Falls in old age: pills, the heart and beyond

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Withdrawal of drugs and screening for cardiovascular causes in older fallers

Medicatie afbouw en screening naar cardiovasculaire oorzaken bij oudere vallers

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Aan mijn oma's

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Chapter 1
Introduction

Fall risk and cardiovascular abnormalities

Falls are among the most common and serious problems facing older persons and are associated with considerable morbidity and mortality.[1] Assessment of falls and fall risk is a complex matter. By now, over twenty risk factors have been identified and often there are multiple causes for falls in a given patient (Table 1). Thus, in the assessment, many risk factors for falls need to be considered.[2] Risk factors for falls vary from direct causal ones, such as impaired mobility, to indirect ones, such as age. Several of these risk factors are of cardiovascular origin.[3] Important cardiovascular disorders that can cause falls are orthostatic hypotension, carotid sinus hypersensitivity and vasovagal collapse.[4] These cardiovascular disorders can also lead to syncope. However, 50% of older patients with witnessed syncopal events do not recall a loss of consciousness and will present with a fall instead.[5] Therefore, it is important that in the differential diagnosis of an older person presenting with a fall, causes for syncope are also considered. Besides the possible diagnoses mentioned above, these include cardiac arrhythmias and structural cardiac disease.[6-8] However, to our knowledge, no studies have been published up to now regarding the association between cardiac abnormalities and fall incidents. Nor are there papers regarding the effectiveness of treatment of these conditions using a reduction of fall incidents and/or syncopal events as an outcome parameter.

Table 1. Summary of identified risk factors for falls

Risk factor group	Elaboration
Age	High age
Gender	Female gender
History of falls	Recalled falls
Fear of falling	
Environmental	Among others: poor lighting, loose carpets or cords
Gait/balance disorders or muscle weakness	Poor TUGT-, Tinetti-, or other mobility test scores, use of walking aid, osteoarthritis, foot problems, peripheral neuropathy
Impaired activities of daily living	Poor ADL function, urinary incontinence, poor self-perceived health, pain
Visual or auditory deficit	Poor visual acuity and poor contrast and/or depth vision
Cognitive impairment	Impaired MMSE score, diagnosis of dementia
Dizziness/vertigo	
Co-morbidity	Among others: depression, Parkinson's disease, stroke, diabetes mellitus, hypertension, orthostatic hypotension, structural cardiac abnormalities, number of comorbid conditions
Use of certain drugs	Among others: psychoactive and hypotensive drugs

Abbreviations: TUGT, Timed Up and Go Test; ADL, activities of daily living; MMSE, Mini-Mental State Examination

The current hypothesis regarding the underlying cardiovascular pathway is that in certain circumstances a transient shortage of cerebral perfusion results in a fall or syncope, sometimes preceded or accompanied by a sensation of dizziness or weakness, blurred vision, headache or pain in the paracervical region (coat hanger ache), and/or chest discom-

fort.[9] In the event of orthostatic hypotension, cerebral hypoperfusion is caused by excessive venous pooling subsequent to standing up due to impaired compensatory actions of the sympathic nervous system. Orthostatic hypotension is thought to contribute to fall incidents in 5 to 32% of cases.[10-12] Several age-related changes predispose older persons to orthostatic hypotension. These alterations include reductions in thirst sensation, in the ability to preserve sodium and water, in the baroreceptor response, and in heart rate response to orthostatic stress, as well as autonomic dysfunction.[8] Vasovagal collapse is thought to be triggered by excessive venous pooling (Bezold-Jarisch reflex), which paradoxically triggers the vagal afferents, resulting in inhibition of the sympathic nervous system.[13] The end result is inappropriate vasodilatation and bradycardia resulting in cerebral hypoperfusion. Vasovagal collapse is the commonest neurally mediated disorder, affecting all age groups with an equal sex incidence. Premonitory symptoms may be attenuated in older persons and falls due to recurrent vasovagal collapse therefore carry substantial risks in terms of morbidity and mortality in this age group.[14] Similar to vasovagal collapse, carotid sinus hypersensitivity also results from an augmented vagal tone, but the pathogenesis is still uncertain.[15,16] Carotid sinus hypersensitivity results in inappropriate firing of the baroreceptors during certain head movements, or when wearing tight collars for example. The outcome can be either temporary asystole or a profound drop in blood pressure or both.[17] Prevalence increases with age from approximately zero in patients under 50 years of age to 40-45% in those aged 80 years and over.[18-22] It is important to realize, however, that a fair number of asymptomatic persons do show carotid sinus hypersensitivity on testing. Therefore, clinical significance of this finding needs to be determined for each patient individually.[19,21] Nevertheless, the diagnostic yield of carotid sinus massage in subjects over 65 years presenting with syncope or falls has been reported to be up to 45%.[18,22-24] Cardiac arrhythmias can lead to a decrease in heart minute volume and if this surpasses the cerebral buffer capacity, cerebral hypoperfusion will result. In the case of bradycardic conditions, the heart minute volume will be too low due to the slow heart rate. In the case of tachycardia, cardiac output is diminished due to the inability of the heart to reach sufficient filling volume of the ventricles per heartbeat to maintain the necessary heart minute volume. Structural cardiac abnormalities that are known to give rise to syncope are aortic valve stenosis, mitral valve prolapse, outflow-tract obstruction, pulmonary hypertension, and acute myocardial infarction or ischemia.[5-7,25,26] Through different pathways they all result in a diminished cardiac output when circulatory demands outweigh the impaired ability of the heart to increase its output. If the circulatory demands cannot be met, this will result in a shortage of cerebral perfusion. This same mechanism is postulated to be true for fall incidents as well, as explained above.[4,5]

Fall risk and drug use

An important risk factor for falls is the use of certain drugs. Nevertheless, up to now data regarding drug-induced falls are predominantly limited to observational studies. A meta-analysis in 1999 suggested that there is a consistent association between the use of psychotropic drugs and falls in older persons.[27,28] In addition, an increased fall risk has been demonstrated for certain cardiovascular drugs and for polypharmacy, defined as the use of three or more prescribed medications.[29] Polypharmacy in itself, however, is not a risk factor unless it includes at least one fall-risk increasing drug.[30] Several drugs have been associated with falls (Table 2). A fall before hospital admission has been shown to be a risk indicator for a severe adverse drug reaction.[31] Although the association between fall incidents and the use of certain drugs is undisputed, to our knowledge only one intervention study has been published.[32] This randomized controlled trial showed a significantly lowered fall risk after withdrawal of sedatives and antidepressants in community-dwelling older persons.

The incidence of falls increases with age. Furthermore, it is generally assumed that the incidence rate of drug-induced falls also increases with age, although, to our knowledge, there are no data available regarding this issue. Apart from the increased utilization of drugs in the elderly, this is attributed to the fact that physical reserves decrease with ageing. Changes in pharmacokinetics and pharmacodynamics make older persons more prone to adverse drug reactions.[33,34] Because of these changes, an adverse drug reaction (for ex-

Table 2. Drugs associated with an increased fall risk

Psychotropic drugs	
Sedatives	Benzodiazepines and others
Neuroleptics	D2 agonists and serotonin dopamine receptor antagonists
Antidepressants	Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors
Cardiovascular drugs	
Antihypertensives	Diuretics, beta-blockers, alpha-blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers
Anti-arrhythmics	Class IA anti-arrhythmics, digoxin and others
Vasodilators	Nitrates and others
Miscellaneous drugs	
Beta-blocker eye drops	
Analgesics	Especially opioids
Anticholinergic drugs	Anticholinergics, antispasmodics, mydriatics, tricyclic antidepressants, certain antiarrhythmics, antihistamines, antipsychotics
Antihistamines	
Anti-vertigo drugs	
Hypoglycemics	

ample a fall) can occur without any recent changes in the drug regimen.[31,34-37] With regard to pharmacokinetic changes, a decline in liver volume and blood flow, and a reduction of in vitro and in vivo metabolic capacity in older persons has been demonstrated. This is the physiological basis of reduced hepatic drug clearance in this age group, giving rise to a lower first pass effect, and slower biotransformation.[38] Changes in body composition with age result in a higher percentage of fat mass and a lower percentage of body water and muscle mass. Therefore, the biological half-life of lipophilic drugs is increased, and a lower loading dose of hydrophilic drugs is needed. Since renal clearance is often diminished in older persons, renal elimination is slower.[39] Due to the reduction in muscle mass with ageing, the serum-creatinine level is also decreased. Hence, in older persons a normal serum-creatinine level should not be interpreted as an indicator of normal renal function. The formula according to Cockroft and Gault or the Siersbaeck-Nielsen nomogram are recommended for clinical use if the assessment of creatinine in a 24-hour urine sample is not feasible.[40] Pharmacodynamic changes with ageing are due to target organ changes, which can be caused by illness, diminished spare capacity of target organs, or a change in receptor function of the target organ. These changes result in a higher sensitivity of the target organ at a given drug plasma level. This is clinically relevant, especially for drugs acting on the central nervous system.[41]

Aims of this thesis

The objective of this thesis is to gain more knowledge about the optimal content of the multifactorial approach of older fallers. Although many studies have demonstrated the effectiveness of a multifactorial approach when treating older fallers, the setting and design of these studies differ substantially.[1] Therefore, we address two aspects on which the literature is scarce. First, we address cardiovascular determinants of fall incidents and second, we describe a potential intervention in older fallers, i.e. withdrawal of fall-risk-increasing drugs. For this goal, we used two population-based data sources: a prospective cohort study of 215 geriatric outpatients of the Erasmus Medical Center in Rotterdam, and the Rotterdam Study, a population-based cohort study among 7983 older adults living in Ommoord, a suburb of Rotterdam.[42]

In chapter 2, we describe a series of cases presenting with fall incidents induced by the use of certain drugs. These cases prompted us to the design of the studies described in chapter 4. In chapter 3, we first describe the association between certain echocardiographic abnormalities and fall incidents in our geriatric outpatient population. Second, we address echocardiographic abnormalities and their association with fall incidents in the Rotterdam Study. Third, we address the optimal measurement of orthostatic hypotension when addressing fall risk. In chapter 4, we first assess the effect of withdrawal of fall-risk-

increasing drugs on fall incidents in our geriatric outpatient cohort. Second, we address possible underlying mechanisms of this effect, i.e. whether withdrawal of these drugs results in improvement of certain mobility tests and/or improvement of tilt-table test outcomes (orthostatic hypotension, vasovagal collapse and carotid sinus hypersensitivity). We conclude chapter 4 with a cost-effectiveness analysis of this intervention. In chapter 5, we reflect on our main findings, and speculate on the implication of our results.

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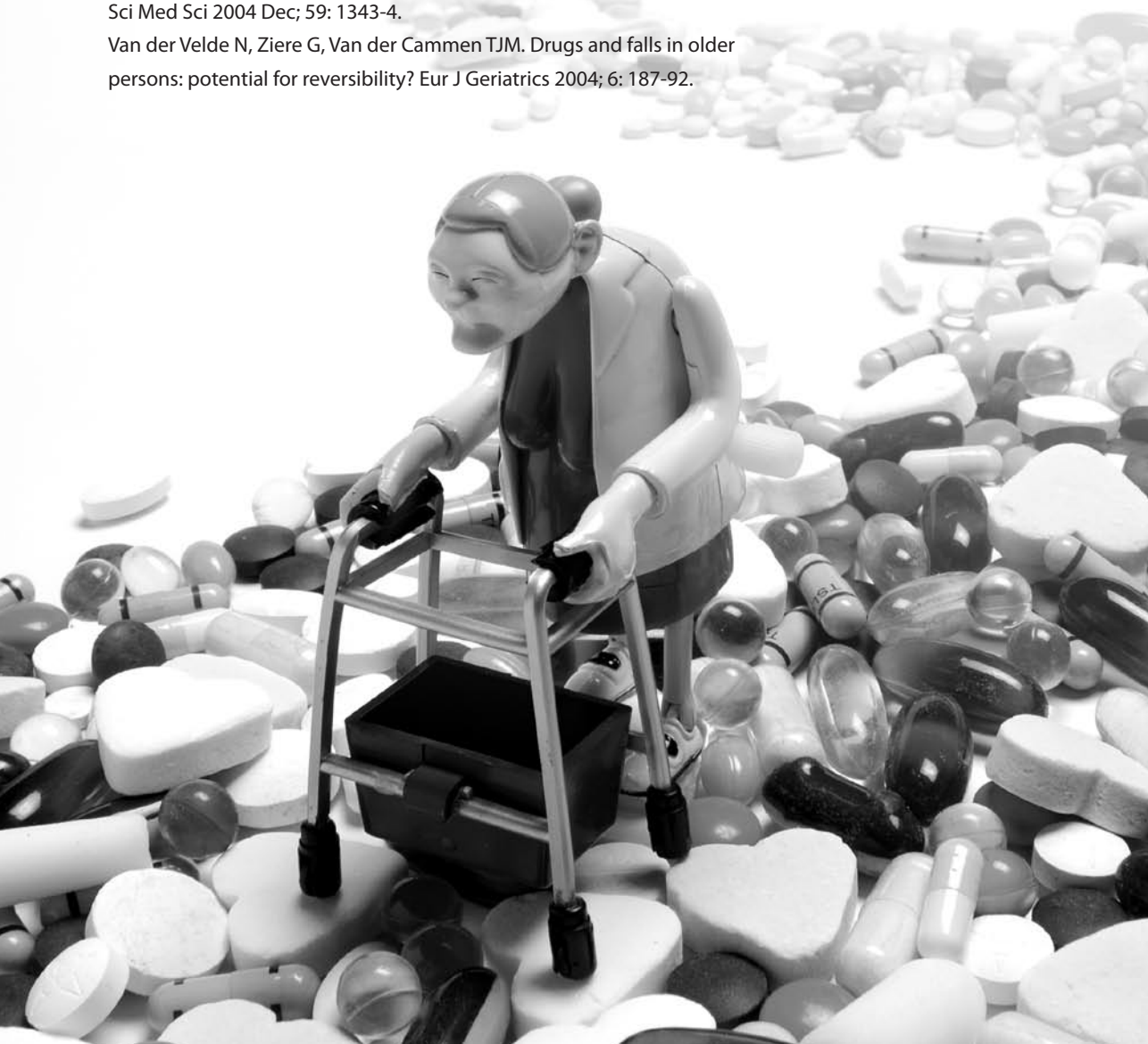
Chapter 2

A series of cases: drug-related falls

Chapter 2 is based on the following articles:
Muller ME, Van der Velde N, Krulder JW, Van der Cammen TJM. Syncope and falls due to timolol eye drops. BMJ 2006; 332: 960-1.
Van der Velde N, Ziere G, Van der Cammen TJM. Falls in three patients due to timolol eye drops, tolterodine, and flecainide. J Gerontol A Biol Sci Med Sci 2004 Dec; 59: 1343-4.
Van der Velde N, Ziere G, Van der Cammen TJM. Drugs and falls in older persons: potential for reversibility? Eur J Geriatrics 2004; 6: 187-92.



Introduction

In this chapter we describe a selection of cases, seen in our geriatric outpatient clinic. In all these patients, falling was attributed to the use of certain drugs and fall incidents ceased after withdrawal of these drugs. However, causality is hard to ensure on the basis of case reports. Therefore, these observations prompted us to conduct a prospective cohort study on this topic, which is described in chapter 4 of this thesis.

Case 1

A 73-year-old woman complained of unexpected falls during the previous five years. Furthermore, she regularly had a feeling of light-headedness and weakness in both arms. She had a five-year history of glaucoma, for which she used latanoprost and timolol eye drops (0.5%, once daily in both eyes). Besides orthostatic hypotension, no other abnormalities were found at physical examination. Her supine blood pressure was 139/68 mm Hg, with a regular pulse rate of 58 beats/min; lowest blood pressure during three minutes of standing was 117/64 mm Hg, with a regular pulse rate of 66 beats/min. Electrocardiography showed sinus bradycardia of 53 beats/min. Laboratory testing showed normal blood count, electrolytes, and renal and liver profiles. On tilt-table testing, orthostatic hypotension was confirmed; supine blood pressure was 160/85 mm Hg, with a regular pulse rate of 58 beats/min, and lowest blood pressure during five minutes of standing was 134/75 mm Hg, with a regular pulse rate of 62 beats/min. There was no vasovagal collapse or carotid sinus hypersensitivity. Her falls were diagnosed as resulting from orthostatic hypotension, induced by timolol eye drops. Because of this, and because of an insufficient reaction of the glaucoma to the eye drops, her ophthalmologist decided to perform eye surgery, after which her eye drops were stopped. Since then (follow-up period of 1 year) she has not experienced any more falls, nor has she experienced any more episodes of light-headedness or weakness in the arms. On repeat tilt-table testing, orthostatic hypotension did not occur.

Case 2

A 74-year-old woman complained of frequent falls for the past three months, mainly at night. Her medical history revealed a hip fracture, percutaneous transluminal coronary angiography, heart failure, diabetes mellitus, and urinary incontinence. Her medication consisted of perindopril 4 mg once daily, furosemide 40 mg once daily, metoprolol slow-release 100 mg once daily, aspirin 100 mg once daily, simvastatin 20 mg once daily, metformin 500 mg twice daily, and colecalciferol 400 I.U. once daily. Three months earlier, tolterodine 4

mg once daily had been added because of urinary incontinence. On physical examination, she had diastolic orthostatic hypotension, her blood pressure supine was 130/75 mmHg, with a regular pulse rate of 68 beats/min. The lowest blood pressure during three minutes of standing was 130/65 mmHg; pulse rate 72 beats/min. Except for a trace of pitting oedema at both ankles, physical examination was normal. Laboratory testing yielded normal blood count, electrolytes, and renal and liver profiles. Non-fasting glucose was 9.5 mmol/l; HbA1c 8.5%. Electrocardiogram showed sinus rhythm and left axis deviation. Because the falls had started around the time of the addition of tolterodine, this drug was thought to be the most probable cause of the falls, as its anticholinergic properties can induce orthostatic hypotension. Therefore, tolterodine was stopped. Metoprolol was halved because of the relatively high dosage. Follow-up for one year revealed that falls had stopped after this change of medication, confirming the diagnosis. The urinary problems had remained unchanged.

Case 3

An 81-year-old man complained of dizziness upon standing up, frequently associated with falls, for several months. He had a history of paroxysmal atrial fibrillation, presbyacusis, and bilateral cataract extraction. He used aspirin 100 mg once daily and flecainide 50 mg twice daily since several years. On physical examination, blood pressure supine was 200/90 mmHg, with a regular pulse rate of 56 beats/min. The lowest blood pressure during three minutes of standing was 120/60 mmHg; pulse rate 64 beats/min. Further physical examination was normal. Laboratory testing showed a normal blood count, serum creatinine level of 104 micromol/l, serum ureum 9 mmol/l, and normal electrolytes. Creatinine clearance according to the Cockroft and Gault formula was 38.7 ml/min. Repeated electrocardiograms showed a sinus rhythm with left axis deviation and left anterior fascicular block. Tilt-table testing showed autonomic insufficiency with an inappropriate catecholamine response. The most probable diagnosis was orthostatic hypotension induced by a negative inotropic cardiac drug (flecainide), superimposed on pre-existing autonomic insufficiency. Therefore, flecainide was stopped. Frequent follow-up for one year showed that the patient remained in sinus rhythm and falls ceased, confirming the diagnosis.

Case 4

A 64-year-old man complained of dizzy spells on standing up and bending over, and the inability to stand for longer periods without experiencing a fall or syncope. These symptoms had started approximately three years earlier, and had been previously diagnosed and

treated unsuccessfully as Menière's disease by a specialist elsewhere. His medical history revealed hypothyroidism. His regular medication consisted of acetazolamide 250 mg once daily, betahistine 16 mg three times daily and levothyroxine 0.025 mg twice daily. Physical examination showed systolic orthostatic hypotension. Blood pressure supine was 129/65 mmHg, with a regular pulse rate of 53 beats/min. Lowest blood pressure during three minutes of standing was 108/63 mmHg, with a regular pulse rate of 54 beats/min. On tilt-table testing he had a vasovagal collapse after twelve minutes of standing, blood pressure 77/56 mmHg; pulse rate 49 beats/min. At that moment he recognised the symptoms as one of his "Menière" attacks. Further physical examination was unremarkable. Laboratory values for serum-creatinine level were 80 µmol/l, urea 5.7 mmol/l, blood count, electrolytes and thyroid stimulating hormone were within the normal range. Renal clearance according to the Cockroft and Gault formula was estimated at 85 ml/min. Electrocardiogram was normal, showing sinus rhythm and a normal heart axis. Betahistine and acetazolamide were stopped. Follow-up up to one year revealed that his symptoms were markedly reduced after this change of medication regimen, and no falls had occurred. Occasional spells of dizziness persisted, but because they were less severe, this gave him the possibility to react to them appropriately (muscle tensing/ sitting down). On retesting at three months no orthostatic hypotension was found. Blood pressure supine was 153/89 mmHg, with a regular pulse rate of 64 beats/min. Lowest blood pressure during three minutes of standing was 152/90 mmHg, with a pulse rate of 65 beats/min. Neither a vasovagal collapse nor onset of symptoms occured on re-challenging during tilt-table testing.

Case 5

A 79-year-old woman complained of monthly falls starting three months earlier; there were never any preliminary symptoms, nor did she lose consciousness. Falling did not occur on specific occasions (for example on standing up, after a meal, on micturition). Her medical history revealed polymyalgia, for which she used prednisolone up to three years ago, neurogenic claudication for which she had decompression surgery one year ago. Her regular medication consisted of zopiclon 7.5 mg once daily ante nocte, alprazolam 0.25 mg once daily ante nocte, furosemide 40 mg once daily and hypromellose eye drops twice daily. On physical examination blood pressure supine was 138/70 mmHg with a regular pulse rate of 70 beats/min. Lowest blood pressure three minutes of standing was 136/68 mmHg with a pulse rate of 69 beats/min. Cardiac examination revealed a systolic murmur, consistent with an aortic valve stenosis. Further physical examination, including neurological examination, was unremarkable. Mobility testing showed the following results: 10-Meter Walking Test duration of 18 seconds, a Timed Up and Go Test duration of 30 seconds and a Functional Reach Test of 13 cm. Laboratory testing showed normal blood count,

electrolytes and liver profiles. The serum-creatinine level was 81 µmol/l, urea 6.0 mmol/l and electrolytes were normal. Creatinine clearance according to the Cockroft and Gault formula was estimated at 60 ml/min. The electrocardiogram was normal, showing a sinus rhythm. An echocardiogram showed a moderate aortic valve stenosis with an aortic velocity of 3.08 m/s, no left ventricular hypertrophy. The aortic valve stenosis was not thought to be severe enough to cause falling, nor was the medical history typical of recurrent syncope caused by aortic valve stenosis. It was thought that the use of the two benzodiazepines resulted in blunted executive motor functions and reduction in muscle strength, resulting in recurrent falls. Therefore, zopiclon was stopped and alprazolam was decreased to three times weekly. Follow-up up to one year showed no more falls and she was also retested: 10-Meter Walking Test had improved to 11 seconds, Timed Up and Go Test had improved to 15 seconds and Functional Reach Test had improved to 20 cm.

Discussion

In these five patients we were able to prevent further falls and improve test results by modifying their drug regimen, despite abundant co-morbidity. We will now discuss the underlying mechanisms.

Case 1 had typical complaints of orthostatic hypotension, which were confirmed both with sphygmomanometer and tilt-table testing of orthostasis. The prevalence of glaucoma increases with age.[1] Timolol, a non-selective beta-blocker, is the first line treatment. This case shows that even a low dose of timolol eye drops may cause severe systemic adverse effects. At least 80% of the administered drop drains through the nasolacrimal duct, where it is absorbed by the nasal mucosa. Thus it spreads systemically, and as there is no hepatic first pass effect, the absorbed dose behaves like an intravenous drug dose.[2] Eye drops with beta-blocking action can have a strong and prolonged systemic effect, especially in older age groups. Beta-blocker eye drops should therefore be prescribed with caution in this age group.[3] If such patients present with syncope, a systemic adverse drug reaction should be considered.

Case 2 had proven diastolic orthostatic hypotension (defined as a drop in diastolic blood pressure of 10 mmHg or more) and obvious polypharmacy. There were a number of drugs that could have caused her symptoms, such as tolterodine, metoprolol, furosemide, and perhaps perindopril, although angiotensin-converting enzyme inhibitors are thought to give less rise to orthostatic hypotension than other antihypertensive drugs.[4] Since the patient's falls began around the time when tolterodine was added, we reasoned that it most likely gave rise to her symptoms and we withdrew it; because of the relatively high dose of metoprolol, we decided to halve this drug at the same time. Furosemide was continued because of the patient's reduced cardiac function and the risk of recurrence of heart failure.

Perindopril was continued because it was less likely to give rise to orthostatic hypotension than other antihypertensive drugs and it was needed to reduce the risk of recurrence of heart failure. The relationship between anticholinergic drugs and falls has not been studied in larger series, but anticholinergics can cause orthostatic hypotension and falls.[5] Since metoprolol, a selective lipophilic beta-blocker, was used in a relatively high dose, it was thought to be partly responsible for the orthostatic response in case 2.

Case 3 was on flecainide, a class Ic anti-arrhythmic drug with a negative inotropic action, because of paroxysmal atrial fibrillation. Tilt-table testing revealed an autonomic insufficiency, which can be primary, secondary, or a combination of the two. Primary autonomic insufficiency in old age is thought to be due to increased baroreceptor sensitivity. One of the causes of secondary autonomic insufficiency is the use of certain drugs, in this case, flecainide. After stopping this drug, the orthostatic hypotension lessened to an extent where the patient did not experience any more falls. He also remained in sinus rhythm. A study on drug withdrawal in a Falls Clinic performed in 2001 showed that chronic cardiovascular medication can often be withdrawn safely.[6] After stopping anti-arrhythmic drugs because of falls, renewal of these drugs was not necessary in 36% of cases; for anti-anginal drugs, renewal was not necessary in 77% of cases; for antihypertensives, no renewal was necessary in 69% of cases.

Case 4 had a long history of invalidating dizziness and falls, for which he had been unsuccessfully treated with betahistine and, experimentally, acetazolamide. On examination, he had systolic orthostatic hypotension and vasovagal collapse. Since acetazolamide has diuretic properties, it was thought that it possibly induced or increased the orthostatic hypotension and the vasovagal collapse. Betahistine has a histaminergic effect, which can cause vasodilatation (orthostasis, hypotension, collapse and tachycardia) when used in high doses. Therefore, both drugs were reduced and eventually withdrawn. This improved the patient's quality of life. And although he did still occasionally experience some dizziness on standing, no more falls occurred. This patient probably has some degree of primary autonomic failure, which makes him prone to orthostasis and vasovagal collapse. Instead of reducing his complaints, the drugs had aggravated them.

In case 5 the causes for falling were most likely mobility (balance) problems due to diminished concentration and prolonged reaction time caused by her use of two different benzodiazepines (zopiclon and alprazolam). This was recorded with three different tests, which have been previously shown to be predictive for falling, i.e. the 10-Meter Walking Test, the Timed Up and Go Test and the Functional Reach Test.[7-10] These mobility tests are all easy to perform clinically, and no (expensive) devices are needed. This makes them attractive for clinical practice. They have been tested in epidemiological studies, and various researchers have tried to determine cut-off points for increased fall risk: < 0.77 meters/seconds for the 10-Meter Walking Test, 15 or 20 seconds for the Timed Up and Go Test and 25,5 cm for the Functional Reach Test. But as far as we know, there are no data on whether

and how big a change in these tests over time is concurrent with a diminished fall risk in patients who present with falls. In this particular patient, the improvement of the tests was clear, and we think they represent markedly improved functioning due to a decrease in benzodiazepine use. This assumption is backed by the fact that the patient experienced no more falls.

Conclusion

In the fall-risk-assessment of older patients, there are many drugs to be considered as the possible cause or contributing factor. Our case reports show that, in older patients with falls, an ADR should be considered as the possible cause of falling. If a suspected drug can be defined, it should be stopped or reduced. In the case of polypharmacy in a patient with falls, besides trying to identify a suspected drug, it is worth the effort to try and limit the number and dosage of prescribed drugs. Even if an underlying pathology is present, drug withdrawal may stop the symptoms. In general, if a patient starts falling, it is wise to evaluate which drugs have been added to the drug-regimen recently. However, since pharmacokinetic and pharmacodynamic properties change with age, drugs that have been used for many years should also be considered as potential culprits.[11] As we have shown with these 5 cases, falls can be reversible after stopping drugs, despite abundant co-morbidity.

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Chapter 3.1

Can echocardiograpic findings predict falls in older persons?

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(submitted)

Abstract

Background

The European and American guidelines state the need for echocardiography in patients with syncope. Fifty percent of older adults with syncope present with a fall. Nonetheless, up to now no data have been published addressing echocardiographic abnormalities in older fallers.

Methods

In order to determine the association between echocardiographic abnormalities and falls in older adults we performed a prospective cohort study, in which 215 new consecutive referrals (age 77.4, SD 6.0) to a geriatric outpatient clinic of a Dutch university hospital were included. During the previous year, 139 had experienced a fall. At baseline, all patients underwent routine two-dimensional and Doppler echocardiography. Falls were recorded during a 3-month follow-up. Multivariate adjustment for confounders was performed with a Cox proportional hazards model.

Results

Fifty-five patients (26%) fell at least once during follow-up. The adjusted hazard ratio of a fall during follow-up was 1.35 (95% CI, 1.08-1.71) for pulmonary hypertension, 1.66 (95% CI, 1.01 to 2.89) for mitral regurgitation, 2.41 (95% CI, 1.32 to 4.37) for tricuspid regurgitation and 1.76 (95% CI, 1.03 to 3.01) for pulmonary regurgitation. For aortic regurgitation the risk of a fall was also increased, but non-significantly (hazard ratio, 1.57 [95% CI, 0.85 to 2.92]). Trend analysis of the severity of the different regurgitations showed a significant relationship for mitral, tricuspid and pulmonary valve regurgitation and pulmonary hypertension.

Conclusions

Echo(Doppler)cardiography can be useful in order to identify risk indicators for falling. Presence of pulmonary hypertension or regurgitation of mitral, tricuspid or pulmonary valves was associated with a higher fall risk. Our study indicates that the diagnostic work-up for falls in older adults might be improved by adding an echo(Doppler)cardiogram in selected groups.

Introduction

Falls are a major public health hazard in countries with ageing populations. Injury is the fifth leading cause of death in older adults, and most of these fatal injuries are related to falls.[1] Falling can be caused by many different risk factors, several of which are cardiovascular.[2,3] A typical presentation of these cardiovascular causes of falls would be syncopal spells, e.g. a brief loss of consciousness due to loss of blood flow to the brain. However, approximately 50% of older persons do not recall losing consciousness and will therefore present with an unexplained fall instead of syncope.[4] Since the distinction between syncope and falls is so difficult to establish, it is important to address causes of syncope when investigating an older faller.

The main cardiovascular disorders that can cause falls or syncope are orthostatic hypotension, carotid sinus hypersensitivity, vasovagal collapse, cardiac arrhythmias and structural cardiac disease.[5,6]. Although guidelines on syncope state that there is causal evidence for aortic valve stenosis, mitral valve prolapse, outflow-tract obstruction, pulmonary hypertension, and acute myocardial infarction or ischemia, only few studies have reported structural cardiac disease as a causal factor.[5-7] According to the American and European guidelines, an echocardiogram is indicated if a patient with syncope is suspected either to have structural heart disease or has an abnormality on the electrocardiogram.[5,6] Up to now, however, there are no studies addressing the yield of echocardiography in patients presenting with falls. Consequently, we undertook a prospective study in a cohort of geriatric outpatients in which we studied this issue.

Methods

Study participants

All new consecutive referrals to the outpatient clinic and the Diagnostic Day Center of the Section of Geriatric Medicine at the Erasmus MC of 65 years or older, with a Mini-Mental State Examination score (MMSE) of 21 points or higher (out of 30 points)[8,9] and the ability to walk 10 meters without a walking aid, were invited to participate between April 1, 2003 and November 30, 2004. The Medical Ethics Committee of the Erasmus MC approved the study protocol and written informed consent was obtained from all patients.

Interventions during follow-up

The only intervention performed during the 3 months of follow-up was withdrawal of drugs known to increase fall risk. This consisted of discontinuation or reduction to the lowest possible dose, where possible, in patients with a history of one or more falls during the previous year. The following drugs were considered for withdrawal, i.e. anxiolytics/hyp-

notics (benzodiazepines and others), neuroleptics (D2 agonists and serotonin dopamine receptor antagonists), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors), antihypertensives (diuretics, beta-blockers, alpha-blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), anti-arrhythmics, nitrates and other vasodilators, digoxin, beta-blocker eye drops, analgesics (mainly opioid analgesics), anti-cholinergic drugs, antihistamines, anti-vertigo drugs, and hypoglycemics. The objectives, methods and results of this intervention have been described in detail elsewhere.[10]

Baseline characteristics

Functional status was measured with the Activities of Daily Living scale and the Instrumental Activities of Daily Living scale.[11,12] We also recorded whether or not study participants used a walking aid. Information on co-morbidity was obtained at baseline in an interview with the study participants. This was verified both with the records of the geriatrics department and with information from the general practitioner. All comorbid diagnoses were recorded, including a.o. heart rhythm disorder, ischemic heart disease, cerebrovascular event, hypertension, neurological disorder, depression, COPD, (osteo)arthritis, visual abnormality and total number of comorbid diagnoses. At baseline, several tests were performed. Mobility testing was among others done with the Functional Reach Test, a test for balance. It evaluates the maximal distance that a person can reach forward while maintaining a fixed base of support.[13,14] Maximal isometric quadriceps femoris muscle strength was measured at both legs with the handheld MicroFET dynamometer.[15] Furthermore, an electrocardiogram was done and a tilt-table test was performed in order to measure orthostatic hypotension, carotid sinus hypersensitivity and vasovagal collapse. Blood pressure was measured performing non-invasive finger arterial pressure measurements as implemented in the Finometer trade mark (Finapres Medical Systems, Amsterdam, The Netherlands).

Falls history and falls follow-up

A fall was defined as coming to rest unintentionally on the ground or at a lower level with or without losing consciousness, but not if this had been induced by acute medical conditions, such as a stroke, or exogenous factors, such as a traffic accident.[16] For registration of fall incidents during follow-up, respondents were asked to report their falls weekly on a falls calendar and to mail the calendar page at the end of every month. Every participant was called by the first author to check compliance with these calendar pages on a monthly basis. This reporting method is considered the golden standard for research on fall incidents.[17,18] Furthermore, subjects with a MMSE of 21 or over (our inclusion criterion) have been shown to be able to reliably recall falls.[9]

Echocardiography

Standard echo/Doppler transthoracic examination was performed using a commercially available ultrasound scanner (Sonos 5500, Philips, Best, The Netherlands). Patients were examined in left lateral recumbent position using a standard broadband S4 transducer (2-4 MHz). Echocardiography was performed according to a standard protocol by one trained operator (NV). A second investigator (WF), who was blinded to falls history, reviewed all test outcomes and decided on the final scoring.

Standard images were recorded from parasternal long axis, parasternal short axis and apical 4 chamber, apical 2 chamber and apical 3 chamber views. Systolic left ventricular function was scored both qualitatively and quantitatively. Qualitative scoring was performed visually as either good, fair, moderate or poor. For quantitative assessment, ejection fraction and fractional shortening were calculated from left parasternal long axis 2D-guided M mode measurements.[19] For estimation of the ejection fraction we used the simplified method of Quinones et al.[20] Standard measurements of the interventricular septum were obtained and a septum thickness of 12 mm or more was considered to be hypertrophic. Valvular functions were assessed using both spectral Doppler and color Doppler. Valvular regurgitation was assessed as mild, moderate, moderately severe or severe on the basis of the jet extension (no regurgitation; trivial; 1: mild; 2: moderate; 3: moderately severe: with a long jet; and 4: severe: with a regurgitant jet along the length of either the left ventricle or the right ventricle).[21] This qualitative assessment is accurate and correlates well with quantitative measures of valvular incompetence.[22,23] In case of eccentric jets the amount of turbulence was used to estimate the severity of the regurgitation. The degree of valvular stenosis was quantified by continuous wave Doppler velocity measurements using the modified Bernouilli.[24] For velocities through the aortic valve, stenosis was defined as higher than 2.2 m/sec. Systolic pulmonary arterial pressure was estimated when tricuspid regurgitation was detected by continuous wave Doppler echocardiogram, using the peak regurgitant velocity. The pressure gradient between the right ventricle and the right atrium at the time of pulmonary valve opening was calculated by applying the simplified Bernoulli equation (pressure = 4 times velocity^2). To this the estimated right atrial pressure was added. Right atrial pressure was estimated at 10 mm Hg if the diameter of the vena cava inferior was 1.5 cm or over and during respiration there was a collapse of 50% or over. Right artrial pressure was estimated at 5 mm Hg if the diameter of the vena cava inferior was less than 1.5 cm.[25] In the absence of tricuspid regurgitation, systolic pulmonary artery pressure was considered normal. In the absence of pulmonary stenosis and right outflow tract obstruction, mild pulmonary hypertension was defined as a systolic pulmonary artery pressure of 35-50 mmHg and severe pulmonary hypertension was defined as a systolic pulmonary artery pressure of 50 mmHg or over.[26-28] Diastolic function was assessed using Doppler recordings of mitral and pulmonary venous flow (PV) velocities and PV pattern. Impaired relaxation was defined as an E/A ratio < 1, atrial reversal flow in the PV > 0.4 msec

and a PV pattern with S > D. A restrictive pattern was defined as an E/A ratio > 1.5, a shortened deceleration time (< 160 msec) and a PV pattern with S < D.[29]

Statistical analysis

Baseline differences between the subgroups with and without fall incidents during follow-up were tested using an independent t-test for continuous variables, and a chi-square test for dichotomous variables.

The association between falls during follow-up and cardiac abnormalities was evaluated using a Cox proportional hazards model. First, hazard ratios of events (first fall during follow-up) were computed as estimates of relative risk in a binary fashion (no or trivial abnormalities, versus mild to severe abnormalities). To adjust for possible confounders, cofactors were included one-by-one in the age- and gender-adjusted multivariate model. Cofactors that changed the hazard ratio of a fall incident according to the different echocardiographic abnormalities by more than 5% or that were biologically plausible, and drug withdrawal as defined above, were maintained in the final model. In order to study the association between categories of increasing severity of the valvular regurgitation and risk of a fall, a trend analysis was performed within the Cox proportional hazards model. Thereafter, the variables were treated as categorical variables, in order to get an estimation of the risks for the separate categories of severity of the abnormality. A Kaplan-Meier analysis was performed in order to provide a figure showing the crude survival for the different valvular regurgitations. If numbers were too low in the upper categories, groups were combined in order to get more reliable results, i.e. moderately severe and severe regurgitations were combined to one category: severe. All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

Results

During the study period, 350 geriatric outpatients were eligible for inclusion; 132 declined participation, mostly because of the burden of extra visits to the clinic. Patients who refused participation were on average older, used more drugs and had more comorbid diseases. We included 218 patients of whom we were not able to collect data on fall follow-up in 3 subjects: 2 subjects died during follow-up and 1 subject refused further participation during the follow-up period. The remaining 215 subjects were included in the analysis (age 77.4, SD 6.0); Fifty-five patients (26%) fell at least once during follow-up. Baseline characteristics are shown in table 1. Prevalence of echocardiographic abnormalities at baseline is shown in table 2. At baseline, 126 participants used a total of 262 fall-risk-increasing drugs. In 75 participants a total of 91 fall-risk-increasing drugs were withdrawn [10].

Table 1. Baseline characteristics of study population

Baseline characteristics	All (N=215)		Falls + (n=56)		Falls – (n=159)		P-value
	n/mean (%/SD)		n/mean (%/SD)		n/mean (%/SD)		
Age, years	77.4	(6.0)	79.1	(6.2)	76.8	(5.9)	0.015
Gender, female	140	(65%)	36	(64%)	104	(65%)	0.88
Referral for falls	109	(51%)	43	(77%)	66	(42%)	0.000
Use of walking aid	86	(40%)	35	(63%)	51	(32%)	0.000
Isometric M. Quadriceps strength (N)	208	(91)	192	(99)	213	(87)	0.133
Functional Reach Test, cm	28	(14)	25	(13)	29	(14)	0.028
ADL score	0.52	(1.4)	0.8	(1.6)	0.4	(1.3)	0.070
IADL score	14.2	(3.0)	13.1	(3.5)	14.6	(2.7)	0.005
MMSE score	27.8	(4.9)	27.6	(2.3)	27.8	(5.6)	0.722
Drugs	4.9	(2.8)	5.8	(2.8)	4.6	(2.8)	0.004
Comorbid conditions	4.0	(1.9)	4.8	(1.9)	3.7	(1.8)	0.000
History of angina pectoris	26	(12%)	8	(14%)	18	(12%)	0.602
History of myocardial infarction	24	(11%)	4	(7%)	20	(13%)	0.154
History of atrial fibrillation	22	(10%)	10	(18%)	12	(8%)	0.021
History of other arrhythmia's	15	(7%)	6	(10%)	9	(6%)	0.221
History of cerebrovascular accident	26	(12%)	8	(14%)	18	(12%)	0.602
History of transient ischemic attack	27	(13%)	6	(11%)	21	(13%)	0.669
History of diabetes mellitus	26	(12%)	8	(14%)	18	(12%)	0.602
History of COPD	31	(14%)	11	(20%)	20	(13%)	0.175
History of (osteo)arthritis	101	(47%)	34	(61%)	67	(42%)	0.016
History of neurological disorders	18	(9%)	8	(14%)	10	(7%)	0.072
History of depression	28	(13%)	10	(18%)	18	(12%)	0.392
History of visual disorders	54	(25%)	14	(25%)	40	(25%)	0.981
Repolarisation abnormalities (ECG)	110	(51%)	28	(50%)	82	(52%)	0.808
Rhythm abnormalities (ECG)	128	(60%)	25	(45%)	59	(37%)	0.470
Conduction abnormalities (ECG)	135	(63%)	30	(54%)	105	(66%)	0.203
Orthostatic hypotension	130	(61%)	36	(63%)	94	(59%)	0.592
Carotid sinus hypersensitivity	35	(16%)	10	(18%)	25	(16%)	0.735
Vasovagal collapse	15	(7%)	1	(2%)	14	(9%)	0.086

Abbreviations: SD: standard deviation; N: Newton; ADL: activities of daily living; IADL: instrumental activities of daily living; MMSE: Mini-Mental State Examination; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram

First, the hazard ratio of fall incidents according to echocardiographic abnormalities was calculated in a binary fashion: relative risk of falls in patients with at least a mild echocardiographic abnormality (regurgitation, stenosis, pulmonary hypertension, left ventricular ejection fraction, fractional shortening, left ventricular hypertension) compared to patients without or with only a trivial abnormality. For the associations, the following potential cofactors were considered and tested for possible confounding: age, gender, referral for falls, cognitive function (MMSE-score), use of fall-risk-increasing drugs, withdrawal of fall-risk-increasing drugs, use of cardiovascular drugs, withdrawal of cardiovascular drugs, comorbid conditions: total number and separately (heart rhythm disorder, ischemic heart

Table 2. Prevalence of cardiac abnormalities on echo(Doppler)cardiography

Baseline characteristics	All (N=215)		Falls + (n=56)		Falls – (n=159)		P-value
	n/mean SD/%		n/mean SD/%		n/mean SD/%		
LV systolic function < good	34	(16%)	11	(20%)	23	(15%)	0.467
LVEF < 40%	6	(3%)	1	(2%)	5	(3%)	0.590
Fractional shortening < 25%	28	(13%)	5	(9%)	23	(15%)	0.308
Diastole: impaired relaxation	160	(74%)	37	(66%)	123	(77%)	0.031
Diastole: restrictive pattern	5	(3%)	4	(8%)	1	(1%)	0.031
Aortic valve stenosis (≥ mild)	20	(9%)	4	(7%)	16	(10%)	0.532
Aortic valve regurgitation (≥ mild)	55	(25%)	16	(29%)	38	(24%)	0.459
Mitral valve regurgitation (≥ mild)	70	(32%)	24	(43%)	46	(29%)	0.064
Tricuspid regurgitation (≥ mild)	97	(45%)	37	(67%)	60	(37%)	0.000
Pulmonary regurgitation (≥ mild)	73	(33%)	26	(47%)	46	(29%)	0.014
Pulmonary hypertension (≥ mild)	47	(22%)	16	(29%)	31	(19%)	0.579
Tricuspid reg. velocity > 2,5 m/s	44	(20%)	16	(29%)	28	(18%)	0.452
LV diameter systole (mm)	30	(8)	30	(8)	29	(7)	0.360
LV diameter diastole (mm)	47	(7)	48	(9)	47	(7)	0.380
LV hypertrophy (> 12 mm)	72	(33%)	21	(36%)	53	(33%)	0.725

Abbreviations: LV, left ventricular; LVEF, left ventricular ejection fraction; reg., regurgitation

Table 3. Hazard ratio of a fall according to echocardiographic abnormalities (N=215)

Echocardiographic finding	HR, Model 1	(95% (CI)	P-value	HR, model 2	(95% CI)	P-value
Aortic valve stenosis (≥ mild stenosis)	0.60	(0.22-1.68)	0.330	0.63	(0.22-1.76)	0.375
Aortic valve regurgitation (≥ mild regurgitation)	1.15	(0.63-2.08)	0.650	1.57	(0.85-2.92)	0.154
Mitral valve regurgitation (≥ mild regurgitation)	1.64	(1.08-2.84)*	0.038	1.66	(1.01-2.89)*	0.049
Tricuspid valve regurgitation (≥ mild regurgitation)	2.51	(1.39-4.53)*	0.002	2.41	(1.32-4.37)*	0.004
Pulmonary valve regurgitation (≥ mild regurgitation)	1.81	(1.06-3.08)*	0.030	1.76	(1.03-3.01)*	0.040
Tricuspid valve regurgitation velocity (linear)	2.85	(1.20-6.76)*	0.018	2.69	(1.09-6.65)*	0.032
Pulmonary hypertension (≥ mild PH)	1.60	(1.02-2.50)*	0.039	1.35	(1.08-1.71)*	0.023
LV hypertrophy (septum >12mm)	1.47	(0.77-2.82)	0.136	1.78	(0.87-3.64)	0.148
LVEF (<40%)	1.61	(0.22-11.65)	0.624	1.51	(0.21-10.97)	0.670
Fractional shortening (<25%)	1.98	(0.71-5.51)	0.335	2.18	(0.78-6.11)	0.255

Model 1: adjusted for age, gender

Model 2: adjusted for age, gender, number of comorbid conditions, Mini-Mental State Examination, drug intervention during follow-up

Abbreviations: HR, hazard ratio; CI, confidence interval; PH, pulmonary hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction

* $P < 0.05$

Table 4. Trend analysis of hazard ratio of a fall and aortic, mitral, tricuspid and pulmonary valve regurgitation and pulmonary arterial systolic pressure (N=215)

	N	HR	(95% CI)	P-value
Trend aortic valve regurgitation (linear)		1.16	(0.90-1.50)	0.248
No aortic valve regurgitation	134	1.00 (reference)		
Aortic valve regurgitation (trivial)	26	1.00	(0.42-2.43)	0.994
Aortic valve regurgitation (mild)	35	1.80	(0.85-3.80)	0.123
Aortic valve regurgitation (moderate)	20	1.30	(0.52-3.24)	0.518
Aortic valve regurgitation (severe)	0	-	-	-
Trend mitral regurgitation (linear)		1.35	(1.07-1.72)*	0.013
No mitral valve regurgitation	61	1.00 (reference)		
Mitral valve regurgitation (trivial)	83	1.32	(0.64-2.74)	0.453
Mitral valve regurgitation (mild)	51	1.70	(0.77-3.73)	0.188
Mitral valve regurgitation (moderate)	16	2.28	(0.88-5.93)	0.091
Mitral valve regurgitation (severe)	4	3.79	(1.05-13.76)*	0.043
Trend tricuspid valve regurgitation (linear)		1.46	(1.17-1.83)*	0.001
No tricuspid valve regurgitation	69	1.00 (reference)		
Tricuspid valve regurgitation (trivial)	48	1.72	(0.68-4.36)	0.255
Tricuspid valve regurgitation (mild)	55	2.94	(1.30-6.65)*	0.009
Tricuspid valve regurgitation (moderate)	35	2.91	(1.19-7.09)*	0.019
Tricuspid valve regurgitation (severe)	8	5.13	(1.71-15.36)*	0.003
Trend pulmonary valve regurgitation (linear)		1.36	(1.08-1.71)*	0.009
No pulmonary valve regurgitation	80	1.00 (reference)		
Pulmonary valve regurgitation (trivial)	63	1.89	(0.91-3.94)	0.090
Pulmonary valve regurgitation (mild)	44	2.17	(1.02-4.65)*	0.045
Pulmonary valve regurgitation (moderate)	25	2.52	(1.09-5.87)*	0.031
Pulmonary valve regurgitation (severe)	3	4.08	(0.87-19.28)	0.076
PAPs (linear)		1.05	(1.01-1.09)*	0.017
PAPs < 35 mmHg (reference)	169	1.00 (reference)		
PAPs 35-50 mmHg (mild PH)	39	1.14	(0.53-2.45)	0.737
PAPs > 50 mmHg (severe PH)	8	3.31	(1.18-9.29)*	0.023

Hazard ratio adjusted for age, gender, number of comorbid conditions, Mini-Mental State Examination, drug intervention during follow-up;
Explanation severity regurgitation: mild, 1+; moderate, 2+; severe, 3+ & 4+
Abbreviations: RR, relative risk; CI, confidence interval; PAPs, pulmonary arterial systolic pressure; PH, pulmonary hypertension
* $P < 0.05$

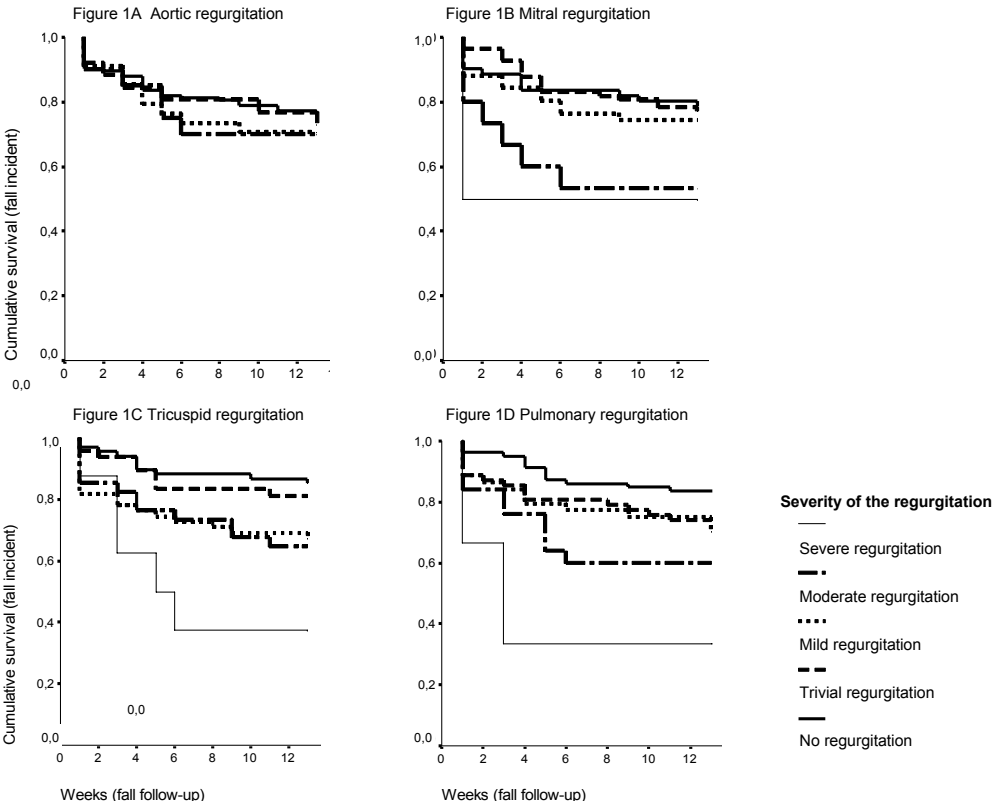

Figure 1. Kaplan-Meier Curve of Valve Regurgitation (Aortic, Mitral, Tricuspid and Pulmonary) According to Falls Incidence, Divided for Severity of the Regurgitation

disease, cerebrovascular event, hypertension, neurological disorder, depression, COPD, (osteo)arthritis, visual abnormality), use of a walking aid, ADL and IADL function, presence of abnormalities on the electrocardiogram, presence of orthostatic hypotension, carotid sinus hypersensitivity, vasovagal collapse, presence of other abnormalities on the echocardiography besides the one under consideration. Our final analysis included age, gender, MMSE-score, number of comorbid conditions and use and withdrawal of fall-risk-increasing drugs as cofactors. This resulted in a higher risk that was statistically significant for mitral valve regurgitation, tricuspid valve regurgitation and pulmonary valve regurgitation (table 3). A statistically significant relationship between increased pulmonary hypertension, as measured with tricuspid regurgitation velocity and systolic pulmonary arterial pressure, and falls during follow-up was also found, which was significant after adjustment for the cofactors mentioned above, including presence of valvular regurgitations. No significant correlation with falls was found for aortic valve stenosis, aortic valve regurgitation, left ventricular function < 40%, fractional shortening < 25%, or left ventricular hypertrophy.

However, the number of participants small, especially for poor left ventricular function, therefore giving rise to uncertain results (table 3). In a second analysis, the association between categories of increasing severity of valvular regurgitation and pulmonary hypertension and the risk of a fall was studied (figure 1). With the exception of aortic valve regurgitation, the relative risk increased with increasing severity of the regurgitation and there was a significant trend for mitral, tricuspid and pulmonary regurgitation (table 4). Trend analysis for pulmonary hypertension was also significant.

Discussion

In our study, several echo(Doppler)cardiographic abnormalities were risk indicators for falls. First of all, risk of falls was increased if regurgitation of the mitral, tricuspid or pulmonary valve was present. The level of risk increased according to the severity of the regurgitation. Valvular disease is known to cause syncope, the main evidence being for aortic valve stenosis and mitral valve prolapse.[5,6,30,31] The guidelines on syncope state that structural heart disease can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output. Valvular regurgitation will impair peak cardiac output, and if the circulatory demands cannot be met, this will result in a shortage of cerebral perfusion. In older patients, this can either present as a fall or as a syncopal spell. Although the recent guidelines pertain to syncope,[5,6] our results suggest that these guidelines may also apply to older fallers. Another possible explanation besides the possible causal chain mentioned above, is the fact that cardiac abnormalities might act as predictors for frailty, since in the Cardiovascular Health Study, frailty has been shown to predict falls in older persons and in this same cohort it has also been shown that subclinical cardiovascular disease was associated with frailty.[32,33] However, no significant relationship between frailty and left ventricular ejection fraction or frailty and mitral valve abnormalities was found, making it unlikely that these abnormalities acted as markers for frailty. They did not provide data on tricuspid, aortic or pulmonary valve abnormalities. Furthermore, in our analysis, cofactors associated with frailty, i.e. sort and number of comorbidities, age, cognitive function, use of a walking device and ADL and IADL function, did not act as confounding factors.

An increased fall risk was also found for high tricuspid regurgitation velocity and high pulmonary systolic pressure, which was used as a proxy for pulmonary hypertension. Our finding is therefore in line with earlier publications showing a high percentage of pulmonary hypertension in syncope patients.[5,6] The number of patients with pulmonary hypertension (defined as a pulmonary systolic pressure ≥ 35 mm Hg) was high in our population, i.e. 22%. This is in line with the findings of a study by Dokainish et al, showing a prevalence of 23% in patients aged at least 90 years old and further normal echocardiography.[28] This is an interesting finding because it may not reflect physiological aging but it possibly in-

dicates a high number of non-identified morbidity in this age group. This would be in line with the high percentage of undetected pulmonary embolisms in this age group, as was found in a recent study of older persons presenting with acute respiratory failure to the emergency department.[34]

Although further research will be needed to confirm our findings and establish the clinical usefulness of echocardiographic screening in older fallers, it is interesting to contemplate on the possible clinical consequences and effects, e.g. treatment and a possible ensuing decrease in fall risk. First of all we want to emphasize the fact that most fall incidents in older persons are of multifactorial origin and therefore treatment of valvular abnormalities will need to be part of a multifactorial intervention. Assuming that there is indeed a causal relationship between falls and valvular abnormalities, care of older fallers may be improved by implementing echocardiography in the clinical work-up for older fallers. However, further research will be needed first to determine the clinical added value of including echocardiography to the falls assessment. Furthermore, the available treatments need some consideration in order to judge the potential decrease in fall risk. Surgical repair might be feasible for a subgroup of geriatric patients. Still, it is likely that the majority will not benefit from such a drastic procedure, partly because their cardiac abnormalities are not severe enough to engage in a surgical procedure and partly because in a fair amount of geriatric patients comorbidity is significant, giving rise to an unacceptably high per-operative risk. Therefore, in most patients diligent review of possible precipitants including tailoring of drug treatments will be the intervention of choice. In case of pulmonary hypertension optimal treatment depends of course on the underlying disorder, but could consist of anticoagulants, optimizing treatment for COPD and other lung disorders including oxygen therapy, a trial period with calcium channel blockers (may be either beneficial or detrimental), digoxin, or advanced therapy including prostanoids, endothelian receptor agonists and PDE5 inhibitors. For patients with mitral regurgitation and atrial fibrillation, cardioversion and antiarrhythmic drugs are recommended. Furthermore, in case of mitral regurgitation a reduction of preload with beta-blockers, calcium channel blockers or diuretics can be advantageous, in severe cases vasodilator therapy including ACE inhibitors and angiotensin II receptor blockers may be of benefit. However, data regarding the beneficial effect of long-term vasodilator therapy are conflicting. ACE inhibitors or angiotensin II receptor blockers may be of use in case of comorbity (hypertension, diabetes or left ventricular dysfunction). Besides surgery, cardiac resynchronization may be of use. Reduction of systolic blood pressure is the primary goal in mitral valve prolapse and rheumatic valve disorders, using either beta-blockers, diuretics, hydrazaline or calcium channel blockers. For pulmonary regurgitation and tricuspid regurgitation evidence regarding optimal conservative treatment is limited, but consists of treatment of pulmonary hypertension if present and lowering of the afterload.[35,36] Since vigilant conservative treatment of valvular abnormalities and pulmonary hypertension includes the use of known fall-risk-increasing drugs, we think that is of utmost

importance to carefully weigh the benefits and dangers of treatment, and for this, certainty of presence of the cardiac abnormality is needed. Therefore, assuming that there is indeed a causal relationship between these cardiac abnormalities and fall incidents, in our opinion, echocardiographic assessment will be needed if treatment is considered.

Well-known causes for syncope are aortic valve stenosis and left ventricular outflow-tract obstructions. Contrary to our expectations, an increased fall risk was not found for these conditions. This is most probably caused by the fact that only 20 cases of aortic valve stenosis were present in our cohort, the majority being mild (n=17) and probably only moderate to severe aortic valve stenosis will result in deficient cardiac output in demanding situations.

Our study has some potential limitations. First, in a subgroup of our cohort drugs known to increase fall risk were withdrawn. This intervention was completed after the first month and reduced fall incidence for the intervention group in the second and third month of follow-up.[10] However, adjustment for the intervention did not change our results (table 3 and 4), thus making it unlikely that this intervention acted as a confounder in the association between echocardiographic abnormalities and falling. A second potential limitation of our study is the substantial number of patients who refused participation. On average this group was older and frailer, which might have given rise to a generalizability problem. It seems unlikely that selection bias explains the positive association between valvular regurgitation and fall risk. On the contrary, we expect that the risk would have been even higher in the non-participants because the old and frail have less effective cardiovascular coping mechanisms.

Furthermore, we have assessed 9 predefined possible associations, giving rise to the possibility of random error due to multiple testing. However, since the associations in question were all defined a-priori on the bases of a clinical hypothesis and a significant result due to chance (random error) occurs only one in twenty times (using $p < 0.05$) we do not think it likely that our findings were caused by chance.

In conclusion, this study has shown that in our cohort of geriatric outpatients there was an increased risk of falls in patients with regurgitations or mitral, tricuspid or pulmonary valves and in patients with pulmonary hypertension. To our knowledge, this is the first study addressing the association between echocardiographic abnormalities and falls in older persons. Our study demonstrates that the incidence of cardiac abnormalities is high and that there is an association between cardiac abnormalities and fall incidents. Therefore, we think that a two-dimensional echo(Doppler)cardiogram might be useful in the diagnostic work-up of selected groups of older fallers. Echocardiographic screening of older fallers can be important for two reasons. First, it can provide a diagnosis in a fair number of cases, and second, it can help select those patients who need careful tailoring of their (drug) treatments. Since this is the first study addressing this topic, more studies will be needed to determine the need for and the yield of standard echocardiography in older fallers.

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TC, NV and BS designed the study. NV performed the data collection and analysis. BC contributed to the data analysis. NV wrote the paper. FT contributed to the design of the study and contributed to the data interpretation. All authors commented on the manuscript, suggested changes, and approved the final version.

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Chapter 3.2

Association between left ventricular function and serious fall incidents in older persons in the Rotterdam Study

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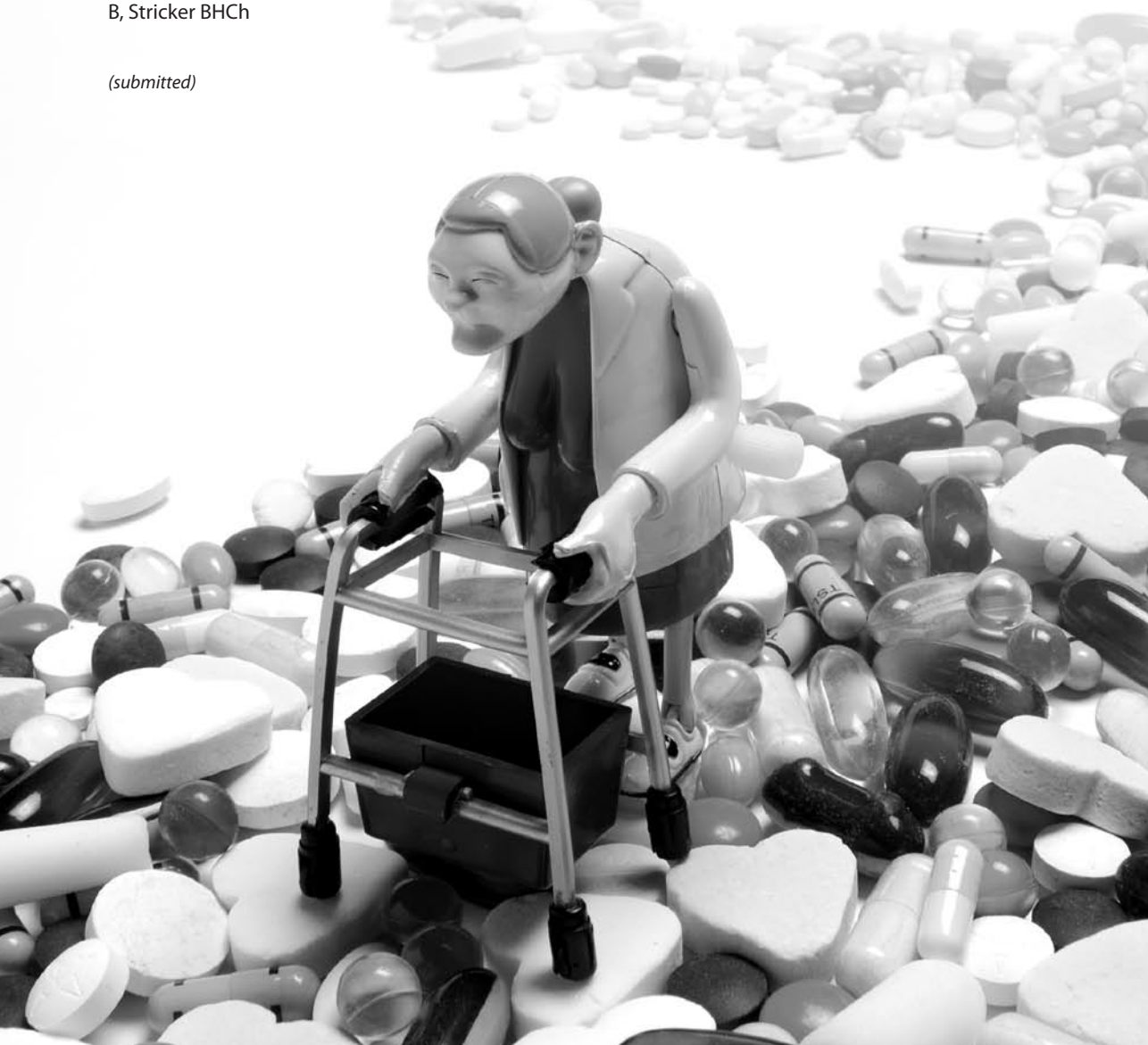
(submitted)



Abstract

Background

Poor left ventricular function can result in a shortage of cerebral perfusion, especially in physically demanding situations. A typical presentation of episodes of cerebral hypoperfusion would be syncope, however, 50% of older syncope patients do not recall the loss of consciousness and will therefore present with a fall instead.

Objective

To investigate the association between left ventricular systolic function and fall incidence in older persons.

Methods

The association between left ventricular systolic function and falls with serious consequences in older adults was tested in the Rotterdam Study, a population-based cohort study in 7983 adults. In 2266 participants left ventricular ejection fraction (LVEF) was measured with two-dimensional transthoracic echocardiography. Events were defined as a fall leading to hospital admission and/or a fracture during follow-up. Data were recorded between 1991 and 2002. Multivariate adjustment for confounders was performed with a Cox proportional hazards model.

Results

The risk of a fall with serious consequences was significantly higher if LVEF was impaired. Trend analysis according to degree of LVEF was significant. The adjusted hazard ratio of a fall was 2.70 for LVEF <35% (95% CI 1.11-6.58) and 1.71 for LVEF 35-50% (95% CI 1.10-2.66).

Conclusions

These findings suggest that poor systolic function as measured with LVEF is a risk indicator for fall incidents with serious consequences, irrespective of cardiovascular drug use, hypertension and atrial fibrillation. Although for the clinical implications of this finding further research is needed, it can be speculated that clinical benefit might be obtainable if systolic function is improved in older fallers.

Introduction

Falls and fall-induced injuries are common among older people, with often devastating results. The incidence of falls ranges from 30-50% per year depending on the population studied, with a mean injury rate of 20%.[1-6] With advancing age, besides a rising number of fall incidents, the percentage of injurious falls also goes up.[7] Furthermore, the costs per injurious fall incident increase with increasing age.[8] All in all, there is a major need for identification of modifiable fall-risk factors. And although many risk factors have been identified in the last two decades, research regarding cardiovascular risk factors is less abundant.[9] The studies present pertain to vascular risk factors, e.g., orthostatic hypotension, systolic hypertension, carotid sinus hypersensitivity and vasovagal collapse.[10] Besides a recent cohort study by our research group, in which echocardiographic abnormalities as fall-risk factors in geriatric outpatients were addressed, to our knowledge there are no data regarding structural cardiac abnormalities as possible risk factor for falls.[11] This is remarkable, since structural cardiac abnormalities are undisputed risk factors for syncope[12,13] and older persons suffering from syncope will present with a fall in approximately 50% of syncope patients, mainly because of amnesia for the temporary loss of consciousness.[14] Syncope, or falls, will occur when circulatory demands outweigh the impaired ability of the heart to increase its output. It is thought that in this situation a transient shortage of cerebral perfusion occurs, resulting in a fall or syncope.[13]

Since so little is known about the association between impaired cardiac function and fall incidents, we tested this in a population-based cohort study of persons of 55 years and older, in which we prospectively assessed the association between poor cardiac function and serious fall incidents.

Methods

Setting

The present study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in older adults. Objectives and methods of the Rotterdam Study have been described elsewhere.[15] In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and had lived in the district for at least 1 year, were invited to participate in the study. Of these 10275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve information from treating physicians. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands, approved the study.

Study population

Baseline data were collected from 1990 until 1993. A trained interviewer visited all subjects at home and collected information using a computerized questionnaire. The obtained information included current health status, medical history, history of falls and drug use. Subsequently, participants came to the research centre for several measurements. In addition, a two-dimensional transthoracic echocardiography was performed in a random sample of participants (n=2823). The presented results are based on the 2266 participants of whom data regarding echocardiography were deemed of sufficient quality to reliably measure left ventricular dimensions. Persons in whom M-mode registrations were unsuccessful were more likely to be older, to have a higher body mass index and to use medication for chronic obstructive pulmonary disease. Cardiovascular disease and diabetes were also more common in participants with an inadequate echocardiographic window.[16]

Cofactors

For the current analysis, the following risk factors for falls were assessed as potential confounders: age, gender, body mass index, a history of diabetes mellitus, hypertension and atrial fibrillation, and cardiovascular drug use.

Medication use was gathered via a linked network, including 7 fully computerized pharmacies of the area.[17] Use at the index date was assessed for all antihypertensives (diuretics, beta-blockers, alpha-blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), anti-arrhythmics, nitrates and other vasodilators, digoxin and beta-blocker eye drops. The date of fall or fracture occurrence was defined as the index date. We defined hypertension as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg, or the use of antihypertensive medication for the indication of hypertension. Diabetes mellitus was defined as the use of blood glucose lowering medication or a random or post-load serum glucose level ≥ 11.1 mmol/l.[18] Height and weight were measured with participants wearing light clothes and without shoes. Body mass index (BMI) was defined as weight divided by height squared (kg/m^2).

Echocardiography interpretation and measurements

Echocardiography was performed with the participant in the partial left decubitus position. A Toshiba SSH-60A was used for all examinations (Nasuworks, Otawara, Japan). Two-dimensional imaging using parasternal long-axis views was performed to aid M-mode studies. Measurements were made according to the recommendations of the American Society of Echocardiography using a leading edge to leading edge convention. Left ventricular internal dimension was measured at end diastole (LVED), as defined by the onset of the QRS complex and at end systole (LVES), as determined at the nadir of septal motion.

Left ventricular ejection fraction (LVEF) was calculated using the simplified method of Quinones, *et al*.[19]

Follow-up procedure

As the primary outcome we studied a fall leading to hospital admission or diagnosis of a fracture. Follow-up started at the baseline examination and for the present study lasted until January 2002. Information on fatal and non-fatal endpoints for the participants enlisted was obtained from a computerized reporting system for general practitioners (LMR). These data cover approximately 80% of the study sample. For participants who were not covered in this system, research physicians performed annual checks on the complete medical records of all general practitioners in the Rotterdam Study.

Two research physicians independently coded all fractures that occurred during the study period using the International Classification of Diseases, 10th revision (ICD-10).[20] This was also done for hospital admissions due to a fall incident. A medical expert in the field who was unaware of the patients' history and medication use reviewed all coded events for a final classification. Definition of an endpoint was either a fall leading to hospital admission or an incident fracture. Vertebral fractures, pathological and post-procedural fractures were excluded from the case definition.

Statistical analysis

Baseline differences between the subgroups with and without impaired LVEF were tested using an independent t-test for continuous variables, and a chi-square test for dichotomous variables.

Cox's proportional hazards analysis was used to estimate the crude and adjusted relative risks of a serious fall incident associated with abnormal left ventricular function. In case of occurrence of death before occurrence of the event the participant was censored in the analysis. Participants with normal left ventricular function, defined as LVEF >50%, were taken as the reference group. Furthermore, abnormal LVEF was divided in participants with an LVEF between 35% and 50% and participants with a LVEF <35%. Both categorical analysis and trend analysis were performed. To adjust for possible confounders, cofactors were included one-by-one in the age- and gender-adjusted model. Cofactors that changed the hazard ratio of a serious fall incident according to LVEF by more than 5% or that were biologically plausible were maintained in the final model. For the assessment of cardiovascular drug use as a potential confounder, a time-varying-exposure analysis was performed, using occurrence of the defined outcome as the index date. All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows baseline characteristics of all participants and of those with a LVEF >35% and < 35%. Mean age of the participants was 65.1 years (SD 7.3) with an approximately equal gender distribution (54% females). An association with LVEF <35% was present for gender only (table 1). Two hundred and forty-nine participants (11%) recalled one or more falls during the previous year. The mean follow-up time was 2996 days (SD 880). During follow-up 251 (11.1%) participants experienced a fracture and 44 (1.9 %) experienced a hospital admission due to a fall incident. Since for 18 participants the fracture was a reason for admission to a hospital, the total number of events added up to 267. Table 2 shows the number of events and the incidence rates for the different categories of LVEF.

In participants with a LVEF <35%, both the crude and the age- and gender adjusted hazard ratios for a serious fall incident were significantly increased (Tabel 3, model 1 and 2). After further adjusting for body mass index, hypertension, diabetes mellitus, and atrial fibrillation (Tabel 3, model 2) both LVEF <35% and 35-50% showed a significantly increased

Table 1. Baseline characteristics, overall and divided for LVEF >/< 35% (N=2266)

Characteristic	All	%/SD	LVEF >35%	%/SD	LVEF <35%	%/SD	P-value
	(n=2266)		(n=2232)		(n=27)		
Age, SD	65.1	7.3	65.1	7.3	67.2	6.1	0.26
Gender, female (%)	1219	53.8	1211	54.3	7	25.9	0.002
At least 1 fall (%)	249	11	245	11.0	1	3.7	0.22
>1 fall (%)	21	0.9	21	0.9	0	0	0.61
BMI (SD)	26.9	3.3	25.9	3.3	25.6	2.7	0.79
Systolic BP, mmHg (SD)	138.4	22.5	138.3	22.5	144.4	26.1	0.38
Diastolic BP, mmHg (SD)	74.6	11.6	74.6	11.5	77.1	13.9	0.19
Diabetes mellitus (%)	160	7.1	157	7.0	2	7.4	0.99
Smoking current (%)	491	21.7	486	21.8	5	18.5	0.32
Smoking former (%)	1021	45.1	998	44.7	16	59.3	0.32
Atrial fibrillation (%)	56	2.4	56	2.5	0	0	0.41

Abbreviations: LVEF, left ventricular ejection fraction; SD, standard deviation; BMI, body mass index

Table 2. Number of events and crude incidence rates per 100 000 person years for all participants and according to LVEF

	Events*	Incidence rate	95% CI
All (N=2266)	267	39	35-44
LVEF >50% (n=2068)	238	38	33-43
LVEF 35-50% (n=171)	23	50	32-75
LVEF <35% (n=27)	6	88	32-192

*Fall incident resulting in a hospital admission and/or fracture

Abbreviations: LVEF, left ventricular ejection fraction; CI, confidence interval

Table 3. Relative risk of a fall resulting in hospital admission according to Left ventricular ejection fraction (LVEF) (N=2266)

LVEF	HR	95% CI	HR	95% CI	HR	95% CI
	Model 1		Model 2		Model 3	
LVEF categorical	1.42	1.05-1.93*	1.47	1.08-2.01*	1.68	1.22-2.31*
LVEF >50% (reference)	1.00		1.00		1.00	
LVEF 35-50%	1.32	0.86-2.03	1.35	0.88-2.08	1.71	1.10-2.66*
LVEF <35%	2.35	1.04-5.28*	2.59	1.15-5.93*	2.70	1.11-6.58*

Abbreviations: LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval
Model 2: adjusted for age and gender
Model 3: adjusted for age, gender, body mass index, diabetes mellitus, hypertension, atrial fibrillation
* $P < 0.05$

risk for serious fall incidents (table 3, model 3). Risk of an event increased with worsening of the LVEF. For the assessment of cardiovascular drug use as a possible confounder, a time-varying-exposure analysis was performed with incidence of a serious fall incident as the index date. Since none of the cardiovascular drugs acted as a confounder they were left out of the final analysis. The respective hazard ratios for LVEF adjusted for the cofactors mentioned above and use of cardiovascular drugs were 1.66 for the trend analysis (95% CI 1.19-2.29), 1.69 for LVEF 35-50% (95% CI 1.09-2.63) and 2.61 for LVEF <35% (95% CI 1.04-6.53).

Discussion

In our study, poor LVEF was a risk factor for serious fall incidents. Fall risk increased with decreasing LVEF, with an almost tripled risk of a serious fall incident in participants with a LVEF below 35%. Our explanatory hypothesis is that persons with a poor LVEF have a limited spare cardiac output capacity, which can result in cerebral hypoperfusion, and hence falls, in physically demanding situations.[13] Another possible explanation would be that poor LVEF might act as a predictor for frailty, since in the Cardiovascular Health Study, frailty has been shown to predict falls in older persons.[21] However, in that study it was also shown that although the incidence of poor LVEF was higher in frail participants, there was no significant association between LVEF and frailty.[22]

As mentioned earlier, falls are a major problem in the healthcare of older persons, because of their high incidence en often devastating consequences. Although in the current guidelines for assessment and treatment of older fallers already many risk factors have been incorporated, the optimal content is still not clear, since studies regarding the multifactorial approach differ regarding the content of the assessment and intervention.[23] The current study suggests that there might be a role for a more thorough cardiovascular assessment, although further research is needed to determine the clinical added value of

including echocardiography to the falls assessment. On any account, regarding the results it can be speculated that clinical benefit might be obtained if cardiac output is optimalized in older fallers.

In our study, we addressed falls with serious consequences, which is merely a fraction of the total number of fall incidents in older persons; approximately 10% in a Dutch cohort study.[24] As a consequence, we cannot be certain whether our finding is generalizable to overall falls in older persons. However, there is no reason to assume that poor LVEF would only lead to serious fall incidents and not falls with less disastrous consequences. Furthermore, our study group has also assessed the association between poor LVEF and fall incidents in a small prospective cohort of geriatric outpatients (N=215) and although the incidence of poor LVEF was too small to draw definite conclusions (3%), we found a comparable, though non-significant, fall risk in this group.[11]

Due to the size of our study population, left ventricular systolic function was estimated by LVEF, rather than by 2D echocardiographic determination of ejection fraction. In the absence of major wall motion abnormalities however, LVEF can be assumed to reliably reflect left ventricular systolic function.[19] Due to a limited availability of echotechnicians, echocardiographic information was only available for 2823 participants. Although no prior rules were set for the performance of echocardiography in certain subgroups, participants who underwent echocardiography tended to be younger and were less likely to have cardiovascular disease as compared to the study group.[16] Furthermore, participants in whom the echocardiographic window was deemed adequate for analysis (N=2266) were also younger and less likely to have cardiovascular disease. Therefore the studied group probably reflects a healthier subgroup of the Rotterdam Study. Nevertheless, one can expect that this only lowered the incidence of poor LVEF and did not affect the relative risk, since there is no reason to expect that with increasing age or presence of cardiovascular disease the relation between fall incidents and poor LVEF alters.

In conclusion, this study suggests that poor LVEF is a risk indicator for fall incidents with serious consequences. This finding was irrespective of cardiovascular drug use, hypertension and atrial fibrillation. Hence, according to our hypothesis, it appears probable that insufficient cardiac spare capacity can lead to periods of cerebral hypoperfusion, which subsequently can result in falls. Although for the clinical implications of our finding further research is needed, this outcome suggests that clinical benefit might be obtained if systolic function is optimalized in older fallers.

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Chapter 3.3

Measuring orthostatic hypotension with the Finometer device: Is a blood pressure drop of one heartbeat clinically relevant?

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Blood Press Monit 2007; in press

Abstract

Objective

The role of orthostatic hypotension (OH) in falls in older people is generally accepted. Because of the high degree of intra- and inter-observer variability in conventional measurements of OH, application of continuous measurement systems has been proposed. However, the clinical relevance of a blood pressure drop lasting one heartbeat is unknown. We therefore investigated which time average of continuous-finger-blood-pressure measurement (Finometer) showed the best association between OH and falls. This was also compared with conventional sphygmomanometer measurements.

Methods

In 217 geriatric outpatients supine and standing (finger) blood pressure to diagnose OH was monitored with Finometry (beat-to-beat and 1, 5, 10, 15, 20 and 30 second averages) and sphygmomanometry. History of fall incidents (previous year) was registered.

Results

The best association (C=0.22, p=0.003) with falls history was found for the 5-second average of Finometry, whereas falls and OH assessed by sphygmomanometry did not correlate. The odds ratio of a fall according to OH using the 5-second average was 2.54 (95% CI: 1.37 to 4.71).

Conclusions

OH and falls are correlated when using Finometry, with the best association found when using 5-second averages. Since the etiology of falls is often multifactorial, OH and falls are poorly correlated, irrespective of the method or time average that is applied.

Introduction

Falls and fall-induced injuries in older people are a major public health problem.[1] Falling is associated with many different risk factors, several of which are cardiovascular.[2,3] Cardiovascular disorders are responsible for as many as 77% of cases presenting to Accident and Emergency departments with unexplained or recurrent falls.[4] The main causative cardiovascular disorders are orthostatic hypotension (OH), carotid sinus hypersensitivity, vasovagal collapse, cardiac arrhythmias and structural cardiac diseases.[5] OH is thought to contribute to fall incidents in 5 to 32% of cases.[4-7]

Incidence of OH in older people varies depending on the chosen population, with values of approximately 50% in institutionalised patients,[8,9] and 7 to 30% in community-dwellers.[10-12] The incidence of OH increases with age, due to the fact that over the years the ability to maintain haemodynamic homeostasis in response to postural changes becomes less effective.[13-17] These alterations in the cardiovascular system combined with a blunted response of the sympathetic nervous system, predispose older people to significant drops in blood pressure when assuming the upright position.[18]

Notwithstanding some conflicting data, the role of OH as one of the causal pathways for falls is generally accepted.[19-21] These conflicting data might in part be caused by the way OH is assessed.[12,22,23] In particular, sphygmomanometer assessment is probably too imprecise and too infrequently repeated during standing-up, in order to measure OH in a sufficiently reliable manner.[24] Therefore, it seems logical to use a more objective and precise measurement method, i.e. a tilt-table and a continuous-blood-pressure measurements system, like Finometer or Finapres.[25] Of late, continuous-blood-pressure-measurement systems are increasingly available in hospital settings. However, a potential problem with these measurement systems could be over-diagnosing of OH.[26] With a Finometer or a Finapres system, finger blood pressure is measured every heartbeat, but to our knowledge, up to now no adjustment of the definition of OH has been proposed when applying these systems. As a result, a systolic drop of 20 mmHg for the duration of only one heartbeat would already be sufficient to diagnose OH. Such a short lasting fall in blood pressure might not be very closely related to OH diagnosed in the conventional way, rendering the clinical meaning of such a test outcome unclear. We therefore tested in a sample of 217 geriatric outpatients with and without a history of falls, which OH measurement (sphygmomanometer measurement and 7 different time averages of the finger-blood-pressure measurement) correlated best with fall incidents.

Methods

Study participants

All new consecutively referred patients to the outpatient clinic and the Diagnostic Day Centre of the Section of Geriatric Medicine of the Erasmus MC were considered to be eligible if they were 65 years or over, had a Mini-Mental State Examination score (MMSE) of 21 points or higher (out of 30 points)[27,28] and were able to walk 10 meters without a walking aid in the test setting.

The study protocol was approved by the Medical Ethics Committee of the Erasmus MC and written informed consent was obtained from all patients. Patient recruitment started April 1, 2003 and ended November 30, 2004.

Falls history

A fall was defined as coming to rest unintentionally on the ground or at a lower level with or without losing consciousness, but not if this had been induced by acute medical conditions, such as stroke, or exogenous factors, such as a traffic accident.[29] Falls history was considered positive if at least one fall had occurred within the previous year.[30]

Baseline characteristics

Functional status was measured with the Activities of Daily Living measurement (ADL)[31] and the Instrumental Activities of Daily Living measurement (IADL).[32] We also recorded whether or not study participants used a walking aid in daily life. Information on co-morbidity was obtained in an interview with the study participants at baseline. This was verified with the record of the geriatrics department and information from the general practitioner. All comorbid diagnoses were recorded, as was total number of comorbid diagnoses. Furthermore, total number of drugs used was recorded, as was the number of cardiovascular active drugs that are known to be able to cause OH. The latter included the following drug groups: antihypertensives, anti-arrhythmics, nitrates and other vasodilators, beta-blocker eye drops, opioid analgesics, anxiolytics/hypnotics, neuroleptics and antidepressants.

Measurement of orthostatic hypotension

OH was defined as a 20 mm Hg fall in systolic blood pressure or a 10 mm Hg fall in diastolic blood pressure.[33,34] Sphygmomanometer blood pressure measurements were performed by trained nurses, using a normal office sphygmomanometer with appropriate size cuffs. Supine blood pressure was measured at the left arm after 10 minutes of rest. Standing blood pressure was measured at 1, 2 and 3 minutes, and of these the lowest blood pressure was used.

Continuous-finger-blood-pressure measurement was performed with a Finometer (Finapres Medical Systems BV, the Netherlands), a non-invasive beat-to-beat blood pressure

measurement device using digital photoplethysmography. The blood pressure signal was analysed by the Beat Scope software program (Finapres Medical Systems BV, the Netherlands). For tilting, a manually operated, motor-driven tilt-table was used. For measuring of OH, the brachial and finger cuffs were placed respectively on the left upper arm and second finger, the height correction system of the Finometer device was active during the whole testing period. The participants first underwent 10 minutes of supine rest; at the end of this period blood pressure was recorded. Subsequently, the participants were tilted head up to 70 degrees. Lowest systolic and diastolic blood pressure was recorded using the first 300 seconds of head up tilt. Finometry allows averaging of blood pressure in pre-defined time periods, using sequential time windows of any chosen length. This makes it possible to use different blood pressure averages. For our study, seven different parameters were used: beat-to-beat values and 1-, 5-, 10-, 15-, 20-, and 30-second averages.

Statistical analysis

Cross-sectional analysis of the association between falls history and the different methods and time averages of measuring OH was performed in two steps. First we used the Chi-square test and association coefficients (Chi-square Contingency Coefficient C: no association=0, perfect association=1) in order to estimate the associations between the different measurements of OH and falls history. Both OH and falls history were coded in a binary fashion. Subsequently, we calculated the odds ratios, using a binary logistic regression model. Odds ratios of OH according to falls history were computed as estimates of relative risk. All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

Results

During the study period, 218 persons were included, of whom 1 dropped out because the test procedure turned out to be too difficult. The remaining 217 individuals were included in our analysis. Out of these, 139 had experienced at least one fall during the previous year. Out of all included patients, 25 (12%) had Finometer files that were unsuitable for analysis due to the loss of signal from the Finometer (n=5) or invalid data storage (n=20).

Baseline subject characteristics are summarised in Table 1. The majority of fallers were frequent fallers (76%). The group of patients with a positive falls history comprised more women and age was higher compared to the group with a negative falls history. They were also more disabled as was shown by a higher use of walking aids and poorer ADL and IADL scores. They had more comorbid conditions, a lower MMSE-score, and used more drugs. Figure 1 shows the prevalence of OH for the different measurement parameters.

Table 2 shows a cross-sectional analysis of sphygmomanometer and Finometer OH measurements for the different time averages, according to falls history. Crude prevalences of OH were higher in patients with a positive falls history than in patients with a negative

Table 1 Baseline characteristics of a cohort of geriatric outpatients (N=217)

	Fall previous year (n=139)		No fall previous year (n=78)		P-value
Age, mean (SD), y	78.7	(±5.7)	75.0	(±6.0)	0.000
Gender: female, no. (%)	107	(76%)	36	(47%)	0.000
Referral b/o falls, no. (%)	106	(76%)	2	(3%)	0.000
>1 fall last year, no. (%)	106	(76%)	-		
Use of walking aid, no. (%)	73	(52%)	14	(18%)	0.000
ADL score, mean (SD), pts.	0.8	(±1.7)	0.1	(±0.3)	0.000
IADL score, mean (SD), pts.	13.6	(±3.3)	15.2	(±1.9)	0.000
MMSE score, mean (SD), pts.	27.1	(±2.7)	28.9	(±7.4)	0.038
Drugs used, mean (SD), no.	5.3	(±2.8)	4.1	(±2.0)	0.005
OH-causing drugs, mean (SD), no.	2.4	(±1.8)	1.7	(±2.0)	0.013
Co-morbidity, mean (SD), no.	4.2	(±1.9)	3.6	(±1.8)	0.025

Abbreviations: SD, standard deviation; no., number; b/o, because of; ADL, activities of daily living; IADL, instrumental activities of daily living, MMSE, Mini-Mental State Examination; OH, orthostatic hypotension

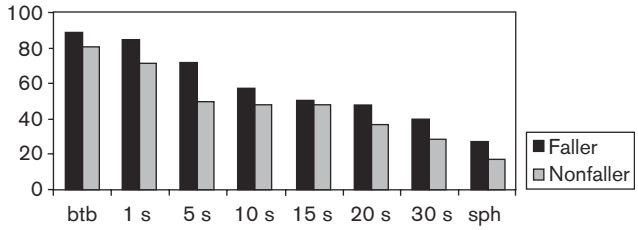

Figure 1. Percentages of subjects with orthostatic hypotension for the different measurement averages
Abbreviations: btb, beat-to-beat; s, seconds; sph, sphygmomanometry

falls history. This difference was significant for the 1-second and the 5-second Finometer averages, but not for the sphygmomanometer measurement. The association coefficient was 0.17 for the 1-second average measurement and 0.22 for the 5-seconds average measurement. For the sphygmomanometer measurement, the association coefficient was 0.11 (non-significant). Table 3 shows the odds ratios for OH according to fall history for the different measurement parameters. The strongest association with falls history was found for

Table 2 Prevalence of orthostatic hypotension according to fall history yes/no

	Fall previous year (n=124)		No fall previous year (n=68)		P-value
Sphygmomanometer	33	(27%)	12	(17%)	0.61
Finometer					
Beat-to-beat	110	(89%)	55	(81%)	0.14
1-second average	105	(85%)	48	(71%)	0.02
5-second average	89	(72%)	34	(50%)	0.03
10-second average	71	(57%)	33	(48%)	0.25
15-second average	62	(50%)	32	(47%)	0.70
20-second average	60	(48%)	25	(37%)	0.21
30-second average	49	(40%)	20	(29%)	0.16

Table 3 Relative risk (odds ratio) of a fall during the previous year according to orthostatic hypotension yes/no for the different measurement possibilities

	Odds Ratio	95% Confidence interval
Sphygmomanometer	1.94	0.78-4.35
Finometer		
Beat-to-beat	1.86	0.82-4.22
1-second average	2.30	1.13-4.71*
5-second average	2.54	1.37-4.71*
10-second average	1.42	0.79-2.57
15-second average	1.13	0.62-2.03
20-second average	1.61	0.88-3.00
30-second average	1.57	0.83-2.96

*$P < 0.05$

the 5-second average. The association was also significant for the 1-second average. We have also performed the analyses addressing frequent fallers only; this resulted in similar outcomes. Therefore, only the data of overall fallers are presented.

Furthermore, we also recorded after which time interval OH occurred. When using the 5-second averages, mean duration from standing up to occurrence of OH was 62 seconds (95% CI: 52 to 71 seconds). Eight patients (6%) developed OH only after 3 to 5 minutes of standing. Of these, 7 had a history of falls.

Discussion

This study shows that the optimal time average for finger-blood-pressure measurements, when addressing OH as a cause of falls, appears to be 5 seconds and not the generally used beat-to-beat reading.[12,22-25,35] Compared to conventional sphygmomanometry, continuous finger-blood-pressure measurement seems to perform better when evaluating OH as a cause of fall incidents in older people. In our population, the risk of a fall (history) was 2.5 times higher if OH was present (odds ratio 2.54, 95% CI 1.37 to 4.71). We therefore are confident to conclude that OH based on 5-second averages is the best, albeit still a poor, predictor of falls.

As mentioned in the introduction, the role of OH as one of the causes of falls is generally accepted.[19-21] Our finding that OH was related to a positive falls history supports this view. However, our study also shows that the association between OH and falls is weak. This is not an unexpected finding, since the aetiology of falls is usually complex, with OH as the predominant factor in only some instances.[19]

Since OH contributes to fall incidents only in a subgroup of persons, it is crucial to diagnose this condition correctly. Conventional sphygmomanometry to assess OH suffers from a high degree of inter- and intra-observer variability, which can be overcome by using an operator-independent continuous-measurement system.[24] When applying such a system,

it is important to realise that within a geriatric population, the number of subjects with OH, either with or without a history of falls, is over 80% when OH is diagnosed on the basis of beat-to-beat readings or 1-second averages. Increasing the time period of blood-pressure averaging results in a progressive decrease in the prevalence of OH, but even with 30-second averages the prevalence of OH was about 50% higher in both fallers and non-fallers than the prevalence of OH assessed by sphygmomanometry (figure 1). To some extent this difference in prevalence might be explained by the difference in experimental conditions, i.e. active standing during sphygmomanometry and passive standing during Finometry. Furthermore, sphygmomanometry will miss blood pressure drops that occur between measurements.[35]

An interesting observation within our study population is the fact that among fallers the use of cardiovascular active drugs that can cause OH is higher than in non-fallers. This observation endorses the idea that these drugs are indeed able to cause falls, most probably by causing OH. We have studied this hypothesis in a follow-up part of this same cohort and found that together with a decrease in fall incidents the presence of OH (among other abnormal test outcomes) decreases after withdrawal of fall-risk-increasing drugs.[36]

A potential limitation of our study is the loss of data, 12% of our study population could not be included in our final analyses, because of technical problems. This loss of data may have influenced the results, however it is unlikely that patients in whom data were inaccessible had different responses compared to the patients in whom data were accessible, since failure of data storage was random. Another potential limitation of our study is the cross-sectional approach. Although we show a clear association between falls and OH, because of the study design one cannot be certain that this association is truly a causal one. For this a double-blinded placebo controlled intervention study would be needed. Furthermore, it is not certain that OH indeed preceded the fall incidents in all participants; this might have given rise to either an over- or underestimation of the association.

In conclusion, OH in older subjects is better assessed with continuous finger blood pressure measurements than with conventional sphygmomanometry. When applying continuous finger blood pressure measurements it is important to realise that the prevalence of OH is grossly overestimated when only beat-to-beat values are considered. For the diagnosis of OH, we recommend to use 5-second averages instead of beat-to-beat finger blood pressure readings. A second recommendation is to take into account an observation period of five minutes of standing when addressing OH, since in our study, 6% of patients developed OH only after the first three minutes and most of these (7/8) were fallers.

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Chapter 4.1

Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study

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Abstract

Aim

Falling in older persons is a frequent and serious clinical problem. Several drugs have been associated with increased fall risk. The objective of this study was to identify differences in falls incidence after withdrawal (discontinuation or dose reduction) of fall-risk-increasing drugs as a single intervention in older fallers.

Methods

In a prospective cohort study of geriatric outpatients, we included 139 patients presenting with one or more falls during the previous year. Fall-risk-increasing drugs were withdrawn, if possible. Falls incidence was assessed within 2 months of follow-up after a set 1-month period of drug withdrawal. Multivariate adjustment for potential confounders was performed with a Cox proportional hazards model.

Results

In 67 patients, we were able to discontinue a fall-risk-increasing drug, and in 8 patients to reduce its dose. The total number of fall incidents during follow-up was significantly lower in these 75 patients, than in those who continued treatment (mean number of falls: 0.3 vs. 3.6; p-value 0.025). The hazard ratio of a fall during follow-up was 0.48 [95% confidence interval (CI) 0.23, 0.99] for overall drug withdrawal, 0.35 (95% CI 0.15, 0.82) for cardiovascular drug withdrawal and 0.56 (95% CI 0.23, 1.38) for psychotropic drug withdrawal, after adjustment for age, gender, use of fall-risk-increasing drugs, baseline falls frequency, comorbidity, Mini-Mental State Examination score, and reason for referral.

Conclusions

Withdrawal of fall-risk-increasing drugs appears to be effective as a single intervention for falls prevention in a geriatric outpatient setting. The effect was strongest for withdrawal of cardiovascular drugs.

Introduction

Falls are a major public health challenge for countries with ageing populations. Approximately 30% of people aged over 65 years and 50% aged over 80 years will fall in a given year.[1] In addition to the morbidity and mortality associated with the injuries they cause, falls are a principal reason for emergency attendance at the hospital, hospital bed utilisation, and transfer to nursing home care.[2] Altogether, falls can have a large negative impact on functioning and quality of life of older persons.

Since falling is a symptom, not a diagnosis, it can be caused by many different factors. In addition, there are often multiple causes for falling in one patient. Therefore, most trials have addressed multi-factorial assessment and intervention.[3,4] This multi-factorial assessment has been shown to lower risk of falling, with a risk ratio of 0.82 (0.72, 0.94) in a recent meta-analysis.[5] But, with the exception of mobility training, it is still unclear which parts of the multi-factorial assessment are effective and how large the effect on fall risk is for every single intervention.[2]

One of the possible single interventions is withdrawal (discontinuation or dose reduction) of fall-risk-increasing drugs (FRID).[5] Although there are hardly any data about the effectiveness of this single intervention, many associations between falls and drugs have been reported. Especially, psychotropic drugs such as antipsychotics, antidepressants, and sedatives,[6-9] and cardiovascular drugs such as diuretics, type IA anti-arrhythmics, and digoxin[10] are considered as risk factors. To our knowledge, only one study has addressed the effect of withdrawal of FRID: in 1999 a randomised-controlled trial was published, showing that discontinuation of a subgroup of possible FRID, i.e. antidepressants and sedatives, indeed lowered fall risk.[11] However, this study did not address other possible FRID, and moreover it did not target geriatric patients with a falls history, but relatively healthy and fit community-dwelling older persons. Therefore, we performed a prospective cohort study in our population of geriatric outpatients, in which we investigated whether withdrawal of FRID was associated with a decrease in fall risk.

Methods

Study participants

All new consecutive referrals to our geriatric outpatient clinic and the diagnostic day centre were considered to be eligible if they were 65 years or over, had a history of falling, had a Mini Mental State Examination score (MMSE) of 21 points or higher (out of 30 points)[12,13] and were able to walk 10 meters without a walking aid. The study protocol was approved by the Medical Ethics Committee of the Erasmus MC and written informed consent was obtained from all patients. Patient recruitment started April 1, 2003 and ended November 30, 2004. During the study period 201 fallers were eligible; 141 gave informed consent; 139

completed follow-up. Non-participants were older (80.2 ± 7.3 years). The main reason for refusing participation was the burden of the extra visits to the clinic.

Assessment of drug use

Before the baseline assessment of the study, a list of drug use during the preceding year was obtained from both the general practitioner and the patient's pharmacist. During baseline assessment the patient, and if applicable a partner or main carer, were consulted on actual drug use, dosages and duration of use. The medication list was checked on a patient basis for use of FRID and for known drug-drug interactions.[5-11,14] During the second assessment after 3 months, the patient was asked whether changes in drug use had occurred. If so, date and changes in dosage were registered. This was crosschecked with the information from letters of consulting physicians, and if there was any doubt a new list was obtained from the pharmacy.

Intervention: withdrawal of FRID

All potential FRID were considered for withdrawal, i.e. anxiolytics/hypnotics (benzodiazepines and others), neuroleptics (D2 agonists and serotonin dopamine receptor antagonists), antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors), antihypertensives (diuretics, beta-blockers, alpha-blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), anti-arrhythmics, nitrates and other vasodilators, digoxin, beta-blocker eye drops, analgesics (mainly opioid analgesics), anti-cholinergic drugs, antihistamines, anti-vertigo drugs, and hypoglycemics. Subsequently, in all fallers FRID were stopped if considered redundant, or else if safely possible, reduced in dose over a 1-month period. The prescribing physicians were consulted if drug changes were intended. During follow-up, no other interventions were performed.

Falls history and falls follow-up

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, e.g. stroke, or exogenous factors, e.g. a traffic accident.[15] At baseline, falls history was considered positive if at least one fall had occurred within the previous year. Other questions concerning falls history were whether more than one fall had occurred in the past year and whether the patient fell on average on a yearly, monthly or weekly basis.

For every participant, we assessed fall incidents during a fixed follow-up period of 2 months, after a set 1-month period, during which we stopped or decreased the dose of FRID. For registration of fall incidents during follow-up, respondents were asked to report their falls weekly on a falls calendar and to mail the calendar page at the end of every

month. Every participant was called by the first author to check compliance with these calendar pages.

Baseline characteristics

Functional status was measured with the Activities of Daily Living measurement (ADL)[16] and the Instrumental Activities of Daily Living measurement (IADL).[17] We also recorded whether or not study participants used a walking aid in daily life. Information on co-morbidity was obtained in an interview with the study participants at baseline and this was crosschecked with the record of the geriatrics department and information from the general practitioner. The following diseases were recorded: hypertension, myocardial infarction, diabetes mellitus, angina pectoris, heart failure, atrial fibrillation, heart rhythm disorders other than atrial fibrillation, stroke, transient ischemic attack, arthritis, Parkinson's disease and parkinsonism, chronic obstructive pulmonary disease, delirium, depression, epilepsy, eye disorder, anxiety disorder, sleeping disorder, history of hip fracture, history of non-hip fracture, thyroid disorder, malignancy, Menière's disease, urinary incontinence, other diseases and total number of comorbid diagnoses.

Statistical analysis

Before starting the study, we estimated that we would need 200 subjects, including 130 fallers, to have 80% power for detection of a relative risk of 0.5, taking into account an alpha of 0.05.

At baseline, all persons with a falls history were stratified according to withdrawal (discontinuation or dose reduction) of FRID. To compare potential confounders between the two groups, an independent t-test was used for continuous variables, and a chi-square test for dichotomous variables. The adjusted mean number of falls (cumulative incidence) during follow-up was calculated with ANOVA.

The association of falls incidence during follow-up according to FRID withdrawal was evaluated using a standard multivariate Cox proportional hazards model in which we tested for collinearity, proportionality and goodness of fit. We tested for effect modification with interaction terms. Hazard ratios of events (first fall during follow-up) were computed as estimates of relative risk. To account for potential confounding, we computed a multivariate model containing the following variables on the basis of the fact that they changed the point estimate by 5% or more, or because they were considered clinically relevant: age, gender, use of FRID, baseline falls frequency, total number of comorbid conditions, MMSE score and reason for referral. A second Cox proportional hazards analysis was performed in which the confounders were replaced by a propensity score.[18] All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

Results

We were able to withdraw one or more FRID in 75 out of the 139 patients. In 67 patients, FRID were discontinued and in 8 patients FRID doses were reduced. For the other 64 fallers FRID withdrawal was not possible, either because they did not use FRID, or because the FRID could not be missed. Also in 8 patients, FRID withdrawal was attempted but failed. During the 3 months of follow-up (i.e. 1 month of FRID withdrawal plus 2 months of falls registration) 1 patient died in the FRID-withdrawal group (due to cancer).

The baseline characteristics of the study population are shown in table 1. Table 2 shows a list of use and withdrawal of FRID. In more detail, we withdrew 17 benzodiazepine derivatives, 5 benzodiazepine related drugs, 6 selective serotonin reuptake inhibitors, 2 monoamine reuptake inhibitors, 2 butyrophenone derivatives, 1 thioxanthene derivative, 9 beta-blockers, 2 alpha-blockers, 14 diuretics, 7 calcium channel blockers, 2 angiotensin converting enzyme inhibitors, 4 angiotensin receptor blockers, 5 nitrates, 3 class III antiarrhythmics, 1 nicotinic acid derivative, 3 beta-blocker eye drops, 5 nonsteroidal antiinflammatoral drugs, 4 opioid analgesics, 7 antivertigo preparations, 1 hypoglycemic and 1 urinary antispasmodic.

During the 2 months of fall follow-up, 17 patients (23%) in the FRID-withdrawal group experienced one or more falls compared to 20 (31%) in the group without FRID withdrawal, resulting in a crude attributable risk of 8%. Mean number of falls during follow-up was 0.8 (95% CI 1.0, 2.6) for the group with FRID withdrawal and 3.1 (95% CI 1.1, 5.0) for the group without FRID withdrawal (p-value 0.10). After adjustment for age, gender, baseline FRID use, baseline falls frequency, number of comorbid conditions, MMSE-score and reason for referral, the mean number of falls was 0.3 (95% CI -1.6, 2.2) and 3.6 (95% CI 1.6, 5.7), respectively (p-value 0.025). There was no effect modification by age and gender. Within our FRID-withdrawal group we did not find any known drug-drug interactions, which could have caused a fall as an adverse drug reaction.

For the 139 fallers in our study, overall-FRID withdrawal and cardiovascular-FRID withdrawal were significantly associated with a lower fall risk after adjustment for potential confounders (as mentioned above) (table 3, model 2). When replacing the confounders with a propensity score, the association was even slightly stronger. Figure 1 shows the cumulative proportional hazard of a fall incident during follow-up according to FRID withdrawal, after adjustment for potential confounders. The cumulative hazard of a fall was 0.18 for the FRID-withdrawal group and 0.37 for the group without FRID withdrawal, resulting in an absolute risk reduction of 19% and a relative risk reduction of 49%.

Table 1. Baseline characteristics of study population (N=139)

	Fallers with drug change (n=75)		Fallers without drug change (n=64)		P-value
Characteristic	n	% (SD)	n	% (SD)	
Mean age (SD)	78.4	(5.2)	78.8	(5.9)	0.66
Female gender	53	71%	52	81%	0.17
Referral for falls	64	85%	43	67%	0.015*
>1 fall last year	58	77%	47	73%	0.59
≥1 fall per month	33	43%	22	35%	0.25
Use of walking aid	40	53%	32	50%	0.69
Mean ADL (SD)	0.72	(1.7)	0.78	(1.6)	0.83
Mean IADL (SD)	13.65	(3.1)	13.59	(3.5)	0.92
Mean MMSE (SD)	27.0	(2.8)	27.2	(2.5)	0.67
Mean no. drugs (SD)	6.2	(2.6)	4.3	(2.5)	0.000*
Mean no. FRID (SD)	2.9	(1.7)	1.7	(1.5)	0.000*
Mean no. Co-morbidity (SD)	4.6	(1.9)	3.7	(1.7)	0.002*

Abbreviations: SD, standard deviation; ADL, activities of daily living; IADL, instrumental activities of daily living, MMSE, Mini-Mental State Examination; no., number of, FRID, fall-risk-increasing drugs
* P<0.05

Table 2. Use and withdrawal of fall-risk-increasing drugs (N=139)

	Baseline use (n=126)		Number of withdrawals (n=75)	
Psychotropic drugs	33	(26%)	29	(39%)
Sedatives	26	(21%)	22	(29%)
Antidepressants	14	(11%)	8	(11%)
Neuroleptics	3	(2%)	2	(3%)
Cardiovascular drugs	62	(50%)	41	(55%)
Antihypertensives	51	(41%)	29	(39%)
Nitrates	15	(12%)	5	(7%)
Anti-arrhythmics	4	(3%)	3	(4%)
Nicotinic acid	1	(1%)	1	(1%)
Beta-blocker eye drops	3	(2%)	3	(4%)
Other drugs	41	(33%)	18	(24%)
Analgesics	68	(54%)	9	(12%)
Antivertigo preparations	11	(9%)	7	(9%)
Hypoglycemics	20	(16%)	1	(1%)
Urinary antispasmodics	4	(3%)	1	(1%)

In the second column, the baseline usage of FRID for the total study population is shown. In total, 126 patients used 262 fall-risk-increasing drugs (FRID). In the third column, the 91 withdrawn FRID in 75 patients are given; clustered in psychotropic-, cardiovascular-, and other drugs.

Table 3. Risk of a fall during follow-up according to drug withdrawal in cohort of older fallers (N=139)

Drug group	Model 1*		Model 2†	
	HR	(95% CI)	HR	(95% CI)
All FRID (n=75)	0.65	(0.33, 1.28)	0.48	(0.23, 0.99)‡
CVD (n=41)	0.48	(0.21, 1.09)	0.35	(0.15, 0.82) ‡
PTD (n=29)	0.71	(0.31-1.61)	0.56	(0.23-1.38)

Abbreviations: CI, confidence interval; FRID, fall-risk-increasing drugs; CVD, cardiovascular drugs; PTD, psychotropic drugs; HR, hazard ratio.
*Model 1: adjusted for age, gender
†Model 2: adjusted for age, gender, FRID use, baseline falls frequency, MMSE-score, number of comorbid conditions, and reason for referral
‡ P<0.05

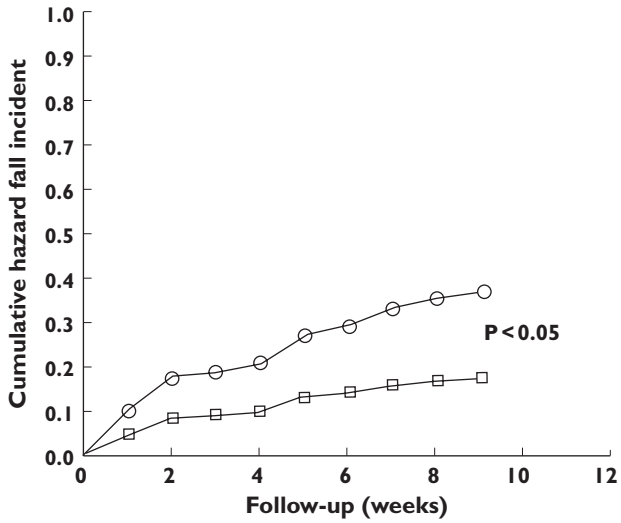

Figure 1. Cumulative hazard of a fall incident in 75 patients with FRID withdrawal and 64 patients without FRID withdrawal

Discussion

To our knowledge, this is the first prospective cohort study in older fallers in which the effect of withdrawal of all fall-risk-increasing drugs was investigated. During follow-up, the risk of a fall incident was halved (p<0.05).

As expected, because of the observational cohort approach, the two groups differed at baseline in that the group of fallers in whom drug change was possible at baseline used more drugs, more FRID, and also had a higher total number of comorbid conditions (table 1). Also, this group was significantly more frequently referred for falls and they had a slightly higher fall incidence at baseline. Consequently, the significant reduction of falls during follow-up after withdrawal is clinically very relevant. After all, any confounding by indication would tend to hide a true protective effect, because the discontinuation group had the highest baseline risk of falling, but despite this showed the lowest cumulative hazard

of falling during follow-up. In addition to multivariate adjustment, analyses with propensity scores for the likelihood to receive the intervention further increased the protective hazard ratio.

Remarkably, the protective hazard ratio of cardiovascular-FRID withdrawal was stronger than that of psychotropic-FRID withdrawal. This is an unexpected finding, because in earlier studies the strongest associations between fall risk and drug use have always been found for psychotropic drugs, not cardiovascular drugs.[6,10] This difference may have been caused by a lack of precision in our study, because the psychotropic-FRID withdrawal group was smaller than the cardiovascular-FRID withdrawal group.

Limitations of the study

A potential limitation of our study is the fact that we were not able to perform a randomized double blind controlled study (RCT) for drug intervention, which would be the ideal research situation to test our hypothesis. The reason not to perform a RCT was that withdrawal of FRID is already implemented in Dutch and international falls guidelines,[3,19] rendering it unethical not to withdraw FRID in patients presenting with a fall. Therefore, we performed a prospective cohort study in which we compared the effect of drug withdrawal on falls incidence to a group of patients in whom FRID withdrawal was not possible. Because of the lack of blinding, we have to consider the possibility of information bias if patients in whom FRID were withdrawn remember fewer falls than those who continued therapy, or vice versa. Information bias by the investigators is unlikely as gathering of data on falling was performed without knowledge of the intervention status. Another potential limitation of our study is the substantial group that refused participation. On average, these patients were older. Although this might have affected generalizability of our results, we have no reasons to suspect that these non-participants would not benefit from FRID withdrawal. Furthermore, in our opinion there is no reason to assume that refusal was differential for the two groups, which makes the possibility of selection bias unlikely.

Conclusions

In conclusion, FRID withdrawal was effective as a single intervention in lowering fall incidence in our study. We have shown that FRID withdrawal is safely possible in a geriatric outpatient setting. The effect on fall incidence was strongest for withdrawal of cardiovascular drugs. On the whole, FRID withdrawal as a single intervention appears to lower fall incidence during short-term follow-up in the frail group of geriatric outpatients. Our findings endorse the guideline advice that withdrawal of fall-risk-increasing drugs should be part of the multi-factorial intervention for patients presenting with falls.

Acknowledgements

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Chapter 4.2

Withdrawal of Fall-Risk-Increasing Drugs in Older Persons:

Effect on Mobility Test Outcomes

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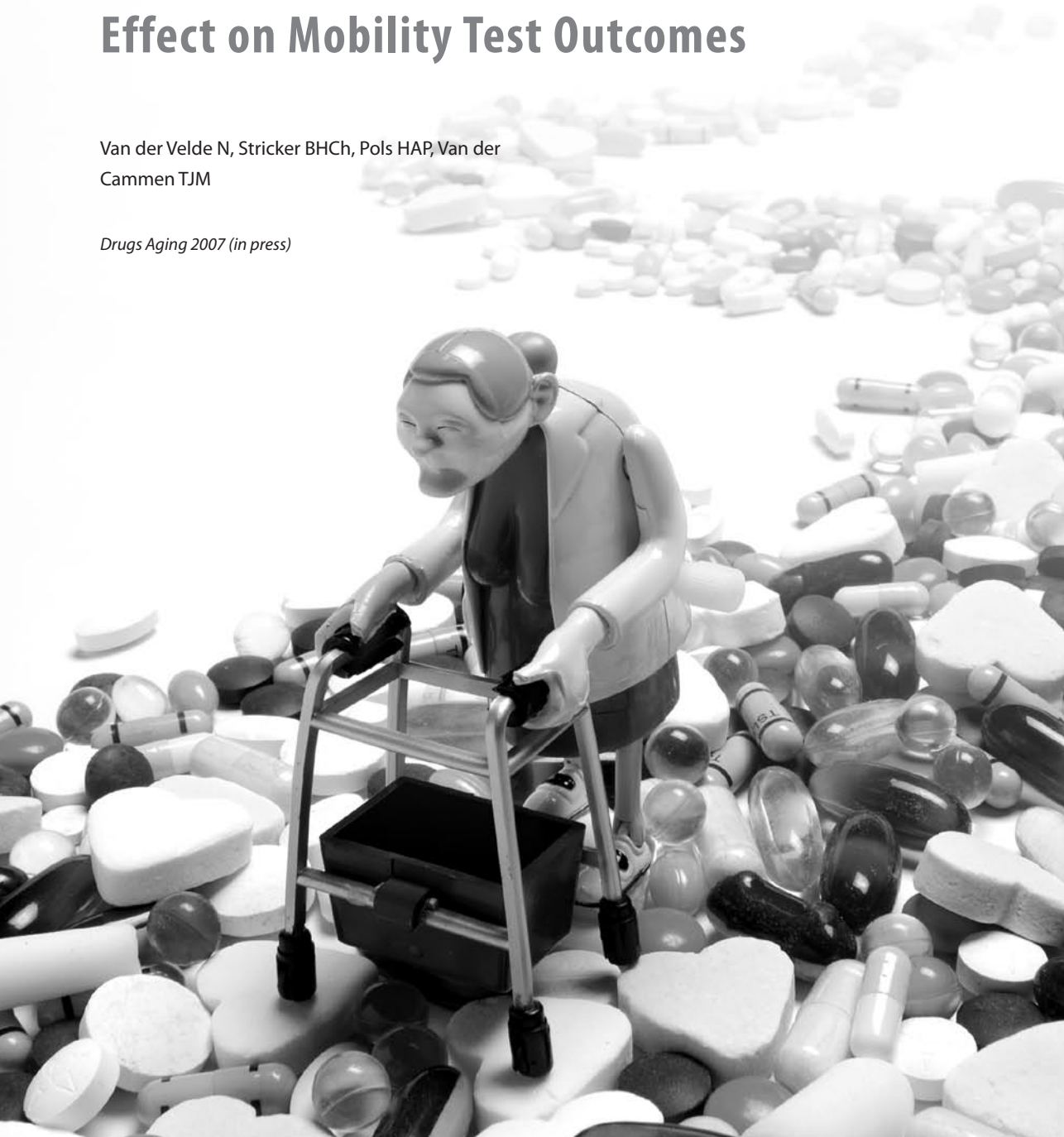

Abstract

Background

Previously, we have shown that withdrawal of fall-risk-increasing drugs (FRID) as a single intervention reduces falls incidence. Herein, improvement of mobility may be an important factor. We therefore tested whether mobility tests improved after withdrawal of FRID.

Methods

In a prospective cohort study of 137 geriatric outpatients (age 77.7 ± 5.7 years) FRID were withdrawn in all fallers, if possible, from April 2003 until November 2004. All patients underwent mobility testing at baseline, including 10m-walking test, Timed Up and Go Test (TUGT), Functional Reach, isometric quadriceps femoris muscle strength and body sway. Retesting occurred at a mean follow-up of 6.7 months. Effect of FRID-withdrawal (discontinuation or dose reduction) on test outcomes were calculated using both a multivariate linear and a binary logistic regression analysis.

Results

In the group of fallers with FRID-withdrawal all mobility tests improved, as opposed to non-fallers and fallers without FRID-withdrawal. After adjustment for confounders, the odds ratio of test improvement was 0.14 (95% CI, 0.03-0.59) for the 10m-walking test, 0.19 (95% CI, 0.04-0.86) for the TUGT, 0.48 (95% CI, 0.14-1.48) for the Functional Reach, 0.46 (95% CI, 0.14-1.48) for Quadriceps strength, and 0.49 (95% CI, 0.15-1.62) for Body Sway.

Conclusion

The results of this study suggest that FRID-withdrawal may be effective as a single intervention in a geriatric setting. Alongside with a reduction in falls, 10m-walking test and TUGT significantly improved during follow-up. These tests may be useful tools for clinical follow-up.

Introduction

Falls are a major health risk for older persons and are associated with abundant morbidity and mortality.[1,2] Of community-dwelling older persons, 25 to 40 percent experience a fall at least once a year.[3-6] For older persons living in residential or nursing homes, this increases to 70 percent.[7-9]

During the last two decades, many risk factors for falls have been identified.[3-11] An important risk factor for falls in older persons is the use of certain drugs.[10] Among these fall-risk-increasing drugs (FRID) are psychotropic drugs[12,13] such as antipsychotics, antidepressants,[14] and sedatives[15] and cardiovascular drugs such as diuretics, type IA anti-arrhythmics and digoxin.[16] Previously, we have shown that intervening on this risk factor, i.e. withdrawing FRID, indeed results in a lower falls incidence. In a prospective cohort of geriatric outpatients, fallers in whom FRID withdrawal was possible were compared to fallers in whom no withdrawal was possible. This study showed that withdrawal of FRID as a single intervention indeed lowered falls incidence, with a significant risk reduction of approximately 50%.[17] This is in line with the findings of Campbell et al, showing a lowered fall risk after discontinuation of a subgroup of possible FRID, i.e. antidepressants and sedatives.[18]

Mobility tests, such as the Timed Up and Go Test, are well-established predictors for fall incidents.[19-22] Falls due to usage of FRID might be largely or at least partly caused by the impairment of mobility that these drugs can generate.[23,24] Consequently, mobility tests may be useful in the clinical follow-up of fallers in whom FRID are withdrawn. However, to our knowledge, studies regarding the effect of FRID on mobility have not yet been published. Therefore, we tested within our prospective cohort of geriatric outpatients whether besides a reduction in fall incidents withdrawal of FRID also resulted in an improvement of mobility-test outcomes.

Methods

Study participants

All new consecutive referrals to our geriatric outpatient clinic and the diagnostic day centre were considered to be eligible if they were 65 years or older, had a Mini Mental State Examination score (MMSE) of 21 points or higher (out of 30 points)[25,26] and were able to walk 10 meters without a walking aid. The study protocol was approved by the Medical Ethics Committee of the Erasmus MC and written informed consent was obtained from all patients. Patient recruitment started April 1, 2003 and ended November 30, 2004.

Falls history

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, e.g. stroke, or exogenous factors, e.g. a traffic accident.[27] At baseline, falls history was considered positive if at least one fall had occurred within the previous year. Other questions concerning falls history were whether more than one fall had occurred in the past year and whether the patient fell on average on a yearly, monthly or weekly basis.

For every participant, we assessed fall incidents during a fixed follow-up period of 2 months, after a set 1-month period, during which we stopped or decreased the dose of FRID. For registration of fall incidents during follow-up, respondents were asked to report their falls weekly on a falls calendar and to mail the calendar page at the end of every month. Every participant was called by the first author to check compliance with these calendar pages.

Mobility testing

Five different mobility tests were performed at two visits. All subjects underwent the tests at baseline. At the end of follow-up (mean duration 6.7 months) a subgroup (65%) was asked back for second testing. This was done for logistic reasons (limited personnel and equipment available) and selection for second testing was random, depending only on the availability of the testing room and availability of personnel.

The following tests were performed: 10-meter walking test, Timed Up and Go Test (TUGT), Functional Reach, isometric quadriceps femoris muscle strength, and body sway. For each test, it was first checked whether the patient knew how to perform the test properly. Thereafter, all tests were performed twice. The best score out of two was used for the analysis. To avoid inter-tester variability, one and the same tester conducted the tests in all patients. To avoid information bias, gathering of data on mobility test outcomes was performed without knowledge of the intervention status.

The 10-meter walking test measures the time (in seconds) that it takes a patient to walk 10 meters (33,3 ft). It assesses short-duration walking speed.[28,29]

The TUGT is a test for balance that is commonly used to examine functional mobility in community-dwelling, frail older adults.[19-21,30] The test requires a subject to stand up, walk 3 m (10 ft), turn, walk back, and sit down. The duration of this test is measured in seconds.

The Functional Reach is a test for balance. It evaluates the maximal distance that a person can reach forward while maintaining a fixed base of support.[31,32]

Maximal isometric quadriceps femoris muscle strength was measured at both legs with the handheld MicroFET dynamometer[33] In this measurement the dynamometer is placed just proximal to the ankle on the front lower leg (on the distal tibia and anterior tibial muscle tendon). The tester then holds the dynamometer stationary while the subject exerts a maximal force against it; therefore the test is essentially isometric.[34]

Body sway was measured with a stabilometric platform through recording of involuntary body sway forwards and backwards and side-to-side, using a platform with vertical force. The total length of displacement from the gravity centre and the surface areas corresponding to this displacement were analyzed by a computer.[24,35,36] Body sway was measured twice for the duration of 1 minute, once with eyes open, and once with eyes closed.

Assessment of drug use and withdrawal of FRID

During the study period, only one fall-reduction intervention was performed, i.e. withdrawal of FRID if possible. All other interventions were postponed to the end of the study period.

Before the baseline assessment of the study, a list of drug use during the preceding year was obtained from both the patient's general practitioner and pharmacist. During baseline assessment the patient, and if applicable a partner or main carer, were consulted on actual drug use, dosages and duration of use. During the second assessment, the patient was asked whether changes in drug use had occurred. If so, date and changes in dosage were registered. This was crosschecked with the information from letters of consulting physicians, and if there was any doubt a new list was obtained from the pharmacy.

All potential FRID were considered for withdrawal, i.e. anxiolytics/hypnotics, neuroleptics, antidepressants, antihypertensives, anti-arrhythmics, nitrates and other vasodilators, digoxin, beta-blocker eye drops, analgesics (mainly opioid analgesics), anti-cholinergic drugs, antihistamines, anti-vertigo drugs, and hypoglycemics. Subsequently, in all fallers FRID were stopped abruptly, if safely possible, or else reduced in dose over a 1-month period to a lower dose or to complete withdrawal. As mentioned above, during follow-up, no other interventions were performed.

Baseline characteristics

Functional status was measured with the Activities of Daily Living measurement (ADL)[37] and the Instrumental Activities of Daily Living measurement (IADL).[38] We also recorded whether or not study members used a walking aid in daily living. Information on co-morbidity was obtained in an interview with the study members at baseline and this was crosschecked with the record of the geriatrics department and written information from the general practitioner. The following diseases were recorded: hypertension, myocardial infarction, diabetes mellitus, angina pectoris, heart failure, atrial fibrillation, heart rhythm disorders other than atrial fibrillation, stroke, transient ischemic attack, arthritis, Parkinson's disease and parkinsonism, chronic obstructive pulmonary disease, delirium, depression, epilepsy, eye disorder, anxiety disorder, sleeping disorder, history of hip fracture, history of non-hip fracture, thyroid disorder, malignancy, Menière's disease, urinary incontinence, other diseases and total number of comorbid diagnoses.

Statistical analysis

Before starting the study, we estimated that for our main study regarding fall incidents we would need 200 subjects, including 130 fallers, to have 80% power for detection of a relative risk of 0.5, taking into account an alpha of 0.05.

To compare potential confounders between the three groups (fallers with FRID withdrawal, fallers without FRID withdrawal, and non-fallers), an independent t-test was used for continuous variables, and a chi-square test for dichotomous variables. Subsequently, we compared the subgroup that was asked back for second testing to the subgroup that was not invited for a second visit because of a limited capacity of the research center. Re-invitation was performed in a random fashion; the only consideration was group sizes. Our aim was to retest approximately equal groups of patients with and patients without drug withdrawal and within the group of non-withdrawal to retest approximately equal groups of fallers and non-fallers.

For each study member, we calculated the difference between the first and second outcome of each mobility test. Differences in mobility tests between the two assessments were assessed with a paired t-test for all three groups. The data for the different groups are reported as mean differences and range.

Secondly, a linear regression analysis was performed in order to address the adjusted association between changes in mobility test outcomes and FRID-withdrawal. Model 1 is adjusted for age and gender. Model 2 is adjusted for age, gender, follow-up time, reason for referral (falls or other), number of comorbid conditions, MMSE-score and baseline use of FRID.

Relative risk of no test improvement due to FRID-withdrawal was estimated by calculation of the odds ratio's with binary logistic regression analysis. In this analysis, improvement at the second assessment was defined as 0 and deterioration or an unchanged outcome as 1. Improvement was classified similar for all mobility tests, i.e. a difference between the first and second test >0. Main covariate was withdrawal of FRID and potential confounders (as mentioned above) where added to the model. We concluded with the association between improvement of mobility test outcomes and fall incidents within the group with FRID withdrawal. For this we calculated the odds ratio of a fall during follow-up according to test improvement. All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

Results

During the study period, 350 subjects were eligible for participation in the study. 131 subjects did not give informed consent, mostly because of the burden of two extra visits. Patients who refused participation were on average older, used more drugs and had more comorbid diseases. Of the 219 included persons, 8 persons dropped out for various reasons. For

three persons, the tests turned out to be too difficult, 2 persons died during follow-up, and the remaining 3 did not wish to continue halfway through the follow-up period. The remaining 211 individuals were included in the cohort. Out of the 211 included patients, 135 had experienced at least one fall during the previous year. Within this subgroup, we were able to discontinue FRID in 65 cases and to reduce its dose in 6 cases.[17] This resulted in a total of 71 patients in our subgroup of patients with FRID withdrawal (figure 1). In 56 fallers FRID withdrawal was not attempted, either because they did not use FRID (n=11), or because the FRID could not be missed (n=45). Furthermore in 8 patients, FRID withdrawal was attempted, but failed. This resulted in a total of 64 patients in the non-withdrawal group (figure 1).

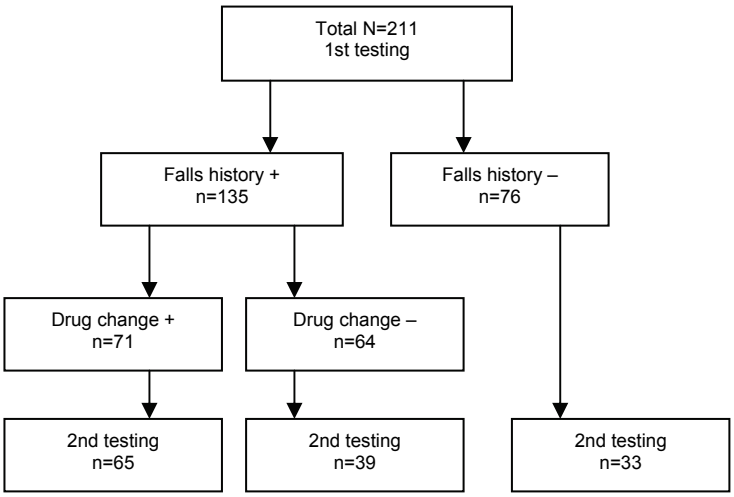

Figure 1. Group sizes

A subgroup from the cohort, i.e. 137 participants, received an invitation for a second visit and subsequently returned for repeated mobility testing (Figure 1). There were no significant differences between the retested and the non-retested group regarding the baseline characteristics and baseline mobility test outcomes. Baseline subject characteristics of all participants that underwent both test episodes (n=137) are summarized in Table 1. The groups with a positive falls history comprised more women and age was higher than in the group with a negative falls history. They were also more disabled as was shown by a higher use of walking aids and higher (worse) scores for Activities of Daily Living scale and Instrumental Activities of Daily Living scale. They had more comorbid conditions, a lower MMSE score and used more drugs.

Table 2 and figure 2 show the change in test outcomes for the three different groups, respectively numerical and in percentages. For the group of fallers with FRID withdrawal, there was a significant improvement of the 10m-walking test (difference –1.3 sec) and

Table 1. Baseline Characteristics of a Cohort of Geriatric Outpatients (N=137)

Characteristics	Fallers with FRID withdrawal (n=65)		Fallers without FRID withdrawal (n=39)		Non-fallers (n=33)	
Age, mean (SD), yrs.	78.2	(±4.9)	78.7	(±6.1)	75.6	(±6.6)
Gender: female (%), no.	47	(72%)	32	(82%)	20	(61%)
Referral for falls (%), no.	56	(86%)	29	(74%)	-	
>1 fall last year (%), no.	52	(80%)	30	(77%)	-	
Use of walking aid (%), no.	36	(55%)	19	(49%)	5	(16%)
ADL score, mean (SD), pts.	0.8	(±1.8)	0.8	(±1.7)	0.1	(±1.3)
IADL score, mean (SD), pts.	13.6	(±3.2)	13.9	(±3.4)	15.0	(±2.3)
MMSE score, mean (SD), pts.	27.1	(±2.8)	27.2	(±2.5)	28.9	(±7.5)
Drugs used, mean (SD), no.	6.1	(±2.6)	4.3	(±2.6)	4.7	(±2.8)
FRID used, mean (SD), no.	3.4	(±1.8)	1.7	(±1.6)	1.9	(±2.0)
Co-morbidity, mean (SD), no.	4.8	(±1.8)	3.9	(±1.8)	3.6	(±1.6)

Abbrevations: FRID, fall-risk-increasing drugs; yrs., years; SD, standard deviation; no., number; ADL, activities of daily living; IADL, instrumental activities of daily living; pts., points; MMSE, Mini-Mental State Examination

the TUGT (difference –3.0 sec). Body sway (lateral sway with eyes closed) did not reach a significant improvement (difference –3.8 cm). Functional Reach and quadriceps strength remained approximately at the same level (difference 0.5 cm and 6 N respectively). The second group, fallers without FRID withdrawal, showed a significant deterioration in the 10m-walking test (difference 3.4 sec), TUGT (difference 3.8 sec) and Functional Reach (-3.0 cm). Quadriceps strength and body sway remained approximately at the same level (4

Table 2. Changes in mobility test outcomes

Mobility test	1st testing	2nd testing	Difference	CI 95%	P-value
Fallers with FRID change (n=65)					
10m-walking test	12.0 sec	10.7 sec	-1.3 sec	-2.3;-0.2	0.021
TUGT	15.3 sec	12.3 sec	-3.0 sec	-5.7;-0.4	0.026
Functional Reach	22.8 cm	23.4 cm	0.5 cm	-1.2;2.2	0.537
Quadriceps strength	196 N	203 N	7 N	-7.3;19.8	0.358
Body sway	23.7 cm	19.9 cm	-3.8 cm	-9.8;1.2	0.133
Fallers without FRID change (n=39)					
10m-walking test	10.0 sec	13.5 sec	3.4 sec	1.2;5.7	0.004
TUGT	12.6 sec	16.4 sec	3.8 sec	1.5;6	0.002
Functional Reach	24.1 cm	21.1 cm	-3.0 cm	-5.6;-0.4	0.023
Quadriceps strength	176 N	180 N	4 N	-14;21	0.670
Body sway	23.6 cm	21.0 cm	-2.6 cm	-8.2;2.9	0.349
Non-fallers, no FRID change (n=33)					
10m-walking test	7.6 sec	8.8 sec	1.2 sec	0.7;1.7	0.000
TUGT	8.5 sec	10.0 sec	1.6 sec	0.6;2.6	0.003
Functional Reach	31.4 cm	27.1 cm	-4.3 cm	-6.5;-2.1	0.000
Quadriceps strength	273 N	246 N	-27 N	-8;-3	0.008
Body sway	12.4 cm	18.4 cm	6.1 cm	2;10.1	0.004

Abbreviations: FRID=Fall-risk-increasing drugs; CI=Confidence interval; TUGT=Timed Up and Go Test

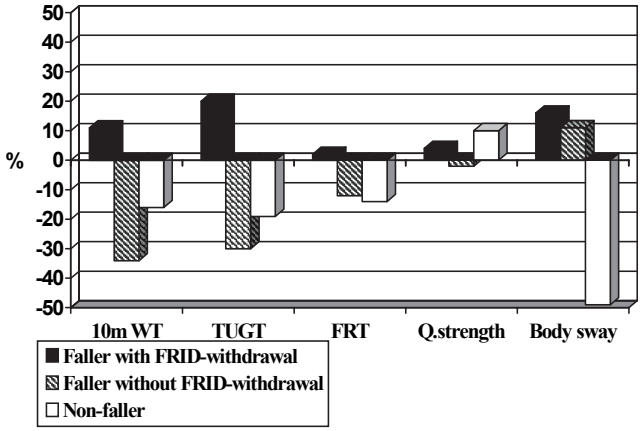

Figure 2. Percentage change in mobility test outcomes
Abbreviations: 10mWT, 10-meter walking test; TUGT, Timed Up and Go Test; FRT, functional reach test; Q-strength, M. Quadriceps strength; FRID, fall-risk-increasing drugs

N and –2.6 respectively). The third group, non-fallers (without change in drug regimen), showed a significant deterioration of the 10m-walking test (difference 1.2 sec), TUGT (difference 1.6 sec), Functional Reach (difference –4.3cm), quadriceps strength (difference –27 N) and body sway (difference 6.0 cm).

Table 3 shows a linear regression model of the changes in the different mobility test outcomes according to FRID-withdrawal. All B's (partial regression coefficients) were directed towards improvement, i.e. negative for 10m-walking test, TUGT and Body sway and positive for Functional Reach and M. Quadriceps strength. After adjustment for potential confounders, i.e. follow-up time, reason for referral (falls or other), gender, age, number of comorbid conditions, MMSE-score and baseline use of FRID, the protective association with FRID-withdrawal remained significant for the 10m-walking test and the TUGT.

Table 4 shows the crude and the adjusted odds ratio (risk of no improvement) according to FRID-withdrawal in the total cohort. The crude analysis shows a significant protective ef-

Table 3. Linear regression analysis of mobility test outcomes according to FRID withdrawal*

	Model 1			Model 2		
Test	B	SE	P-value	B	SE	P-value
10m walking test	-2.75	0.88	0.002	-3.03	0.97	0.009
TUGT	-5.55	1.43	0.000	-4.63	2.21	0.032
Functional Reach	4.07	1.20	0.001	2.26	1.83	0.219
Quadriceps strength	16.00	9.28	0.087	16.62	14.31	0.248
Body Sway (lateral)	-3.63	2.38	0.130	-6.61	3.61	0.069

Abbreviations: FRID=Fall-risk-increasing drugs; CI=Confidence interval; TUGT=Timed Up and Go Test; MMSE=Mini Mental State Examination
Model 1: adjusted for age and gender
Model 2: adjusted for follow-up time, referral, gender, age, FRID-use, number of comorbid conditions, MMSE-score
* In these analyses, the group where FRID could not be withdrawn served as the reference

Table 4. Odds ratio's of no improvement of mobility test outcomes in case of FRID-withdrawal*

	Model 1		Model 2	
Test	OR	(95% CI)	OR	(95% CI)
10m-walking test	0.08	(0.03-0.22)†	0.19	(0.04-0.86)†
TUGT	0.10	(0.04-0.26)†	0.14	(0.03-0.59)†
Functional Reach	0.33	(0.16-0.69)†	0.48	(0.14-1.57)
Quadriceps strength	0.47	(0.23-0.89)†	0.46	(0.14-1.48)
Body sway (lateral)	0.43	(0.21-0.88)†	0.49	(0.15-1.62)

Abbreviations: FRID=Fall-risk-increasing drugs; OR=Odds ratio; CI=Confidence interval; TUGT=Timed Up and Go Test; MMSE=Mini Mental State Examination

Model 1: adjusted for age and gender

Model 2: adjusted for follow-up time, referral, gender, age, FRID-use, number of comorbid conditions, MMSE-score

* In these analyses, the group where FRID could not be withdrawn served as the reference

† P<0.05

fect in the following mobility tests: 10m-walking test, TUGT, Functional Reach, quadriceps strength and body sway (lateral sway with eyes closed). After adjustment for the confounders mentioned above, the protective effect of FRID-withdrawal in the 10m-walking test and TUGT remained significant. For all other tests the associated odds ratio favored FRID-withdrawal, but did not reach significance.

We also performed a subgroup analysis for specific drug-groups. For the subgroup of psychotropic FRID (e.g. sedatives, neuroleptics, and antidepressants), withdrawal led to significant improvement of all mobility tests. After adjustment for potential confounders the odds ratio of FRID withdrawal remained significant only for the 10m-walking test and TUGT (table 4). For the subgroup of cardiovascular FRID, improvement was not significant after adjustment for potential confounders (table 5).

Finally, within the group of fallers with FRID withdrawal the risk (odds ratio) of a fall during follow-up according to test improvement was calculated, showing a significant association for the Timed Up and Go Test (adjusted OR 0.21; 95% CI 0.05-0.88). For the 10 meter walking test the adjusted odds ratio was 0.23 (95% CI 0.05-1.03).

Table 5. Odds ratio of no improvement of mobility test outcomes according to psychotropic- and cardiovascular FRID-withdrawal*

		Model 1		Model 2	
Drug group	Test	OR	(95% CI)	OR	(95% CI)
Psychotropic (n=28)	10m-walking test	0.12	(0.05-0.32)†	0.27	(0.10-0.75)†
	TUGT	0.14	(0.06-0.35)†	0.23	(0.08-0.65)†
Cardiovascular (n=40)	10m-walking test	0.27	(0.12-0.62)†	0.44	(0.11-1.37)
	TUGT	0.37	(0.17-0.82)†	0.32	(0.12-1.03)

Abbreviations: FRID, Fall-risk-increasing drugs; OR, Odds ratio; CI, Confidence interval; TUGT, Timed Up and Go Test; MMSE, Mini Mental State Examination

Model 1: adjusted for age and gender

Model 2: adjusted for follow-up time, referral, gender, age, FRID-use, number of comorbid conditions, MMSE-score

* In these analyses, the group where FRID could not be withdrawn served as the reference

† P<0.05

Discussion

Our study shows that if FRID-withdrawal is possible, this results in a positive effect on mobility test outcomes for older fallers. Analysis of fallers with FRID-withdrawal revealed a significant improvement for the 10m-walking test and TUGT. By comparison, in our study, the natural course of mobility test outcomes in older persons attending a geriatric outpatient clinic (non-fallers) appears to be deterioration or at best constancy. This is in accordance with follow-up results of other study populations.[39,40]

Because baseline characteristics differed for the subgroups in our cohort (fallers with FRID withdrawal, fallers without FRID withdrawal, and non-fallers), we conducted a regression analysis (binary logistic and linear) in which we adjusted for possible confounders. In these analyses the chance of improvement was over five times higher for the 10m-walking test and TUGT in case of FRID-withdrawal. Because our risk estimates were odds ratios rather than relative risks, these estimates may be slightly overestimated. Nevertheless, our results consistently show the value of discontinuation of FRID on mobility tests. All other tests showed a trend towards improvement of mobility tests due to FRID withdrawal. When addressing subgroups of FRID, i.e., psychotropic and cardiovascular drugs, the effect appeared to be strongest for psychotropic FRID-withdrawal. Although also the discontinuation of cardiovascular FRID seemed to be favorable for mobility tests outcomes, these results did not reach statistical significance. This is in line with the literature, which suggests the strongest and most consistent improvement occurs after discontinuation or dose reduction of psychotropic drugs.[12,16] However, our study was not powered for subgroup analysis, therefore this difference might be caused by a type I error.

Known adverse effects of psychotropic drugs that can result in a deterioration of mobility with possibly ensuing fall incidents are diminished concentration, prolonged reaction time, impaired balance and orthostatic hypotension.[23,24] This holds also true for opioid analgesics. For cardiovascular drugs we postulate that the main adverse drug reaction leading to falls via a deterioration of mobility is most likely dizziness or unstable gait caused by inadequate blood pressure regulation resulting in episodes of insufficient cerebral perfusion. This study focussed on the association between FRID-withdrawal and mobility test improvement, and although it is likely that an improvement of mobility will lead to a decrease in fall incidents, this is not necessarily the case. However, since the association between mobility test improvements and non-occurrence of fall incidents was also significant, we think it probable that part of the FRID related falls in this cohort were mediated through the side effects mentioned above.

A potential limitation of our study is the fact that we were not able to perform a randomized double blind controlled trial (RCT) for drug intervention, which would be the ideal research situation to test our hypothesis. The reason not to perform a RCT was that withdrawal of FRID is already implemented in Dutch and international Falls Guidelines,[10,11]

rendering it unethical not to withdraw FRID in patients presenting with a fall. Therefore, we performed a prospective cohort study in which FRID-withdrawal was the only intervention during follow-up. Because of the lack of blinding, we have to consider the possibility of information bias of the patient, i.e. patients with FRID-withdrawal may have performed better during the second testing because of confidence in the intervention. Information bias by the investigators is unlikely as gathering of data on mobility test outcomes was performed without knowledge of the intervention status. Another potential limitation of our study is the substantial group that refused participation. On average, these patients were older. Although this might have affected generalizability of our results, we have no reasons to suspect that these non-participants would not benefit from FRID-withdrawal. Furthermore, in our opinion there is no reason to assume that refusal was differential for the three groups, which makes the possibility of selection bias unlikely.

In conclusion, our study has shown that if withdrawal of FRID is possible, mobility appears to be favorably influenced. The mobility tests we have used, and especially the TUGT, have proven to be sensitive and specific predictive measures for falls. In an earlier study we showed that within our cohort falls incidence indeed decreased after FRID-withdrawal, and now we have demonstrated that alongside mobility test outcomes improved also. Therefore, we think that the 10m-walking test and TUGT can be useful when monitoring the clinical effect of FRID-withdrawal.

Acknowledgements

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None of the authors have a conflict of interest to declare.

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Chapter 4.3

Withdrawal of Fall-risk-increasing Drugs in Older Persons: Effect on Tilt-table Test Outcomes

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Abstract

Objectives

Several drugs can cause cardiovascular adverse effects, e.g. orthostatic hypotension, vasovagal collapse, and carotid sinus hypersensitivity. Consequently, fall incidents can ensue. We therefore tested whether tilt-table test outcomes improved after withdrawal of fall-risk-increasing drugs (FRID).

Design

Prospective cohort study

Setting

Geriatric outpatient clinic

Participants

211 new consecutive outpatients, recruited from April 2003 until December 2004.

Measurements

Tilt-table testing was performed in all participants at baseline. Subsequently, FRID were withdrawn in all fallers, in whom this was safely possible. At a mean follow-up of 6.7 months, tilt-table testing was repeated in 137 participants. Tilt-table testing addressed carotid sinus hypersensitivity, orthostatic hypotension and vasovagal collapse. Odds ratios of tilt-table test normalization according to withdrawal (discontinuation or dose-reduction) of FRID were calculated using multivariate logistic regression analysis.

Results

After adjustment for confounders, the reduction of abnormal test outcomes (odds ratio) according to overall FRID withdrawal was 0.34 (95% CI=0.06-1.86) for carotid sinus hypersensitivity, 0.35 (95% CI=0.13-0.99) for orthostatic hypotension, and 0.27 (95% CI=0.02-3.31) for vasovagal collapse. For the subgroup of cardiovascular FRID, the adjusted odds ratio for carotid sinus hypersensitivity was 0.13 (95% CI=0.03-0.59), for orthostatic hypotension 0.44 (95% CI=0.18-1.0) and for vasovagal collapse 0.21 (95% CI=0.03-1.51).

Conclusion

Orthostatic hypotension improved significantly after withdrawal of FRID. Subgroup analysis of cardiovascular FRID withdrawal showed a significant reduction in both orthostatic hypotension and carotid sinus hypersensitivity. These results imply that FRID withdrawal can cause substantial improvement of cardiovascular homeostasis. Derangement of cardiovascular homeostasis may be an important mechanism by which FRID use results in fall incidents.

Introduction

Cardiovascular disorders are responsible for as many as 77% of cases presenting to Accident and Emergency departments with unexplained or recurrent falls.[1] Since classic clinical features, including typical symptoms of syncope, are often absent in older fallers, one cannot rely on history taking for diagnosis.[2] The head-up tilt-table test, over half a century old, has retained a central place in the investigation of syncope of unknown origin, orthostatic intolerance and dysfunction of the autonomous nervous system. It has also proven its merit in the assessment of older fallers.[3,4] Tilt-table testing can assess three important cardiovascular causes of falls and syncope: carotid sinus hypersensitivity (CSH), vasovagal collapse (VVC), and orthostatic hypotension (OH).

OH is thought to contribute to fall incidents in 5 to 32% of cases.[1,5,6] OH can either be tested on active standing or during passive standing, using a tilt-table.[7,8] With the passive head-up tilt, stress on the sympathetic nervous system is maximized by excluding the influence of voluntary inferior limb musculoskeletal contractions that increase venous return.[3] VVC is the commonest neurally mediated disorder, affecting all age groups. Premonitory symptoms may be attenuated in older persons and recurrent VVC therefore carries substantial risks in terms of morbidity and mortality in this age group.[9] For diagnosis, besides clinical history, prolonged tilt-table testing is warranted.[10] CSH is a frequently overlooked phenomenon. In patients over 65 years of age the diagnostic yield of carotid sinus massage has been shown to be up to 45%.[1,3,11] Since in approximately one third of patients CSH can only be demonstrated upon standing, it is recommended to perform carotid sinus massage both in supine position and during head-up tilt.[12,13]

An important risk factor for falls in older persons is the use of certain drugs.[14] Among these fall-risk-increasing drugs (FRID) are psychotropic drugs such as antipsychotics, antidepressants, and sedatives and cardiovascular drugs such as diuretics, type IA anti-arrhythmics and digoxin.[15,16] It has been shown in two populations that withdrawal (discontinuation or dose-reduction) of FRID in older fallers is an effective single intervention for the prevention of further falls.[17,18]

The majority of the drugs mentioned above are known to be able to induce OH, VVC and/or CSH. These cardiovascular abnormalities may be important in the causal pathway of drug-induced fall incidents. In order to ascertain whether withdrawal of FRID also results in normalization of cardiovascular abnormalities, we investigated whether withdrawal of FRID was associated with improvement of tilt-table test outcomes.

Methods

Study participants

A detailed description of our prospective cohort study has been published elsewhere.[17] In short, all new consecutive referrals to our geriatric outpatient clinic and the diagnostic day center were considered to be eligible if they were 65 years or over, had a Mini Mental State Examination score (MMSE) of 21 points or higher (out of 30 points)[19,20] and were able to walk 10 meters without a walking aid. The geriatric outpatient clinic included both general geriatric referrals and Memory Clinic referrals; the diagnostic day center included general geriatric referrals as well as Falls Clinic referrals. The study protocol was approved by the Medical Ethics Committee of the Erasmus University Medical Center and written informed consent was obtained from all patients. Patient recruitment started on April 1, 2003 and ended on November 30, 2004.

Baseline characteristics and assessment of falls

Functional status was measured with the Activities of Daily Living measurement (ADL) and the Instrumental Activities of Daily Living measurement (IADL).[21,22] We also recorded whether the patient had a positive falls history, and whether study participants used a walking aid in daily life. A fall was defined as coming to rest unintentionally on the ground or at a lower level with or without losing consciousness, but not if this had been induced by acute medical conditions, such as stroke, or exogenous factors, such as a traffic accident.[23] At baseline, falls history was considered positive if at least one fall had occurred within the previous year. Other questions concerning falls history were whether more than one fall had occurred in the past year and whether the patient fell on average on a yearly, monthly or weekly basis.[24] For every participant, we assessed fall incidents during a fixed follow-up period of 2 months, after a set 1-month period, during which we stopped or decreased the dose of FRID. For registration of fall incidents during follow-up, respondents were asked to report their falls weekly on a falls calendar and to mail the calendar page at the end of every month. Every participant was called by the first author to check compliance with these calendar pages. Information on co-morbidity was obtained in an interview with the study participants at baseline and this was crosschecked with the record of the geriatrics department and information from the general practitioner.

Tilt-table testing

All participants underwent tilt-table testing at baseline. Carotid sinus massage was performed if no contra-indication was present (n=207). At the end of follow-up (mean duration 6.7 months) a subgroup (65%) was asked back for second testing. This was done for logistic reasons (limited personnel and equipment available) and selection for second test-

ing was random. Besides drug withdrawal, no other interventions were performed during the follow-up period.

All tilt-table measurements were performed with a Finometer (Finapres Medical Systems BV, the Netherlands), a non-invasive beat-to-beat finger blood pressure measurement device. For tilting a manually operated, motor-driven tilt-table was used.

Carotid sinus massage was performed according to the Newcastle protocol,[25] starting with supine position and if negative, proceeding to a head up tilt position of 70 degrees. CSH was defined as a fall in blood pressure greater than 50 mm Hg and/or asystole of 3 seconds or more. Contra-indications to carotid sinus massage were presence of a carotid bruit on examination; myocardial infarction, stroke or TIA within the previous 3 months; and a history of ventricular tachy-arrhythmias.

For measurement of orthostatic changes, participants first underwent a period of 10 minutes of quiet supine rest. Subsequently, the participants were tilted to 70 degrees head-up tilt. Lowest systolic and diastolic blood pressure was recorded using the 5-second averages of the first 5 minutes of head-up tilt. OH was defined as a 20 mm Hg fall in systolic blood pressure and/or a 10 mm Hg fall in diastolic blood pressure.[7,26]

For provocation of VVC, head-up tilt was continued until collapse occurred or 30 minutes of head-up tilt was reached. VVC was defined as a fall in blood pressure greater than 50 mm Hg and/or asystole of 3 seconds or more. [4,27]

Assessment of drug use and withdrawal of FRID

Before the baseline assessment of the study, a list of drug use during the preceding year was obtained from both the general practitioner and the patient's pharmacist. During baseline assessment the patient, and if applicable a partner or main caregiver, were consulted on actual drug use, dosages and duration of use. During the second assessment, the patient was asked whether changes in drug use had occurred. If so, date and changes in dosage were registered. This was crosschecked with the information from letters of consulting physicians, and if there was any doubt a new list was obtained from the pharmacy.

All potential FRID were considered for withdrawal, i.e. anxiolytics/hypnotics, neuroleptics, antidepressants, antihypertensives, anti-arrhythmics, nitrates and other vasodilators, digoxin, beta-blocker eye drops, analgesics (mainly opioid analgesics), anti-cholinergic drugs, antihistamines, anti-vertigo drugs, and hypoglycemics. Subsequently, in all fallers FRID were stopped if considered redundant, or else if possible, reduced in dose over a 1-month period. The prescribing physicians were consulted if drug changes were intended. Patients were informed about the intended withdrawal, including an explanation of why and how the withdrawal was planned. During follow-up, no other interventions were performed.

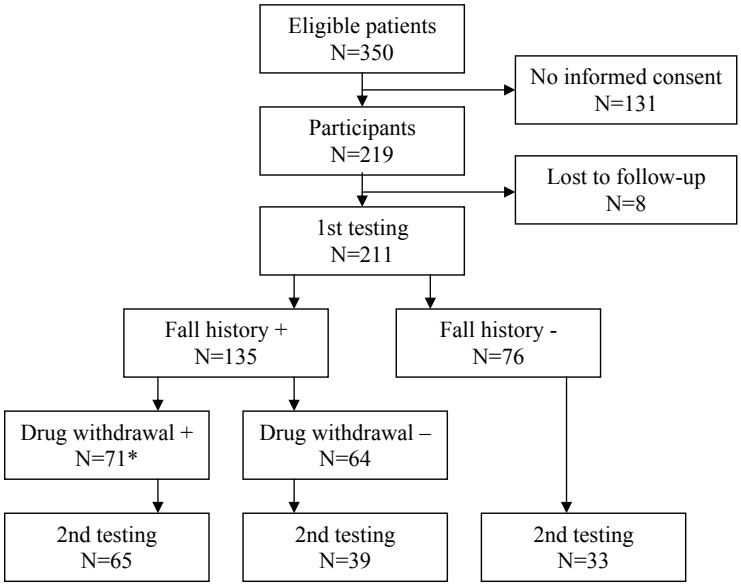
Statistical analysis

In the study, we performed 2 analyses. First, we performed a cross-sectional analysis of the association between falls history and tilt-table test abnormalities, which was performed in two steps. For this, we calculated crude percentages of tilt-table test outcomes and falls history. Subsequently, we estimated the relative risk adjusted for confounders, using a binary logistic regression model. Odds ratios of abnormal tilt-table test results and falls history were computed as estimates of relative risk.

The association between tilt-table test outcomes according to withdrawal of FRID and according to withdrawal of cardiovascular FRID was evaluated using a binary logistic regression model. Odds ratios of events (normalization of test outcomes) were computed as estimates of relative risk. To account for possible confounding, we computed a multivariate model containing all variables that caused a change in the point estimate of more than five percent. A second logistic regression analysis was performed in which the confounders were replaced by a propensity score.[28] Finally, we used a multinomial logistic regression model in order to be able to take into account deterioration of test outcomes, deterioration was defined +1, improvement as −1 and unaltered test results were coded as 0. In this model we adjusted for confounders as mentioned above. We concluded with the association between normalization of tilt-table test outcomes and fall incidents within the group with FRID withdrawal. For this we calculated the odds ratio of a fall during follow-up according to test normalization. All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

Results

During the study period, 350 subjects were eligible for participation in the study (figure 1); 131 subjects did not give informed consent, mostly because of the burden of 2 extra visits and fear of an adverse effect of carotid sinus massage. Of the 219 included persons, performance of the tests turned out to be too difficult in 3 persons, 2 persons died during follow-up, and 3 refused to continue during the follow-up period. The remaining 211 individuals were included in our analysis. Out of the 211 included patients, 135 had experienced at least one fall during the previous year. Within this subgroup, we were able to discontinue FRID in 65 cases and to reduce its dose in 6 cases. This resulted in a total of 71 patients in our subgroup of patients with FRID withdrawal (figure 1). In 56 fallers FRID withdrawal was not attempted, either because they did not use FRID, or because the FRID could not be missed. Furthermore in 8 patients, FRID withdrawal was attempted, but failed. This resulted in a total of 64 patients in the non-withdrawal group (figure 1). Baseline subject characteristics are summarized in Table 1. The groups with a positive falls history comprised more women and age was higher compared to the group with a negative falls history. They were also more disabled as was shown by a higher use of walking aids and impaired ADL scores and IADL scores. They had more comorbid conditions, had a lower



* In 65 of cases drugs were totally withdrawn, and in 6 cases doses were reduced.

Figure 1. Flow sheet patient enrolment

MMSE-score and used more drugs. Table 2 shows a cross-sectional analysis of tilt-table test abnormalities at baseline according to falls history. Crude prevalence of CSH and OH was higher in patients with a positive falls history compared to non-fallers. After adjustment for confounders only OH was significantly associated with falls history.

Baseline use of FRID differed significantly: 89% of patients with a positive falls history versus 76% of non-fallers ($P<0.05$). For sedatives the difference was also significant: 43% versus 28% ($P<0.05$). For cardiovascular drugs, baseline use was respectively 63% versus 53% (non-significant). The major drug-groups that were withdrawn were sedatives and cardiovascular drugs (table 3).

In table 4 the odds ratios of test normalization according to FRID withdrawal are presented as estimates of the relative risk. Overall FRID withdrawal appeared favorable for normalization of all tilt-table test outcomes, but significance was only reached for OH. Normalization of test outcomes according to cardiovascular FRID withdrawal was significant for both OH and for CSH. For VVC, cardiovascular FRID withdrawal appeared favorable, but this was not statistically significant. Multi-nomial logistic regression analyses of the outcomes in table 4 showed similar results. Therefore, only the odds ratios of the binary logistic regression analysis are presented.

Table 1. Baseline Characteristics of a Cohort of Geriatric Outpatients (N=211)

Characteristics	Fallers with FRID withdrawal (n=71)		Fallers without FRID withdrawal (n=64)		Non-fallers (n=76)	
Age, mean (SD), yrs.	78.7	(±5.2)	78.8	(±5.9)	75.2	(±5.9)
Gender: female (%), no.	51	(72%)	52	(81%)	35	(46%)
Referral for falls (%), no.	61	(86%)	43	(67%)	2*	(3%)
>1 fall last year (%), no.	57	(80%)	47	(73%)	-	
Use of walking aid (%), no.	39	(55%)	32	(50%)	14	(18%)
ADL score, mean (SD), pts.	0.8	(±1.8)	0.8	(±1.6)	0.1	(±1.3)
IADL score, mean (SD), pts.	13.5	(±3.2)	13.6	(±3.5)	15.2	(±1.9)
MMSE score, mean (SD), pts.	27.1	(±2.8)	27.2	(±2.5)	28.9	(±7.5)
Drugs used, mean (SD), no.	6.1	(±2.6)	4.3	(±2.5)	4.2	(±2.9)
FRID used, mean (SD), no.	3.3	(±1.8)	1.7	(±1.5)	2.0	(±2.0)
Co-morbidity, mean (SD), no.	4.7	(±1.9)	3.7	(±1.7)	3.6	(±1.9)

*Two patients without a history of falls were referred for falls, which turned out to be fear of falling

Abbrevations: FRID, fall-risk-increasing drugs; yrs., years; SD, standard deviation; no., number; ADL, activities of daily living; IADL, instrumental activities of daily living; pts., points; MMSE, Mini-Mental State Examination

Table 2. Cross-sectional Analysis of Abnormalities during Baseline Tilt-Table Testing in Patients with and without a Fall during the previous Year

	Fall history +		Fall history -		Abnormal test*	
	Number (%)		Number (%)		OR	(95% CI)
Carotid sinus hypersensitivity	23	(17)	11	(15)	1.1	(0.4-2.6)
Orthostatic hypotension	91	(67)	36	(47)	2.7	(1.4-5.2) †
Vasovagal collapse	8	(6)	6	(8)	1.6	(0.4-5.8)

The number of subjects with an abnormal test outcome is shown per item (e.g. orthostatic hypotension, vasovagal collapse or carotid sinus hypersensitivity). A subject will therefore be in more than one cell if he/she has multiple abnormalities. Furthermore, subjects without any abnormality do not appear in the table (n=64).

* Adjusted for age, gender, number of comorbid conditions and Mini-Mental State Examination

†$P < 0.05$

Abbreviations: OR: odds ratio; CI: confidence interval

Finally, within the group of fallers with FRID withdrawal the risk (odds ratio) of a fall during follow-up according to test normalization was calculated, showing a significant association (OR 0.24; 95% CI 0.11-0.54).

Table 3. Subgroups of Withdrawn FRID (n=71)

Psychotropic drugs	n=28
Sedatives	22
Antidepressants	7
Neuroleptics	2
Cardiovascular drugs	n=40
Antihypertensives	28
Nitrates	5
Anti-arrhythmics	3
Nicotinic acid	1
Timolol eye drops	3
Other drugs	n=16
Analgesics	9
Antivertigo preparations	5
Hypoglycemics	1
Urinary antispasmodic	1

Numbers in the table depict the number of times a specific drug was withdrawn; multiple drugs could be withdrawn in one single patient.
Abbreviations: FRID, fall-risk-increasing drugs

Table 4. Effect of FRID Withdrawal on Tilt-Table Test Outcomes

	Model 1		Model 2	
	OR	(95% CI)	OR	(95% CI)
Overall FRID withdrawal				
Carotid sinus hypersensitivity	0.47	(0.15-1.50)	0.34	(0.06-1.86)
Orthostatic hypotension	0.35	(0.16-0.75)*	0.35	(0.13-0.99)*
Vasovagal collapse	0.17	(0.02-1.54)	0.27	(0.02-3.31)
Cardiovascular FRID withdrawal				
Carotid sinus hypersensitivity	0.19	(0.06-0.63)*	0.13	0.03-0.59)*
Orthostatic hypotension	0.38	(0.17-0.89)*	0.44	(0.18-1.00)*
Vasovagal collapse	0.18	(0.03-1.12)	0.21	(0.03-1.51)

The odds ratios were calculated using the entire sample, including both fallers and non-fallers
* $P \leq 0.05$
Abbreviations: FRID, fall-risk-increasing drugs; OR, odds ratio; CI, confidence interval.
Model 1: adjusted for age and gender
Model 2: adjusted for age, gender, use of fall-risk-increasing drugs, Mini Mental State Examination score, total number of comorbid conditions, follow-up time

Discussion

Our study showed that OH improved significantly after withdrawal of FRID. For the subgroup of cardiovascular FRID withdrawal, there was a significant reduction of both OH

and CSH. This outcome indicates that a substantial subgroup of geriatric patients experiences drug-induced cardiovascular adverse effects, which are reversible after withdrawal of these drugs. This is in agreement with our finding that compared to withdrawal of FRID in general or psychotropic FRID withdrawal, withdrawal of cardiovascular FRID resulted in the largest reduction of falls in this same cohort.[17]

The role of OH as one of the causal pathways for falls is generally accepted[9] and is in line with our finding that OH was related to a positive falls history in this study. OH has been associated with a wide variety of drugs, the main groups being antihypertensives, vasodilators, antidepressants, neuroleptics, sedatives and anti-Parkinson medication.[29-34] The reversibility of OH after withdrawal of these drugs was demonstrated in our study. Given the significant association between normalization of tilt-table test outcomes and non-occurrence of fall incidents, we think it likely that part of the reduction of fall incidence after FRID withdrawal in this same cohort of geriatric outpatients[17] was indeed due to improvement of OH. Similarly, we think it probable that part of the reduction of falls incidence was due to improvement of CSH. Many researchers believe that CSH and VVC are part of a continuum of neurally mediated reflex syncope.[4,35] Therefore, a usual advice has been to withdraw the same drugs as one would for VVC, i.e. vasodilating and hypotensive drugs.[36] To our knowledge, only one randomized study addressed vasodilator drug withdrawal in patients with symptomatic SCH.[37] Although there was a tendency towards improvement, the difference in positive carotid sinus massages was not significant. Contrary to the reduction of OH and CSH in our study, we did not observe a significant normalization for VVC after overall FRID withdrawal or cardiovascular FRID withdrawal. This is most likely due to the small incidence of VVC in our cohort, resulting in too small a sample size for significant subgroup analysis.

There is some discussion in the literature regarding the reliability of tilt-table testing with carotid sinus massage. For VVC testing, reproducibility appears to be 65-85%, and negative initial tests are more likely to be reproducible than positive initial tests.[39,39] Moreover, the rate of positive responses appears to decrease with short-term sequential head-up tilt tests, although the number of tests performed does not appear to modify the rate of positive responses.[40-42] Measurement of OH through passive head-up tilting shows more consistent outcomes, with a high reproducibility (r=0.82-0.98) in older persons.[3,43] Reproducibility of CSH varies between 41 and 100%, depending on the duration to re-testing and patient selection.[44] Nevertheless, for our study there is no reason to assume that reproducibility of abnormal tilt-table test outcomes was differential for the different groups.

A potential limitation of our study is the lack of randomization. The reason not to perform a randomized controlled trial was that withdrawal of FRID is already implemented in Dutch and international Falls Guidelines,[14,45] rendering it unethical not to withdraw FRID in patients presenting with a fall. Therefore, we performed a prospective cohort study in which FRID withdrawal was the only intervention during follow-up. We adjusted for pos-

sible confounders, and for the use of FRID at baseline. Information bias by the investigators is unlikely as gathering of data on tilt-table test outcomes was performed without knowledge of the intervention status. Another potential limitation of our study is the substantial group that refused participation. On average, these patients were older. Although this might have affected generalizability of our results, we have no reasons to suspect that these non-participants would not benefit from FRID withdrawal. In fact, we have no reason to assume that being older weakens the relation between use of FRID and tilt-table test abnormalities. On the contrary, one would expect a stronger correlation, because of a smaller physiological reserve.

Conclusion

To our knowledge, this is the first prospective cohort study of geriatric patients in which the effect of withdrawal of all FRID on tilt-table test abnormalities has been investigated. It demonstrates that cardiovascular adverse drug reactions are considerable, since both presence of OH and CSH decreased significantly after withdrawal of FRID. This effect was clearest for the subgroup of fallers in whom cardiovascular FRID were withdrawn. Since the association between these cardiovascular improvements and non-occurrence of fall incidents was significant, we think it likely that part of the FRID related falls in this cohort were mediated through cardiovascular side effects. Therefore, we think that in individual patients repeated tilt-table testing can be a useful tool to measure the effect of the intervention.

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Author contributions

N. van der Velde initiated and contributed to the study concept and design, to the acquisition of subjects and data, and to the interpretation of the data, and the preparation of the manuscript. B.H.Ch. Stricker contributed to the study concept and design, and to the interpretation of the data, and the preparation of the manuscript. A.H. van den Meiracker contributed to the study concept and design, to the acquisition of data, and to the interpretation of the data, and the preparation of the manuscript. H.A.P. Pols contributed to the study concept and design and the preparation of the manuscript. T.J.M. van der Cammen

initiated and contributed to the study concept and design, to the acquisition of subjects, and to the interpretation of the data, and the preparation of the manuscript.

Sponsor's role

The study's sponsors had no role in the design and conduct of the study, in the subject recruitment, the collection, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

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Chapter 4.4

Cost-effectiveness of withdrawal of fall-risk-increasing drugs in geriatric outpatients

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(submitted)

Abstract

Background

Withdrawal of fall-risk-increasing drugs has been proven to be effective in older persons, resulting in a short-term fall-risk reduction of approximately 50%. However, given the enormous rise in healthcare costs during the last decades, next to effect on health the effect on healthcare costs also needs consideration.

Methods

Within a common geriatric outpatient population, patients with a history of falls were assessed for falls risk (n=139). Fall-risk-increasing drugs were withdrawn if possible (n=75). All participants had a 2-month follow-up for fall incidents. Number of prevented falls was calculated using a loglinear regression model. The savings on health expenditures due to prevented injuries (estimated from a literature review) and reduced consumption of pharmaceuticals was compared to the intervention costs. Subsequently, a sensitivity analysis was performed.

Results

After adjustment for age, gender, drug use, baseline falls frequency, co-morbidity and mental status, drug withdrawal resulted in a falls reduction of 0.89 (95% CI 0.33, 0.98) per patient. Net cost savings were € 1691 (95% CI 662, 2181) per patient in the cohort. This resulted in a cost saving of € 491 per prevented fall (95% CI 465, 497).

Discussion

Withdrawal of fall-risk-increasing drugs results in a decrease of falls incidence, and generates significant cost savings. Although the effect is likely to decrease over time, cost savings are already generated in the short run. On a national scale this was estimated to result in a reduction of € 60 million of healthcare expenditures, 15% of fall-related health costs.

Introduction

Falls and fall-related injuries in older people are a major public health challenge because of their high incidence, severe disabling consequences, and high associated healthcare costs.[2,3] Around 30% of persons aged 65 years and older living in the community and more than 50% of those in assisted living facilities fall every year; approximately half of those who fall, do so repeatedly.[4-6] Twenty percent of these falls need medical attention, 5% result in a fracture, and 5-10% result in other serious injuries.[4,7-10] The burden continues to grow because of a rising incidence of falls per age category and because of an increasing number of older people worldwide.[11]

It is increasingly recognized that certain drugs increase fall risk. In 1999, Campbell et al. demonstrated in a randomised controlled trial that fall risk was reduced with two-thirds after withdrawal of sedatives and antidepressants among community-dwelling older people.[12] Recently, we published a prospective cohort study among a geriatric outpatient population, showing that withdrawal of a broader group of fall-risk-increasing drugs, including cardiovascular drugs, psychoactive drugs, and certain analgesics, resulted in a 50% risk reduction of fall incidence (hazard ratio 0.48; 95% CI 0.23, 0.99).[13]

However, given the continuous pressure on healthcare costs during the last decades, it is important to also address the cost-effectiveness of medical interventions. Therefore, we investigated the cost-effectiveness of withdrawal of fall-risk-increasing drugs in a common geriatric outpatient population.

Methods

In order to determine the cost-effectiveness of withdrawal of fall-risk-increasing drugs, we estimated costs of the intervention, the number of prevented falls and injurious falls, and the savings on health expenditures due to prevented injuries and reduced consumption of pharmaceuticals.

Intervention

A detailed description of our prospective cohort study has been published elsewhere.[13] New consecutive referrals to the geriatric outpatient clinic were invited to participate between April 1, 2003 and November 30, 2004.

For all participants the medication list was checked for use of fall-risk-increasing drugs as defined in literature, i.e., anxiolytics/hypnotics, neuroleptics, antidepressants, antihypertensives, anti-arrhythmics, nitrates and other vasodilators, digoxin, beta-blocker eye drops, analgesics (mainly opioid analgesics), anti-cholinergic drugs, antihistamines, anti-vertigo drugs, and hypoglycemics.[11,14-19]

If a participant had fallen at least once during the previous year, fall-risk-increasing drugs were stopped if considered redundant, or reduced in dose over a 1-month period if considered safe. Patients were informed about the intended withdrawal, including an explanation of why and how the withdrawal was planned. During follow-up, no other interventions were performed. During the 1-month withdrawal period subjects had regular telephone consultations according to need, to assess the safety and compliance with drug withdrawal and reduction of doses.

Outcomes

For every participant, we recorded fall incidents during a fixed follow-up period of 2 months, after the set 1-month period during which we stopped or decreased the dose of fall-risk-increasing drugs. Respondents were asked to report their falls weekly on a falls calendar and to mail the calendar page at the end of every month. This is a valid method for measuring falls incidence.[20]

We estimated the number of falls prevented due to withdrawal of fall-risk-increasing drugs using a loglinear regression analysis (Poisson), with the cumulative number of falls during month 2 and 3 as outcome, and with the intervention as exogenous dummy variable. Because of the observational study design, we adjusted for possible confounders. Information regarding confounders was collected during the baseline assessment. Confounders were selected because of their known association with falls: age, gender, use of fall-risk-increasing drugs, baseline falls frequency, total number of comorbid conditions and cognitive dysfunction as measured with the MMSE score.[21] The definitive prediction model was restricted to those that were significant ($P < 0.05$).

Costs

We assessed costs from the perspective of health service providers, including acute and long-term effects. All costs were calculated for the 2005 financial year.[22]

All new consecutive referrals to the geriatric outpatient clinic and the diagnostic day centre underwent a full geriatric assessment by their treating geriatrician and were subsequently invited to participate in our study. Costs of the intervention included extra time needed for assessment of falls history, drug use, and patient education in case of drug withdrawal (on average 15 minutes per patient), and time needed for extra telephone consultations assessing safety and compliance with drug withdrawal and further lowering of doses (on average 5 minutes per telephone call). Personnel time needed for the intervention was converted to personnel costs of medical staff. We added 72% to the direct personnel costs to account for costs of overhead and housing.[23]

Cost savings

Since we used fall incidents as health outcome measure, we multiplied the number of prevented falls with the probability of an injury given a fall in a random population of community-dwelling persons of 55 years and older in the Netherlands, i.e., 9.8%.[24] Injuries were restricted to those that needed at least treatment in a hospital-based Emergency Department (ED), so patients with minor injuries who were fully treated by primary care practitioners or at the injury scene were excluded. The mean healthcare costs of fall-related injuries in older persons (age ≥ 65 years) that are treated in the ED were derived from an incidence-based injury cost model. The model includes the lifetime healthcare costs per injury, estimated with data on health care consumption from national surveillance registers (e.g. the hospital discharge register) and a patient follow-up study.[22] All health services that are relevant for treatment and rehabilitation of fall-related injury patients were included.

We calculated cost savings of medication withdrawal by multiplying the reduced individual drug consumption with drug costs according to the national pharmacy listing.[25] The prescription costs were also added.

Statistical analysis

The number of prevented falls was estimated using a prediction model, by simulating how many falls would have occurred without the intervention. Because the number of falls cannot be regarded independent of events, the model was adjusted for overdispersion.

Total costs were calculated by subtracting from the intervention costs the savings in pharmaceutical consumption and medical savings due to prevented injuries. These net costs were divided by the mean number of prevented falls during follow-up, resulting in costs per prevented fall. Confidence intervals of net costs and costs per fall prevented were determined with bootstrapping, a resampling technique that does not require prior assumptions about the parameter distributions.[26] We accounted for the statistical uncertainty of falls reduction by drug withdrawal, the number of telephone contacts, and the proportion of patients with drug withdrawal. Because the cost savings related to prevented injuries were the largest component of total costs, we reduced the proportion of injurious falls by 50% in the sensitivity analysis. All statistical analyses were performed using Splus software.

Results

Patients

During the study period 201 fallers were eligible; 141 gave informed consent; 139 completed follow-up. Non-participants were older (80.2 ± 7.3 years). The main reason for refusing participation was the burden of the extra visits to the clinic. We were able to withdraw one or more fall-risk-increasing drugs in 75 out of the 139 patients (54%) (table 1).

Outcomes

Mean number of falls during follow-up was 0.8 (SD 2.4) for the group with drug withdrawal and 3.1 (SD 11.5) for the group without drug withdrawal (p-value 0.03). For the group with drug withdrawal mean number of withdrawn drugs was 1.2 (SD 0.8), resulting in drug cost saving per month of € 12.3 (SD 13.2). The mean number of telephone consultations was 4.1 (SD 2.5).

Table 1. Baseline characteristics of study population (N=139)

	Fallers with drug change (n=75)		Fallers without drug change (n=64)		P-value
Characteristic		(SD)		(SD)	
Mean age (SD)	78.4	(5.2)	78.8	(5.9)	n.s.
Female gender	71%		81%		n.s.
>1 fall last year	77%		73%		n.s.
≥1 fall per month	43%		35%		n.s.
Mean number of drugs (SD)	6.2	(2.6)	4.3	(2.5)	<0.001
Mean number of FRID (SD)	2.9	(1.7)	1.7	(1.5)	<0.001

Abbreviations: SD, standard deviation; FRID, fall-risk-increasing drugs

Table 2. Falls reduction due to withdrawal of fall-risk-increasing drugs: results of poisson regression on number of falls in month 2 and 3.

	Beta	SE	T-statistic
Constant	-11.05	7.95	-1.39
Drug withdrawal	-2.22	0.91	-2.44
Age – 70	0.59	0.35	1.71
(Age - 70)^2	-0.04	0.02	-1.82
History of falls	1.12	0.46	2.42
Cognitive dysfunction*	-0.07	0.14	-0.49
Number of chronic conditions	4.21	2.45	1.72
(Number of chronic conditions)^2	-0.37	0.23	-1.60

Model is adjusted for overdisperson, with parameter value 30.39.
SE, standard error
*MMSE-score

Table 3. Cost-effectiveness analysis: assumptions

Parameters	Baseline estimate (95% CI)	Source
Falls		
Reduction in number of falls due to drug withdrawal	0.89 (0.98, 0.33)	Own data (table 2)
Proportion of study population with FRID withdrawal	0.54 (0.46, 0.62)	Own data
Proportion of injurious falls needing hospital treatment	0.098 (0.049 in sensitivity analysis)	Stel et al., 2004
Costs, resource use		
Assessment costs (15 minutes)	€ 42	Expert estimate
Follow-up: telephone calls	4.1 (3.7, 4.6)	Own data
Telephone call (5 minutes)	€ 4	Expert estimate
Follow-up visit (30 minutes)	€ 84	Expert estimate
Savings in pharmaceuticals consumption per month	€ 12 (€ 8, € 18)	Own data
Medical costs per injury due to a fall	€ 5250	Meerding et al., 2006

Table 4. Costs and savings of withdrawal of fall-risk-increasing drugs in older fallers (n=139)

	Baseline		Sensitivity analysis*	
	Mean	(95% CI)	Mean	95% CI
Prevented number of falls in month 2 and 3	3.4	(1.4, 4.5)	3.4	(1.4, 4.5)
Incremental costs per person assessed (€)				
Intervention costs	98	(89, 106)	98	(89, 106)
Savings in pharmaceutical consumption	13	(20, 9)	13	(20, 9)
Medical savings due to prevented injuries	1775	(2270, 744)	889	(1136, 371)
Total savings	1691	(2181, 662)	804	(1046, 286)
Savings per prevented fall	491	(497, 465)	233	(239, 208)

* Proportion of falls with injury reduced from 0.098 to 0.049 (-50%).

After adjustment for confounders, drug withdrawal significantly reduced the number of falls by $1\text{-}e^{(-2.22)} = 0.89$ (95% CI 0.33, 0.98) (table 2). The number of falls prevented was 3.4 per patient in month 2 and 3 (95% CI 1.4, 4.5).

Cost effectiveness analysis

The intervention costs were € 98 (95% CI 89, 106) per patient, the pharmaceutical savings € 13 (95% CI 9, 20) and the medical savings per prevented injury € 1775 (95% CI 744, 2250) (table 3&4). The mean total cost savings per patient was € 1691 (95% CI 662, 2181), resulting in a cost saving per prevented fall of € 491 (95% CI 465, 497) (table 4). When the proportion of injurious falls was reduced by 50% (sensitivity analysis), cost savings per patient remained significant (€ 804; 95% CI 286, 1046).

Discussion

We have shown that withdrawal of fall-risk-increasing drugs reduces falls and is cost saving in a geriatric outpatient population. The intervention costs were small compared to the estimated medical savings, resulting in considerable cost savings per subject and per prevented fall. Already after short-term follow-up (2 months) withdrawal of fall-risk-increasing drugs in older fallers is cost-effective. Furthermore, if these findings are generalized to all older patients who receive medical attention for fall incidents during a given year (in the Netherlands 7% of persons of 65 and older),[20] the resulted cost savings would be approximately € 60 million per year in the Netherlands alone (assuming a 50% participation rate). This would amount to 15% of the fall-related health care costs.

A potential limitation of our study is the fact that we did not account for possible health hazards due to withdrawal and reduction of drugs. However, since we only withdrew drugs if this was considered safely possible, e.g. as is current practice in geriatric care, we do not think that this will have caused major health hazards. This is confirmed by a recent study that showed that for the majority of patients, renewal of cardiovascular drugs was not needed in a geriatric falls clinic.[27]

Regarding the long-term effectiveness of withdrawal of fall-risk-increasing drugs, it is likely that a subset of patients will resume their medication, or get new fall-risk-increasing drugs prescribed. This will of course dilute the effectiveness. Long-term management of drug withdrawal will therefore require extra efforts, but is also likely to sustain the risk reduction. In order to gain more knowledge about the long-term effects of this intervention, further research is needed. But even if it would turn out to be modestly cost increasing in the long run, it would be worthwhile in view of the positive health outcomes, physical and social functioning, and its cost-effectiveness would be favorable compared to many other common interventions in injury control and other health care problems.

In conclusion, besides being effective with respect to health care outcomes, i.e., a reduction of fall incidents, withdrawal of fall-risk-increasing drugs in older persons appears to be successful also in terms of health expenditures. Although further research is needed in order to assess long-term effects, considerable cost savings are already generated in the short run. These data provide sufficient argument for a similar experiment in a more broadly defined patient population, for example older fallers presenting at the ED.

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Chapter 5
General Discussion

Introduction

The main objective of this thesis was to gain more knowledge about two sets of possible risk factors for falls, e.g. certain drugs and cardiovascular abnormalities. In this chapter, we will start with a short discussion regarding the importance of addressing individual components of a composite intervention, e.g. the multifactorial approach at the Falls Clinic. Subsequently, we will reflect on our main findings and discuss the current status of the two examined sets of risk factors, consider the methodological issues, the broader context of clinical practice and possible future implications.

The multifactorial approach, optimizing the content

One of the main challenges in geriatric medicine is to correctly diagnose and treat a patient presenting with vague and/or atypical symptoms. With increasing age, disease presentation becomes more atypical, with less than 50% of older patients fitting the classical medical model of illness.[1] There are four main reasons why disease presentation in this age category is often atypical: co-morbidity may be present which may mask the presentation of another disease, a causal chain of problems may lead to a certain complaint, patients and physicians may attribute symptoms of a new disease to a chronic problem, or longstanding, unrecognised morbidity may be unmasked by a certain event.[1] All in all, the presenting complaint appears to reflect the most recent, easily recognisable or familiar symptom, the composite burden of illness, or the legitimate medical problem with which to gain entry into the health care system. An 'atypical' symptom, e.g. functional decline, delirium, cognitive decline or falls, appears to be the presenting symptom in approximately 25-59% of older patients.[2]

In this thesis we aim to get a clearer view on one of these atypical, but characteristic, symptoms, e.g. falls. As mentioned in the introduction, fall incidents are not a disease entity in itself, but a symptom. Therefore, fall incidents can be caused by many different factors and many of these factors are interrelated (figure 1).[3,4] For this reason the majority of the studies regarding this issue have addressed a multifactorial approach, with a recent meta-analysis showing that this multifactorial approach is indeed effective.[5] However, this same article also states that the assessment of the literature on effectiveness of the multifactorial approach to fall incidents is rather problematic, because in the various studies, the content of assessment and intervention differs extensively. This brings us right to the heart of the problem of these kinds of studies. Namely, although it is very important and correct to assess the effectiveness of a certain multifactorial intervention or approach, it is even more important to first test which parts of the intervention are effective on an individual basis. Only when the individual components have been proven to be effective separately, then subsequently the multifactorial model/approach can be tested. This is of importance not only for financial reasons, but also more crucially, because every assessment and treatment

can have adverse effects. This holds especially true for older persons due to their diminished physiological reserves. First of all, every assessment and treatment will present an extra burden for the overall frail geriatric patient. Second, many tests and treatments have potentially harmful consequences, such as an adverse drug reaction when prescribing a certain drug. Third, a non-relevant finding can possibly deflect the patient and treating physician from the real problem, leaving the disease that needs targeting untreated.

For the assessment and treatment of fall incidents, the only individual component that has been extensively studied is mobility training.[6,7] Further individual components for which one or a few studies have shown some effectiveness are psychotropic drug withdrawal,[8] correction of visual disorders,[6] and cardiac pacing in carotid sinus hypersensitivity.[9,10]

Cardiovascular determinants of falls

With age, the incidence of cardiovascular disorders, including structural cardiac abnormalities, rises.[11] Due to the often non-specific disease presentation of older persons, as mentioned above, a relatively high percentage of these abnormalities remain unrecognised in current clinical practice. A typical presentation for a geriatric patient would be overall deterioration, fatigue or fall incidents. However, evidence regarding cardiac abnormalities as fall-risk factors is scarce and most studies have specifically focussed on syncope.[12,13] In view of the classical medical model this is a logical, straightforward approach, because it is common knowledge that certain cardiac abnormalities can lead to syncopal events.[12-14] However, approximately 50% of older fallers do not recall losing consciousness and will therefore present with an unexplained fall instead of syncope.[15]

Furthermore, since it has been shown that syncope and falls overlap substantially in older persons, with approximately half of the syncope patients presenting with falls, causes of falls and syncope are often intermingled and are both assessed in older fallers.[16] It is important to realise that although this train of thought is very reasonable, it is not certain whether the risk factors for syncope are also significant risk factors for falls in older persons. This is relevant for several reasons. First of all, since the prevalence of cardiovascular abnormalities rises with age, the pre-test probability of finding abnormalities on testing rises. If these abnormalities are unrelated to fall incidents, wrong attribution of diagnoses will result, followed by potentially unnecessary treatments. This can result in possibly harmful (side) effects, either due to treatment, or due to non-treatment of the actual cause of the fall incidents. Second, as mentioned above, unneeded testing gives rise to an avoidable burden both in a patient-related and in a financial sense.

In light of the above we have studied two possible cardiovascular fall risk factors. In chapter 3.1 and 3.2 we describe the association between several echocardiographic abnormalities and fall incidents.

In chapter 3.1 we determined the association between echocardiographic abnormalities and falls in a prospective hospital-based cohort study, in which 215 new consecutive refer-

rals to a geriatric outpatient clinic in a Dutch University hospital were included. At baseline, all patients underwent two-dimensional and Doppler echocardiography. Fall incidents were recorded during a 3-month follow-up. Presence of pulmonary hypertension or valvular regurgitation, except aortic regurgitation, was associated with a higher fall risk. Trend analysis of the severity of the different regurgitations showed a significant relationship. These findings also indicate that echo(Doppler)cardiography can be useful in order to identify risk indicators for falling.

Chapter 3.2 contains a prospective, population-based cohort study regarding the association between left ventricular systolic function and falls with serious consequences (e.g. fractures and/or hospital admission) in older adults. This was tested in the Rotterdam study, in which 2266 participants underwent two-dimensional transthoracic echocardiography. In this study, the risk of a fall with serious consequences was significantly higher if left ventricular ejection fraction (LVEF) was impaired. Trend analysis according to degree of LVEF was also significant. These findings suggest that poor systolic function as measured with LVEF is a risk indicator for fall incidents with serious consequences.

Our hypothesis behind these findings is that persons with a poor cardiac function have a limited reserve cardiac output capacity, which can result in cerebral hypoperfusion, and hence falls, in physically demanding situations.[13] Another possible explanation would be that poor cardiac function might act as a predictor for frailty, since frailty has been shown to predict falls in older persons in the Cardiovascular Health Study.[17] However, although the incidence of clinical cardiovascular disease was higher in the frail participants, the Cardiovascular Health Study showed no significant association between frailty and LVEF or mitral valve abnormalities.[11] The authors did not provide data on other valvular abnormalities.

Chapter 3.3 describes the optimal measurement method for orthostatic hypotension when addressing fall risk. This was done with a cross-sectional analysis of data from our hospital-based cohort of geriatric outpatients. The best association with falls history was found, not for the regularly used beat-to-beat reading of continuous finger-blood-pressure measurement (Finometer), but for the 5-second average of the Finometer readings. Furthermore, falls and orthostatic hypotension assessed by sphygmomanometry did not correlate. These findings show that although measurement of orthostatic hypotension is already implemented in the falls guidelines,[3,4] the assessment may not yet be performed in an optimal fashion if the current guidelines are followed.

All in all, the studies mentioned above suggest that there is still room for improvement of the cardiovascular assessment in older fallers, although further research is needed to determine the clinical added value of including echocardiography in the falls assessment. On any account, in view of our results it can be speculated that clinical benefit might be obtained if cardiac output is optimized in older fallers and if orthostatic hypotension is measured with a continuous-blood-pressure measurement system using the 5-second average reading.

Withdrawal of fall-risk-increasing drugs

As was mentioned in the introduction, several studies have shown that certain drugs are risk factors for falls. However, the fact that certain drugs have been shown to increase fall risk does not necessarily mean that withdrawing these drugs will result in a decrease in fall incidence. And although this had not yet been tested, except for one study regarding withdrawal of sedatives and antidepressants,[8] withdrawal of fall-risk-increasing drugs is already part of the current guidelines[3,4] and common practice in many falls clinics. In view of the plausibility of the effect, this is certainly not unreasonable. However, one must realise that withdrawal of drugs may have negative effects too. Although many drugs may be withdrawn safely -either because they are given for the wrong indication, the indication has ceased to exist, or because alternatives with fewer side effects are available- for other patients the withdrawal of fall-risk-increasing drugs might have short- or long-term consequences. To our knowledge, only one study has touched on this issue, showing that withdrawal of cardiovascular drugs in a falls clinic had no adverse consequences during a mean follow-up of 30 months.[18]

For this reason, we assessed whether withdrawal of fall-risk-increasing drugs was indeed an effective intervention on its own. As described in chapter 4.1, we showed in a prospective cohort study that drug withdrawal, including both cardiovascular and psychotropic drugs, was indeed an effective intervention. During short-term follow-up the risk of a fall was halved compared to the group of patients in whom withdrawal was not possible. We cannot be certain that all confounders were adjusted for, because for ethical reasons we could not perform a prospective randomised controlled study, since the intervention of drug withdrawal is already part of de Dutch Falls Guideline.[4] However, even if the unbiased risk reduction would be 50% less than the one we found in our study, this still would remain clinically very relevant.

Since the drugs that have been stated as fall-risk increasing in the literature are very diverse, including drugs with very diverse effects and known side effects, we were interested which mechanisms would be of clinical relevance in the pathway leading to falls. For this reason the studies in chapter 4.2 and 4.3 were performed. For the first study we performed several mobility tests that are known to predict falls in older persons. And indeed, there was a significant improvement of these tests after withdrawal of the fall-risk-increasing drugs. Although this does not provide direct evidence that the decrease in fall incidence was a result of the improvement of mobility, it does make it likely. Furthermore, the association between falls and test improvement was also significant, strengthening the hypothesis. However, in order to confirm this probably causal chain, it would have been necessary to test the mobility of all participants (cases and controls) at the occurrence of each fall incident, so that the delta of the test outcome could be linked to the intervention status (yes or no drug withdrawal). For obvious reasons, this was not feasible. An alternative would be to assume that mobility at the end of the follow-up period was the same as at the occurrence of the fall incident, but as such an assumption in probability is unjustified, we decided to solely address the test outcomes.

Because of the high number of cardiovascular drugs within the group of fall-risk-increasing drugs, we also addressed possible cardiovascular adverse effects as is described in chapter 4.3. As could be expected the greatest test improvement was found for cardiovascular drug withdrawal (both for orthostatic hypotension and carotid sinus hypersensitivity), but orthostatic hypotension also improved significantly when the overall group of fall-risk-increasing-drugs withdrawal was assessed. This is not unexpected, because many drugs, including antidepressants, neuroleptics, sedatives and analgesics, are known to be able to cause orthostatic hypotension as an adverse effect.[19-24]

According to our findings, drug withdrawal is a very effective individual intervention for lowering fall risk. However, a few points of concern need to be addressed. First of all, our study addressed only short-term effects. We have no information regarding the long-term effectiveness of withdrawal of fall-risk-increasing drugs, but it is likely that a subset of patients will resume their medication, or get new fall-risk-increasing drugs prescribed. This will of course dilute the effectiveness. Long-term management of drug withdrawal will require extra efforts, but is also likely to sustain the risk reduction. In order to gain more knowledge about the long-term effects of this intervention, further research is needed. Second, we did not account for possible health hazards due to withdrawal and reduction of drugs. However, since we only withdrew drugs if this was considered safely possible, e.g. as is current practice in geriatric care, we do not think that this will have caused major health hazards. This is confirmed by the study mentioned above[18] that showed that for the majority of patients, renewal of cardiovascular drugs was not needed in a geriatric falls clinic. Third, overall quality of life needs some consideration. Since obviously the drugs were prescribed for a reason, it is very well possible that withdrawal of these drugs would lead to unwanted clinical effects. In our study, in the case of apparent adverse effects of withdrawal such as, for example, cardiac failure after withdrawal of a diuretic, the withdrawn drug was of course restarted as is current practice in geriatric care. However, less obvious clinical signs of unwell-being may have been overlooked, resulting in a lower effective quality of life. Therefore, we tested this in our study population.

Effect of drug withdrawal on quality of life

As mentioned above, it is important to also address possible negative effects of drug withdrawal in older fallers. Because of the 'atypical' disease-presentation in the majority of geriatric patients it is important not only to act on obvious negative effects of drug withdrawal, e.g. recurrence of the symptoms for which the drug was prescribed, but to also be alert to health deterioration in a general sense. For this, a quality of life assessment such as, for example, the SF-36 questionnaire can be used.

The SF-36 contains 36 items for which subjects can indicate whether the presented statements about health apply to him/her and can also relate the intensity of symptoms or symptom impact in the preceding 4 weeks. Questionnaires are scored on 8 domains

including physical and social function, limitations due to emotional and physical problems (role emotional and role physical, respectively), mental health, vitality, bodily pain and general health. Summary scores for physical (physical function, role physical, bodily pain and general health) and mental components (social function, role emotional, vitality and mental health) can be derived.[25]

In our cohort we asked 171 participants to complete a SF-36 questionnaire at baseline and at the end of the follow-up period. If they had trouble completing it on their own, a family member or the researcher helped, explaining the questions. In case the participants failed to send or give the questionnaire back to the investigator at the end of the follow-up period, the answers were obtained by telephone two weeks later.

For each study member, we calculated the difference between the first and second SF-36 questionnaire. The relative risk of improvement/deterioration of the SF-36 questionnaire according to drug withdrawal was tested for all 8 individual domains, using a binary logistic regression analysis. The following cofactors were assessed as possible confounding factors: age, gender, follow-up time, use of fall-risk-increasing drugs at baseline, total number of comorbid conditions, cognitive function (MMSE-score) and reason for referral.

All 171 participants completed the first questionnaire. The second questionnaire was returned by 159 participants. The adjusted odds ratio was significantly in favour of drug withdrawal for the subgroups vitality and social function, and the physical summary score (table 1). For all other domains the odds ratio was non-significant. In conclusion, drug withdrawal does not appear to have a negative effect on quality of life, including both mental and physical functioning. Moreover, withdrawal of fall-risk-increasing drugs may even have a small favourable effect on quality of life.

Future implications

The studies presented in this thesis indicate that there is still room for improvement of the multifactorial assessment and treatment of older fallers. With regard to the assessment of possible cardiovascular risk factors for falls, our study shows that measurement of orthostatic hypotension with a continuous-blood-pressure-measurement system has a better association with falls than conventional measurement methods. Since this was a cross-sectional study, however, a prospective research set-up is needed to confirm this finding. Furthermore, in patients with unexplained falls, echocardiography might improve the falls assessment. We have shown that there is an association between falls and certain cardiac abnormalities in two different populations of older persons. Nevertheless, before implementing a new diagnostic tool, further research will be needed to confirm these findings. Moreover, the clinical benefit of diagnosing these abnormalities will also need attention. Studies regarding improvement of clinical care and general health, e.g., a reduction in falls and

improvement of quality of life after the diagnosis of cardiac abnormalities, are needed first. This is necessary in order to make sure that we do not add unnecessary tests without clinical consequences to the extensive battery that is already performed in a falls assessment.

We also showed that another individual part of the approach, e.g., drug withdrawal, was indeed an effective intervention in our cohort, indicating that drug withdrawal has been implemented in the multifactorial approach for fall incidents with good reasons. Specifically, we showed that not only the already studied psychotropic drugs form a serious risk factor for older fallers, but that cardiovascular drugs also appear to play an important role. The adverse effects that give rise to fall incidents can be tested with both mobility and cardiovascular testing and these tests could be of use in the follow-up in a clinical setting. In our opinion, an official recognition of falls as a possible adverse drug reaction would result in a major improvement of medical care for older persons. However, we have only addressed short-term effects. More research will be needed to address the long-term merits and possible adverse effects of this intervention.

Finally, as mentioned above, due to lack of data, the currently advised content of the multifactorial approach for older fallers is not yet completely evidence based, with the exception of mobility training. We have now provided data regarding the cardiovascular and the drug withdrawal part of the approach, but many more parts of the intervention need further consideration. The effect of for example treatment of visual impairment, hearing impairment, cognitive dysfunction, certain neurological disorders, poor nutritional status, fear of falling and optimal treatment of co-morbidity also need further research (figure 1). Preferably, this is to be done in large multi-center trials.

Table 1. Relative risk (Odds ratio) of improvement of perceived quality of life (SF-36) according to drug withdrawal (n=171)

Domains of SF36	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Physical functioning	1.8	0.6-5.1	1.1	0.4-3.3
Role-physical	1.2	0.4-3.8	1.3	0.4-4.2
Bodily pain	1.7	0.6-4.6	1.8	0.6-5.2
General health	0.9	0.3-2.2	1.1	0.4-3.2
Vitality	1.2	0.9-4.2	4.2	1.3-13.3*
Social functioning	1.8	0.7-4.9	6.4	1.4-30.1*
Role-emotional	1.9	0.6-5.9	1.2	0.4-3.5
Mental health	0.5	0.2-1.4	0.9	0.3-2.5
Physical summary	3.2	1.1-8.7*	5.9	1.6-22.4*
Mental summary	0.9	0.4-2.4	1.4	0.5-4.3

* $P < 0.05$

Model 1: adjusted for age and gender

Model 2: adjusted for age, gender, baseline use of fall-risk-increasing drugs, follow-up time, number of comorbid conditions, Mini-Mental State Examination score, reason of referral

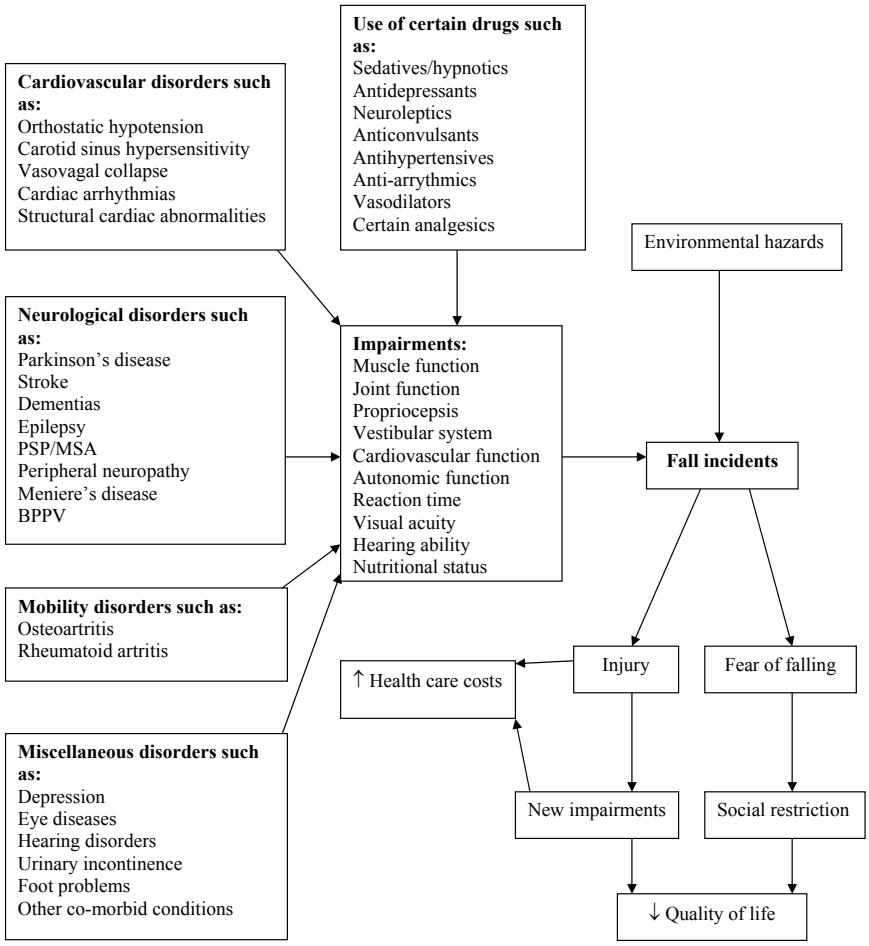

Figure 1. Determinants and effects of fall incidents in older persons
Abbreviations: PSP, progressive supranuclear palsy; MSA, multi system atrophy; BPPV, benign paroxysmal positional vertigo

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Chapter 6

Summary/Samenvatting

Summary

Fall incidents are common in old age, with a rising injury rate with increasing age. Falling is not a diagnosis per se, but a symptom that can result from a number of diseases and abnormalities. However, even though there are abundant studies addressing possible causes of fall incidents in older persons, there are still quite a few unresolved questions. In this thesis, we focus on two groups of (possible) fall-risk factors. First, we address cardiovascular risk factors for falls and second, we elude on the effects of withdrawal of drugs that are known in the literature to increase fall risk.

Chapter 1 gives a general introduction to this thesis. **Chapter 2** contains a selection of case reports regarding drug-related falls. These patients prompted us to conduct a prospective cohort study on this topic. In all these patients, falling was attributed to the use of certain drugs and fall incidents ceased after withdrawal of these drugs.

Chapter 3 focuses on cardiovascular determinants of falls. In **chapter 3.1** the association between echocardiographic abnormalities and fall incidents was investigated in a prospective cohort of geriatric outpatients. It is generally accepted that certain structural cardiac abnormalities, like for example aortic valve stenosis, mitral valve regurgitation and pulmonary hypertension can result in syncopal events. We showed that there was a significant association with fall incidents for both valvular regurgitations and pulmonary hypertension. Fall risk increased with increasing severity of the abnormality. No relation was found between aortic valve stenosis and fall incidents, probably due to a lack of moderate and severe stenoses in our follow-up group. In **chapter 3.2** the association between left ventricular systolic function, as measured with echocardiography, and fall risk was examined in the Rotterdam study. The risk of a serious fall incident during follow-up was significantly higher if left ventricular ejection fraction was impaired. In **chapter 3.3** the optimal measurement method of orthostatic hypotension in relation to falls was studied. Within a cohort of geriatric outpatients it was investigated which time average of continuous-finger-blood-pressure measurement showed the best association between OH and falls. This was also compared with conventional sphygmomanometer measurements. The best association was found when using 5-second averages of the continuous measurement method. Since the aetiology of falls is often multifactorial, orthostatic hypotension and falls remained poorly correlated, irrespective of the method or time average that was applied.

The studies described in **chapter 4** concern the relationship between the use of fall-risk-increasing drugs and falls, including the pathway leading to these fall incidents. In **chapter 4.1** fall risk after withdrawal of certain drugs is tested in a cohort of geriatric outpatients. Several drugs have been associated with an increased fall risk, but it is not yet known if withdrawal of these drugs leads to a decrease in fall incidents. This study indicates that withdrawal of all fall-risk-increasing drugs, including both cardiovascular and psychotropic drugs, is an effective intervention for lowering falls incidence. The effect was highest for

withdrawal of cardiovascular drugs. The effect of withdrawal of fall-risk-increasing drugs on mobility test outcomes is shown in **chapter 4.2**. Mobility tests, such as the Timed Up and Go Test are well-established predictors for fall incidents. Falls due to usage of certain drugs might be largely or at least partly caused by the impairment of mobility that these drugs can generate. This was confirmed by our study, since alongside with a reduction in falls, 10-meter walking test and Timed Up and Go Test significantly improved during follow-up. Other adverse drug effects that might be important in the causal pathway of drug use and ensuing fall incidents are cardiovascular abnormalities, e.g. orthostatic hypotension, vasovagal collapse, and carotid sinus hypersensitivity. This was investigated in **chapter 4.3**. For this, the effect of withdrawal of fall-risk-increasing drugs on tilt-table test outcomes was tested. In our study orthostatic hypotension improved significantly after drug withdrawal. Subgroup analysis of cardiovascular drug withdrawal showed a significant reduction in both orthostatic hypotension and carotid sinus hypersensitivity. These results indicate that derangement of cardiovascular homeostasis may be an important mechanism by which drug use results in fall incidents. **Chapter 4.4** deals with the cost-effectiveness of the intervention. Chapter 4.1-4.3 show that withdrawal of fall-risk-increasing drugs is clinically effective. However, given the continuous pressure on healthcare costs during the last decades, it is important to also address the cost-effectiveness of medical interventions. In our cohort, the intervention, i.e. drug withdrawal, was not only cost-effective; it also generated significant cost savings. Although the effect is likely to decrease over time, cost savings were already generated in the short run. Long-term management of drug withdrawal will require extra efforts, but is also likely to sustain the risk reduction. In the general discussion, **chapter 5**, the main findings of this thesis are discussed and put in a broader perspective. The results indicate that there is room for improvement in the multifactorial approach of older fallers. This appears to be true both for the assessment of cardiovascular abnormalities and for the withdrawal of fall-risk-increasing drugs.

Vallen bij ouderen is een veelvoorkomend en ernstig probleem. Met het vorderen van de leeftijd neemt niet alleen het aantal valincidenten toe, ook de kans op letsel ten gevolge van een val stijgt. Valneiging is geen op zichzelf staande diagnose, maar betreft in feite een symptoom dat veroorzaakt kan worden door meerdere ziekten en aandoeningen. Ondanks het feit dat er inmiddels vele studies zijn uitgevoerd naar mogelijke oorzaken van valincidenten, is er nog een aantal vragen onbeantwoord gebleven. In dit proefschrift richten wij ons op twee groepen van (mogelijke) valrisicofactoren. Enerzijds wordt de relatie tussen bepaalde cardiovasculaire aandoeningen en valincidenten beschreven en anderzijds wordt gekeken naar het effect van afbouwen of staken van medicatie die de kans op vallen zou kunnen verhogen.

Hoofdstuk 1 betreft een algemene introductie over de onderwerpen beschreven in dit proefschrift. **Hoofdstuk 2** behelst een selectie van patiëntenbeschrijvingen over medicatiegerelateerde valincidenten. Naar aanleiding van deze casus besloten wij om een prospectieve studie op te zetten naar dit onderwerp. Bij al deze patiënten werd het vallen toegeschreven aan het gebruik van bepaalde medicijnen. Dit werd ondersteund door het feit dat na het afbouwen van deze medicatie geen valincidenten meer plaatsvonden.

Hoofdstuk 3 richt zich op cardiovasculaire aandoeningen als mogelijke oorzaken voor valincidenten. In **hoofdstuk 3.1** is de associatie tussen echografische afwijkingen van het hart en valincidenten onderzocht in een prospectief cohort van geriatrische poliklinische patiënten. Uit eerder onderzoek is bekend dat bepaalde structurele hartafwijkingen, zoals bijvoorbeeld aortaklepstenose of mitralisklepinsufficiëntie (vernauwing respectievelijk lekkage van bepaalde hartkleppen) en pulmonale hypertensie (verhoogde druk van de longvaten), kan leiden tot wegrakingen. Wij vonden een significante associatie tussen het voorkomen van valincidenten met zowel hartklepinsufficiënties als pulmonale hypertensie. De kans op vallen steeg met toenemende ernst van de afwijking. Er werd geen relatie gevonden tussen aortaklepstenose en valincidenten, wat vermoedelijk verklaard kan worden door het feit dat er vrijwel geen deelnemers waren met een matige of ernstige aortaklepstenose. In **hoofdstuk 3.2** wordt de associatie tussen de linker ventrikelfunctie -gemeten met echocardiografie- en valincidenten beschreven. Het onderzoek werd uitgevoerd binnen de ERGO- (Erasmus Rotterdam Gezondheid en Ouderen) studie. De kans op een ernstige val gedurende follow-up was significant hoger bij een gestoorde linker ventrikelfunctie. **Hoofdstuk 3.3** beschrijft de optimale meetmethode voor orthostatische hypotensie (bloeddrukdaling bij het overeind komen) in relatie tot valincidenten. Binnen het cohort van geriatrische poliklinische patiënten werd onderzocht welk tijdsgemiddelde van een continue vinger bloeddrukmeting (Finometer) de beste associatie tussen vallen en orthostatische hypotensie laat zien. Dit werd eveneens vergeleken met conventionele bloeddrukmetingen. Alleen bij de continue meetmethode werd een significante associatie

tussen valincidenten en orthostatische hypotensie gevonden. De beste associatie werd gezien indien bij deze continue meetmethode de 5-seconden gemiddelden werden gebruikt. Aangezien de oorzaak van vallen veelal multifactorieel bepaald is, bleef de correlatie matig, ongeacht de gebruikte meetmethode.

De studies beschreven in **hoofdstuk 4** betreffen de relatie tussen het gebruik van valrisico verhogende medicatie en valincidenten, inclusief de mogelijke oorzakelijke ketens van medicatiegerelateerde valincidenten. In **hoofdstuk 4.1** wordt de kans op valincidenten na het afbouwen van bepaalde medicijnen bij geriatrische poliklinische patiënten beschreven. In de literatuur zijn meerdere medicijnen geassocieerd met een verhoogd valrisico, maar het is niet eerder aangetoond, met uitzondering van sedativa en antidepressiva, dat afbouwen van deze medicatie leidt tot een afname van het aantal valincidenten. De uitkomsten van deze studie duiden erop dat afbouwen van valrisico verhogende medicijnen, inclusief zowel psychotrope als cardiovasculaire medicijnen, een effectieve interventie is voor het verlagen van het valrisico. Het grootste effect werd behaald door het verminderen van cardiovasculaire medicatie. De effecten van het afbouwen van valrisico verhogende medicatie op de mobiliteitstest uitkomsten worden beschreven in **hoofdstuk 4.2**. Mobiliteitstesten, zoals de Timed Up and Go Test, zijn erkende predictoren voor valincidenten. Valincidenten ten gevolge van het gebruik van bepaalde medicijnen worden waarschijnlijk voornamelijk, of in ieder geval deels veroorzaakt door de gestoorde mobiliteit die deze medicijnen kunnen veroorzaken. Dit werd bevestigd door onze studie waarin naast een afname van het aantal valincidenten de 10-meter looptest en de Timed Up and Go Test significant verbeterden. Andere bijwerkingen die belangrijk zouden kunnen zijn in de oorzakelijke keten van medicatie gerelateerde valincidenten zijn cardiovasculaire aandoeningen, zoals orthostatische hypotensie, vasovagale collaps (flauwvallen) en sinus caroticus overgevoeligheid. Dit is onderzocht in **hoofdstuk 4.3**, waarin het effect van verminderen of staken van medicatie op kanteltafeltest uitkomsten werd getest. In deze studie werd een significante afname aangetoond van orthostatische hypotensie na afbouwen van valrisico verhogende medicatie. Subgroepanalyse van het effect van verminderen of staken van cardiovasculaire medicatie toonde een significante afname van zowel orthostatische hypotensie als sinus caroticus overgevoeligheid. Deze resultaten duiden erop dat verstoring van de cardiovasculaire homeostase een belangrijk mechanisme zou kunnen zijn binnen de oorzakelijke keten van medicatie gerelateerde valincidenten. **Hoofdstuk 4.4** behandelt de kosteneffectiviteit van de interventie. Hoofdstuk 4.1-4.3 laten zien dat de interventie klinisch effectief is. Echter, gezien de continue druk op de kosten van de gezondheidszorg gedurende de afgelopen decennia is het van eminent belang om ook de kosteneffectiviteit van de medische interventies mee te wegen. In ons cohort bleek de interventie niet alleen kosteneffectief, er was eveneens een aanzienlijke besparing van de kosten. Hoewel het effect waarschijnlijk afneemt met de tijd, werden de besparingen al op korte termijn

bereikt. Lange termijn management van medicatievermindering vergt waarschijnlijk extra investeringen, maar zal naar verwachting ook de risicoreductie doen behouden.

In de algemene discussie in **hoofdstuk 5** worden de belangrijkste bevindingen besproken en in een breder perspectief geplaatst. De uitkomsten duiden erop dat er ruimte is voor verbetering van de multifactoriële aanpak van oudere vallers. Dit lijkt het geval te zijn voor zowel het testen op cardiovasculaire afwijkingen als voor het afbouwen van valrisico verhogende medicijnen.

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Curriculum vitae

Nathalie van der Velde werd geboren op 1 oktober 1974 in Kingston, Jamaica. Zij behaalde het VWO diploma aan het Comenius College te Hilversum, waarna zij geneeskunde heeft gestudeerd aan de UvA. Aansluitend aan het behalen van haar artsexamen in 2001 heeft zij nog een extra keuze co-schap Klinische Geriatrie gelopen aan de Harvard Medical School te Boston. Vervolgens heeft zij 2 maanden als ANIOS (arts niet in opleiding tot specialist) gewerkt op de afdeling Klinische Geriatrie van het Slotervaart Ziekenhuis te Amsterdam en aansluitend 4 maanden als ANIOS Interne Geneeskunde in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Sinds 2002 is zij in opleiding tot klinisch geriater aan het Erasmus MC te Rotterdam (opleider Dr. Tischa J.M. van der Cammen). Tevens startte zij in 2002 onder begeleiding van Dr. Tischa J.M. van der Cammen en Prof. dr. Bruno H.Ch. Stricker op de afdeling Klinische Geriatrie van het Erasmus MC met de voorbereidingen van het onderzoek naar medicatie- en cardiovasculair gerelateerd vallen, wat uiteindelijk heeft geleid tot dit proefschrift. In juni 2006 heeft zij haar opleiding tot Master of Science in Clinical Epidemiology aan het NIHES (Netherlands Institute of Health Sciences) afgerond. Naast haar klinische en onderzoeks- werkzaamheden heeft zij ook bestuurswerkzaamheden verricht voor de VAKG (Vereniging voor AIOS Klinische Geriatrie): van 2002 tot 2006 was zij vertegenwoordiger van de VAKG binnen het NVKG-bestuur (Nederlandse Vereniging voor Klinische Geriatrie) en vanaf 2003 tot eind 2006 bekleedde zij de positie van voorzitter van de VAKG.

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