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Review Article

The Association of Cardiovascular Disorders and Falls: A Systematic Review

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A B S T R A C T

Objective: Cardiovascular disorders are recognized as risk factors for falls in older adults. The aim of this systematic review was to identify cardiovascular disorders that are associated with falls, thus providing angles for optimization of fall-preventive care.
Design: Systematic review.
Data Sources: Medline and Embase. Eligibility criteria for selecting studies: studies addressing persons aged 50 years and older that described cardiovascular risk factors for falls. Key search terms for cardiovascular abnormalities included all synonyms for the following groups: structural cardiac abnormalities, cardiac arrhythmia, blood pressure abnormalities, carotid sinus hypersensitivity (CSH), orthostatic hypotension (OH), vasovagal syncope (VVS), postprandial hypotension (PPH), arterial stiffness, heart failure, and cardiovascular disease. Quality of studies was assed using the Newcastle-Ottawa Scale.
Results: Eighty-six studies were included. Of studies that used a control group, most consistent associations with falls were observed for low blood pressure (BP) (4/5 studies showing a positive association), heart failure (4/5), and cardiac arrhythmia (4/6). Higher prevalences of CSH (4/6), VVS (2/2), and PPH (3/4) were reported in fallers compared with controls in most studies, but most of these studies failed to show clear association measures. Coronary artery disease (6/10), orthostatic hypotension (9/25), general cardiovascular disease (4/9), and hypertension (7/25) all showed inconsistent associations with falls. Arterial stiffness was identified as an independent predictor for falls in one study, as were several echocardiographic abnormalities.
Conclusion: Several cardiovascular associations with falls were identified, including low BP, heart failure, and arrhythmia. These results provide several angles for optimizing fall-preventive care, but further work on standard definitions, as well as the exact contribution of individual risk factors on fall incidence is now important to find potential areas for preventive interventions.

Falls are the leading cause of injury in older people.[1,2] Approximately 1 in 3 people older than 65 will suffer a fall each year, with injuries occurring in at least 1 in 5 of these.[3] As the world's aging population increases, health care costs associated with falls are set to rise over the next 30 years.[4] As it is estimated that up to 40% of falls may be preventable, evidence for causative, treatable factors is essential.[5]

Cardiovascular disorders are among the several risk factors that have been identified to cause falls; in particular, unexplained falls (defined as those for which no attributable mechanical cause such as a trip or slip can be found) and recurrent falls.[6] Syncope secondary to underlying cardiovascular disease (CVD) is more common in older adults and may lead to injurious falls.[7]

As there is considerable overlap between the symptoms of falls and syncope in older adults, there is likely an underestimation for the role of cardiovascular abnormalities in fall risk.[8] Orthostatic hypotension (OH), carotid sinus hypersensitivity, vasovagal syncope (VVS), and

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cardiac arrhythmias are the main cardiovascular disorders that can cause syncope in older adults, but evidence linking these abnormalities to falls included in current falls guidelines is scarce.

Up to now, 1 systematic review has been published that addressed cardiovascular causes of falls.[9] However, no quality assessment of included articles was performed in this review, and a first selection of articles was based on titles alone, potentially causing certain articles to have been overlooked. Two recent reviews have studied the association between OH and falls, but these studies did not assess other potential cardiovascular causes of falls.[10,11] Furthermore, as the subject has gained attention in the past 5 years, there is a need to update earlier reports. The aim of this review was to identify cardiovascular risk factors for falls systematically and to thereby provide a broad overview of the available literature.

Methods

A systematic search was conducted to include all articles that addressed the question of possible cardiovascular contributions to falls in adults older than 50 years. Our review methodology and reporting followed standard guidance.[12]

Search Strategy

In collaboration with a clinical librarian (JD), a systematic search was conducted in PubMed and Embase for articles published until the date of the search (March 30, 2015). A customized search strategy was conducted for each database. A manual search of references in the selected articles was also conducted to identify additional studies. Key search terms were "falls," "aged," and "cardiovascular." Full details of the search strategy are available as supplementary data, Appendix 1, as well as the actual search strategy used: supplementary data, Appendix 2.

Two reviewers (SJ and JB) first independently screened titles and abstracts for inclusion and then read the full text of the eligible articles found during this first selection. In case of differences between the 2 reviewers, a third independent reviewer was consulted (NV).

Inclusion/Exclusion Criteria

Studies were included if they were published as a primary research paper in a peer-reviewed journal, included persons 50 years or older, defined falls as an outcome measure, and included diagnosis or assessment of cardiovascular abnormalities.

Search terms for cardiovascular abnormalities included all synonyms and differentiations for structural cardiac abnormalities (impaired ventricular function, heart valve abnormalities), cardiac arrhythmia (CA), blood pressure (BP) abnormalities (systolic BP [SBP] and diastolic BP [DBP]), carotid sinus hypersensitivity (CSH), OH, postprandial hypotension (PPH), arterial stiffness (AS), heart failure (HF), angina, myocardial infarction (MI), and general cardiovascular or circulatory disease (CVD). Cardiovascular assessments included electrocardiogram (ECG), Holter monitoring (HM), prospective external event recorders, external loop recorders (ELR), implantable loop recorders (ILR), remote telemetry, echocardiogram, carotid sinus massage (CSM), assessment of OH or impaired BP recovery on active stand, head-up tilt table testing (HUT), electrophysiological studies, exercise stress testing, and/or cardiac catheterization. Articles using self-report of doctor-diagnosed cardiovascular abnormalities or disease were included also, but only for the following conditions: hypertension (HTN), general CVD, angina, arrhythmia, and HF. We also included studies in institutions, nursing homes, hospitals, or other non–community-dwelling settings, which were performed on cognitively intact participants. Hospital-based studies were included only if falls had occurred before admission.

Articles were excluded if the sample comprised a specific disease-defined population (such as Parkinson disease, diabetes, or individuals with significant cognitive impairment); if they were intervention studies; if they were reviews, case reports, or conference abstracts; and if they were not written in English. If 2 or more articles had included the same populations for the same exposure, only 1 was included. For the latter, priority was given to studies that used a control group or larger sample size.

Data Extraction and Quality Assessment

Data were collected on study design, setting, type of and method of cardiovascular assessment, and definition of cardiovascular abnormality. Demographic data, clinical characteristics, number of falls, and method and interval for reporting of falls were also collected. If applicable, data on the association between cardiovascular abnormalities and falls were collected. To appropriately describe reported associations, a breakdown into categories was made: ++ denoted association multivariably adjusted for potential confounders, + denoted univariable association or higher prevalence compared with the control group, and − denoted an absent association or similar prevalence.

To reduce the risk of reporting bias, all cardiovascular exposures that were evaluated were extracted from individual studies, even if they were not part of the main outcome variables. Cardiovascular exposures that were not included in a multivariable model because they were not associated with falls in the univariable model were considered to not be associated with falls.

Quality of included studies was assessed by the same reviewers (SJ, JB). Because of the variety of nonrandomized study designs included, the Newcastle-Ottawa Scale (NOS) was used to evaluate risk of bias in the case-controlled and cohort studies.[13] A detailed description of the quality assessment can be found in Appendix 3. A score of 0 to 3 was considered low quality, 4 to 6 of intermediate quality, and 7 or above was considered high quality. No studies were excluded based on their grading of quality, but quality grades were used in the critical review of the results.

Data Synthesis and Analysis

As included studies were heterogeneous in design and assessment methods, a descriptive approach was used to summarize study characteristics and outcomes. Studies that were included were categorized per exposure. No statistical pooling was conducted.

Results

Search Results

After removing duplicates, the initial combined search retrieved 5420 journal articles. Of these, 194 full texts were assessed for eligibility, of which 86 were included in this systematic review (Figure 1).

Characteristics of the Studies

Table 1 shows the characteristics of included studies. Forty-eight studies were cohort studies, 13 were case-control studies, and 25 were observational series. Numbers of study participants in each study varied from 13 to 135,433. Mean age varied from 50 to 88 years.

Of included studies, 39 were conducted in the community, 9 in long-term care facilities, 1 in both community and long-term care, 24 in outpatient clinics (20 in specialized falls and syncope clinics), 8 in emergency departments, and 5 in acute hospital settings.

Fifty-one studies used any falls as an outcome measure, 8 used recurrent falls, 8 used unexplained falls, 12 studies used falls and/or

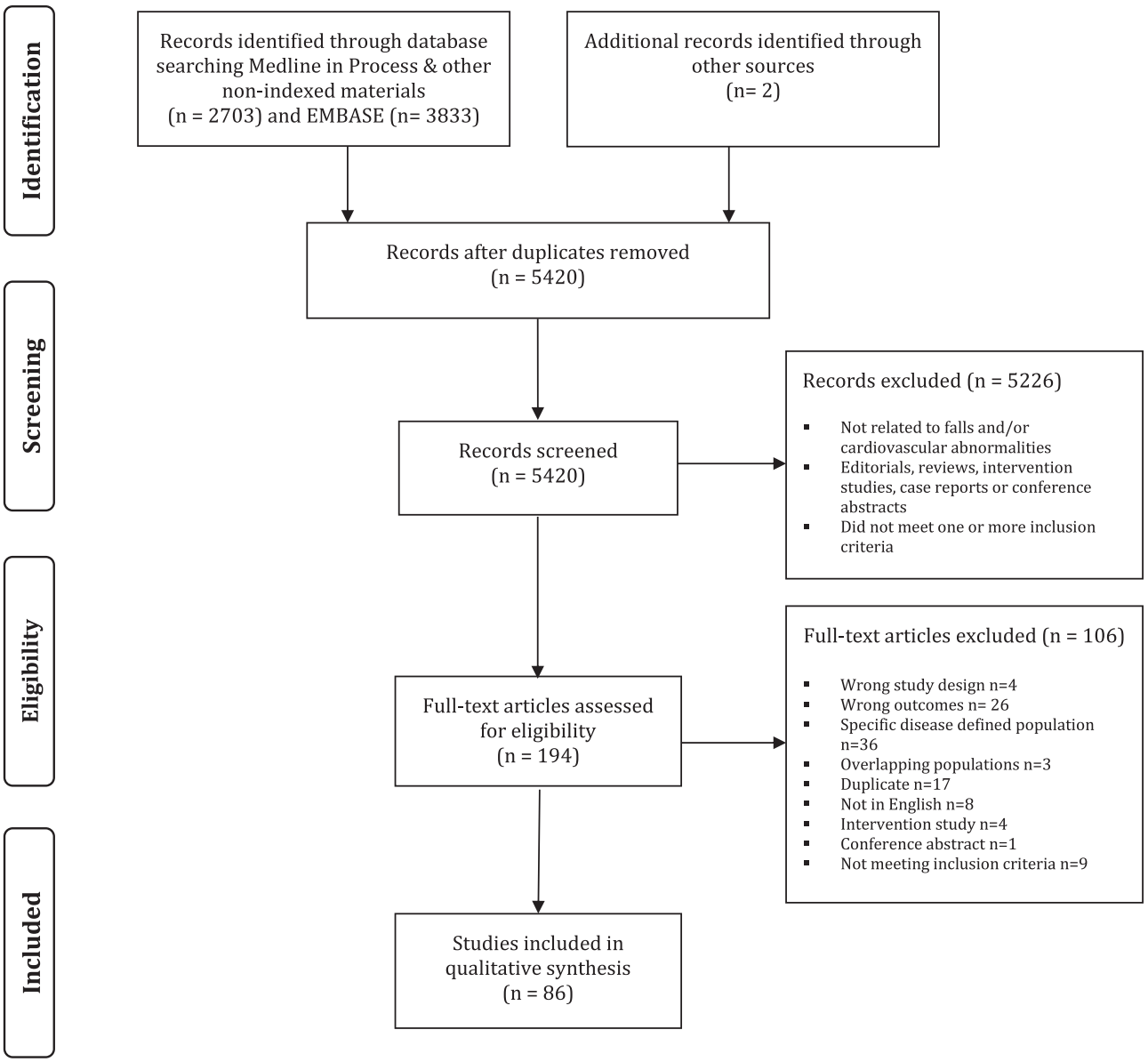

Fig. 1. Flow diagram of study screening and inclusion.

syncope as an outcome, and 2 studies used unexplained falls described as "drop attacks."

Eleven types of cardiovascular abnormalities (exposures) were identified with 39 studies assessing more than 1 risk factor. OH as a risk factor for falls was examined in (36), followed by HTN (27), CSH (21), general CVD (9), angina and MI (grouped as coronary artery disease [CAD]) (14), arrhythmia (12), VVS (10), HF (6), low BP (5), PPH (4), and structural cardiac abnormalities (3).

Tables 2–11 show results of includes studies, categorized per cardiovascular risk factor and type of study.

Orthostatic Hypotension

OH (Table 2) was studied as an exposure in 36 studies, 23 of which were designed as cohort studies and 2 as case-control studies. Six studies reported a positive multivariably adjusted association with falls; 3 studies reported a higher prevalence of OH in fallers. Eleven observational design studies reported a prevalence of between 5% and 56% of fallers.

OH was defined as a drop of greater than 20 mm Hg SBP and/or greater than or equal to 10 mm Hg DBP drop in 20 studies, greater than 20 mm Hg SBP drop in 12 studies, and 4 studies did not report a value. Fifteen studies used intermittent BP measurements, 12 studies used continuous measurement with photoplethysmography, 2 studies used both methods, and 7 studies did not specify their study instrument. Seven studies were scored as high quality with the remainder (29) scoring low and intermediate on the NOS scale.

Carotid Sinus Hypersensitivity

Twenty-one studies investigated CSH (Table 3) as an exposure. Five were designed as case-control studies, 1 reported a positive association between neurally mediated syncope and unexplained falls compared with accidental falls, and 3 reported a higher prevalence of CSH in fallers compared with controls. Fifteen observational series were performed that reported a prevalence of between 8% and 73%.

Eighteen studies performed both supine and upright (70°) CSM; 2 were supine only. All studies defined CSH as asystole greater than 3 seconds on ECG or a vasodepressor drop of 50 mm Hg in SBP. Five studies used symptom reproduction during CSM to differentiate carotid sinus syndrome from CSH. All studies had a low to intermediate NOS quality level.

Vasovagal Syncope

Ten studies investigated VVS (Table 4) as an exposure for falls; 2 used a case-control design, both of which reported that VVS was more common in fallers. Eight observational series reported a prevalence of VVS between 3% and 46%. All studies had used an HUT test as the measurement method. All were graded as low to intermediate on the NOS quality score.

Hypertension

Twenty-seven studies assessed HTN (Table 5) as an exposure for falls; 22 were designed as cohort studies, 3 as case controls. Of the 25 studies with a control group, 5 reported a positive multivariably adjusted association between HTN and falls and 2 reported a higher prevalence of HTN among fallers compared with controls. Two studies reported a negative association between HTN and falls.

The 2 observational series reported a prevalence of HTN among fallers of between 34% and 73%. Nine studies used only self-report of HTN, 5 used medical charts only, 6 studies used an objective measurement of BP and/or use of antihypertensive to diagnose HTN, 5 used a combination of self-report and medical charts, 1 used both objective and self-reporting methods, and 1 study did not report the measurement method. Of studies that used an objective measurement, different cutoffs for HTN were used, ranging from higher than 130/80 mm Hg to higher than 160/95 mm Hg. Only 2 studies were considered high quality on the NOS scale, neither of which showed a positive association between HTN and falls.

Low BP

Five studies looked at low BP (Table 6) as an exposure in cohort studies. Four showed a positive, multivariably adjusted association between low BP and falls; 1 did not. Prevalence of hypotension among fallers varied, from 7% to 74%.

All studies used an objective measurement of BP, but various thresholds for diagnosing hypotension were used, ranging from 100 mm Hg to 142 mm Hg for SBP, and from 60 mm Hg to 80 mm Hg for DBP. The 1 study that did not show an association also used the lowest BP cutoff (SBP/DBP $\leq$100/60). Four of 5 studies were rated high quality on the NOS scale.

Coronary Artery Disease

Fourteen studies assessed the association between MI or angina (grouped as coronary artery disease [CAD]) and falls (Table 7). Ten studies used a control group, of which 5 reported a positive multivariably adjusted association between CAD and falls and 4 reported no association. The 4 observational series reported a prevalence of 0.9% for acute MI, to 76% for ischemic heart disease (IHD).

Six studies used self-reported history of MI or angina, 4 used medical chart history of MI or angina, 3 used a combination of medical records and self-report, and 1 used a clinical definition to define MI (myocardial infarct evidenced by chest pain and/or serial ECGs). All cohort studies scored intermediate or high on the NOS scale, whereas the observational series scored low to intermediate on the NOS scale.

General CVD

Nine studies looked at general CVD (Table 8) without breakdown into specific CVDs. Seven used a cohort design; 1 was a case-control study. Two of these 9 studies showed a multivariably adjusted association between CVD and falls, 2 studies showed a higher prevalence of CVD among fallers, and 4 studies did not show an association. The 1 observational study reported a prevalence of CVD of 52%. Four used self-report of CVD, 3 used medical records, and 2 used both methods. All studies were graded as low to intermediate on the NOS scale.

Postprandial Hypotension

Four papers studied PPH (Table 9) as an exposure for falls: 2 cohort and 2 case-control studies. One reported a positive, multivariably associated association between PPH and falls and 1 reported no association. The case control studies both reported a higher prevalence of PPH in fallers compared with controls. PPH was defined and measured in different ways in all studies. All studies were rated as low to moderate on the quality rating scale.

Cardiac Arrhythmia

Twelve studies studied CA (Table 10) as an exposure; 3 were designed as cohort studies, 3 were case-control studies. Of these 6 studies, 4 reported a positive, multivariably adjusted association between arrhythmia and falls, of which 3 were studies on atrial fibrillation (AF).

Six observational design studies reported a prevalence of between less than 1% and 27%. There were a variety of measurements performed: ILR (for extended arrhythmia monitoring beyond 30 days) in 1 study, ELR (for arrhythmia monitoring up to 30 days) in 1 study, HM (for arrhythmia monitoring up to 24 hours), 12-lead ECG, cardiac telemetry (in-patient arrhythmia monitoring), and medical chart review. This resulted in a variety of definitions used for CA. Two studies were graded as high quality on the NOS scale, whereas the remainder were of low or intermediate quality.

Heart Failure

Six studies looked at HF (Table 11) as an exposure; 5 cohort studies, with 4 reporting a positive, multivariably adjusted association between congestive HF and falls. One study used the New York Heart Association Classification for HF and 1 study used the National Health Service–Read coding for classification. All studies that reported an association measure were of intermediate or high quality.

Structural Abnormalities

Three studies looked at exposures that could not be categorized under other exposures (Table 12).

Wong et al[14] studied AS in a prospective cohort, and found that the top quintile of pulse wave velocity (indicating AS) was an independent predictor of future falls.

Schoon et al[15] studied head-turning–induced hypotension in a case-control study in a falls and syncope clinic. Prevalence of a drop in SBP following these movements was high, but not different between cases and controls.

Van der Velde et al[16] assessed the association between echocardiographic abnormalities and future falls. Several heart valve abnormalities were independent predictors of future falls: mitral, tricuspid, and pulmonary valve regurgitation and pulmonary hypertension.

Discussion

Main Results

A systematic review of the literature shows strong associations between cardiovascular disorders and falls. Of studies that used a control group, the most consistent associations with falls were observed for low BP (4/5), HF (4/5), and CA (4/6), as most of these studies showed a positive association with falls after performing multivariable adjustment for potential confounders. For CSH (4/6), VVS (2/2), and PPH (3/4), most studies reported a higher prevalence of the exposure in fallers compared with controls, but only a few multivariable adjusted associations were reported. CAD (6/10), OH (9/25), general CVD (4/9), and HTN (7/25) all showed inconsistent associations with falls, with a similar or smaller number of studies reporting positive associations as studies reporting no associations with falls. HTN even showed a protective effect on falls in 2 of 25 studies. Finally, AS was identified as an independent predictor for falls in 1 study, as were several echocardiographic abnormalities.

Although OH, carotid sinus syndrome, and VVS are most frequently cited as important cardiovascular causes of falls, the evidence on the association between these BP syndromes and falls was inconsistent, mainly due to a lack in adequate control groups and reporting of association measures that were adjusted for potential confounders. Surprisingly, more consistent positive associations were found for low BP, HF, and CA. A range of studies examining the association of BP and falls was evaluated. Although these studies differed significantly in their methods, certain trends were apparent.

Low BP showed a consistent association with falls. It has been hypothesized that transient reduction in cerebral perfusion pressure may not only lead to immediate effects of cerebral hypoperfusion (eg, syncope or falls during exertion or postural changes), but may also lead to chronic damage to the areas of the brain that govern balance and gait[17] through neurodegeneration. In addition to an association with falls, low BP has been associated with stroke and cognitive impairment.[18–20] Conversely, hypertension was associated with falls after adjustment for confounders in only a small number of studies reviewed, and HTN even showed a protective effect on fall incidence in 2 studies. It has been reported previously that BP behavior is not uniform throughout all age groups and may demonstrate a U-shaped curve, especially with regard to its effect on the incidence of stroke and mortality.[21,22] Adults in the oldest age categories have not been shown to benefit from aggressive lowering of their BP and in fact may be harmed by low BP.[22] However, whether low BP, or conditions causing low BP can been seen as causative or contributory factors to falls remains unclear. A consistent association with falls was also seen for HF (4/5). HF can lead to a reduction in cardiac output in demanding situations such as exertion and postural changes, which may explain this finding, and strengthens the finding of the association between low BP and falls. Further work on the effects of transient changes in BP is needed to delineate thresholds by which older adults are more prone to falling and elucidate treatment strategies for this.

Most studies on arrhythmia and falls showed a positive association. Both length of monitoring time and the definition used for CA had a large influence on the reported associations. Those studies that used a monitoring time longer than 24 hours showed a positive correlation with CA and falls. Studies that focused on finding a causative arrhythmia detected a prevalence of between 15% and 46%; however, these were in predominantly observational series, limiting the applicability of this finding. Interestingly, the 3 studies that exclusively defined AF as an arrhythmia reported a positive association with falls. As these were done in cross-sectional studies, causation could not be ascribed. Cardiac arrhythmias are a potentially treatable cause of falls and this review highlights the inconsistencies with which they are reported on, limiting the ability to make a definitive statement of the contribution of CA to falls risk.

Although OH is a commonly accepted cardiovascular cause of falls in older persons, only a minority of studies reported a positive association with falls. However, quality of included studies varied and several assessment methods to detect OH were used. We included studies that used intermittent methods of BP detection as well as continuous methods, neither of which showed a consistent association with falls. Finucane et al[23] recently reported new normative data for definitions of OH, using noninvasive, beat-to-beat BP measurements. Although they reported that initial OH (within 15 seconds) occurred in up to a third of the population, impaired BP stabilization at 40 seconds was present in 16% of individuals and "classical" OH at or after 1 minute of standing was present in a much smaller number of individuals (7%). Most studies included in this review assessed OH at 1 minute of standing or beyond, potentially explaining why only a minority of studies found a positive association between OH and falls. In addition, only a small number of studies included symptom correlation for diagnosing OH or did not specifically report these results, leaving a gap regarding the value of symptom correlation in diagnosing OH. It does appear that OH does not follow a uniform distribution in the population, and intermittent measurements (such as those with a standard sphygmomanometer) may underestimate the true prevalence of OH and its clinical importance. With the rise of the use of continuous measurement of OH, more complete research can be performed to determine the full association between OH and falls.

CVD, which comprised angina, IHD, and arterial disease, showed a positive association with falls in a few studies, as did AS. However, CVD represents a diverse group of disorders, rendering it difficult to establish individual mechanisms that may contribute to falls risk. Potential interacting mechanisms include direct damage to affected end organs, such as the heart or brain or downstream impacts on physiological homoeostasis. Macro- or microvascular arterial disease may impair muscle capacity and motor and sensory nervous function with deleterious effects on gait. Frailty syndromes also have been shown to have a higher prevalence in CVDs, contributing to increased falls risk.[24] Last, treatments used for cardiovascular disorders have been linked to increases in falls both through direct effects of drugs on the cardiovascular system as well as polypharmacy.[25] There is evidence that withdrawal of cardiovascular drugs may reduce falls rates in practice,[26] potentially through an improvement in postural BP changes.[27] Although the exact mechanisms remain difficult to elucidate, this review has shown that clinicians should regard those patients with a diagnosis of CVD at a higher risk of falls.

There is a lack of evidence regarding interventions to reduce falls risk by treating cardiovascular disorders alone. Up to now, only OH and CSH (which are commonly classified as syncope syndromes[28]) have been included in intervention trials, which have shown benefit in preventing recurrent syncope and falls. Multifactorial interventions that include recognition and treatment of OH have been shown to be effective in reducing falls.[6] Furthermore, a recent Cochrane review on interventions aimed at reduction of falls rates has identified only dual-chamber pacemaker insertion as having a proven benefit for reduction of falls in those patients with carotid sinus syndrome (CSS).[29] This review demonstrates a strong overlap between cardiovascular conditions that commonly lead to syncope and those that lead to falls. It thus enhances previous guideline conclusions that have aimed to incorporate the potential impact that cardiovascular abnormalities were thought to have on falls.[6]

The European Society of Cardiology has stated the need to consider syncope as the cause of a fall in those with unexplained falls.[28] Syncope mistaken for falls presents a difficult clinical challenge, as up to 50% of older persons suffer from retrograde amnesia after VVS, and eyewitnesses are often absent.[30] This may in part have accounted for the large variation in prevalence rates of VVS reported. Carotid sinus

hypersensitivity is a condition that is also considered a form of reflex syncope.[28] Prevalence rates of between 10% and 40% were consistently reported in fallers with 2 notable outliers. In addition, studies conducted in patients with unexplained and recurrent falls were able to attribute CSH as the cause of these falls. As dual-chamber pacemaker insertion has been found to be beneficial for treating cardio-inhibitory CSS, this has important implications for clinical practice.[31] Controversy exists over terminology and definitions, as some authors define CSS as an abnormal response to CSM only when accompanied by symptom reproduction of syncope.[32] This is distinct from CSH, which would produce an abnormal response to CSM without definite symptom reproduction. In this review, only 5 studies had included the presence of symptoms in their definition of CSS, but 13 studies reported on CSS as being present. Despite difficulties in terminology, this review does reveal a higher incidence of CSH in fallers; however, the prevalence rates reported may be skewed by definitions used.

Clinical Implications and Future Perspectives

This systematic review has highlighted a number of studies that have shown easily measurable cardiovascular parameters that may contribute to falls risk in older patients. The clinical implications of these associations are important in evaluation of falls risk reduction. Consensus is needed to adopt standard definitions of cardiovascular risk factors, as well as the resources and settings needed to systematically evaluate older adults at risk of falls for the presence of CVD. As up to 40% of falls may be preventable, a standardized assessment of cardiovascular risk factors is essential for falls prevention.[5] There is a need for treatment trials to be designed and carried out to gauge the treatment benefits, which may accrue by systematic review and treatment of underlying cardiovascular abnormalities in older patients.

Limitations

Differences in disease definition and the disparities between the quality of included studies make it impossible to perform a proper meta-analysis. This in turn limits our ability to describe the strength of associations between cardiovascular disorders and falls. Therefore, as mentioned previously, it is of major importance to reach consensus for standard definitions. As we have pointed out, falls can be very difficult to distinguish as a distinct clinical entity, and overlap syndromes, such as syncope, have been reported. Therefore, caution is warranted when interpreting the data. A large majority of the studies used only self-reported falls that had occurred in the past, and only a small minority studied falls in a prospective manner. As such, it is difficult to attribute causation to any one risk factor in isolation. Further prospective studies are therefore needed. The exact effect of cardiovascular drugs on falls risk remains a confounder in most studies. As this review specifically excluded articles in which there were therapeutic interventions made, the contribution of individual medications to falls risk is beyond the scope of this article.

Conclusion

Cardiovascular disease has a high prevalence in older adults with falls. There is a clear association between hypotension and falls, whereas conversely those patients with HTN demonstrate a lower prevalence of falls in some studies. Furthermore, both HF and arrhythmia (in particular AF) are consistently associated with falls. There is also a positive association demonstrated between syndromes that cause syncope, such as CSH, VVS, and OH, and falls, although the evidence regarding the association between OH and falls remains inconsistent. Efforts at unlocking the exact contribution of each variable to falls risk are hampered by a lack of standard definitions, methods of assessment, and the low quality of available studies. Further work on standard definitions, as well as the exact contribution of individual risk factors is of major importance to find potential areas for intervention.

Supplementary Data

Supplementary Data related to this article can be found online at http://dx.doi.org/10.1016/j.jamda.2015.08.022.

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