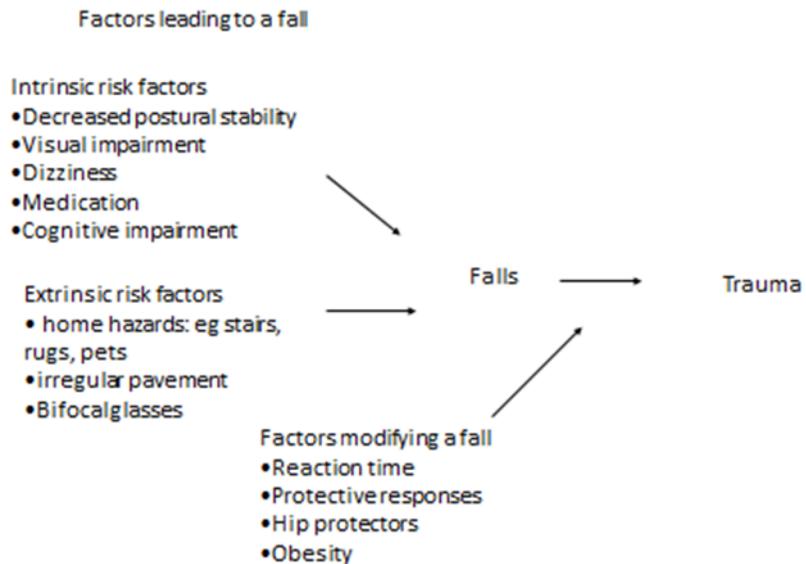


Introduction

Fall incidents occur frequently in older persons. Annually, about 30% of persons older than 65 years falls at least once and 15% falls at least twice.¹⁻³ The consequences of falling may be severe: about 5% of the falls leads to a fracture and about 5% causes other serious injuries.^{4;5} About one in four fallers consults a hospital emergency department or primary care physician after the fall. Other consequences are loss of function and mobility, fear of falling, loss of independence leading to institutionalisation and death.⁵ Apart from the loss of function and quality of life attributable to falls, the financial impact on society is considerable.⁶ These facts emphasize the necessity to study the risk factors of falls and the most effective measures to prevent falling in older persons. Several relevant risk factors are presented in figure 1. This thesis describes research that was done to elucidate the fall risks attributable to several classes of medication and the association between frailty and fall risk. The current knowledge about fall risk factors was subsequently used in a multifactorial intervention studied in a randomised clinical trial aimed at the prevention of new falls in older persons with intermediate to high fall risk.

Risk factors for falls have been extensively studied. Previous falls, female sex, fear of falling, dizziness, urinary urgency, functional limitations and walking speed were among the factors that several studies found to be associated with increased fall risk.⁷⁻¹⁰ The use of psychotropic medication, such as benzodiazepines and tricyclic antidepressants, is also associated with increased fall risk.^{11;12} Moreover, their use was not only associated with increased risk of injurious falls but, also with increased risk of hip fractures.^{13;14} Although most studies applied adjustment for co-morbid conditions, confounding by indication cannot be ruled out as an explanation of the association of psychotropic drug use with increased fall risk.¹⁵



The STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) is an explicit medicine review tool that has rapidly gained importance in geriatric medicine. Among the prescriptions that are active in the central nervous system, the tool deems the use of "long-term (i.e. > 1 month), long-acting benzodiazepines" potentially inappropriate because of the risks of prolonged sedation, confusion, impaired balance and falls.¹⁶ Despite this advice, several aspects of the fall risk increasing properties of psychotropic drugs are uncertain. Differences in fall risk resulting from the use of these drugs may be due to their pharmacodynamics properties but also to pharmacokinetic differences like metabolic route, volume of distribution and excretion. The pharmacokinetic properties result in differences in elimination half-life and duration of drug activity. Mainly due to methodological difficulties, like lack of longitudinal data and lack of data on potential confounders, the debate on the influence of the elimination half-life of benzodiazepines on fall risk was undecided.^{17;18 19;20} In most studies the maximum elimination half-life of benzodiazepines of agents that were considered "short-acting" was 24 hours. However, we hypothesised that benzodiazepines with a half-life shorter than 10 hours may be associated with a lower fall risk than benzodiazepines with a longer elimination half-life. In two separate prospective cohort studies among non-institutionalised old persons with a low to intermediate and a high risk of falls, respectively, we addressed the association between the use

of benzodiazepines with short and long elimination half-life and accidental falls. The results of these studies are presented in Chapter 2.

In 2006, Yang et al. reported an increased risk of hip fractures in persons of 50 years and older using proton pump inhibitors (PPI).²¹ The authors hypothesized that decreased calcium solubility and intestinal malabsorption of calcium secondary to acid suppressive therapy may explain this association. The use of H2 receptor antagonists (H2RA), an alternative drug class for treatment of acid induced gastrointestinal complaints, was not associated with increased risk of hip fracture. Other studies confirmed their findings.

None of these studies did take into account the number of fallers and falls. We studied the possible associations between the use of PPI or H2RA and falls and fractures with the data that were available from LASA. In addition to prospective falls and fracture data, heel bone ultrasound reflecting bone mass density was also available in this study. The results are presented in Chapter 3.

The concept of frailty in older adults expresses an expectation of increased risk of adverse health outcomes such as disability, complications and institutionalisation. Although frailty is a useful concept for both clinical and research purposes in older adults, the definition and methods of assessment are heterogeneous. In 2001 Fried et al. described a phenotype of frailty that has been widely followed in geriatric and gerontological research.²² They defined frailty as a clinical syndrome that is present in persons who fulfil 3 or more of the following criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. A subsequent debate in the literature has revolved around the question whether or not frailty definitions should include cognitive and mental factors.²³

In LASA frailty was assessed using similar markers complemented with indicators of psychological and cognitive function. Frailty, defined by the LASA frailty instrument, was associated with decline of physical performance and self-reported functional ability after a follow-up of 3 years.²⁴ Most of the indicators of the LASA frailty instrument coincide with risk factors for falls and fractures.^{1;9;25-28} Fall and fracture risk have been demonstrated to be associated with frailty assessed by instruments that do not include aspects of psychological or cognitive functions.^{29;30} We hypothesised that frailty assessed by the LASA frailty instrument would be associated with increased fall and fracture risk. In addition we examined which individual frailty markers were associated with falls and fractures, and we compared the predictive value of frailty with that of falls history, an established

risk factor for falls and fractures.^{1;9;25-28} The results of this study are presented in Chapter 4.

Based on the knowledge of the most relevant potentially reversible fall risk factors numerous fall prevention studies have been done. In 1999, Wolf et al. published a landmark study in which they showed effectiveness of tai chi exercise training for the prevention of falls in relatively healthy older adults.³¹ Other research groups showed effectiveness of strength and balance exercises in similar study populations.^{32;33} Separately addressing other fall risk factors like home hazards showed only minor reductions of fall risk.³⁴ Day et al. studied exercise, visual improvement and home hazard reduction separately and in combinations. Whereas combining all three interventions showed the most benefit, of the separate interventions only exercise reduced fall risk significantly.³⁵ Multifactorial trials adding more interventions were also performed in older adults with co-morbid conditions. These studies resulted in conflicting outcomes.³⁶⁻³⁹ A meta-analysis published in 2004 showed minor effectiveness of multifactorial fall prevention in older adults living in the community.⁴⁰ The Dutch CBO guideline “Preventie van Valincidenten bij Ouderen” (Prevention of falls in older persons) was also published in 2004. It advised to perform a multifactorial analysis and intervention in all community dwelling older persons who had fallen more than once in the year before and those who presented themselves at an emergency department after a fall. Based on the evidence that was available in 2004 the guideline committee advised to perform analysis and intervention in older adults with manifest risk factors for falls and fractures. They also concluded that, although multifactorial intervention trials seemed more successful than single interventions, specific implementation trials were not available at that time.⁴¹ They advised to add a medication review and possibly withdrawal of psychotropic medication based on limited evidence from one RCT.⁴² The conclusions and advice of the national guideline combined with the positive results of the recently published multifactorial intervention study of Close et al.⁴³ formed the inspiration to design our own study to address the research questions that needed an urgent answer.

We designed a study to test the hypothesis that older adults with the combination of several fall risk factors and an incident fall would benefit from a multifactorial evaluation and targeted intervention. Although the results of some previously performed multifactorial fall prevention studies in unselected participants were promising,^{38;44} the meta-analysis by Chang et al. showed that it is uncertain whether participants with a high fall risk would also benefit from such an

evaluation and intervention.⁴⁰ Our study was conducted in Amsterdam between April 2005 and July 2008. We selected older adults who visited the emergency department or their general practitioner after a fall. They were asked to participate in the study when they had an elevated fall risk according to the LASA (Longitudinal Aging Study Amsterdam) fall risk profile.⁹ After randomisation, intervention participants were evaluated in the geriatric out-patient clinic of the VU university medical center. An intervention aimed at all fall risk factors that were identified was performed in close cooperation with their general practitioner and with primary care physical and occupational therapists. The design of this study is presented in Chapter 5 and the results are presented in Chapter 6.

To test whether discontinuation of fall-risk increasing drugs (FRID) would lead to a reduction of the number of falls and fallers we participated in a multicentre study in collaboration with the department of Geriatric Medicine of the Erasmus MC in the IMPROVeFALL study. In this prospective, multi-centre, randomised controlled trial the effect of a structured medication assessment including the withdrawal of fall-risk increasing drugs was compared with 'care as usual' in older adults presenting at the Emergency Department after a fall.⁴⁵ All patients received a full geriatric assessment at the research outpatient clinic. Patients were randomised between a structured medication assessment including withdrawal of fall-risk increasing drugs and 'care as usual'. After twelve months, a second visit to the research outpatient clinic was performed and changes in the medication regimen both in the intervention and control group were assessed. The design and results of this study are presented in Chapter 7.

The discussion, the implications and the perspectives on future research following from the results of the studies that are reported in this thesis are presented in Chapter 8.

Reference List

- (1) Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls. A prospective study. *JAMA* 1989;261:2663-2668.
- (2) Tinetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury during falls by older persons in the community. *J Am Geriatr Soc* 1995;43:1214-1221.
- (3) Tromp AM, Pluijm SM, Smit JH, Deeg DJ, Bouter LM, Lips P. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *J Clin Epidemiol* 2001;54:837-844.
- (4) CBO. Osteoporose. Tweede herziene richtlijn. Alphen aan den Rijn, the Netherlands: Van Zuiden Communications B.V., 2002.
- (5) Stel VS, Smit JH, Pluijm SM, Lips P. Consequences of falling in older men and women and risk factors for health service use and functional decline. *Age Ageing* 2004;33:58-65.
- (6) Panneman MJ, Goettsch WG, Kramarz P, Herings RM. The costs of benzodiazepine-associated hospital-treated fall injuries in the EU: a Pharmo study. *Drugs Aging* 2003;20:833-839.
- (7) Luukinen H, Koski K, Laippala P, Kivela SL. Predictors for recurrent falls among the home-dwelling elderly. *Scand J Prim Health Care* 1995;13:294-299.
- (8) Luukinen H, Koski K, Kivela SL, Laippala P. Social status, life changes, housing conditions, health, functional abilities and life-style as risk factors for recurrent falls among the home-dwelling elderly. *Public Health* 1996;110:115-118.
- (9) Pluijm SM, Smit JH, Tromp EA et al. A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. *Osteoporos Int* 2006;17:417-425.
- (10) Stel VS, Pluijm SM, Deeg DJ, Smit JH, Bouter LM, Lips P. A classification tree for predicting recurrent falling in community-dwelling older persons. *J Am Geriatr Soc* 2003;51:1356-1364.
- (11) Hartikainen S, Lonroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci* 2007;62:1172-1181.
- (12) Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999;47:30-39.

- (13) Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. *CNS Drugs* 2003;17:825-837.
- (14) Wagner AK, Zhang F, Soumerai SB et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med* 2004;164:1567-1572.
- (15) Bartlett G, Abrahamowicz M, Grad R, Sylvestre MP, Tamblyn R. Association between risk factors for injurious falls and new benzodiazepine prescribing in elderly persons. *BMC Fam Pract* 2009;10:1.
- (16) Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008;46:72-83.
- (17) Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA* 1989;262:3303-3307.
- (18) Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics and sedatives and risk of fractures: effects of half-life. *Calcif Tissue Int* 2008;82:34-43.
- (19) Hanlon JT, Boudreau RM, Roumani YF et al. Number and dosage of central nervous system medications on recurrent falls in community elders: the Health, Aging and Body Composition study. *J Gerontol A Biol Sci Med Sci* 2009;64:492-498.
- (20) Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Zolpidem use and hip fractures in older people. *J Am Geriatr Soc* 2001;49:1685-1690.
- (21) Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947-2953.
- (22) Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-M156.
- (23) Morley JE, Perry HM, III, Miller DK. Editorial: Something about frailty. *J Gerontol A Biol Sci Med Sci* 2002;57:M698-M704.
- (24) Puts MT, Lips P, Deeg DJ. Static and dynamic measures of frailty predicted decline in performance-based and self-reported physical functioning. *J Clin Epidemiol* 2005;58:1188-1198.
- (25) Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. *J Gerontol* 1991;46:M164-M170.
- (26) Stalenhoef PA, Diederiks JP, Knottnerus JA, Kester AD, Crebolder HF. A risk model for the prediction of recurrent falls in community-dwelling elderly: a prospective cohort study. *J Clin Epidemiol* 2002;55:1088-1094.

- (27) Tromp AM, Smit JH, Deeg DJ, Bouter LM, Lips P. Predictors for falls and fractures in the Longitudinal Aging Study Amsterdam. *J Bone Miner Res* 1998;13:1932-1939.
- (28) Tromp AM, Ooms ME, Popp-Snijders C, Roos JC, Lips P. Predictors of fractures in elderly women. *Osteoporos Int* 2000;11:134-140.
- (29) Ensrud KE, Ewing SK, Taylor BC et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med* 2008;168:382-389.
- (30) Romero-Ortuno R, Cogan L, Foran T, Kenny RA, Fan CW. Continuous noninvasive orthostatic blood pressure measurements and their relationship with orthostatic intolerance, falls, and frailty in older people. *J Am Geriatr Soc* 2011;59:655-665.
- (31) Wolf SL, Barnhart HX, Kutner NG, McNeely E, Coogler C, Xu T. Reducing frailty and falls in older persons: an investigation of Tai Chi and computerized balance training. Atlanta FICSIT Group. Frailty and Injuries: Cooperative Studies of Intervention Techniques. *J Am Geriatr Soc* 1996;44:489-497.
- (32) Fiatarone MA, O'Neill EF, Ryan ND et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med* 1994;330:1769-1775.
- (33) McMurdo ME, Millar AM, Daly F. A randomized controlled trial of fall prevention strategies in old peoples' homes. *Gerontology* 2000;46:83-87.
- (34) Cumming RG, Thomas M, Szonyi G et al. Home visits by an occupational therapist for assessment and modification of environmental hazards: a randomized trial of falls prevention. *J Am Geriatr Soc* 1999;47:1397-1402.
- (35) Day L, Fildes B, Gordon I, Fitzharris M, Flamer H, Lord S. Randomised factorial trial of falls prevention among older people living in their own homes. *BMJ* 2002;325:128.
- (36) Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet* 1999;353:93-97.
- (37) Coleman EA, Grothaus LC, Sandhu N, Wagner EH. Chronic care clinics: a randomized controlled trial of a new model of primary care for frail older adults. *J Am Geriatr Soc* 1999;47:775-783.
- (38) Hornbrook MC, Stevens VJ, Wingfield DJ, Hollis JF, Greenlick MR, Ory MG. Preventing falls among community-dwelling older persons: results from a randomized trial. *Gerontologist* 1994;34:16-23.

- (39) Tinetti ME, Baker DI, McAvay G et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med* 1994;331:821-827.
- (40) Chang JT, Morton SC, Rubenstein LZ et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. *BMJ* 2004;328:680.
- (41) CBO. Richtlijn Preventie van valincidenten bij ouderen. Alphen aan den Rijn: Van Zuiden Communications B.V., 2004.
- (42) Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc* 1999;47:850-853.
- (43) Close JC, Hooper R, Glucksman E, Jackson SH, Swift CG. Predictors of falls in a high risk population: results from the prevention of falls in the elderly trial (PROFET). *Emerg Med J* 2003;20:421-425.
- (44) Wagner EH, LaCroix AZ, Grothaus L et al. Preventing disability and falls in older adults: a population-based randomized trial. *Am J Public Health* 1994;84:1800-1806.
- (45) Hartholt KA, Boye ND, van der Velde N et al. [Cost] effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROVeFALL-study). *BMC Geriatr* 2011;11:48.