Polypharmacy in geriatric patients: too little or too much?

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Polypharmacy in geriatric patients: too little or too much?

Polyfarmacie in geriatrische patiënten: te veel of te weinig?

(met een samenvatting in het Nederlands)

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Clarinda Rixt Tulner
geboren 4 oktober 1964 te Aduard, Groningen

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Co-promotor:	Dr D.P.M. Brandjes

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Chapter 3 Treatment of cardiovascular disorders

Preface

Barely ten years ago, older patients commonly were excluded from trials.[1,2] One of the reasons was the fear that due to co-morbidity, they could be at increased risk from the participation in the study. Since then, trials have been performed targeting older people.[3,4,5] However, the inclusion of the most healthy patients limits their external validity. In usual care, older patients frequently have more than one condition. This results in polypharmacy, defined as the use of multiple drugs. It is associated with increased non-adherence, inappropriate prescribing by physicians and adverse drug reactions (ADRs).[6]

The reduction of suboptimal medication use, is one of the goals of comprehensive geriatric assessment (CGA). Geriatricians are in a unique position to critically review medication use for all the separate conditions a patient suffers from. Susceptibility to ADRs calls for reducing polypharmacy, while refraining from drug prescription may result in unnecessary undertreatment. The most important challenge is that for individual patients, with different complex combinations of illnesses and medications, no clear cut evidence is available for the preferred treatment regimen for all co-existing diseases and risk factors simultaneously, and may never be. So, a treatment regimen best matching the priorities of the patient should be the goal.

In our geriatric practice adjustment of medication is one of the most frequent, and often rewarding interventions. Miraculous recoveries can occur when for instance the use of a combination of several sedatives or antihypertensives is discontinued. It is not only the frequent presence of polypharmacy which is responsible for less desirable consequences of drug treatment. Patients of any age may suffer from ADRs. However, the effects of ADRs may be much more deleterious to the frail geriatric patient, whose equilibrium is increasingly susceptible to disturbances of any kind. This vulnerability of geriatric patients resulting in frequent adverse events, induces cautiousness in prescribing medication which could well be beneficial. It should alert caregivers to be especially meticulous in drug treatment choices, prescription and delivery.

I am frequently in doubt whether I should add a ninth, tenth or eleventh drug to an already complicated drug regimen. These doubts have prompted me to evaluate which choices my colleagues and I make in the usual care of the frail patients visiting our own department, and explore an area were the most difficult choices have to be made.

This thesis starts with a chapter on accidents in medication prescription and reporting. Changes in pharmacotherapy regarding geriatric patients in usual care are described. In addition, controversies encountered in the treatment of frequently present cardiovascular conditions are identified and discussed.
Two case reports demonstrate how seemingly small accidents in prescription can result in serious ADRs, in one patient leading to an Emergency Department visit, with quick recovery, in another patient resulting in nursing home placement. A chapter on discrepancies between the reporting of drug use by patients, general practitioner (GP) and pharmacy will highlight the importance of medication review with the patient to establish concordance regarding actual drug use. The trends in changes of medication use in geriatric patients over the last decades are also described. The next topic is the influence of comprehensive geriatric assessment (CGA) on medication use, especially the reduction of undertreatment, despite the presence of contraindications. In the last chapter, the focus is on the treatment of cardiovascular disorders; hypertension and anticoagulation in patients with atrial fibrillation.
It will be shown that age is still often associated with undertreatment of some conditions, while for other conditions hardly any undertreatment and maybe even treatment without sufficient evidence is present.

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Chapter 1

Accidents in medication prescription and description

Chapter 1.1

Intoxication with trazodone caused by dirty fax machine.

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CASE REPORT

A 85 year old woman was diagnosed with advanced dementia, possibly caused by Lewy Body disease or Alzheimer's disease. She showed subtle signs of parkinsonism, with an intermittent tremor of her right arm, and walked with small steps. Her Mini-Mental State Examination score was 11/30 at presentation. Besides cognitive decline, she also had subclinical hyperthyroidism. Treatment with an acetylcholinesterase-inhibitor was discussed and declined. In the following months, she became agitated more often, was restless and became very fearful when her husband left her even for only a few moments. She sometimes thought a stranger was in the house. Often, she woke up trembling, but could not describe the reasons for her anxiety. Because of these complaints, hyperthyroidism with a slightly increased T4, 28 pmol/l (normal values 10-23), and a TSH of 0.05 mU/l (normal values 0.35-4.70) was treated with carbimazol. This did not improve her agitated and anxious mood. It was decided to try and treat her anxiety with a starting dose of 50 mg trazodone (Trazolan®) in the evening, with oxazepam as break through medication as needed.

In the outpatient clinic, a handwritten prescription for trazodone 100 mg, a half tablet once in the evening was given to the husband. The receptionist faxed the prescription to their public pharmacy. The same evening, the patient was presented at the Emergency Department. After taking the trazodone for the first time, she had collapsed: she was described as very sleepy and dizzy. At presentation, her blood pressure was 160/65 mmHG, pulse 80, she was somnolent without neurological deficits. No other abnormal findings were seen. It transpired she had been given 200 mg of trazodone. Her husband told us he had followed the orders on the box, which read 1 dd 200 mg. The next day, the pharmacy sent us the prescription they had received by fax. A grey line had obliterated part of the prescription, so that it could be read as 1 dd 2 (tablets) instead of 1 dd ½. In Dutch, dd signifies qd. (See illustrations). In the Netherlands, trazodone is available only in formulations containing 100 mg. The pharmacist had been called by her assistant to interpret the prescription, but since the usual starting dose of trazodone as advocated by the Pharmaceutical Compass in the Netherlands is 150 mg, had not deemed 200 mg as a starting dose to be too high. By sending faxes to this pharmacy again and other departments in our hospital, we found out our fax machine caused grey stripes to appear on the faxes received by others from our outpatient clinic due to dirt.

The patient recovered quickly, and could return home from the Emergency Department the same evening. She started with 50 mg of trazodone, which was increased to 100 mg after a week. This treatment did improve her anxiety. A month later, she was admitted with a delirium due to urinary tract infection, and subsequently developed a pneumonia, to which she succumbed.

DISCUSSION

This report shows a combination of mechanical defect (the dirty fax), and lack of knowledge about appropriately adjusting starting doses of medication in geriatric patients can result in accidental overdosing. In geriatric patients starting doses of 50 to 100 mg are advocated.[1] This adverse drug reaction could have been avoided if trazodone had been available in smaller tablets than 100 mg a piece, or the pharmacy had been requested to cut the tablets in half instead of assuming the husband would be able to do this.

Use of fax-based order systems has been demonstrated to decrease medication order turnaround time. However, already in 1991 problems such as order clarity and legibility were identified.[2] Faxing prescriptions is an appreciated service for immobile patients. However, with this case, we have demonstrated this may introduce another cause of error in drug delivery. Prescriptions received by fax transmission and mail have been shown to be the most likely to require clarification by pharmacists prior to dispensing.[3]

CONCLUSION

This case illustrates the continued importance of a pharmacist carefully judging whether a (handwritten) prescription is readable and understandable, if the dose is correct and if not confer with the prescribing physician to ascertain that the interpretation of the prescription is in accordance with the intentions of the prescriber.

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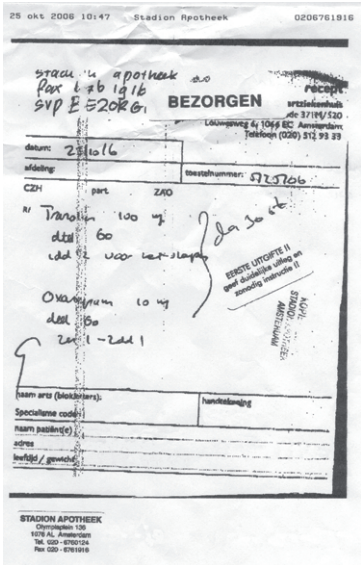
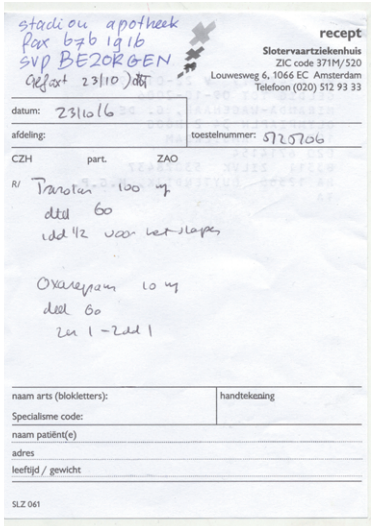
Illustrations





Chapter 1.2

Prescription error resulting in valproic acid intoxication

S.V. Frankfort, C.R. Tulner, W. Knol,

J.P.C.M. van Campen, H.M. Schellens, J.H. Beijnen

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CASE REPORT

An 81-year-old female with a history of atrial fibrillation, constipation, subclinical hypothyroidism, a wrist fracture and an ischemic cerebrovascular accident in 2002 followed by a seizure was admitted to a nursing home for rehabilitation for 8 months. Recently she was discharged home in a good condition. She was able to walk with a walking-aid. Three days before presentation she became increasingly somnolent and was unable to stand up and she fell repeatedly. She became for the greater part functionally dependent and wheelchair dependent. Finally she was admitted to the geriatric ward of a general hospital.

The medication at admittance to the geriatric ward, as prescribed by her general practitioner, consisted of digoxin (0.0625 mg qd), acenocoumarol (a coumarone derivative), valproic acid 40 mg/mL oral solution (10 ml bid), ascorbic acid (500 mg qd), acetazolamide (250 mg bid), magnesiumoxide (1000 mg qd), omeprazole (40 mg qd), levothyroxine (25 µg qd) and lactulose (15 ml bid).

Physical examination revealed a blood pressure of 160/100 mm Hg, an irregular pulse rate of 92 beats/minute and a temperature of 36.5 °C. She was somnolent, her attention was diminished and her thinking was slow. At neurological investigation the function of the cranial nerves was intact. Sensory testing revealed no disorders. She had bilateral flexion when testing her foot sole reflex. Motor- and coordination testing, revealed no abnormalities.

At admission, a subdural haematoma was considered, but a computerized tomography scan of the brain did not show this or a new infarction or intracerebral bleeding. The initial laboratory studies revealed no hematological abnormalities or disturbances in renal and hepatic function, glucose, electrolytes and thyroid function, but the serum level of valproic acid on the day of admission was 234.5 mg/L (therapeutic range 40.0-100 mg/L). Valproic acid was discontinued immediately. The patient received intravenous fluids for rehydration and recovered gradually.

During the week between discharge from the nursing home and admission to the geriatric ward the patient's husband took care of the distribution of the medication. Valproic acid (Depakine®) is available in the Netherlands as oral drops (for children, 300 mg/ml, 60 ml) and as an oral solution (40 mg/ml, 300 ml). At our request the patient's husband took the bottle of oral solution of valproic acid to the hospital. The label of the bottle of the patient showed 300 mg/ml drops in a dosage of 10 ml twice a day, instead of the oral solution of 40 mg/ml as provided by

the general practitioner's information at admittance. The general practitioner prescribed electronically via the computer.
In the software package, the oral solution and the oral drops are listed as consecutive lines, but the general practitioner prescribed the drops in combination with the dosage of the solution. The community pharmacy did not receive an error warning and delivered this unusual combination of concentration and dosage scheme.
Nine days after admission, her serum level of valproic acid was below 0.5 mg/L and valproic acid was restarted as tablets in a dosage of 300 mg twice daily. Although the patient recovered well, she continued to need care and was discharged to a nursing home. Two weeks after discharge the serum level of valproic acid was 76 mg/L, remaining within the therapeutic range.

DISCUSSION

In geriatric medicine, oral solutions are often used because of convenience for elderly patients and the advantage of accurate dosing. This case shows the importance of the general practitioner and the community pharmacist checking the concentration of oral solutions in combination with daily dosages, leading to appropriate doses.
Another point that we can learn from this case is to be careful with prescribing electronically and errors occurring with consecutive lines in a spreadsheet. In this case the serum level of valproic acid was in the toxic range after changes in patient setting (discharge from the nursing home). If place of care changes from an inpatient to an outpatient setting, at least one medication error is observed in 42% of patients[1].

CONCLUSIONS

Geriatric patients are prone to medication errors because they often use multiple drugs. Communication between different prescribers, especially at the time of discharge from hospital or nursing home, is very important. Because geriatric patients are also more vulnerable to adverse medication events it is important for the prescriber and the delivering community pharmacy to prevent medication dosage errors.

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Chapter 1.3

Discrepancies in reported drug use in geriatric outpatients. Relevance to adverse events and drug-drug interactions.

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ABSTRACT

The main goal of the current study was to describe the frequency and relevancy of discrepancies in drug use in Dutch geriatric outpatients as reported by the patients and their caregivers, documented by the referring general practitioner (GP), and registered by the public pharmacy. The frequency of medication discrepancy adverse patient events (MDAPEs) was also recorded. In addition, possible contributing factors—such as increasing age, cognitive status and depressive symptoms, the number of medications used, the presence of a caregiver, and the number of physicians visited by the patient—were studied. This was a prospective descriptive study conducted at the geriatric day clinic of a teaching hospital. Between January 1 and May 1, 2005, consecutive patients were included if they were aged >65 years, reported use of ≥1 medication, and if they could understand the goals and consequences of participating in the study. The medication described by geriatric patients and their caregivers were compared with the drugs listed by their GP. The pharmacies of the referred patients were asked to send a description of the drugs distributed in the 6 months preceding the patient's visit to the geriatric outpatient clinic. The classification of ADRs and undertreatment as clinically relevant was done by study investigators who were blinded for the presence of discrepancy. A total of 120 outpatients were included; 90 patients had discrepancies in drug use and 30 did not. The mean (SD) age of the study patients was 82.3 (6.8) years; 71.7% were women. Of the 120 patients, 113 patients reported taking >1 drug (94.2%) and 88 were prescribed ≥4 drugs (73.3%). At least one discrepancy between the medication lists of patients, GP, or pharmacy was present in 104 of 120 patients (86.7%). In 90 patients, there was ≥1 discrepancy between the medication reported by the patient and the GP (75.0%). Patients with ≥1 discrepancy reported taking a higher mean number of drugs and had more prescribing physicians in addition to their GP. Twenty-nine patients (24.2%) experienced an MDAPE involving the use of drugs the GP had not correctly described in the letter of referral. The pharmacy was unaware of the use of medication involved in an MDAPE in 2 patients. Geriatricians should assume that the medication lists supplied by GPs are incomplete or incorrect, and be aware that in ~25% of patients, symptoms may be caused by medication use inaccurately described in the referral. Reports by the community pharmacy may supply valuable additional information. Because there are also discrepancies between patients and pharmacies, medication use from a database—with data from prescribing physicians and pharmacy systems—will still have to be confirmed by the patient.

INTRODUCTION

Increased age is associated with polypharmacy.[1] Polypharmacy is a risk factor for severe adverse drug reactions (ADRs)[2] and is associated with an increased risk of mortality.[1] An ADR, as defined by the World Health Organization, is a reaction that is noxious and unintended, and which occurs at dosages normally used in humans for prophylaxis, diagnosis or therapy.[1] Adverse drug events have been defined as any injury resulting from the use of a drug (ADEs).[3] In an ambulatory clinical setting, including patients with a mean age of 74.7 years, the incidence of ADEs was 50.1 per 1000 person-years, with a rate of 13.8 preventable ADEs per 1000 patient-years.[3] ADR-related hospitalizations were estimated to account for between 2.4% and 16.4% of all hospital admissions in The Netherlands in 2001.[4] After discharge from a general internal medicine service, the most common preventable ADEs were therapeutic errors involving medication prescription or monitoring. In univariate analysis, patients were significantly more likely to experience an ADE if they were older, but age was not an independent predictor in this study.[5]

Medication histories are frequently incomplete, not only in older patients. Discrepancies between the use of medications as reported by patients and lists of medications as compiled by their physicians have been shown to occur in >95% of patients in general practice and patients referred to outpatient clinics or geriatric services.[6–11] In hospital admission and discharge studies, discrepancy rates range from 14% to >70%.[12–21]

Several different predictors for discrepancies in drug use have been found. Age and the number of drugs were inconsistently associated with the presence of a discrepancy.[7,8,11,12,18,19,22] Other patient characteristics shown to be associated with drug discrepancies include female gender,[9,11] the participation of other physicians in the care of the patient,[8] and low patient understanding of medications.[23] These results are based only on univariate analysis, however, and have not been consistently reported.

In a prospective cohort study conducted at a geriatric outpatient center, medication changes between visits were the principal causes of errors in medication records.[6] In another study, elderly patients (N = 256) with lower cognition who were discharged with several new medications were at the highest risk of ADEs.[24] Number of prescribing physicians was also shown to be an independent risk factor for ADEs in a study of 405 elderly patients, although no data were supplied for drug discrepancies.[25] Most hazardous drug combinations in general practice are the

result of using medications initiated by hospital physicians.[26] Up to 13% of identified drug discrepancies have the potential to cause harm.[22,23]
Discrepancies can be divided into deletions (i.e., patients not taking medication listed in their GPs' reports), additions (i.e., patients taking medications not listed in their GPs' reports), and differences in dosage. The clinical adverse effects of discrepancies can be categorized as ADEs due to the addition of a medication by the patient that the treating physician is not aware of, and undertreatment either due to intentional or unintentional nonadherence and undertreatment due to addition by the patient or another physician of a drug, which leads to a drug–drug interaction that diminishes the therapeutic effect of an earlier prescribed drug.
Potential interaction rates associated with discrepancies have been reported in up to 19% of elderly patients.[9,27] Medication lists obtained from patients showed more potential drug–drug interactions than their physicians' lists (12.7% vs. 7.3%).[9] The frequency of possible ADEs caused by these potential interactions were not described.[9,27] The reported clinical relevance of potential interactions ranged from 0 to 70%. In a previous study by Tulner et al,[28] drug–drug interactions possibly leading to either ADRs or inadequate reaction to therapy were reported in 25.5% of all patients using >1 drug.
Because geriatric patients often suffer from multiple conditions including cognitive disorders and are therefore often treated by >1 physician, they may be at a higher risk of discrepancies that result in ADEs.[24,25,26] Because of the vulnerability and frequent presence of polypharmacy in geriatric patients, one would expect careful evaluation of their drug use. Yet, despite technologic improvements such as electronic prescribing and computerized monitoring of drug use, it still is a common experience of geriatricians that drug lists provided by GPs are incomplete, as was described in 1987.[27] In addition to discrepancies between the medication lists of the patient and the GP, there can also be substantial differences between the GP's perception of the medication used and the pharmacy record. In terms of prescription drugs, the community pharmacy records in The Netherlands were almost completely accurate when drugs found at a patient's home were taken as the gold standard representing drug use.[29] Due to the reimbursement system in The Netherlands, most patients obtain drugs prescribed by all their physicians from 1 community pharmacy, so the pharmacist of an individual patient can be requested to report more complete information on the medication history, than individual prescribers.[13,30] The pharmacy's records may thus be more accurate than the GP's records.

The main goal of the current study was to describe the frequency and relevancy of discrepancies in drug use in Dutch geriatric outpatients as reported by the patients and their caregivers, documented by the referring GP, and registered by the public pharmacy. The frequency of medication discrepancy adverse patient events (MDAPEs) was also recorded. In addition, possible contributing factors—such as increasing age, cognition, the number of medications used, and the number of physicians visited by the patient—were studied.

PATIENTS AND METHODS

This was a prospective descriptive study conducted at the geriatric day clinic of a teaching hospital (Slotervaart Hospital, Amsterdam, The Netherlands). The clinic offers patients 1-day comprehensive geriatric assessment (CGA) with follow up if necessary for further diagnosis or treatment on an outpatient basis. The most frequent reasons for referral by the GP are cognitive and functional decline.
Between January 1 and May 1, 2005, consecutive patients were included if they were aged >65 years, reported use of ≥1 medication, and if they could understand the goals and consequences of participating in the study. All patients signed written informed consent forms before participation, and the study was approved by the institutional Medical Ethical Review board.

Determination of Discrepancies in Drug Use
The public pharmacies of the referred patients were asked to send a description of all the drugs distributed in the 6 months preceding the patient's visit to the hospital's geriatric department. Medication use as reported by the patient, the GP, and the pharmacy were collected on separate research forms by one of the investigators (I.M.J.A.K.).
Using data from the public pharmacy, medications prescribed to the patient and supplied by the pharmacy and the relevant time period during the preceding 6 months were determined. These data were used to determine if there was a difference in the number of discrepancies between the records of the pharmacy and the GP; the goal was to determine whether pharmacy data more accurately reflected medication use than data supplied by the GP on referral. If the GP referral did not provide the treating geriatrician with information on this subject, one of the investigators (I.M.J.A.K.) interviewed the GP by telephone. There was no discrimination between prescription and non-prescription drugs, nor were herbal or homeopathic products or as-needed medications ex-

cluded. Until 2003, drugs such as NSAIDs and laxatives were imbursed if they had been prescribed by a physician in The Netherlands, and were therefore generally supplied by the same community pharmacy where the patient obtained all their prescription drugs. These drugs were included because they might contribute to ADEs or interactions.
Because the focus of the current study was on the accuracy of the description of medication use in the referral by the GP, and not the prevalence of nonadherence, there was no distinction made between deletion of drugs by the patients because of intentional or unintentional nonadherence.
These data were compared with the lists of drugs completed at home by the patients and their caregivers. Discrepancies were labeled *deletions* when the patients did not report using a drug that was listed on the reports of their GP or pharmacy, and *additions* when the patient stated using a drug not reported by the GP or pharmacy. The third possible discrepancy was a difference in dosage between the reports of the patient, GP, and/or pharmacy.

Outcomes
Study physician L.R.T. assessed the signs and symptoms observed and described after CGA by the treating physicians and evaluated whether these could be an ADE caused by one or more of the drugs reported to be used by the patient, or could be the result of an inadequately treated condition previously diagnosed. This assessment was based on the medication use as reported by patients and caregivers and blinded for the registration of medications as an addition or deletion by I.M.J.A.K.
ADEs can be caused by patients taking drugs their physicians do not know about (i.e., additions). Treatment failure can also be caused by patients not using medication the GP had prescribed or using additional medication the GP was not aware of, which reduce the effectiveness of other medications through drug–drug interactions. These possible effects of discrepancy were labeled MDAPEs.
The clinically relevant, possible drug–drug interactions recognized by the treating and study physicians were noted. The methods for evaluating medication lists for potential and possible interactions has been described previously.[28] Drug–drug interactions were defined as clinically relevant if, according to the clinical judgment of the treating physician and the study physician (L.R.T.), there were still symptoms present of a disorder treated with medication whose effect was countered by another drug (undertreatment due to interaction) or there was an enhanced drug effect potentially due to interaction with a possible adverse effect. This

assessment was made using the Naranjo ADR probability scale.[31] This algorithm assigns a weighted score to 10 criteria. A possible ADR has a score of 1 to 4; a definite ADR has a score ≥9.[31] This procedure resembles the manner in which geriatricians evaluate the drug regimens of their patients in daily practice.

Undertreatment was assessed by noting conditions from the patient record that could have been treated pharmacologically by other drugs than the patient reported taking. This assessment by one of the investigators (L.R.T.) was blinded for the medication lists supplied by the GP and the pharmacy. After the conditions were labeled as undertreatment, the medication lists of the GP and pharmacy were searched for medications that could have been used for the undertreated conditions but were discontinued by the patient. Severity of possible ADRs and undertreatment were independently assessed after the visit on a separate data collection form using the patient records by 2 of the investigators (L.R.T. and J.P.C.M.C.) who were blinded for the classification of drug discrepancies. The patient records used for this assessment contained medication use as confirmed by the patients or their caregiver and not medication use as described by the GP or the pharmacy. ADEs were labeled significant, serious, or life-threathening.[3] If there was a difference in opinion, the investigators met and reached a consensus. The interrater reliability was good (κ = 0.90).

Three components of the MDAPEs were therefore included: undertreatment due to deletion (patient not taking a drug the GP described), drug–drug interaction leading to undertreatment by addition (less effectiveness caused by patient taking interacting medication not prescribed by their GP), and ADRs due to addition (patient taking a drug not prescribed by the GP).

Other Variables Collected

When deemed necessary by the treating physicians, patients' cognitive status was assessed using the Mini–Mental State Examination (MMSE).[32] A score <24 out of 30 on the MMSE may indicate the presence of dementia. Depressive symptoms were evaluated with the Geriatric Depression Scale (GDS).[33] A score >5 on the 15-item GDS suggests the presence of depressive symptoms. The patients and caregivers were asked how many other physicians, in addition to their GP, were involved in their treatment and whether their medication use was supervised.

Statistical Analysis

Statistical calculations were performed with SPSS for Windows (version 16.0, SPPS Inc., Chicago, Illinois). The number of drugs used reported by patients, GPs, and pharmacies and the differences in the number of drug discrepancies between patients, GPs, and pharmacies were compared using a paired sample *t* test.

Patients with or without ≥1 discrepancy with the medication list supplied by the GP, and patients with or without MDAPEs, were compared using a χ^2 test for the dichotomous variables sex and presence of a caregiver to supervise medication use. Age, MMSE and GDS scores, number of medications, number of prescribing physicians, and level of patient education were evaluated using the Student *t* test.

$P < 0.05$ was considered statistically significant. The interrater reliability for severity of ADRs and undertreatment was evaluated with Cohen's κ statistic.

RESULTS

Patients

During the first 4 months of 2005, 190 patients were recruited and assessed for study eligibility. Thirty-three patients were excluded because they did not use any medication (n = 21), could not give informed consent (n = 10), or were aged <65 years (n = 2). An additional 37 patients were excluded because of incomplete data (i.e., the GP did not supply medication lists [n = 20], the pharmacy did not supply medication lists [n = 12], or neither the pharmacy nor the GP supplied medication lists [n = 5]). A total of 120 patients were evaluated in the final analysis (Figure).

The mean (SD) age of the study patients was 82.3 (6.8) years; 71.7% were women. Of the 120 patients, 113 patients reported taking >1 drug (94.2%) and 88 were prescribed ≥4 drugs (73.3%). Table I shows the characteristics of the patients with (n = 90) and without discrepancies (n = 30) in drug use. There was no difference in level of education.

When the lists of patients, GPs, and pharmacies were compared, a mean (SD) of 6.4 (3.3) different medications (range, 1–18) was reported per patient. The mean number of drugs reported by the patients (5.4) was higher than that reported by the GP (4.4; P< 0.001;95% CI, 0.66–1.37) and the pharmacy (4.9; P< 0.01; 95% CI, 0.144–0.83).

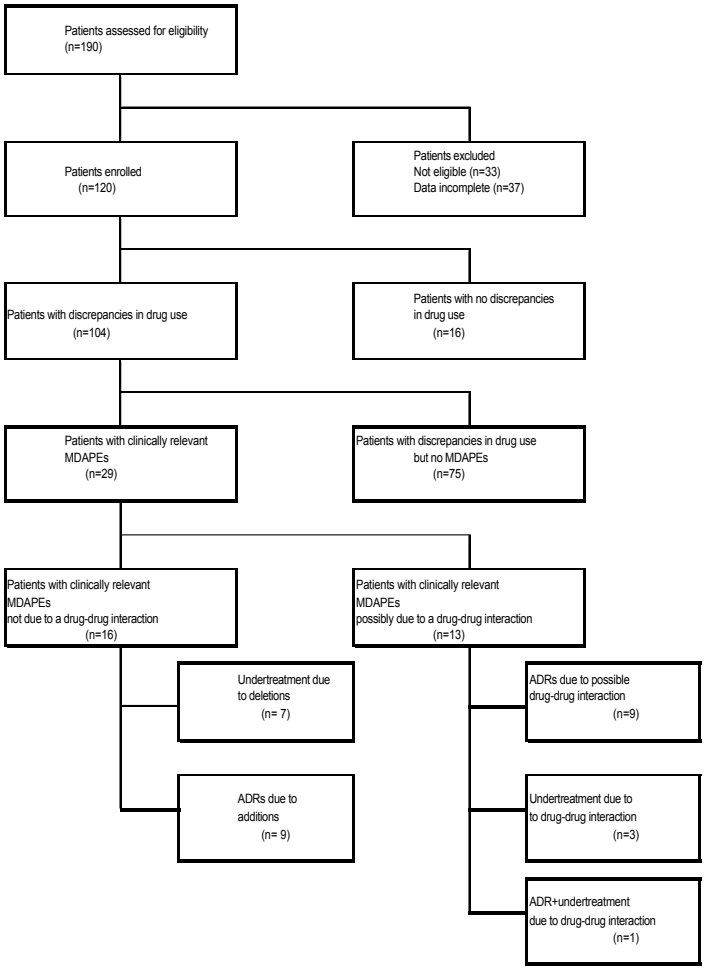

Figure. Classification of patients. MDAPEs = medication discrepancy adverse patient event; ADR = adverse drug reaction.

Table I.

Patient characteristics and presence of drug use discrepancies based on patient and general practitioner (GP) medication lists. N = 120 unless otherwise specified.

	Discrepancies Present (n = 90)	Discrepancies Absent (n = 30)
Age, y*	82.3 (6.8)	82.4 (6.8)
Female, no. (%)	63 (70.0)	23 (76.7)
No. of medications according to patients*	5.9 (2.8)†	4.0 (2.2)†
No. of other prescribing physicians*	1.1 (1.1)†	0.43 (0.68)†
Presence of a caregiver to supervise medication use, no. (%)	40 (44.4)	18 (60.0)
MMSE (n = 111)*‡	22.3 (5.4)	20.1 (5.8)
GDS (n = 96)*§	5.3 (3.6)	3.9 (2.6)

MMSE = Mini–Mental State Examination; GDS = Geriatric Depression Scale.
*Mean (SD). †$P < 0.05$. ‡Based on a scale of 0 to 30; scores <24 may indicate the presence of dementia. §Based on a 15-item scale; scores >5 suggest the presence of depressive symptoms.

Discrepancies

A total of 771 drugs were listed (649 by the patients, 594 by the pharmacies, and 527 by the GPs). At least one discrepancy (deletion, addition, or difference in dosage) between the medication lists from patients, GP, or pharmacy was present in 104 patients (86.7%) involving 386 drugs. There were 272 discrepancies between patients' lists and information supplied by the GP, and 233 discrepancies between patients' reported use of medication and the drug history supplied by the pharmacy. Of the 104 patients, in 74 (71.2%), there were discrepancies between their lists and the lists of both the GPs and the pharmacies; in 14 (13.5%), the discrepancy was between the patient and the pharmacy; and in 16 (15.4%), the discrepancy was between the patient and the GP. discrepancy between the medication reported by the patient and the pharmacy (73.3%).

Therefore, 90 of 120 patients had ≥1 discrepancy between the medication reported by the patient and the GP (75.0%), and 88 had ≥1 The highest rates of discrepancies were seen for acetaminophen (86.7%), laxatives (82.9%), and formulations for dermatologic or opthalmologic diseases (81.3%). Other medications with discrepancies >35.0% were corticosteroids, NSAIDs, chronic obstructive pulmonary disease medications, drugs for osteoporosis, antacids/proton pump inhibitors, antipsychotics, benzodiazepines, ACE-inhibitors and Angiotensin II-antagonists, antidepressants, diuretics, and coumarin (Table II).

There was a trend toward more discrepancies between patients and GPs than between patients and pharmacies. However, the difference in number of discrepancies between the patient and the GP or between the patient and the pharmacy (2.3 vs. 1.9) did not reach statistical significance (Table III).

Table II.

Types of drug use discrepancies in most prescribed and clinically relevant drugs Values are given as no. (%) of drugs present on lists from the patient, the general practitioner (GP), or the pharmacy (unless otherwise indicated).

Drug Class	No. of Patients Possibly Using Drug	Total of Patients with Discrepancies	Discrepancies Between Pharmacy and Patient Only	Discrepancies Between GP and Patient According to Type		
				Addition*	Deletion*	Difference in Dosage
β-blockers	31	7 (22.6)	0	3 (9.7)	1 (3.2)	3 (9.7)
Diuretics	70	28† (40.0)	12 (17.1)	10 (14.3)	6 (8.6)	1 (1.4)
RAAS inhibitors	39	16 (41.0)	5 (12.8)	7 (17.9)	3 (7.7)	1 (2.6)
Calcium antagonists	16	4 (25.0)	2 (12.5)	2 (12.5)	0	0
Nitrates	21	6 (28.6)	2 (9.5)	2 (9.5)	2 (9.5)	0
Statins	16	4 (25.0)	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)
Digoxin	12	4 (33.3)	0	2 (16.7)	1 (8.3)	1 (8.3)
Coumarin	14	5 (35.7)	1 (7.1)	4 (28.6)	0	0
Antithrombotics	46	12 (26.1)	3 (6.5)	6 (13.0)	1 (2.2)	2 (4.3)
NSAIDs	24	16 (66.7)	4 (16.7)	6 (25.0)	5 (20.8)	1 (4.2)
Acetaminophen	30	26 (86.7)	7 (23.3)	16 (53.3)	3 (10.0)	0
Antidepressants	22	9 (40.9)	4 (18.2)	2 (9.1)	2 (9.1)	1 (4.5)
Antipsychotics	9	4 (44.4)	1 (11.1)	3 (33.3)	0	0
Benzodiazepines	57	25 (43.9)	7 (12.3)	10 (17.5)	6 (10.5)	2 (3.5)
COPD inhalation agents	36	21 (58.3)	5 (13.9)	13 (36.1)	2 (5.6)	1 (2.8)
Antidiabetic agents	40	13 (32.5)	5 (12.5)	7 (17.5)	0	1 (2.5)
Anti-osteoporosis agents	24	12 (50.0)	2 (8.3)	8 (33.3)	1 (4.2)	1 (4.2)
Corticosteroids	8	6 (75.0)	0	4 (50.0)	0	2 (25.0)
Antiepileptic agents	6	2 (33.3)	0	0	2 (33.3)	0
Antacids/PPIs	26	12 (46.2)	4 (15.4)	4 (15.4)	2 (7.7)	2 (7.7)

RAAS = renin-angiotension-aldosterone system; COPD = chronic obstructive pulmonary disease; PPIs = proton pump inhibitors. * Additions and deletions on patient lists compared with the lists of the GP. † There was one patient with an addition of a diuretic, as well as a difference in dosage in another diuretic

Table III.

Frequency and types of discrepancies in drug use. Values are given as mean (SD) [%] (percentage of all medications described per patient).

Type of Discrepancy	Discrepancies Between Patient and GP	Discrepancies Between Patient and Pharmacy
Deletions in patient lists*	0.55 (0.98) [8.6]	0.68 (1.1) [10.6]
Additions in patient lists†	1.6 (1.8) [25.0]	1.1 (1.5) [17.2]
Different dosages‡	0.15 (0.46) [2.3]	0.14 (0.44) [2.2]
Total	2.3 (2.1) [35.9]	1.9 (1.9) [29.7]

GP = general practitioner. *Patients did not report using a drug that was listed on the reports of their GP or pharmacy. †Patient stated using a drug not reported by the GP or pharmacy. ‡Difference in dosage between the patient, GP, and/or pharmacy.

Prevalence of Adverse Drug Reactions, Undertreatment, and Possible Interactions

Using the Naranjo ADR probability scale, 64 patients (53.3%) were classified as having possible ADRs. MDAPEs were identified in 29 patients (24.2%).

In 67 patients, 188 medications were classified as additions, 19 of these drugs (in 12.8% of patients) were implicated in 24 ADRs, in 9 of these possibly due to interaction.

Undertreated conditions were seen in 7 of 37 patients with 66 deletions (10.6% of deletions) and in 4 of 67 patients with 188 additions (2.1% of additions) with possible interactions due to these additions.

Two patients had serious MDAPEs (1 admitted to the hospital for dehydration and 1 with worsening heart failure and renal dysfunction); their use of diuretics had not been correctly reported. Other MDAPEs classified as serious were renal failure in 2 patients, anemia in 2 patients, hyponatremia in 2 patients, hypotension in one patient and apathy in one patient. All other MDAPEs were classified as significant (Table IV).

Table IV.
Medication discrepancy adverse patient events (MDAPEs)

Possible ADRs	**No. of Patients (n = 29)***	**Type of Medication Addition**
Renal dysfunction	6*	Diuretics 4 ACE inhibitor 3 NSAID 2
Anemia	3*	Salicylate 2 Clopidogrel 1
Electrolyte disorder	2*	ACE inhibitor 1 Diuretic 1
Dehydration	1†	Diuretics 1
Orthostatic hypotension	3*	Diuretics 3
Dyspepsia	2	NSAIDs 2
Constipation	1	Codeine 1
Depression	1‡	Benzodiazepine 1
Apathy	1	Benzodiazepine 1
Possible ADRs/undertreatment		**Type of Medication Addition**
Depression	1‡	Benzodiazepine 1
Hyperglycemia	3*	Diuretics 3
Undertreated Conditions	**No. of Patients**	**Type of Medication Deletion**
Pain	3	NSAID 2 Acetaminophen 1
Hypertension	1*	ACE inhibitor 1
Heart failure	1†	Diuretic 1
Tachycardia	1	Digoxin 1
Dyspnea	1	Flixotide 1
Dyspepsia	1	Proton pump inhibitor 1
Sleeping disorder	1	Benzodiazepine 1
Folic acid deficiency	1	Multivitamin 1

ADR = adverse drug reaction; ACE = angiotensin-converting enzyme. *There were patients with >1 MDAPE or >1 drug possibly contributing to the MDAPE. †One patient was admitted to the hospital with dehydration with furosemide as an addition not described by the general practitioner (GP); another patient was admitted with worsening heart failure and renal dysfunction with furosemide as a deletion not described by the GP. ‡Two patients were depressed while using benzodiazepines not listed by the GP; only one was treated with an antidepressant.

Of the 113 patients who reported taking >1 drug, 75 (66.4%) were taking combinations of drugs with a potential drug interaction. Of these, 32 (42.7%) used combinations not reported by the GP.
In 25 of the 29 patients with MDAPEs (86.2%), the pharmacy correctly reported the drug use relevant for these adverse events. The pharmacy was unaware of the medication use involved in 2 patients who had an MDAPE. In 7 of the 29 patients (24.1%), the drugs involved in the MDAPEs could have been procured as prescription drugs or over-the-counter (OTC) medication. However, the pharmacy was aware of the past use of NSAIDs in 6 of these patients. One patient with folic acid deficiency did not use the multivitamins the GP assumed were taken, the pharmacy also did not report the use of these multivitamins.

Discrepancies and Patient Characteristics
Patients with ≥1 discrepancy compared with the lists of their GP reported using a higher mean number of drugs (5.9 vs. 4.0; $P < 0.05$) and had more prescribing physicians in addition to their GP (1.1 vs. 0.43; $P < 0.05$) (Table I). In 70 patients (58.3%), drugs were prescribed by ≥1 provider in addition to the GP, with a maximum of 5 in one patient.
Both the presence of discrepancies (Pearson's *r*, 0.293; $P \leq 0.05$) and MDAPEs (Pearson's *r*, 0.230; $P = 0.012$) were significantly correlated with the number of medications reported by the patient, but only 8.6% of the variance in the presence of discrepancies could be explained by the number of medications. The number of prescribing physicians was also correlated with the presence of discrepancy (Pearson's *r*, 0.271; $P = 0.003$) but not with the frequency of MDAPEs (Pearson's *r*, 0.102; $P = 0.266$). Age, sex, MMSE and GDS scores, level of education and the presence of a caregiver to supervise medication use were not associated with the presence of a discrepancy or MDAPEs (Table V).

Table V.
Patients characteristics (N = 120 [unless otherwise specified]) and presence of medication discrepancy adverse patient events (MDAPEs).

	MDAPEs Present (n = 29)	MDAPEs Absent (n = 91)
Age, y*	83.1 (8.2)	82.1 (6.3)
Female, no. (%)	19 (65.6)	67 (73.7)
No. of medications according to patients*	6.6 (2.8)†	5.06 (2.7)†
No. of other prescribing physicians*	1.1 (1.2)	0.86 (0.73)
Presence of a caregiver to supervise medication use, no. (%)	14 (48.3)	44 (48.4)
MMSE score*† (n = 111)	22.1 (6.7)	21.7 (5.2)
GDS*‡ (n = 96)	5.8 (3.5)	4.7 (3.3)

* Mean (SD); MMSE = Mini–Mental State Examination; GDS = Geriatric Depression Scale.

†$P < 0.05$. †Based on a scale of 0 to 30; scores <24 may indicate the presence of dementia. ‡Based on a 15-item scale; scores >5 suggest the presence of depressive symptoms.

DISCUSSION

There was a high frequency of discrepancy in drug use in this Dutch geriatric outpatient population. Although the prevalence is comparable to other studies,[8,9,12] a lower rate had been expected due to the fact that Dutch patients obtain their prescription drugs in one public pharmacy and GPs in the region of Amsterdam can easily gain access to pharmacy records.

There was also a trend toward fewer discrepancies between patients and pharmacies than between patients and GPs. During visits, patients may not always recall their current medication use due to cognitive decline or because their medications are supplied by nursing staff from community services. It is common practice in such cases to consult the GP. Consultation of pharmacy records by treating physicians may yield valuable additional information. A shared registry for medication that is used by prescribing physicians and pharmacies could further improve the accuracy of these records. However, because there are also discrepancies between patients and pharmacies, data on medication use from such a registry would still have to be confirmed by the patient.

Only the number of medications and treating physicians were significantly higher in those patients with ≥1 discrepancy. We did not find a higher number of discrepancies for women; inconsistent results for this factor have been reported before.[9,11] The failure to capture changes in medication by other prescribing physicians has been reported previously and may explain the higher number of prescribing physicians in patients with discrepancies.[6]

Bedell et al[8] found an association between number of drugs and number of discrepancies in patients visiting cardiologists and internists and a trend in the association with the number of prescribing physicians. It has also been reported that having providers in addition to a regular GP increases the odds of patients reporting ADEs.[25] However, because patients in The Netherlands generally procure their drugs from the same pharmacy, even if prescribed by different physicians, one would expect multiple providers to be less of a problem than in countries where more pharmacies are visited and confusion caused by multiple providers could be countered by closer communication between pharmacy and GP. We had expected the number of discrepancies between public pharmacies and patients to be significantly lower than between GP and patient, because drugs prescribed by other physicians are also procured at the same public pharmacy. This difference did not reach statistical significance in this relatively small sample.

In patients with drug use discrepancies, cognitive decline and depressive symptoms did not occur more frequently. The risk of unintentional nonadherence caused by cognitive decline or depression may have been off-set by the frequent presence of supervision.

Unlike other research,[8] our study patients with discrepancies in drug use were not significantly older than the patients not showing discrepancies. This may be explained by selection bias, as our population had a high mean age, as expected in a geriatric outpatient clinic.

As in other studies, addition of drugs on the medication lists of patients was the most frequent cause of discrepancies.[9,12,13,27] These may be caused by the use of OTC drugs, use of drugs prescribed to others (e.g., family members), the continued use of drugs prescribed previously, or the use of drugs prescribed by other physicians. Other physicians may also instruct the patient to discontinue medications without notifying the GP, causing deletions by intentional nonadherence. Deletions may also be caused by unintentional nonadherence, which is associated with the number of drugs prescribed. Nonadherence was shown to be the most common reason for therapeutic failure in 106 frail, hospitalized elderly patients.[34]

Contrary to the presence of discrepancies in general, patients with MDAPEs did not have significantly more prescribing physicians than patients not reporting MDAPEs. This illustrates the influence of including clinical relevance in the evaluation of the importance of discrepancy. One may speculate that discrepancies resulting in adverse events may be detected earlier when more physicians are involved, while discrepancies not resulting in adverse events may be less likely to be noticed.

To our knowledge, the current study is the first description of the frequency of MDAPEs in outpatients referred for geriatric assessment. Our rate of 24.2% of patients with MDAPEs in a group of community-dwelling elderly was higher than that described in an earlier study of elderly patients being discharged from the hospital to a nursing home.[20] Reconciliation of drugs in this latter population reportedly reduced the frequency of discrepancy-related ADEs. Medication reconciliation is the process of identifying discrepancies in drug regimens in different care settings or at different time points. The preintervention group in that study had a 14.5% rate of discrepancy-related ADEs after a hospital stay.[20] It may be that in addition to incurring discrepancies, part of the discrepancies are actually being resolved during the hospital stay, which would explain the lower rate of discrepancy-related events than found in our study in community-dwelling elderly. However, discharge from hospital was associated more often with discrepancies than admission.[18,23]

In this geriatric outpatient population, almost half of the patients with potential interactions may not be identified if the information of the GP is supposed to be complete and not confirmed with the patient or the pharmacy. Chen et al[26] also found that in 56% of patients who were prescribed potentially hazardous or contraindicated drug combinations, the prescribing physician was not aware of the medications the patient was taking or the patient's disease history. In a study by Coleman et al,[19] more patients who experienced medication discrepancies were rehospitalized compared with patients who did not experience a discrepancy. We did not investigate whether MDAPEs were associated with a comorbidity such as heart failure, as was reported in this prior study.[19] However, in our study, diuretics, ACE-inhibitors, NSAIDs and benzodiazepines were most frequently responsible for MDAPEs. This is not surprising, as these agents are among the most frequently prescribed drugs in elderly patients,[3] in our study as well. In heart failure patients, dosage of medication, especially diuretics may often need to be adjusted.[19]

The frequency of untreated conditions possibly due to deletions in the drug regimen or interactions possibly resulting in diminished effective-

ness was about half as high as the frequency of possible ADRs. Especially renal dysfunction, orthostatic hypotension, anemia and hyperglycaemia were possibly caused or aggravated by addition of medication the GP had not reported. The most frequent undertreated condition for which prescribed medication was not reported to be taken by the patient was pain. In a previous study, undertreatment due to interactions was frequent.[28]

LIMITATIONS

Our study did have some limitations. We assumed that patients and caregivers accurately reported either using or not using a drug. This information may not always be accurate, as patient medical histories based on interviews are frequently incomplete.[14] We tried to make the reports by the patients as complete as possible by asking them to compile the lists at home with their caregiver, just before their visit. Yet there may be either more or less discrepancy in actual drug use versus drug reports than we have reported, due to underreporting or nonadherence to reported prescribed medication by the patients.

We did not confront the GPs and the patients with the discrepancies nor asked them for possible explanations, so we have only indirect evidence for prescriptions by other physicians as one of the possible causes. Because the MDAPEs might have been prevented if the GP had been aware of the actual medication use earlier, we cannot conclude that the adverse events were caused by the discrepancy but only that it may have contributed to a delay in recognition. We also do not know which part of the discrepancies are caused by a difference in physician–patient congruence and intentional or unintentional nonadherence. Congruence is defined as agreement between physician and patient regarding all prescription medications, dosages, and frequency. Bikowski et al[10] reported a mean congruence of 70%. If there is no agreement on the intended regimen, intentional nonadherence may result. Another cause for intentional nonadherence may be ADRs recognized by the patient: in a study by Gray et al,[24] almost 10% of elderly patients experiencing an ADE made changes in their own therapy. This may contribute to the high prevalence of MDAPEs.

The results of our study may not be generalizable to other patient populations or other settings. Discrepancy rates in other groups or settings could be even higher. First, of our original individuals recruited, only 63% had data from all groups (patients and their caregivers, the GP, and the pharmacy). However, one could expect the discrepancy rate to

be higher in patients and their caregivers not supplying the information, because they may have refrained from doing so because there was uncertainty (or ignorance) about actual medication prescription or use. Secondly, because the Dutch health system facilitates patients procuring their medication in 1 public pharmacy, in countries were patients often go to several pharmacies, the data on medication use will be less complete. Furthermore, our patients were generally referred by their own GP. When patients are referred to emergency departments by other GPs who do not know them as intimately, the medications lists may be even less reliable.
This study comprises cross-sectional data. We did not assess whether the individuals evaluated with discrepancies had a better outcome when these discrepancies were discussed with the patients and the GPs. However, given the very high rate of discrepancy and the high rate of MDAPEs, this study showed the importance of questioning patients and caregivers on actual drug use as an indispensable part of the geriatric assessment.

CONCLUSIONS

Geriatricians should assume that the medication lists supplied by GPs are incomplete or incorrect, and be aware that in ~25% of patients, symptoms may be caused by medication use inaccurately described in the referral. A higher number of medications used and the presence of other prescribing physicians should alert the treating physicians and be an incentive to discuss the actual drug regimen frequently with their patients. Reports by the community pharmacy may supply valuable additional information. Because there are also discrepancies between patients and pharmacies, medication use from a database—with data from prescribing physicians and pharmacy systems—will still have to be confirmed by the patient.

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CHAPTER 2

Evaluation of polypharmacy in geriatric inpatients and outpatients

Chapter 2.1

The effect of admission to a geriatric ward on medication use: 2002 versus 1985

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ABSTRACT

The aim of this study was to investigate the changes in pharmacotherapy of patients during and after admission to a geriatric ward in 2002 and to investigate if this goes along with reduction of drugs. And to describe the differences of the admitted patients and their medication in 2002 compared to 1985.

Included patients were admitted to the geriatric ward of a general hospital in the Netherlands during 2002 (n= 258, mean age 84.2 years). Medication at admission, during admission and at discharge was described after retrospective reviewing of medical charts. A comparable study was performed at the same ward in 1985.

In 2002, most frequently used medication at admission was acetylsalicylic acid (30.2%). Pantoprazole was during admission used in 38.8% of patients and at discharge in 31.8%. Folic acid that was at admission used by 11.6% of patients was at discharge increased to 23.4%. At discharge, vitamin D was used in 21.5% of patients, whereas lisinopril was used in 17.8% of patients. Both in 1985 and 2002 vitamins were added and use of antibiotics was increased during admission. A mean addition of 1.0 drug in 1985 and of 0.7 drugs in 2002 was observed.

Geriatric hospital admission resulted both in 1985 and 2002 in addition of medication. In both periods reductions in medication were nullified by addition of medication for reason of therapy optimisation. Compared to 1985 admitted patients receive more medication resulting from new insights into pharmacotherapy and more use of preventive medicine.

INTRODUCTION

Polypharmacy is an important issue in geriatric medicine[1,2]. The frail elderly are often diagnosed with multiple diseases and may thus have to use several drugs, resulting in an increased risk of drug interactions and adverse events[3]. In addition, the number of drugs prescribed is inversely correlated with adherence to the therapeutic regimen[4]. Therefore, a balance between optimising pharmacotherapy and reduction in number of drugs used is essential. During hospital admission changes in drug use may result from optimisation of drug regimen by addition of medication for new diagnoses and discontinuation of inappropriate medication.

During the last decennium, health care in the Netherlands has changed. Long admissions to geriatric wards have been partly substituted by admissions of shorter duration and by more visits to diagnostic day clinics, where complete geriatric assessment (CGA) is carried out. These changes may possibly result in different characteristics of admitted patients and their medication use.

The primary aims of this study are to investigate the changes in pharmacotherapy of newly admitted patients in 2002 during and after admission to a geriatric ward and to investigate if this goes along with reduction of drugs. The secondary aim of this study is to describe the historical differences of the admitted patients and their medication in 2002 compared to 1985.

METHODS

Patients and data collection

This retrospective chart study was carried out at the geriatric ward of a general hospital in the Netherlands during 2002. Patients were excluded if their medical records were incomplete. Origin of patient (i.e. home, nursing home), date of birth, gender, date of admission and discharge, medication at admission, during admission and at discharge were anonymously collected from the medical records and incorporated in a database in Visual FoxPro 6.0 (Microsoft Corporation, Redmond, WA).

Design

The cohort of admitted patients is defined as cohort 1 (n_1) and the cohort of discharged patients is defined as cohort 2 (n_2).

Drugs were classified according to the anatomical therapeutical chemical (ATC) classification index[5].
A descriptive analysis was performed for demographic variables, medication used at admittance to, during admission at and at discharge from the geriatric ward. Because in 1985 a comparable study[6] has been performed at the same geriatric ward changes in pharmacotherapy between 1985 and 2002 could be described.

RESULTS

Patients

In 2002, a total of 258 patients were included. One patient was excluded, because of incomplete medical information.
Table I shows patient demographics and characteristics of hospital admission of the studied populations in 2002 (n=258) and 1985 (n=724). Both cohorts consisted of more women, patients lived primarily at their own homes and comparable percentages of deaths during admission were shown. Mean duration of admission was remarkably shorter in 2002 (25 days) compared to 1985 (52 days).

Medication at admission, during admission and at discharge

ATC code groups A, gastrointestinal tract and metabolism; group B, blood and blood-forming organs; group C, cardiovascular agents; and group N, central nervous system agents, were frequently used at admission. Hospital admission resulted in a strong increase in almost all ATC code groups, except oncolytics (L). At discharge a slight increase in group A and a slight decrease in group C and N was noticed, whereas groups B, J (systemic antimicrobial drugs) and R (respiratory tract agents), were almost comparable to admission. Table II shows the top 10s of individual medication at admission, during admission and at discharge in 2002 and the top 5s of medication groups in 1985 and 2002, all expressed as percentage of patients.
In 2002, most frequently used medication at admission was

Table I.

Descriptives of demographics, hospital admission and medication use in 1985 and 2002.

Characteristics	1985[6] (n_1=724)	2002 (n_1=258)
Demographics		
Gender, Male (%) / Female (%)	521 (72.0) / 203 (28.0)	162 (62.8) / 96 (37.2)
Age at admission (years), mean ± SD (range)	83 (64-104)	84.2 ± 6.6 (65.2-99.4)
Place of living, Own home (%) / Other (%)	474 (65.5) / 250 (34.5)	189 (73.3) / 69 (28.3)
Hospital admission		
Discharged patients (n_2) (%) / Deaths (%)	622 (85.9) / 102 (14.1)	214 (83.0) / 44 (17.0)
Inpatient days, mean ± SD (range)	52 (1-144)	25.1 ± 26.4 (1-166)
Medication use		
At admission, mean ± SD (range)	2.8 ± 2.3	5.2 ± 3.3 (0-16)
During admission, mean ± SD (range)	6.4 ± 3.4	10.6 ± 5.0 (0-25)
At discharge, mean ± SD (range)	3.8 ± 2.2	5.9 ± 3.1 (0-22)
Drugs added during hospital admission, mean (range)	1.0 (-6-+8)	0.7 (-7-+10)

Table II. Medication use at and during admission to and at discharge from the geriatric ward in 1985 and 2002. Numbers between square brackets reflect the rank at admission.

	2002			2002			1985[6]		
	Top 10 individual medication (% of patients)			**Top 5 medication groups (% of patients)**			**Top 5 medication groups (% of patients)**		
	At admission (n_1)	**During admission (n_1)**	**At discharge (n_2)**	**At admission (n_1)**	**During admission (n_1)**	**At discharge (n_2)**	**At admission (n_1)**	**During admis-sion (n_1)**	**At discharge (n_2)**
1	Acetylsalicylic acid (30.2)	Paracetamol (41.9) [3]	Pantoprazole (31.8) [21]	Diuretics (60.9)	Anticoagulants (140.3) [2]	Anticoagulants (93.0) [2]	Diuretics (34.0)	Laxatives (50.8) [7]	Laxatives (42.1) [7]
2	Furosemide (28.7)	Furosemide (40.7) [2]	Acetylsalicylic acid (30.0) [1]	Anticoagulants (56.9)	Antibiotics (103.1) [10]	Vitamins (44.9) [5]	Analgesics (22.4)	Antibiotics (45.8) [8]	Vitamins (31.4) [5]
3	Paracetamol (21.3)	Fraxiparine (39.9) [81]	Furosemide (25.7) [2]	Analgesics (27.5)	Neuroleptics (68.2) [4]	Proton Pump Inhibitors (34.6) [13]	Sedatives/ Hypnotics (22.0)	Vitamins (44.4) [5]	Diuretics (29.6) [1]
4	Digoxin (15.5)	Pantoprazole (38.8) [21]	Folic acid (23.4) [7]	Neuroleptics (27.5)	Analgesics (56.2)[3]	ACE inhibitor (28.5) [6]	Digoxin (14.9)	Diuretics (42.1) [1]	Sedatives/ Hypnotics (24.8) [3]
5	Acenocoumarol (13.2)	Acetylsalicylic acid [1] (36.4)	Paracetamol (22.4) [3]	Vitamins (22.9)	Vitamins (49.2) [5]	Iron / Minerals (27.6) [7]	Vitamins (13.7)	Sedatives/ Hypnotics (39.4) [3]	Analgesics (22.5) [2]
6	Temazepam (12.4)	Heparine (35.7) [-]	Vitamin D (21.5) [11]						
7	Folic acid (11.6)	Temazepam (30.6) [6]	Magnesium Oxide (21.0) [25]						
8	Isosorbide dinitrate (10.9)	Amoxicillin (29.1) [-]	Acenocoumarol (20.5) [5]						
9	Spironolactone (10.9)	Folic Acid (28.7) [7]	Digoxin (19.2) [4]						
10	Lactulose (10.0)	Digoxin (24.8) [4]	Lisinopril (17.8) [12]						

acetylsalicylic acid (30.2%), followed by furosemide (28.7%). During admission therapy with proton-pump-inhibitors (PPIs), pantoprazole, was used in 38.8% of patients and 31.8% of discharged patients used pantoprazole. Folic acid that was at admission used by 11.6% of patients, was at discharge increased to 23.4%. At discharge vitamin D was used in 21.5% of patients, whereas lisinopril, an angiotensin converting enzyme (ACE) inhibitor, was used in 17.8% of patients.
In 1985, the percentage of patients using diuretics at admission was lower compared to 2002, however at discharge this percentage was higher in 1985 compared to 2002. Introduction of ACE inhibitors in routine clinical practice was shown in 2002. In 2002, more than half of the admitted patients already used anticoagulants and this was further increased at discharge. Both in 1985 and 2002, vitamins were added and use of antibiotics was increased during admission. In 2002, use of analgesics was markedly increased during admission, whereas in 1985 use of laxatives was increased during admission, which was not shown in 2002. Use of neuroleptics was increased in 2002 compared to 1985.

Change in number of drugs at admission, during admission and at discharge

The mean number of drugs used per patient at admission, during admission and at discharge both in 1985 and 2002 is shown in Table I. Patients received more medication in 2002 compared to 1985. In both periods admission resulted in addition of drugs, partly discontinued at discharge, but a substantial part is continued and thus resulted in a mean addition of 1.0 drug (range from reduction of 6 to addition of 8) in 1985 and of 0.7 drugs (range from reduction of 7 to addition of 10) in 2002.
Reduction of medication has been achieved in a minority (30.4%) of patients. In 47 patients (22.0%) medication was not changed or number of added drugs equalled discontinued ones. In 47.6% of patients addition has been experienced.

DISCUSSION

Geriatric hospital admission results in addition of drugs. During admission more antibiotics, analgesics, anticoagulants and neuroleptics are used. Heparin and amoxicillin are discontinued at discharge, but for example pantoprazole, folic acid and vitamin D are continued. These

changes in pharmacotherapy result in a mean addition of 0.7 drugs at discharge and only in 30.4% of patients medication has been reduced. Comparable numbers of added drugs were shown in 2002 and 1985. During both periods, antibiotics and vitamins were added during hospital admission. Laxatives, sedatives and diuretics were more used at discharge in 1985 compared to 2002. Use of ACE inhibitors and PPIs in routine clinical practice is apparent nowadays.

During admission to the geriatric ward an important goal is the optimisation of pharmacotherapy and we showed a primary role for preventive therapy, for example vitamin supplementation. It is known that an inadequate folate status is associated with an increased risk for chronic diseases that may have a negative impact on the health of the aging population[7]. Studies showed a relative risk of 6.8 for folate deficiencies in elderly living at home versus elderly living in institutions[8] and its prevalence increases with age[9]. Elderly populations aged over 65 and residents of nursing homes showed prevalence of vitamin D deficiencies between 25 and 54%. This deficiency is an important risk factor for osteopenia and bone fractures. Supplementation of 800IE vitamin D daily showed substantially reduced risks of osteoporotic fractures[10].

The risk of developing gastroduodenal ulcers or complications is recognised as a problem in patients using NSAIDs. Important risk factors are increasing age and a past history of upper gastrointestinal ulcer or bleeding[11]. Once daily pantoprazole that showed efficacy in preventing peptic ulcers[12], is often co-prescribed with NSAIDs in our setting.

Optimisation by means of an ACE inhibitor, for example lisinopril, is favourable in type 1 diabetes mellitus with microalbuminuria, because blood pressure control is a key element in slowing the progression of diabetic nephropathy[13]. ACE inhibitors are also of primary importance after acute decompensated heart failure because of proven prolonged life expectance[14].

Geriatric health care has changed. In 1985, the geriatric ward of our hospital counted 108 beds[6] compared to only 24 beds in 2002. However, the geriatric day clinic counted 702 first-time visitors in 2002 and plays an important role in diagnostics resulting in less and shorter durations at the ward. In 2002, patients used almost twice as much medication as the studied population in 1985. This can be explained by the introduction of new medication groups since 1985, introduction of more guidelines and guidelines advising drug combinations. For example, patients with heart failure resulting from left ventricular dys-

function are now often treated with a combination of an ACE inhibitor, diuretic, a beta blocker and spironolactone[15].

CONCLUSIONS

Geriatric hospital admission resulted in both 1985 and 2002 in addition of medication. In both periods, reductions in medication were nullified by addition of medication for reason of therapy optimisation. Changes in healthcare structure resulted in less and shorter admissions. Compared to 1985 admitted patients receive more medication resulting from new insights into pharmacotherapy and more use of preventive medicine.

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Chapter 2.2

Evaluation of pharmacotherapy in geriatric patients after performing Complete Geriatric Assessment (CGA) at a diagnostic day clinic

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ABSTRACT

Elderly patients often take multiple drugs. It is known that polypharmacy, i.e. use of five or more drugs, may lead to drug interactions and adverse events. However, undertreatment of conditions or illnesses is also a concern in geriatric patients. A centralised review of both diagnoses and medication may play a key role in optimising pharmacotherapy in geriatric patients. The aims of this study were to evaluate quality and appropriateness of medication after performing complete geriatric assessment (CGA) and medication review at a diagnostic geriatric day clinic, to investigate reasons for drug changes, and to determine whether medication review leads to a reduction in the number of drugs used.

A chart review was performed in 702 patients (mean age 82.0 years, range 57.1-104.1) who underwent a CGA at a diagnostic geriatric day clinic. Medication at admission, changes in medication and reasons for changes were noted.

Vitamins, for example folic acid and vitamin B12 (cyanocobalamin), and trimethoprim for urinary tract infections were the most frequently started medications after CGA and medication review. The number of drugs used was reduced in only a minority of patients (11.7%); reasons for discontinuation were a diagnosis that was not longer relevant (38.8%), adverse events (33.2%) and identification of better pharmacotherapeutic options (21.9%). In 69.2% of the cases, a new diagnosis was the reason for starting new medication, followed by osteoporosis prophylaxis (15.0%) and improvement in pharmacotherapy (10.6%). At admission, patients were taking a mean number of 4.6 drugs (range 0-17). A mean of 0.8 drugs (range from reduction of 5 to addition of 7) had been added per patient resulting in a mean number of 5.4 (range 0-18) prescribed drugs at discharge.

Evaluation of medication in patients after performing CGA at the geriatric day clinic resulted in relevant medication changes. The main reason for prescribing new drugs was a new diagnosis. Absence of a relevant medical indication was the main reason for stopping drugs. CGA and medication review resulted in a mean net addition of 0.8 drugs per patient.

INTRODUCTION

Healthcare for older patients has undergone many changes during the last decade. In The Netherlands, the emphasis has shifted from inpatient to ambulatory care. The diagnostic day clinic, for example, has been a unique part of the department of geriatric medicine in our hospital since 1995 and has been introduced into 30 hospitals in The Netherlands since then. At such clinics, a complete geriatric assessment (CGA) is carried out by a geriatrician, predominantly in outpatients, most of whom have been referred by a general practitioner. These patients are referred to a geriatrician because they have both acute and chronic problems, mostly in combination with multiple morbidities and medication use and often accompanied by psychiatric illnesses or functional decline. Review of medical history, physical examination, laboratory tests, medication review, chest x-ray, testing of functional state, cognition and mood are all carried out over a period of one day. At the end of this day, diagnoses are made and medication is sometimes changed or pharmacotherapeutic advice is given to the general practitioner. Further treatment can take place through the general practitioner or the geriatrician and in some patients involving other specialists as well. From the patient's point of view, it is of great value that all diagnostic tests are conducted over one day so that the patient does not need to visit the outpatient department several times. From the geriatrician's standpoint, the day clinic is a practical setting to perform CGA and thereby obtain insight into patients' diagnoses and drug use.

Frail elderly patients are often diagnosed with multiple diseases and visit several specialists besides their general practitioner. This may lead to multiple prescriptions and specialists not knowing which drugs are being prescribed by their colleagues. A centralised review of both medications and diagnoses may therefore play a key role in optimising pharmacotherapy in geriatric patients. The diagnostic process can lead to new diagnoses and prescriptions, but may also reveal inappropriate drug use. This should of course be minimised in the geriatric population, for whom there is strong evidence of a sizeable and consistent negative effect of inappropriate drug use on patients' health status[1] and an associated increase in use of outpatient services and more rapid hospitalisation[2]. It is preferable to reduce polypharmacy, defined as the use of five or more drugs[3], because this can lead to drug-drug interactions and adverse events[4], and the number of drugs is inversely correlated with adherence to the therapeutic regimen[5]. On

the other hand, however, undertreatment has also been described.[6,7] Therefore, evaluation of medication in geriatric patients should aim to reduce polypharmacy on the one hand and prevent undertreatment on the other. To our knowledge, this is the first study describing medication evaluation at a geriatric diagnostic day clinic.
The aims of this study were: (a) to evaluate the quality and appropriateness of pharmacotherapy after performing a CGA and medication review at a geriatric day clinic; (b) to investigate reasons for changes in pharmacotherapy; and (c) to investigate if medication review is associated with a reduction in drugs used.

PATIENTS AND METHODS

Patients and data collection

This study was carried out at the geriatric day clinic of a general hospital (Slotervaart Hospital) in Amsterdam, The Netherlands, in 2002. Patients were included and underwent CGA if it was their first visit to the day clinic. Patients were excluded if their medical records were incomplete.
A retrospective chart review was performed that included date of visit, date of birth, sex, medication at admission and medication that was started and discontinued, reasons for changes in medication and new diagnoses after performing CGA. Medication at admission was counted as the medication that was brought to the day clinic and that was actually ingested by the patient. Reasons for changes were sometimes explicitly noted. In other cases, reasons were assumed by the person doing the chart review. In addition, changes are sometimes based upon protocols that are created and used at the geriatric department. Only changes in medication were counted; changes in dosage were not taken into account.
Data were incorporated in a database in Visual FoxPro 6.0 (Microsoft Corporation, Redmond, WA).

Design

Illnesses or conditions diagnosed after geriatric assessment at the day clinic were classified according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10)[8]. Drugs were classified according to the Anatomical Therapeutical Chemical (ATC) classification index[9].
Descriptive analyses of the medication used on admission to the geriatric day clinic and changes in medication after therapy evaluation

were carried out. The change in number of drugs was also counted in each patient to determine whether medication review was associated with a reduction in the number of drugs.

RESULTS

Patients

Seven hundred and two patients were included in this study; 11 patients were excluded because their medical records were incomplete. The cohort consisted of 464 women (66.1%) and 238 men (33.9%). Mean age of these patients at admission was 82.0 years (SD 6.8 years) with a range of 57.1-104.1 years.

Diagnoses

The most frequently made diagnosis was dementia, including mild cognitive impairment, (45.0% of patients), followed by vitamin deficiencies as confirmed by laboratory tests (26.4%), constipation (16.0%), depression (15.8%), urinary tract infection (13.0%), osteoporosis (9.5%), anaemia from chronic diseases (7.8%), arthrosis (6.8%), diabetes mellitus (6.6%) and electrolyte disorders (5.4%), Parkinson disease (5.4%) and atrial fibrillation (5.4%).

Medication at admission

The ATC codes for drug groups that were frequently used on admission to the geriatric day clinic were: (A) gastrointestinal tract and metabolism; (B) blood and blood-forming organs; (C) cardiovascular agents; and (N) central nervous system agents. Table I lists the top ten of medications being taken at admission. Acetylsalicylic acid (25.8%), paracetamol (acetaminophen) (20.9%) and furosemide (18.0%) were the most frequently used medications.

Evaluation of medication

Table I shows the top ten medications started and the medications discontinued after evaluation at the day clinic. Hydrochlorothiazide was discontinued in 3.6% of patients, haloperidol in 2.6% of participants, pipamperone (an antipsychotic agent) in 2.1% and ferrous fumarate in 1.6% of patients. Vitamins, for example folic acid, vitamin D and vitamin B12 (cyanocobalamin), were started frequently, in 18.9%, 13.4% and 7.3% of participants, respectively. Trimethoprim was added to drug regimens in 4.6% of subjects, and risperidone in 4.2%.

Tabel I.
Top ten medications on admission to and top ten medications started or discontinued at the geriatric day clinic (% of total patients; n=702).

	Medication		
	On admission [n (%)]	Discontinued at day clinic [n (%)]	Started at day clinic [n (%)]
1	Acetylsalicylic acid [181 (25.8)]	Hydrochlorothiazide [25 (3.6)]	Folic acid [133 (18.9)]
2	Paracetamol (acetaminophen) [147 (20.9)]	Haloperidol [18 (2.6)]	Vitamin D [94 (13.4)]
3	Furosemide [126 (18.0)]	Betahistine [18 (2.6)]	Magnesium oxide [82 (11.7)]
4	Lactulose [86 (12.3)]	Pipamperone [15 (2.1)]	Vitamin B12 [51 (7.3)]
5	Temazepam [81(11.5)]	Lactulose [13 (1.9)]	Calcium carbonate [41 (5.8)]
6	Digoxin [79 (11.2)]	Ferrous fumarate [11 (1.6)]	Citalopram [38 (5.4)]
7	Acenocoumarol [77 (11.0)]	Triamterene [11 (1.6)]	Trimethoprim [32 (4.6)]
8	Isosorbide dinitrate [70 (10.0)]	Furosemide [10 (1.4)]	Risperidone [29 (4.2)]
9	Oxazepam [65 (9.3)]	Cinnarizine [8 (1.1)]	Paracetamol [28 (4.0)]
10	Hydrochlorothiazide [63 (9.0)]	Diclofenac [7 (1.0)]	Acetylsalicylic acid [27 (3.8)]
		Tramadol [7 (1.0)]	
		Paracetamol [7 (1.0)]	

Reason for change of medication after pharmacotherapy evaluation

The reasons for changes in pharmacotherapy after CGA and medication evaluation are presented in Table II. In 69.2% of started medication, a new diagnosis was the reason for starting new medication, followed by osteoporosis prophylaxis (15.0%) and improvement in pharmacotherapy (10.6%). Examples of medications started for new diagnoses were trimethoprim, for urinary tract infections, and citalopram for depression, whereas calcium carbonate and vitamin D were started for osteoporosis prophylaxis. Risperidone, usually to replace

the typical antipsychotic haloperidol, is an example of a drug that was started to improve pharmacotherapy.
No longer existing or relevant diagnosis accounted for 38.8% of all discontinued drugs, followed by adverse events (33.2%) and availability of better pharmacotherapeutic options (21.9%). Hydrochlorothiazide, ferrous fumarate and betahistine are examples of medications that were often discontinued because they were prescribed for diagnoses that no longer appeared to be significant after geriatric assessment. Pipamperone was discontinued because of cholinergic adverse events. Haloperidol was discontinued because a better pharmacotherapeutic alternative was available.

Table II.
Reasons for medication changes at the geriatric day clinic (% of total discontinued or total started medication).

Reason	Started [no.(%)]	Discontinued [no. (%)]
Adverse events		130 (33.2)
Better pharmacotherapeutical options	101 (10.6)	86 (21.9)
Diagnosis not relevant anymore		152 (38.8)
Insufficient effect		15 (3.8)
New diagnosis (including folic acid and vitamin B12 deficiencies)	659 (69.2)	
Osteoporosis prophylaxis (vitamin D, calcium)	142 (15.0)	
Preventive cardiac medication (acetylsalicylic acid, acenocoumarol)	26 (2.7)	
Prevention adverse event other medication	12 (1.3)	
Other	12 (1.2)	9 (2.3)
Total	952 (100)	392 (100)

Change in number of drugs after pharmacotherapy evaluation
The mean number of drugs used per patient at admittance was 4.6 (range 0-17). A mean addition of 0.8 drugs (range from reduction of 5 to addition of 7) per patient resulted in a total of 5.4 (range 0-18) drugs used per patient after CGA and medication review at the day clinic.
The number of drugs was reduced only in a minority of patients (11.7%). Reduction of one drug was achieved in 52 patients (7.4%), whereas a reduction of two drugs was achieved in only 20 patients (2.8%). In 246 patients (35.0%), the number of added drugs equalled the number of discontinued drugs or medication remained unchanged.

However, in a majority (53.3%) of the day clinic patients, the number of drugs increased. Addition of one, two and three drugs occurred in 183 (26.1%), 106 (15.1%) and 57 (8.1%) patients, respectively.

DISCUSSION

After CGA and medication review at our diagnostic geriatric day clinic, primarily vitamins, magnesium oxide, calcium carbonate, trimethoprim, citalopram and risperidone were added to the pharmacotherapeutic regimen, whereas diuretics, antipsychotics (pipamperone, haloperidol) and medication for dizziness/vertigo (betahistine, cinnarizine) were discontinued most frequently. New diagnoses, including folic acid and vitamin B12 deficiencies, accounted for most of the newly prescribed drugs. Discontinuation of drugs, although relatively uncommon, was mostly because the indications for prescription no longer appeared to be relevant. Evaluation of pharmacotherapy at our geriatric day clinic thus resulted primarily in addition of medication with only a minority of patients experiencing discontinuation of medications, resulting in a mean net addition of 0.8 drugs per patient.

Optimisation of geriatric pharmacotherapy involves initiating new therapy in case of a new diagnosis, improving drug use or discontinuing medication when its use is no longer appropriate. Vitamin supplementation was frequently started at the day clinic; two diagnosed deficiencies were treated (folic acid and vitamin B12) and purely preventive supplementation with vitamin D was also started. It is known that an inadequate folate status is associated with increased risk for chronic diseases that may have a negative impact on the health of the aging population[10]. A moderately reduced vitamin B12 level is associated with vascular disease and neurocognitive disorders such as depression and impaired cognitive performance. Furthermore, poor vitamin B12 status is assumed to be involved in the development and progression of dementia[11]. Vitamin D and calcium carbonate were often started at the day clinic because these reduce the risk of hip fracture and other nonvertebral fractures among elderly women[12]. Depression was one of the most frequent diagnoses made at the day clinic and is one of the leading causes of poor quality of life in the elderly[13]. If medical treatment is warranted, then citalopram is one of the better alternatives in the elderly, because it is efficacious in this age group, has negligible cholinergic and histaminergic adverse events[14] and has a low potential for pharmacokinetic interactions because of its low affinity for metabolising cytochrome P450 enzymes[15].

Discontinuation of drugs if they are no longer useful is necessary, particularly in older people who are often taking multiple drugs. Discontinuation of drugs at the day clinic was, however, achieved only in a minority of patients. Iron supplementation, for example, was discontinued in patients demonstrating a regular iron state. This is important as iron may induce constipation, the incidence of which increases with age[16].

Optimisation of drug treatment is also possible when better pharmacotherapeutic options are available, for example in our cohort with the change of haloperidol to risperidone for treatment of behavioural and psychological symptoms of dementia. In this condition, for which long-term antipsychotic treatment is expected, risperidone is preferred because of possibly fewer adverse events[17,18].

CONCLUSION

Evaluation of medication in patients after CGA at our geriatric day clinic resulted in many changes in pharmacotherapy. In a majority of patients, new drugs were prescribed and preventive medicine played an important role in these changes. The most frequent reason for prescribing additional drugs was the diagnosis of a new condition and only in a minority of day clinic visitors was medication discontinued because diagnoses no longer appeared relevant.

In The Netherlands, general practitioners play a key role in healthcare as they refer patients to specialists. We therefore recommend that if a general practitioner sees a geriatric patient with multiple morbidities and associated medication use that is possibly causing psychiatric illnesses, functional decline or other adverse events, the patient should be referred to a geriatric day clinic for CGA and medication review.

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Chapter 2.3

Changes in undertreatment after geriatric assessment

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Submitted

ABSTRACT

Geriatric patients are often undertreated. Moreover, as these patients often have several medical conditions, polypharmacy and contraindications to indicated drugs are also common. The aim of this study was to describe the prevalence of undertreatment with frequently indicated medications before and after Comprehensive Geriatric Assessment (CGA) and to determine the prevalence of contraindications to these medications. Data on demographics, medical history, comorbidity, and medication use and changes in use were available for patients who had participated in a prospective descriptive study in 2004. The use of drugs indicated for frequently undertreated conditions before and after CGA was compared. Undertreatment with a drug for a certain condition was defined as omission of drug therapy indicated for the treatment or prevention of a disease or condition. Comorbid conditions were independently classified as contraindications to these drugs by two geriatricians. In 2004, 807 geriatric patients were referred for CGA. Of these, 548 patients had at least one of the selected conditions known to be frequently undertreated. Before CGA, 170 patients were undertreated (32.9%) and after CGA 115 (22.3%). Contraindications were present in 102 of the patients (19.8%) and were more often present in the undertreated patients. After CGA, mean drug use and the prevalence of polypharmacy increased. Five times more drugs were prescribed for a new diagnosis than were prescribed to correct undertreatment of previously diagnosed conditions. Patients with contraindications to indicated drugs are more frequently undertreated than patients without contraindications. CGA leads to a significant reduction in undertreatment and to an increase in polypharmacy, mainly because new conditions are diagnosed and despite frequent discontinuation of medications.

INTRODUCTION

Many older individuals suffer from medical conditions for which effective drugs are available but often do not receive these medications. This undertreatment is more common than inappropriate treatment in patients using fewer than eight medications.[1] In the Netherlands, a study has shown that 61% of home-dwelling older patients receiving polypharmacy are undertreated,[2] and another study reported rates of underprescription of indicated drugs of 31% in patients referred for geriatric evaluation.[3] Advancing age has been found to be associated with diminished use of statins, β-adrenoreceptor antagonists, ACE inhibitors, and antithrombotic therapy.[4-10] Indeed, failure to prescribe indicated medications was found to be more common than the prescription of inappropriate drugs in a study of pharmacological care in vulnerable community-dwelling individuals.[11]

However, if patients were to be prescribed all the drugs recommended by treatment guidelines, then the rate of polypharmacy would increase. Indeed, up to 12 medications may be needed to treat patients with several comorbid diseases if appropriate guidelines are followed.[12] General practitioners (GPs) may be reluctant to prescribe more than a certain number of drugs because of fear of adverse drug reactions (ADRs), drug-drug interactions, and poor adherence due to complex drug regimens. That physicians are concerned about potential ADRs was shown in a study in which GPs expressed more concern about the risks of ACE inhibitors and oral anticoagulants (OAC) than cardiologists.[13]

Moreover, there may be valid reasons to refrain from prescribing medications, such as contraindications. For this reason, it is important to distinguish between undertreatment and underprescription of drugs for a certain medical indication. Undertreatment is defined as omission (for whatever reason) of drug therapy indicated for the treatment of a diagnosed disease or condition.[14] In contrast, underprescription is defined as the lack of drug therapy for a diagnosed disease, for which drug therapy is indicated according to clinical practice guidelines, and for which there are no contraindications, therapy failure, or relevant adverse effects.[3] While contraindications to drug use are likely to be present among patients with multiple comorbidities, they are not the sole explanation for undertreatment. In patients with heart failure, those with increasing risk are less likely to be prescribed ACE inhibitors and β-adrenoreceptor antagonists, even after taking potential contraindications, such as hypotension, bradycardia, and renal failure,

into account.[15] Underprescription was found to be more common among patients receiving polypharmacy, defined as the use of five or more drugs.[3]
Because Comprehensive Geriatric Assessment (CGA) has been shown to reduce undertreatment,[16] the objective of this study was to describe the prevalence of undertreatment before and after CGA in a geriatric outpatient population. We also investigated the prevalence of contraindications to those drugs that are most frequently not prescribed, and whether it is justified, according to the literature, to refrain from prescribing these drugs because of these (relative) contraindications.

METHODS

Patients and setting

The study was performed at the geriatric day clinic of the Slotervaart Hospital in Amsterdam. In this department of a large teaching hospital, CGA is performed in one day, with follow up if necessary for further diagnosis or treatment on an outpatient basis. The main reasons for referral by the GP are cognitive decline or functional dependence.

Data collection and endpoints

The patients included in this study had participated in a prospective descriptive study in 2004. Patients were evaluated by geriatricians or geriatric medicine residents, using the Medication Appropriateness Index (MAI).[17] The treating physicians were advised by the study physician (LT) and study pharmacist (SF) regarding changes in medication, including prescribing medication for hitherto untreated or undertreated conditions. Demographic data, medical history, comorbidity (Charlson Index),[18] and medication use and changes in use were registered.
For this study, patients were included if their records showed the GP had diagnosed one or more of the following conditions that require pharmacotherapy but which is often omitted[3]: hypertension, angina pectoris, stroke or transient ischemic attack (TIA), peripheral arterial disease, myocardial infarction, heart failure, atrial fibrillation, diabetes mellitus, and osteoporosis. We recorded whether, according to the guidelines of the Dutch General Practitioners, patients had indications for treatment with antihypertensives, antithrombotics, OAC, ACE inhibitors, β-adrenoreceptor antagonists, antidiabetics, or bisphospho-

nates. Moreover, we considered steroid use, NSAID use, and morphine use to be indications for the use of bisphosphonates, proton pump inhibitors (PPIs), and laxatives, respectively. We classified the omission of any of these indicated drugs as undertreatment, regardless of possible reasons for the failure to prescribe these drugs. We recorded whether additional drugs were started after CGA for hitherto undertreated conditions, and how many drugs should have been prescribed to prevent undertreatment. If the CGA identified new conditions for which the patients were not referred, and for which they remained untreated, these patients were also classified as being undertreated after CGA. Lack of statin use was not classified as undertreatment because we did not have information about cholesterol levels. We also recorded how many drugs were prescribed for reasons other than hitherto undertreated conditions. These reasons were either explicitly described or deduced from the records by the geriatrician who performed the chart review (LT). Patients were excluded if their health and prognosis precluded maximum therapy, if insufficient information was present about the use of medication over a sufficient period of time in the past, or if medication use after CGA was unknown because the patient had been referred elsewhere. Patients who refused drug therapy were also excluded.

General Practitioner Guidelines available in 2004 for heart failure, TIA diabetes mellitus, angina pectoris, osteoporosis, peripheral arterial disease, acute coronary syndrome, hypertension, atrial fibrillation, stomach complaints, and pain were used to classify whether a medication was indicated. These guidelines are available on request from the author LT. In 2004, there were no Dutch General Practitioner guidelines for stroke and myocardial infarction, and so national and international interdisciplinary guidelines were used.[20, 21] Patients were classified as being undertreated if their medication regimen on referral lacked at least one indicated drug. If the reason for GP referral of the patient was the potentially undertreated condition and advice about this was requested, the patient was not classified as undertreated. The symptoms, signs, or diseases classified as contraindications were derived from the GP guidelines and the Summary of Product Characteristics (SPCs) provided by manufacturers .[19 21] Two geriatricians (LT and JvC) independently classified comorbid conditions as contraindications. In a case of disagreement consensus was reached. Cohen's κ was 0.71, indicating good inter-rater agreement.

The primary endpoint was the prevalence of undertreatment of the above-mentioned conditions or the absence of protective medications

before and after CGA. A second endpoint was the prevalence of relative contraindications to these indicated drugs, as defined in Dutch GP guidelines and the SPCs.

Statistical Analysis

Dichotomous variables are reported as proportions with comparisons made using chi-square tests. Continuous variables are given as means ± SD. Comparisons were made for medication use before and after CGA with paired Student-T tests. Differences in age, gender, number of drugs, Charlson comorbidity index, presence of dementia, and contraindications after CGA in relation to undertreatment were analyzed. A p-value of less than 0.05 was considered statistically significant. Statistical calculations were performed with SPSS for Windows (version 16.0, SPPS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

In 2004, 807 patients were evaluated, 548 of whom had at least one indication for medical treatment, according to the GP guidelines. Thirty-two of these patients were excluded for different reasons (Figure I), and so the data of 516 patients (53% women; mean age (± SD) 81.5 ± 7.6 years) were analyzed. The mean Charlson Comorbidity Index was 2.3±1.4 (range 0-9): it was significantly higher (2.45±1.45) in patients receiving polypharmacy (≥5 drugs) than in patients not receiving polypharmacy (2.01 ± 1.35).

Differences in drug use before and after CGA

The differences in drug use before and after CGA are shown in Table I. Fewer patients were undertreated after CGA (115 patients, 22.3%) than before CGA (170 patients, 32.9%). The number of drugs used increased from 3177 before CGA to 3424 after CGA. After CGA, 92 drugs were prescribed for previously diagnosed but hitherto undertreated conditions, and 548 drugs were started for other reasons ($p<0.01$): 507 drugs were prescribed for newly diagnosed conditions and 41 drugs were prescribed as additional treatment for conditions already being treated. A total of 393 drugs were discontinued. The reasons for discontinuation, collected from the patients' medical records, were: no indication present (n=184), ADRs (n=155), lack of effectiveness n=(41), simplifying drug regimen (n=9), duplications of

similar drugs (n=2) and contraindications (n=2). Of the discontinued medications, 85 contributed to possible drug-drug interactions.

Table I.
Differences in medication use before and after CGA, regardless of contraindications

N=516	Before CGA	After CGA
Mean ±SD no. of drugs (range)	6.2±3.3 (0-21)	6.6±3.2 (0-18)*
Polypharmacy: no. (%) of patients with 5 or more drugs	340 (65.9%)	364 (70.5 %)*
Undertreatment: no. (%) of patients with ≥ 1 missing drug	170 (32.9%)	115 (22.3 %)*
No. of missing drugs (mean ± SD)	215 (0.41±0.67)	133 (0.26±0.51)*
No. (%) of patients with contraindications who are under-treated	53 (51.9 %)	57 (55.9%)*

*P < 0.05

Mean drug use and the prevalence of polypharmacy increased and fewer patients were undertreated after CGA. In total, 102 patients had contraindications to drug therapy (19.8%) (Figure). The proportion of patients with contraindications who were undertreated increased from 51.9% before CGA to 55.9% after CGA. Of patients receiving polypharmacy, 111 of 340 (32.6%) were undertreated before and 86 of 364 (23.6%) were undertreated after CGA. Of undertreated patients, 65.7% were receiving polypharmacy before CGA and 75.4% after CGA

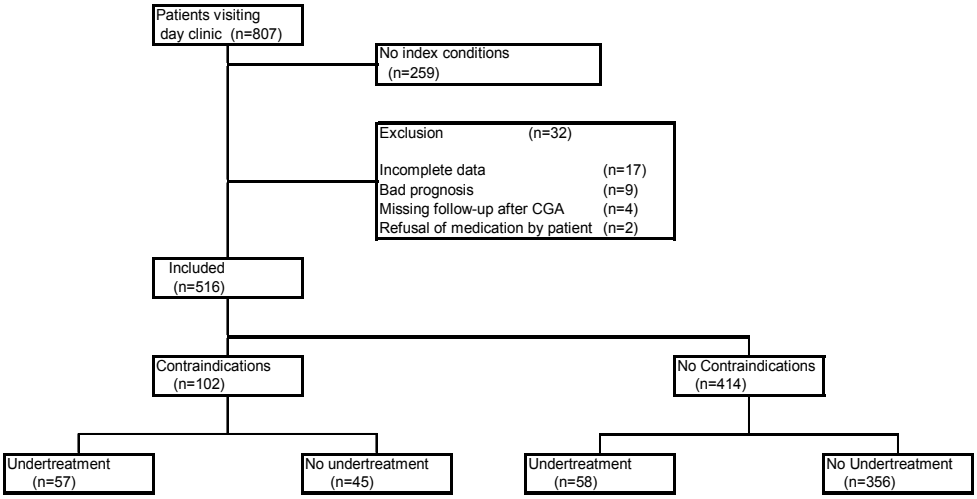

Figure. Classification of patients: undertreatment after CGA

Differences in patients with and without undertreatment after CGA

Patients receiving polypharmacy tended to be undertreated more often than patients not receiving polypharmacy (p=0.068). After CGA, undertreated patients had a higher Charlson Index, were more often male, and more frequently had contraindications than adequately treated patients. Undertreatment was not higher in patients with dementia (Table II). Correction of undertreatment, regardless of the presence of contraindications, would have increased the number of drugs to a mean of 6.8 drugs per person in the whole population, and to 7.5 per person in the undertreated population.

Table II. Differences between patients with and without undertreatment after CGA

N=516	Undertreatment (n=115)	No undertreatment (n=401)	Confidence Interval, p-value
Age (mean± SD)	83.1± 7.1	81.0±7.7	CI 0.55-3.70, p<0.01
Charlson Index	2.57± 1.5	2.22±1.4	CI 0.04-0.64, p<0.05
Female gender, no (%)	52 (45.2%)	275 (68.6%)	P < 0.01
Presence of contraindications, no (%)	57 (49.6%)	45 (11.2%)	P < 0.01
Presence of polypharmacy, no (%)	88 (76.5%)	276 (68.8%)	P = 0.068
Presence of dementia, no (%)	54 (47.0%)	186 (46.4 %)	P = 0.916

Table III.

Use of indicated drugs before and after CGA

Condition	Indicated drug	Indicated before CGA	Indicated after CGA	Present before CGA (*)	Present after CGA (*)
Myocardial infarction, angina pectoris, TIA, stroke, peripheral arterial disease	Antithrombotic treatment	251	255	213 (84.9)	225 (88.2)
Hypertension	Antihypertensive	225	229	213(94.6)	220 (96.1)
Atrial fibrillation	OAC	87	109	64 (73.6)	63 (57.8)
Myocardial infarction	β-adrenoreceptor antagonist	63	66	35 (55.6)	35 (53.0)
Heart failure	ACE inhibitor	54	56	50 (92.6)	55 (98.2)
Osteoporosis and steroid use	Bisphosphonate	62	73	30 (48.4)	57 (78.1)
NSAID use	Gastroprotective drug	51	40	20 (39.2)	29 (72.5)
Morphine use	Laxative	10	7	7 (70.0)	5 (71.4)

(*): percentage of patients with indication

Table IV.
Contraindications (CIs) and undertreatment in patients after CGA

No. of patients with indication for drug	Patients with CIs	No (%) of Patients with CIs who are treated	No (%) of patients with CIs who are undertreated	CIs in undertreated patients*
Cumarin derivatives N= 109	80 (73.4%)	41 (51.2 %)	39 (48.8%)	Dementia[x] n=25 Falls[x] n=13 Anemia n=7 Recent bleeding n=5 Non-adherence n=1 Alcohol abuse[x] n=1 Subdural hematoma n=1 Intracerebral Bleeding n=1
Antithrombotic treatment N=255	10 (3.9%)	0	10 (100%)	Anemia n=6 Bleeding n=4 Renal dysfunction n=1
β-adrenoreceptor antagonist N=66	15 (22.7%)	5 (33.3%)	10 (66.7%)	Bradycardia n=5 Hypotension n=4 Serious COPD n=2

* Patients had 1-3 contraindications. [X] These were contraindications described by the GP guideline, but not by the SPC.

After CGA, more patients received bisphosphonates and gastroprotective drugs and fewer received OAC for atrial fibrillation (see Table III). We found contraindications to the use of only three classes of drug, namely, OAC, antithrombotic treatment, and β-adrenoreceptor antagonists. However, patients with contraindications to the use of these drugs were often treated with them. The most common contraindications were those for OAC (Table IV).

DISCUSSION

Prevalence of undertreatment

The prevalence of undertreatment (33% before CGA) was lower than described by Lipton and Steinman, who reported medication underuse in 55–64% of elderly patients, with an average of 1.0 underused

medication per patient.[14,1] However, Kuijpers et al found underprescription of indicated drugs in 31% of patients referred for geriatric evaluation.[3] Kuijpers et al excluded patients with ADRs, therapeutic failure, or contraindications whereas we included these patients in our study, which could explain the slightly higher proportion of undertreated patients in our study.
We noticed marked differences in drug underuse: almost all patients with hypertension were prescribed antihypertensives, and antithrombotics and ACE inhibitors were also prescribed very frequently, whereas in patients with myocardial infarction in the history were frequently not taking β-adrenoreceptor antagonists, and patients with atrial fibrillation often were not prescribed OAC. Underuse has previously been reported to be common, but not for all conditions. The high rate of antihypertensive prescription may be because more is known about antihypertensive therapy than for other conditions.[7] Moreover, advanced age does not seem to influence the prescription of hypoglycemic or antihypertensive drugs,[7] and the availability of different antihypertensives means that a patient can be switched to another drug if he/she does not tolerate the first one. The differences in the rate of undertreatment of different conditions or underuse of different medicines could suggest that the risks of available treatment may be considered more important than the expected benefits. Contrary to Kuzuya et al, we did not find patients with dementia to be undertreated more often than other patients.[7]

Differences in medication use before and after CGA

The proportion of patients who were undertreated decreased significantly after CGA, by 10.6%. Schmader et al. reported a decrease in the number of conditions with omitted drugs from 1.4 per patient to 1.0 after discharge from an inpatient geriatric unit, and a decrease in undertreatment has also been reported in a geriatric outpatient clinic.[16] Like others, we found that undertreatment was not abolished. Possible reasons for continued undertreatment include the presence of contraindications, since these are associated with more frequent undertreatment, and the high prevalence of polypharmacy, as also shown by Kuijpers et al.[3] The prescription of biphosphonates and gastroprotective drugs increased after CGA. The identification of new conditions and the optimization of drug therapy for existing conditions resulted in a five-fold greater increase in medicines prescribed than the correction of previously existing undertreatment. Because drugs were often dis-

continued after CGA, medication use increased by only a mean of 0.5 drugs per patient. Like other studies,[16,22] we found that CGA resulted in an increase in polypharmacy, which was already common in our study population, despite a discontinuation of a substantial number of drugs because of ADRs or lack of indication.

The influence of recognized contraindications

Undertreatment with OAC was common in our study population, possibly because many patients had contraindications to OAC use, and undertreatment even increased after CGA. This might be because CGA often detects contraindications, such as dementia or falls. We did not ask GPs or geriatricians why they did or did not treat patients with an indicated medication, so we also do not know whether GPs and geriatricians gave contraindications a similar "weighting" when deciding to prescribe a drug. Interestingly, contraindications were rarely mentioned in the records as a reason to discontinue medicines.

The most frequently identified contraindications for OAC were falls and dementia, which are given as contraindications to OAC in the GP guidelines but not in the SPCs. The extent to which these conditions should influence the decision to anticoagulate a patient is strongly debated. Go and colleagues showed that the presence of contraindications for OAC in usual care did not influence the reduced risk of all-cause mortality associated with OAC use in patients with a mean age of 71 years.[23] Man Son Hing et al found that the risk of falling was not an important factor in determining the optimal antithrombotic therapy.[24] In multivariate analysis, fall-related major hemorrhagic injury during an admission was associated with female gender and use of aspirin or clopidogrel, and less likely with OAC.[25] Gage et al reported that the rate of ischemic stroke per 100 patient-years was 13.7% in patients at high risk of falls and 6.9% in other patients. Patients using OAC with a high risk of stroke and a high risk of falls had a 25% relative lower risk of death or hemorrhage. In these patients at high risk of falls, neuropsychiatric impairment was an independent risk factor for intracranial hemorrhage.[26] While dementia is mentioned as a contraindication in the GP guidelines but not explicitly in the SPCs, both mention non-adherence, which can be caused by dementia, as a reason to refrain from prescribing OAC. In patients with dementia, microbleeds are relatively often present.[27] The presence of such abnormalities is independently related to the incidence of OAC-related intracerebral hemorrhage.[28,29] However, neither the GP guidelines or the SPCs warn of the potentially higher risk of intracerebral bleeding in patients with

dementia resulting from structural changes in the brain. The importance of emerging possible contraindications, such as microbleeds, needs to be established.[28,29]

When deciding to withhold medication because of possible contraindications, it is important to consider the risks of alternative therapies. For instance, the choice of aspirin instead of OAC in patients with dementia is not clear-cut because the use of aspirin in patients with Alzheimer's disease is accompanied by a cumulative rate of bleeding complications necessitating hospital admission of 8% after 3 years, with fatal cerebral bleeds occurring in 2% of patients.[32] The most recent landmark trial of risk of bleeding in elderly patients, the BAFTA, showed an absolute risk reduction of 2% in the combined endpoint of stroke, hemorrhagic complications, and systemic emboli in favor of OAC compared to aspirin.[33] Furthermore, falls are not associated with a worse outcome in patients at high risk of stroke who are prescribed OAC.[24,26] Thus it may be preferable to educate the caregivers of patients with cognitive decline more thoroughly and to monitor anticoagulant therapy more intensely than to replace OAC with aspirin. The contraindications to medications mentioned in guidelines may be insufficiently evidence-based to be accepted as mandatory reasons to refrain from prescribing relevant medications. Our study shows that patients with contraindications are more frequently undertreated, so it is crucial to consider only really significant contraindications when deciding to refrain from treatment.

One study showed that patients with heart failure at greatest risk of dying were the least likely to receive ACE inhibitors, even after taking potential contraindications into account and after exclusion of patients with ACE inhibitor intolerance.[15] We found no contraindications for ACE inhibitors, and prescription rates (over 90%) were higher than those reported by others (around 50 %).[8,9] Hypotension and bradycardia were frequently mentioned reasons not to prescribe β-adrenoreceptor antagonists. Some investigators argue that β-adrenoreceptor antagonists are unnecessary in patients with resting bradycardia, and others claim that a decrease in heart rate is possibly not the only mediator of the clinical benefits of β-adreno-receptor antagonists after myocardial infarction. Since the benefit of β-adrenoreceptor antagonist therapy in patients with bradycardia-related contraindications has not been established, a study is currently investigating whether pacemaker implantation is warranted in patients with β-adrenoreceptor antagonist associated bradycardia.[35] Another contraindication to β-adrenoreceptor antagonist therapy is "serious"

chronic obstructive pulmonary disease (COPD). Nearly 33% of patients admitted with heart failure were found to have airway disease and therefore a potential contraindication,[9] and the presence of pulmonary disease has been found to decrease the odds of patients receiving a β-adrenoreceptor antagonist.[8] However, in most patients the benefit of prescribing selective β-adrenoreceptor antagonist will outweigh the risk of worsening dyspnea.[36] CGA in our population did not increase the rate of β-adrenoreceptor antagonist prescription in patients with a history of myocardial infarction, despite the low prevalence of observed contraindications. A previous study has concluded physicians treating survivors of myocardial infarction seem to rely on the initiative of the hospital department from which the patient is discharged to prescribe β-adrenoreceptor antagonists after myocardial infarction. [37]

So, in this population, ACE inhibitors were not frequently underused whereas β-adrenoreceptor antagonists were, even in the absence of contraindications. Many patients treated with OAC and β-adrenoreceptor antagonist had contraindications to the use of these drugs, yet physicians seemingly considered these contraindications not important enough to refrain from prescribing indicated drugs. This shows that the relevance of contraindications should be better defined in guidelines, since there seem to be differences of opinion about the way contraindications should be weighed in the decision to treat patients at high risk of dying if not treated or of having complications if treated with a given medication. The dilemma is best exemplified by patients with atrial fibrillation who are demented and prone to falling, who are at high risk of both stroke and major bleeding.[26] Lastly, many patients were undertreated even though they did not have contraindications for a specific drug, for example, bisphosphonates, proton pump inhibitors, and laxatives. This suggests that physicians have other reasons to withhold indicated therapy, such as fear of increasing polypharmacy.[3]

Strengths and Limitations

We found a significant reduction in undertreatment after CGA, as has been reported earlier, and a difference in the frequency of undertreatment between conditions. Furthermore, we found that the post-CGA decrease in undertreatment resulted in only a relatively small increase in the proportion of patients receiving polypharmacy; medicines were added for newly diagnosed conditions while others were withdrawn because of ADRs and lack of indication. Contraindications

were rarely explicitly described as a reason to discontinue medication. Unlike earlier studies, we described the prevalence of contraindications as defined by GP guidelines and SPCs.
We did not ask the GPs or geriatricians why they decided not to prescribe an indicated medication. Current comorbid conditions were the only contraindications to treatment that we could reliably identify in the patient charts, and therefore the influence of past ADRs or patient preferences could not be determined. For this reason, we cannot refer to the undertreatment of patients without contraindications as “underprescription” nor can we assume the presence of a contraindication to be a reason for undertreatment. Another limitation is that we studied a patient cohort for whom data were collected prospectively in 2004, and treatment indications were defined according to then current guidelines. Since then, some guidelines for GPs have changed. For instance, the indications for ACE inhibitors in heart failure have been expanded. We also did not evaluate other frequently undertreated conditions, such as depression or undertreatment with statins, because of lack of sufficient data. Therefore, we may have underestimated the prevalence of undertreatment.

Conclusion

Geriatric patients are often undertreated, and undertreatment can be reduced by carrying out a CGA. Undertreatment may be due, in part, to the frequent presence of contraindications. Since the CGA evaluates all previously diagnosed conditions and possible new conditions, geriatricians are in a unique position to review medication use for all comorbid conditions. ADRs, omission of indicated medication because of contraindications, and potential drug-drug and drug-disease interactions can be identified, while taking into account the clinical condition and preferences of the patient regarding the goals of pharmacological treatment. This will lead to individually optimized drug therapy, which often will result in an increase in polypharmacy despite frequent discontinuation of medications.

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Chapter 2.4

Drug-drug interactions in a geriatric outpatient cohort: prevalence and relevance.

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ABSTRACT

The prevalence of drug-drug interactions (DDIs) in a geriatric population may be high because of polypharmacy. However, wide variance in the clinical relevance of these interactions has been shown. The objective of the study was to explore if adverse drug reactions (ADRs) due to drug-drug interactions (DDIs) can be identified by clinical evaluation, to describe the prevalence of ADRs and diminished drug effectiveness as a result of DDIs, and to verify whether the top ten most frequent potential drug-drug interactions known to public pharmacies are of primary importance in geriatric outpatients in the Netherlands. All adverse events, classified by the Naranjo algorithm as being a possible ADR, and drug combinations resulting in diminished drug effectiveness, were identified prospectively in 807 geriatric outpatients (mean age 81) at their first visit. The setting was a diagnostic day clinic. The Medication Appropriateness Index (MAI) and Beers criteria were used to evaluate drug use and identify possible DDIs. The ten most frequent potential interactions according to a 1997 national database of public pharmacies in 1997 ('Top Ten') and possible adverse events as a result of other interactions were described. The effects of changes in medication regimen were recorded by checking the medical records.

In 300 patients (44,5% of the 674 patients taking more than one drug), 398 potential DDIs were identified. In 172 (25,5%) of all patients taking more than one drug, drug combinations were identified that were responsible for at least one ADR or which possibly resulted in reduced effectiveness of therapy. Eighty-four of the 158 possible ADRs effects resulting from enhanced action of combined drugs forming combinations listed in the 'Top Ten' were seen in 73 patients. Only four DDI resulting in less effective therapy that involved drug combinations in the 'Top Ten' were identified. Changes in drug regimens pertaining to possible interactions were proposed or put into effect in 111 of these 172 (65%) patients with possible DDIs. Sixty-one (55 %) returned for follow-up. Of these, 49 (80 %) were shown to have improved after changes were made to their medication regimen.

In this study, nearly half of geriatric outpatients attending a diagnostic day clinic who were taking more than one drug were candidates for DDIs. One-quarter of these patients were found to have possible adverse events or diminished treatment effectiveness which may have been at least partly caused by these DDIs. These potential interactions can be identified through clinical evaluation. In the majority of patients (99 of 172) the potential interactions resulting in possible ADRs or diminished effectiveness was not present in the 'Top Ten' interactions described by a national database of public pharmacies, a finding that emphasizes that the particular characteristics of geriatric patients (e.g. frequent psychiatric co-morbidities) need to be considered when evaluating their drug use. At least 7% of the patients taking more than one drug, and 80% of those with possible drug interactions whose drug regimen was adjusted, benefited from changes made to their drug regimen.

INTRODUCTION

The prevalence of polypharmacy, defined as taking four or more medications,[1] increases with age. In the Netherlands, 8 to 22 % of the elderly patients living at home, and up to about 40 % of patients in nursing homes take more than 4 drugs.[2]

Polypharmacy is a risk indicator for adverse drug reactions (ADRs). In the elderly, ADRs are estimated to account for between 2.4% and 16.4% of all hospital admissions, especially gastrointestinal bleeding and falls being the most frequent causes.[3]

ADRs can be side effects of appropriately prescribed drugs, but they can also be caused by enhanced drug action or diminished therapeutic effect due to drug-drug interaction (DDIs). The frequency of ADRs, and inappropriate drug-drug and drug-disease combinations is correlated with the number of drugs taken.[1,4-8] The frequency of potential DDIs also increases with age and number of medications and ranges from <5 % in outpatients to 60% in patients living in long term care facilities. However, not all potential drug interactions, defined as drug combinations that may lead to DDIs, inevitably result in ADRs: the reported clinical relevance of potential interactions ranges from 0 to 70%. [1,5,9-13] These figures are probably an underestimation because interactions resulting in reduced drug action are as frequent as those resulting in enhanced drug action and may be overlooked more easily than the interactions with a potentiating effect.[1,14]

Ideally, ADRs should be prevented by avoiding clinical important DDIs. On the other hand, drug combinations with the potential for interaction should still be used judiciously when there is an appropriate indication for their use in order to avoid undertreatment. Indeed, this is common practice. On discharge from the emergency room or hospital ward, up to half of the patients are intentionally prescribed drug combinations with the potential for interactions.[5,10,15-19] In one study, potential DDIs were detected at hospital discharge in 88.8 % of patients with heart failure.[20]

Use of a computerised drug-interaction program for drug prescription will identify all drug combinations with potential interactions. However, a large proportion of these combinations will not result in adverse effects or diminished drug action, making evaluation of relevant clinical effects of all these possible interactions a time-consuming inefficient procedure.[13,21]

In summary, the prevalence of potential drug interactions in a geriatric population may be high, but wide variance in the clinical relevance has been shown.
The aim of this study was to determine whether potential interactions, ADRs and diminished drug effectiveness possibly arising from interactions could be identified by clinical evaluation alone in a 2004 cohort of geriatric outpatients. The second aim was to investigate the frequency of possible clinical relevant effects of the ten most frequently prescribed drug combinations resulting in potential interactions, as described in a national database of public pharmacies in the Netherlands in 1997 ('The Top Ten'[22]). We were also interested in determining whether identification of possible ADRs or diminished drug effectiveness as a result of interactions would lead to changes in drug prescription in clinical practice, and when possible, to changes in patient's condition.

METHODS

Population

The study was part of a prospective descriptive study at the diagnostic geriatric day clinic of the Slotervaart Hospital in Amsterdam between January 2004 and January 2005. In this teaching hospital, patients are offered geriatric assessment over the course of 1 day with follow up if necessary for further diagnostics or treatment on an outpatient basis. The most frequent reasons for referral to the clinic by the general practitioners are cognitive decline, functional dependence or a combination of these.

Collection of data

All 807 patients visiting for the first time in 2004 were appraised using Comprehensive Geriatric Assessment (CGA) including a medical history, medication review, physical and functional evaluation, laboratory investigations, ECG and chest X-ray. The Mini Mental State Examination (MMSE)[23] is a short screening test for cognitive decline. A score of <25 out of 30 on the MMSE indicates the presence of impaired cognitive function. The MMSE was administered only when the history pointed to possible cognitive decline of new onset. The Charlson Comorbidity Index,[24] a measure of the presence of multiple co-morbid diseases such as diabetes, heart failure, malignancy and others, was scored on the basis of the clinical history and evaluation. The higher the score, the more severe the comorbidity.

In this study, medication use in all patients was evaluated using the Medication Appropriateness Index (MAI)[25] and the Naranjo's algorithm (see following paragraph) for assessing the probability of adverse drug reactions[26] at the time of the first visit of the diagnostic day clinic.
With the MAI, the clinician scrutinizes the drug regimen for the presence of possible inappropriate prescriptions and weighs the clinical relevance of the MAI's ten items. Separate items on the MAI include, for example, indication, dosage, drug duplication, DDIs and drug-disease interactions. The MAI can be used as a checklist to identify adverse effects and ineffective treatment and may be used in conjunction with a standard medication text. (in our study the Dutch *Farmocotherapeutic Compass*). We did not use a computerized drug-interaction program. Medication deemed inappropriate according to the updated Beers criteria for potentially inappropriate medication use[27] were rated as ineffective, as instructed in the MAI. The Beers criteria lists drugs and drug-disease combinations which are contraindicated in the elderly because of frequent ADRs.
Naranjo's algorithm[26] is a method for assessing the probability of an ADR. Points are given, for example, for time relationship and dose dependency of drug administration and adverse effect, reversibility after discontinuing the drug, toxic concentrations and other objective measures. Points are taken away when there are other possible causes for the adverse reaction or when placebo has the same result. Between 1 and 4 points denotes possible ADR, 5 to 8 points denotes a probable ADR and >8 points denotes a certain ADR. When, according to clinical judgment of the treating physician and the study physician, a treatment was not effective enough, or when a possible side effect was present, the drug regimen was scrutinized for known possible drug interactions. This procedure resembles the way geriatricians evaluate drug regimens of their patients in daily practice.
First, we established the prevalence of possible DDIs identified as clinically relevant inappropriate combinations by the MAI (with at least one possible ADR identified by Naranjo's algorithm) or combinations possibly resulting in reduced effectiveness of therapy. Potential DDIs were defined as combinations of different drugs with previously described pharmacokinetic or pharmacodynamic interactions. We chose not to describe all potential pharmacodynamic interactions. We excluded as potential interactions those combinations in which the ADR would be an exaggerated result of the intended therapeutic goal, such as the potential hypotensive effect of a combination of drugs prescribed for treatment of hypertension. We also excluded combinations

of drugs which both might cause vague subjective complaints like dizziness or vaguely described gastrointestinal complaints as a possible ADR. We excluded these because in our opinion it would misclassify overdosing of combinations of drugs with the identical intended effect as an interaction, which would in turn have resulted in an overestimation of the prevalence of clinically relevant potential interactions. Second, possible DDIs were then divided in DDIs included in the top ten most prevalent potential interactions identified earlier in 1997 by public pharmacies in the Netherlands('Top Ten' [22]) and other interactions.
Third, after the medication review the treating physicians were advised by the study physician and study pharmacist about inappropriate prescriptions and given suggestions about changes in medication that would enhance the effectiveness of therapy or address ADRs. Subsequently, we conducted retrospective chart reviews to determine which adjustments in medication regimen had been made, and whether these resulted in measurable improvements of at least 10% or reported benefit in the clinical status of the affected patients.
Descriptive statistical calculations were performed with SPSS for Windows (version 12.0, SPPS Inc.,Chicago, IL, USA).

RESULTS

807 patients were included in the study. The characteristics of these patients are shown in Table I. 513 of the patients (64 %) were taking four or more drugs. 674 (84%) patients were taking more than one drug, excluding applications for dermatological diseases. The percentages mentioned in the results presented in this section pertain to these patients.
The following were identified as potential interactions:

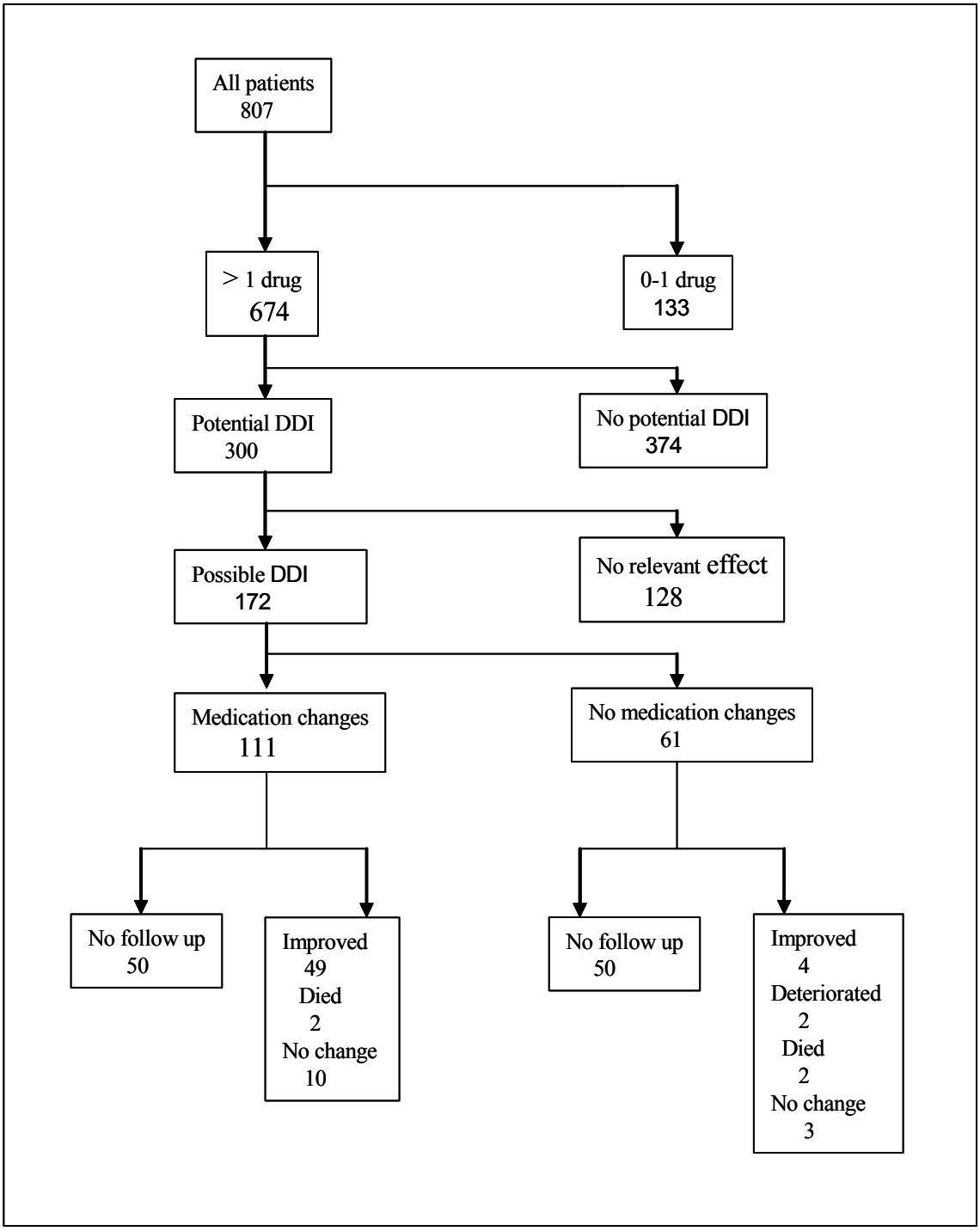
- A combination of two or more of the following drugs resulting in renal dysfunction, electrolyte disorders, hypotension, inadequately treated hypertension or fluid retention: renin-angiotensin system inhibitors ± diuretics ± NSAIDs.
- A combination of two or more of the following drugs resulting in bradycardia or hypotension: β-adrenoreceptor antagonists ± digoxin ± diuretics ± calcium channel antagonists ± renin-angiotensin system inhibitors.
- A combination of two or more of the following drugs resulting in inadequately controlled obstructive pulmonary symptoms: β-adrenoreceptor antagonists and β-sympathomimetics.

- A combination of two or more of the following drugs resulting in inadequately controlled diabetes mellitus: antihyperglycaemics and β-adrenoreceptor antagonists ± diuretics ± antipsychotics ± corticosteroids ± antibacterials.
- A combination of two or more of the following drugs resulting in sedation or inadequately treated depression: antidepressants ± antipsychotics ± benzodiazepines ± antiepileptics ± opioids.
- A combination of two or more of the following drugs resulting in anaemia or bleeding complications: NSAIDs ± salicylates ± selective serotonin reuptake inhibitors; NSAID ± salicylates ± corticosteroids ± coumarins; coumarins and antibacterials.
- A combination of two or more of the following drugs resulting in inadequately treated hypothyroidism: iron supplements and bisphosphonates ± thyroxin (levothyroxine sodium).
- A combination of two or more of the following drugs resulting in constipation: iron supplements ± antipsychotics ± calcium channel antagonists ± opioids.
- A combination of two or more of the following drugs resulting in inadequately treated gout: gout medication and diuretics
- A combination of two or more of the following drugs resulting in hypercalcaemia: thiazide diuretics ± calcium ± activated vitamin D (calcitriol).

Table I.
Characteristics of the population (N=807)

Age (y)[mean ± SD]	81.7 ± 7.4
Female (%)	67
Living (%)	
At own home,	78.5
Assisted living	15.4
Nursing home	3.7
Other 2.4	
Charlson Comorbidity Index (mean ± SD)	2.05 ± 1.46
Clinical diagnosis, history and present (%)	
dementia and mild cognitive impairment	59,2
cerebrovascular disease	21.7
parkinsonism	3.6
one or more falls in previous year	21.0
syncope	2.5
osteoporosis	14.7
diabetes mellitus	18.6
hypertension	42.8
atrial fibrillation	17.6
heart failure	16.2
coronary artery disease	25.5
urinary incontinence	25.5
Mini-Mental State Examination	20.6 ±6
(n= 608) [mean ± SD]	
Number of medications (mean ± SD) [range]	5.1 ± 3.6 [0-23]

Figure Classification of patients. DDI=drug-drug interaction



398 potential interactions were seen in 300 (44.5%) patients, with a range from one to five interactions per patient. Of these 300 patients,172 (25.5%) were clinically identified as having at least one possible ADR or a less than adequately treated chronic condition that could be to the result of a DDI. In these 172 patients, 158 possible ADRs and 78 less effective treatments that were possibly the result of DDIs were found.
In 99 (14.7%) patients, the only possible ADRs identified were those that may have resulted from enhanced drug effects, possibly caused in part by DDIs, were identified. Inadequately treated conditions, that were possibly the result of reduced drug actions secondary to DDIs, were found in 48 (7.1%) patients. An additional 25 (3.7%) patients were taking drug combinations that resulted in both possibly enhanced ánd possibly reduced effectiveness.
Pharmacokinetic interaction were possibly present in six patients: two patients taking digoxin and verapamil, three patients taking cytochrome P450 (CYP) enzyme inducers and antidepressants concomitantly, and one patient taking a combination of thyroxin and iron supplement. All other possible interactions were pharmacodynamic, such as adverse effects on renal function associated with taking NSAIDs and ACE inhibitors, or the combined use of several medications with sedating properties.
Changes in drug regimens pertaining to possible interactions were proposed or effectuated in 111 of the 172 (16.5%) patients having at least one possible ADR or a less than adequately treated chronic condition that could be the result of a DDI. Sixty-one (9.1%) of these patients returned for follow-up. Of these, 49 (7.3%) reported their condition had improved or showed improvement in, for instance, renal function after changes had been made in their medication regimen. Ten showed no change in clinical condition, one died of heart failure after a new myocardial infarction and one died of a pulmonary tumour.
In 61 patients no adjustments were made to address the possible DDI. In 14 of these patients, it was not clear why the possible DDI wasn't addressed. In 17 patients with severe heart failure and in 13 patients with several other diseases, the chosen treatment was deemed more important than the DDI. One of these patients died of heart failure, two had worsening heart failure, one died of a malignant lung tumour. In seven patients with renal dysfunction, other explanations for their renal dysfunction were deemed more important than the DDI. In ten patients the treating psychiatrist had chosen to accept the long-term

use of benzodiazepines by depressed patients. The figure shows how patients were finally classified.

The number and type of ADRs possibly resulting from DDIs leading to enhanced drug action is shown in Table II.

Table II.
Possible adverse drug reactions resulting from interactions leading to drug action

Adverse drug reaction	No. of patients taking the interacting drug	No. of patients taking the interacting drug who had their medications changed	Patients who benefited after changes to their medication regimen
Renal dysfunction and/or dehydration	65	42	18
Sedation and/or Mobility disorder	32	32	11
Hypotension	17	15	6
Bradycardia	7	7	4
Electrolyte disturbance	15	13	6
Gastrointestinal	13	13	4
Anaemia	7	6	2

The adverse effects of combinations of sedating drugs in particular were prominent in this geriatric outpatient population. In all patients taking a combination of sedatives, tapering or discontinuation of one or both offending drugs was attempted, with documented benefit in a third of these patients.

Cases of insufficient therapeutic efficacy possibly caused by DDIs that resulted in reduced drug action are shown in Table III.

Continuation of depressive symptoms in patients being treated with benzodiazepines and antidepressants was the most frequent finding. However, benzodiazepines were reduced in only half of these patients. Changes to drug regimens in patients with DDIs causing possible diminished effectiveness were associated with benefits in 13 patients.

Table III.
Interactions resulting in potential and possible decreased effectiveness of treatment and outcome of changes to drug regimen

Interactions resulting in potential reduction of effect of drugs (n = 144) [a]	No. benefiting from change in regime/no. changed
Benzodiazepines and antidepressants (n = 32)	5/13
Depressive symptoms in remission (n = 6)	
Antihypertensive drugs and NSAIDs (n = 37)	1/3
Blood pressure >160/90 mmHg (n = 10)	
Blood pressure ≤ 160/90 mmHg (n = 27)	
Thiazide diuretics and antihyperglycaemics (n = 22)	2/7
Blood glucose > 10 mmol/L (n = 12)	
Blood glucose ≤ 10 mmol/L (n = 10)	
β-Adrenoceptor antagonists and sulfonylureas (n = 21)	3/6
Blood glucose > 10 mmol/L (n = 12)	
Blood glucose ≤ 10 mmol/L (n = 9)	
NSAIDs and diuretics (n= 7)	2/5
Signs of heart failure present (n = 6)	
Signs of heart failure absent (n = 1)	
CYP enzyme inducers and antidepressants (n = 7)	1/3
Depressive symptoms present (n = 4)	
Depressive symptoms in remission (n = 3)	
Depressive symptoms present (n=26)	
β-Adrenoceptor antagonists and β-sympathomimetics (n = 7)	0
Dyspnoea present (n = 4)	
Dyspnoea absent (n = 3)	
CYP enzyme inducers and calcium channel antagonists	0
Blood pressure ≤ 160/90 mmHg (n = 3)	
CYP enzyme inducers and thyroxine (levothyroxine sodium)	0
Thyroid function well regulated (n = 2)	
Corticosteroids and antihyperglycaemics	0
Blood glucose > 10 mmol/L (n=2)	
Atypical antipsychotics and antihyperglycaemics	0
Blood glucose > 10 mmol/L (n = 1)	
Thyroxine and ferrous sulphate (n = 3)	0
Thyroid-stimulating hormone >4.7 mIU/L (n = 1)	
Thyroid-stimulating hormone ≤ 4.7 mIU/L (n = 2)	

a Treatment actually inadequate in 78 patients (55%).
CYP = cytochrome P450; mIU = million international units

Table IV shows the prevalence in the study population of the ten most frequently identified potential interactions involving public pharmacies in the Netherlands (the 'Top Ten' [22]). Eighty-four of the 158 possible ADRs effects resulting from enhanced action of drugs forming combinations listed in 'Top Ten' were seen in 73 patients. Only four DDIs resulting in less effective therapy that involved drug combinations in the 'Top Ten' were identified. Therefore, in the majority of the patients (99 of 172) the potential interactions resulting in possible ADRs or diminished effectiveness were not listed in the 'Top Ten' interactions.
Table V shows the ten most prevalent DDIs with a possible clinical relevant effect in the study.
In the next section we describe some of these results in more detail to illustrate some of the difficulties encountered when attempting to establish the occurrence of specific DDIs and formulating the appropriate response.

Table IV.
Prevalence in the study population of the ten most frequently identified potential interactions involving public pharmacies in the Netherlands in 1997 (the 'Top Ten' [22])

Top Ten of most frequent interactions in public pharmacies in the Netherlands 1997[22]	Prevalence of combination in geriatric day clinic patients using >1 drug(%)
1. ACE-inhibitors and diuretics	75 (11.1%)
2. Loop diuretics and NSAID's	22 (3.2%)
3. Verapamil and digoxin	4 (0.6%)
4. Potassium salts and potassium savers	24 (3.6%)
5. β-adrenoreceptor antagonists and verapamil/diltiazem	5 (0.7%)
6. Coumarins and NSAID's	10 (1.5%)
7. β-Adrenoreceptor antagonists and betasympaticomimetics	7 (1.0%)
8. Coumarins and salicylates	2 (0.3%)
9. Theofyllin and diltiazem	0 (0 %)
10. Valproate and phenytoin	1 (0.1%)

Table V. Prevalence of possibly clinically relevant interactions in the study

Top Ten of most frequent possibly clinically relevant interactions	Prevalence of combination in patients taking more than one drug (%)
1. Renin-angiotensin system inhibitors and diuretics	45 (6.7%)
2. Combined diuretics	32 (4.7%)
3. Antidepressants and benzodiazepines	26 (3.9%)
4. Diuretics and NSAID's	24 (3.6%)
5. β-Adrenoreceptor antagonists and antihyperglycaemics	12 (1.8%)
6. Thiazide diuretics and antihyperglycaemics	12 (1.8%)
7. Antipsychotics and benzodiazepines	7 (1.0%)
8. Opiods and benzodiazepines	6 (0.9%)
9. Antipsychotics and antidepressants	5 (0.7%)
10. β-Adrenoreceptor antagonists and renin-angiotensin system inhibitors	4 (0.6%)

Interactions with possible Adverse Drug Reactions.

Renin-Angiotensin System Inhibitors in Combination with Diuretics.
Combining a renin-angiotensin system inhibitors and a diuretics may lead to (pre)renal dysfunction, electrolyte disturbances and hypotension. In this study, a combination of ACE inhibitors and diuretics was being taken by 75 patients (11.1%). The indication for this combination was hypertension in 38 patients and heart failure in 33 patients. In three patients the indication was a combination of heart failure and hypertension. Forty patients (53%) had impaired renal function as defined by a creatinine level above the upper limit of 90 Umol/l for women and above 110 Umol/l for men. We could not establish creatinine clearance by the Cockroft formula because the patients' weights were not systematically recorded.
Hypotension (systolic blood pressure < 100 mmHg) was diagnosed in 7 (9.3%)patients, of whom six were taking the drugs for heart failure and one for hypertension. Use of the ACE inhibitor was discontinued in nine patients, resulting in partial (4) or complete (2) recovery of

renal function in six patients. Diuretic dosage was reduced or tapered in 19 patients, resulting in partial (8) or complete (3) recovery of renal function in 11 patients.
The combination of angiotensin II type 1 (AT_1) receptor antagonists with a diuretic was used by 23 patients, in all cases to treat hypertension. Of these, nine had renal dysfunction. In these nine patients, diuretic dosage was decreased with partial improvement in renal function in one patient and was increased because of heart failure in another patient.
Forty-five patients (Table V) had renal dysfunction or hypotension while using rennin-angiotensin system inhibitors combined with diuretics. In 22 patients one or both of the drugs were adjusted. In the other 23 patients the medication was not adjusted because the treating physician chose to continue treatment of heart failure or hypertension despite the possible adverse effects of such treatment on the kidney, or because the patient's renal dysfunction was ascribed to chronic renal failure and not to the use of medications.
Three patients with renal dysfunction while using renin-angiotensin system inhibitors combined with diuretics had deteriorating heart failure, one of whom died.

Loopdiuretics and NSAID's
Renal dysfunction is also the main adverse effect of the interaction between loop diuretics and NSAIDs. This combination was used by 22 (3.3%) patients. Of these 13 (59%) had impaired renal function. In nine patients either the NSAID (five) or the diuretic (four) was discontinued with (partial) recovery of renal function in four (44%) cases. NSAIDs were continued if the pain couldn't be relieved with paracetamol (acetaminophen). One of the patients experienced hydronephrosis as a result of a malignant tumour, another patient died of sepsis. In the other patients the reversibility of renal dysfunction couldn't be evaluated because they did not return to the hospital for follow-up.

Verapamil and Digoxin
Verapamil increases the plasma digoxin level, and both medications by themselves can cause bradycardia. Only four patients in this study were taking this combination for atrial fibrillation. All were suspected of digoxin toxicity because of bradycardia or anorexia. Three of these patients had renal impairment and two were hypokalaemic. Clinical symptoms led to discontinuations of digoxin in three patients and discontinuation of verapamil in one patient. Bradycardia improved in two

patients, one patient died of a myocardial infarction and the fourth did not return for follow-up. Plasma digoxin concentrations were measured in only two patients: 0.7 and 1,0 ug/l, respectively, which are not indicative of toxicity but do not preclude an ADR caused by a therapeutic level.

Valproic Acid and Phenytoin
An interaction between valproic acid and phenytoin may result in a higher phenytoin level through inhibition of CYP2C9 enzyme by valproic acid. The only patient who was taking both drugs had a low normal phenytoin level (8.0 mg/l).

Combinations of Psychotropic Medications
In 32 patients, various combinations of sedatives, antidepressants, neuroleptics and/or opioids resulted in sedation, apathy or falls. In all patients the use of psychotropics was tapered or discontinued with good result shown at follow-up in nine of them.

Combinations with Risk of Anaemia
In seven patients, DDIs between anticoagulants, NSAIDs, corticosteroids, selective cyclo-oxygenase (COX)-2 inhibitors (coxib) and selective serotonin reuptake inhibitors (SSRIs) might have contributed to existing anaemia.
Concomitant use of SSRIs is important in this context because SSRIs in combination with NSAIDs are associated with an increased risk of bleeding.[28]
In five of these seven patients with anaemia who were taking combinations that increase the risk of anaemia, NSAIDs (two) or selective coxibs (three) were discontinued or reduced. Anaemia improved in one of these patients; the other four did not return for follow-up.
In one patient, who was also taking an SSRI, an NSAID and coumarin, a proton pump inhibitor was started with a slight increase in haemoglobin. This patient died of malignancy. Finally, one patient taking a combination of salicylate with acenocoumarol, had no changes made to his treatment regimen.

Interactions resulting in reduced effect of treatment

Antidepressants and Benzodiazepines
Treatment of depression was the most likely regimen to be made less effective because of a reduced treatment effect caused by DDIs. (Table III). Eighty-one percent of patients taking a combination of benzodiazepines and antidepressant drugs still showed some signs of depression. Benzodiazepines were reduced in only 12 of them.

Sympaticomimetics and β-Adrenoreceptor Antagonists
In two of four patients with dyspneu treated with β-adrenoreceptor antagonists and sympaticomimetics, other causes for shortness of breath besides chronic obstructive pulmonary disease, such as pneumonia and heart failure, were present. In two patients, sotalol was changed to selective β-adrenoreceptor antagonists with either an unknown or no effect on the shortness of breath.

DISCUSSION

Potential drug interactions causing enhanced or reduced drug action were frequent in the study population, as was expected given the presence of known risk factors[1,4,-8] such as high co-morbidity burden (mean Charlson Comorbidity Index 2.05) and the frequent presence of polypharmacy (64 %).
However, some considerations must be kept in mind when interpreting the results of this study. First, the study describes a selected population of geriatric patients, whose drug regimens were evaluated when they had been using the drug combinations on a long-term basis; this may explain differences between this study's results and data pertaining to pharmacy alerts on first prescriptions and from primary care. Second, it remains difficult to ascertain whether a possible ADR or seemingly less effective drug treatment can be ascribed to a DDI rather than the use of single drugs or co-morbid conditions. These issues will be discussed below.
In this study, fewer potential DDIs and ADRs listed in the 1997 'Top Ten' for public pharmacies in the Netherlands[22] were identified than events that could have been due to other interactions. In addition, most inadequately treated conditions possibly caused by reduced drug effect as a result of DDIs identified in this study, were not found in the 'Top Ten'.

A more recently published study, based not on the national database, but rather on prescriptions filled at 63 Dutch pharmacies, showed that in 2004 approximately 6% of all prescriptions generated a DDI alert.[29] The most frequent 20 alerts only partially overlapped with the 'Top Ten' used in the current study. As with our results, particularly cardiovascular drug classes and NSAID's were frequently identified in this study. Frequent alerts in 2004, not present in the 'Top Ten' in 1997, were the combinations ACE inhibitors with NSAID's, NSAID's with SSRI and corticosteroids with NSAIDs. These combinations did not give rise to frequent possible DDIs in our study. As in the 1997 'Top Ten', no drug alerts pertaining to sedative use were presented in the recent study.[29]

Differences between the prevalence of drug alerts for potential drug interactions in public pharmacies as opposed to the frequency of possible interactions in our geriatric outpatient population may be explained by referral bias. Geriatric patients use more medications and cognitive decline is often an important reason for psychotropic medication use. In addition, we identified possible interactions involving drugs used on a long-term basis, whereas public pharmacies generally focus on potential interactions of newly prescribed drugs. Some of these potential interactions are probably dealt with by general physicians changing drug regimens in response to drug alerts by the pharmacies and hence are no longer present when the relevant patients visit our outpatient clinic.

We showed that in a geriatric outpatient population, many possible interactions can be identified by addressing and evaluating possible ADRs and the insufficient effect of medications through the use of a structured instrument such as the MAI. Use of a computerized drug-interaction program might have identified even more drug combinations with the potential for interaction, given that up to 70% of patients in primary health care are reported to be exposed to drugs with the risk of drug interaction.[30] However, because we did not find these by the analysis of the adverse effects caused by increased or diminished drug action, these would have been classified as irrelevant in this study.

The relevance of potential interactions can be determined only by clinicians who have up-to-date knowledge of both the drugs used and the clinical condition of the patient. Close cooperation between pharmacies and treating physicians is mandatory. Recently, it was shown that public pharmacies in the Netherlands can remain unaware of ADRs recorded during hospital stay because of poor transfer of infor-

mation to primary carers.[3,31] In another study, physicians judged 36.5% of drug alerts to be inappropriate and overrode 89.4 % of high-severity drug alerts.[32] Therefore, drug interactions for inclusion in computerized drug interaction surveillance systems should be chosen selectively.[30]

This study shows that careful evaluation of drug regimens can result in reductions in renal dysfunction, hypotension and sedative use with good result being obtained in at least 7% of geriatric outpatients who taking more than one drug. However, these findings apply to patients who returned for follow-up and whose improvement was noted by the treating physician in the medical records. We don not know whether the same proportion of the other patients who continued to be treated by their general practitioner benefited from our interventions, and it is therefore possible that the percentage of patients who benefited might have been higher for the total study population.

Possible ADRs resulting from DDIs in the study population were identified most frequently in relation to the use of cardiovascular drugs and sedating agents. This could be expected, because the majority of the 'Top Ten' interactions in 1997[22] and DDI alerts in 2004 [29}] involved combinations of cardiovascular drugs. Our population differed from the general population in terms of the high prevalence (59.2%) of cognitive decline in the sample, a factor that may have given rise to behavioural disorders and a concomitant increased likelihood of use of psychotropic medication. Neuropsychiatric impairment as a frequent adverse effect of DDIs has been previously shown in geriatric inpatients.[10]

Few patients in the study population had anemia that was possibly caused by drug interactions. This was surprising, given that gastrointestinal bleeding is one of the most frequent causes of hospitalisation due to preventable ADRs.[3,4,12,33] Such serious complications are probably either caused by one drug, or by combinations of drugs not prescribed on a long-term basis, such as coumarins in combination with antibacterials.[34,35]

Over 60% of the patients aged > 75 years in the Dutch general practices are prescribed benzodiazepines, β-adrenoreceptor antagonists, ACE inhibitors or loop diuretics.[36] Yet, Veehof [37] identified less potential interactions in < 3% of the elderly population of general practice in the Netherlands. In the current study, 25,5% of patients taking more than one drug were identified as having possible DDIs, as determined by possible ADRs or diminished effects of drug therapy. The higher prevalence of possible interactions in this study was probably caused

by selection of more vulnerable and elderly patients as shown by the higher mean number of drugs (5.1 vs. 3.9 in the study by Veehof et al[37]). Comorbidity or polypharmacy can be one of the reasons for referral of patients to the geriatric department.

Not all the adverse events or cases of reduced therapy effectiveness identified in this study could be attributed to DDIs with certainty. The physician who prescribes medications that give rise to potential interactions is in a better position to judge causality than the physician who identifies the adverse event some time later. The physician in the latter case must take into account that the drugs prescribed could well be innocent bystanders and that the symptoms were caused by comorbidities such as atrial fibrillation and heart failure in dyspnoeic patients taking β-adrenoreceptor antagonists or longstanding hypertension in patients with current renal dysfunction. Also, the identified adverse effect might well have been the result of one of the agents, rather than the combination.

It is tempting, for example, to ascribe all adverse effects of ACE-inhibitors and the diuretics to use of these drugs in combination. However, the prevalence of adverse effects of single agents in patients with similar conditions may be just as high. For example, the prevalence of renal dysfunction in women using only diuretics was 49%, only ACE inhibitors 17%, and neither of both 20.3%. Thus, the small number of patients whose renal function improved after discontinuing one of these two drugs might have been experiencing the adverse effect of that drug only or the combination of the drug with disease such as dehydration, rather than adverse effects from the combination of the two suspected drugs *per se*. Nevertheless, discontinuing one or both of the drugs possibly causing renal dysfunction is worthwhile as an attempt to preserve renal function, and even in those patients who did not improve, this step may have prevented further declines in renal function.

It is also important to note the fact depressive symptoms, for instance, were still present in patients taking a combination of antidepressants and benzodiazepines does not necessarily mean that absence of benzodiazepine use in these particular patients would have resulted in complete remission of their depressive symptoms. We therefore choose to label the suspected unwanted effects of drug combinations ‘possible ADRs’ and ‘possible reduced effectiveness’ to avoid the possibility of overestimating the prevalence of actual drug interactions.

Few important pharmocokinetic interactions were identified in the study. Lack of ADRs resulting from pharmacokinetic interactions may

be explained by non-compliance, or careful titration of the drugs by the treating physician, as illustrated by appropriate levels of a combination of valproic acid and phenytoin when these drugs are used in combination. Furthermore, pharmacies may adjust drug regimens to avoid pharmacokinetic interactions by separating ingestion of, for instance, thyroxin and ferrous sulfate, or bisphosphonates and calcium-salts during the day.

Patients' history of medication use and the duration of symptoms and abnormal laboratory values could often not be confirmed due to the effects of patient cognitive decline. Geriatric patients generally tend to avoid hospitals. We therefore have a policy of asking the general practitioner to follow up changes in medication. Consequently, this study was based largely on cross-sectional data with follow-up information available for only 55% of patients whose drug regimens were changed. We did not rechallenge patients when drugs were discontinued and subsequent improvements were noted because the adverse effects in question are all well documented in the literature. The cause and effect relationship of specific symptoms with drug interactions in this aged and frail population remain difficult to establish.

However, it can be argued that use of any recognized drug combination in the presence of inadequately controlled symptoms or possible side effects merits the attention of treating physicians and can therefore be justifiably called clinically relevant. The possibility of DDIs should be evaluated not only at the introduction of a new combination of drugs but also particularly when an ADR occurs or drug therapy does not seem to be effective.

CONCLUSION

Nearly half of the geriatric outpatients using more than one drug in this study were candidates for potential DDIs. A quarter of these patients had possible adverse events or diminished treatment effectiveness which may have been at least partly caused by DDIs, although co-morbidity and ADRs from use of just one of these medications may also have contributed to less desirable treatment outcomes. Possible interactions can be identified through clinical evaluation with using the MAI and without the use of a computerised drug-interaction program. The majority of possible interactions identified in this study were not listed in 'Top Ten' interactions described by public pharmacies in the Netherlands in 1997 and 2004, a finding which reflects selection in this study of geriatric patients characterised by frequent psychiatric co-morbidity and the special factors that need to be considered when evaluating drug regimens in this patient group. Finally, in this study, adjustment of the drug regimen was beneficial in at least 7% of the patients using more than one drug and in 80% of the patients with possible drug interactions.

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Chapter 2.5

Do geriatric outpatients adhere to medication changes advised after assessment? An exploratory pilot study.

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ABSTRACT

The most frequent intervention after Comprehensive Geriatric Assessment (CGA) is adjustment of medications. Adherence to recommendations is often incomplete. Patients at high risk of nonadherence should be identified.

The objective was to explore if changes in drug-use after CGA are carried out by the patient and to identify factors influencing non-adherence.

Co-morbidity and medication use were recorded. Patients, and when cognitively impaired, a caregiver, were questioned about advised changes. Drug-use before and after CGA was assessed. Patients were asked whether they would discontinue their drugs either with or without consulting their physician. Univariate logistic regression analysis to identify factors influencing non-adherence, was performed with SPSS.

Forty patients were included. Of the changes in medication advised, 90 % were reported to be carried out. 65 % of the patients were compliant. Only the presence of a caregiver was associated with reported complete adherence to drug therapy.

Most patients can't describe for how long they will have to continue taking the drugs that are prescribed to them. Most geriatric patients carry out changes in medication made after CGA. Supervision by caregivers may explain a high rate of reported adherence despite the presence of polypharmacy and cognitive decline.

In the absence of caregivers special attention should be paid to adherence to medication changes. Information about intended duration of drug therapy should be improved.

INTRODUCTION

The prevalence of polypharmacy increases with age. Most commonly it is defined as the concomitant use of four or more medications.[1] Of the patients over 65 years living at home in the Netherlands, 8 to 22 % use more than 4 drugs. This percentage is reported to be even higher, up to about 40 %, in patients in nursing homes.[2] In geriatric outpatients who were presented at our clinic the prevalence of polypharmacy was 64%.[3]

Both polypharmacy and non-adherence have been shown to be risk factors for adverse drug events, and medication related hospital admissions.[1,4,5] Geriatric patients may be especially at risk for non-adherence and subsequently for hospital admissions which might have been prevented if they had adhered to their prescribed drug regimen. A frequently mentioned cause of non-adherence is forgetfulness.[5] Besides accidental omissions, elderly patients may also be non-adherent for reasons with a rational basis, for instance reducing (too high) doses to address perceived side-effects.

Earlier studies have shown that recommendations after comprehensive geriatric assessment (CGA) often are not carried out. In CGA, the health status and functional capacities of elderly patients are evaluated. Interventions may comprise changes in drug regimen and a range of other recommendations on for example life style, physical exercise, diet and use of support services. Adherence rates with recommendations by a geriatric service range from 46-76%.[6] Adherence can be influenced by several factors. Implementation of CGA recommendations on medication management by physicians is more likely to be followed compared to more complex or preventive recommendations and has been reported to be 79%.[7] A key predictor for adherence appears to be a stable caregiver. Patients who self-administer their medications may be less adherent.[6,8,9] Follow-up by the geriatric service has also been shown to be one of the determinants of outcome after geriatric consultation.[10]

Adjusting medication is one of the most frequent interventions in our outpatients. Examples are the discontinuation of contraindicated drugs, changing doses in response to the clinical condition of the patient, or adding drugs because of newly diagnosed or hitherto undertreated diseases.[11] We wanted to know whether these changes are understood and carried out by our outpatients and their caregivers, since these instructions could easily be forgotten or misunderstood due to the complexity of other proposed diagnostic procedures and

interventions being discussed after CGA. A distinction has to be made between adherence to recommendations made on a specific moment and adherence to medication prescriptions on a chronic basis.

Adherence to chronic medication use in the elderly is reported to be between 40-100%.[5,9] The reported adherence is influenced by the criteria used and the studied patients: non-adherence rates in a given population may range from 20 to 70% depending on the definition.[12] The use of more drugs, the frequency of drug intake per day, prescriptions from more than one doctor, probability of dementia and living alone are among the factors correlated with deviations from the drug regimen.[12,13]

In this study we wanted to explore how many patients carried out the advice given on changes in medication use after CGA, and which were the most important factors influencing the adherence to these specific recommendations. There are several methods of establishing adherence over a time period like pill counts, electronic counting medication dispensers, checking on refills at the pharmacy or interviewing the patient. Neither of these methods can reliably rule out overestimating adherence, since they are prone to socially desirable reporting or feigned behaviour. For instance: results from interviews correlated with serum digoxin concentrations while pill counts did not.[14]

Because there is no real gold standard in measuring adherence,[15] the percentages reported for non-adherence remain an estimate. In community dwelling elderly the combined use of computerized medication records and direct questioning are advocated as optimal. Direct questioning alone underestimates non-adherence.[5] However, it can be assumed that patients who report to be non-adherent indeed are.[9] 80% of true non-compliers can be identified by interview.[16]

We chose for the interview to assess adherence in this prospective pilot study. For our main objective, to establish if advised changes are understood and remembered directly after CGA, the personal interview is a reliable tool, because it can be verified if the proposed changes are described accurately after the CGA. Whether the changes in drug use persevere on the long run is more difficult to establish because this will be influenced by adherence to chronic medication regimens and changes in the medical condition of patients. In this pilot study, an additional question to assess adherence to the drug regimen in general for our population was the most practical to organize.[9]

METHODS AND PATIENTS

The study was part of a prospective descriptive study at the geriatric day clinic of the Slotervaart Hospital in Amsterdam. In this large department of a teaching hospital geriatric assessment is offered during a one day program with follow up if necessary for further diagnosis or treatment. Comprehensive Geriatric Assessment (CGA) consists of a medical history, medication review, physical and functional evaluation, laboratory investigations, EKG and Chest X-ray.

Reasons for referral by the general practitioner are most frequently cognitive decline and/or functional decline. Medication use was evaluated with the MAI index[17] and the updated Beers criteria[18] at the time of the first visit of the diagnostic day clinic. With the MAI index, the clinician scrutinizes the drug regimen for the presence of possible inappropriate prescriptions and weighs the clinical relevance of the 10 items. Separate items are for instance indication, dosage, drug duplication, drug-drug interactions, and drug-disease interactions. The treating physicians used the MAI index to identify inappropriately prescribed medication and were advised by the study physician (LT) and study pharmacist (SF) regarding changes in medication. The Beers criteria lists drugs and drug-disease combinations which are contraindicated in the elderly because of frequent adverse drug reactions.

Medication use and changes, demographic data, Mini Mental State Examination score (MMSE)[19], medical history and co-morbidity (Charlson Index)[20] were recorded. The Charlson Comorbidity Index[24] is a measure of the presence of multiple co-morbid diseases like diabetes, heart failure, malignancy and others.

In this usual care setting of CGA, after the first intake, patients and their caregivers receive a lot of information. Advice on drug use and changes in drug regimen is part of the concluding discussion at the end of the day. Besides changes in drug regimens, recommendations may me made among others about consultations by other medical specialists and other disciplines like physiotherapists or occupational therapists, further diagnostic procedures indicated, starting a diet, use of elastic stockings, physiotherapy, changes in living accommodations etc.

When new or other drugs are deemed indicated by the treating doctor, the patient personally receives a handwritten prescription which must be delivered subsequently to the public pharmacy. The general practitioner is notified of medication changes by a handwritten note, sent the same day and a more elaborate report later on. Important changes

are discussed with the referring physician by telephone on the same day.
Patients were asked to participate in this pilot study if they were older than 60 years, used at least one prescription drug after their visit to the hospital for CGA, a medication change was suggested and they lived in or near to Amsterdam. They were excluded if no appointment could be made or no caregiver could be interviewed in the case of cognitive decline.
Patients were either interviewed by telephone or when information was incomplete visited at home between two and four weeks after their visit. In cognitively impaired patients a caregiver was asked to be present. In a semi-structured interview with open-ended questions the patients were asked to tell and show which drugs were used, to explain the reason, and to describe the frequency of not taking or forgetting (part) of the medications. Asking the patients about their medication use in a non-judgmental way without leading questions enhances the validity of their answers.[21] Furthermore the patients were asked to tell whether they would discontinue their drugs either with or without consulting their physician. It was noted whether aids for medication use like boxes were used.
Non-adherence was defined as a reported deviation from the prescribed regimen at least once a week or more.
Recommendations about other interventions were recorded from the patient notes.
Univariate logistic regression analysis to identify factors influencing non-adherence, was performed with SPSS for Windows (version 11.0, SPPS Inc.,Chicago, IL, USA).

RESULTS

Patients
Between 24th of May and 13th of August 2004, 166 patients visited the geriatric day clinic of the Slotervaart Hospital for the first time. Forty patients and/or caregivers were eligible and willing to participate. Twenty-four were visited at home at the time of the appointment, sixteen could answer all questions by telephone. The characteristics of these patients are shown in Table I.

Table I.
Characteristics of the population, (N=40)

Mean Age, years mean ± SD	81.2 ± 6.4
Female %	65%
Living %	
At own home,	72.5
Assisted living/Nursing home	27.5
Charlson Comorbidity Index, mean	2.1
Range	0-4
Reason for referral	
Cognitive decline	11
Somatic complaints	13
Combination of somatic and cognitive problems	16
Mini Mental State Examination	22.2 ±6.1
(n= 34) mean ± SD	
Number of medications, mean ± SD	5.3 ± 2.7
and range	0-12

Twenty-seven were referred for cognitive evaluation,16 of whom also had somatic complaints. Twenty-five (62,5%) had more than 6 years of schooling.
Fourteen patients took their medication without help from others, 13 were assisted by family members, 13 by community nurses. Of the 26 people assisted, 24 were aided with their drug ingestion on a daily basis. Eleven used a medication box, 8 of whom also were aided by other people. 82.5 % (33) used four or more drugs.
In 6 patients there was no MMSE-score because they showed no signs of cognitive decline.

Adherence to CGA recommendations on changes in medication
After comprehensive geriatric assessment a mean of 2.8 changes in medication regimens per patient were proposed. Of these changes, 90% were reported to be followed. 77.5 % of the patients had adjusted their medication use as the geriatricians had prescribed. Two patients had not carried out any of the advice. One patient was depressed and stated she did not feel like it, the other was a patient with cognitive decline and alcohol abuse who refused any assistance in his home and presumably stuck to his old medication regimen from habit. Be-

sides medication changes, a mean of 2.4 (range 0-7) other interventions like referral to a neurologist or recommendations like starting physiotherapy or day care were discussed.
Because there were only 9 patients included whose medication was not adjusted by them as advised after CGA, no further statistical analysis was possible.

Reported adherence to and knowledge about chronic drug prescription regimens

Of the patients, 65% were classified as adherent to their drug regimens as they reported to deviate from the prescribed medications less than once a week. Only the absence of a caregiver who checked medication use was associated with reported non-adherence to drug therapy in univariate analysis (O.R. 0.147, 95% C.I. 0.035-0.627, p-value 0.010). Polypharmacy, MMSE and the presence of a medication distribution device had no significant influence on non-adherence in this small population (Table II). Because of the small number of patients no other variables were entered.
Twenty-four (60%) of the patients properly described the reasons for which their medications were prescribed, 9 (22,5%) knew none of the reasons for their medication use, but in all of them the changes had been carried out. The others could tell for only a part of their drugs why they had to take them. All patients except two, took their medication on fixed times.
Of the patients, 90% reported they would only make changes in their drug regimen after consulting their physician. Sixteen (40%) could tell for how long they should continue taking the medication, the predominant answer was not a time period, but sounded as an intention: “as long as my doctor tells me to”.

Table II.

Factors influencing non-adherence, univariate analysis

	Odds Ratio	95% CI	p-value
Polypharmacy	0.667	0,126-3.516	0.633
MMSE score	2,133	0,519-8,761	0,293
Medication box	0,756	0,184-3,105	0,69
Supervision	0,147	0,035-0,627	0,010*

*:p<0.05

DISCUSSION

Adherence to recommendations given by geriatricians is often incomplete.[7] Our small pilot study shows that the majority of geriatric outpatients intends to adhere to the advice on medication use as given by their doctors. Even those patients who do not know why they have to take certain prescriptions or for how long told us they would follow their doctor's orders. An adherence of 90 % of the medication changes in 77.5% of our patients is comparable to the results of Bogardus.[7]

Reported non-adherence is low despite the high frequency of polypharmacy. This probably is an optimistic estimation of adherence in geriatric outpatients in general. It can be assumed that the patients who were not willing or able to enter in this study are more likely to be non-adherent and do not concord with proposed changes in medication. Adherence may also be overestimated by the patients who did participate, giving socially desirable answers. However, by asking open ended, non-threatening and non-judgmental questions, we do think we have established a reasonable correct estimate of the number of patients following the advised changes in this sample, though the reported adherence rate to the drug regimen after a longer period of time will probably decline since adherence tends to deteriorate after longer use of chronic medication.[15,21] Only 24% of the patients who visited the diagnostic day clinic during the study period were included. The presence of polypharmacy in this sample was more frequent than in the whole day-clinic population of 2004 (82,5% versus 64%). This may be explained by selection bias since they were included when changes were made in drugs prescription after CGA and this may be more frequent in patients with polypharmacy. Since their other demographic and medical characteristics including cognition showed no relevant differences with our outpatient population as a whole, we do consider them representative of "usual" geriatric outpatients.[3]

The presence of supervising caregivers probably explains the relatively low reported non-adherence.[7] Adherence to the changes on the long run will probably be lower. When drugs have been discontinued because of adverse drug reactions, approximately a quarter are re-prescribed within 6 months.[22] This emphasizes the importance of concordance between geriatricians, general physicians, caregivers and patients on the reasons for discontinuing and restarting medication after CGA.[23]

We did not find deterioration in cognition to be contributing to non-adherence in this population. This may be explained by insufficient sample size. It may also be explained by the observation that in these patients this risk factor, known from previous studies[5], was already effectively accounted for by the supervision of medication use by family or community services, even before a diagnosis of dementia was established.

Beckman has shown that in an elderly population, 66.6% had at least one limitation of capacity related to taking medicine. Of these 31.8% lived alone with no home-help.[24] This highlights the importance of establishing the capability of patients to understand their medication regimen and willingness to actually take the drugs, and provide assistance when needed.

One might assume that if adherence is improved by supervision, this would result in better outcomes, since poor adherence accounts for worsening of disease states, death and health care costs.[15] However, 79% of patients aged 70 and over can adequately recognize adverse effects of drugs.[25] If part of non-adherence is an appropriate reaction of a patient to experienced side effects or overdosing, adherence imposed by caregivers might result in more adverse drug reactions. Whether this is a clinically relevant phenomenon remains to be studied.

Noteworthy is the large part of patients and caregivers who don't know for how long the prescribed medication is intended to be used. This does not imply they have not been told, since 40-80% of medical information provided by health care practitioners is forgotten immediately.[26] The ageing process engenders difficulty in encoding and subsequently remembering medical information, especially that which contradicts pre-existing beliefs. In our study, only 2 patients knew how long they should take their anticoagulants, and they did not know the expected period of use of their other prescriptions. Even when patients reported they knew how long they would have to continue, their answer showed they could not describe the intended length of treatment precisely, but stated intentions like "until the doctor says I should stop". This clearly needs to be improved.

Improving adherence will remain a challenging task since the effects demonstrated thus far by interventions involving cognitive or educational strategies are small.[27]

Our study confirms the importance of caregivers for carrying out medication changes and adherence. Patients are at risk for non-adherence if the continuity of drug-use and implementation of changes depends

only on communication with the general physician and caregivers are not present at the time of CGA.

CONCLUSION

The large majority of geriatric outpatients and their caregivers effectuate changes in drug regimens after comprehensive geriatric assessment. This study confirms that the presence of caregivers supervising medication is an important factor in establishing adherence.

Practice implications

In the absence of caregivers special attention should be paid to adherence to medication changes. Although the adherence to our recommendations on medication changes is acceptable, more attention should be paid in our clinic to informing patients and their caregivers why drugs are prescribed and the intended length of treatment. In our opinion medical education about the aims of the medication prescribed should be extended to the primary caregivers and supported by written information. We plan to implement this in our clinic and evaluate the effects on adherence in a larger follow-up study.

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Chapter 3

Treatment of cardiovascular disorders

Chapter 3.1

Treatment of hypertension in a geriatric outpatient population

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ABSTRACT

Treatment of older hypertensive patients has been controversial. The recently published HYVET trial, however, has shown that lowering blood pressure in people 80 years or older may result in decreased morbidity and mortality.

We investigated how many of our geriatric outpatients aged 80 years and older, were being prescribed medication for hypertension. Secondly, we judged how many of these patients would have been included in or excluded from the HYVET trial, based on their co-morbidity. Thirdly, we investigated how many of our hypertensive geriatric patients reached the goals for adequate blood pressure control as set in HYVET. Lastly, we investigated whether reaching these goals was associated with number and types of antihypertensive medication and being eligible for HYVET. We retrospectively included geriatric outpatients, aged 80 years or older, whose history showed hypertension and were treated with anti-hypertensive medication or showed hypertension, defined as systolic hypertension of 160 mmHg or higher on their visit, but not treated with antihypertensives. Medication use and changes, demographic data, medical history and co-morbidity had been previously registered prospectively.

During 2004, 518 geriatric patients 80 years or older visited the geriatric diagnostic day clinic. In this cohort, 141 of the 147 patients who could be included for this study with hypertension in the history were treated with antihypertensive medication (95.9%). Of these patients, 52 (35.4 %) would have been eligible for HYVET, 95 patients (64.6%) would have been excluded. The 147 geriatric patients included in our study showed more co-morbidity than the HYVET population e.g. dementia, strokes and cardiovascular disorders besides hypertension. Adequate blood pressure control defined as systolic blood pressure lower than 150 mmHg and diastolic blood pressure lower than 80 mmHg, the target pressures of HYVET, was seen in 50.3 % of the patients. The patients who would have been excluded from HYVET had similar levels of blood pressure control as the patients who would have been included.

The only significant difference between the patients who showed an adequately controlled blood pressure and those who did not was the mean number of antihypertensive medications: 2.2 (± 1.0) versus 1.8 (± 1.1) respectively.

Although the HYVET study has provided important evidence showing benefit in the treatment of relatively healthy older people, results of treating hypertension in geriatric patients may be less beneficial than shown in this trial, since most of them wouldn't have been included. Yet, almost all of these patients were already being treated before the study was published. The results of HYVET will probably not increase the intention to treat hypertension but may induce more intensive treatment to reach systolic blood pressure below 160 mmHg. Our study supports the current advice to treat hypertension with more than one antihypertensive if adequate control isn't achieved with one low dosed antihypertensive. However, we also emphasize that further studies are needed including more vulnerable geriatric patients to justify antihypertensive treatment in this patient category.

INTRODUCTION

Treatment of older hypertensive patients is controversial. There has been uncertainty regarding target blood pressure in the very old, and concerns exist that excessive lowering of blood pressure could result in adverse events like falls, strokes and cognitive problems, causing additional morbidity and mortality.[1] In observational studies, blood pressure was demonstrated to be strongly and directly related to vascular and overall mortality without any evidence of a threshold down to at least 115/75 mmHG. The proportional differences in vascular mortality were about half as extreme at ages 80-89 years as at ages 40-49 years but the annual absolute differences in risk were greater in old age.[2] This means a beneficial effect of treatment may be greater if expressed as an absolute risk reduction in older people, because older people have a greater base line risk of cardiovascular disease without treatment than younger people. Drug treatment of isolated systolic hypertension showed a larger benefit in patients aged 70 or more and those with previous cardiovascular complications.[3] However, there have also been population based studies which showed low systolic blood pressure to be associated with higher risk of death[1,4] or did not show any effect of hypertension on mortality from cardiovascular causes or all cause mortality.[5] The observed inverse relationship between blood pressure and the risk of death among people aged 80 years of age and older may reflect an increased risk of antihypertensive treatment or reverse causation due to conditions causing lower blood pressure like heart failure.

A subgroup meta-analysis of antihypertensive treatment in very old people, aged 80 years or older suggested that treatment prevented 34% of strokes and reduced rates of major cardiovascular events and heart failure by 22% and 39% respectively. However, there was a non-significant 6% relative excess of death from all causes and the meta-analysis was not robust; one additional properly designed trial with no treatment effect shown would be enough to make the result non-significant. Yet the authors concluded that their results did not suggest an age threshold above which hypertension should not be treated.[6] The HYVET study aimed to resolve these persistent areas of clinical uncertainty about the relative benefits and risks of antihypertensive treatment in patients 80 years and older.[7] This trial, with 1933 patients in the active-treatment group, not only showed a 30% reduction in the rate of fatal or nonfatal stroke and a 39% reduction in the rate of death from stroke, but also 21% reduction in rate of death from any cause.

More than 90% of these patients were known to be hypertensive, of whom approximately one third had not been previously treated.
We have now investigated whether the results of this landmark trial, which seems to have solved the dilemma of clinicians treating hypertension in the very old, could affect our clinical practice. Therefore we studied:

1. how many of our patients aged 80 years and older, were being prescribed medication for hypertension prior to geriatric evaluation;
2. how many of these patients would have been included in or excluded from the HYVET trial, based on their co-morbidity, to establish whether these trial results could be applicable to our outpatient population;
3. how many of our patients reached the goals for adequate blood pressure control as set in HYVET, and
4. if reaching these goals was associated with number and types of antihypertensive medication and being eligible for HYVET.

METHODS AND PATIENTS

The study was retrospectively conducted with the data acquired in a prospective descriptive study at the geriatric diagnostic day clinic of the Slotervaart Hospital in Amsterdam. In this large department of a teaching hospital geriatric assessment is offered during a one day program with follow up if necessary for further diagnosis or treatment. Reasons for referral by the general practitioner are most frequently cognitive decline and/or functional decline. Medication use and changes, demographic data, medical history and co-morbidity were registered prospectively.
Included were those patients, aged 80 years or older, whose history showed hypertension and were still treated with antihypertensive medication or were still showing hypertension, defined as systolic blood pressure (SBP) of 160 mmHg or higher on their visit, when not treated with antihypertensives.
Patients were excluded if (1) insufficient data were present on their medication use, (2) no blood pressure was recorded, or (3) the general practitioner (GP) had abstained from antihypertensive treatment for a documented reason.
It was recorded how many antihypertensive drugs the patients used and from which classes. Patients were classified as having not been potential participants in the HYVET trial by the presence of contraindi-

cations like heart failure, a serum creatinine level greater than 150 µmol per liter, a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, a diagnosis of gout or clinical dementia.
The treatment goal was defined as achieved when the systolic blood pressure was less than 150 mmHg and the target diastolic blood pressure (DBP) was less than 80 mmHg.

Statistical evaluation
Continuous variables were analysed with Student-T tests, dichotomous variables using chi-square testing with SPSS for Windows (version 16.0, SPPS Inc., Chicago, IL, USA).

RESULTS

During 2004, 807 patients visited the geriatric day clinic for the first time. Of these, 518 were 80 years or older of age. In 149 of these patients (29%) the referring physician or the patient described hypertension in the history. One patient was excluded because she had previously refused any treatment. In one other patient no blood pressure was recorded. So, included were 147 patients, who were either using antihypertensives or the SBP was still ≥ 160 mmHG. Antihypertensive medications were prescribed to 141 patients (95.9%). Six patients were not treated on referral, and still had a systolic blood pressure of above 160 mmHg. The characteristics of the patients are shown in Table I, juxtaposed to the characteristics of the patients included in the active treatment group of HYVET. In our population, there was a preponderance of females, and more patients had strokes, myocardial infarction, heart failure, diabetes mellitus and dementia in the history.
Fifty-two (35.4 %) of these patients would have been eligible for HYVET. Excluded would have been 95 patients (64.6%), the most important reason for exclusion would have been the presence of dementia in 70 patients (47.6 %).Systolic blood pressure lower than 150 mmHg and a diastolic blood pressure lower than 80 mmHg, the target pressures of HYVET, were found in 78 patients (50.3 %). The patients used a mean of 6.3 (±3.4) medications, of which a mean of 2.0 (±1.1) were antihypertensives. The history of these 147 geriatric patients more frequently showed strokes, myocardial infarctions, heart failure and diabetes than the patients in HYVET.

The only significant differences between the patients who showed an adequately controlled blood pressure and those who did not was the number of antihypertensive medications (Table II).

Table I.
Characteristics of the population

	Study population (n=147)	HYVET active treatment group (n=1933)
Mean Age, years mean ± SD	85.8 ± 4.1	83.6 ± 3.2
Female sex no.(%)	115 (78.2)	1174 (60.7)
Stroke no.(%)	33 (22.4)	130 (6.7)
Myocardial infarction no.(%)	11 (7.5)	59 (3.1)
Heart failure no.(%)	17 (11.6)	56 (2.9)
Diabetes no.(%)	31 (21.1)	132 (6.8)
Dementia no.(%)	70 (47.6)	0*
Serum creatinine –µmol/l (± SD)	104 (±38)	88.6± 20.5
Antihypertensive treatment no.(%)	141 (95.9)	1241 (64.2)
Blood pressure-mmHg		
Before treatment	unknown	173 ± 8.4/90.8±8.5
While on treatment	149.0 ± 28.5/77.7 ±12.8	143.5 / 77.9**
Target blood pressure %	50.3	48

*: dementia was an exclusion criterium for HYVET. **: blood pressure computed from intention to treat group after two years of treatment

Table II.
Factors possibly associated with reaching target blood pressure

	Target blood pressure reached	Target blood pressure not reached
Total population no. (%)	74 (50.3)	73 (49.7)
Female sex no. (%)	59 (80.0)	56 (77)
Age ± SD	86.1 ± 4.1	85.6 ± 4.0
No. of antihypertensives ± SD	2.2 ±1.0 *	1.8 ± 1.1*

*:p<0.05

Hypertension without CVA, heart failure, myocardial infarction or diabetes in the history was present in 75 (51%) of the patients. Neither the presence of a CVA, heart failure, myocardial infarction, diabetes or

dementia in the history, nor being eligible for HYVET was associated with a different proportion of patients showing adequate pressure control.
Dementia or heart failure also wasn't associated with lower mean blood pressure. Of all patients, 68% were treated with diuretics, 43% with a beta-blocker, 41 % with an ACE-inhibitor or Angiotensin-II antagonist, 24 % with a calcium antagonist, and 2 % with an alpha-blocker. No significant differences in blood pressure control were found for the use of these individual types of medications.
Interestingly, patients who would have been eligible for HYVET more often had suffered myocardial infarction: 15.4% versus 3.2% ($p<0.005$), then those not eligible for HYVET. There were no significant differences in blood pressure control and the presence of stroke or diabetes in the history between the patients who would or would not have been eligible for participation in HYVET (Table III).

Table III. Eligibility for HYVET, co-morbidity and blood pressure control

	Eligible for HYVET (n=52)	Not eligible for HYVET (n=95)
Diabetes no. (%)	11 (21.2)	20 (21.1)
Stroke no. (%)	14 (26.9)	19 (21.1)
Myocardial Infarction no. (%)	8 (15.4)	3 (3.2)*
Target blood pressure no. (%)	24 (46.2)	50 (52.6)

*p<0.05

DISCUSSION

Our first question was how many of our geriatric patients were treated for hypertension. The fact that almost all of our patients were prescribed antihypertensives was surprising, since undertreatment in older patients has been shown in many other disorders besides hypertension, like heart failure, myocardial infarction and osteoporosis.
It has been reported that only 59% of hypertensive patients receive treatment.[8]
A much larger proportion of our patients was being treated than in the population included in HYVET. In earlier studies in the Netherlands, 55% of the hypertensive patients older than 80 were not pharmacologically treated [9] and 71% of patients of all ages newly identified with

hypertension.[10] In a population aged up to 59 years, only 17.9% of the hypertensive men, and 38.5% of the hypertensive women were receiving antihypertensive medication.[11] Thus, it seems that older and less healthy persons are more often being treated for hypertension, which stands to reason if one considers their absolute cardiovascular risk to be the highest.[2] However, in our population, the presence of vascular morbidity like strokes and myocardial infarction in the history, was not associated with more adequate control.

Our second question was how many of our patients would have been included in the HYVET study. By far, most geriatric patients wouldn't have been eligible for this, the only trial clearly demonstrating a beneficial effect on mortality. On the one hand, reasons to exclude patients from HYVET will have been motivated by foreseeing difficulties in obtaining informed consent due to cognitive decline, other patients were probably excluded because adequate treatment of comorbidity would have demanded prescription drugs also lowering blood pressure, like heart failure or renal insufficiency requiring ACE-inhibitors and diuretics. The preponderance of females and more frequent comorbidity compared to the HYVET population shows this geriatric population differs significantly from the population included, even though both patients groups consisted of persons aged 80 years and older.

It may be that a greater perceived risk of cardiovascular and cerebrovascular disorders, has motivated the general practitioners to treat these older vulnerable patients, even though in 2004, there was insufficient conclusive evidence from randomized trials in patients aged 80 years and older that the benefits would outweigh the risks yet.

Our third objective was to investigate in how many patients blood pressure had been effectively lowered by drug therapy. A large part of the patients didn't reach the goals for treatment as set in the HYVET. The guideline of the Dutch General practitioners current in 2004 also described a target systolic blood pressure less than 160 mmHg in healthy people over 60 years of age.[12] It is well known that treatment targets are often not achieved, even in high risk patients. For example, a German study showed that although 87.9% of patients with cerebrovascular disease received types of antihypertensives, 54.5% had elevated blood pressure.[13]

Since our study consists of retrospective cross-sectional data, we cannot establish whether the treatment of octogenarians, who would not have been eligible for HYVET, results in improvement of outcome. We can conclude that the treatment with antihypertensives of these

vulnerable patients was started and had been continued by the GPs into high age. Seemingly, the GPs had considered the treatment sufficiently safe, otherwise the drugs would have been discontinued in an earlier stage because of adverse drug events or perceived contraindications.

The fourth question we investigated was which factors were associated with adequate blood pressure control. In our study, the only factor associated with achieving target blood pressure was the number of antihypertensives used and not one of the individual classes of antihypertensive drugs. The current advice in the Dutch guideline is to preferably add another low dosed antihypertensive in stead of increasing the dose of one antihypertensive when control is insufficient.[14]

In Italy, community-dwelling persons aged 65 and over were most often treated with ACE-inhibitors, calcium antagonists and diuretics[15], while in our patients diuretics and beta blockers were the most commonly prescribed drugs, which was in accordance with the guidelines from the Dutch General Practitioners which advocated to start with diuretics and add betablockers.[12] We couldn't demonstrate whether certain classes of medication were more efficacious. It has been shown that female gender was associated with an increased chance of being treated.[11] We didn't find any patient characteristic associated with adequate control of hypertension. We also did not find an association between adequate control of hypertension and different type's antihypertensive medication. However, our study was probably underpowered to do so. Because almost all our patients were being treated we could not analyze factors influencing the choice whether to prescribe different types of antihypertensive medication.

Being eligible for HYVET was only associated with more frequent myocardial infarction in the history. This was surprising: since myocardial infarction is one of the causes of heart failure, and the presence of heart failure was an exclusion criterium, one would expect more patients with myocardial infarction in the history, in the population who would have been excluded.

In this usual care study, patients who would have been excluded from HYVET had similar levels of blood pressure control as patients who would have been included. It is reassuring that the level of blood pressure control was not associated with being eligible for HYVET. Although we cannot conclude from our cross-sectional data that the long-term benefit from treatment for these patients will be the same as the HYVET population, we can conclude that blood pressure control can be similarly effective.

CONCLUSION

We can conclude that although the landmark HYVET study has provided important evidence showing benefit in treating hypertension in relatively healthy older people, results of antihypertensive treatment in geriatric patients could be less beneficial than shown in this trial, since most of them wouldn't have been included. Because of more frequent co-morbidity, especially cognitive decline, strokes and heart failure, they could be more susceptible to adverse events caused by antihypertensive treatment. Yet, almost all of these patients were already being treated, with similar levels of blood pressure control, without sufficient evidence, probably on the assumption that their increased absolute risk for vascular disease was enough justification. Since the treatment was continued by the GPs into high age, treatment probably was tolerated without significant adverse events.
Contrary to expectations, important co-morbid vascular conditions did not increase the chance of adequate blood pressure control, since the goals often weren't met. The results of HYVET will probably not change the intention to treat hypertension but may support more intensive treatment to reach systolic blood pressure below 150 mmHg. Future studies should use less strict exclusion criteria, including for instance geriatric patients with cognitive decline to gather evidence that the current practice of treating hypertension also in these patients is good clinical practice.

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Chapter 3.2

Contraindications for anticoagulation in older patients with atrial fibrillation; a narrative review

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ABSTRACT

Oral anticoagulation (OAC) is the most effective treatment to prevent strokes in patients with atrial fibrillation (AF). Many older patients are not prescribed OAC out of fear for bleeding complications.

The objective was to explore which co-morbid conditions in older patients with AF have been associated with undertreatment with oral anticoagulation, or were used as exclusion criteria for trials, or have been associated with increased risk of bleeding complications.

A Pubmed search was conducted with the terms elderly, atrial fibrillation, stroke risk, bleeding risk, intracranial haemorrhage, cognition, fall risk, renal dysfunction, alcohol abuse, malignancy, polypharmacy, NSAID, undertreat-ment, underuse and underprescription.

Higher age is associated with undertreatment. Patients with a higher risk of stroke show higher rates of bleeding complications. The associations of major bleeding rates with age and other possible contraindications are inconsistent. The bleeding risk in older patients in usual care is higher than in trials.

Published bleeding rates reflect selection bias, describing mainly relatively healthy older patients. The use of stratification schemes for stroke risk and for bleeding risk will have to be implemented. Because the rates of stroke have been seen to decline, risk estimates need to be validated repeatedly.

The decision to prescribe OAC in older patients with AF remains a challenging task since bleeding risk is difficult to estimate reliably. Stratification schemes may be helpful, but the careful evaluation of individual characteristics and preferences of the patients should remain the mainstay for a well informed decision by the patient and their caregivers.

Introduction

Prevalence of atrial fibrillation

The prevalence of atrial fibrillation (AF) increases with age to about 10% in people over the age of 80 years, and over 15% in those over age 85.[1-4] AF patients are almost five times more likely to experience a stroke compared to non-AF patients. In patients older than 75 years, the estimated annual stroke risk is 6% or higher despite aspirin therapy.[5] In the Framingham study, the risk of stroke attributable to AF rises to 23.5% in the age group 80 to 89 years.[1] Stroke risk is similar for patients with paroxysmal versus permanent and persistent AF.[6,7]

Patients with stroke and AF have a worse prognosis regarding mortality and residual handicap as compared to patients with stroke without AF. Embolic stroke results in death or severe neurological deficit in 50% to 70% of cases.[8,9,10]

The prevalence of AF in the USA has been extrapolated on the basis of currently available health care data to increase to 5.6 - 15.9 million patients by 2050, with more than half of the affected individuals aged 80 years or older.[2,11]

Effectiveness of anticoagulant treatment

Treatment with oral anticoagulation (OAC) unequivocally reduces the risk of stroke in patients with AF. A meta-analysis comprising nineteen clinical trials with 17833 patients estimated that adjusted standard-dose OAC could prevent 28 ischemic strokes at the expense of 11 major or fatal bleeding episodes. Aspirin could prevent 16 ischemic strokes at the expense of 6 major or fatal bleeding episodes.[12] A subsequently published meta-analysis including twenty-nine trials, comprising 28044 patients showed an 64% (95% CI,49% to 74%) reduction in stroke with adjusted-dose OAC and an 22% (95% CI,6% to 35%) reduction with antiplatelet agents. The absolute rates of major extracranial and intracranial haemorrhage were only 0.2% per year. All cause mortality was reduced by 26% (95% CI, 3% to 43%) by adjusted-dose OAC.[13]

Anticoagulation also reduces stroke severity and mortality, presumably by preventing more severe embolic strokes.[10,14]

The relative benefit of OAC vs. aspirin in stroke prevention appeared to be greater for patients younger than 75 years vs. those who were 75 years or older and for women vs. men.[15]

Undertreatment with oral anticoagulants.

The use of anticoagulants has been steadily increasing since the early 1980s: in 1980-1981 the percentage of patients with nonvalvular AF to whom OAC were prescribed was 7.1%, in 1990-1993 32% and by 2002 over 55%.[16,17] Yet, in many older patients, treating physicians do not prescribe OAC. This controversy is caused by observations that older patients probably may benefit the most from anticoagulation, but are also at the highest risk for bleeding complications. Nonetheless, good estimates on major haemorrhage rates are lacking. Possible causes for the reluctance to prescribe OAC in older patients have been the difficulty of evaluating the risk of bleeding, the time-consuming INR monitoring, the fear of increasing drug-drug interactions in patients with polypharmacy and the lack of knowledge about the pharmacology and efficacy of OAC in older patients.[18] Underuse of OAC has been shown to be associated with worse outcomes, even in the presence of (perceived) contraindications.[19] Of patients without OAC, 83% had ≥ 2 major risk factors or stroke, and 98% were felt to have contraindications.[20]

The most feared complication of anticoagulation is intracranial haemorrhage. Patients with OAC had an approximately 10 times higher risk of hemorrhagic stroke as compared to the general population.[21] The intracranial haemorrhage 30-day mortality was 51.8% in patients on OAC and 33.6% in patients who had not been prescribed OAC.[22] However, this complication occurs infrequently.

The problem is that some of the risk factors for anticoagulation-related bleeding like history of ischemic heart disease and cerebrovascular disease are also indications for the use of anticoagulants.[23]

So, the question remains which patient characteristics and co-morbid conditions increase the risk of bleeding complications in such a degree that OAC is not the best option.

The objective of this review is to discuss the recent literature about conditions that have been linked to undertreatment and are frequently present in older patients, which have been described in recent trials as exclusion criteria, and which have been shown to be associated with bleeding complications in trials and usual care studies. In addition, we discuss the possible role of prediction models for bleeding risk.

METHODS

A Pubmed search was conducted with the terms elderly, atrial fibrillation, stroke risk, bleeding risk, intracranial haemorrhage, cognition, fall

risk, renal dysfunction, alcohol abuse, malignancy, polypharmacy, NSAID, undertreatment, underuse and underprescription. The references of relevant reviews and original papers were searched for further publications regarding bleeding risk in patients treated with OAC. We did not exclude studies on the basis of strict quality criteria, since we did not want to exclude possible contraindications from this review because they had been observed only in smaller or less well designed studies.

UNDERTREATMENT WITH ORAL ANTICOAGULATION

Current prevalence of undertreatment

In different studies, terms are used like “ineligible”, “underuse”, ”undertreatment” and “underprescription“ indicating patients who do not receive OAC treatment. The definition is often unclear. Classifying a patient as “undertreated” or “ineligible” depends on the contraindications to OAC treatment the investigator considers valid. So, one should bear in mind the distinction between underprescribing and appropriately abstaining from treatment is ill defined.

In 597 Missouri Medicare beneficiaries with chronic AF, 34% received OAC and 21% received aspirin.[19]In primary care 78-84% of patients with AF was treated with OAC in the 60-89 age group, only 52% was treated over the age of 90.[4]

Prescriptions for OAC from 7 days preceding to 30 days after the development of AF were filled in only 9.7% of all patients, and 11.9% of those without apparent contraindications.[24] In a Spanish study 69% of patients seen in an emergency department with AF were not taking anticoagulants.[25]

Of old patients admitted to hospital with AF, 25%-34% were prescribed OAC.[26,27] Only 54% of eligible patients discharged from hospital were receiving OAC.[28] Of patients who had suffered an ischemic stroke, in 39.8% anticoagulation treatment was omitted, without a contraindication.[29]

In European university and specialized centres, OAC were prescribed to 67 and 49% of eligible and ineligible patients respectively.[30]

So, currently up to 75% of frail elderly patients with AF are not being prescribed anticoagulants.[26] We will discuss which factors have been linked to undertreatment.

Underprescription of anticoagulation

Advanced age is associated with underuse of OAC in many studies.[9,19, 20,24,28,31-37]

Female gender has also been linked to underuse of antithrombotic therapy in some studies.[19,32,36] Rural residents were less often anticoagulated.[19,32]

Major bleeding, intracranial haemorrhage and perceived risk of bleeding are frequently reported to influence prescribing practices.[20,24,27,33,34,37,38] Other perceived contraindications associated with underuse are falls,[20,24,33] cognitive impairment[31,20] and conditions perceived as barriers to compliance.[20,24] Alcohol or drug abuse and renal impairment were associated with decreased prescription,[24] as was paroxysmal atrial fibrillation.[28] Monte described obstructive pulmonary disease and the presence of malignancy as deterrents for use of anticoagulants.[27]

In observational studies, contraindications to the use of anticoagulation like these are present in 21-69% of patients.[25,28,39,40] According to Deplanque, the reason evoked by treating physicians why patients were not on anticoagulation was most frequently an inappropriate interpreted potential contra-indication, for instance falls.[41] Fall-related subdural haematomas and intracranial haemorrhages are extremely infrequent. It has been calculated that persons taking OAC must fall almost daily, about 295 times in 1 year, for OAC not be the optimal therapy.[42] So, factors interpreted as barriers to OAC probably should often not influence the choice of stroke prophylaxis.

Yet, physicians may be reluctant to prescribe OAC to part of their older patients because they assume the most frail patients have been excluded from the trials that have demonstrated benefit. This selection bias makes it difficult to extrapolate the reported beneficial effect to the patients with AF in usual care. In the next section we will discuss the exclusion of patients in recent studies regarding the efficacy of OAC in older patients with AF.

Exclusion in recent trials.

BAFTA was a prospective randomized open-label trial in patients aged 75 and over. In Table I exclusion criteria used in this and other recent trials including also younger patients are described. For BAFTA, patients were also excluded if their primary care physician judged on the basis of risk factors for stroke and haemorrhage, that the patient either should or should not be on OAC. Of the whole cohort, only 21% of primary care patients were included because inclusion was restricted to patients for whom there was clinical uncertainty. The majority of the patients was excluded because the primary care physician expected OAC to be more beneficial than aspirin. It is unclear how many patients were included or excluded with for instance a high fall risk or cognitive decline: 6.1% of the excluded patients did not meet inclusion criteria because of reported contraindications to OAC, in another 12 % of the excluded patients the primary care physician had judged the patients should not be OAC.[44]

In WASPO, patients aged >80 and <90 were included in a randomized open labelled prospective study of primary thromboprophylaxis for AF. In this study patients were referred by clinicians for the study, so there were no accurate data regarding the percentage of octogenarians being ineligible.[45]

So in these two most recent studies in older patients at least about 20%, or an unknown proportion of patients were excluded, and it is unclear because of which contraindications. In other trials it is also often unclear how many patients had been excluded for which reason. In Table I exclusion criteria used in other recent trials including also younger patients are summarized.[44-53]

In the next caption we will discuss which co-morbid conditions have actually been associated with increased bleeding risk in trials and usual care studies.

BLEEDING COMPLICATIONS.

In trials, the risk of bleeding will be underestimated because of the exclusion of older and vulnerable patients and strict monitoring of INR levels. Therefore, the rates of bleeding complications could be expected to be higher in usual care. However, a systematic review showed there was a higher rate of minor bleeding in clinical practice than in trials, but the rates of ischemic stroke, intracranial bleeding and major bleeding were similar.[54]

Table I.
References for described possible contraindications for OAC.

	Defined as exclusion criterium	Associated with underuse	Associated with bleeding risk
Female gender		16,19,20,32,36	5,56,63,67,76,77,78
Rural residency		19,32	
Nonadherence	46	20,24	52,59,73
Intracranial haemorrhage	44,45,51,49,52	16,24	
(Recent) Previous TIA or stroke	45,46,47,50,52		22,55,77
Leukoaraiosis /microbleeds			68, 69,70,71
History of (major) bleeding	44,52	19,20,24,27,34,37,38	22,56,105
Recent gastrointesti-nal/ urinary bleeding	44,45,47,50,52	16,24	
Recent ulcer/ oesophageal varices	44,47,51,52		
(Major) surgical procedure or trauma	44,47,52,53	19	
(History) of hypertension	44,45,46,47,50,52	37	65,80
Haemorrhagic disorder	47,51,52		
Use of platelet inhibitor drugs			56,57,61,79,89
Use of NSAIDs	46,50,52		56,57,61,89
Polypharmacy			69,91,84,90
Renal insufficiency	47,49,55,53	16,19,24	57
Hepatic disease	47,49,52	16,19	57,61
Alcohol abuse	45,46,50,52	24	73
Fall risk	45,50	16,20,24,31,37	22,87
Epileptiform seizures	45,50	16	
Cognitive decline	45,46,47	20,31	22
Myocardial infarction	49,52		64,65
Heart failure	47,49,52		64,65
Diabetes mellitus			55,57,77,91
Chronic obstructive pulmonary disease		27	
Malignancy	49	27	63,86
Hyperthyroidism	49,50		

Trial results can be used to identify risk factors for bleeding, if patients with these conditions weren't excluded. Other risk factors for bleeding not identified in trials may become evident from usual care studies. The results of the different studies cannot be easily compared because there are multiple methods reported in estimating the bleeding risk. Furthermore, because different variables are entered in multivariate analysis in different studies, some conditions will be identified in one study as an independent risk factor, while in other studies the association with bleeding risk is not confirmed as an independent factor. The introduction of confounding variables, not previously included, like for instance the presence of leukoaraiosis or microbleeds, may render hitherto identified independent variables insignificant in multivariate analysis in the future.
In 2007 Hughes systematically reviewed the literature for some of the possible risk factors of anticoagulation-related bleeding complications in AF patients. Supporting evidence was found for: advanced age, uncontrolled hypertension, history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents.[23] Fall risk and cognitive disorders were not reviewed. We will describe some studies which have shown these and other clinically relevant condition at least once as a possible risk factor for bleeding. For the interpretation of the described risk, one has to bear in mind that even in usual cares studies, some selection bias will be present because treating physicians decide which patients are receiving OAC, so confounding by contraindication remains present, probably resulting in underestimation of bleeding risk. In addition, part of these studies also included patients on anticoagulation for other reasons than AF.

Patient characteristics

Age
Age has been identified most frequently as a major independent risk factor for bleeding complications in several studies.[19,55-62] A reported relative risk up to 6.6 (95% CI, 1.2-37) for bleeding complications in patients aged > 75 years compared with those aged <75 was found, with a cumulative incidence of major bleeding up to 10.8% (95% CI, 1.8-19.8).[55] There have also been studies showing increasing age was not a risk factor.[63-67] We will discuss some observational population studies in more detail.

In 4202 Dutch patients including 696 patients older than 80 years, the incidence rate of major haemorrhage rose with age to 4.2 per 100 patient years for patients older than 80 years.[58] Currie also demonstrated a higher bleeding risk with higher age, but also a survival advantage in even the oldest patients OAC.[59] Of patients ≥ 80 years of age, 26% stopped taking OAC within the first year.[62] In another study in octogenarians, OAC resulted in no serious bleeding episodes or side effects, with fewer adverse events than 300 mg aspirin. In this trial there was a lower than expected mortality rate, which could be explained by selection bias since patients were excluded if their history revealed one or more falls without formal gait assessment.[45]
In the landmark BAFTA trial, there was no increased risk of major haemorrhage in patients on OAC compared with those on 75 mg aspirin. An absolute risk reduction of 2% was demonstrated. The main benefit was seen for severe or disabling stroke, rather than fatal strokes. Risks of bleeding rose by similar amounts with age in both patients on OAC and aspirin.[44]
One explanation for the often found association between age and bleeding complications may be the presence of leukoaraiosis or microbleeds. The prevalence of these increases with age. The presence and severity of leukoaraiosis on CT scan correlated strongly and independently with the occurrence of intracranial haemorrhage in patients with a previous ischemic stroke.[68] Yet, patients anticoagulated because of cerebral ischemia with AF did not have an increased risk of intracranial haemorrhages compared with patients anticoagulated without AF, despite the more frequent presence of leukoaraiosis in patients with AF.[69] The presence of microbleeds was independently related to the incidence of OAC-related intracerebral hemorrhage.[70,71]
History of AF was an independent risk factor for the presence of cerebral microbleeds in acute ischemic stroke and TIA patients.[72]
Another explanation for higher bleeding risk could be that doses of OAC should be lower with increasing age, and especially in older women.[73,74] It is often not clear from studies whether at initiation, doses have been adjusted for age.
So, since treatment of carefully selected older patients has proven to be safe, the bleeding risk seen to be associated with higher age, may be incurred by co-morbid conditions associated with higher age, but not controlled for in previous studies, like the presence of leukoaraiosis or microbleeds.

Gender

There have been studies showing increased bleeding complications in women using anticoagulants, but results are inconsistent.[55,56,63,67,75-78] When only high quality studies are considered in patients with AF, only two studies [56,67] showed borderline significance.[23]

Ethnicity

Asians, Hispanics and blacks were at greater risk for OAC related intracranial haemorrhage. Overall 54.5% of patient-time was in the therapeutic range, with blacks having a lower percentage of patient time in the therapeutic range (INR 2 to 3). There was no difference in the patient time with INR > 3 (9%).[78]

History of bleeding

A history of bleeding was associated with future bleeding as was a history of anemia.[56] Prior major bleeding has been associated with intracranial bleeding.[22]

Gitter did not find a history of gastrointestinal haemorrhage or peptic ulcer to be significantly associated with major hemorrhage.[63]

Non-bleeding peptic ulcer disease has not been associated with subsequent gastrointestinal bleeding[75] and when patients have had upper gastrointestinal bleeds they are not at an increased risk of re-bleeding once they have been treated adequately.[43] Risks for upper gastrointestinal bleeding were similar for low-dose aspirin and vitamin K antagonists.[79] So, the evidence for history of bleeding as a risk factor is inconsistent.

Hypertension

The prevalence of a history of hypertension was higher in patients with bleeding complications than in patients with no complications.[65] Others did not find a relation between major bleeding and (history of) arterial hypertension.[55,63,77] In the SPORTIF III and V, event rates for stroke and systemic embolic events increased with systolic blood pressures of ≥ 140 mmHg, but there was no relationship between quartiles of systolic blood pressure and rates of bleeding.[80] Treatment of hypertension may explain lower stroke rates observed during antiplatelet therapies in recent trials.[51] So, although the evidence for risk for bleeding with hypertension is inconsistent, treatment of hypertension should be strongly advocated because it may not only reduce risk of bleeding, but it will further reduce the risk of stroke, which is also the goal of OAC treatment.

Cerebrovascular disease

There have been studies showing no significant association between a history of stroke or thromboembolism and bleeding risk.[55,65] Other studies did find previous cerebrovascular disease to be a significant independent risk factor for major bleeding or intracranial hemorrhage.[22,60,77] In 343 surgical cases of chronic subdural haematoma, both antiplatelet and anticoagulant therapy had no significant effect on the recurrence of subdural haematoma, but the time interval between the injury and operation for patients with antiplatelet or OAC was shorter, suggesting these drugs both facilitate the growth of chronic subdural hematoma.[81]

With a Markov state transition decision model, Eckman demonstrated in patients with prior lobar intracranial haemorrhage or deep hemispheric intracranial haemorrhage, withholding OAC was preferred. However, patients with deep hemispheric intracranial haemorrhage at particularly high risk for thromboembolic stroke might still benefit from long-term anticoagulation.[82] So, not even in all patients with intracranial bleeding episodes in the history, OAC should be unequivocally considered contraindicated.

Cognitive disorders

MMSE score <23 was independently associated with inadequate INR control, mainly because of an increased number of supratherapeutic INR values.[83] In 323 patients 80 years and older, receiving anticoagulant treatment after discharge from geriatric and internal medicine departments, cognitive function measured with the MMSE was not a significant predictive factor for bleeding complications, while insufficient education on anticoagulant treatment as perceived by the patient or caregiver was.[84] Neuropsychiatric impairment was an independent risk factor for intracranial haemorrhage in patients at high risk for falls.[22] When one considers the importance of a possible contraindication, while deciding to withhold the contraindicated medication, the risks of alternative therapies should also be taken into account. For instance, the choice to treat patients with AF and dementia with aspirin instead of OAC is not a clear cut better choice. In a study of patients with Alzheimers disease treatment with aspirin resulted in a cumulative rate of bleeding complications necessitating hospital admission of 8% after 3 years, fatal cerebral bleeds occurred in 2%.[85]

So, educating caregivers more thoroughly and monitoring anticoagulant treatment in patients with cognitive decline more intensely may be preferred over replacing OAC treatment with salicylate.

Heart disease
A history of myocardial infarction or ischemic heart disease was associated with bleeding complications defined as a minor or major bleed, but no association was found when only major bleeds were considered.[64,65] In the AFFIRM trial, the presence of congestive heart failure increased the risk of major bleeding.[57]

Diabetes Mellitus
History of diabetes was associated with an increased risk of major bleeding [57,77] but not consistently.[55,61,65,67]

Renal insufficiency
In the AFFIRM trial renal disease was associated with major bleeding disease. Aspirin increased the risk of major bleeding as much as OAC.[57]

Liver disease
Hepatic disease was associated with major bleeding.[57] Previous liver disease was also associated with increased risk of bleeding in a pooled analysis of the SPORTIFF III and V trials.[61] Gitter did not find an association between alcohol abuse and major hemorrhage.[63] In patients on prophylactic OAC after hip fracture, history of alcohol abuse was associated with bleeding complications.[73]

Malignancy
Malignant disease at initiation of OAC was associated with both major haemorrhage and thromboembolism.[63] In patients treated for venous thrombo-embolic disease, the rates of minor and major bleeding were significantly higher in cancer patients compared with patients without cancer.[86]

Falls
In a Markov model study, it was found that OAC was the preferred option if the baseline stroke rate was over 2% per year. Sensitivity analysis demonstrated the risk of falling was not an important factor in determining the optimal antithrombotic therapy.[42] In patients who suffered a fall during an admission in a tertiary-care teaching hospital, fall-related major hemorrhagic injury was independently associated with female gender, and use of aspirin or clopidogrel, but not OAC.[76] Gage demonstrated that in patients at high risk for falls, OAC prescription at discharge after a prior hospitalisation was not associated with

intracranial haemorrhage occurrence. Ischemic stroke rates per 100 patient-years were 13.7% in patients at high risk for falls and 6.9 % in other patients. Rates of traumatic intracranial haemorrhage were 2.0 per 100 patient-years (95% CI:1.0-1.3) versus 0.34 (95% CI, 0.270.45) per 100 patient-years in patients without high risk for falls. Still, patients at high risk for falls did show a 25% relative risk reduction in the composite outcome, which included death or hemorrhage.[22]
In a study using a statewide hospital database 47.717 patients aged 65 years or older hospitalized as a result of a fall were included. Overall mortality did not differ by the use of OAC, but the mortality after intracranial haemorrhage was significantly higher (21.9 % vs. 15.2%).[87] These mortality rates are markedly lower than previously reported.[22]
So, falls do not increase mortality in patients with OAC in general, and OAC may still benefit patients who fall, especially when they are at high risk for stroke.

Treatment characteristics
Besides patients characteristics which increase the risk for bleeding, there are also situations which are associated with higher bleeding risk. One should take these high risk situations into account, so one may lower bleeding risk by careful monitoring, in patients who are at higher risk due to their co-morbidity.

Initiation of anticoagulation therapy
The incidence of major haemorrhage was 6.9 % per year in patients who had recently begun OAC therapy, compared with 1.7% per year in the group who were receiving warfarin therapy for more than 3 months.[66] In usual care studies, more major bleeds occurred in the first months of treatment.[26,60,62,88] In the AFFIRM study, the first episode of AF was associated with major bleeding. The incidence of major bleeding through five years of follow up was constant, approximately 2 % per year.[57] In ACTIVE W the yearly risk of a major haemorrhage in patients who were started on OAC as part of the trial, was 2.9% compared to 2% in the people assigned to OAC who were already on the drug.[51] Often in these studies, starting doses are not described.

Aspirin
The concomitant use of aspirin was demonstrated to increase the risk of bleeding.[56,61,79,90] In patients with a prior stroke/TIA the major bleed-

ing rate was 1.5% per year with OAC and 4.95% with OAC plus aspirin.[52,89] So, concomitant use of aspirin should be avoided as much as possible.

Polypharmacy

There have been conflicting results regarding polypharmacy as a risk factor. Several studies showed patients taking more than three medications in addition to anticoagulants had an increased risk of bleeding.[69,84,91] Another study failed to demonstrate additional medications as a risk factor when risk was measured against an increase of each additional drug.[56] Gorter, found patients taking three or more drugs in addition to anticoagulants had a significantly higher risk of major bleeding on univariate analysis, but in a multivariate model together with leukoaraiosis and age older than 65 years, the use of more than three drugs no longer was predictive.[69]

Of patients discharged on OAC, 54% were prescribed another medication that could increase bleeding risk, and more than one interacting drug was prescribed for 20% of the patients.[92] Combined use of ≥ 1 interacting drugs was associated with a 3 to 4.5 fold increased risk of serious bleeding in patients on long-term OAC.[90] In a usual care study, NSAID use during OAC considerably increased the bleeding risk compared with OAC alone. The relative risk of NSAID use with regard to bleeding complications was 5.8.(95% CI,2.3-13.6).[93]

One can conclude especially the use of other interacting medication increasing bleeding risk, like NSAIDs, should be disencouraged.

INR control

The risks of haemorrhage and thromboemboli are lowest at international normalized ratios of 2-3.[62,86, 94,95]

There have been reports linking poor control to bleeding complications, while others have not. Increasing INR was an independent risk factor.[64] Bleeding complications are lower with moderate and good INR control compared to poor control. Poor control was linked to higher rates of stroke and mortality.[52,59] However, Johnson demonstrated the INR level was within or below the therapeutic range in 58.5% of major haemorrhage episodes.[26] Poli did not find differences in bleeding risks with the quality of anticoagulation control, and the median INR related to major bleeding events was 2.5.[77]

The percentage of follow-up time above target ranges was not higher in patients older than 80 in usual care, compared with patients under 60.[58] Higher odds of non-adherence with education beyond high

school and impaired cognition was demonstrated. Adherence was somewhat improved in unemployed and retired subjects. Disabled subjects over age 55 had worse adherence than younger disabled subjects.[96]
So, patient characteristics frequently present in older people which have been described to be associated with higher bleeding risks at least once, although not always undoubtedly as an independent risk factor for bleeding in AF are: higher age, female gender, high fall risk, disability, history of major bleeding, uncontrolled hypertension, cerebrovascular disease, neuropsychiatric impairment, presence of leukoaraiosis, myocardial infarction, heart failure, diabetes mellitus, renal insufficiency and liver disease.
Other risk factors for bleeding are initiation of anticoagulation, poor INR control, concomitant use of anti-platelet agents, NSAIDs and polypharmacy with drugs interacting with OAC.
In Table I these risk factors are summarized. The question is whether the presence of any one of these putative contraindications increases the risk of major bleeding in such a degree anticoagulants should not be prescribed. In usual care, patients often use OAC despite having more than one contraindication to anticoagulants.[30] Does the use of OAC in usual care result in a higher rate of bleeding complications, when more patients like these will be on OAC than in trials?

THE ABSOLUTE RISK OF BLEEDING COMPLICATIONS.

The annual rates of bleeding complications from trials have been reassuringly low even in patients over 80 years of age, up to 6% for major bleedings and 0.7% for intracranial hemorrhage.[44] However, one may not conclude that these rates could be extrapolated to the kind of patients that have not been included in trials. Observational studies may give a more accurate estimation of bleeding risk, but in these studies the most vulnerable patients will also have been excluded by their treating physicians because their bleeding risk was perceived to outweigh their risk of stroke. Also, in many trials and observational studies the initial phase of therapy was not included, and this may result in an underestimation of bleeding risk, since the start of anticoagulation treatment is associated with increased bleeding risk.[26,60,62,66,88]
In the Netherlands the Anticoagulation services reported only 1 major haemorrhage per 100 treatment years over the years 1998-2002.[97]

Pengo found a cumulative incidence of 10.8% major bleeding in patients over 75 years of age.[55] In the Framingham Heart Study, major bleeding was seen in 25% of patients using OAC and 22 % in patients treated with aspirin ≤ 5 years after initial AF, vs. 12% of patients with no antithrombotic treatment.[67] The cumulative incidence of major haemorrhage for patients ≥ 80 years was 13.1 per 100 person-years in patients with trial-level anticoagulation control. Of patients ≥ 80 years of age, 26% stopped taking OAC within the first year. Even in this study, only 4 % of patients had a history of falling, and only 3 % suffered from dementia. Of the 9 intracranial bleeds, 2 were associated with documented falls.[62]

The annual rate of major haemorrhage, requiring emergency treatment, in an old frail cohort was 10% and included five fatal bleeds. The annual rate of fatal haemorrhage was 0.9%. Yet, more than 90% of these patients with major haemorrhage survived with nearly no permanent sequelae. The annual stroke rate after initiation was 2.6%, demonstrating the effectiveness of OAC.[26]

The presence of contraindications for OAC in usual care didn't influence the reduced risk of all-cause mortality associated with OAC use in patients with a mean age of 71 years. The rate of intracranial haemorrhage was moderately higher among those taking vs. those not taking OAC (0.46 vs. 0.23 per 100 person years).[98]

When patients at high risk for falls had multiple additional stroke risk factors, OAC appeared to protect against a composite endpoint of stroke, intracranial haemorrhage, myocardial infarction and death.[22]

So in usual care, patients with AF who are treated with OAC, major haemorrhage has occurred in up to 13 % of patients [62], and an annual rate of fatal haemorrhage up to 0.9%.[26]

Although the frequency of bleeding is higher in usual care than in trials, it is still unclear whether there are identifiable subgroups of patients in whom the chance of bleeding complications predictably surpasses the expected benefit of OAC. It may be that bleeding rates from older patients treated with anticoagulation for other indications are a more reliable estimate of bleeding risks from OAC since there may be less confounding by contraindication in studies where the treatment goal is not prevention of embolism, like it is in AF, but the treatment or prevention of for instance venous thromboembolism. In patients treated for idiopathic deep venous thrombosis or pulmonary embolism OAC during a period of one year, 4 to 10% had major bleeding. These patients had mean ages of 65 to 67.7.[99,100,101] In patients aged ≥ 80 years treated for venous thromboembolism, major

bleeding occurred in 3.4% during three months, over a third during the first week of treatment.[102] In patients treated with oral anticoagulant after total hip replacement up to 5.5% major bleeding occurred.[73,103]
Randomized trials in patients with established venous thromboembolism generally have found an overall frequency of major bleeding of ≤ 3% during 3 months of therapy and up to 3.8% /year in patients who were continued to receive anticoagulants.[75]
These patients were often treated for periods substantially shorter than is expected in patients with AF. Hemorrhagic complications of anticoagulation are more frequent early in the course of therapy. Therefore one cannot just extrapolate these bleeding risks to long term anticoagulation. Many of the population based studies concerning AF included patients after they had been discharged from the hospital, and the first stage of treatment with OAC had been completed, which may explain relatively lower bleeding rates.
Over all, these rates of bleeding complications do seem to be higher than the rates of major bleeding seen in patients treated in trials for AF but still lower than in patients with AF in usual care.
In Table II the bleedings risks in different types of studies are demonstrated.

THE NEED FOR RISK STRATIFICATION

Antithrombotic undertreatment of high-risk patients with AF is associated with a worse cardiovascular prognosis, whereas over-treatment according to the ACC/AHA/ESC guidelines[104] is nonsignificantly associated with a higher risk for major bleeding.[105] In a prospective survey in 5203 patients, in 35 European countries in 2003 and 2004, 86% of this population (in 27.7% aged ≥75) had at least one additional risk factor for stroke, so many patients would probably benefit from anticoagulation.[30]
Patients can be stratified according to the risk of stroke. The best validated score is the $CHADS_2$. The acronym denotes Congestive heart failure, Hypertension, Age over 75 years, Diabetes mellitus and prior Stroke or TIA. A prior Stroke or TIA as risk factor is assigned two points, the other conditions one point. Absolute risk for stroke has been shown to increase with 1.5 % for each point, and patients with a score higher than 3 have the highest stroke risk, >6.4% per year.
Patients with zero points had a risk of stroke of 1.2% per year when treated with aspirin.[106]

Table II.

Observed major bleeding rates in patients using OAC

Study, year [Reference]	% of patients excluded because of contra-indications	No of Patients on OAC	Mean age	Major bleeding Complications per year	Intracranial haemorrhage per year
Trials					
AFASAK 2 1998 [46]	Unclear	43	73.2	1.1 %	0.6 %
PATAF 1999 [47]	9 %	131	70		0.3 %
JNAFESP 2000 [49]	Unclear	55	65.7	6.6%	1.1%
Vemmos et al. 2006 [50]	Unclear	16	80.1	0	0
SPORTIF III&V 2005 [52]	Unclear	3665	70.9	2.68 %	0.2%
ACTIVE W 2006 [51]	Unclear	3371	70.2	2.21 %	0.4%
WASPO 2007 [45]	Unclear	36	83.5	0	
BAFTA 2007 [44]	18.1%	488	81.5	6 %	0.7%
AMADEUS 2008 [53]	9%	2271	70.2	1.4 %	0.4 %
Usual Care					
Pengo 2001 [55]		433	67.9	1.8 %	0.3%
Go 2003 [98]		11526	71	1.52%	0.5%
Johnson 2005 [26]		228	81.1	10%	0.4 %
Poli 2007 [77]		290	82	2.1%	1.4%
Hylek 2007 [62]		472	77	13.1%	2.5%

Risk stratification schemes for strokes like the $CHADS_2$ are increasingly being validated and incorporated in guidelines.[104]

However, risk of major haemorrhage and OAC termination were also highest among patients with higher risk of stroke.[62,77,107] Because of the high prevalence of possible contraindications, for many geriatric patients the current guidelines do not aid the difficult decision whether or not to prescribe OAC. The prevalence of contraindications rose with age to 14 % in men and 16 % in women ≥ 75 years.[108] These percentages are strongly influenced by the choice of contraindications

included and the type of population studied. Carroll did not classify fall risk as a contraindication. In 41.7% of the population studied by Waldo, fall risk was reported as a bleeding risk factor, and in 25 % of the patients studied by Hylek.[20,38,56] Over 60 % of patients treated in veterans affairs hospitals not being prescribed OAC had a documented contraindication including bleeding risk or history, fall risk, dementia, and alcohol abuse.[39,40]
The presence of such contraindications as well as medical background, have been shown to influence withholding treatment.[20,109,110] It has also been described that physicians tend to overestimate the risks of OAC use.[37,109,111]
Physician's experience with bleeding events associated with OAC was shown to decrease prescription of OAC, whereas adverse events possibly associated with underuse of OAC didn't seem to increase subsequent prescribing.[112] Treating physicians were shown not to estimate the probability of major bleeding with OAC better than chance.[113]
So, it may be that treating physicians are aware of the conditions important for risk stratification for stroke, but still need more solid data or guidelines on risk for bleeding complications. Bleeding risk scores could be of assistance.

Bleeding Risk Stratification
Beyth validated the Outpatient Bleeding Risk Index, but included only 6% patients aged ≥ 80. This Index performed better in predicting major bleeding than physicians.[113] Since age 65 years or greater was included as a risk factor, older patients are classified as having at least an intermediate risk of 12% major bleeding in 12 months: an estimated base-line risk which about equals the highest rate of major bleeding observed in trials and population based studies. So, this index will overestimate the bleeding risk for otherwise healthy older patients.
On the other side, of the patients who did sustain a major haemorrhage in the study by Hylek, only 3 of 26 would have been classified as high risk according to this index.[62]
Another bleeding risk score was validated in patients with a mean age of approximately 60 years suffering from venous thrombo-embolism. A combination of age, sex and the presence of known malignancy could identify a subgroup of 20% of patients with the highest risk suffering 7% major bleedings.[114] In 2006 Shireman developed a risk model in atrial fibrillation patients aged > 65 with bleeding rates of 5.4% in the

high risk group. However, this risk model was validated in a cohort of patients discharged from the hospital while receiving OAC, therefore also representing an already selected non-inception cohort, and it may therefore underestimate the risk of bleeding in patients starting with OAC.[115]

Risk stratification schemes may successfully identify patients with low rates of ischemic stroke. However, the number of patients classified as low, medium or high risk may vary markedly because the different schemes have been derived from different studies. This was demonstrated by Thomson, who showed in selected patients with AF, a difference in estimated stroke risk of up to 8% could occur. The authors propagated the general principle that one should choose a risk estimation scheme based on a population as similar as possible to the population to which it is applied.[116]

So the question is also whether the patients included in studies used for the validation of bleeding risk scores are sufficiently comparable to older patients with AF. Important possible contraindications to anticoagulation like falls and cognitive impairment were either not described [113,114] or nearly as prevalent in the development and validation cohorts for these risk models as in older patients in usual care.[115]

Gage more recently constructed a new bleeding risk scheme, HEMORR$_2$HAGES, in a data set from quality improvement organisations covering 3791 Medicare beneficiaries with a mean age of 80.2 years. HEMORR$_2$HAGES is scored by adding two points for a prior bleed, and one point for each of the other risk factors: hepatic or renal disease, ethanol abuse, malignancy, older (age > 75 years), reduced platelet count or function, hypertension (uncontrolled), anemia, genetic factors, excessive fall risk (including neuropsychiatric disease) and stroke. The risk of major bleeding in this cohort exceeded 10 % in patients with ≥ 4 points. This risk scheme can quantify the risk of haemorrhage for a wider range of co-morbid conditions than the previous ones. It was a valid predictor of bleeding in patients who were prescribed OAC or aspirin.[117]

However, since in some studies the bleeding risk of OAC was not greater than the risk of aspirin, and the presence of contraindications was not associated with higher mortality, it remains a challenging task to decide on the preferred strategy since both the risk of stroke and the risk of bleeding because of present contraindications increase with age and vascular co-morbidity.[108] Also, the large majority of major bleeds do not cause permanent health damage [26] while strokes associated with AF frequently do.[8,9]

Discussion

The current United States and European cardiology guidelines do not mention which contraindications for OAC should be considered.[104] The 2006 national guideline on AF of the Royal College of Physicians states particular attention should be paid to the assessment of bleeding risk but does not provide a more specific advice on how to weigh contraindications.[118]

It is debatable whether the currently often listed contraindications are adequate, since part of them can now be treated, like peptic ulcer disease, and the relative risk of others possible contraindications are as yet unknown, like leukoaraiosis or microbleeds in the brain of demented patients.[69,119] Microbleeds were seen in 65% of patients with vascular dementia and 18% of Alzheimer disease patients.[119] It is questionable whether the less effective alternative therapy, aspirin, is safer in the presence of contraindications. There are studies where the risk of major non-intracranial bleeding for aspirin and for OAC were similar.[56,57,98] There are also data that the rates of subdural haematoma and intracranial haemorrhage may be similar for OAC and aspirin.[44,47] Studies with markedly higher rates of intracranial bleeding are mainly older studies which have mostly aimed at target INRs well above 3.0.[94]

There is a rise in the use of OAC. In the UK, intracerebral haemorrhage in the population aged 75 and over associated with antithrombotic use increased, while the incidence associated with premorbid hypertension decreased. In the USA the incidence of anticoagulant-associated intracerebral haemorrhage in persons aged ≥ 80, increased from 2,5/100.000 in 1988 to 45,9/100.000 in 1999. So, we are probably exchanging ischemic strokes for hemorrhagic strokes, which may be less in number but even more invalidating.[120,121]

The expected event rate of stroke as predicted by a score like $CHADS_2$ also changes in time. There may be a decline in the frequency of stroke due to changes in management of other risk factors than AF such as hypertension and high cholesterol; lower than anticipated event rates were reported.[44,51] Reduction in blood pressure in patients with AF, irrespective of the use of anticoagulants or the presence of hypertension, resulted in a 34% reduction of strokes.[122] A 40% reduction in age-specific incidence of major stroke over the past 20 years was shown with a substantial reduction in the proportion of smokers, mean total cholesterol, blood pressures and increases in

treatment with anti-platelet, lipid-lowering and blood pressure lowering drugs.[123]
This may mean the absolute risk reduction for stroke with anticoagulants in AF will be less than in previous decades. However, improved control of hypertension may also reduce the rates of anticoagulation related bleeding.

CONCLUSION

In conclusion, the landmark trial in older patients with AF, the BAFTA, showed an absolute risk reduction of 2 % in the combined endpoint strokes, hemorrhagic complications and systemic emboli.[44]
Aspirin may increased the risk of major bleeding as much as OAC.[57]
In population studies survival benefit of OAC was shown even in older vulnerable patients with high fall risk on OAC.[22] However, an incidence of up to 13.1 % major bleedings per year has also been described and an incidence of fatal bleedings up to 0.9%.[26,62]
The significance of contraindications to anticoagulant use in older patients still needs to be better studied to be able to choose the most adequate treatment. At present the choice still seems to be predominantly based on age. The risks of questionable contraindications like the propensity to fall are in our opinion too much emphasized. A single contraindication should not preclude anticoagulation treatment, especially in patients at high risk for stroke. Bleeding risk scores are more adequate in predicting bleeding complications than physicians, since in usual care age is still the predominant deterrent for OAC, and physicians have been demonstrated to predict bleeding complications not better than chance.
Since in physician decision making, errors of commission are considered more serious than errors of omission, physicians should use more objective models for stratifying bleeding risk like the $HEMORR_2AGES$. Treatment with OAC should only be initiated with adequate patient education, adjusting starting doses to the age of the patient, reviewing co-medication and treating all co-morbidity which either increases stroke risk or bleeding risk like uncontrolled hypertension and high fall risk.

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Chapter 3.3

Undertreatment with oral anticoagulants in atrial fibrillation in frail geriatric outpatients is only associated with age.

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ABSTRACT

The main aims of the study were to explore if oral anticoagulation (OAC) in atrial fibrillation (AF) in geriatric outpatients is prescribed in accordance with the international (ACC/AHA/ESC) and national guidelines for the general practitioner (GP) and to identify if age and selected co-morbid conditions are associated with under-treatment. As a secondary objective, we wanted to establish how many patients discontinue OAC because of major bleeding.

During 2004, during the first visit of all patients to the geriatric day clinic of the Slotervaart Hospital in Amsterdam demographic data, Mini Mental State Examination (MMSE), medical history, comorbidity and medication use and changes were registered. The presence of AF was established by assessing information from the GP about the medical history, history taken from patients and caregiver and the clinical evaluation including EKG. Associations between the use of OAC, demographic data and co-morbid conditions which were registered in the Dutch NHG standard for general practitioners as risk factors for stroke or contraindications for OAC were being analyzed. The reasons for discontinuing OAC were assessed after 4 years by questioning the anticoagulation services or the GP.

At the time of the visit, 17.5% of the 807 outpatients showed chronic (135) or paroxysmal AF (6). The mean age of the 141 patients in this cohort was 84.3 years (SD 6.2), Comorbid conditions increasing the risk of stroke are present in 129 (91%) patients. Contraindications to the use of OAC were observed in 118 (84.7%) patients. Of the 116 patients with AF in their history before their visit, 57.8% were treated with OAC at the time of their visit. After comprehensive geriatric assessment, 73 (51.8%) of the 141 patients with continuing chronic or paroxysmal AF were continued on OAC.

Of the 141 patients 110 (78.0%) had both extra stroke risk factors, and contraindications to the use of OAC.

Only increasing age was significantly associated with the chance not to be prescribed anticoagulants ($p<0.001$).

At follow up after 4 years, OAC were discontinued in 5.5% of the patients because of major bleeding; 3 (4.1%) patients using OAC had died due to major bleeding, one other patient discontinued treatment because of a major, non-lethal, bleeding episode.

Applying the NHG standard for appropriate prescription, and disregarding age as a risk factor or contraindication, in this population 14 of 141 patients (9.9 %) were inappropriately prescribed OAC, salicylates or neither. Since in this study only age was associated with refraining from prescription of OAC, age still seems to be considered the most important contraindication for anticoagulation. Implementation of better models for stratifying bleeding risk in the frail elderly is needed. After 4 years, the cumulative rate of bleeding in this usual care study of frail older patients causing discontinuation of anticoagulation was comparable to other usual care studies.

INTRODUCTION

The prevalence of atrial fibrillation (AF) increases with age. It is the most important single cause of stroke in patients >75 years, and associated with higher mortality. Over the age of 80 yearly stroke risk rises to up to 23.5% in high risk patients.[1,2]
Treatment of patients with AF with anticoagulation (OAC) should be considered, according to the 2001 and 2006 guidelines of American and European cardiologists (the ACC/AHA/ESC guidelines) and the American College of Chest Physicians in 1998, in people aged > 75 years even when no other risk factors for strokes are present.[2,3,4] The 2003 guidelines of the Dutch general practitioners, the NHG standard, advocate anticoagulation when in addition to AF, more risk factors like previous stroke, history of hypertension, heart failure, coronary artery disease, rheumatic valvular disease or diabetes mellitus are present. In the absence of these additional risk factors or contraindications for OAC, antithrombotic treatment by salicylate is advocated, age is not included as a risk factor warranting anticoagulation.[5]
So, a difference in opinion exists about whether or not to treat patients with AF above age 75 with OAC when no additional risk factors are present. This controversy is caused by observations that older patients probably may benefit most from anticoagulation, but are also at the highest risk for bleeding complications.
Age and the intensity of anticoagulation are the most powerful predictors of bleeding complications. The incidence of bleeding complications per se is not higher in elderly patients in all trials, but a up to 3- to 4- fold increased risk of life threatening or fatal bleeding has been described in those aged >80 compared with patients <50 years.[1,2] In trials, the risk of bleeding will be underestimated because of the exclusion of vulnerable patients and strict monitoring of INR levels. In an observational study, patients receiving usual care with oral anticoagulation had a 10 times higher risk of haemorrhagic stroke compared to the general population.[6] The increase of bleeding complications with age may be influenced by increasing co-morbidity. Age was a predictor of all anticoagulation-related haemorrhages with a hazard ratio of 1.9 in patients with cerebral ischemia of presumed arterial origin. The presence of leukoaraiosis increases with age and is also a strong independent risk factor for intracranial haemorrhages with a hazard ratio of 2.7.[7]

In observational studies, perceived contraindications to the use of anticoagulation are present in 25-67% of patients.[8,9,10] These patients are generally excluded from trials.
Besides higher age, especially a history of falls, haemorrhage and cerebrovascular disease have been reported to influence prescribing practices.[11] Family physicians overestimated risks of OAC for AF.[12]
Repeatedly it has been shown that in the many elderly patients, physicians do not prescribe OAC, although no contraindications for anticoagulation are present, and even when according to their risk profile they could benefit the most from anticoagulation.[1,13,14] Some argue many of the factors interpreted as barriers to anticoagulant therapy probably should not influence the choice of stroke prophylaxis. Fall-related subdural haematomas and intracranial haemorrhages are extremely infrequent. It has been calculated that persons taking OAC must fall almost daily, about 295 times in 1 year, for OAC not be the optimal therapy. Persons who fall are much more likely to suffer other serious morbidity. Similar arguments can be raised about upper gastrointestinal bleeding in the history, which relative contraindication may be sufficiently be abandoned by eradicating Helicobacter pylori, or prescribing a proton pump inhibitor. For other possible contraindications like alcoholism, bleeding diathesis and non-compliance with monitoring, there is little or conflicting evidence.[15,16]

In this study we investigated the prevalence of clinically diagnosed AF in a cohort of geriatric outpatients, the type of medication they used for stroke prophylaxis, and the association of age and co-morbidity with possible undertreatment. In addition, we wanted to determine the reasons for discontinuing OAC.

METHODS

Patients

The study was part of a prospective descriptive study at the geriatric day clinic of the Slotervaart Hospital in Amsterdam. In this department of a large teaching hospital patients are offered comprehensive geriatric assessment (CGA) in one day with follow up if necessary for further diagnosis or treatment on an outpatient basis. Reasons for referral by the general practitioner are most frequently cognitive decline or functional dependence. The treating physicians were advised by the study physician (LT) and study pharmacist (SF) regarding changes in medication. Demographic data, Mini Mental State Examination (MMSE)[17],

medical history, co-morbidity (Charlson Index)[18] and medication use and changes were registered. In the $CHADS_2$ risk factors for cerebrovascular incidents in combination with atrial fibrillation are incorporated, with points given for Congestive heart failure(1), Hypertension(1) Age over 75 years(1), Diabetes mellitus (1) and prior Stroke or TIA(1). A higher score is associated with a higher risk of stroke.[19] The presence of these risk factors was established by assessing information from the general practitioner about the medical history, history taken from patients and caregiver and the clinical evaluation with EKG and Chest X-ray. As possible contraindications for anticoagulation were registered: systolic hypertension>180 mmHg, diastolic hypertension> 110 mmHg, bleeding lesions in the digestive tract, recent serious bleeding, serious renal or hepatic dysfunction, haemorrhagic diathesis, diabetic or hypertensive retinopathy with bleeding, at least one fall reported in the previous year, dementia and other reasons for non-compliance with medication regimen, alcoholism, frequent use of NSAID's and illnesses which shorten life expectancy like malignancies. These are the contraindications as described in the NHG standard for the Dutch general practitioners.[5] Contraindications were not classified as absolute or relative contraindications. The reasons for discontinuing OAC were assessed after 4 years by questioning the anticoagulation services or the GP.

Analysis

Continuous variables are presented as means ± SD, with comparisons between the age of OAC users and non-users using the Student *t* test, dichotomous variables are described as proportions with comparisons made using chi-squared tests, ordinal variables were tested with the Mann Whitney test. Patients using no antithrombosis prophylaxis were grouped with patients using salicylates versus patients using OAC. A p-value of less than 0.05 was considered statistically significant. Statistical calculations were performed with SPSS for Windows (version 16.0, SPPS Inc,Chicago, IL, USA).

RESULTS

Prevalence of atrial fibrillation.
In 2004, a total of 807 geriatric outpatients visited the geriatric day clinic for the first time. Of these, 20.1% (162) had episodes of AF in the past or present (Table I). 137 patients were reported to have had at least one episode of AF in the past, of whom 9 were known to suffer from paroxysmal atrial fibrillation (PAF) before their visit. 19 showed normal sinus rhythm at present and one showed an ectopic atrial rhythm. Of the 9 patients with PAF 2 showed chronic atrial fibrillation of unknown duration and one had a pacemaker. 116 patients who had shown AF in the past, still suffered from it at the time of the visit.
New AF of unknown length of duration was diagnosed in 25 other patients. So at the time of the visit 141 patients, 17.5% showed chronic (135) or paroxysmal atrial fibrillation (6), (Figure I).

Presence of atrial fibrillation and additional risk factors.
Of all patients with AF in past or present, 150 (92,6%) had in addition to their age, one or more of the following additional risk factors for stroke: heart failure, coronary artery disease, diabetes mellitus, hypertension or a stroke in the past. No additional risk factors besides their advanced age were present in 12 patients.
All 116 patients with known and present AF had at least one additional risk factor.
Of the 141 patients still suffering from AF, 129 (91%) suffered from one or more of the above described co-morbid conditions.

Table I.

Characteristics of the population, (N=807)

Mean Age, years mean ± SD	81.7 ± 7.4
Female %	67
Living %	
At own home,	78.5
Assisted living	15.4
Nursing home	3.7
Other	2.4
Charlson Comorbidity Index, mean ± SD	2.05 ± 1.46
Clinical diagnosis, history and present %	
Dementia and Mild Cognitive Impairment	59,2
Cerebrovascular disease	21.7
Parkinsonism	3.6
≥ 1 Fall reported over previous year	21
Syncope	2.5
Osteoporosis	14.7
Diabetes Mellitus	18.6
Hypertension	42.8
Atrial Fibrillation	20.1
Heart failure	16.2
Coronary heart disease	25.5
Urinary Incontinence	25.5
Mini Mental State Examination (n= 608) mean ± SD	20.6 ±6
Number of medications, mean ± SD and range	5.1 ± 3.6 0-23

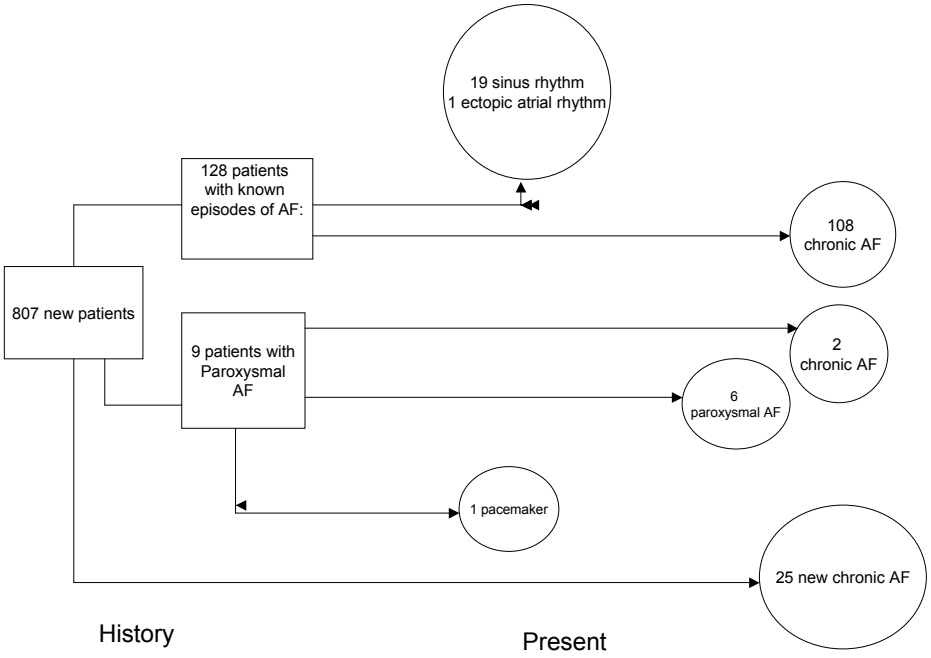


Figure I. Prevalence of atrial fibrillation

Presence of contraindications to anticoagulation

In all patients with AF in the past or present (162), 144 (88,9%) had one or more of the conditions described as (relative) contraindications to the use of OAC in the NHG standard. 25 (15.4%) had no contraindications for OAC. Of the 141 patients with current AF, 118 (84.7%) had contraindications to the use of OAC.

Type of antithrombotic profylaxis, risk factors, and contraindications to OAC

At least one additional risk factor besides age was present in 129 of the 141 patients (91%) who at the time of the visit had chronic AF (123) or paroxysmal atrial fibrillation (6) (Table II).

No additional risk factors for stroke besides their age were present in 12 of the 141 patients suffering from chronic or paroxysmal AF at the time of the visit. These all had chronic AF. The type of antithrombotic treatment after geriatric assessment in the different subgroups is shown in Figure II. So, 73 (51.8%) of the 141 patients with present chronic or paroxysmal AF were continued on OAC.

Changes in prescriptions by geriatricians

Of the 116 patients known with episodes of AF before visiting the diagnostic day clinic, and still suffering from AF until their visit, 11 patients (8.6%) received no salicylate or OAC, 39 patients (33.6%) were treated with only salicylate, 67 (57.8%) with OAC, one of these patients used a combination of salicylate and OAC. So, in the 116 patients known with current AF who still suffered from it, 67 were on anticoagulation before their visit (57.8%). Of these patients, 5 changed from no prophylaxis to coumarines, 5 others changed from coumarins to salicylate (4) or no thrombosis prophylaxis. So in 8.6 % of the patients with continued AF the geriatrician changed the antithrombotic strategy.

In the 25 newly diagnosed patients 14 were prescribed salicylate (of whom 7 already used this for other indications), 2 additionally were started on salicylate with the intention to switch to OAC after further diagnostic procedures, 5 were started on OAC who had used no antithrombotics, 1 changed from salicylate to OAC, and 3 weren't prescribed any antithrombotic prophylaxis because of iron deficiency anemia, in two of unknown origin, in 1 caused by colon cancer.

Inappropriate prescription

After their visit, of the 141 patients with actual paroxysmal or chronic AF 10 patients (7.1%) didn't receive either salicylate or OAC . 58 (41.1%) were treated with salicylate, 73 (51.8%) with OAC. Of the 141 patients 110 (78.0%) had both extra risk factors supporting the use of OAC, and contraindications to the use of OAC. Disregarding age as a risk factor or contraindication, if one would classify adherence to the NHG standard as appropriate prescription, in this population 14 of 141 patients (9.9 %) were inappropriately prescribed OAC (6) or salicylates (6), or neither (2). An additional 8 patients with contraindications received no thrombosis prophylaxis at all (Figure II).

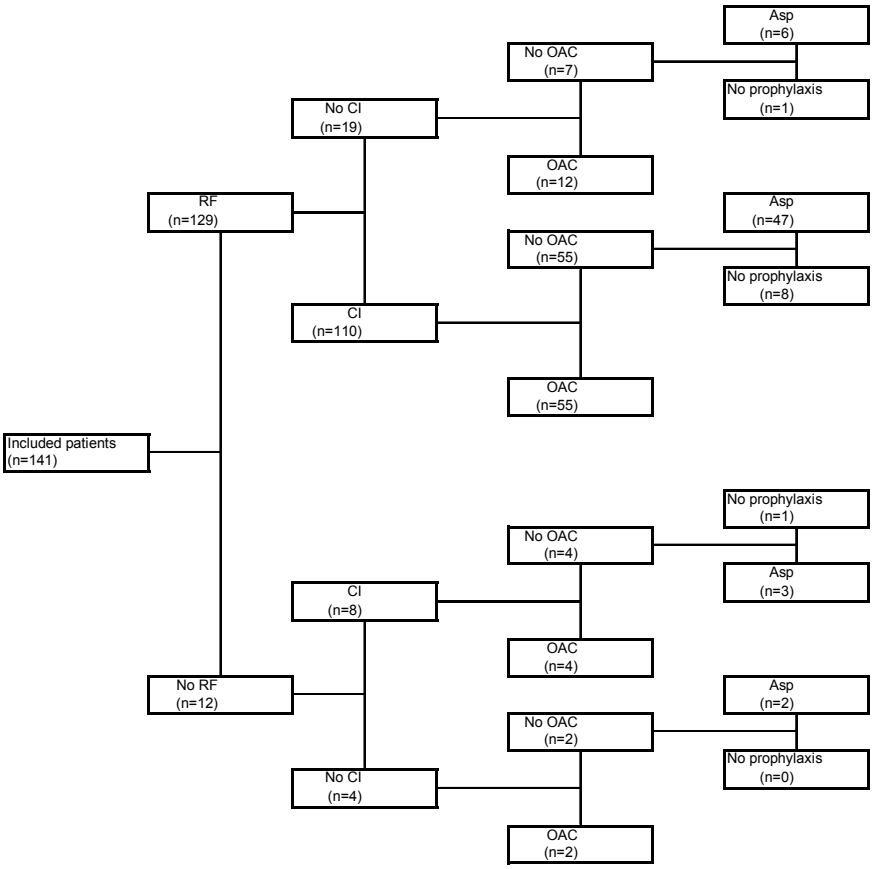
63% of the patients with risk factors on top of their age and no contraindications were treated with OAC, and 50% of the patients with no additional risk factors besides their age, with contraindications to anticoagulation. We could not deduce from the notes why the 2 patients with no contraindications for anticoagulation weren't prescribed any antithrombotic prophylaxis.

Influence of specific co-morbid conditions on anticoagulation use

Although the percentage of patients treated with OAC was higher in the group not showing any contraindication to the use of anticoagulants (Table II), this difference wasn't statistically significant.

Neither the $CHADS_2$ score, nor the presence of one or more contraindications nor the registered individual conditions which increase the risk of a stroke or may be a risk factor for bleeding complications was associated with the prescription of anticoagulation.

Only increasing age was significantly associated with the chance not to be prescribed anticoagulants ($p<0.001$).



RF= Extra risk factors for stroke besides AF and age
CI= Contraindications present for anticoagulant use
OAC= Oral Anti Coagulant treatment
Asp= Treatment with salicylate

Figure II . Antithrombotic treatment, risk factors and contraindication

Table II.

Type of antithrombotic prophylaxis, risk factors, and contraindications to OAC: after CGA.

N=141	Risk factors present* No (%treated with OAC)	Risk factors absent* No (%treated with OAC)
Contraindications for OAC Present	110 (50.0%)	8 (50%)
Contraindications for OAC Absent	19 (63.2%)	4 (50%)

*Age was not included here as a risk factor

Table III.

Univariate analysis comparing demographic and co-morbidity variables between patients prescribed OAC and not prescribed OAC after CGA

	OAC (n=73)	No OAC (n=68)	P-value
Age (Mean ± SD) (years)	82.3 ± 6.3	86.3 ± 5.3	<0.001
Female	45/73 (62%)	38/68 (56%)	0.487
Charlson Index (Mean ± SD)	2.51 (±1.52)	2.47 (±1.47)	0.934
$CHADS_2$ (Mean ± SD)	2.85 (±1.2)	2.75 (±1.1)	0.769
Previous stroke or TIA	18/73 (24.7%)	13/68 (19.1%)	0.427
Hypertension	45/73 (61.6%)	42/68 (61.8%)	0.988
Heart failure	35/73 (48.0%)	33/68 ((48.5%)	0.945
Diabetes Mellitus	24/73 (32.9%)	20/68 (29.4%)	0.657
Dementia	34/73 (46.6%)	33/68 (48.5%)	0.816
Falls	20/73 (27.3%)	23/68 (33.8%)	0.408
Presence of ≥ 1 contraindication	60/73 (82.2%)	58/68 (85.3%)	0.618

Follow-up

At the end of 2008, 20 of the 73 patients were still using OAC. OAC was no longer used by 53 patients. We asked the anticoagulation services or the GP why patients were no longer treated with OAC**.** Of the 53 patients no longer on OAC, 48 patients had died.

Major bleeding had contributed to death in three patients: one died of an infected haematoma after a fall, one died of an intracerebellar bleeding, another patient died of heart failure after a gastrointestinal bleed. Despite the use of OAC, 4 patients suffered a stroke, in three of them fatal. One patient had major gastrointestinal bleeding associated with the combined use of NSAID and anticoagulant without proton pump inhibitor. Of the four patients with major bleeding, two had both contraindications to the use of OAC, and additional risk factors for stroke. One patient had contraindications without extra risk factor, one had extra risk factor without contraindications. In eleven patients, death was sudden or unexplained with no indication of bleeding. One patient was found dead after he had fallen.

The other 30 patients died of co-morbid conditions not associated with bleeding complications or stroke.

We could not trace four of the patients who had discontinued the treatment with anticoagulant (Table IV).

Table IV.

Follow-up of patients taking OAC

Discontinued	No of patients (n=53)	% of patients prescribed OAC (n=73)
Major bleeding (fatal)	4 (3)	5.5 % (4.1%)
Discontinued for unknown reason	4	5.5 %
Other causes of death		
Stroke (fatal)	3 (3)	4.1 %
Sudden death	4	5.5 %
Death caused by		
unknown cause	7	9.6 %
fall (intracranial bleeding ?)	1	1.4 %
heart failure	9	12.3%
infection	6	8.2 %
respiratory insufficiency	3	4.1 %
malignancy	6	8.2 %
terminal general condition	6	8.2 %

DISCUSSION

The prevalence of AF in this geriatric outpatient population is similar to prevalences of 10-18 % described in the general population.[1,14,20, 21]
In a European survey, it was shown that OAC was prescribed to 67 and 49% of eligible and ineligible patients respectively. In this study only major bleeding and malignancy were described as contraindications.[22] These figures are comparable to the rates of anticoagulation of 63.2% and 50% we found for eligible and ineligible patients, according to the indications and contraindications of the NHG standard.
Besides a higher age, neither of the investigated individual co-morbidities nor higher co-morbidity indexes like the Charlson or the $CHADS_2$ showed a statistically significant relationship with treatment choice.
The underuse of OAC with increasing age found in our study, is understandable since in many studies higher age is associated with higher bleeding risk.[23-27] Age has also been associated with under treatment by many others.[11,28-,35]
However, age should not be the most important consideration regarding the prescription of anticoagulation. Currie demonstrated a higher bleeding risk with higher age, but also a survival advantage in even the oldest patients on OAC.[36] Also in trials including octogenarians with AF, improved outcomes associated with the use of OAC have been demonstrated.[37,38]
In over 80% of the geriatric outpatients in this study, (relative) contraindications to anticoagulation are present, almost as much as the prevalence of 92% of patients with risk factors for stroke besides their age. These figures depend on the definition of which comorbid conditions are considered contraindications. We also included dementia and falls as a contraindication, because they were labelled as such in the GP guideline. Presumably due to selection bias, the proportion of patients with contraindications is higher than previously described in other observational studies, which reported contraindications in 21-69 % of patients.[8,9,10,39] It is unjustified to refrain from prescribing OAC indiscriminately because of all possible contraindications, since the presence of contraindications for OAC in usual care didn't influence the reduced risk of all-cause mortality associated with OAC use in patients.[40]
If one would classify adherence to the NHG standard as appropriate prescription, and disregarding age as a risk factor or contraindication, in this population 14 of 141 patients (9.9 %) were inappropriately pre-

scribed OAC, salicylates or no prophylaxis. Geriatric assessment did not increase the prescription rate of anticoagulants. This might be explained by increased recognition of contraindications like dementia or falls during CGA or a difference in opinion about the importance of such contraindications by GPs and geriatricians.
In the Netherlands, patients on OAC are kept under surveillance by centralized anticoagulation services. This enabled us to trace and ascertain the causes of death in most of our patients on OAC. We could not establish this for the patients treated with salicylate, since these were treated by their own GPs. After 4 years, the cumulative rate of bleeding causing discontinuation of OAC was 5.5%, and in 4.1% of the patients major bleeding contributed to, or caused death. This is much lower than demonstrated by Hylek. She described a cumulative incidence of major haemorrhage for patients ≥ 80 years of 13.1 per 100 person-years, while these patients may have been less prone to bleeding, since only 4 % of patients had a history of falling, and only 3 % suffered from dementia.[27] This difference could however be explained by selection of patients, since all the patients in the latter study were started on OAC, while in our study patients who were already treated with OAC were included and bleeding occurs more frequently in the first months of treatment. Johnson also found an annual higher rate of major haemorrhage of 10%, but a comparable annual rate of fatal haemorrhage of 0.9%.[41]
So, prescription rates of OAC in this geriatric outpatient population were comparable to the rates in less vulnerable patient groups, and yet the bleeding rates were not alarmingly higher than in other usual care studies.

Strengths and limitations
We demonstrated even in an already old population, higher age is associated with undertreatment. We showed stroke risk factors and contraindications to OAC use frequently coexist, and are not associated with more or less prescription of OAC. We did not question either the patients, caregivers, GPs nor the geriatricians for the reasons for refraining from prescription. Only co-morbid conditions identified and described in the charts were identified as contraindications. Therefore, we cannot conclude either higher age or the presence of contraindications was the cause of undertreatment. We only registered major bleeding complications when they had resulted in discontinuation. Furthermore, the cause of death was unclear in about 15 % of pa-

tients. So, we may have underestimated the rate of major and fatal bleeding complications.

CONCLUSION

Age is an important risk factor for stroke, but has also been associated with increased bleeding risk. Since in this study only age was associated with refraining from prescription of OAC, age still seems to be considered the most important contraindication for anticoagulation. In many geriatric patients OAC are prescribed and tolerated despite the presence of (relative) contraindications. A careful evaluation of risk factors for stroke and risk factors for bleeding complications which may be adequately treated is mandatory.
Because there is uncertainty regarding the best strategy to avoid major and lethal bleeding complications, implementation of better models for stratifying bleeding risk in frail old patients is needed.

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Conclusions and perspectives

Polypharmacy, defined as the use of multiple drugs is more frequent in the elderly. It is associated with a higher risk of non-adherence, inappropriate prescribing by physicians and adverse drug reactions (ADRs). Increased mortality has been described. The reduction of suboptimal medication use, is one of the goals of CGA. After CGA, medications are discontinued because of ADRs and because an indication for the pharmacological treatment is not present (anymore).
The importance of medication review with the patient to identify ADRs, undertreatment and non-adherence has been demonstrated. It was shown, in the last years there is increased use of medication by geriatric patients. CGA increases medication use, due to the recognition of previously undiagnosed conditions and the reduction of undertreatment. Even after geriatric assessment, undertreatment is still often present for conditions like myocardial infarction in the history and the prevention of stroke in the presence of atrial fibrillation. Fear of polypharmacy or co-morbid conditions constituting contraindications may be responsible for continuing undertreatment.
The comorbid conditions now labelled as contraindications for anticoagulants for instance should be further evaluated in future research to justify refraining from treating those who are prone to worse outcomes if treatment is withheld. In contrast, for other conditions like hypertension hardly any undertreatment is shown and maybe even over treatment of subgroups for whom no treatment benefit has been proven in trials yet. So, at the moment, treatment shown to be beneficial in relatively healthy older patients is also extended to those patients in usual care, who may be more vulnerable to adverse effects.
In the future, interventions in usual care should become better targeted by excluding from treatment those patients in whom the chance of adverse effects of treatment supercedes the chance of benefit. Currently however, simply excluding patients from treatment because of possible contraindications is as insufficiently evidence-based as including the kind of patients who have not been participating in the trials. For several conditions, studies have demonstrated that the presence of co-morbid conditions described and perceived as contraindications to treatment result in underuse of indicated medication and worse outcomes.The next phase in research should therefore be the identification of those subgroups of elderly patients in whom potential benefit from treatment outweighs the potential harm versus those in

whom treatment justifiably should be withheld. Especially those subgroups of patients who have been shown to be frequently undertreated should be included in trials. Exemplary of this treatment dilemma is the decision to prescribe anticoagulants in older patients with atrial fibrillation. This will remain a challenging task since bleeding risk is difficult to establish reliably. Stratification schemes may be helpful, but the careful evaluation of individual characteristics and preferences of the patients should remain the mainstay for a well informed decision by the patient and their caregivers.
In conclusion, for an evidence-based balance between reducing polypharmacy and unjustifiably excluding patients from treatment which could be very beneficial also for frail older people, more research should be focused on this subgroup. Frail older people should not be excluded from randomised trials on account of age or comorbidity. Analysing the results of investigated treatments should be focused also on factors identifying those with the least chance of benefit, or the greatest chance of adverse events.

Recommendations for future research
For medications with high risk of clinically relevant adverse events and no available alternative treatments which are equally effective, case control studies and observational prospective studies should be designed to establish the relative importance of contraindications which are more prevalent in older people. For example in the study of oral anticoagulants, these should include cognitive decline, the presence of microbleeds in the brain and high risk of falls.
Because prescription of medications is extended to patients in usual care who were not analysed in trials, like children and frail older patients, these patients may be at increased risk of ADRs. Until frail older patients are not selectively excluded from trials, future research will have to include observational studies in usual care, to evaluate whether risk and benefit of treatment, demonstrated to be effective in trials, are comparable in patients groups which have not been evaluated in these randomised trials.
As long as physicians have to treat frail patients without evidence from clinical trials, they will have to make choices based on a combination of evidence from subgroup analysis including patients as similar possible and observations from epidemiological usual care studies, while taking into account the specific vulnerability and preferences of the individual patient.

Summary

Introduction

Barely ten years ago, older patients commonly were excluded from clinical trials. There are several barriers described to their participation. Increased variance introduced by a heterogeneous population of older patients makes them less desirable study subjects. Obtaining informed consent from the patient and the caregivers can be a time consuming and complicated task. There can be fear that due to co-morbidity and frailty, they may be at increased risk for complications from the treatment being studied. Despite these barriers, in recent years trials have now been completed in people aged over 80 years, for conditions like hypercholesterolemia, hypertension and anticoagulation in atrial fibrillation. These have demonstrated that higher age in itself should not be a contraindication to treatment aimed at prolonging life expectancy. The selection of relatively healthy older patients, however, does limit the external validity of these trials for the older patients in the general population, since they would not all have been included in the trials, because of their co-morbidity.

Medications prescribed in usual care can be less beneficial or associated with more adverse events than in trials for the same treatment. Since Comprehensive Geriatric Assessment (CGA) comprises the evaluation of all the conditions an elderly patient is afflicted with, geriatricians are in a unique position to critically review medication use for all the separate conditions. The most important challenge is that for a selection of patients, with different complex combinations of illnesses and medications, no clear cut evidence is available for the preferred treatment regimen for all co-existing diseases and risk factors simultaneously, and may never be. So, the identification of those conditions whose treatment best matches the priorities chosen by the patient should be the goal of every treating physician. This leads to one of the challenges in geriatric medicine: the careful evaluation of polypharmacy, since it is associated with a higher risk of non-adherence, inappropriate prescribing by physicians, adverse drug reactions (ADRs), increased mortality, but also underprescribing of indicated medication.

This thesis deals with accidents happening in usual care regarding medication use. The evaluation of polypharmacy during geriatric assessment is described. Finally, the dilemmas in the treatment of frequently present cardiovascular diseases are discussed.

Chapter 1

Accidents in medication prescription and description

In **chapter 1.1** a case report is presented about dirt in a fax machine causing a grey stripe on a faxed prescription of trazodone. This obliterated part of the prescription, leading to an instruction label with a fourfold increase of the daily dose resulting in an anxious patient with dementia collapsing after the first dose.

In **chapter 1.2** it is described how a patient becomes intoxicated with valproic acid due to accidental overdosing after a transfer from a nursing home. The cause was an incorrect combination of the amount and concentration of valproic acid prescribed, probably because accidentally the wrong solution was marked during electronic prescribing.

Chapter 1.3 describes a prospective study about discrepancies in the drug use of geriatric outpatients as reported by the patient and their caregivers, the GP and the pharmacy. Included were 120 patients. At least one discrepancy between the medication lists of patients, GP or pharmacy was present in 104 out of patients (87%). In 90 patients there was at least one discrepancy between the medication reported by the patient and the GP (75%). Patients with at least one discrepancy reported using a higher mean number of drugs and more treating physicians besides their GP. Twenty-nine patients (24.2%) experienced possible medication discrepancy adverse patient events. The public pharmacy was unaware of the use of medication involved in a medication discrepancy adverse patient event in only 2 of these patients.

Chapter 2

Evaluation of polypharmacy in geriatric inpatients and outpatients.

In **chapter 2.1** the effects of admission to a geriatric ward on medication use are retrospectively analysed. A comparison is made between the 724 patients admitted in 1985 versus the 258 patients admitted during 2002. The main difference shown between drug use before and after admission, was an increase in the amount of drugs used, especially because of the prescription of vitamins. Compared to 1985, in 2002 more preventive medications were prescribed, and new medica-

tion groups like ACE inhibitors and proton pump inhibitors were frequently present.

The evaluation of pharmacotherapy in geriatric patients after performing geriatric assessment at a diagnostic day clinic during 2002 was also retrospectively analysed.

Chapter 2.2 describes that medications were frequently discontinued because the diagnosis was no longer relevant (39% of discontinued medication), adverse events (33%) and better pharmacotherapeutical options (22%). Since also frequently medications were added because of new diagnoses (69.2%), osteoporosis prophylaxis (15%) and improvements in pharmacotherapy (10.6%), after geriatric assessment patients used a higher mean number of drugs (4.6 before CGA versus 5.4 after CGA).

Chapter 2.3 describes the prevalence of undertreatment in geriatric outpatients. The presence of contraindications to medications for undertreated conditions was prospectively evaluated in 807 patients who were referred for CGA in 2004. Of these, 548 patients had at least one of the conditions known to be frequently undertreated. Before CGA, 170 patients were undertreated (32.9%), after CGA 115 (22.3%). Contraindications were present in 102 of the patients (19.8%) and more frequent in undertreated patients. Correction of all undertreatment regardless of the presence of contraindications would have increased the number of drugs with 97 used to a mean of 6.8 drugs in the whole population, and to 7.5 in the population still undertreated after CGA.

In **chapter 2.4** the prevalence and clinical relevance of drug-drug interactions (DDIs) in the 807 geriatric outpatients visiting the day clinic in 2004 are described. In 300 patients, 44,5% of patients using more than one drug, 398 potential DDIs were identified. In 172 patients,25,5% of all patients using more than one drug, drug combinations were found with either adverse drug reactions possibly due to combinations of culprit drugs or inadequate reaction to therapy. Changes in drug regimens pertaining to possible interactions were proposed or effectuated in 111 of these 172 patients (65%). 61 of these (55 %) returned for follow up. Of these, 49 (80 %) were shown to have improved after changes in their medication regimen.

A prospective exploratory pilot study is described in **chapter 2.5**. After CGA, 40 patients and their caregivers were questioned and if necessary visited at home to assess whether changes in medication advised after CGA were reported to be followed. The medication use was adjusted completely as the geriatricians had prescribed in 77.5 % of the patients. Of the changes in medication advised after CGA, 90% were reported to be followed. Only the presence of a caregiver who checked medication use was associated with complete adherence to drug therapy.

Chapter 3
Treatment of cardiovascular disorders

In **chapter 3.1** the treatment of hypertension in geriatric outpatients, 80 years or older, is described and compared with the patients included in the landmark HYVET trial. During 2004, 141 of the 147 patients in this age group with hypertension in the history were treated with antihypertensive medication (95.9%). Of these patients, 52 (35.4 %) would have been eligible for HYVET, 95 patients (64.6%) would have been excluded . The 147 geriatric patients included in our study showed more co-morbidity than the HYVET population e.g. dementia, strokes and cardiovascular disorders besides hypertension. Adequate blood pressure control defined as the target pressures of HYVET, was seen in 50.3 % of the patients. The patients who would have been excluded from HYVET had similar levels of blood pressure control as the patients who would have been included. The only significant difference between the patients who showed an adequately controlled blood pressure and those who did not was the mean number of antihypertensive medications: 2.2 (± 1.0) versus 1.8 (± 1.1) respectively.

In **chapter 3.2** the contraindications for anticoagulation in elderly patients with atrial fibrillation are reviewed. It is described how higher age is associated with undertreatment. Patients with a higher risk of stroke also show higher rates of bleeding complications. The association of major bleeding rates with age and other possible contraindications are inconsistent. The bleeding risk in usual care is higher than in trials. Published bleeding rates reflect selection bias, describing mainly relatively healthy elderly patients. The use of stratification schemes for stroke risk and for bleeding risk will have to be imple-

mented. However, their validation needs to be adjusted, because the rates of stroke have been seen to decline.

In **chapter 3.3** it is shown that in geriatric outpatients with atrial fibrillation, risk factors for stroke favouring the use of anticoagulants and contraindications to coumarins frequently coexist in the same patients. After CGA, 73 (52%) of the 141 patients with continuing chronic or paroxysmal AF were continued on coumarins. Extra risk factors supporting the use of warfarin, as well as contraindications to the use of coumarins were present in 110 patients (78.0%). Neither the presence of risk factors nor the presence of contraindications was associated with coumarin use. Only increasing age was significantly associated with the chance not to be prescribed anticoagulants.

Hopefully, in this thesis, the opportunities geriatric assessment offers for the critical evaluation of polypharmacy were brought into view. Future research offering more evidence for treatment of specific conditions including frail older patients remains necessary, since these patients are frequently undertreated, despite their high risk for worse outcomes. On the other hand, they are also receiving treatments without proven benefit, taken into account their complex comorbidity profile.

Samenvatting

Nauwelijks 10 jaar geleden was het nog gewoon dat ouderen geëxcludeerd werden uit onderzoek. Er zijn verschillende barrières beschreven voor de deelname van ouderen. Toegenomen variabiliteit door inclusie van de heterogene populatie van oudere patiënten maakt hen minder aantrekkelijke deelnemers. Het verkrijgen van toestemming van de patiënt en de mantelzorger kan tijdrovend en gecompliceerd zijn. Er kan angst bestaan dat door co-morbiditeit en kwetsbaarheid zij een verhoogd risico lopen op complicaties door de te bestuderen behandeling. Ondanks deze barrières, zijn er in de laatste jaren studies verricht bij patiënten ouder dan 80 jaar voor aandoeningen als hypercholesterolemie, hypertensie and antistolling bij atrium fibrilleren. Deze studies hebben aangetoond dat een hogere leeftijd op zich geen contra-indicatie is voor behandeling gericht op levensverlenging. De selectie van relatief gezonde ouderen beperkt de externe validiteit van deze studies voor ouderen in de algemene bevolking, daar dezen niet allen geïncludeerd zouden zijn, vanwege hun co-morbiditeit.

Medicijnen voorgeschreven in de normale praktijk kunnen minder effectief zijn of meer bijwerkingen geven dan in studies naar dezelfde behandeling. Omdat geriatrisch onderzoek de evaluatie omvat van alle aandoeningen waar een oudere aan lijdt, zijn geriaters bij uitstek in staat om het medicatie gebruik kritisch te beoordelen voor de verschillende aandoeningen. Het grootste dilemma is dat voor een deel van de patiënten, met verschillende complexe combinaties van aandoeningen en medicijnen, geen evident bewijs beschikbaar is voor het totale behandelings regime voor alle gelijktijdig aanwezige ziektes en risicofactoren, en misschien ook nooit zal zijn. Dus moet het identificeren van die aandoeningen waarvan de behandeling het beste overeenkomt met de prioriteiten van de patiënt het doel zijn van iedere behandelend arts. Dit geeft richting aan een van de uitdagingen in de geriatrie: de zorgvuldige evaluatie van polyfarmacie, daar dit geassocieerd is met een hoger risico op therapieontrouw, ongepast voorschrijven, bijwerkingen, hogere mortaliteit, maar ook onderbehandeling door het achterwege laten van geïndiceerde medicatie.

Dit proefschrift beschrijft ongelukken met medicatie in de dagelijkse praktijk. De effecten op polyfarmacie van geriatrisch onderzoek worden geëvalueerd. Tenslotte worden dilemma's in de behandeling van vaak voorkomende cardiovasculaire aandoeningen besproken.

Hoofdstuk 1. Ongelukken in voorschrijven en beschrijven van medicatie.

In **hoofdstuk 1.1** wordt een gevalsbeschrijving gepresenteerd over een vieze fax machine, waaroor een grijze streep ontstond op een gefaxt recept voor trazodon. Dit leidde tot een label met een vier keer hogere dosering dan bedoeld. Hierdoor collabeerde een angstige, demente patiënte na de eerste dosis.

In **hoofdstuk 1.2** wordt beschreven hoe een patiënt geïntoxiceerd wordt met valproïnezuur waardoor een accidentele overdosering na overplaatsing vanuit een verpleeghuis. De oorzaak was een onjuiste combinatie van de hoeveelheid en concentratie van de voorgeschreven valproïnezuur, waarschijnlijk door het per abuis aanklikken van de verkeerde oplossing bij elektronisch voorschrijven.

Hoofdstuk 1.3 beschrijft een prospectieve studie over discrepanties in medicijn gebruik zoals gerapporteerd door de patiënt en diens verzorgers, de huisarts en de apotheek. Geïncludeerd werden 120 patiënten. Tenminste één discrepantie tussen de medicatie lijsten van patienten, huisarts en apotheek was aanwezig in 104 patiënten (87%). In 90 patiënten was er tenminste één verschil tussen de medicijnen zoals gemeld door de patiënt en de huisarts(75%). Patiënten met tenminste een discrepantie rapporteerden het gebruik van méér medicijnen en meer behandelend artsen naast hun huisarts. Negenentwintig patiënten (24.2%) ervoeren een mogelijk nadelig effect bij discrepante medicatie. De apotheek was onbekend met het gebruik van de hiervoor relevante medicatie in slechts twee patiënten.

Hoofdstuk 2. Evaluatie van polyfarmacie in opgenomen en ambulante geriatrische patiënten.

In **hoofdstuk 2.1** zijn de effecten van opname op een geriatrische afdeling op medicatie gebruik retrospectief geanalyseerd. Een vergelijking is gemaakt tussen de 724 patiënten opgenomen in 1985 versus de 258 patiënten opgenomen gedurende 2002. Het belangrijkste verschil tussen medicatie gebruik voor en na opname was een toename in het aantal gebruikte medicijnen, vooral vitamines. Vergeleken met 1985, werden in 2002 meer preventieve geneesmiddelen voorgeschreven, en nieuwe types medicijnen zoals ACE remmers en proton pomp remmers.

De evaluatie van farmacotherapie bij geriatrische patiënten na geriatrisch onderzoek werd ook retrospectief geanalyseerd voor een diagnostische dag kliniek gedurende 2002.

Hoofdstuk 2.2 laat zien dat frequent medicijnen worden gestopt omdat de indicatie niet meer bestond (39% van de gestopte medicijnen), vanwege bijwerkingen (33%) en omdat er betere farmacotherapeutische mogelijkheden waren (22%). Omdat ook vaak geneesmiddelen werden toegevoegd voor nieuw gediagnosticeerde aandoeningen (69.2%), voorkomen van osteoporose (15%) en verbeteringen in farmacotherapie (10.6%), werden na geriatrisch onderzoek gemiddeld meer medicijnen gebruikt (5.4 versus 4.6).

Hoofdstuk 2.3 beschrijft de prevalentie van onderbehandeling in ambulante geriatrische patiënten. De aanwezigheid van contra-indicaties voor medicijnen voor onderbehandelde aandoeningen werd prospectief geëvalueerd bij 807 patiënten die werden verwezen voor geriatrisch onderzoek op de dagkliniek gedurende 2004. Van hen hadden 548 tenminste één aandoening waarvan bekend was dat deze vaak wordt onderbehandeld. Vóór geriatrisch onderzoek werden 170 patienten onderbehandeld (32.9%), erna 115 (22.3%). Contra-indicaties waren aanwezig bij 102 patiënten(19.8%) en vaker in onderbehandelde patiënten. Correctie van alle onderbehandeling ongeacht de aanwezigheid van contra-indicaties zou het aantal medicijnen met 97 hebben verhoogd naar gemiddeld 6.8 geneesmiddelen in de hele populatie, en 7.5 in de patiënten die na het onderzoek nog steeds onderbehandeld werden.

In **hoofdstuk 2.4** wordt de prevalentie en klinische relevantie beschreven van geneesmiddel interacties bij 807 ambulante patiënten die in 2004 de dagkliniek geriatrie bezochten. Bij 300 patiënten, 44,5% van de patiënten die meer dan één geneesmiddel gebruikte, werden 398 potentiële interacties geïdentificeerd. Bij 172 (25,5%) van de patiënten die meer dan één geneesmiddel gebruikte werden geneesmiddel combinaties gevonden met óf bijwerkingen door combinaties en/óf onvoldoende effect. Veranderingen in medicatie met mogelijke interacties werden voorgesteld of geëffectueerd voor 111 van deze 172 patiënten (65%).Van deze patiënten kwamen 61 (55 %) op controle. Van hen bleken 49 (80 %) verbeterd na veranderingen in hun medicatie regime.

Een prospectieve verkennende studie wordt beschreven in **hoofdstuk 2.5**. Na geriatrische evaluatie werden 40 patiënten en hun mantelzorgers bevraagd en waar nodig thuis bezocht om te beoordelen of voorgestelde wijzigingen in medicatiegebruik waren uitgevoerd. Het geneesmiddelen gebruik was bij 77.5% van de patiënten volledig aangepast volgens het advies van de afdeling geriatrie. Van de geadviseerde veranderingen rapporteerden de patiënt en de mantelzorgers dat 90% was uitgevoerd. Alleen de aanwezigheid van een verzorger die toezag op het medicatiegebruik was geassocieerd met therapietrouw.

Hoofdstuk 3. Behandeling van vasculaire aandoeningen.

In **hoofdstuk 3.1** wordt de behandeling van hypertensie in geriatrische patiënten ouder dan 80 jaar vergeleken met de belangrijkste studie hiervoor, het HYVET onderzoek. In 2004, werden 141 van de 147 patiënten uit deze leeftijdsgroep met hypertensie in de voorgeschiedenis behandeld met antihypertensieve medicatie (95.9%). Van deze patiënten hadden 52 (35.4%) geïncludeerd kunnen worden in HYVET, 95 patiënten (64.6%) zouden zijn geëxcludeerd. De 147 geriatrische patiënten in deze studie toonden meer co-morbiditeit dan de HYVET populatie, bijvoorbeeld dementie, beroertes en cardiovasculaire aandoeningen naast hypertensie. Goede bloeddruk behandeling zoals gedefinieerd volgens HYVET, was bereikt in 50.3% van de patienten. De patiënten die geëxcludeerd zouden zijn uit HYVET hadden een bloeddruk vergelijkbaar aan de bloeddruk van patiënten die wel geïncludeerd hadden kunnen worden.
Het enige significante verschil tussen patiënten met een adequate bloeddruk controle en de patiënten met een nog hoge bloeddruk was het gemiddelde aantal antihypertensieve medicijnen: respectief 2.2 (± 1.0) versus 1.8 (± 1.1).

In **hoofdstuk 3.2** worden de contra-indicaties voor antistolling in ouderen met atrium fibrilleren besproken. Besproken wordt dat een hogere leeftijd geassocieerd is met onderbehandeling. Patiënten met een hoger risico op beroertes hebben ook een hoger risico op bloedings complicaties. Het verband tussen grote bloedingen en andere mogelijke contra-indicaties is inconsistent. Het bloedings risico in de normale praktijk is hoger dan in studies. Gepubliceerde aantallen bloedingen reflecteren selectie bias, omdat het vooral relatief gezonde ouderen betreft. Het gebruik van risico stratificaties voor de bepaling

van het risico op beroerte en bloedingen moet worden geïmplementeerd. Echter, deze dienen opnieuw gevalideerd te worden omdat is geobserveerd dat het risico op beroertes dalende is.

In **hoofdstuk 3.3** wordt getoond dat bij geriatrische patiënten met atrium fibrilleren, risico factoren voor beroerte die het gebruik van antistolling nodig maken en contra-indicaties voor coumarine vaak tegelijkertijd aanwezig zijn in patiënten. Na geriatrisch onderzoek, werden 73 (52%) van de 141 patiënten met chronisch of paroxismaal atrium fibrilleren behandeld met antistolling. Extra risico factoren die het voorschrijven van coumarine ondersteunden, tegelijkertijd met contra-indicaties voor het gebruik van coumarine waren aanwezig in 110 patiënten (78.0%). Noch de aanwezigheid van risico factoren, noch het hebben van contra-indicaties was geassocieerd met coumarine gebruik. Alleen hogere leeftijd was significant geassocieerd met de kans geen antistolling voorgeschreven te krijgen.

Hopelijk zijn in dit proefschrift de mogelijkheden die geriatrisch onderzoek biedt voor de kritische evaluatie van polyfarmacie voor het voetlicht gekomen. Toekomstig onderzoek blijft nodig om meer bewijs te verkrijgen voor het behandelen van specifieke aandoeningen in kwetsbare ouderen, daar deze patiënten nog steeds vaak onderbehandeld worden, ondanks hun hoge risico op een slechtere uitkomst dan jongere patiënten. Anderzijds krijgen kwetsbare patiënten ook behandelingen, zonder dat deze bewezen gunstig zijn, als men rekening houdt met hun complexe comorbiditeit.

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Paranimf Maarten: dat er een punt achter dit hoofstuk van mijn leven kan komen te staan is jouw verdienste. Je prikkelt, stimuleert, geeft gas maar remt ook op tijd en gooit je humor, relativeringsvermogen en zorgzaamheid op de goede momenten in de strijd. Nooit teveel, en nooit te weinig.

Curriculum Vitae

Clarinda (Linda) Rixt Tulner werd geboren op 4 oktober 1964 te Aduard in de provincie Groningen. Na het Praedinius Gymnasium volgde vanaf 1982 de studie geneeskunde aan de Rijks Universiteit Groningen. Het coassistentschap klinische geriatrie in het Slotervaart Ziekenhuis leidde to de keuze voor dit vak. Eerst werd ruim een jaar ervaring op gedaan als dokter Linda, AGNIO in het Diakonessenhuis te Groningen. Daarna werden vergezeld door Arany, en later ook Lon de verschillende stages van de specialisatie doorlopen:
Interne Geneeskunde in IJmuiden bij Anton Kerst, Psychogeriatrie in Venray bij Gertie Goluke en de Somatische Geriatrie in Amsterdam bij Carla Thijssen en Gerard de Ruyter, en vervolgens in Nijmegen bij Willibrord Hoefnagels. Op 1 april 1997 werd zij klinisch geriater, en ging terug naar de bakermat waar het enthousiasme voor de geriatrie zijn vorm kreeg. Sinds 4 oktober 2002 is zij erkend als opleider voor de klinische geriatrie.