General discussion

In this thesis the methods and results of three longitudinal fall risk studies and of two falls prevention studies have been presented. In the longitudinal cohort studies we confirmed the fall risk associated with short-acting benzodiazepine use, with H2-receptorantagonist use and with frailty. Both a multifactorial intervention study in high risk patients and a study of reduction of fall risk increasing drugs (FRID) failed to show the expected benefit for the mostly multi-morbid older persons who came to the emergency room of a hospital or their primary care physician after a fall.
In this chapter the role of the risk factors for falls to detect those who are at an increased risk of falls will be discussed. Furthermore difficulties in the design, conduction and interpretation of results of the intervention studies will be discussed and recommendations for future directions of research will be made.

Fall risk factors

The characteristics that are associated with increased fall risk in older persons have been extensively studied.[1;2] The fall risk factors that have been found in several studies vary greatly due to the differences in the populations that were studied and the methods used. In the Longitudinal Aging Study Amsterdam (LASA) a community based population was studied. Based on a three year fall follow-up, a fall risk profile was constructed that contained 9 risk factors and 2 interactions.[3] However, this risk profile is valid for community based populations only. For example, although recommendations from the Dutch fall prevention guideline state that orthostatic hypotension is probably a risk factor that should be addressed in both community based and institutionalised older persons, it was not among the significant risk factors in the LASA population.[4] In contrast, in frailer older persons living in care homes, orthostatic hypotension is associated with increased fall risk.[5] This finding illustrates the need to define relevant risk factors separately for each population that is the target of an intervention. It also raises the question whether the LASA risk profile was the proper instrument to select the persons with the highest fall risk among the older persons who participated in our multifactorial intervention study and who were not average community-dwelling subjects because they had already experienced a fall.
Although we added to the knowledge base of pharmacological fall risk factors, especially short acting benzodiazepines and H2-antagonists, the IMPROveFALL intervention, in which we tried to withdraw fall risk increasing drugs (FRIDs)

including these two substances, did not lead to a decreased fall risk.[6] In the study design no differentiation was made in the strength of the fall risk increasing properties of the separate drug classes. This might have led to prioritisation of the withdrawal of the drugs with the weakest fall risk increasing properties. Furthermore, very little is known about pharmacokinetic and pharmacodynamic drug interactions leading to an even further increased fall risk of FRIDs when used simultaneously. In our pharmaco-epidemiological studies adjustment for co-medication was not feasible, thus we were not able to rule out the possibility of confounding by interaction with other medication. It would be logical to expect pharmacodynamic interactions such as increased muscle relaxation due to combination of sedating drugs. However, no robust data are available on this topic. Furthermore, systematic research is desperately needed to elucidate potentially increased fall risk due to pharmacokinetic interactions leading to e.g. elevated serum levels of "low potency" FRIDs or even of drugs without previously known fall risk increasing properties.

Most of the available frailty definitions contain several items that are associated with fall risk. In several studies and in our study, frailty was shown to be significantly associated with fall risk. The discriminative ability of frailty is, however, smaller than that of falls history, which has been found to be the strongest predictor of falls.[7-9] In a meta-analysis of risk factors in community dwelling older persons this finding was corroborated; one or more falls in the last year proved to be the strongest predictor of future falls.[2] Because the measurement of the separate frailty parameters is more time-consuming than recording fall history we would not recommend using frailty to predict the outcomes fall risk or fall rate.

Although fall prevention guidelines suggest limiting multifactorial fall prevention programs to the older persons with the highest fall risk, it is not clear what the fall risk factors or other characteristics are of those persons who will benefit most from these costly intervention programs.[4]

Fall prevention strategies

Fall prevention strategies in older persons have been extensively studied. Multiple single intervention trials and multifactorial intervention trials have been published.[10] Before we published the design of our multifactorial falls prevention study,[11] most falls prevention studies reported positive results. Several hallmark studies like the single intervention FICSIT trial (Frailty and Injuries: Cooperative Studies of Intervention Techniques) and the multifactorial intervention trials of

Tinetti et al. and the PROFET study (Prevention of Falls in the Elderly Trial) showed a reduction of fall risk in participants with a low to intermediate fall risk at baseline.[12-14] Shortly before and directly after publication of the results of our multifactorial falls prevention trial,[15] several other negative multifactorial fall prevention studies have been published.[16-20] In these studies as well as our study, participants with a high fall risk were selected for participation. The common denominator of this elevated risk was a (recent) history of falls. In these high risk participants a multifactorial evaluation and intervention neither led to a lower proportion of fallers nor to a reduction of falls and fractures. After performing a meta-analysis of the data of 19 and 34 trials respectively, a recent Cochrane review concluded that multifactorial intervention reduced fall rate (number of falls per person) but neither the risk of falling (the number of persons who fell) nor fracture risk was reduced.[10]

In order to develop intervention strategies that will successfully decrease fall risk in this target group, the mechanisms that led to a failure to demonstrate benefit of multifactorial interventions have been discussed extensively. These discussions revolved around the following characteristics of the negative studies: selection of the target group, selection of the most effective types of intervention and the strategies used to "administer" the interventions.[10;21;22] Analysis of these characteristics hopefully will enable research developments that should lead to more effective strategies to prevent falls in older persons with an elevated fall risk.

Selection of the intervention group

In our multifactorial study we were able to include only 21.9% of the persons who met the inclusion criteria. The majority of the potential participants refused to participate. In other fall prevention studies the percentage of eligible participants who agreed to participate was high in studies that did not select participants based on increased fall risk and was much lower in the studies that selected their participants based on fall risk. In the studies of Tinetti et al. and Close et al. more than 75% of those eligible agreed to participate.[12;13] In contrast, in the studies of Conroy et al. and Faes et al. less than 25% of those eligible eventually participated in the study.[16;17] It is likely that the low inclusion rate has affected the outcomes of our and other studies selecting high risk participants. The participants who agreed to participate were most likely the most highly motivated persons in the eligible population. Both intervention and control groups were probably inclined to change dangerous habits, seek help for their health problems and perform their exercises. This conjecture is corroborated by our results that showed a lower risk of falling in

both intervention and control groups compared with self-reported fall risk in the year prior to the start of the study.
A much discussed characteristic of fall prevention studies is the choice of inclusion and exclusion criteria. Since the prevalence of cognitive decline in older persons is high and the fall risk double that of cognitive healthy persons, the exclusion of persons with cognitive impairment is much debated. The VUmc medical ethical committee did not approve the inclusion of older persons with dementia or other relevant cognitive decline. In most other fall prevention studies older persons with cognitive decline were excluded or, if included, were underrepresented. Because cognitive decline may influence the uptake of the intervention the results of most fall prevention studies cannot be extrapolated to older persons with dementia. Frailty in older persons, both according to the criteria of Fried et al. and those of LASA (Longitudinal Aging Study Amsterdam), is associated with an increased fall risk. Selecting older persons based on falls history also leads to selection of participants with an elevated fall risk. Future research should address the question whether selecting older persons based on either frailty, fall risk or fall history criteria will lead to more benefit from multifactorial interventions to prevent falls.[9;23]

Selection of interventions

Fall prevention studies using multifactorial interventions usually have two elements in common: exercise programs or physical therapy and addressing the individual fall risk factors that are identified. Regarding the first element; the exercise programs that are used are very heterogeneous. Although most studies claim that their exercises are aimed at increasing balance and strength, the methods or techniques that are used are not specified. In a limited number of studies single exercise methods were evaluated. Tai Chi was used to prevent falls in the hallmark study of Wolf et all.[14] Meta-analysis of the results of 5 and 6 studies showed the positive effects of Tai Chi in lowering both risk of falls and rate of falling respectively. Subgroup analysis according to fall risk at enrolment showed that Tai Chi was more effective in unselected older persons.[10] The ineffectiveness of Tai Chi in older persons with a high fall risk might be due to high withdrawal and low adherence rates possibly as a result of the high level of coordination, balance and strength required at baseline.[24] Studies in which gait, balance and functional training were applied showed that the rate of falling (the number of falls per participant) decreased but not the risk of falling (the number of participants who fell).[10] Although advanced techniques such as force platforms and accelerometers

have improved the precision of measuring risk factors for falls, no studies have been published that demonstrate benefits resulting in falls prevention facilitated by the diagnostic insights that these instruments provide.[25;26] Strength training did neither lower the rate nor the risk of falling.[10]

Regarding the second element of multifactorial fall prevention programs; one of the important aspects of addressing individual fall risk factors is a reduction of so called fall risk increasing drugs (FRIDs). Because a randomised trial cannot be done due to ethical reasons, the pharmacodynamic fall-promoting effects of several drug classes cannot be studied. Most pharmaco-epidemiological studies presenting associations between several drug classes and falls do not elaborate on possible causal relationships.[27] However a review of pharmacodynamics in older adults identified several pharmacodynamic effects and changes in older persons that might increase fall risk.[28] The common denominator appears to be postural instability. Most psychopharmacological drugs are associated with loss of alertness and sedation leading to decreased reaction time. The use of benzodiazepines additionally results in increased body sway and memory dysfunction.[29] Insecurity resulting from these cognitive and motor effects of the use of sedatives will lead to fear of falls and avoidance of activities that are seen as high risk and ultimately physical deconditioning resulting in a further increased fall risk. Although the Dutch fall prevention guideline of 2004 advises to evaluate medication and stop unnecessary and especially psychotropic medication, many aspects of the fall risk increasing properties of several groups of medication still have to be studied.[4] Old beliefs have to be re-evaluated: contrary to results from the nineteen nineties we found evidence from our observational longitudinal study that the use of short acting benzodiazepines is at least as much associated with increased fall risk as the use of long acting benzodiazepines. Withdrawal or dose reduction of potential FRID's has demonstrated a decrease of fall rate in a cohort study and in a placebo-controlled study.[30;31] Van der Velde et al. also studied the effects of medication withdrawal on mobility and tilt-table test outcomes.[32;33] Based upon a decrease in the prevalence of both orthostatic hypotension and carotid sinus hypersensitivity they concluded that the effects of FRID and especially cardiovascular medication withdrawal are possibly due to better cardiovascular homeostasis.[33] A study of medication review and FRID reduction in older persons with an increased fall risk selected through the records of their pharmacy did however not result in reduction of either fall rate or fall risk.[34]

The results of our Dutch multicenter prospective study of withdrawal of FRID's in high risk older persons (the IMPROvefALL study) was also negative.[6;35] The only

difference in treatment between the intervention group and the control group was the withdrawal of mainly psychotropic and cardiovascular medication, which suggests that the elevated fall risk in older persons probably results from multiple aetiological factors and may only benefit from FRID withdrawal when it is part of a multifactorial falls prevention program.[36]

Adverse effects of interventions

Interventions that are designed to reduce fall risk may also lead to improvement of mobility through improved balance and strength, increased physical condition and reduction of fear of falls. The result of the improvement of mobility will be that the "time at risk" for falls will increase. This may paradoxically negate the fall risk reduction that may have been achieved. This effect may partly explain the negative results in other studies that studied participants with an increased fall risk. It may be postulated that increasing the time-at-risk will have a different effect on the fall risk in low risk compared with high risk older persons. In healthy low risk older persons time that is spent standing or walking, apart from the formal exercise sessions may further increase stability, strength and endurance. Conversely, in high risk older persons the level of stability, strength and endurance that is achieved by the exercise sessions may be inadequate to compensate for more time at risk. This hypothesis is corroborated by the results of the FARAO (FAll Risk Assessment in Older adults) study. Van Schooten et al. demonstrated that in older adults with gait instability as reflected by decreased harmonicity of medio lateral trunk accelerations, the fall risk increased with higher levels of physical activity.[37] Falls cannot be prevented completely. Therefore, in older persons with a high fall risk the consequences of falls, especially fractures should be addressed as well. Bisphosphonates, selective estrogen receptor modulators (SERM's), parathyroid hormone analogues and several other drugs have been shown to reduce fracture risk.[38] Furthermore, the use of hip protectors seemed feasible and has been widely advocated and refuted because of non-compliance and the dangers accompanying their use.[4;39;40] However, fracture risk reduction of hip protectors has only been consistently shown in frail older people in nursing care.[41]

Administration of interventions

Some non-effective multifactorial interventions used a combination of assessment of fall risk factors and a referral to the primary care provider to carry out the interventions that were deemed necessary. One of these trials was performed in The Netherlands and its negative result was partly attributed to the fact that less

than half of the participants received the interventions that were recommended.[18] Gates et al. concluded in their review of fall prevention strategies that interventions leading to immediate treatment may be more effective than those that provide only diagnosis and referral.[42] Another point is the application and implementation of multiple interventions. The probability of compliance is higher with one intervention and even with two interventions than with multiple interventions. This may explain that a single or double intervention with a factorial design is more successful than a multifactorial intervention involving many simultaneous actions (Table 1). For example, the administration of vitamin D and calcium in vitamin D deficient older persons compared to placebo was effective in the prevention of falls, according to several double blind trials and meta-analyses.[10] This may however, also be the effect of the selection of the study subjects.

Table 1.

Study design	Randomised clinical trial on the effect of 1 intervention	Randomised clinical trial on the effect of 2 or 3 interventions: factorial design	Randomised clinical trial on the effect of many interventions: multifactorial design
Study example	Double blind randomised clinical trial on the effect of vitamin D	Randomised clinical trial on the effect of vitamin D and exercise: factorial design, 4 groups	Randomised clinical trial on the effect of multifactorial intervention compared with usual care
Compliance check	Easy	More difficult	Very difficult

Future developments

Future research should focus on two aspects of fall risk factors. First, their use should be studied in primary prevention to select the older persons with a high fall risk who have not (yet) fallen and offer them a community based fall prevention program. Second, the use of fall risk factors and other characteristics should be studied to be able to select those older persons who will benefit from a fall prevention program Thus we might also be able to identify those who will not benefit from the currently available fall prevention programs and perform studies with new fall prevention strategies with them.In order to develop more effective strategies to prevent falls and fractures in older persons we have to better understand the mechanisms of the effect of the separate components of multifactorial interventions. Studies using tilt-tables, treadmills, force plates and accelerometers have already greatly improved the knowledge base of the mechanisms of instability, gait disorders and falls.[26;43;44] Particularly the use of accelerometers in measuring fall risk and assessing the effect of preventive strategies looks very promising: training effects leading to correction of balance loss and prevention of a (near) fall can be measured and analysed. This analysis might give feedback leading to adjustment of exercise techniques. Although martial arts derived training strategies, and mainly tai chi has been proven effective in reducing fall risk, martial arts techniques may also be useful to prevent fractures. Practicing martial arts based fall techniques may prevent fractures whenever a fall occurs. Evidence of reduction of impact force on the trochanter by using these techniques has already been obtained.[45] However, a very large scale RCT would be necessary to demonstrate fracture risk reduction using martial arts fall techniques because of the relatively low incidence of hip fractures.

Decline of cognitive function is an important fall risk factor.[46] Cognitive function is highly influenced by lack of attention and concentration. The fall risk lowering properties of tai chi may, next to balance and strength training also be due to training of concentration. The possibilities of lowering fall risk by training attention and concentration using cognitive training or meditation techniques should be studied.

Furthermore, drugs leading to improved performance are known from sports medicine (and have been banned). Drugs improving muscle strength (e.g. anabolic steroids and selective androgen receptor modulators), endurance (erythropoietin analogues) and concentration (amphetamine) have been widely used in sports or would be theoretically favourable to prevent falls. Some of these drugs are known for their adverse effects like elevated blood pressure, hirsutism and voice changes

in women in anabolic steroid use and tachycardia in amphetamine use.[47] However, the oldest old have a limited life expectancy and can possibly profit from the performance increasing effects of some of these drugs without suffering from the adverse effects within the rest of their lifetime. Persons with a high serum testosterone concentration had a lower fall risk as has been shown in a study by Bischoff-Ferrari et al.[48] However, Schaap et al. could not demonstrate an association between the testosterone serum level and muscle strength or physical performance in older men.[49] In a randomised controlled trial by Emmelot-Vonk et al. testosterone supplementation was studied in healthy older men. The use for 6 months did not result in more muscle strength or an improved physical performance. Fall risk was not measured in this study.[50] Multiple drugs are currently being developed aimed at increasing muscle mass and muscle strength. These drugs use different pathways to attain this goal: e.g. selective androgen receptor stimulation, myostatin inhibition, ghrelin receptor stimulation and very recently supplementation of oxytocin (in mice).[51;52] These drugs can, after having shown effect and safety in phase 3 trials, be tested in populations with an elevated fall risk. These drug trials should be performed in a relevant target population of older persons, without excluding frail persons or those who are using other drugs. A standardised exercise program should be added to these drug trials, to promote mobility improvement and fall risk reduction in addition to the increase of muscle mass and strength. Although most older persons will not be familiar with the use of video gaming, the use of commercially available games that stimulate mobility is promising. The effect of games like Wii Fit on fall risk has not yet been studied, but favourable effects on balance in small groups of older persons have already been published.[53]

Last but not least should motivational strategies be studied to improve both implementation and adherence to fall prevention interventions. Interventions aimed at reduction of fear of falls reduce activity avoidance but have not shown to effectively reduce the rate of falls nor the risk of falling.[54;55] Probably the several components of multifactorial intervention all need their separate way of attaining optimal adherence: e.g. adherence to the advice to discontinue benzodiazepine use will need motivational techniques from addiction care whereas adherence to physical therapy exercises will need techniques similar to those used in sports. Generally, I would like to encourage fellow researchers to think “out of the box” in developing and testing new fall prevention strategies. Both demographical developments and dramatic individual consequences of falls call for far more effective interventions than are currently available.

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