CI)
All	918	19.2	(16.6-21.7)	18.4	(15.9-20.9)
Age (years)					
75-79	307	16.0	(11.8-20.1)	14.7	(10.7-18.6)
80-84	347	21.6	(17.3-26.0)	20.7	(16.5-25.0)
≥85	264	19.7	(14.9-24.5)	19.7	(14.9-24.5)
Sex					
Women	540	19.6	(16.3-23.0)	20.0	(16.6-23.4)
Men	378	18.5	(14.6-22.5)	16.1	(12.4-19.9)
Housing					
House or apartment	742	15.5	(12.9-18.1)	15.1	(12.5-17.7)
Sheltered housing*	143	31.5	(23.8-39.2)	28.7	(21.2-36.2)
Nursing home	33	48.5	(30.5-66.5)	48.5	(30.5-66.5)
Comorbidity index †					
0	248	13.3	(9.0-17.6)	14.5	(10.1-18.9)
1	241	15.4	(10.8-19.9)	14.9	(10.4-19.5)
2	205	20.5	(14.9-26.1)	19.0	(13.6-24.4)
≥ 3	193	30.1	(23.5-36.6)	26.9	(20.6-33.3)
Number of regular drugs					
0-1	255	2.7	(0.7-4.8)	4.3	(1.8-6.8)
2-4	378	14.8	(11.2-18.4)	15.1	(11.5-18.7)
≥ 5	285	39.6	(33.9-45.4)	35.4	(29.9-41.0)

* Service home, home for the elderly, group living for the demented. † Classified according to the modified Charlson Comorbidity Index used in Study II (31 with missing data). ‡ Inappropriate drug use: Study II and IV criteria are described in 'Methods – Potentially inappropriate drug use'.

one acute hospitalization during three years after data collection as the outcome variable, controlling for sociodemographic, health-related factors, and medical conditions. The 785 participants with complete data on selected exposure, outcomes, and covariates were included. In the analyses that were stratified for housing, there was an association for community residing participants, OR (95% CI): 2.75 (1.66-4.55) between IDU and hospitalization. No association was found for participants living in some form of institution, and also, there was no association between IDU and mortality.

Continuity of IDU was investigated in the 561 participants who had drug use data both at baseline and follow-up. At baseline, 76 persons (13.5%) were users of at least one inappropriate drug compared to 107 (19.1%) at follow-up (p=0.001). Twenty-eight (37%) of the users at baseline had discontinued at follow-up, and 59 (55%) of the users at follow-up were non-users at baseline. Women were more often users than men, and the difference was significant at follow-up (p=0.037).

Discussion

This thesis focuses on quantitative and qualitative issues regarding elderly people's consumption of pharmaceutical drugs. In the following section, methodological issues and the main results will be discussed. More detailed discussion of minor results is available in the discussion parts of the attached **Studies I-IV**.

Internal validity

The study populations

The Kungsholmen Project is a population-based study, where all inhabitants of the Kungsholmen parish, Stockholm, October 1, 1987 and all inhabitants of Nordanstig municipality September 1, 1995, were invited to participate. The overall aim of the project was to study ageing from a medical, psychological, and social point of view, with special focus on dementia. The Kungsholmen parish was originally chosen for the first cohort because of the high concentration of elderly inhabitants at that time [91]. As Kungsholmen is an inner city area in the capital of Sweden, the area of Nordanstig was added eight years later to represent a rural area to enable regional comparisons. In Nordanstig, there was also a high concentration of elderly inhabitants at the time of baseline [92].

The participation rate was high at both the Kungsholmen and Nordanstig baseline investigations, with fairly small differences regarding age and sex distribution between non-participants and participants. Thus, the study populations are likely to be representative for their source populations. However, the remaining participants in K5 (**Study I**) were those who had survived since baseline, and no new participants (i.e., persons who declined participation in earlier phases and still lived in the parish, or persons who had moved into the parish after baseline) were included. As the majority of the dropouts (73%) died, this may have led to a selection bias, as those who remained at follow-up were probably the healthiest persons at baseline.

At baseline, 76% of the inhabitants in Kungsholmen and 58% in Nordanstig were women, compared to a figure of 62% in the age group 75 years and older in the whole of Sweden during the corresponding periods [112, 113]. This trend may be a result of migration patterns within Sweden during part of the 20th century, when people left the rural areas. More women and people with higher education relocated to urban regions, which explains the differences in sex and educational distribution between the studied participant groups. These differences may, to some extent, limit the generalizability to other populations, but there would be similar populations in most western societies where the results could be applicable.

Drug data collection and classification

Several methods of drug data collection have been described in methodologically different studies. Comparisons between drug use data obtained by telephone interviews and pharmacy databases have shown a probable under-reporting of drug use, but there is little evidence concerning an over-reporting [114]. Recall of medications may differ depending on type of drug and length of treatment [115]. Self-administered questionnaires may underestimate the use of drugs, especially if the questions are open-ended [116]. Most researchers consider an at-home assessment procedure as the most valid and reliable method when ascertaining drug use in elderly people [117, 118].

No “golden standard” for validation of drug use data exists at present. Medical records are often incomplete and pharmacy databases, if available, may give limited information, e.g., only include prescribed drugs. In addition, records do not give any information on how the drug is actually used by the patient. Comparisons between these different sources of drug data are measures of agreement rather than validation [119]. At the time of Kungsholmen and Nordanstig data collection, pharmacy-dispensing registers on an individual basis were not available in Sweden. An early Swedish study on drug utilization collected drug data at home visits, and validated the stated use of digoxin by comparing serum digoxin in those who claimed they used the drug with a sample of those who reported being non-users. None of the claimed non-users of digoxin but 91% of the claimed users had a measurable concentration of digoxin. These results suggest a fairly good validity for the home interview method, at least for digoxin [120]. However, it is not feasible to analyze blood samples for all possible drugs in all participants in a large population-based study.

The drug data for the studies in this thesis were collected at home visits (including institutions) in the vast majority of the participants in Nordanstig and for two thirds of the participants in K5. The participants who visited the research facilities were asked to bring their medications and prescriptions with them for the examination. However, there is still a possibility that drug use was not accurately reported in some cases. Over-reporting is less probable than under-reporting, and important drugs that may lead to immediate symptoms if discontinued are less likely to have been forgotten, e.g., insulin and drugs for HF or COPD. However, participants may have forgotten some medications, especially those which are used 'as needed', e.g., hypnotics, and non-prescription drugs. This may, for example, have had some impact on our classification of IDU, probably resulting in an underestimation, although it is not expected that the misclassifications would be differential regarding the hospitalization and death outcomes in **Study II**.

The drug data were collected by physicians (Kungsholmen) and skilled nurses (Nordanstig), but it is not expected that the profession of the investigator would lead to differences in reporting medications. Moreover, in the comparisons between K5 and N84+ participants, place of drug data collection (home or centre) was considered in the analysis. Persons with knowledge of pharmacology (pharmacist or physician) entered or revised the entry of collected drug data into the database. Classifications were then made automatically with the help of computer software and the database was checked for data entry or programming errors. Therefore, there were probably few misclassifications of drugs during the data handling process.

Misclassification of exposure, outcomes, and other main variables

All data sets may include misclassifications for different reasons. Both the sensitivity and specificity of a diagnostic or data collection method cannot be expected to be 100%, and there may be mistakes in entering the data into databases. However, as long as a misclassification of a dichotomous exposure is non-differential in relation to the outcome, and vice versa, it tends to weaken the possible association (bias towards the null hypothesis). Differential misclassifications can affect the results in an unpredictable way, as well as misclassifications of potential confounders that will lead to residual confounding. Misclassification of exposure, outcomes, and other main variables is discussed below.

Potentially inappropriate drug use

A main concern regarding **Study II** is an unknown number of misclassifications of IDU. First, as mentioned above, some participants may not have reported the use of an inappropriate drug, and thus been classified as non-users. Secondly, and most importantly, is that data on the exposure were collected only at one time point, and the outcome was ascertained during three years of follow-up. Users of inappropriate drugs could have discontinued use at any point of time or used the drug irregularly, and non-users could have started using an inappropriate medication during the observation period.

This problem is well demonstrated in a study of calcium channel blockers as a risk factor for cancer, which compared drug data collected at an interview at baseline with longitudinal medication records from the pharmacy. A good agreement was found between reports of use from interviews at baseline with the records, but there were a fairly large number of false negatives, where non-users at the baseline interview became chronic users of the drug during follow-up according to the pharmacy records [121].

The main aim of **Study IV** was to address this concern by exploring continuity of drug use, using the two available data collections, but continuous drug use data were unavailable. Close to two thirds of the users of at least one inappropriate drug were users at both time points, but they could, of course, have discontinued and restarted between data collection periods. Just over half of the users at follow-up were new users. This shows that the turnover of users is noteworthy but does not indicate at which occasion the drug was discontinued or started. Drug prescriptions are often changed during a hospital stay, and thus no attempt was made to analyze the number of hospitalizations as an outcome. However, up to the first hospitalization there is no indication that the misclassifications would be differential regarding the outcome (at least one hospitalization or death). Hospitalization was also included as a possible confounder in the regression models for mortality.

Hospitalization and mortality

Hospitalization data are collected by local county councils and reported to the Swedish National Board of Health and Welfare. The annual under-reporting of hospital stays is stated to be <1% [122]. Statistics Sweden, the authority responsible for registration of the deceased, states that there is no under-reporting at all from 1997 onwards [123]. Thus, the validity of the outcomes in **Study II** is good.

Heart failure

It is well known that a clinical diagnosis of HF has limitations and that both false positive and false negative diagnoses are common [72, 124, 125]. Different definitions of the syndrome and different diagnostic tools have been used to determine the prevalence of HF in the population, giving different results. A study comparing the diagnostic criteria according to the Framingham study [73], the Boston instrument [126], the Gothenburg criteria [127], and the European Society of Cardiology's 1995 criteria [124] in an Italian community residing population of 553 participants aged ≥65 years, showed prevalences of 12%, 11%, 21%, and 9%, respectively [128]. This illustrates the difficulty of determining the prevalence even when using defined criteria.

In the Kungsholmen Project, there were no defined criteria but the diagnosis was left to the physician's judgment. Although it is known that cardiovascular disease is more common in Nordanstig compared to the whole of Sweden [129, 130], the prevalence of 30.5% in Nordanstig baseline and 37.3% in K5 (**Study I**) are high compared to the prevalence of 10% in octogenarians in the Framingham study [74], suggesting that a number of false positives may be present. These probable misclassifications are important when HF is studied as an exposure, outcome, or confounder, but in studies of drug utilization in relation to diagnosis, they are less important, as a clinical diagnosis is the basis for treatment decisions. Thus, the possible over-diagnosis may be of some importance in **Study II** where HF is included as a component in the comorbidity index (contributing one point to a possible maximum score of eleven), but less so in **Study I** where HF is studied as an indication for different drugs. However, in **Study III** where treatment of HF is discussed, use of at least one cardiovascular drug was required for inclusion in an attempt to reduce the number of HF misclassifications.

Cognitive impairment and dementia

The MMSE score was categorized as 0-23 and 24-30, where probable cognitive impairment was defined as a score of 0-23. A score of 0 on the MMSE could be due to either refusal to complete the task or a failure on all items, and thus cognitively intact persons who refused the test could have been misclassified. However, none of the 20 participants in Kungsholmen with a MMSE score of 0, and only two out of the 34 in Nordanstig, were considered to be 'normal' after the dementia diagnostic procedure.

The Kungsholmen Project was designed with focus on dementia. Thus, the determination of dementia diagnosis was careful, with a consensus procedure between three independent physicians. In Kungsholmen the first diagnosis was decided by the physician who examined the participant and the second, and eventually third, diagnoses were based solely on the protocols. In Nordanstig the protocols were used in all steps. The procedure was validated in the initial part of the project. With the introduction of the category questionable dementia, the overall agreement on diagnosis of dementia, questionable dementia, or no dementia was fairly good, with a κ=0.70 [131]. Although there may be some misclassifications, it is likely that it was non-differential in relation to cardiovascular drug use. Some drugs may affect cognition, e.g., anticholinergics, psychotropics, digoxin, and beta-blockers may cause delirium [132]. However, delirium is an exclusion criterion in the DSM-III-R criteria for dementia.

Housing

There are some small discrepancies in some of the results from **Study I and II**, between those reported in the results sections of this thesis and those reported in the original articles included in the thesis. This is due to the fact that a few misclassifications of the housing variable were discovered after the publication of these articles, despite the 'cleaning' process. After this discovery, all analyses that included the housing variable were rerun. Only minor differences were found with no significant impact on the outcome considered in the studies.

The main results and external validity

Overall drug use

Nine out of ten participants in Nordanstig and K5 used at least one drug. The results from the K5 participants correspond well with earlier published studies from the Kungsholmen parish, where 84% used at least one drug at baseline 1987-1989 [9] and 94% at the second follow-up 1994-1996 (when the participants were 81 years or older) [133]. The three most used drugs in Kungsholmen and Nordanstig baseline and follow-up were drugs from the main ATC-groups C, N, and A (Table 4 and 5). This reflects the pattern of morbidity in old age, and other population- or community-based studies have found similar distributions [7, 8, 11, 13, 14, 134, 135]. Also, the trends are close to drug sales patterns in Sweden during the corresponding times of data collection (Figure 2).

Observations in Nordanstig

The increased drug use in persons with sheltered living conditions in Nordanstig corresponds with findings in phase IV of the Kungsholmen cohort [133]. A sample of 33 Swedish nursing homes, investigated in 1994, with a mean age of the residents of 83 years, showed similar average number of used drugs (7.7 compared to 8.8 in Nordanstig) [136]. Two national surveys of nursing homes in the USA found that the residents used seven to eight medications during a month [137]. The high drug utilization found in nursing homes is probably mainly due to higher morbidity, and more severe cases with functional decline among the nursing home residents, but over-medication cannot be excluded.

Gender differences in drug utilization by elderly people have been described by others, both in Sweden [7, 13, 134], and in other countries, as well as in different settings [8, 11, 15, 138-141]. The differences in **Study I** and **IV,** where women used more drugs than men, and the drug class patterns in **Study IV** may be explained by well-known gender differences in morbidity and symptoms, e.g., women have a higher prevalence of thyroid disease, osteoporosis with pain, and chronic venous insufficiency with leg oedema, whereas men are affected by ischemic heart disease earlier than women. However, there is considerable literature on gender-related differences in healthcare utilization, and factors such as health differences, health behaviour differences, and physician treatment biases have been discussed [142-144]. However, little is known concerning very old people.

Other cross-sectional studies including subjects over 85 years [8, 138] have found increasing numbers of prescribed drugs with increasing age. Our findings partly support these reports. Morbidity could be expected to increase with age and thus explain the increase in drug use [13], but in a population of the oldest old, one may also expect to find a cohort survival effect, which could explain why we did not detect a significant increase in drug use in the oldest age groups in Nordanstig.

The mean number of used drugs increased between baseline and follow-up in Nordanstig, and with few exceptions there was an increase of users for most of the main ATC-groups. This is in concordance with earlier reports of an increasing number of prescription drugs over time in population- or community-based studies, comparing longitudinal drug use in a cohort or cohort comparisons, in Sweden and elsewhere [145-148], as well as with earlier phases of the

urban part of the Kungsholmen Project [133]. The trend is also in concordance with drug sale patterns in Sweden at the time (Figure 2). The increased use of drugs with increasing age may reflect an increase in morbidity, but can also – as cohort comparisons of the same age groups at different time points suggest - reflect change in therapeutic patterns, e.g., the development of new, more effective drugs used in addition to older ones, and new therapy guidelines.

The most prominent increase in drug use was in SSRIs, reflecting an increasing interest in treating depression in elderly people. Depression is common in old age and is sometimes difficult to diagnose [149, 150]. Earlier generations of antidepressants had numerous adverse reactions, especially in elderly patients, in contrast to the SSRIs' more benign profile [150, 151]. However, the under-treatment of depression may have been recently replaced by an over-treatment in some settings, as indicated in recent Swedish nursing home studies [152, 153]. Although the ADR profile for SSRIs is more favourable than for earlier antidepressants, there are reports of serious ADRs, e.g., hyponatremia with serious neurologic or psychiatric symptoms [154], and upper gastrointestinal bleeding [155]. Several of the SSRIs have been reported to induce QT prolongation in susceptible individuals, with risk for severe cardiac arrhythmias (Torsades de Pointes) [156]. Therefore, it has been suggested that electrocardiogram control, especially of patients with cardiovascular disorders, should be considered [157]. As elderly patients have a high prevalence of heart pathology – diagnosed or not – this recommendation is highly relevant, and over-medication with SSRIs should be avoided.

Polypharmacy was common, especially in the oldest age group at baseline and at follow-up, with about half of the participants using five drugs or more. Considering that multimorbidity is common in this age group, all polypharmacy is not necessarily inappropriate, but the finding still raises concern. Although the literature is somewhat inconsistent, results suggest that an increased number of drugs decreases the level of adherence to drug treatment. The relatively few studies on complexity of drug regimens (e.g., multiple drugs, multiple dosages) suggest either decreased adherence with increased complexity or no effect on adherence [158, 159]. Also, interactions within multiple medications are not well understood, and may be more complex when several drugs are involved. Finally, earlier studies have shown increasing risk of adverse effects with increasing number of drugs [62, 63], and increasing prevalence of inappropriate prescribing [20-22].

Cardiovascular drug use in Nordanstig

Although HF is common in the elderly [74], and has a considerable impact on the healthcare system [81, 82], old patients have been under-represented or under-reported in HF clinical trials [66], including the major clinical trials of ACEIs [160]. Still, the available data resulted in Swedish guidelines at the time of data collection recommending treatment with ACEIs for patients with low left ventricular ejection fraction and HF or earlier myocardial infarction, irrespective of age [161, 162]. Use of ACEIs in HF in older patients has also been recommended in the geriatric literature [163], but with consideration of possible contraindications and the increased risk for adverse effects [164, 165]. These recommend-dations were later supported by observational studies of elderly HF patients in different settings [166-168].

The findings from **Study I** that approximately only one fifth of the participants 84 years and older with HF used ACEIs, and in **Study III that** one fourth of the HF participants 75 years and older used them, are in concordance with other data describing low utilization of ACEIs by elderly patients. Most studies are from hospital settings [69, 169]. A review of the literature from 1966 up to early 2000, found six studies from ambulatory non-specialist settings with a utilization median of 26%. These data were collected during 1988 to 1995, which could partly explain the low utilization, but the studies included all ages of HF patients, suggesting even lower utilization for elderly patients [170]. The National Corporation of Swedish Pharmacies publishes yearly drug sales statistics, and earlier performed diagnosis and therapy surveys. In the 1998 diagnosis and therapy survey, 27% of Swedish HF patients aged 75 years and older were prescribed ACEIs compared to 1% in 1988 [171, 172]. This reflects the increasing awareness of the benefits of ACEIs and also shows that the use of ACEIs in Nordanstig was similar to the use in the whole of Sweden at that time (Figure 3).

If 50% of HF patients in this age group have normal left ventricular function [76, 77], the expected maximum prevalence of ACEI use in HF would not exceed 50% (unless hypertension predominantly was treated with ACEIs), as the Swedish guidelines for treatment of HF at the time of the baseline data collection recommended ACEIs for HF with left ventricular dysfunction. Also, the very old could have several concurrent diseases, polypharmacy, and be generally frail, all of which could contraindicate the use of ACEIs.

The low utilization of 'agents acting on the angiotensin system' in participants with HF at baseline, and the finding of an even lower utilization by participants with low MMSE, and the increasing interest in cardiovascular disease in relation to cognitive decline and dementia [87, 173] formed the basis of the analyses of differences in ACEI use related to dementia status in **Study III**. Although HF was probably over-reported in Nordanstig, there was no significant difference in HF prevalence by dementia status. However, we cannot exclude differences in HF severity. It has often been argued that dementia patients run a risk of under-diagnosis of somatic disorders due to difficulties in reporting symptoms. This could bias the study results if the demented participants were generally diagnosed with HF later, and thus on average had more serious heart disease.

The lower use of ACEIs by participants with dementia seems, instead, to be closely correlated to living conditions. Although the OR was <1 for being an ACEI user, if classified as demented or questionably demented with the non-demented as reference, the significance disappeared when controlling for covariates in the regression model, where living in an institution and age over 90 years were significantly associated with lower use of ACEIs. This suggests that the choice of therapy is guided not by dementia per se, but rather by frailty leading to increased risk of side effects and possibly also lower access to cardiologists in institutions. The finding of a low utilization rate in institutions corresponds with earlier nursing home studies [174]. To our knowledge there are no clinical trials of ACEIs in HF in nursing home settings or with frail elderly people. However, a retrospective cohort study in nursing homes, with a mean age over 80, suggested beneficial effects of ACEI use in HF on survival and physical function [175]. Notwithstanding this, it is still unclear to what extent this part of the population benefits from ACEI treatment.

In **Study III**, impaired renal function was not associated with refraining from ACEI treatment, but with reduced dosage, reflecting a desired individualization of treatment. Low systolic BP (<110 mmHg) had no significant effect on the use of ACEIs in our study, probably due to low numbers. Presence of atrial fibrillation was associated with ACEI use. This was probably because HF was, to some extent, over-diagnosed in the study, and the presence of atrial fibrillation probably correlated with correctly classified cases of HF.

There was a fairly low utilization of beta-blockers in the HF participants in the Nordanstig baseline investigation. Beta-blockers were introduced in the Swedish 1996 HF treatment

guidelines as a drug class only for specialists [162], and were recommended without this restriction, except for treatment of severe HF in the 2000 guidelines [176], which may explain the low utilization at the time of data collection. At the time in Sweden, only 3% of the patients aged 75 years and older who were receiving medications for HF were treated with beta-blockers on this indication [177], reflecting the slow introduction.

The majority of HF patients with calcium channel blockers had preparations with known negative inotropic effects on the myocardium, which is a practice that is not recommended. Also, 10% used NSAIDs, a drug class that inhibits renal prostaglandin synthesis. This decreases the renal blood flow and can cause sodium and water retention, which can aggravate HF in susceptible individuals. In addition, it has been reported that NSAIDs reduce the effects of diuretics, beta-blockers, ACEIs, and possibly digitalis. Thus, in general, NSAIDs should be avoided in HF and be used with caution in patients with a history of cardiovascular disease or renal dysfunction [178-180], in addition to the well known risk of gastric ulcers and bleeding [181].

As shown in **Study IV**, there was a marked increase in the number of users of high-ceiling diuretics between baseline and follow-up. There was also a significant increase in users of ACEIs in women. The prevalence of HF would not be expected to increase as rapidly as the use of these drugs. Instead, this increase probably reflects an increasing severity of prevalent cases with increasing age, especially as the use of ACEIs in HF would otherwise be expected to reduce the need for diuretics. In addition, the dominating high-ceiling diuretic, furosemide, was also the most prescribed diuretic for treatment of hypertension in ages 65 years and older at that time in Sweden [177]. Thus, part of the increase could reflect an increasing inclination to treat hypertension in this age group following the new guidelines [182]. The increase of ACEIs could probably partly be caused by an increasing awareness and adherence to the guidelines for treatment of HF with impaired left ventricular function [162], or increased use for hypertension and ischemic heart disease, which were the other main indications for ACEIs at the time of data collection [183, 184].

Somewhat surprisingly, there was an increase in the use of cardiac glycosides (mainly digoxin), significantly in women, contrary to other reports that have described a decreased use in Sweden [147, 177] and elsewhere [185]. At the time, digoxin was recommended for symptomatic use in HF, especially with concurrent atrial fibrillation [162] and for atrial

fibrillation also without HF. However, several studies from different settings have reported use of digoxin without a recommended indication in 30% to 47% of the elderly digoxin users [186-189]. This is a potential problem, as digoxin has a narrow therapeutic window, especially in elderly people [190], and digoxin intoxication may have atypical symptoms in elderly patients [188] and thus should be used with caution.

The increased use of low dose aspirin reflects an increased awareness of the preventive effects against a wide range of vascular events in at-risk patients [191]. However, there are no controlled trials conducted in the very old, and elderly patients are at higher risk of adverse reactions, mainly gastric bleeding. Retrospective studies have found beneficial effects of aspirin in elderly patients, and as the risk of cardiovascular events are higher in the elderly, the benefits may exceed the risk of adverse events, especially in secondary prevention. Thus, it is very important to perform an individual risk-benefit assessment when considering a prescription of aspirin to an elderly person [192]. However, the ongoing trial 'Aspirin in Reducing Events in the Elderly' (ASPREE) of placebo-controlled low-dose aspirin treatment for primary prevention of major cardiovascular events and vascular dementia in participants 70 years and older [193], and the ongoing trial 'Drugs and Evidence Based Medicine in the Elderly' (DEBATE) of multi-factorial cardiovascular disease prevention in participants 75 years and older [194], may provide additional information in due time.

Regional differences

There were few differences in drug utilization between N84+ and K5 participants, after adjustment for covariates. However, some differences remained, such as higher use of antithrombotics (mainly low dose aspirin) in Kungsholmen, and higher use of cardiovascular drugs, namely vasodilators used in cardiac disease (mainly nitrates), and high-ceiling diuretics in Nordanstig. Hypertension, which is often treated with diuretics in the Swedish elderly [177], was more often diagnosed in Kungsholmen, yet the utilization of diuretics was lower. These differences in drug utilization might reflect regional differences in physicians' prescribing behaviours, as there was no difference in cardiac disease or CVD prevalence. The cross-sectional design of the comparisons precludes causal inferences, and the comparison must be interpreted with caution, as the Kungsholmen participants were part of a follow-up, and thus probably were a healthier part of the original source population. Still, the difference

raises questions as to whether there is an inverse association between the use of low dose aspirin and the use of nitrates and diuretics, suggesting protective effects from aspirin.

Although the measurements of drug utilization in Nordanstig and in Sweden in general as shown in Figure 2 and 3 are not directly comparable, it is possible to see that the trends in drug use are similar, with two exceptions: an increase in use of cardiac glycosides and a decrease in use of calcium channel blockers in Nordanstig, and the opposite at the national level. Also, the overall patterns are similar with the exception that ATC-group B (blood and blood forming organs) and B01 (antithrombotics) seem to be more represented in Sweden overall than in Nordanstig. This is in concordance with the results from the comparison between Nordanstig baseline and K5. It also highlights that possible regional differences in prescribing behaviours must be accounted for when generalizing drug use data, even if morbidity patterns are similar.

Potentially inappropriate drug use

Quality indicators for drug use in elderly patients were not systematically introduced in Sweden until 2003, after a report from The National Board of Health and Welfare [97]. Although the quality indicators for drug use in elderly people used in this thesis did not cover all potentially inappropriate drug regimens described in the literature, more than one out of ten were IDU users at baseline, and almost one out of five at follow-up in **Study IV**. Studies of inappropriate prescribing using Beers criteria or modified (reduced) Beers criteria have shown a prevalence between 3% and 48% depending on setting and design, as summarized in Table 1. One large American register study found a decline in use between 1995 and 1999 [37], which may partly be attributable to the publication of the revised 1997 Beers criteria [24].

The baseline data collection for **Study II and IV** was performed between 1995 and early 1998, and the follow-up between 1999 and 2001. The international publication of Beers quality criteria in 1997 had no measurable effect on the prevalence of IDU in this population. However, the use of these drugs cannot be expected to cease completely as long as they are available. The recommendations are targeted to the general elderly population, and individual medical decisions to prescribe potentially inappropriate medications can sometimes be justified depending on the clinical situation. Besides, no ‘acceptable’ prevalence has been

suggested. However, the increasing use of potentially inappropriate drugs is of concern, considering the risks for severe adverse reactions in elderly people, e.g., delirium associated with use of multiple psychotropics and drugs with prominent anticholinergic effects [132].

Study II and **IV** did not address the question of possible risk factors for IDU, but the crude data are in agreement with earlier studies where an association with increasing number of used drugs and increasing prevalence of IDU is the most common finding [20-22].

The hypothesis in **Study II** was that IDU often leads to detected or undetected ADRs resulting in negative events such as hospitalization or death. Therefore, all-cause acute hospital stays and mortality were used as outcomes, controlling for morbidity and other possible confounders. The finding of an association of IDU with acute hospitalization of community dwelling participants in Nordanstig must be interpreted with caution considering the limitations in exposure classification discussed above, and the possibility of residual confounding. However, hospital-based studies on elderly patients support this finding, as IDU is often related to ADRs leading to hospitalization [59, 195], and a meta-analysis of hospitalizations caused by ADRs, with a subgroup analysis of 17 studies of elderly patients, found that a mean of 17% of hospital admissions were related to ADRs [61]. Two of the studies in the meta-analysis also dealt with prevention and found that 88% of the adverse reactions were preventable.

Moreover, other studies of IDU in elderly people have found associations with different health outcomes: DUR criteria were associated with decline in basic self care [54] and increased utilization of outpatient services [196], and Beers criteria was associated with more rapid hospitalization [196] in studies of the Duke 'Established Populations for Epidemiologic Studies of the Elderly' (EPESE) cohort. Other studies in different settings using Beers criteria found an association between IDU and higher costs, and healthcare utilization [30], lower self-perceived health [38], and lower self-reported health-related quality of life [29]. In yet another study, no association of IDU with healthcare utilization was found, but it was limited by a cross-sectional design and restriction to psychotropic drug use [197].

We found no association between IDU and hospitalization in institutionalized participants. This was probably because residents in sheltered accommodation had better access to physicians and nurses in their homes, and thus were less likely to be sent to hospital. Lack of

power (n=124) may also be a reason for failing to detect an association among the institutionalized participants. As opposed to our results, two Beers criteria-based studies in nursing homes in the USA (n=1117 and n=3372), found an association between IDU and an adverse health outcome (emergency department visit, hospitalization, or death) [39] and an association with hospitalization and death [198].

In **Study II** no association was found between IDU and death. The true incidence of drug-related death is not known. Although it is mandatory to report new or serious ADRs in Sweden, it is believed that a large number of ADRs are not reported and not even detected, especially in elderly persons with multimorbidity, which may disguise drug-related problems. A study of persons 65 years and older in an ambulatory setting in the USA reported an incidence of ADRs of 50 per 1000 person-years, of which 0.7% were fatal [199]. Hospital-related events were not included in the USA study. In 2004, the Swedish Medical Product Agency Pharmacovigilance Unit received 115 reports of deaths in all ages where a relationship to drug use could not be excluded [200] in the 9 million inhabitants of Sweden. Considering these data, it is clear that **Study II** lacked sufficient power to detect mortality as an outcome.

Continuity of drug use

Time trends and continuity of drug use is partly discussed in the earlier discussion sections. The general pattern of fairly stable use of drugs for chronic diseases is not surprising, nor is the large turnover of users of opioids and other analgesics, as they would often be used for conditions with temporary pain. However, chronic pain is also common in elderly persons, and the prevalence of pain has been reported to be between 25% and 50% in community-dwelling seniors, and between 45% and 80% in nursing home residents [201] and this contributes to the persistent high utilization of ATC-group N.

The high turnover of laxative users reflects the fact that periods of constipation are common in elderly people. This partly reflects a more sedentary lifestyle or immobilization caused by periods of illness or disability, especially as these people may also be using drugs in which constipation is a common side effect, e.g., opioids and calcium channel blockers. The prevalence of peptic ulcers or gastro-oesophageal reflux disease in old age are not well known, but the common use, and high turnover of users of ‘drugs for treatment of peptic

ulcer' suggests a widespread symptomatic use without specific diagnosis [202]. Antacids were available over-the-counter at both examination times, and some H_2-receptor antagonists and proton pump inhibitors were made available in low doses without prescription during the follow-up period.

Conclusions

- Drug utilization was high in the very old participants investigated, both with a very high proportion of drug users, and with a high and increasing mean number of drugs per person over time.

- Polypharmacy, defined as use of five drugs or more, was common.

- There was an increase of users between the investigations in 1995-98 and 1999-2001 of all the nine main drug classes with at least 10% of users.

- The three most commonly used main drug classes were in good agreement with the pattern of morbidity in old age: Cardiovascular system drugs, nervous system drugs (including analgesics and psychotropics), and drugs for the alimentary tract and metabolism.

- There was continuity in use of drug classes mainly targeted at chronic diseases and conditions, but a considerable turnover of users of symptom relieving drugs.

- There were some regional differences not explained by morbidity, suggesting some variations in prescribing behaviours within Sweden.

- Inappropriate drug use, as defined by consensus-based criteria, was common and increased with increasing number of used drugs, and also increased over time.

- Inappropriate drug use was associated with an increased risk of hospitalization in community residing elderly people.

- There were quality issues concerning treatment of heart failure in very old people:

    - Possible under-use of ACE-inhibitors despite therapy guidelines
    - Slow introduction of beta-blockers in heart failure
    - Use of calcium channel blockers with negative inotropic effects
    - Use of non-steroid antiinflammatory drugs

- There was no significant difference in ACE-inhibitor use in heart failure between non-demented and demented participants, but utilization was lower in the oldest and most frail (institution residing) participants.

- There is a need for continuous quality assessment and discussion of drug utilization in the Swedish healthcare system, especially for elderly patients.

Finally:

Drug use in the elderly – are quantity and quality compatible?

The development of new drugs and pharmacological strategies mean that a single disease may be treated with several different drugs. For example ischemic heart disease (with myocardial infarction and heart failure) could be treated with five different drugs: aspirin, an ACE-inhibitor, a beta-blocker, a diuretic, and a lipid-lowering agent. As a large proportion of elderly people have more than one disease, the number of drugs can be high and the treatment still be of good quality. Inversely, a low number of drugs can be due to under-treatment and thus of low quality. A potentially inappropriate drug can be present irrespective of the number of drugs used by a person. However, a large number of drugs generally increases the risk of drug-drug interactions, and may also be a sign of insufficient monitoring – i.e., review of earlier prescriptions and discontinuing of ineffective and unnecessary treatments.

In brief:

The answer is yes… and no!

Future directions

The scarcity of randomized controlled trials (RCTs) including sufficient numbers of true geriatric participants, the high drug utilization, and the demonstrated quality issues regarding drug utilization in elderly populations, emphasize the need for continuous monitoring of drug use. Population-based and healthcare system-based observational studies are important tools, which presently substitute RCTs. It is not possible, though, to replace observational studies with conventional RCTs, as the RCT generally represents an ideal situation with well-informed patients, highly motivated staff at all levels, and a level of monitoring rarely feasible in 'real life' clinical situations. Thus, there will be a need for both kinds of study designs in the future.

The Kungsholmen Project finished at the end of the Nordanstig follow-up, but was succeeded in 2001 by the Swedish National Study on Aging and Care (SNAC) in Nordanstig and Kungsholmen, with the addition of two new locations in Sweden [203]. This large, population-based, longitudinal study will provide detailed information through direct examination of individuals in a variety of domains. These data, together with the new research possibility initiated in July 2005, with the National Corporation of Swedish Pharmacies' register of prescription drug sales based on individuals, will allow population-based research on health outcomes with more accurate drug exposure data than previous studies.

It is important that epidemiological results are applied in clinical practice. Considering the high prevalence of potential IDU in elderly patients, this is an important field for intervention. Some research has been done in this field in Sweden, and interventions have been found to improve prescribing patterns [49, 204, 205], but there is also a need for more studies in this area of research. In addition, pharmacological studies of frail patients with several concurrent diseases in clinical situations will add knowledge and facilitate the process of improving the quality of drug use in elderly people.

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