Falling: should one blame the heart?
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CHAPTER

TEN

SUMMARY AND PERSPECTIVE
Falls in older adults form an important health care burden and with the ageing of the population, this burden is only expected to grow, both in number and in volume. Falls rarely have one single cause, and timely recognition and treatment of all (modifiable) risk factors for falls is therefore necessary to prevent new falls or injury. Although many studies have addressed risk factors for falls and recurrent falls, only a limited number of studies have specifically looked at cardiovascular risk factors for falls. Cardiovascular abnormalities, such as arrhythmia or valve abnormalities resulting in decreased cardiac output, can lead to falls when they cause cerebral hypoperfusion resulting in syncope (a transient loss of consciousness characterized by spontaneous recovery). Older adults with syncope frequently present with falls due to amnesia for loss of consciousness. Near-syncope evoking dizziness or unstable gait can also lead to a fall in an older individual with multiple other risk factors for falls. Several cardiovascular risk factors and other causes for syncope in older adults have been recognized, but evidence linking these abnormalities to falls is limited.

**Association of cardiac abnormalities and falls**

To provide an overview of the existing literature addressing cardiovascular risk factors for falls, and to identify potential gaps in the available evidence, a systematic review of the literature was performed. The results of this review are described in **CHAPTER ONE**, and show that in studies that used a control group, the most consistent associations with falls were observed for low blood pressure, heart failure and cardiac arrhythmia. The majority of these studies showed however a positive association with falls after performing multivariable adjustment for potential confounders. For carotid sinus hypersensitivity, vasovagal syncope and post-prandial hypotension, the majority of studies reported a higher prevalence of the exposure in fallers compared to controls, but only few studies with multi-variable adjusted associations were reported. Orthostatic hypotension, coronary artery disease, general cardiovascular disease and hypertension all showed inconsistent associations with falls, with the same number of studies reporting a positive association as the number of studies not reporting an association. Finally, arterial stiffness was identified as an independent predictor for falls in one study, as were several echocardiographic abnormalities. Studies looking at cardiac arrhythmias showed mixed results, due to great heterogeneity in measurement strategies and in definitions of cardiac arrhythmia. Furthermore, structural cardiac abnormalities, such as heart valve abnormalities and heart failure were only studied in a small number of studies, although several positive associations between these abnormalities and falls were found.

Although various observational studies showing a relationship between cardiovascular abnormalities and falls have been published, current fall guidelines have not yet included these risk factors. Furthermore, intervention studies that studied the effectiveness of treatment of cardiovascular abnormalities have been limited to trials looking at treatment of carotid sinus syndrome and orthostatic hypotension, leaving cardiac arrhythmias, heart valve abnormalities, low blood pressure and other cardiovascular abnormalities out of the scope.

The main aim of this thesis was therefore to study associations between cardiac arrhythmias, structural abnormalities and falls, as well as to explore potential mechanisms responsible for these associations. The second aim of this thesis was to study whether adding a comprehensive cardiovascular work-up to the routine fall-assessment is feasible and effective. Furthermore, we aimed to identify which older adults prefer to undergo a falls preventive intervention, to aid in the optimization of fall-preventive care.

In **CHAPTER TWO**, we studied a large sample of the Irish Longitudinal Study on Ageing, to investigate which self-reported, but doctor-diagnosed cardiovascular abnormalities were associated with falls and recurrent falls in older community dwelling adults. Cardiovascular conditions associated with one or more falls in the past year were cardiac arrhythmia, heart murmur, heart failure, angina and a history of myocardial infarction. This study also showed that likelihood of having one of these abnormalities was even greater for individuals with recurrent (two or more) falls in the past year. As the findings of this study were based on self-report, we aimed to validate these findings with objective measurements, such as electrocardiograms (ECGs) and echocardiograms, in different populations and settings. In **CHAPTER THREE**, we therefore performed a case-control study within hospitalized older adults admitted for hip surgery, in which we found that several ECG abnormalities (atrial fibrillation, prolonged QTc-interval and sinus tachycardia) were more prevalent in hip fracture patients, compared to age- and gender matched controls who underwent planned hip surgery. In **CHAPTER FOUR**, we found that in the same population, left ventricular (LV) dysfunction was more prevalent in hip fracture patients compared to controls undergoing planned hip surgery.
As studies within hospitalized populations are limited in generalizability, we aimed to validate these findings in the general population as well. In a large cohort study among community dwelling older adults, we found that ECG-diagnosed atrial fibrillation (AF), was associated with falls, fainted and blackouts in the past year (CHAPTER FIVE). Comparable to the study described in chapter two, the likelihood of having AF grew stronger for individuals with an increasing amount of fall events in the past year. The results of chapters two to five provide additional evidence that links objectively diagnosed cardiac arrhythmia (in particular atrial fibrillation) and ventricular dysfunction to falls and hip-fractures, as well as self-reported heart failure, angina and myocardial infarction.

**Cardiovascular disorders as risk factors for falls**

The abnormalities that were associated with falls in our studies could lead to (recurrent) falls through multiple pathways, for which a framework is presented in **Figure 1**. Firstly, cardiovascular conditions can cause impairment in cardiac output, resulting in cerebral hypoperfusion. Subjects who subsequently experience syncope may present with falls instead, when they suffer from amnesia for loss of consciousness (LOC). Amnesia for LOC following syncope has a reported prevalence of 30% of subjects with vasovagal syncope, up to 70% in subjects with carotid sinus syndrome. Falls in older adults are often not witnessed, making it even more difficult to distinguish between multi-causal falls and falls due to syncope. Furthermore, cerebral hypoperfusion can lead to dizziness without resulting in LOC. In subjects who already suffer from impaired mobility and have other risk factors for falls as well, this dizziness can contribute easily to a fall. AF may result in decreased cardiac output because of increased and/or irregular ventricular rate, and a reduction in the atrial contribution to ventricular filling. Other cardiovascular conditions, such as heart failure, orthostatic hypotension and heart valve abnormalities can also reduce cardiac output, thus causing falls in conjunction with other fall risk increasing factors.

Secondly, cardiovascular abnormalities can also evoke or contribute to falls by affecting conditions that are known to increase risk of falls. Intermittent hypotension has the potential to induce permanent cerebral changes, but cardiovascular conditions such as atrial fibrillation can also cause cerebral damage via thrombo-embolic events, reflected through white matter lesions. These cerebral changes in turn are associated with important fall-risk increasing conditions, such as depression, impaired cognition and impaired mobility and gait. The latter pathway was explored in chapter six and is described below.

The pathways described above may be further strengthened by the models of geriatric syndromes, of which falling is a main one. A geriatric syndrome primarily refers to one symptom or a complex of symptoms, resulting from multiple aetiological factors with multiple interacting pathways. The model of geriatric syndromes is therefore different from the standard medical model of diagnoses, where clinical symptoms and signs usually correspond to one clear pathological disease process. Fried et al. have proposed different diagnostic models for disease presentation of older persons with complex conditions, of which one is the synergistic morbidity model. In this model, multiple (unrelated) conditions amplify their respective symptoms, until a functional threshold is crossed, and a
geriatric syndrome, such as a fall, is manifested. Although not all cardiovascular conditions may directly cause falls, the synergistic effect of cardiovascular conditions (such as AF) and other fall-risk increasing factors (such as urinary incontinence and visual impairment) eventually leads to falls.

**AF and impaired mobility**

Impaired mobility is one of the most important risk factors for falls; common causes of impaired mobility include decreased muscle strength, balance problems and osteoarthritis. In **CHAPTER SIX**, we found that subjects with AF had significantly slower gait speed and mobility tasks (timed up-and-go test) in community dwelling older adults. The association with slower gait speed was evident from age 70 years and onwards and became more pronounced with increasing age.

Exercise capacity may be diminished in subjects with AF, due to a loss of the atrial kick during heart rate acceleration. This reduction in exercise capacity could directly affect walking speed and mobility, explaining the association between AF and slower walking speed. However, AF could also impair walking and mobility on a central nervous system level. Both walking and mobility are regulated in the motor cortices of the brain, which are affected by vascular pathology. AF can accelerate or cause vascular cerebral pathology in the brain through different mechanisms. AF is linked to the development of white matter lesions (WMLs) 9,10, which in turn have been shown to be a risk factor for gait impairment and falls. Furthermore, AF has been linked to impaired cognition and depression, both important risk factors for falls. AF may also lead to vascular pathology in the brain by a reduction in cardiac output, causing cerebral hypoperfusion and subsequent degenerative changes. This theory is strengthened by the fact that impaired cerebral blood flow regulation is associated with slow gait speed 11. Secondly, hypertension is a common risk factor for both WMLs and AF, and AF could thus be a mediator in this association. Finally, AF can lead to the formation of left atrial thrombi that can in turn lead to occlusion of small or large brain arteries, resulting in micro-infarction (including white matter) or stroke 12. A recent study identified a novel phenotype of older adults with poor executive function, slow gait speed and depressive symptoms 11, and both hypertension and congestive heart failure were independently associated with having this phenotype. This strengthens the theory that cardiovascular abnormalities could lead to falls through cerebral pathology by affecting fall-risk increasing conditions.

**AF and impaired blood pressure recovery**

So far, orthostatic hypotension (OH) has been the most extensively described cardiovascular risk factor for falls 1, as it can reduce cerebral perfusion upon standing, causing dizziness and subsequent falls. However, OH has a high prevalence in the older population, and an important trigger to examine the presence of OH is the report of symptoms of cerebral hypoperfusion upon standing. From current literature it is unclear whether the finding of OH is clinically relevant when symptoms of OH are absent, and the question arises whether the same holds for the cardiac abnormalities that were associated with falls, syncope and hip fractures in this thesis. Most of the cardiovascular abnormalities that we found (atrial fibrillation, decreased left ventricular function, heart failure, history of myocardial infarction) have not been reported as causes of syncope 13, unless they evidently lead to impairment in cardiac output with subsequent symptoms of cerebral hypoperfusion.

Postural changes may reduce cerebral oxygenation in older subjects without causing typical symptoms of reduced cerebral blood flow 15,16. When these postural changes lead to hypoperfusion of the prefrontal cortex, this could lead to impairments in executive function, such as gait and mobility, without subjects reporting typical symptoms of OH. This suggests that the chronic effects of cardiovascular abnormalities on cerebral perfusion may be subtle, causing degenerative cerebral changes without evident symptoms in time. AF has been reported a risk factor in the development of dementia 17. Repeated episodes of hypotension due to AF may contribute to this association, as an emerging body of evidence supports the association between OH and cognition as well 16,19.

Presence of multiple cardiovascular risk factors for falls could also interact, thus magnifying their effects. Hypertension is a risk factor for OH, and symptoms of OH can be further triggered by the use of antihypertensive medication. Cardiac arrhythmia, reducing cardiac output, could further aggravate drop in blood pressure upon standing and delay blood pressure recovery. This hypothesis was confirmed in a study reported in **CHAPTER SEVEN**. Subjects with AF showed a greater drop in diastolic BP upon active stand and had more sustained OH from baseline compared to those without AF, indicating that recovery to baseline blood pressure was delayed. These orthostatic changes were most pronounced at 40 and 50 seconds after active stand, and associations were strongest in the younger age group (50-64 years) within this cohort. One study has described this association before, in which OH was identified as a risk
factor for developing AF, rather than vice versa. Regardless of the direction of the association however, the link between AF and OH could further explain the association between AF and falls.

The role of the heart in optimizing interventions for falls
The associations demonstrated between cardiovascular abnormalities and falls in this thesis show that clinically relevant cardiovascular abnormalities are frequently present in older fallers. The designs of these studies were all cross-sectional, and further longitudinal studies need to be performed to conform these abnormalities as risk factors or causal factors for (recurrent) falls as well. Furthermore, there is a need of randomized clinical trials that study the effectiveness of a cardiovascular evaluation and subsequent treatment in older fallers. The identification of these abnormalities as causes or risk factors for falls has clinical implications, as it warrants awareness of these abnormalities in fall preventive care, and potentially treatment of these abnormalities to reduce fall risk. Abnormalities that clinicians should be aware of comprise at least: atrial fibrillation and other cardiac arrhythmias, impaired LV function (with or without associated heart failure), heart valve abnormalities, history of myocardial infarction, carotid sinus syndrome and orthostatic hypotension. Furthermore, awareness of OH in subjects with AF and vice versa is warranted. A simple diagnostic tool to detect AF and some structural cardiac abnormalities is the electrocardiogram, and when structural cardiac abnormalities are suspected, an echocardiogram. For detection of orthostatic hypotension and carotid sinus syndrome continuous blood pressure measurement is recommended. In current clinical practice OH is usually measured with conventional sphygmomanometers, but as the most important dip in BP upon standing appears to be around 40 seconds, OH may be easily underestimated in clinical practice. This is further highlighted in a study in which sphygmomanometer measured OH did not correlate with falls, whereas continuously measured OH was associated with falls in the same cohort during the same episode. Furthermore, continuous BP measurement provides the benefit of giving direct biofeedback about BP changes to patients and showing the positive results of counter maneuvers when OH is diagnosed.

Treatment of cardiac abnormalities and the effect on fall incidence
As recognition of cardiovascular abnormalities as a risk factor for falls immediately leads to the question whether treatment of these abnormalities results in a reduction of falls, we studied in Chapter Eight whether it was feasible and effective to add a cardiovascular evaluation and intervention to the routine fall clinic assessment. The result of this study shows that almost half of fallers that underwent additional cardiovascular testing, were diagnosed with a cardiovascular abnormality that could be considered a new and contributing factor to their fall incident. The most important abnormality was orthostatic hypotension, for which several treatment options exist. Adding the work-up to routine care was challenging, but feasible. The study lacked a control group to observe whether treatment of these abnormalities influenced fall incidence, but the results nevertheless show that a cardiovascular evaluation leads to recognition of important cardiovascular abnormalities that would potentially be overlooked in regular fall preventive care.

Current practice guidelines for falls prevention recommend assessment of postural hypotension and of cardiac rhythm and rate, and treatment recommendations are limited to cardiac pacing for cardio-inhibitory carotid sinus syndrome and treatment of postural hypotension. The results of this thesis show that several other cardiovascular abnormalities are associated with falls, and if further prospective studies might confirm these abnormalities as modifiable risk factors for falls, this may give rise to several other treatment options. Appropriate treatment would depend on the nature of the abnormality, but the main aim of treatment would be to optimize cardiac output, thus diminishing the short- and long-term consequences of cerebral hypoperfusion. For arrhythmia, in particular AF, this treatment could consist of adequate rhythm control. Current treatment of AF mainly aims at prevention of thrombo-embolic events by starting anti-coagulant therapy, and acute improvement of cardiac function (AF guideline). Restoration of sinus rhythm is only pursued in those with severe symptoms, as rhythm control has not shown improved survival over rate control. Furthermore, rhythm control is less successful when AF is longstanding; therefore older subjects, with few AF related symptoms, will often receive rate control, especially when rhythm control fails. However, our studies have shown that AF is associated with falls, syncope and impaired mobility; all of which could be regarded as ‘non-cardiovascular’ outcomes of AF. Longstanding AF may have already impaired cardiac output and exercise capacity, hereby accelerating vascular pathology in the brain. This is supported by the fact that the association between AF and impaired gait and mobility was more pronounced with increasing age.
It has been shown that long-term maintenance of sinus rhythm leads to improved LV function \(^2\) as well as better health related quality of life, in particular physical functioning and vitality, and exercise capacity \(^23,24\). However, as rhythm restoration is often unsuccessful with progression of AF, the majority of older patients still receive rate control \(^12\). This would plead for early recognition of AF with subsequent restoration of sinus rhythm, potentially even in a screening setting. Nevertheless, although LV function improves with maintaining sinus rhythm after restoration; LV function does not deteriorate under adequate rate control \(^22\). However, rate control is often established with beta-blockers, calcium-channel blockers and digoxin, all of which have been reported as fall risk increasing drugs (FRIDs). Over-strict rate control might therefore unintentionally lead to an actual increase in fall risk. Moreover, an increasing body of evidence shows that strict rate control (<80 bpm) shows no benefit over lenient rate control (<110 bpm) in terms of cardiovascular morbidity, mortality, symptoms and quality of life \(^25,26\). This is promising for the treatment of AF with respect to fall- and syncope risk, as reduction of the amount of cardiovascular drugs could subsequently reduce fall risk.

Treatment of severe ventricular dysfunction could consist of cardiac resynchronization therapy; however, in current clinical practice this therapy is only reserved for individuals with poor ejection fraction (≤ 35%), which does not improve under pharmacologic treatment. Pharmacologic treatment of heart failure with reduced ejection fraction consists of beta-blockers and ace inhibitors, both of which are known to increase fall risk. Pharmacological treatment of heart failure and other cardiovascular abnormalities therefore poses a clinical dilemma that can only be tackled by applying tailor made care and careful monitoring of the patient.

**Interventions to reduce falls**

As multifactorial fall preventive interventions have shown inconsistent effectiveness in recent studies, the question arises whether adherence to fall preventive intervention could be improved. In \(\text{CHAPTER NINE}\) we therefore explored which patient-characteristics determine whether older adults prioritize for falling in a multifactorial treatment plan, when several geriatric problems are diagnosed. It was found that only ten percent of older adults at risk of falls acknowledged this risk, and prefer to prioritize for it in a preventive intervention to reduce functional decline. Severe fear of falling, recurrent falls and use of a mobility aid were associated with this prioritization for falls prevention. The identification of these characteristics could aid in the recognition of patients that will benefit most from preventive interventions, thus optimizing fall preventive care. Several studies in this thesis have shown that cardiovascular abnormalities were associated with a single fall in the past year; however, multiple abnormalities were even stronger (or only) associated with recurrent falls. Hip fracture patients form the most vulnerable category of fallers, as they are usually older and have several comorbidities. This may indicate that further cardiovascular evaluation and subsequent treatment should be reserved for those with recurrent or injurious falls. However, one of the proposed mechanisms through which cardiovascular abnormalities could contribute to falls is that of cerebral hypoperfusion resulting in permanent cerebral damage, affecting executive functions such as gait and cognition. If this mechanism is indeed responsible, timely identification of cardiovascular abnormalities and optimization of cardiac output and thus cerebral blood flow is warranted to prevent further damage. This would plead against only selecting patients with injurious or recurrent falls for further evaluation and treatment, as preventive strategies may be too late in this group. However, too early identification and treatment of fall risk may not be effective, as adherence to the intervention could be low in subjects who have had no or single falls, due to a lack of motivation. This subject is still debated on and requires further research.
Future perspectives and research opportunities

This thesis shows that several cardiovascular abnormalities are associated with falls in older adults, giving rise to the question whether these abnormalities cause falls, and whether recognition and treatment of these abnormalities will reduce fall risk. Most of the studies describing associations between cardiovascular abnormalities and falls have a cross-sectional design assessing falls retrospectively, or only were prospective with only short follow-up time. Therefore, more longitudinal studies are needed to determine which cardiovascular abnormalities can be considered actual risk factors or causes for future falls. As the association between cardiovascular abnormalities and falls is potentially also caused by more long-term progressive decline in mobility and gait, prospective studies should at least include a couple of years of follow-up.

Secondly, it is needed to determine whether an intervention consisting of cardiovascular evaluation and intervention would prevent falls through a randomized controlled clinical trial, in which controls will undergo care as usual. A particular study could be carried out in older persons presenting with one or more falls to study the effect of such an intervention on recurrent falls. Another potential design would be to include older adults without falls, to study whether intensive vascular care will lead to the prevention of falls in a primary care setting. Cost-effectiveness should be included in these trials as well, as demonstration of cost-effectiveness for such an intervention would make it easier to implement such strategies into current healthcare. Furthermore, increasing awareness of fall risk among older adults is necessary, as only a small percentage of older adults at risk of falls recognizes this risk and prefers to undergo a preventive intervention for falls.

CONCLUSION

The results of this thesis show that several cardiovascular abnormalities are associated with falls in older adults, in particular atrial fibrillation, LV dysfunction, heart failure and low blood pressure. Atrial fibrillation is associated with two important fall-related outcomes, providing additional pathways to support the framework in which cardiovascular abnormalities could lead to falls. These results fill a gap in current literature addressing cardiovascular risk factors for falls. Extending current fall preventive care with a cardiovascular evaluation and intervention is feasible, but more longitudinal studies and randomized controlled trials investigating the effect of such an intervention on falls incidence are needed.
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