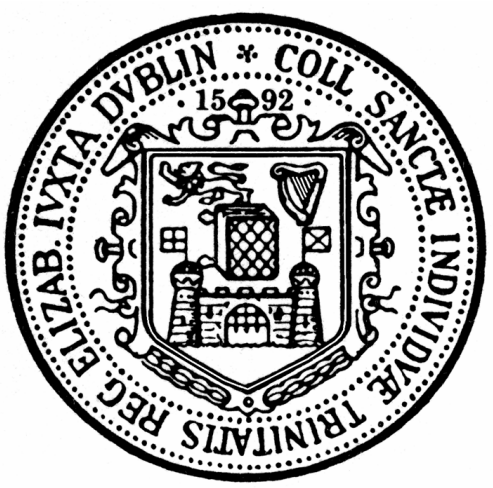


University of Dublin, Trinity College
School of Medicine,
Department of Gerontology

Cardiovascular Associations of Falls and Syncope in the Elderly

PhD Thesis Submission
Submission date: September 2016

Jaspreet Bhangu
Principal supervisor: Professor Rose Anne Kenny
Co-Supervisor: Dr Geraldine Mc Mahon

Declaration

I declare that no part of the material contained within my thesis has been submitted as an exercise for a degree in Trinity College Dublin or any other institution.

I certify that I performed all work contained within this thesis, from analysis and interpretation of data to manuscript preparation. Professor Rose Anne Kenny and Dr Geraldine Mc Mahon provided guidance and direction to the issues addressed within this thesis and acted as supervisors.

Following acceptance of my PhD submission, I agree that the library may lend or copy my thesis upon request

Jaspreet Bhangu

Signed: _____

Date: _____

Acknowledgements

I wish to acknowledge my supervisors Professor Rose Ann Kenny and Dr Geraldine Mc Mahon, for their clinical supervision, research guidance and teaching. Without their knowledge and ideas this work would not have been possible. I am eternally grateful for having the opportunity to work with two inspirational figures.

To my beautiful wife Dervla. This work would not be possible without you.

I have been helped by many others along the way – the staff in the Falls and Blackouts unit, the staff in TILDA, my co-authors, co-workers, co- researchers and, most of all, the patients who participated in the study.

Lastly, I would like to dedicate this thesis to the memory of my father Hans Pal Singh Bhangu. His unwavering belief in me empowered me to continually strive for greater pursuits of knowledge.

Dissemination of Thesis

Publications accepted

1. **The Association of Cardiovascular Disorders and Falls: A Systematic Review.**

Jansen S, **Bhangu J**, de Rooij S, Daams J, Kenny RA, van der Velde N. J Am Med Dir Assoc. 2016 Mar 1;17(3):193-9. doi: 10.1016/j.jamda.2015.08.022. Epub 2015 Oct 9.

2. **Syncope Chapter**

Kenny R.A, Bhangu J, 2016 . Syncope Howard M. Fillit, MD, Kenneth Rockwood, MD, FRCPC and John B Young, MD In: Brocklehurst's Textbook of Geriatric Medicine and Gerontology, 8th Edition, Elsevier

3. **Epidemiology of syncope/collapse in younger and older Western patient populations.**

Kenny RA, **Bhangu J**, King-Kallimanis BL. Prog Cardiovasc Dis. 2013 Jan-Feb;55(4):357-63. doi: 10.1016/j.pcad.2012.11.006. Review

4. **Long-term cardiac monitoring in older adults with unexplained falls and syncope.**

Bhangu J, McMahon CG, Hall P, Bennett K, Rice C, Crean P, Sutton R, Kenny RA. Heart. 2016 May;102(9):681-6. doi: 10.1136/heartjnl-2015-308706. Epub 2016 Jan 28. PMID: 26822427

5. **The relationship between syncope, depression and anti-depressant use in older adults**.

Bhangu JS, King-Kallimanis B, Cunningham C, Kenny RA. Age Ageing. 2014 Jul;43(4):502-9. doi: 10.1093/ageing/afu003. Epub 2014 Feb 3

Submitted for publication

1. **Unexplained falls are common with advancing age - implications for cardiovascular assessment in older patients with falls**

Bhangu J, King-Kallimanis BL, Donoghue OA, Carroll L, Kenny RA

Submitted to the Journal of the American Geriatrics Society

2. **Transient Loss Of Consciousness (T-LOC) In The Emergency Department – Implications For Resource Use In Older Adults**

Bhangu J, Hall P, Devaney N, Bennett K, Carroll L, Kenny RA, Mc Mahon CG

Submitted to Age and Ageing

Table of Contents

ABBREVIATIONS 12

INTRODUCTION 14

CHAPTER 1: FALLS IN THE ELDERLY 17

Definitions 17

CHAPTER 2: THE ASSOCIATION OF CARDIOVASCULAR DISORDERS AND FALLS: A SYSTEMATIC REVIEW 24

INTRODUCTION 24

METHODS 26

RESULTS 30

Orthostatic hypotension (OH), table 2 31

Carotid sinus hypersensitivity (CSH), table 3 31

Vasovagal syncope (VVS), table 4 32

Hypertension (HTN), table 5 32

Low blood pressure (LBP), table 6 33

Coronary artery disease (CAD), table 7 33

General Cardiovascular Disease (CVD), table 8 34

Postprandial hypotension, table 9 34

Cardiac arrhythmia, table 10 34

Heart failure, table 11 35

Structural abnormalities, table 12 35

DISCUSSION 37

Clinical implications and Future perspectives 42

Limitations 43

Conclusion 43

Table 1. Overview of studies published on cardiovascular abnormalities and falls, included in systematic review 45

Table 2. Orthostatic hypotension and falls 62

Table 3. Carotid sinus hypersensitivity and falls 77

Table 4. Vasovagal syncope and falls 85

Table 5. Hypertension and falls 89

Table 6. Low blood pressure and falls 99

Table 7. Coronary artery disease (Angina, ischemic heart disease and myocardial infarction) and falls 102

Table 8. General cardiovascular disease and falls 108

Table 9. Postprandial hypotension (PPH) and falls 112

Table 10. Cardiac arrhythmias and falls 115

Table 11. Heart failure and falls 121

Table 12. Structural cardiovascular abnormalities and falls 124

Figure 1. Flow diagram of study screening and inclusion 127

Identification **127**

Screening **127**

Eligibility **127**

Included **127**

Appendix S1. Search strategy and actual search 127

Appendix S2. Actual searches for MEDLINE and EMBASE. 129

Appendix S3. Quality Assessment 132

Quality review for- case-control studies or observational series 133

CHAPTER 3: SYNCOPE IN THE ELDERLY **138**

DEFINITION **138**

ORTHOSTATIC HYPOTENSION **140**

POST-PRANDIAL HYPOTENSION **143**

CAROTID SINUS SYNDROME AND CAROTID SINUS HYPERSENSITIVITY **143**

Cardiac Syncope **144**

Table 45-3: Causes of Syncope **148**

CHAPTER 4: EPIDEMIOLOGY OF SYNCOPE/COLLAPSE IN YOUNGER AND OLDER WESTERN PATIENT POPULATIONS **152**

Syncope and the Framingham studies **152**

Syncope in the young **154**

Syncope in Older Populations **154**

Syncope and hospital attendance **156**

Syncope in general practice. **157**

Syncope in the ER **158**

Prevalence and causes of syncope. **158**

Table 1 161

Table 2. Syncope Frequency Depends on the Setting in Which the Measurement Is Made..... 163

Figure 1 164

Incidence Rates of Syncope According to Age and Sex..... 164

Figure 2 165

Age-specific lifetime prevalence of syncope..... 165

CHAPTER 5: UNEXPLAINED FALLS ARE COMMON WITH ADVANCING AGE - IMPLICATIONS FOR CARDIOVASCULAR ASSESSMENT IN OLDER PATIENTS WITH FALLS 170

Methods 171

***Measures*..... 172**

***Statistical Analysis*..... 173**

Results 174

Discussion 176

***Conclusions*..... 179**

Table 1 Baseline variables for all participants reporting all falls (n=1,579), unexplained falls (UF) (n=406) and syncope (n=363) in wave one of TILDA 180

Table 2 Univariate and adjusted (OR) ods ratios for all falls, unexplained falls (UF) and syncope in the 12 months prior to wave 1 based on self-reported health variables for all TILDA participants (n=8172)..... 183

Table 3 Multi-variate analysis of participants reporting all falls (n=1,579), unexplained falls (UF) (n= 406) and syncope (n= 363) in wave one of TILDA (n = 8,172)..... 186

Figure 1 Prevalence (wave one) and incidence (wave two) of all falls, unexplained falls (UF) and syncope based on self-reported data from TILDA participants (n= 8504) 188

CHAPTER 6: TRANSIENT LOSS OF CONSCIOUSNESS 189

(T-LOC) IN THE EMERGENCY DEPARTMENT – IMPLICATIONS FOR RESOURCE USE IN OLDER ADULTS.....189

Introduction.....189

Methods.....190

***Statistical Analysis*.....192**

Results.....193

Discussion.....195

***Limitations*.....197**

Figure 1- Flow sheet of recruitment, exclusion numbers and subsequent analysis.....204

Figure 2- Age breakdown of patients over the age of 50 who had presented the emergency department (ED) in a six month period. Numbers represent percentages of patients in each category who presented to ED, numbers admitted from ED and mean length of stay (LOS) with regression line.....205

CHAPTER 7- FALLS AND SYNCOPE IN THE EMERGENCY DEPARTMENT (FUSE) – BENEFITS OF LONG-TERM CARDIAC MONITORING.....206

Introduction.....206

Methods.....208

Results.....211

Secondary end points.....213

Discussion.....214

Limitations.....218

Conclusion.....218

Table 1- Baseline characteristics of patients with ILR inserted.....220

..... 222

Table 2 - Description and classification of arrhythmias detected in patients with ILR inserted at a mean of 9 months 223

Table 3 – Univariate analysis of patients with an ILR inserted who experienced further falls during a mean follow-up of 9 months 225

CHAPTER 8 –THE RELATIONSHIP BETWEEN SYNCOPE, DEPRESSION AND ANTI-DEPRESSANT USE IN OLDER ADULTS ..226

Introduction 226

Methods 227

Measures 228

Statistical Analysis 230

Results 231

Discussion 234

Table 1. Demographic and Clinical Characteristics of Participants (n = 7,993) 239

Table 2. Weighted Prevalence and Standard Errors of Syncope by Medication and Depression 242

Table 3. Bivariate Multinomial Regression Results Comparing a Single and Multiple Syncopal Episode to No Syncopal Episode in the Past 12 Months (n = 7,993) 243

Table 4. Multivariate Multinomial Regression Results Comparing a Single and Multiple Syncopal Episode to No Syncopal Episode in the Past 12 Months (n = 7,993) 244

Figure 1. Prevalence of Syncope by age and history of depression 246

CHAPTER 9 - CONCLUSIONS 247

Limitations 254

Future directions **257**

REFERENCES **261**

Abbreviations

AD = Alzheimer's disease

Ad = Adrenaline

A-LOC = Amnesia for loss of consciousness

ATC = Anatomical therapeutic classification

BMI = Body mass index

BP = Blood pressure

CA = Cardiac arrhythmia

CAPI = Computer-assisted personal interview

CES-D = Centre for epidemiological studies depression scale

CBF = Cerebral blood flow

CNS = Central nervous system

CSH = Carotid sinus hypersensitivity

CSS = Carotid sinus syndrome

CT = Computed tomography

CVD = Cardiovascular disease

DBP = Diastolic blood pressure

DLB = Dementia with Lewy bodies

DM = Diabetes mellitus

ECG = Electrocardiogram

FTD = Frontotemporal dementia

HR = Heart rate

LOC = Loss of consciousness

MCI = Mild cognitive impairment

MI = Myocardial infarction

MMSE = The Mini-Mental State Examination

MOCA = The Montreal Cognitive assessment

MRI = Magnetic resonance imaging

NCVI = Neurocardiovascular instability

OH = Orthostatic hypotension

RCT = Randomised controlled trial

SBP = Systolic blood pressure

SCQ = Self-completion questionnaire

SD = Standard deviation

T-LOC = Transient loss of consciousness

TILDA = The Irish longitudinal study on ageing

VaD = Vascular dementia

VCD = Vascular cognitive disorder

VVS = Vasovagal syncope

WHO = World Health Organisation

WML = White matter lesions

Introduction

In chapter one I will include the concept and formal definition of unexplained falls and its links with cardiovascular disease. Chapter two will examine the links in greater detail and forms a systematic review of falls and cardiovascular disease in the literature to date. It provides the reader with a detailed review of the literature which has explored the association between falls and cardiovascular disease. It provides succinct summaries of each study and establishes the associations already explored to date and any gaps which exist in the literature. It also firmly establishes the need for greater exploration of these associations and further emphasizes the overlap between falls and syncope- especially in those older adults who experience unexplained falls.

Chapter three has been taken partly from the textbook chapter which was co-written by myself and Professor Kenny. It introduces the current definitions and pathophysiology of syncope and introduces the reader to concepts which are explored in greater detail throughout this thesis alongside their underlying pathophysiology. It allows an introduction and further exploration of the syncope syndromes which were discussed in the literature review and finally focuses on some of the links between syncope and falls, its unusual presentation in the elderly and the controversy surrounding the associations to date.

The fourth chapter focuses on the epidemiology of syncope in the literature to date. This will introduce the concepts of the overlap between falls and syncope in elderly adults and will lay the foundation for the research questions explored in the thesis.

Chapter 5 is an epidemiological study of the associations between falls, syncope and unexplained falls in a longitudinal population study. Using the TILDA sample, I have firstly established the incidence and prevalence of these three conditions in the community dwelling population. I then undertook an exploration of associated cardiovascular and chronic diseases with each of the conditions. This paper allowed me to establish whether the observed associations from the literature review were present in an Irish population sample. It also allowed specific associations to be discerned from the TILDA database.

Chapter 6 identifies the clinical characteristics of older adults who present to the emergency department with a fall or syncopal event. It highlights the prevalence of accidental falls, unexplained falls and syncope which present to the emergency room. This chapter will also further highlight the difficulties in trying to classify patients into fall sub-type based on their presenting complaint. It also allowed for a picture into the resource use associated with these conditions within a hospital setting.

In chapter seven I have focused on an exploration of one of the associations in more depth. I had undertaken a clinical trial using a prospective, observational design to explore the association of arrhythmia with unexplained falls and attribute possible causation.

Chapter 8 is also an exploration of one of the associations commonly mentioned with regards to syncope and falls- specifically the association of depression and anti-depressant medications. Using the TILDA database again I had focused on the patients who had reported depressive symptoms as well as the anti-depressant medications which they may have been on. Chapter 9 will form the conclusions from the thesis

Chapter 1: Falls in the Elderly

Definitions

Falls have many different definitions in the literature. For this thesis, I will be using the World Health Organization (WHO) definition which defines a fall as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level (1). This definition was chosen as it does not focus solely on those falls which occurred from a standing position. It also does not specifically exclude syncope or seizures. Other definitions of falls stipulate that there must be no known loss of consciousness (2). This definition would exclude syncope as a cause of falls and therefore exclude potentially important causes of falls in older adults as will be discussed in this thesis.

The exact incidence of falls in most western populations can be difficult to measure and compare directly. This is due to different methodologies of obtaining the results, differences in definitions used and differences in populations studied. A systematic review of falls incidence by Rubenstein had reported the incidence to be 0.2 to 1.6 falls per person per year with an average of 0.7 falls per person per year (3). This gave an average incidence of 34% of the older population who fall per year. However, looking in more detail at the individual studies used to calculate this we can see significant heterogeneity in the methods used to estimate incidence. Most prospective reporting, using falls diaries along with regular follow-up by a member of the investigating team, has reported an annual falls incidence of 30-40% in community dwelling cohorts (2)

. This compares to the reported incidence of 25-30% when falls are measured

using retrospective recall (4-6). This may point to problems with recall bias with regards to incident falls reporting which will be highlighted later in this thesis.

The incidence of falls in hospital and institutionalised cohorts also considerably differed from community dwelling cohorts. It is estimated that institutional fall incidence is 1.5 falls/bed per year. (3) This was 3x greater than that measured in community dwelling older adults. As a result, in the large differences between community and institutional dwelling older adults I have not included institutionalised adults in this thesis. Instead I have focused on older adults who were considered community dwelling adults.

Consequences of falls

1. Injury – This is the single most common and feared consequence of falls. Falls will most often result in so called fragility fractures. These can be defined as fractures which occur as a result of a low energy trauma (7). Hip fractures are one such type of fragility fracture. According to the WHO, falls are the leading cause of hip fractures worldwide (1). They result in prolonged periods of immobility, significant pain and subsequent loss of independence (8). Patients who have suffered a hip fracture have a 26% excess disability in their activities of daily living attributable to the hip fracture when compared those patients who did not suffer a hip fracture (9). Up to 29% of older people who suffer a hip fracture will not return to their previous functioning within one year post fracture (10). In fact, it is estimated that 1/3rd of older adults will die within 6 months of suffering a hip fracture (11). In addition to functional loss and mortality there is a considerable increase in rates of depression, cognitive decline and loss of

independence. Other fragility fractures include Colles' fracture of the wrist, femoral fractures and osteoporosis related fractures also commonly result from falls (12). Although these fractures have not been as well studied as hip fractures they also result in considerable morbidity (13). Head injuries are also a common consequence of falls and result in significant morbidity and mortality (14).

2. Fear of falling – The psychological impact of falling cannot be underestimated. A significant number of older adults will describe fear of falling which is defined as an ongoing concern about falling which ultimately limits the performance of activities of daily living (15). The prevalence of this disorder varies widely but it has been reported as high as 80% in older adults who have experienced a fall. (16). Most studies have reported it in 40-50% of older adults who suffer falls (16). Fear of falling will compound any physical injury suffered and has been shown to lead to increases in depressive symptoms, physical decline and loss of activities of daily living (17).
3. Institutionalisation and death- Falls have been quoted as the most common reason for admission to a nursing home facility (18). This risk appears to increase depending on the number of falls experienced and the type of injury suffered (18). In addition to nursing home admission falls are the commonest reason for an elderly patient to present to an emergency department (19). They are the commonest reason for older adults to be admitted to hospital and are often associated with prolonged hospital stays(20). Both the Center for disease control and prevention (CDC) and the WHO list falls as the second commonest cause of death from accidental or unintentional injury(1, 21). Overall falls are the fifth

leading cause of death in the United States and there is evidence that this rate has been increasing over time(22). Falls are estimated to account for at least €400 million (3.7%) of the total health care expenditure in Ireland (23), £2 billion (4%) in the UK(24) and $34 Billion in the US (25).

Associations and causes of falls

Falls risk factors are often divided into intrinsic and extrinsic risk factors(26). Intrinsic risk factors are those which are unique to the individual affected by the condition such as age and medications. Extrinsic factors usually refer to environmental risk factors or exposures which can contribute to falls such as uneven surfaces or footwear. Often these risk factors do not occur in isolation but instead are combined in one patient leading to a fall- i.e. an older adult with visual impairment who is walking on an uneven surface. Therefore, most falls are considered multifactorial with a combination of risk factors contributing to overall falls risk (27). The more common associations with falls risk are summarized below:

Intrinsic risk factors

- Increasing Age (doubling in prevalence in the over 80s age group)
- Female Gender
- Gait and mobility deficits-
    - Self-reported use of assisted walking aids
    - objective gait deficits arising from prior disability
    - intrinsic lower limb weakness
    - Muscle weakness
    - objectively measured gait deficits such as a slowed time up and go test

- Sedentary behavior
- Foot deformities
    - Cognitive deficits
    - Visual deficits
- Psychosocial factors
    - depression
    - social isolation
    - fear of falling
- Previous falls
- Disability as measured by impairment of activities of daily living
- Medications (commonest reported associations listed below):
    - Benzodiazepines and hypnotic (sedative) medications
    - Anti-depressant medications
    - Anti-psychotic medications
    - Anti-hypertensive medications
    - Anti-arrhythmic medications
    - Dopaminergic medications
    - Anti-cholinergic medications
    - Diuretic medications
- Cardiovascular disease
- Multi-morbidity as measured by number of chronic diseases
- Nutritional status
    - Sarcopenia
    - Vitamin D deficiency

Extrinsic risk factors

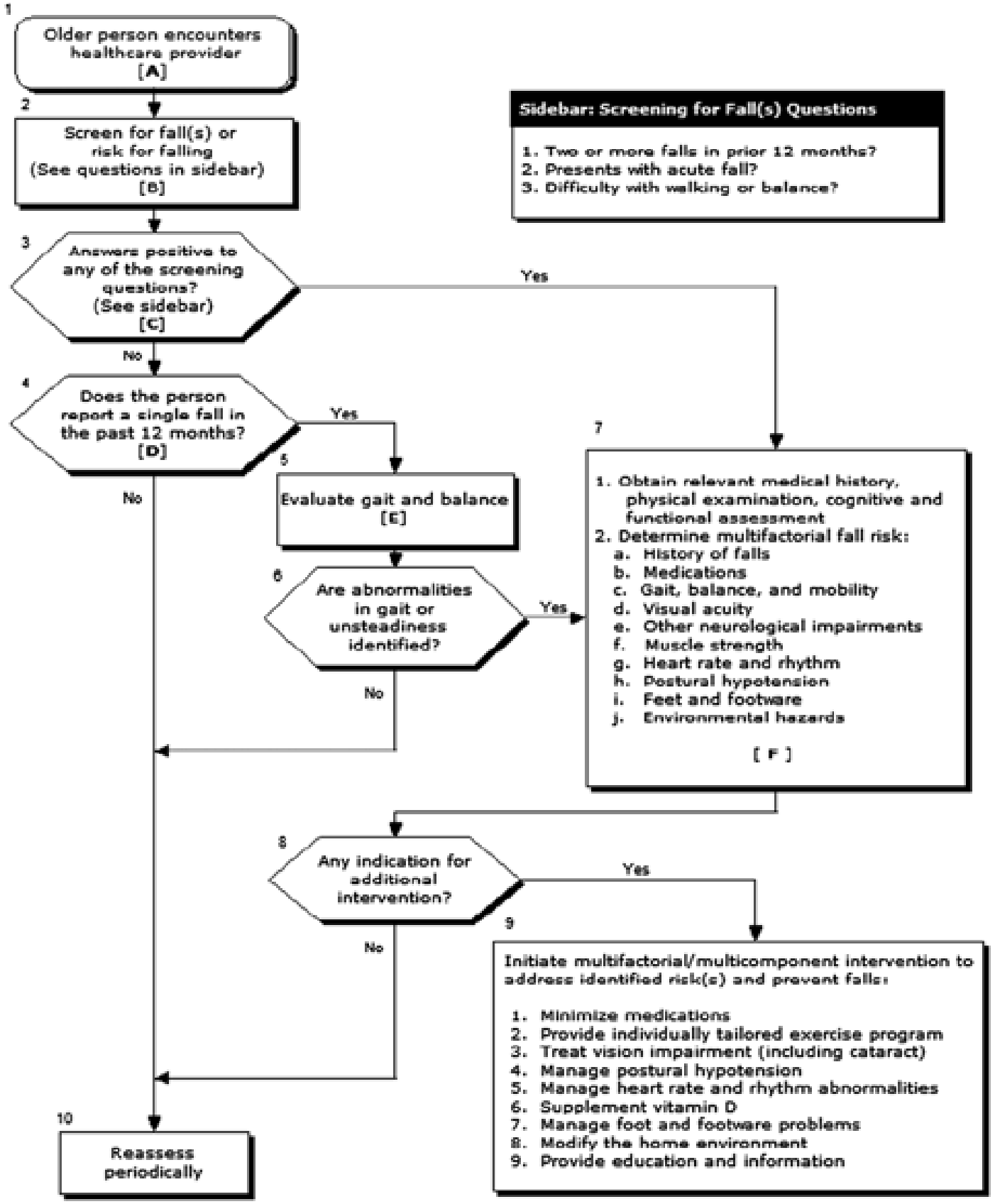
Poor footwear

Environmental hazards

Falls assessment

The American and British Geriatric society last released guidelines on the prevention of falls in the elderly in 2011 (28). These guidelines are quoted extensively in this thesis. They have emphasized the importance of a multifactorial assessment of older adults to prevent falls. This approach has been validated in prior studies using a multi-component intervention (29). In this way patients would be initially screened for the presence of multiple risk factors and then have these addressed in a more comprehensive manner. An algorithm summarizing this is contained below

Prevention of Falls in Older Persons Living in the Community



Chapter 2: The association of cardiovascular disorders and falls: a systematic review

INTRODUCTION

Falls are the leading cause of injury in older people (18, 21). Approximately one in three people over the age of 65 will suffer a fall each year, with injuries occurring in at least one in five of these (25). As the world's ageing population increases, healthcare costs associated with falls are set to rise over the next 30 years (8). As it is estimated that up to 40% of falls may be preventable, evidence for causative, treatable factors is essential (30).

Cardiovascular disorders are among the several risk factors which 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 (28). Syncope secondary to underlying cardiovascular disease is more common in older adults and may lead to injurious falls (31).

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 (32). Orthostatic hypotension, carotid sinus hypersensitivity, vasovagal syncope and 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, one systematic review has been published that addressed cardiovascular causes of falls (33). 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 orthostatic hypotension and falls, but these studies did not assess other potential cardiovascular causes of falls (34) (35). Furthermore, as the subject has gained attention in the last five 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 over the age of 50 years. Our review methodology and reporting followed standard guidance (36).

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 S1* as well as the actual search strategy used; *Supplementary data, Appendix S2.*

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 two 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 aged 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 abnormalities (SBP and DBP), carotid sinus hypersensitivity (CSH), orthostatic hypotension (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 orthostatic hypotension or impaired BP recovery upon active stand, 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, general cardiovascular disease, angina, arrhythmia and heart failure. 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 only included if falls had occurred prior to admission.

Articles were excluded if the sample comprised a specific disease-defined population (such as Parkinson's disease, diabetes or subjects 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 two or more articles had included the same populations for the same exposure,

only one 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 was 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 to control group, - 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 (37). A detailed description of the quality assessment can be found in appendix S3. A score of 0-3 was considered low quality, 4-6 intermediate and 7 or above 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 result

After removing duplicates, the initial combined search retrieved 5,420 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, thirteen 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, nine in long-term care facilities, one in both community and long-term care, 24 in outpatient clinics (20 in specialized falls- and syncope clinics), eight in emergency departments and five in acute hospital settings.

Fifty-one studies used any falls as an outcome measure, eight used recurrent falls, eight used unexplained falls, twelve studies used falls and/or syncope as an outcome, and two studies used unexplained falls described as 'drop attacks'.

Eleven types of cardiovascular abnormalities (exposures) were identified with 39 studies assessing more than one risk factor. OH, as a risk factor for falls was examined in (36), followed by hypertension (27), CSH (21), general cardiovascular disease (9), Angina and MI (grouped as coronary artery disease) (14), arrhythmia (12), vasovagal syncope (10), heart failure (6), low BP (5), post prandial hypotension (4), and structural cardiac abnormalities (3).

Tables 2-11 show results of included studies, categorized per cardiovascular risk factor and type of study

Orthostatic hypotension (OH), table 2

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

OH was defined as a drop of greater than 20 mmHg SBP and/or greater than or equal to 10 mmHg DBP drop in twenty studies, greater than 20mmHg SBP drop in twelve studies while the four studies did not report a value. Fifteen studies used intermittent BP measurements, twelve studies used continuous measurement with photopletysmography, two studies used both methods, and seven studies did not specify their study instrument. Seven studies were scored as high quality with the remainder (how many) scoring low and intermediate on the NOS scale

Carotid sinus hypersensitivity (CSH), table 3

Twenty-one studies had investigated CSH as an exposure. Five were designed as case-control studies; one reported a positive association between neurally mediated syncope and unexplained falls compared to accidental falls; three reported a higher prevalence of CSH in fallers compared to controls. Fifteen observational series were performed which reported a prevalence of between 8-73%. Eighteen studies performed both supine and upright (70^0) carotid sinus massage; two were supine only. All studies defined CSH as asystole greater than 3 seconds on ECG or a vasodepressor drop of 50mmHg in systolic blood

pressure. Five studies used symptom reproduction during carotid sinus massage to differentiate carotid sinus syndrome from carotid sinus hypersensitivity. All studies had a low to intermediate NOS quality level.

Vasovagal syncope (VVS), table 4

Ten studies had investigated vasovagal syncope as an exposure for falls; two 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 3-46%. All studies had used a head up tilt table test as the measurement method. All were graded as low to intermediate on the NOS quality score.

Hypertension (HTN), table 5

Twenty-seven studies assessed hypertension as an exposure for falls; 22 were designed as cohort studies, three as case controls. Of the 25 studies with a control group, five reported a positive multivariably adjusted association between HTN and falls and two reported a higher prevalence of HTN among fallers compared to controls. Two studies reported a negative association between HTN and falls.

The two observational series reported a prevalence of HTN among fallers between 34-73%. Nine studies only used self-report of HTN; five used medical charts only, six studies used an objective measurement of BP and/or use of anti-hypertensive to diagnose HTN, five used a combination of self-report and medical charts, one used both objective and self-reporting methods and one study did not report the measurement method. Of studies that used an objective measurement, different cut-offs for HTN were used, ranging from >130/80 mmHg to >160/95 mmHg. Only two studies were considered high quality on the

NOS scale, neither of which showed a positive association between HTN and falls.

Low blood pressure (LBP), table 6

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

All studies used an objective measurement of blood pressure, but various thresholds for diagnosing hypotension were used, ranging from 100 mmHg to 142 mmHg for systolic blood pressure (SBP), and from 60 mmHg to 80mmHg for diastolic blood pressure (DBP). The one study that did not show an association also used the lowest BP cut-off (SBP/DBP ≤100/60). Four out of five studies were rated high quality on the NOS scale.

Coronary artery disease (CAD), table 7

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

Six studies used self-reported history of MI or angina; four used medical chart history of MI or angina, three used a combination of medical records and self-report and one used a clinical definition to define MI (myocardial infarct evidenced by chest pain and/or serial ECG's). All cohort studies scored intermediate or high on the NOS scale whilst the observational series scored low to intermediate on the NOS scale

General Cardiovascular Disease (CVD), table 8

Nine studies looked at general CVD without breakdown into specific cardiovascular diseases. Seven used a cohort design; one was a case control study. Two out of these nine studies showed a multivariably adjusted association between cardiovascular disease and falls, two studies showed a higher prevalence of cardiovascular disease among fallers and four studies did not show an association. The one observational study reported a prevalence of cardiovascular disease of 52%. Four used self-report of CVD, three used medical records while two used both methods. All studies were graded as low to intermediate on the NOS scale.

Postprandial hypotension, table 9

Four papers studied post-prandial hypotension (PPH) as an exposure for falls; two cohorts and two case control studies. One reported a positive, multivariably associated association between PPH and falls and one reported no association. The case control studies both reported a higher prevalence of PPH in fallers compared to 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, table 10

Twelve studies studied cardiac arrhythmia as an exposure; three were designed as cohort studies, three were case-control studies. Of these six studies, four reported a positive, multivariably adjusted association between arrhythmia and falls, of which three were studies on AF.

Six observational design studies reported a prevalence of between less than 1% and 27%. There was a variety of measurements performed; Implantable loop

recorder (ILR) (for extended arrhythmia monitoring beyond 30 days) in one study, external loop recorder (ELR) (for arrhythmia monitoring up to 30 days) in one study, holter monitoring (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 cardiac arrhythmia. Two studies were graded as high quality on the NOS scale whilst the remainder were of low or intermediate quality.

Heart failure, table 11

Six studies looked at heart failure as an exposure; five cohort studies, with four reporting a positive, multivariably adjusted association between CHF and falls. One study used the New York Heart Association Classification for heart failure and one study used the NHS–Read coding for classification. All studies that reported an association measure were of intermediate or high quality.

Structural abnormalities, table 12

Three studies looked at exposures that could not be categorized under other exposures.

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

Schoon et al. 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. 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 blood pressure (4/5), heart failure (4/5) and cardiac arrhythmia (4/6), as the majority of these studies showed a positive association with falls after performing multivariable adjustment for potential confounders. For carotid sinus hypersensitivity (4/6), vasovagal syncope (2/2) and post-prandial hypotension (3/4), the majority of studies reported a higher prevalence of the exposure in fallers compared to controls, but only few multivariable adjusted associations were reported. Coronary artery disease (6/10), orthostatic hypotension (9/25), general cardiovascular disease (4/9) and hypertension (7/25) all showed inconsistent associations with falls, with a similar or smaller amount of studies reporting positive associations as studies reporting no associations with falls. Hypertension even showed a protective effect on falls in two out of 25 studies. Finally, arterial stiffness was identified as an independent predictor for falls in one study, as were several echocardiographic abnormalities.

Although orthostatic hypotension, carotid sinus syndrome and vasovagal syncope are most frequently cited as important cardiovascular causes of falls, the evidence on the association between these blood pressure 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 LBP, heart failure and cardiac arrhythmia. A range of studies examining the association of

blood pressure and falls was evaluated. Although these studies differed significantly in their methods, certain trends were apparent.

Low blood pressure 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 (e.g. syncope or falls during exertion or postural changes) but may also lead to chronic damage to the areas of the brain which govern balance and gait (38) through neurodegeneration. In addition to an association with falls, LBP has been associated with stroke and cognitive impairment (39) (40) (41). Conversely, hypertension was associated with falls after adjustment for confounders in only a small number of studies reviewed, and hypertension even showed a protective effect on fall incidence in two studies. It has been reported previously that blood pressure behaviour 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 (42, 43). Adults in the oldest age categories have not been shown to benefit from aggressive lowering of their blood pressure and in fact may be harmed by low blood pressure (43). However, whether LBP, or conditions causing LBP can been seen as causative or contributory factors to falls remains unclear. A consistent association with falls was also seen for heart failure (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 LBP and falls. Further work on the effects of transient changes in blood pressure is needed to delineate thresholds by which older adults are more prone to falling and elucidate treatment strategies for this.

The majority of 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 employed 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 15-46%. However, these were in predominantly observational series, limiting the applicability of this finding. Interestingly, the three studies which exclusively defined atrial fibrillation 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. have recently reported new normative data for definitions of OH, using non-invasive, beat-to-beat BP measurements (44). Whilst they reported that initial OH (within 15 seconds) occurred in up to a third of the population, impaired blood pressure stabilization at 40 seconds was present in 16% of subjects and 'classical' OH at or after one minute of standing was present in a much smaller number of subjects (7%). Most studies included in this review assessed OH at one 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 amount 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.

Cardiovascular disease, which comprised angina, ischemic heart disease and arterial disease, showed a positive association with falls in a few studies, as did arterial stiffness. However, cardiovascular disease 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 have also been shown to have a higher prevalence in cardiovascular diseases contributing to increased falls risk (45). Lastly, 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 (46). There is evidence that drug withdrawal of CV drugs may reduce falls rates in practice (47), potentially through an improvement in postural blood pressure changes (48). Although the exact mechanisms remain difficult to elucidate, this review has shown that clinicians

should regard those patients with a diagnosis of cardiovascular disease 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 (49)) 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 (28). 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 CSS (50). This review demonstrates a strong overlap between CV 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 (28).

The European Society of Cardiology (ESC) has stated the need to consider syncope as the cause of a fall in those with unexplained falls (49). Syncope mistaken for falls presents a difficult clinical challenge as up to 50% of older persons suffer from retrograde amnesia after vasovagal syncope, and eye-witnesses are often absent (51). 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 (49). Prevalence rates of between 10-40% were consistently reported in fallers with two 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 (52). Controversy exists over terminology and definitions, as some authors define carotid sinus syndrome (CSS) as an abnormal response to carotid sinus massage (CSM) only when accompanied by symptom reproduction of syncope (53). This is distinct from carotid sinus hypersensitivity (CSH), which would produce an abnormal response to CSM without definite symptom reproduction. In this review only five studies had included the presence of symptoms in their definition of CSS but thirteen 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 many studies, which 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 cardiovascular disease. As up to 40% of falls may be preventable, a standardised assessment of cardiovascular risk factors is essential for falls prevention (30). There is a need for treatment trials to be designed and carried out in order to gauge the treatment benefits, which may accrue by systematic review and treatment of underlying CV abnormalities in older patients.

Limitations

Differences in disease definition and the disparities between the qualities of included studies make it impossible to perform proper meta-analyses. This in turn limits our ability to describe the strength of associations between cardiovascular disorders and falls. Therefore, as mentioned above, 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 only used 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 where 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, whilst conversely those patients with hypertension demonstrate a lower prevalence of falls in some studies. Furthermore, both heart failure 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.

Table 1. Overview of studies published on cardiovascular abnormalities and falls, included in systematic review

Author	Year	Design	Setting	Data gathering	Outcome of falls	Measurement of falls	Reporting interval	N	Age, years	% female	Exposure (s)
Alamgir (54)	2015	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 3 months	5996	65+	not given	CVD
Allcock (55)	2000	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls and syncope	Referred for unexplained falls and syncope	n/a	120	78 (range 66-94)	70%	CSH, OH, VVS, CA
Anpalahan (48)	2011	Case-control	Acute hospital	Retrospective	Unexplained falls and accidental falls	in ER or admitted for falls	n/a	21 / 17	80 [±6] / 77[±5]	55%	CSH, VVS, CAD
Armstrong (56)	2003	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls and syncope	Retrospective	n/a	15	73, range 61-89	87%	CA

Aronow (57)	1997	Cohort	Long-term care	Prospective	Any fall	Incident reports	29 [±10] months	499	80 [±9]	Not given	PPH
Assantachai (58)	2003	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 6 months	1043	Men 69 [± 6], women 68 [±7]	64%	HTN
Benchimol (59)	2007	Case-control	Falls & syncope clinic	Retrospective	Unexplained falls and syncope	Referred for unexplained falls and syncope	n/a	259 / 55	50 [±24], 57 [±21]	66% / 58%	CSH, VVS
Berg (60)	1997	Cohort	Community (home)	Prospective	Recurrent falls	Prospective	2-weekly for 12 months	96	72 [±7], range 60-88	60%	Low BP
Bergland (33)	2003	Cohort	Community (home)	Prospective	Any fall	Prospective	3-monthly for 12 months	307	81 (range 75-93)	100%	HTN
Boddaert (61)	2004	Observational series	Acute hospital	Cross-sectional	Any fall	In ER or admitted for falls	n/a	57	84 [±7]	81%	OH

Brassington (62)	2000	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	n/a	1526	64-99	64%	HTN, CVD
Bumin (63)	2002	Cohort	Long-term care	Cross-sectional	Any fall	Retrospective	Ever	33	fallers 73 [±2], non-fallers 68 [±2]	Not given	OH
Campbell (64)	1981	Cohort	Community (home and residential facility), Acute hospital	Cross-sectional	Any fall	Retrospective	Past 12 months	559	65+	Not given	OH
Campbell (65)	1989	Cohort	Community (home and residential facility)	Prospective	Any fall	Prospective	Monthly for 12 months	761	70+	68%	OH, Low BP
Chan (66)	1997	Cohort	Community	Cross-	Any fall	Retrospective	Past 12	401	69 (range 60-	48%	OH, HTN

			(home)	sectional			months		90)		
Chang (67)	2010	Cohort	Community (home)	Cross-sectional	Injurious falls	Retrospective	Past 12 months	1361	72 [±5]	40%	OH, HTN
Chen (68)	2008	Cohort	Long-term care	Cross-sectional	Any fall	Incident reports	Past 6 months	585	81 [±5]	0%	HTN, CVD
Damian (69)	2013	Cohort	Community (residential facility)	Cross-sectional	Any fall	Incident reports	1 month	733	83	76%	HTN, CA, CAD, HF
Davies (70)	1996	Observational series	Emergency department	Cross-sectional	Unexplained falls and recurrent falls	Retrospective	n/a	26	79 (SE 8)	75%	OH, CSH, VVS, CA
Davies (41)	2001	Case-control	Emergency department	Cross-sectional	Unexplained falls	Retrospective	n/a	26 / 54	79 [±7], 78 [±7]	80% / 80%	OH, CSH

Davison (71)	2005	Case-control	Emergency department	Cross-sectional	Recurrent falls	Retrospective	24 hours (during ECG recording)	128 / 100	77 [±6], 75 [±6]	67%, 59%	CA
Dey (72)	1997	Observational series	Falls & syncope clinic	Cross-sectional	Drop attacks (unexplained falls)	Retrospective	n/a	35	75 (range 50-95)	80	OH, CSH, VVS
Downton (73)	1991	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 12 months	203	83 [±5], range 75-97	70%	OH, HTN
Eltrafi (74)	1999	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls and syncope	Retrospective	n/a	CSS: 139 / VVS: 149	CSS: 74 [±11]. VVS: 66 [±20]	CSS: 59%, VVS: 60%	CSH, VVS
Ensrud (33)	1992	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	12 months	9704	72 (range 65-99)	100%	OH
Freitas (75)	2004	Case-contro	Falls & syncope clinic	Cross-sectional	Any falls and syncope	Retrospective	not described	386 / 108	>42, >40		CSH

		l									
Gangavati (76)	2011	Cohort	Community (home)	Prospective	Recurrent falls	Prospective	Monthly, range 183-365 days	722	78 [±5]	64%	OH
Graafmans (77)	1996	Cohort	Community (home and residential facility)	Prospective	Any fall and recurrent falls	Prospective	Weekly, returned 2-monthly for 28 weeks	354	70+	84%	OH
Heckenbach (78)	2014	Cohort	Community (home)	Cross-sectional	Any fall	ICD-10 codes	n/a	5124	73	65%	HTN, CVD, HF
Heitterachi (40)	2002	Cohort	Community (home)	Prospective	Any fall	Prospective	Monthly for 12 months	70	77 [±6]	80%	OH
Herndon (58)	1997	Case-control	Community (home)	Cross-sectional	Injurious falls	in ER or admitted for falls	Past 7 days	467 / 691	65+	Not given	HTN, CAD

Hung (79)	2013	Observational series	Acute hospital	Cross-sectional	Any fall	Retrospective	Past 3 years	401	82 [±0.2]	24%	CA, HTN
Jansen (80)	2015	Cohort	Community (home)	Cross-sectional	Any fall and recurrent falls	Retrospective	Past 12 months	8173	64 [10], range 51-105	54%	HF, HTN, CAD
Jansen (72)	2015	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 12 months	4886	62 [8]	54%	CA
Jitapunkul (81)	1998	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 6 months	4480	69 [±8)	60%	HTN
Kao (82)	2012	Cohort	Community (home)	Cross-sectional	Recurrent and injurious falls	Retrospective	Past 12 months	360	76 (range 64-91)	61%	HTN, CVD
Kario (83)	2001	Cohort	Community (home)	Prospective	Any fall	Prospective and retrospective	Monthly for 12 months	266	76 [±5]	54%	HTN, Low BP, OH

Kelly (84)	2003	Case-control	Community (home)	Retrospective	Injurious falls	recording of fall in medical history	1 year	2278 / 9112	78.5 (7.7) / 74.5 (6.7)	69%, 57%	HTN, CVD
Kenny (85)	1991	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls and syncope	Referred for falls	not given	130	77 (67-89)	55%	CSH
Klein (86)	2013	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 3 months	3544	70 (60-97)	56%	HTN, Low BP
Kumar (87)	2003	Case-control	Falls & syncope clinic	Retrospective	Unexplained falls	Referred for falls	not given	265 / 44	79.5 (60–92) / 71.3 (63–86	76%, 36%	CSH
de Castro Lacerda (88)	2008	Observational series	Falls & syncope clinic	Prospective	Unexplained falls	Referred for falls	Past 12 months	502	65 [±10]	49%	CSH
Lagro (89)	2013	Observational	Falls & syncope	Cross-	Any fall	Referred for falls	not given	175 (with	75+	Not given	OH, PPH,

		series	Clinic	sectional				falls)			CSH
Lawlor (90)	2003	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 12 months	4050	71	100%	OH, CAD, HTN, Low BP
Le Couteur (36)	2003	Observational series	Community (residential facility)	Cross-sectional	Any fall	Incident reports	Past 12 months	179	83 [±7]	80%	PPH
Lee (91)	2006	Cohort	Community (home)	Cross-sectional	Any fall and recurrent falls	Retrospective	Past 12 months	4000	73 [±5]	50%	CVD
Lee (65)	2009	Cohort	Community (home)	Cross-sectional	Recurrent falls	Retrospective	Past 12 months	11,113	65-75 years 55%, 76 plus 45%	58%	CAD
Liao (92)	2012	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 12 months	1165	75 [±7)	54%	HTN

Lipsitz (59)	1991	Case-control	Long-term care	Cross-sectional	Recurrent falls	Retrospective	Past 6 months	70 / 56	87 [±6] / 87 [±5]	73% / 48%	OH, HTN
Liu (93)	1995	Cohort	Community (residential facility)	Prospective	Any fall	Prospective	Weekly for 12 months	100	83 [±6], range 62-96	83%	OH
Luukinen (94)	1996	Cohort	Community (home)	Prospective	Recurrent falls	Prospective	3-montly during 12 months	1016 / 650	76 [±5]	63%	OH
Mader (95)	1987	Cohort	Outpatient clinic, community clinic	Cross-sectional	Any fall	Retrospective	Past 12 months	300	70 (range 56-93)	77%	OH
Marechaux (96)	2009	Observational series	Emergency department	Prospective	Any fall	in ER or admitted for falls	immediate	60	81+/- 8 years	58,4	HTN

Maurer (97)	2004	Cohort	Long-term care	Prospective	Any fall	Incident reports	Weekly during 270-day FU (range 8–657)	111	88 [±7]	82%	OH
Maurer (98)	2005	Cohort	Long-term care	Prospective	Any fall	Incident reports	12 months	139	88+/-7	85%	HTN
Midttun (99)	2011	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls	Retrospective	not given	207	83 years (58–95)	70%	CA
Milton (100)	2009	Observational series	Falls & syncope clinic	Cross-sectional	Unexplained falls	Retrospective	not given	1464	78 [±10]	72%	CSH, OH
Mitchell (101)	2013	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	12 months	5681	65+	55%	CAD, HTN
Murphy (102)	1986	Cohort	Long-term care	Prospective	Any fall	Incident reports	33 months	100	80, range 63-97 / 83, range 61-97	75%	CSH

Ooi (103)	2000	Cohort	Long-term care	Prospective	Any fall and recurrent falls	Incident reports	Incident reports during 18 months	844	60+	80%	OH
Paling (42)	2011	Observational series	Falls & syncope clinic	Cross-sectional	Unexplained falls	Referred for unexplained falls	n/a	111 (with falls)	82, range 61-99	59%	CSH, VVS, OH
Parry (104)	2005	Observational series	Falls & syncope clinic	Cross-sectional	Any falls and syncope	Referred for falls nd syncope	n/a	34 (falls) / 34 (syncope)	77 [9] / 75 [9]	79%, 47%	CSH
Parry (75)	2005	Observational series	Falls & syncope clinic	Cross-sectional	Drop attacks (unexplained falls)	Retrospective	Past 6 months	93	77 [±9], range 55-92	75%	CSH, OH, VVS, CA
Pasma (105)	2014	Cohort	Outpatient clinic	Cross-sectional	Any fall	Retrospective	Past 12 months	197	82	60%	OH
Philips	1999	Observational	Emergency	Cross-	Any falls and	in ER or admitted	n/a	142	83, range 76-	63%	CAD

(106)		series	department	sectional	syncope	for falls			99		
Prudham (107)	1981	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 12 months	2357	65+	59%	CVD, HTN
Puisieux (108)	2000	Case-control	Acute hospital	Cross-sectional	Any fall	in ER or admitted for falls	n/a	45 / 36	80.9 [8.5] / 78.5 [7.2]	73%, 68%	PPH
Rafanelli (109)	2014	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls	Referred for falls	n/a	298	75 [±11]	not given	CSH, OH, VVS
Rafiq (110)	2014	Cohort	Community (home)	Cross-sectional	Any fall	GP visit for fall	30 months baseline, 30 months FU	135.433	75 [±8], range 65-104	56%	CAD, HF
Richardson (111)	1997	Observational series	Emergency department	Cross-sectional	Unexplained falls and recurrent	in ER or admitted for falls	in ER for fall	279	50+	not given	CSH

					falls						
Romero-Ortuno (112)	2011	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	Past 6 months	598	72	72%	OH
Rosado (113)	1989	Case-control	Long-term care, Community (residential facility)	Cross-sectional	Any fall	Incident reports	Past 7 days	51 / 27	86	not given	CA
Rutan (114)	1992	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	12 months	4931	OH+: 73.6, OH-: 72.6	56%	OH
Sanders (15)	2012	Case-control	Emergency department	Retrospective	Unexplained falls and accidental falls	Retrospective	n/a	211 / 231	82 [±9] / 79 [±7]	62%, 62%	CA
Schoon	2013	Case-contro	Falls & syncope	Cross-	Any falls and	Referred for falls	n/a	105 / 25	79 [±7] / 74	67%, 20%	HTIH

(115)		l	Clinic	sectional	syncope				[±4]		
Sibley (116)	2014	Cohort	Community (home)	Cross-sectional	Any fall	Retrospective	12 months	16.357	65+	55%	HTN, CAD
Smebye (117)	2014	Observational series	Falls & syncope clinic	Cross-sectional	Any fall	Referred for falls	n/a	111	82 [±7]	82%	OH, CVD, CSH, CA
Stenhagen (94)	2013	Cohort	Community (home)	Prospective	Any fall	Retrospective	Past 6 months, at 3 and 6 years	1763	60-93	54%	HF, CAD
Tan (118)	2008	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls and syncope	Retrospective	n/a	302	71 [±11] (range 38–98)	Not given	OH, VVS
Tan (114)	2009	Observational series	Falls & syncope clinic	Retrospective	Unexplained falls and syncope	Retrospective	n/a	302	71 [11], range 38–98	56%	CSH

Tinetti (119)	1986	Cohort	Long-term care	Prospective	Recurrent falls	Incident reports	3 months	79	81 [±7], 78 [±7]	78%, 62%	OH
van der Velde (120)	2007	Cohort	Outpatient clinic	Prospective	Any fall	Prospective	Monthly during 3 month FU	215	77.4 [± 6.0]	65%	HV abn
van der Velde (121)	2007	Cohort	Outpatient clinic	Cross-sectional	Any fall	Retrospective	12 months	217	Fallers 79 [±6], non fallers 75 [±6]	66%	OH
van Nieuwenhuizen (122)	2010	Observational series	Emergency department	Cross-sectional	Any fall and Recurrent falls	In ER or admitted for falls	n/a	639	79 [±8]	73%	CAD, HTN
Vu (54)	2011	Observational series	Acute hospital	Retrospective	Injurious falls	In ER or admitted for falls	n/a	44.942	median 82 (IQR 76-87)	70%	HF, CAD

Wong (123)	2014	Cohort	Community (home)	Prospective	Any fall	Prospective	Monthly for 12 months	481	80 [±4]	51%	Arterial stiffness, OH, HTN, CAD

Prospective falls reporting: fall diaries or calendars and/or frequent telephone interviews

CA, cardiac arrhythmia. CAD, coronary artery disease (angina, Ischemic heart disease, myocardial infarction). CVD, general cardiovascular disease (unspecified). CSH, carotid sinus hypersensitivity/syndrome. HF, heart failure. HTN, hypertension. HTIH, head turning induced hypotension. HV, heart valve abnormality. OH, orthostatic hypotension. Low BP, low blood pressure. VVS, vasovagal syncope.

N/A: Not applicable. 95% CI: 95% confidence interval.

SD (±): standard deviation. IQR: interquartile range.

Table 2. Orthostatic hypotension and falls

First author	N	Age, Years	Population, setting, design	Falls Outcome	Assessment method	Main findings and prevalence of OH	OR/RR/HR	Conclusion	OH	Association	NOS
Cohorts											
Bumin 2002 (63)	33	Fallers 73 [±2], non-fallers 68 [±2]	Cohort, long-term care, cross-sectional	Any fall, ever	Sitting and standing at 3 min, 20 SBP	44% of fallers, 18% of non fallers		OH was univariately associated with falls		+	3
Campbell 1981 (64)	559	65+	Cohort, community and acute hospital, cross-sectional	Any fall in the past 12 months	Supine and standing at 1 and 3 min, sphyg., 20 SBP	13% (74/559) of total sample, considered attributable cause of a fall in 3%.		OH considered an attributable cause of a fall in 3%.	∞	-	4 62

Campbell 1989 (65)	761	70+	Cohort, community, prospective	Any fall during 12 month FU	Lying and standing at 1 and 3 min. sphyg, 20 SBP	40% in female fallers and 31% in female non-fallers, 22% in male fallers and 29% in male non-fallers.	Postural hypotension & falls RR 1.5 (0.95-2.3) in women	OH was not significantly associated with future falls.	∞	-	8
Chan 1997 (66)	401	69 (range 60-90)	Cohort, community, cross-sectional	Any fall in the past 12 months	Standing at 3 min., sphyg, 20 SBP	7.2% (n=5) in fallers and 10.5% (n=35) in non-fallers.	OH & falls unadjusted OR 0.7 (0.3-1.8)	OH was not associated with falls.	∞	-	4
Chang 2010 (67)	1361	72 [±5]	Cohort, community, cross-sectional	Any injurious fall in the past 12 months	Supine and standing, immediately,20/10	36% in fallers, 24% in non-fallers. Prevalence of OH in injurious fallers higher than in non-injurious fallers.	OH & injurious falls vs. non-injurious falls OR 2.3 (1.1-5.12) OH & remarkable injury vs. no injury: OR 4.0	OH and any falls were not associated. OH was associated with injurious falls compared to		++	6

							(1.6-10.0).	non-injurious falls			
Downton 1991 (73)	203	83 [±5], range 75-97	Cohort, community, cross-sectional	Any fall in the past 12 months	Sitting and standing at 1 and 2 min., 20 SBP	31% of subjects; equal between fallers and non-fallers.		OH was not associated with falls		-	4
Ensrud 1992 (33)	9704	72 (range 65-99)	Cohort, community, cross-sectional	Any fall in the past 12 months	Supine and standing at 1 minute, sphyg, 20 SBP		Falls and OH: OR 1.0 (0.9-1.2)	OH was not associated with a history of falls	∞	-	5
Gangavati 2011 (76)	722	78 [±5]	Cohort, community (home), prospective	Recurrent falls during FU (min. 183 days)	Supine and standing at 1 and 3 min., sphyg, 20/10	Falls similar in those with and without OH. : 39% of participants with uncontrolled HTN and OH had recurrent falls, vs. 17% in those without	Recurrent falls & OH at 1 min in uncontrolled HTN: HR 2.5 (95% CI 1.3–5.0).	OH was associated with future recurrent falls in those with uncontrolled	∞	++	8

						OH.		HTN.			
Graafmans 1996 (77)	354	70+	Cohort, community, prospective	Any and recurrent falls during 28 week FU	Supine and standing at 1 minute, 20/10		OH & falls: OR 1.4 (0.8-4.8) (n/s). OH & recurrent falls: OR 2.0 (1.0-4.2)	OH was associated with future recurrent falls but not with any falls		++	8
Heitterachi 2002 (40)	70	77 [±6]	Cohort, community, prospective	Any fall during 12 month FU	HUT at 60 degrees, continuous, 20 SBP	OH at 3 min.: 22% of fallers, 6% of non-fallers.	OH at 3 min. & falls: RR 1.7 [±1.1-2.6].	OH at 3 min. after HUT was associated with future falls.	§	++	7
Kario 2001 (83)	266	76 [±5]	Cohort, community, cross-sectional	Any fall during 12 month FU	Supine, immediately after standing and at 2 min. Sphyogmomanomet	OH not different between fallers and non-fallers		OH was not associated with future falls	∞	-	9

					er, 20/10						
Lawlor 2003 (90)	4050	71 (95% CI 70 - 71)	Cohort, community, cross-sectional	Any and recurrent falls in the past 12 months	Mean of two standing measurements with sphyg, 20/10	17.6% of fallers and 17.1% of non-fallers		OH was not associated with falls in the past year	∞	-	6
Liu 1995 (93)	100	83 [±6], range 62-96	Cohort, Community, Prospective	Any fall during 12 months FU	Immediately on standing and after 5 min., sphyg, 20/10	Prevalence OH 3-15%, no difference between fallers and non-fallers		OH is not associated with future falls	∞	-	6
Luukinen 1996 (94)	1016	76 [±5]	Cohort, community, prospective	Recurrent falls during 12 month FU	Sitting and standing at 1 minute, sphyg, 20 SBP	35% in fallers, 29% in non-fallers	RR 1.3 (0.8-1.9)	OH was not associated with future falls	∞	-	8
Mader 1987 (95)	300	70 (range 56-93)	Cohort outpatient community	Any fall in past 12 months	Supine and standing at 1 minute sphyg, 20 SBP.	7% of fallers, 12% of non-fallers	n/s	OH was not associated with falls in	∞	-	3

			clinic, cross-sectional					the past year			
Maurer 2004 (97)	111	88 [±7]	Cohort, long-term care, prospective	Any fall during a median FU of 270 days	Sitting and standing for 5 min., continuous, 20/10		OH at 1-minute & falls HR 0.98 (0.5–2.0), OH at 3 min. & falls HR 1.3 (0.7–2.5)	OH was not associated with future falls		-	6
Ooi 2000 (103)	844	60+	Cohort, long-term care, prospective	Any fall during 18 months	Supine and standing at 1 & 3 min., 8 measurements sphyg. 20/10	50% in fallers and non-fallers.	OH & recurrent falls in previous fallers aRR 2.1 (1.4 - 3.1). Risk of subsequent falls was greatest in previous fallers with OH at two or more	OH was associated with recurrent falls in those who had previous falls	∞	++	5

							measurements, RR 2.6 (1.7 - 4.6)				
Pasma 2014 (105)	197	82	Cohort, outpatient clinic, cross-sectional	Any fall in the past 12 months	Supine and standing at 1 & 3 min. with sphyg & continuous,20/10	Intermittent OH not different between fallers and non-fallers. Patients with a larger drop in BP during 15-60 seconds after standing more likely to have fallen in the past 12 months.	Continuous: OH overall (0-180 s) & falls, OR 2.45 (0.75-8.06). SBP decrease 15-60s: OR 1.95 (1.08-1.45), DBP decrease 15-60s (OR 2.08 (1.20-3.61).	Continuous OH was not associated with a history of falls. Greater DBP and SBP drop at 15-60 seconds were associated with a falls. Intermittent OH was not associated	∞§	-	5

								with falls.			
Romero-Ortuno 2011 (112)	598	72	Cohort, community, cross-sectional	Any fall in past 6 months	Active stand for 3 min, continuous. COH: >20 SBP or 10 DBP drop. IOH: 40 SBP / 20 DBP drop < 15 seconds	Falls in those with IOH (24.7%) vs no-IOH (10.4%), p<0.001. No difference in falls between those with consensus OH		IOH was univariately associated with a history of falls in the past 6 months	§	+	3
Rutan 1992 (114)	4931	OH+: 74, OH-: 73	Cohort, community, cross-sectional	Frequent falls in the past 12 months	Supine and standing at 3 min., sphyg. 20/10	OH in frequent fallers: 27%, OH in non-fallers: 17%	OR 1.5 (1.0 - 2.2)	OH was associated with a history of frequent falls in the past year	∞	++	5
Tinetti 1986 (119)	79	Rec. fallers	Cohort, long-term care,	Recurrent falls during 3 month FU	Supine and standing at 1 & 3 min., 20	12% (3/25) of recurrent fallers, 0% (0/54) of		OH was more prevalent in		+	3

		81 [±7], single/non-fallers 78 [±7]	prospective		SBP.	single/non fallers		recurrent fallers than single/non-fallers			
Van der Velde 2007 (121)	217	Fallers 79 [±6], non fallers 75 [±6]	Cohort, outpatient clinic, cross-sectional	Any fall in past 12 months	Passive (HUT) at 70°, continuous. Supine and standing at 1,2 & 3 min. with sphyg. 20/10	Sphyg OH 27% of fallers (n=33), 17% (n=12) of non-fallers. Continuous OH: 72% (n=89) of non-fallers vs 50% (n=34) of non-fallers.	Sphyg OH & falls OR 1.9 (0.8–4.4). Continuous 1-s average & falls OR 2.3 (1.1–4.7). Continuous 5 sec average & falls OR 2.5 (1.4–4.7). Unadjusted for	Continuous measured OH was associated with falls in the past year, sphyg measured OH was not.	∞§	+	3

							confounders.				
Wong 2014 (123)	481	80 [±4]	Cohort, community, prospective	Any fall during 12 month FU	Passive (HUT), supine and at 70 deg, immediately and at 1,2,3,4,5 min, sphyg, 20/10	23% of fallers, 21% of non-fallers	OH & falls: univariate RR 1.1 (0.9–1.4)	OH was not associated with future falls	∞	-	9
Case control											
Davies 2001 (41)	26	79 [±7], 78 [±7]	Case-control, Emergency department, cross-sectional	Cases: non-accidental falls. Controls: accidental falls or other	Active stand for 2 min, continuous, 20 SBP	31% cases, 19% controls		Prevalence of OH was higher in accidental fallers than controls.	§	+	6
Lipsitz	70	87 [±6] / 87	Case-control, long-term	Cases: recurrent falls in past six	Supine and standing at 1 & 3 min. sphyg,	21% of fallers, 20% in non-fallers	OR 1.0 (0.4-2.6)	OH was not associated	∞	-	5

1991 (59)		[±5]	care, cross-sectional	months, controls: no falls in past six months, or no more than one in past 2 years	20/10			with recurrent falls			
Series											
Allcock 2000 (55)	120	78 (range 66-94)	Observational series, falls & syncope clinic, retrospective	Referred for unexplained falls and syncope	Active stand, immediately after and at 30-second intervals for 2 min. continuous, 20/10	29%		OH is common in patients with unexplained falls and syncope	§		3
Boddaert 2004 (61)	57	84 [±7]	Observational series, acute hospital, cross-	In ER or admitted for falls	Supine and standing at 1,2 & 3 min., automatic oscillometric	32%		OH is common in patients admitted for			3

			sectional		monitor. 20/10			falls			
Davies 1996 (70)	26	79 (SE 8)	Observational series, emergency dept., cross-sectional	Unexplained and recurrent falls (RF)	Supine and standing at 1 minute, continuous. 20 SBP	19%		OH was a frequent finding in those with unexplained falls	§		3
Dey 1997 (72)	35	75 (range 50-95)	Observational series, falls & syncope clinic, cross-sectional	Drop attacks (unexplained falls)	Morning active standing, continuous.	14%		OH was not very common in this series	§		3
Lagro 2013 (89)	175 (with falls)	75+	Observational series, falls & syncope clinic, cross-	Referred for falls	Active stand for 10 min., continuous, 20/10	55%		OH is common in patients with falls	§		3

			sectional								
Milton 2009 (100)	1464	78 [±10]	Observational series, falls & syncope clinic, cross-sectional	Referred for unexplained falls	Passive (HUT) for 3 min., continuous. 20/10	8%		OH was present in a small amount of fallers	§		2
Paling 2011 (42)	111	82 (range 61-99)	Observational series, falls & syncope clinic, cross-sectional	Referred for unexplained falls and syncope	Active stand with continuous recording, 20/10	7%		OH was not very common in patients with unexplained falls and syncope	§		3
Parry 2005 (75)	93	77 [±9], range 55-92	Observational series, falls & syncope	Drop attacks (3 or more unexplained falls in the past 6	Active stand for 3 min., continuous, 20/10	5%		OH was not diagnosed frequently in	§		3

			clinic, cross-sectional	months)				patients with recurrent drop attacks			
Rafanelli 2014 (109)	298	75 [±11]	Observational series, falls & syncope clinic, retrospective	Referred for unexplained falls	Passive (HUT), Supine and tilted at 0,1 & 3 min. Continuous, 20/10.	35%		OH is common in patients with unexplained falls	§		3
Smebye 2014 (117)	111	82 [±7]	Observational series, falls & syncope clinic, cross-sectional	Any fall	Supine and standing at 1 & 5 min. 20/10	24%		OH is common in older fallers			3
Tan 2008 (118)	302	71 [±11]	Observational series, falls & syncope	Referred for unexplained falls and syncope	Active stand for 2 min., continuous recording.20/10	56%		OH is common in patients with	§		3

			clinic, retrospective					unexplained falls and syncope			

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa Scale.

∞, sphygmomanometer BP measurement

§, continuous BP measurement

20/10, ≥20 mmHg SBP and/or ≥10 mmHg DBP drop cut-off for OH

20 SBP, >20mmHg SBP drop cut-off for OH

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 3. Carotid sinus hypersensitivity and falls

First author	N	Age, years	Population, design, setting	Falls outcome	Assessment method	Main findings and prevalence of CSH	Conclusion	CSS	Association	NOS
Cohorts										
Murphy 1986 (102)	100	80, (63-97) / 83, (61-97)	Cohort, Long-term care, prospective	Any fall during 33 month FU	CSM L+R, supine & upright (70°)	Prevalence of CI CSH was 11% in fallers and 21% in non fallers, difference n/s. VD CSS not measured.	CI CSH was not associated with future falls	¥	-	5
Case-control										
Anpalahan 2011 (48)	38	80 [±6] / 77[±5]	Case-control , Retrospective, Acute hospital	Referred for unexplained and accidental falls	CSM L+R, supine & upright (70°)	19% of unexplained fallers had CSS (2 CI, 2 VD), 0% of accidental fallers. Overall diagnosis	Neurally mediated syncope (CSS or VVS) was associated with unexplained falls	¥	++	5

						of NMS & unexplained falls: OR 5.3 (95% CI 0.6-10.4, p 0.050)	when compared to accidental falls			
Benchimol, 2007 (109)	259 / 55	50 [±24], 57 [±21]	Case-control, falls & syncope clinic, retrospective	Referred for unexplained falls and syncope	CSM L+R, supine & upright (70°)	11% of fallers had CSH (28/259) compared to 7% (4/55) of controls	CSH was not associated with falls	¥	-	5
Davies 2001(41)	26 / 54	79 [±7], 78 [±7]	Case-control, Emergency department, cross-sectional	In ED for unexplained (non-accidental) or accidental falls	CSM L+R, supine & upright (70°)	CI CSS: 46% (12/26) cases, 13% (7/54) of controls. VD CSS: 69% (18/26) cases, 22% (16/54) controls	CSS was more prevalent in non-accidental fallers than accidental fallers and other controls	¥	+	6
Freitas 2004 (75)	386 / 108	40+	Case-control, falls & syncope clinic, cross-	Referred for unexplained falls and	CSM supine, repeated if negative after 45	CSM+ in 20%, reproduction of symptoms in 19% of	Patients with unexplained falls and syncope more often	∞	+	5

			sectional	Syncope	minutes of HUT at 70º, CSM left and right for 10 seconds with an interval of 2 minutes	cases (Mixed 50%, CI response 28%, VD response 22%). One control (<1%) had CSM+ without symptom reproduction.	had CSS compared to healthy controls			
Kumar 2003 (87)	265 / 44	80 (60–92) / 71 (63–86)	Case-control, falls & syncope clinic, retrospective	Referred for falls	CSM L+R, supine & upright (70°)	Prevalence of CSS in fallers was 17% and 0% in asymptomatic controls.	CSS was more prevalent in fallers compared to asymptomatic controls	¥	+	6
Series										
Allcock 2000 (124)	120	78 (range 66-94)	Observational series, falls & syncope clinic, retrospective	Referred for unexplained falls and syncope	CSM L+R, supine & upright (70°)	37% CSH (22% CI and 15% VD)	CSS was common in patients with unexplained falls	¥		3

Davies 1996 (70)	26	79 (SE 8)	Observational series, emergency department, cross-sectional	Unexplained and recurrent falls	CSM L+R, supine & upright (70°)	73%	CSH was common in patients with unexplained falls	¥		3
Dey 1997 (125)	35	75 (range 50-95)	Observational series, falls & syncope clinic, cross-sectional	Drop attacks (unexplained falls)	CSM L+R, supine & upright (70°)	CSH 51%, CI or mixed CSS in 15, VD CSS in 3	CSS was common in those with unexplained falls	∞		3
Eltrafi 1999 (126)	139	66 [±20]	Observational series, falls & syncope clinic, retrospective	Unexplained falls	CSM L+R, supine & upright (70°)	21%.	CSS is responsible for recurrent falls and syncope in 21% of patients referred to a medical outpatient clinic.	¥		3
Kenny	130	77,	Observational	Referred for	Supine CSM only	13%	CSS is present in a	¥		2

1991 (85)		range 67-89	series, falls & syncope clinic, retrospective	unexplained falls and syncope			small number of patients who present with unexplained falls, dizziness or syncope			
De Castro Lacerda 2008 (88)	502	65 [±10]	Observational series, falls & syncope clinic, cross-sectional	Unexplained falls in the past 12 months	Supine CSM only	14%	CSH was present in large number of patient with unexplained falls	¥		3
Lagro 2013 (89)	175 (with falls)	75+	Observational series, falls & syncope clinic, cross-sectional	Unexplained falls	CSM L+R, supine & upright (70°)	84%	CSH was common in unexplained fallers	¥		3
Milton	1464	78 [±10]	Observational series, falls &	Falls and syncope	CSM L+R, supine & upright (70°)	8%	CSH was present in a small amount of	¥		2

2009 (127)			syncope clinic, cross-sectional				patients with unexplained falls			
Paling 2011 (128)	111 (with falls)	82, range 61-99	Observational series, falls & syncope clinic, cross-sectional	Unexplained falls	CSM L+R, supine & upright (70°)	44% (n=28 VD, n=16 mixed, n=5 CI) of unexplained fallers 42% of those with syncope	CSS was common in patients with unexplained falls,	∞		3
Parry 2005 (75)	93	77 [±9], range 55-92	Observational series, falls & syncope clinic, cross-sectional	Drop attacks (3 or more unexplained falls)	CSM L+R, supine & upright (70°)	40% (n=35 CI/mixed, n=2 VD)	CSS was common in patients with drop attacks	¥		3
Parry 2005 (104)	34 (falls) / 34 (syncope)	77 [9] / 75 [9]	Observational series, falls & syncope clinic, cross-sectional	Referred for unexplained falls or syncope	CSM L+R, supine & upright (70°)	CSS in fallers 71%, with LOC 64%. CSS in those with syncope: 85%, with LOC 44%	CSS was common in patients with unexplained falls and syncope	¥		3

Rafanelli 2014 (129)	298	75 [±11]	Observational series, falls & syncope clinic, retrospective	Referred for unexplained falls	CSM L+R, supine & upright (70°)	CSS 14.3% (n=42), CI n=34, VD n=5, mixed n=3.	CSS was common in patients with unexplained falls	∞		3
Richardson 1997 (111)	279	50+	Observational series, emergency department, cross-sectional	Unexplained falls, recurrent falls (3 or more in the past year)	CSM L+R, supine & upright (70°)	23% with (23% CI/mixed and 11% VD)	CSH was common in patients with unexplained and recurrent falls	¥		3
Smebye 2014 (130)	111	82 [±7]	Observational series, falls & syncope clinic, cross-sectional	Referred for falls	CSM L+R, supine & upright (70°)	11%	CSH was common in older fallers	¥		3
Tan	302	71 [±11],	Observational series, falls &	Unexplained falls, Falls and	CSM L+R, supine & upright (70°)	CSH 25%, CSS 14%.	CSH was common in patients with	∞		3

2009 (114)		range 38–98	syncope clinic, retrospective	syncope, drop attacks			unexplained falls			

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa Scale

CI: cardioinhibitory, VD: vasodepressor, CSM: carotid sinus massage, CSH: carotid sinus hypersensitivity, CSS: carotid sinus syndrome, NMS: neurally mediated syncope

¥ CSS defined as either vasodepressor drop of 50mmHG SBP and/or >3 second asystole on ECG

∞CSS defined as either vasodepressor drop of 50mmHG SBP or >3 second asystole on ECG with symptom reproduction

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 4. Vasovagal syncope and falls

First author	N	Age, years	Population, setting, design	Falls outcome	Assessment method	Prevalence of VVS and main findings	Conclusion	VVS	Association	NOS
Case Control										
Benchimol 2007 (59)	259 / 55	50 [±24], 57 [±21]	Case-control, falls & syncope clinic, retrospective	Unexplained falls and syncope	HUT 2x25 mins sphygmomanometer, Oscillometer..	HUT positive in 65% of cases, and in 5% of controls.	VVS is more common in those with unexplained falls and syncope than controls	∞	+	5
Anpalahan 2011	21 / 17	80 [±6] / 77[±5]	Case-control, acute hospital, retrospective	Unexplained and accidental falls	HUT 40mins with continuous monitoring	5% of unexplained fallers had VVS, vs. 0% of accidental fallers	VVS was more common in unexplained fallers	¥	+	5

(48)							compared with accidental fallers			
Series										
Allcock 2000 (55)	120	78, range 66-94	Observational series, falls & syncope clinic, retrospective	Unexplained falls and syncope	HUT 30mins with sphygmomanometer.	3%	VVS is not common in those with unexplained falls and syncope	∞		3
Davies 1996 (70)	26	79 (SE 8)	Observational series, emergency department, cross-sectional	Unexplained and recurrent falls	HUT 30mins.	15%	VVS was a common finding in unexplained or recurrent fallers	∞		3
Dey 1997 (72)	35	75, range 50-95	Observational series, falls & syncope clinic,	Unexplained falls (drop attacks)	HUT with continuous monitoring.	3%	VVS was not common in those with drop attacks	∞		3

			cross-sectional							
Eltrafi 1999 (74)	149	66 [±20]	Observational series, falls & syncope clinic, retrospective	Unexplained falls and syncope	HUT 45mins with continuous monitoring.	9%	HUT positive in 9% of patients referred for unexplained falls and syncope	∞		3
Paling 2011 (42)	111	82, range 61-99	Observational series, falls & syncope clinic, cross-sectional	Unexplained falls	HUT 15mins + 20 mins	11%	Combination of HUT/CSM provided a positive result in 62% of subjects	∞		3
Tan 2008 (118)	302	71 [±11]	Observational series, falls & syncope clinic, retrospective	Unexplained falls and syncope	HUT 20mins (no GTN) + 15mins (GTN) using continuous monitoring.	46%	VVS is common in those with unexplained falls and syncope	¥		3
Parry	93	77 [±9]	Observational	Unexplained	HUT 40mins with	3%	VVS is not common in	π		3

2005 (75)			series, falls & syncope clinic, cross-sectional	falls (3 or more drop attacks)	continuous monitoring. HUT induced hypotension with or without bradycardia/asystole and reproduction of symptoms.		those with drop attacks			
Rafanelli 2014 (109)	298	75.3 [±11.1]	Observational series, falls & syncope clinic, retrospective	Unexplained falls	HUT 15 mins or longer with continuous monitoring.	36%	VVS is common in those with unexplained falls and syncope	¥		3

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa scale.

VVS, vasovagal syncope. HUT, head-up tilt.

∞ HUT induced hypotension/ bradycardia with symptom reproduction

¥ VASIS classification used for definition of VVS [ref?]

Π HUT induced hypotension/bradycardia without symptom reproduction

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 5. Hypertension and falls

Author, year	N	Age Years	Population, setting, design	Falls outcome	Assessment method	Main findings and prevalence of HTN	OR/RR/HR	Conclusion	HTN	Association	NOS
Cohorts											
Assantachai 2003 (58)	1043	Men 69 [±6], women 68 [±7]	Cohort, community, cross-sectional	Any fall in past 6 months	SR, medical diagnosis of HTN	42% (n=87) of fallers, 25% (n=223) of non-fallers	OR 1.6 (1.1-2.3)	HTN was associated with falls	∞	++	3
Bergland	307	81 (range	Cohort,	Any fall during	SR, medical		OR 1.8, p<0.02	HTN was	∞	++	6

2003 (33)		75-93)	community, prospective	12 month FU	diagnosis of HTN			associated with future falls			
Brassington 2000 (62)	1526	Range 64-99	Cohort, community, cross-sectional	Any fall	SR, medical diagnosis of HTN	54% of fallers, 44% of non-fallers	Unadjusted OR 1.5 (1.1-1.9)	HTN was univariably associated with falls	∞	+	4
Chan 1997 (66)	401	69 (range 60-90)	Cohort, community, cross-sectional	Any fall in past 12 months	Not given	52.2% (n=37) of fallers and 37.9% (n=126) of non-fallers.	Unadjusted OR 1.8 (1.1-3.0)	HTN was univariably associated with falls		+	6
Chang 2010 (67)	1361	72 [±5]	Cohort, community, cross-sectional	Injurious falls in past 12 months	SR, medical diagnosis of HTN	49% of fallers, 43% of non-fallers		HTN was not associated with falls	∞§	-	4
Chen 2008 (68)	585	81 [±5]	Cohort, long-term care, cross-sectional	Any fall	MR	50.5% of non-fallers, 56.3% of fallers, p=0.442		HTN was not associated with falls	§	-	5

Damian 2013 (69)	733	83 (95% CI, 83-84)	Cohort, community, cross-sectional	Any fall in past month	MR	45% of cohort, not given for fallers	RR 1.0 (0.6-1.8)	HTN was not associated with a fall in the past month	§	-	5
Downton 1991 (73)	203	83 [±5]	Cohort, Community, cross-sectional	Any fall in past 12 months	Sitting blood pressure	Mean SBP was not different between groups		Mean SBP was not associated with falls	¶	-	3
Heckenbach 2014 (78)	5124	73	Cohort, Community, cross-sectional	GP visit for any fall	GP MR	44% of fallers, 37% of non-fallers.	not associated after adjustment	HTN was not associated with falls	§	-	6
Hung 2013 (79)	401	82 [±0.2]	Cohort, acute hospital, cross-sectional	Any fall in past 3 years	Average SBP calculated from SBP (2-4x/day) before discharge (for 3 days).	SBP>140 mmHg was 27% in non-fallers and 23% in fallers. Medical history of HTN 76% in fallers and 79% in non-		HTN was not associated with falls in the past year	¶	-	6

						fallers.					
Jansen 2014 (80)	8173	64 [±10]	Cohort, community, cross-sectional	Any fall in past 12 months	SR, medical diagnosis of HTN	38% of fallers, 37% of non-fallers.	HTN & any falls OR 0.9 (0.8-1.0), HTN & recurrent falls 1.0 (0.8-1.2)	HTN was not associated with falls	∞§	-	6
Jitapunkul 1998 (81)	4480	69 [±8)	Cohort, community, cross-sectional	Any fall in past 6 months	SR	28% of fallers, 25% of non-fallers.	HTN multivariably associated with falls, association not reported	HTN was a risk factor for falls in males	∞	++	5
Kao 2012 (82)	360	76 (range 64-91)	Cohort, community, cross-sectional	Recurrent and injurious falls in past 12 months	SR	52% of fallers, 52% of non-fallers OR 0.8 (0.5–1.3)		HTN was not associated with falls	∞	-	7

Kario 2001 (83)	266	76 [±5]	Cohort, community, prospective	Any fall during 12 months FU	Supine, immediately, 2 min after stand. Untreated hypertensive: SBP/DBP >140/90 mmHg, untreated	Falls less common in treated (17%) and untreated (20%) hypertensive subjects compared with normotensives (34%).	Objectively measured SBP (10 mmHg increase) & falls: RR 0.8 (0.7–0.9)	HTN was associated with a decreased risk of falls	¶	!	6
Klein 2013 (86)	3544	70 (range 60-97)	Cohort, community, cross-sectional	Any fall in past 3 months	SBP and DBP measured in sitting position with mercury sphygmomanometer. SBP/DBP HTN	24.8% of female fallers had SBP HTN 14.1% of male fallers had SBP HTN 12.7% of females had DBP HTN	DBP HTN women & falls OR 0.6 (0.4-0.9). DBP HTN men & falls OR 0.9 (0.5-1.5). SBP HTN	HTN was associated with a decreased risk of falls in women, but not in men.	¶	!	6

					>140/90	9% of males had DBP HTN	women & falls OR 0.7 (0.5-0.99). SBP HTN in men & falls OR 0.7 (0.4-1.2)				
Lawlor 2003 (90)	4050	71 (95%CI 70 to 71)	Cohort, Community, cross-sectional	Any fall in past 12 months	Oscillometer, 2x seated, SBP >160/95mmHg or receiving treatment for blood pressure	51.6% of fallers and 50.6% of non-fallers (p 0.39)		HTN was not associated with falls	¶	-	5
Liao, 2012 (92)	1165	75 [±7)	Cohort, community, cross-sectional	Any fall in past 12 months	Sphyg., SBP/DBP >130/85mmHg or use of antihypertensive	60% fallers, 50% non-fallers		HTN was no more prevalent in fallers than non-fallers	¶	-	6

					medication						
Maurer 2005 (98)	139	88 [±7)	Cohort, long-term care, prospective	Any fall during 12 month FU	MR and SR, continuous; SBP/DBP >140/90 or use of anti-hypertensive	55% of cohort	OR 2.0 (1.1–3.7)	Patients with HTN are more likely to suffer future falls	∞§¶	++	4
Mitchell 2013 (101)	5681	65+	Cohort, community, cross-sectional	Any fall in past 12 months	SR, medical diagnosis of HTN	54% of fallers, 51% of non-fallers.	Unadjusted OR 1.1 (0.97-1.3)	HTN is not associated with falls	∞§	-	5
Prudham 1981 (107)	2357	65+	Cohort, community, cross-sectional	Any fall in past 12 months	MR, SR and previous HTN	23% of fallers, 22% of non-fallers		HTN is not associated with falls	∞§	-	2
Sibley 2014 (116)	57	65+	Cohort, community, cross-sectional	Any fall in past 12 months	SR, medical diagnosis of HTN	21% of those with HTN fell, compared to 18% of people	A cluster 'hypertension' was associated	HTN is associated with falls	∞	++	5

						without HTN	with falls, OR 1.2				
Wong 2014 (123)	481	80 [±4]	Cohort, community, prospective	Any fall during 12 month FU	SR	55% of fallers and 62% of non-fallers.	HTN & falls unadjusted RR 0.9 (0.7–1.0)	HTN is not associated with falls	∞	-	9
Case control											
Herndon 1997 (58)	467	65+	Case-control, community, cross-sectional	In ER or admitted for falls	SR, medical diagnosis of HTN	7% of respondents had HTN, adjusted	OR 0.7 (0.5-0.9)	HTN is associated with a decreased risk of injurious falls	∞	-	5
Lipsitz 1991 (59)	70	87 [±6] / 87 [±5]	Case-control, long-term care, Prospective	Any fall in past 6 months	MR	41% of fallers, 39% of non-fallers		HTN was not associated with falls	§	-	5
Kelly	2278	79 [±8]	Case-control,	Injurious falls	MR and SR	31% of cases and 31%	Adjusted OR	HTN was not	∞§	-	4

2003 (84)			community, retrospective	reported in ED		of controls	0.9 (0.8-1.0)	associated with injurious falls			
Series											
Marechaux 2009 (96)	60	81 [±8)	Observational series, emergency department, cross-sectional	In ED for falls	MR	73%		HTN was present in the majority of patients who presented with a fall	§		2
Van Nieuwenhuizen 2010 (122)	639	79 [±8]	Observational series, emergency department, cross-sectional	In ED for fall	SR	34%		HTN was not highly prevalent in patients in the ED with a fall	∞		2
N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted for potential confounders unless otherwise specified											

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa Scale. HTN, hypertension. MR, medical record. SR, self-report

∞, Self-report. §, Medical records. ¶, Objective assessment.

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 6. Low blood pressure and falls

First author	N	Age, years	Population, setting, design	Outcome of falls	Assessment method	Main findings and prevalence of LBP	OR/RR/HR	Conclusion	LBP	Association	NOS
Berg 1997 (60)	96	72 [±7], range 60-88	Cohort, community, prospective	Falls during 12 month FU	Not stated	Low SBP 74% of fallers, 37% of non-fallers. Low DBP 52% of fallers, 35% of non-fallers.	Low SBP & recurrent falls OR 4.8 (1.6-20.1). Low DBP & recurrent falls OR 2.0 (0.7-5.6)	Low SBP was associated with recurrent future falls	SBP <142 mmHg	++	7
Campbell 1989 (65)	761	70+	Cohort, community, prospective	Falls during 12 month FU	Sphygmomanometer, supine or standing	11% in female fallers and 3% in female non-fallers, 7% in male fallers and 5% in male non-fallers.	Systolic hypotension & falls RR 3.3 (1.3-8.3) in women.	Low systolic BP was associated with future falls in women	SBP ≤110 mmHg	++	8
Kario	266	76	Cohort,	Falls	Sphygmoman	Falls 2.8 times more often in	Standing SBP level &	Lower standing	SBP<140	++	9

2001 (83)		[±5]	community, prospective	during 12 month FU	ometer,	low SBP than higher). 10 mmHg increase in standing SBP reduced falls by 22%	falls (RR 0.78 for 10 mm Hg increase, p=0.005)	SBP was an independent predictor of future falls. DBP was not related to falls.	mmHg		
Klein 2013 (86)	3544	70, range 60-97	Cohort, community, cross-sectional		Sphygmomanometer,	Low SBP 13% of male fallers, 6% of male non-fallers,	Low SBP& falls in men OR 2.5 (95%CI 1.1-5.5), low DBP & falls OR 1.8 (1.0-3.1)	Low SBP or DBP was associated with falls in men in the past 3 months	SBP/DBP <120/80 mmHg	++	7
Lawlor 2003 (90)	4050	71	Cohort, community, cross-sectional	Any falls in the past 12 months	Oscillometer,	7.3% in fallers, 7.6% in non-fallers		Low standing BP was not associated with recurrent future falls	SBP/DBP ≤100/60 mmHg	-	6

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa Scale.

DBP: diastolic blood pressure. SBP: systolic blood pressure. LBP, definition of low BP

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 7. Coronary artery disease (Angina, ischemic heart disease and myocardial infarction) and falls

First author	N	Age , Years	Population setting, design	Outcome of falls	Method of CAD assessment	Main findings and prevalence of CAD	OR/RR/HR	Conclusion	CAD	Association	NOS
Cohort											
Damian 2013 (69)	733	83	Cohort, community, cross-sectional	Any fall in the past month	MR, interview with physician,	17% in cohort	IHD & falls RR 0.6 (0.3 – 1.2)	IHD was not associated with falls	∞	-	
Jansen 2015 (80)	8173	64 [±10], range 51-105	Cohort, community (home), cross-sectional	Any fall in the past 12 months	SR	Angina 7.1% of fallers, 5.1% of non-fallers. MI 4.5% of fallers , 4.6% of non-fallers.	Angina & falls OR 1.1 (0.9-1.4), & recurrent falls OR 1.4 (1.0 -1.9). MI & falls OR 0.8 (0.6- 1.1), &	MI is not associated with falls, angina is associated with recurrent	∞	++	6

							recurrent falls OR 1.2 (0.8-1.7)	falls			
Lawlor (90)	4050	71 (95%CI 70 to 71)	Cohort, Community, cross-sectional	Any fall in past 12 months	SR and MR	23% of fallers, 14% of non-fallers	CAD & falls OR 1.5 (1.2-2.0), CAD & recurrent falls OR 2.1 (1.5-3.0)	CAD was associated with falls	∞	++	5
Lee 2009 (65)	11 ,113	55%: 65-75 years. 45%: 76+	Cohort, community (home), cross-sectional	Recurrent falls in the past 12 months	SR	23% of patients who had a fall had CAD compared to 16% of the overall population		CAD was more prevalent in fallers compared to non fallers	∞	+	6
Mitchell 2013 (101)	5681	65+	Cohort, community (home), cross-	Any fall in the past 12 months	SR	Heart disease/angina 30% of fallers, 24% of	Circulatory system disease & falls: OR 1.4	Circulatory disease was associated	∞	++	5

			sectional			non-fallers, poor circulation in legs/peripheral vascular disease 28.1% of fallers, 17.4% of non-fallers.	(1.2–1.6)	with falls			
Rafiq 2014 (110)	135,433	75 [±8], range 65-104	Cohort, community, prospective	GP visit for any fall	MR	IHD 15%, CAD 5%, MI 4%. IHD & falls	OR 1.2 (1.1-1.2)	IHD was independently associated with falls; CHF, CAD and MI were not	∞	++	6
Sibley 2014 (116)	16,357	65+	Cohort, community, cross-sectional	Any fall in the past 12 months	SR	24% of those with heart disease fell, compared to 19% of those without	OR 1.3, p 0.06	Cluster 'heart disease' was not significantly	∞	-	4

						heart disease		associated with falls			
Stenhagen 2013 (94)	1763	60-93	Cohort, community (home), prospective	Any fall at 6 months, at 3 and 6 years	MR (ICD codes)	Heart disease in 30% of fallers, 20% of non-fallers.	OR 1.4 (1.0-1.8).	Heart disease was associated with future falls	∞	++	8
Wong 2014 (123)	481	80 [±4]	Cohort, community (home), Prospective	Any fall during 12 month FU	SR	MI in 10% of fallers, 9% of non-fallers. MI & falls unadjusted	RR 1.0 (0.7–1.5)	MI was not associated with future falls	∞	-	9
Case control											
Herndon (58)	467	65+	Case-control, community, cross-sectional	In ER or admitted for falls	SR	14% of cases, 12% of controls	OR 1.2 (0.8-1.7)	MI was not associated with falls	¥	-	5

Series											
Anpalahan 2011 (48)	38	80 [±6], 77 [±5]	Observational series, acute hospital, cross-sectional	In ED for unexplained or accidental falls	SR, MR	When combined with HTN 76%		CVD with HTN is common in older fallers	∞		4
Phillips 1999 (106)	142	83, range 76-99	Observational series, emergency department, cross-sectional	In ER or admitted for falls or syncope	Chest pain, serial ECGs, cardiac enzymes	10%		Prevalence of acute MI in patients admitted with falls or syncope	¥		3
van Nieuwenhuijzen 2010 (122)	639	79 (±8)	Observational series, emergency department, cross-sectional	in ER for falls	SR, MR	11%		History of MI in fallers presenting in the ED	¥		2

Vu 2011 (54)	44,942	median 82 (IQR 76-87)	Observational series, acute hospital, retrospective	In ER or admitted for falls	MR (ICD codes)	0.9% (95% CI 0.9-1.0)		acute MI is not common in patients admitted for injurious falls	¥		1

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk.. OR/HR/RR is adjusted unless otherwise specified.

SD (±): standard deviation. IQR, interquartile range. CAD, coronary artery disease, CHF, congestive heart failure, CVD, cardiovascular disease, ED, emergency department. GP, general practitioner, HTN, hypertension, IHD, ischemic heart disease, MI, myocardial infarction. MR, medical record. WHO, world health organization. SR, self-report. ∞ Both MI/Angina, ¥ Acute MI only. ++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! Negative association.

Table 8. General cardiovascular disease and falls

First author	N	Age, years	Population, setting, design,	Outcome of falls	Assessment method	Main findings and prevalence of CVD	OR/RR/HR	Conclusion	Association	NOS
Cohort										
Alamgir (54) 2015	5996	65+	Cohort, community (home), cross-sectional	Any fall in the past 3 months	SR of CVD	Not given	CVD & falls RR 1.1 (0.6-1.8)	CVD was not associated with falls	-	6
Brassington 2000 (62)	1526	64-99	Cohort, community (home), cross-sectional	Any fall	SR of CVD	30% of fallers, 22% of non-fallers.	Unadjusted OR 1.5 (1.1-2.0)	CVD is univariately associated with falls	+	4
Chen	585	81 [±5]	Cohort, long-term	Any fall in		CVD 5.2% in non-	n/s	CVD was not	-	4

2008 (68)			care, cross-sectional	the past 6 months	MR of CVD	fallers, 12.5% in fallers		associated with falls		
Heckenbach 2014 (78)	5124	73	Cohort, community (home), cross-sectional	GP visit for any fall	MR (GP, ICD code of diseases of arteries/arterioles/capillaries)	30% of fallers, 18% of non-fallers.	OR 1.5 (1.2-1.9).	Arterial disease was associated with falls	++	5
Kao 2012 (82)	360	76 (range 64-91)	Cohort, community (home), cross-sectional	Recurrent or Injurious falls in the past 12 months	SR of CVD	37% of fallers and 26% of non-fallers.	OR 1.5 (0.9-2.6)	CVD was not associated with falls	-	6
Lee 2006 (91)	4000	72 [±5]	Cohort, community (home), cross-sectional	Any fall in the past 12 months	SR of heart disease	Total prevalence 17%	OR 1.6 (1.4-2.0)	Heart disease was associated with single and recurrent falls	++	7
Prudham	2357	65+	Cohort, community	Any fall in	SR , MR of CVD	CVD 21% of fallers		CVD is more	+	2

1981 (107)			(home), cross-sectional	the past 12 months		vs. 16% of non-fallers (p<0.05)		prevalent in fallers than non-fallers in the community		
Case control										
Kelly (84)	2278	79 [±8]	Case-control, community, retrospective	Injurious falls reported in ED	SR , MR of CVD	25% of cases, 19% of controls	OR 1.1 (0.95-1.2)	CVD was not associated with falls	-	4
Series										
Smebye 2014 (117)	111	82 [±7]	Observational series, falls & syncope clinic, cross-sectional	Referred for any fall	MR of CVD	52%		CVD is common in older fallers		3
N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified										

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa Scale.

CVD: cardiovascular disease, GP: general practitioner. (C)HF: (congestive) heart failure.

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 9. Postprandial hypotension (PPH) and falls

First author	N	Age, years	Population, Setting, Design	Outcome of falls	Assessment method	Main findings and prevalence of PPH	OR/RR/HR	Conclusion	Association	NOS
Cohort										
Aronow 1997 (57)	499	80 [±9]	Cohort, long-term care, prospective	Any fall during 20 month FU	Baseline BP before lunch and at 15, 30, 45, 60, 75 and 120 minutes after lunch. Resident in sitting position for at least 2 minutes before measuring.	mean maximal decrease in fallers 20 [±5]mmHg, in non-fallers 12 [±4]mmHg.	RR 1.2 (1.2 - 1.2)	PPH is associated with future falls	++	6

Le Couteur 2003 (36)	179	83 [±7]	Cohort, community (residential facility), cross-sectional	Any fall in the past 12 months	Postprandial BP measurements at 60 min after the meal in both supine and upright position	38% of subjects had PPH.	PPH & falls OR 1.0 (0.6–1.9), & recurrent falls OR 0.9 (0.4–1.9). SBP <=115 mm Hg after a meal & falls OR 3.7 (1.3–11.1)	PPH was not associated with falls or recurrent falls, but SBP postprandial drop below 115 mmHg was	-	3
Case control										
Puisieux 2000 (108)	45	81 [±9] / 79 [±7]	Case-control, acute hospital, cross-sectional	Admitted for any fall	24 hour. Recordings every 15 minutes during the day, every 30 minutes during the night.	PPH 27% in the syncope group, 18% in the fall group, 9% in the control group.		PPH is common in patients admitted for falls and syncope	+	5

Schoon 2013 (115)	105 / 25	79 [±7] / 74 [±4]	Case-control, falls & syncope clinic, cross-sectional	Any fall and syncope	10 minutes of rest, standardized fluid meal consumed within 10 mins (292 calories). HR and BP continuously measured until 75 minutes after the meal.	53% of cases, 14% of controls		PPH is more common in those referred for falls than cases without falls	+	6

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle-Ottawa-Scale score

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 10. Cardiac arrhythmias and falls

First author	N	Age, Years	Population, Setting, Design	Outcome of falls	Assessment method	Main findings and prevalence of CA	OR/RR/HR	Conclusion	CA	Association	NOS
Cohort											
Damian 2013 (69)	733	83	Cohort, Community, Cross-sectional	Any fall in the past month	Medical chart, interview with physician	Arrhythmias in 22.3% of fallers	Arrhythmias RR 3.4 (1.8-6.3)	Medical history of arrhythmia was associated with a fall in the past month	Π	++	6
Hung 2013 (79)	401	82 [±0.2]	Cohort, acute hospital, Cross-sectional	Any fall in the past 3 years	12-lead ECG, Telemetry, Medical chart history	AF 20% of fallers, 11% of non-fallers, p 0.029	AF & falls 2.0 (1.1-3.6)	AF was independently associated with	μ	++	5

								history of falls.			
Jansen 2015 (72)	4886	62 [±8]	Cohort, Community, cross-sectional	Any fall in the past 12 months	ECG	AF 3.6% in fallers, 2.1% in non-fallers	AF & any fall OR 1.4 (0.9-2.2). Age 65-74: OR 2.0 (1.0-4.1)	AF is associated with any fall in the past year in those aged 65-74, but not in the overall age group	µ	++	6
Case Control											
Davison 2005 (71)	128	77 [±6]	Case-control, emergency department, cross-sectional	Recurrent falls in the past 12 months	24-hour ambulatory ECG recorder.	One or more ECG abnormalities were identified in 49% of fallers and 41% of controls. No causative arrhythmias were	Any ECG abnormality & falls: RR 1.2 (0.9–1.6).	No causative arrhythmias identified in recurrent fallers compared to controls without a history of falls.	Π	-	8

						identified.					
Rosado 1989 (113)	51	86	Case-control, long-term care and community, cross-sectional	Any fall in past 7 days	Holter monitoring	82% ventricular arrhythmias in both groups, 100% supraventricular arrhythmias in both groups.		Cardiac arrhythmia was not more prevalent in those who had falls	¥	-	8
Sanders 2012 (15)	211	82 [±9]	Case-control, emergency department, retrospective	In ER for accidental and non-accidental falls	12-lead ECG, medical history (chart review)	26% of non-accidental fallers had a medical history of AF, compared to 15% of those with accidental falls	History of AF & non accidental falls OR 1.2 [1.0-2.7] compared to non-accidental falls. Objectified AF not associated with falls	AF is associated with non-accidental (unexplained) falls compared to accidental falls	µ	++	5
Series											

Allcock 2000 (55)	120	78, range 66-94	Observational series, falls & syncope clinic, retrospective	Referred for unexplained falls and syncope	12-lead ECG and Holter monitoring	<1%		Cardiac arrhythmia was not frequently observed in subjects with unexplained falls	П		3
Armstrong 2003 (56)	15	73, range 61-89	Observational series, falls & syncope clinic, retrospective	Referred for unexplained falls and syncope	ILR (up to 3 years)	27%		Cardiac arrhythmia was frequently observed in subjects with unexplained falls and syncope with no other attributable diagnosis for their fall	П		2

Davies 1996 (70)	200	79 (SE8)	Observational series, emergency department, cross-sectional	In ED for unexplained and recurrent falls	12-lead ECG and/or ambulatory heart rate monitoring	8%		Arrhythmia was common in unexplained fallers	Π		3
Midttun 2011 (99)	207	83, range 58–95	Observational series, falls & syncope clinic, retrospective	Referred for unexplained falls	External Loop Recorder (7 days)	16%		Cardiac arrhythmia was not frequently observed in subjects with unexplained falls	∞		1
Parry 2005 (75)	93	77 [±9], range 55-92	Observational series, falls & syncope clinic, cross-sectional	Unexplained falls, (3 or more drop attacks) in the past 6 months	12-lead ECG and Holter monitoring	18% arrhythmia. 6% significant arrhythmia		Cardiac arrhythmia is a frequent finding in subjects with unexplained falls	μ,∞		3

Smebye 2014 (117)	111	82 [±7]	Observational series, falls & syncope clinic, cross-sectional	Referred for any fall	12-lead ECG	AF 8% Atrioventricular block, grade I 6% Branch block 2% (n=2/106)		Arrhythmias were common in older fallers	∞		3

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR is adjusted unless otherwise specified.

SD (±): standard deviation. IQR: interquartile range. SE: standard error. NOS, Newcastle-Ottawa-Scale

AF: atrial fibrillation. ECG: electrocardiogram. ILR, internal loop recorder

¥ Ventricular/ Superventricular arrhythmias. ∞ Bradycardia/heart block only. Π Any arrhythmia. µ atrial fibrillation

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 11. Heart failure and falls

First author	N	Age, years	Population, setting, design	Outcome of falls	Assessment method	Main findings and prevalence of OH	OR/RR/HR	Conclusion	CHF	Association	NOS
Cohorts											
Damian 2013 (69)	733	83	Cohort, community, cross-sectional	Any fall in the past month	Medical chart, interview with physician,	20% in cohort	RR 2.2 (1.2- 4.0)	HF was associated with a fall in the past month		++	6
Heckenbach 2014 (78)	5124	73	Cohort, community, retrospective	GP visit for any fall	Medical chart, ICD-codes GP	19% of fallers, 9% of non-fallers.	OR 1.7 (1.3-2.3)	HF was associated with previous falls		++	5
Jansen 2015 (80)	8173	64 [±10]	Cohort, community,	Any fall in the past 12 months	Self-reported doctor-diagnosed	1.6% of fallers, 0.9% of non-fallers	HF & falls OR 1.4 (1.1-1.7)	HF was associated with		++	6

			cross-sectional				HF & recurrent falls OR 1.5 (1.0-2.1)	falls and recurrent falls			
Rafiq 2014 (110)	135,433	75 [±8]	Cohort, community, retrospective	GP visit for any fall	Medical chart, GP charts,	4% in whole cohort	Not given	HF was not associated with falls	∞	-	6
Stenhagen 2013 (94)	1763	Range 60-93	Cohort, community, prospective	Any falls in the past 6 months, at 3 and 6 years	Medical chart, ICD-10 examination by a physician	11% of fallers and 4% of non-fallers.	OR 1.9 (1.2-3.0)	HF was associated with future falls	¥	++	8
Series											
Vu 2011 (54)	44,942	82 (IQR 76-87)	Observational series, acute hospital, retrospective	In ER or admitted for falls	Medical chart, ICD codes	3%	n/a	HF is not common in patients admitted for			1

								injurious falls			

N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa Scale. (C)HF: (congestive) heart failure. ∞ NHS read criteria for CHF. ¥. NYHA class II-IV symptoms

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Table 12. Structural cardiovascular abnormalities and falls

First author	N	Age, years	Population, setting, design	Falls outcome	Type of abnormality	Assessment method and definition of abnormality	Main findings and prevalence of abnormality and main findings	Conclusion	Association	NOS
Schoon 2013 (115)	105	79 [±7] / 74 [±4]	Case-control, falls & syncope clinic, cross-sectional	Any fall or syncope leading to referral	Head turning induced hypotension	10 min. active stand, continuous BP. Three head movements (rotation right, left and hyperextension). SBP calculated as mean of three beats with lowest SBP during the HTT. HTT defined as a drop in SBP of ≥20 mmHg.	39% of cases had HTIH, compared to 44% of controls.	HTIH is not different between those presenting with falls and syncope compared to healthy controls	-	6
Van der Velde	215	77.4 [± 6.0]	Cohort, geriatric	Any fall during 3	Structural cardiac	Echocardiography. Aortic valve stenosis, aortic valve	AVS 7% fallers, 10% non-fallers. AVR 29% of fallers, 24% non-	Mitral, tricuspid and pulmonary	++	4

2007 (120)			outpatient clinic, prospective	month FU, monthly calendars	abnormalities	regurgitation, mitral valve regurgitation, tricuspid valve regurgitation, pulmonary valve regurgitation, pulmonary hypertension, LV hypertrophy (septum >12mm), LVEF <40%	fallers. MVR. 43% of fallers, 29% non-fallers, HR 1.7 (1.0–2.9). TVR 67% fallers, 37% non-fallers, HR 2.4 (1.3–4.4). PVR. 47% fallers, 29% non-fallers, HR 1.7 (1.0–3.0). PH 29% fallers, 19% non-fallers, HR 1.35 (1.1–1.7). LVH 36% fallers, 33% non-fallers, HR 1.8 (0.9–3.6).	valve regurgitation and pulmonary hypertension were associated with future falls		
Wong 2014 (123)	531	80 [±4]	Cohort, community, prospective.	Any fall during 12 month FU, monthly calendars	Arterial stiffness	Carotid–femoral PWV measured supine using a semi-automated pulse wave analysis system. High PWV was taken as the top quintile (>13 m/s)	Pulse wave velocity 11.5 [2.6] m/s in fallers and 11.0 [2.2] m/s in non-fallers (RR 1.05 (1.01–1.09)). Top quintile of PWV & falls RR 1.37 (1.06–1.78), adjusted for age, gender and	Arterial stiffness is an independent predictor of future falls	++	9

							other confounding factors			

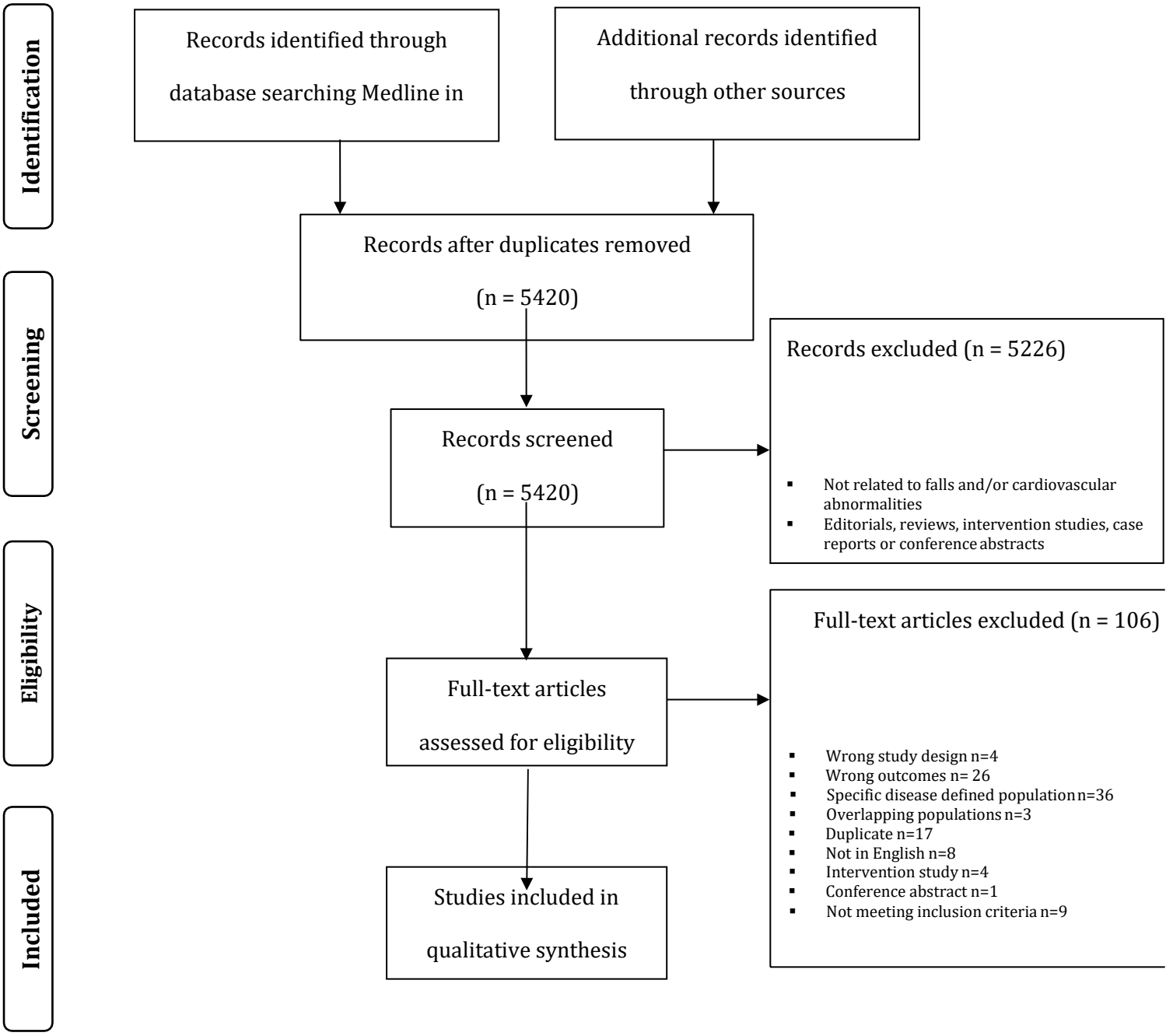
N/A: Not applicable. 95% CI: 95% confidence interval. OR: odds ratio. HR: hazard ratio. RR: relative risk. OR/HR/RR are adjusted unless otherwise specified

SD (±): standard deviation. IQR: interquartile range. NOS, Newcastle Ottawa Scale.

VS, aortic valve stenosis. AVR, aortic valve regurgitation. MVR, mitral valve regurgitation. TVR, tricuspid valve regurgitation. PVR, pulmonary valve regurgitation. PH, pulmonary hypertension. LVH, left ventricular hypertension.

++ Association multivariably adjusted for potential confounders, + univariable association or higher prevalence compared to control group, - absent association or similar prevalence, ! negative association

Figure 1. Flow diagram of study screening and inclusion



Appendix S1. Search strategy and actual search

Key search terms were 'falls', 'aged' and 'cardiovascular'.

Search terms for falls included: falling, stumbling, slipping or tripping.

Search terms for ‘aged’ included: aging, frail elderly, old, senior, geriatric and postmenopausal women.

Search terms for 'cardiovascular' included: cardiovascular, circulatory or heart diseases, hypertension, blood pressure, arrhythmia, sinus node disease, heart conduction abnormality, atrial fibrillation, bradycardia, heart valve disease, cardiomyopathy, myocardial ischemia or infarction, heart failure, carotid sinus syndrome, orthostatic or postural hypotension, postprandial hypotension, vasovagal and neurocardiogenic syncope.

Appendix S2. Actual searches for MEDLINE and EMBASE.

Medline in process & other non-indexed materials, 20141110, OvidSP

(2703 hits)

1. accidental falls/

2. Geriatric assessment/ OR aging/ OR frail elderly/ OR exp aged/ OR middle aged/

3. 1 and 2

4. ((fall? OR fell OR falling OR fallen OR faller OR stumble? OR stumbling OR stumbles OR slip OR slips OR slipping OR slipped OR trip OR tripped) adj3 (old OR older OR senior OR elder OR elderly OR aged OR geriatric* OR middle-age? OR geriatric OR frailty OR Ageing OR elders OR Mci OR postmenopausal women OR Geriatric assessment OR aging)).ab,kw,ti

5. 3 or 4 [population]

6. exp cardiovascular diseases/ or exp hypertension/ or hypotension/ OR exp cardiac arrhythmias/ OR heart diseases/ or cardiac output, low/ or cardiomegaly/ or cardiomyopathies/ or heart failure/ or heart valve diseases/ or myocardial ischemia/ or ventricular dysfunction/ or ventricular outflow obstruction/

7. (cardiovascular disease? or hypertension or hypotension or circulatory disease?).ab,kw,ti

8. blood pressure/ or myocardial ischemia/ or prehypertension/

9. (blood pressure or systolic pressure or diastolic pressure).ab,kw,ti

10. (((cardiac OR cardiovascular OR heart) adj3 (disorder? or disease? or abnormalit* or failure or dysfunction*)) OR irregular heartbeat OR Sinus node disease OR Atrial fibrillation OR Bradycardia OR valve disease* OR (valv* adj3

(insuffic* OR incompet* or stenos* or disease? or regurgitation)) OR cardiomyopath* OR Myocardial ischemia OR Myocardial infarction OR carotid sinus OR orthostasis OR orthostatic hypotension OR postural hypotension OR postprandial hypotension OR vasovagal syncope OR Neurocardiogenic syncope OR arrhythmia or ventricular dysfunction).ab,kw,ti

11. or/6-10 [cardiovascular diseases and -parameters]

12. 5 and 11

13. 11 and (fall? OR fell OR falling OR fallen OR faller OR stumble? OR stumbling OR stumbles OR slip OR slips OR slipping OR slipped OR trip OR tripped).ab,kw,ti

14. (older adult? or elderly).ab,kw,ti.

15. 13 and 14

16. 12 or 15

Embase 1947 to Present, 20141110, OvidSp (3833 hits)

1. falling/

2. Geriatric assessment/ OR aging/ OR frail elderly/ OR exp aged/ OR middle aged/

3. 1 and 2

4. ((fall? OR fell OR falling OR fallen OR faller OR stumble? OR stumbling OR stumbles OR slip OR slips OR slipping OR slipped OR trip OR tripped) adj3 (old OR older OR senior OR elder OR elderly OR aged OR geriatric* OR middle-age? OR geriatric OR frailty OR Ageing OR elders OR Mci OR postmenopausal women OR Geriatric assessment OR aging)).ab,kw,ti

5. 3 or 4 [population]

6. cardiovascular disease/ or exp hypertension/ OR exp heart arrhythmias/ or ecg abnormality/ or exp heart arrhytmia/ or exp heart failure/ or exp ischemic

heart disease/ or exp myocardial disease/ or exp valvular heart disease/ or exp coronary artery disease/

7. (cardiovascular disease? or hypertension or circulatory disease?).ab,kw,ti

8. blood pressure/

9. (blood pressure or systolic pressure or diastolic pressure).ab,kw,ti

10. (((cardiac OR cardiovascular OR heart) adj3 (disorder? or disease? or abnormalit* or failure or dysfunction*)) OR irregular heartbeat OR Sinus node disease OR Atrial fibrillation OR Bradycardia OR valve disease* OR (valv* adj3 (insuffic* OR incompet* or stenos* or disease? or regurgitation)) OR cardiomyopath* OR Myocardial ischemia OR Myocardial infarction OR carotid sinus OR orthostasis OR orthostatic hypotension OR postural hypotension OR postprandial hypotension OR vasovagal syncope OR Neurocardiogenic syncope OR arrhythmia or ventricular dysfunction).ab,kw,ti

11. or/6-10 [cardiovascular diseases and -parameters]

12. 5 and 11

13. 11 and (fall? OR fell OR falling OR fallen OR faller OR stumble? OR stumbling OR stumbles OR slip OR slips OR slipping OR slipped OR trip OR tripped).ab,kw,ti

14. (older adult? or elderly).ab,kw,ti.

15. 13 and 14

16. 12 or 15

Appendix S3. Quality Assessment

Quality of included studies was assessed by the same reviewers. 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 (37). The scale was adjusted to allow for appropriate quality assessment of falls. As prospective reporting of falls through calendars or diaries is considered the gold standard for falls reporting [refs], studies using this method were allotted two stars. All other types of falls reporting were allotted one star. A score of 0-3 was considered low quality, 4-6 intermediate and 7 or above high quality

Cohort studies could be allotted a maximum of eleven stars and case control studies could be allotted a maximum of nine stars. As observational series were also included in our review, the NOS for case-control studies was used, omitting the items on comparability and selection and ascertainment of controls, allowing a maximum of three stars for these studies.

Quality review for- case-control studies or observational series

Selection

Is the case definition adequate?

Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as medical/hospital records).

- Yes, with independent validation *
- Yes, with record linkage (e.g. ICD codes in database) or self-report
- No description

Representativeness of the cases

All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample)

- Consecutive or obviously representative series of cases *
- Not satisfying requirements or not stated.

Selection of Controls (n/a for obs series)

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

- community controls * (i.e. same community as cases and would be cases if had outcome)
- Hospital controls, within same community as cases (i.e. not another city) but from a hospitalised population
- No description

Definition of controls (n/a for obs series)

If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.

- no history of disease (endpoint) *
- no mention of history of outcome
- N/A

Comparability

Comparability of cases and controls on the basis of the design or analysis (n/a for obs series)

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

- Controlled for age and/or gender *
- Controlled for other factors *
- no description

Exposure

Ascertainment of exposure (risk factor)

- secure record (cardiovascular assessment) *
- structured interview where blind to case/control status *

- interview not blinded to case/control status
- written self-report or medical record only
- no description

Same method of ascertainment for cases and controls (n/a for obs series)

- yes *
- no

Non-response rate (n/a for obs series)

- same rate for both groups *
- non-respondents described
- rate different and no designation
- no description

Quality review for cohort studies

Selection

Representativeness of the exposed cohort

- truly representative of the average older persons in the community *
- somewhat representative of the average older persons in the community *
- selected group of users eg volunteers
- no description of the derivation of the cohort

Selection of the non-exposed cohort

- drawn from the same community as the exposed cohort *
- drawn from a different source
- no description of the derivation of the non-exposed cohort

Ascertainment of exposure (cohort)

- Some form of independent validation (e.g. cardiovascular assessment) *

- structured interview *
- written self-report or medical record only
- no description

Demonstration that outcome of interest was not present at start of study

yes *

no

Comparability

Comparability of cohorts based on the design or analysis

Either exposed or non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

- Controlled for age and/or gender *
- Controlled for other factors *
- No description

Outcome

Assessment of outcome

- Prospective self-report through fall calendars **
- Incident report (e.g. in nursing homes) *
- Medical record (e.g. patient with fall-related injury in ED) *
- Retrospective self-report
- No description

Was follow-up long enough for outcomes to occur (N/A for cross-sectional studies)?

- yes (six months or more) *
- no

Adequacy of follow up of cohorts (N/A for cross-sectional studies)

- complete follow up - all subjects accounted for *
- subjects lost to follow up unlikely to introduce bias - small number lost *
- subjects lost to follow up likely to introduce bias
- No description

Reference

1. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2000.

Chapter 3: Syncope in the Elderly

DEFINITION

Syncope is a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion, and is characterized by rapid onset, short duration and spontaneous complete recovery T-LOC is a term that encompasses all disorders characterized by self-limited loss of consciousness, irrespective of mechanism. (131).

PATHOPHYSIOLOGY

The temporary cessation of cerebral function that causes syncope results from transient and sudden reduction of blood flow to parts of the brain (brain stem reticular activating system) responsible for consciousness. Regardless of the aetiology, the underlying mechanism responsible for syncope is a drop in cerebral oxygen delivery below the threshold for consciousness. Cerebral oxygen delivery, in turn, depends on both cerebral blood flow and oxygen content. Any combination of chronic or acute processes that lowers cerebral oxygen delivery below the "consciousness" threshold may cause syncope. In general, it is agreed that sudden mild to moderate declines in blood pressure can affect cerebral blood flow markedly and render an older person particularly vulnerable to presyncope and syncope. Syncope may thus result either from a single process that markedly and abruptly decreases cerebral oxygen delivery, or from the accumulated effect of multiple processes, each of which contributes to reduced oxygen delivery.

CLINICAL PRESENTATION-

Syncope in the older patient is under-recognised, particularly in acute care settings, because the presentation is frequently atypical. The older patient is less likely to have a warning or prodrome prior to syncope, commonly has amnesia for loss of consciousness and frequently experiences an unwitnessed event, (132) thus presenting with a fall rather than T-LOC (133-135). These events are typically described as non-accidental (not a trip or slip) or unexplained falls. Therefore, history alone cannot be relied upon when assessing the older patient. Injurious events such as fractures and head injuries are also more common, further emphasising the importance of thorough early investigations and diagnosis (136) In some forms of syncope there may be a premonitory period in which various symptoms (e.g., light-headedness, nausea, sweating, weakness, and visual disturbances) offer warning of an impending syncopal event (137). Often, however, loss of consciousness occurs without warning or recall of warning (134, 138). Recovery from syncope is usually accompanied by almost immediate restoration of appropriate behavior and orientation. The post-recovery period may be associated with fatigue of varying duration.

EVALUATION

The presence of heart disease is an independent predictor of a cardiac cause of syncope, with a high sensitivity of 95% but a low specificity of 45%(139). In order to attribute a diagnosis, patients should have symptom reproduction during investigation and preferably alleviation of symptoms with specific intervention. It is not uncommon for more than one predisposing disorder to

coexist in older patients, rendering a precise diagnosis difficult. In older persons treatment of potential causes without clear verification of attributable diagnosis may be often be the only option.

An important issue in patients with unexplained syncope is the presence of structural heart disease or an abnormal ECG. These findings are associated with a higher risk of arrhythmias and a higher mortality at one year (140). In these patients, cardiac evaluation consisting of echocardiography, stress testing and tests for arrhythmia detection such as prolonged electrocardiographic and loop monitoring or electrophysiological study are recommended. In patients without structural heart disease and a normal ECG, evaluation for neurally mediated syncope should be considered. The tests for neurally mediated syncope consist of tilt testing and carotid sinus massage.

ORTHOSTATIC HYPOTENSION

Pathophysiology

Traditionally, orthostatic hypotension is defined as a reduction in systolic BP of at least 20 mmHg or in diastolic BP of at least 10 mmHg within 3 minutes of standing (141). Orthostatic intolerance refers to symptoms and signs with upright posture due to circulatory abnormality (131). The heart rate and blood pressure responses to orthostasis occur in three phases: 1) an initial heart rate rise and blood pressure drop, 2) an early phase of stabilization, and 3) a phase of prolonged standing. All three phases are influenced by aging. In older persons with hypertension and cardiovascular disease receiving vasoactive drugs, these circulatory adjustments to orthostatic stress are disturbed, rendering them vulnerable to postural hypotension (27).

Evaluation

The diagnosis of orthostatic hypotension involves a demonstration of a postural fall in blood pressure after active standing. Reproducibility of orthostatic hypotension depends on the time of measurement and on autonomic function. Sphygmomanometer measurement will detect hypotension which is sustained. Phasic blood pressure measurements are more sensitive for detection of transient falls in blood pressure. Where possible these methods should be employed

VASOVAGAL SYNCOPE-

Pathophysiology

Vasovagal syncope has been classified into cardioinhibitory (bradycardia), vasodepressor (hypotension) and mixed (both) subtypes depending on the blood pressure and heart rate response. The precise sequence of events leading to vasovagal syncope is not fully understood. The possible mechanism involves a sudden fall in venous return to the heart, rapid fall in ventricular volume and virtual collapse of the ventricle due to vigorous ventricular contraction. The net result of these events is stimulation of ventricular mechano-receptors and activation of Bezold-Jarisch reflex leading to peripheral vasodilatation (hypotension) and bradycardia. Several neurotransmitters, including serotonin, endorphins and arginine vasopressin, play an important role in the pathogenesis of vasovagal syncope possibly by central sympathetic inhibition, although their exact role is not yet well understood (92).

Healthy older persons are not as prone to vasovagal syncope as younger adults. Due to an age-related decline in baroreceptor sensitivity, the paradoxical responses to orthostasis (as in vasovagal syncope) are possibly less marked in older persons. However, hypertension, atherosclerotic cerebrovascular disease, cardiovascular

Medications, impaired heart rate response and impaired baroreflex sensitivity can cause dysautonomic responses during prolonged orthostasis (in which blood pressure and heart decline steadily over time) and render older persons susceptible to vasovagal syncope. Diuretic or age-related contraction of blood volume further increases the risk of vasovagal syncope (142).

Presentation

In most patients, the manifestations occur in three distinct phases: a prodrome or aura, loss of consciousness and post-syncopal phase. A precipitating factor or situation is identifiable in most patients. Common precipitating factors include extreme emotional stress, anxiety, mental anguish, trauma, physical pain or anticipation of physical pain (e.g. anticipation of venesection), warm environment, air travel and prolonged standing. The commonest triggers in older individuals are prolonged standing and vasodilator medication. Some patients experience symptoms in specific situations such as micturition, defecation and coughing. Prodromal symptoms include extreme fatigue, weakness, diaphoresis, nausea, visual defects, visual and auditory hallucinations, dizziness, vertigo, headache, abdominal discomfort, dysarthria and paresthesias. Older patients may have poor recall for prodromal symptoms. The syncopal period is usually brief during which some patients develop involuntary movements usually myoclonic jerks but tonic clonic movements also occur. Thus, vasovagal syncope may masquerade as a seizure. Recovery is usually rapid but older patients can experience protracted symptoms such as confusion, disorientation, nausea, headache, dizziness and a general sense of ill health.

Evaluation

Head-up tilting as a diagnostic tool was first reported in 1986(143) and since then validity of this technique in identifying susceptibility to neurocardiogenic syncope has been established. Subjects are tilted head up for 40 minutes at 70 degrees. Heart rate and blood pressure are measured continuously throughout the test. A test is diagnostic or positive if symptoms are reproduced with a decline in blood pressure of greater than 50 mmHg or to less than 90 mmHg. This may be in addition to significant heart rate slowing.

The sensitivity of head up tilting can be further improved by provocative agents which accentuate the physiological events leading to vasovagal syncope such as glycerol trinitrate spray or isoprenaline.

POST-PRANDIAL HYPOTENSION

Defined as: In healthy older subjects, systolic blood pressure falls by 11-16 mmHg, and heart rate rises by 5-7 beats/minute 60 minutes after meals of varying compositions and energy content. However, the change in diastolic blood pressure is not as consistent. In older persons with hypertension, orthostatic hypotension and autonomic failure, the post prandial blood pressure fall is much greater and without the corresponding rise in heart rate. The clinical significance of a fall in blood pressure after meals is difficult to quantify. However, post-prandial hypotension is causally related to recurrent syncope and falls in older persons.

CAROTID SINUS SYNDROME AND CAROTID SINUS HYPERSENSITIVITY

Pathophysiology

Defined as episodic bradycardia and/or hypotension resulting from exaggerated baroreceptor mediated reflexes or carotid sinus hypersensitivity characterize the syndrome. The syndrome is diagnosed in persons with otherwise unexplained recurrent syncope who have carotid sinus hypersensitivity. The latter is considered

present if carotid sinus massage produces asystole exceeding 3 seconds (cardioinhibitory), or a fall in systolic blood pressure exceeding 50 mmHg in the absence of cardioinhibition (vasodepressor) or a combination of the two (mixed) (144, 145).

Presentation

The syncopal symptoms are usually precipitated by mechanical stimulation of the carotid sinus such as head turning, tight neckwear, neck pathology and by vagal stimuli such as prolonged standing. Other recognized triggers for symptoms are the postprandial state, straining, looking or stretching upwards, exertion, defecation and micturition. In a significant number of patients, no triggering event can be identified. Abnormal response to carotid sinus massage (see below) may not always be reproducible, necessitating repetition of the procedure if the diagnosis is strongly suspected. Dual chamber cardiac pacing is the treatment of choice in patients with symptomatic cardioinhibitory carotid sinus syndrome. With appropriate pacing, syncope is abolished in 85-90% of patients with cardioinhibition. Carotid sinus reflex sensitivity is assessed by measuring heart rate and blood pressure responses to carotid sinus massage. Symptom reproduction during carotid sinus massage is preferable for a diagnosis of carotid sinus syndrome. This reproduction of symptoms aids in attributing the episodes to carotid sinus hypersensitivity especially in patients with unexplained falls who deny loss of consciousness. In one third of patients a diagnostic response is only achieved during upright carotid sinus massage.

Cardiac Syncope

One third of cases of syncope in the older patient are caused by cardiac disorders (146) (see Figure 45- 3). There is a higher morbidity and mortality associated with cardiac syncope (147, 148). Cardiac syncope is characterised by little or no prodrome, occurrence when supine or during exercise and association with palpitations or chest pain (149). However, the older patient may not recall these symptoms. Heart disease is an independent predictor of cardiac syncope – sensitivity 95% and specificity 45% (150) The prevalence of cardiac disease, including structural heart disease and arrhythmias, rises dramatically with age as detailed in Figure 45- 2 and 3(151, 152) (153) and cardiac syncope should be considered when the surface ECG is abnormal or left ventricular systolic dysfunction is present (149).

Investigations

The gold standard for the diagnosis of cardiac syncope is symptom rhythm correlation i.e. contemporaneous HR and rhythm recording during syncope. Cardiac monitoring may also identify diagnostic abnormalities such as asystole in excess of three seconds and rapid supraventricular (SVT) or ventricular tachycardia (VT) (154-156). The absence of an arrhythmia during a recorded syncopal event excludes arrhythmia as a cause unless the patient has a dual diagnosis. In patients, over 40 years with recurrent unexplained syncope who do not have structural heart disease or abnormal ECG, the attributable cause of syncope is bradycardia in over 50% (157-160).

Cardiac Monitoring

Prompt hospital admission or intensive monitoring is recommended when cardiac disease is present in the setting of syncope (see Table 45-6). Although telemetry or in-patient monitoring is indicated if the patient is at high risk of a

life-threatening arrhythmia as per ECG abnormalities detailed in Table 45-5, the diagnostic yield from telemetry is low – 16% in one series (161).

Diagnostic yield from Holter monitoring is only 1 – 2 % in unselected populations (131). Incidental arrhythmias are much more common in older persons, for example, atrial fibrillation occurs in one in five men over 80 years (162). External loop recorders have a higher diagnostic yield in older patients but some older patients may have difficulty operating the devices (163, 164) and automated arrhythmia detection is therefore preferred (165). Normal ambulatory ECG (Holter or external loop or otherwise) in the absence of symptoms does not exclude a causal arrhythmia (149) and monitoring for longer intervals is imperative to capture rhythm during symptoms. Diagnostic rates are much higher in older patients using an implantable loop recorder (ILR) (166, 167) and are helpful in up to 50% in patients with syncope and unexplained falls (168-170). Early insertion of ILRs in the older person is important to consider in view of the disproportionately high number of cardiac causes of syncope in this group (168). This approach is also more cost-effective (171, 172). Difficulties with ILRs include inability to activate the device, particularly if patients have cognitive impairment. However, automated recordings and remote monitoring have much improved diagnostic yield (173). Magnetic resonance imaging (MRI) brain scans are increasingly used for investigation of other symptoms in elderly persons therefore MRI compatible devices should always be used.

Echocardiography

Echocardiography (ECHO) should be performed in syncope patients in whom a structural abnormality is suspected. The prevalence of structural cardiac abnormalities increases with age (153). The test is of most benefit in older patient

with aortic stenosis (174) and to evaluate ejection fraction. Cardiac arrhythmias are evidence in up to 50% of patients with an ejection fraction of less than 40%(175).

Ambulatory BP Monitoring

Patterns of blood pressure behaviour including post-prandial hypotension, hypotension after medication ingestion, orthostatic and exercise induced hypotension and supine systolic hypertension can be readily identified by this investigation. Modification of timing of meals and medications is guided by BP patterns (176),

Exercise Stress Testing

Exercise Stress Testing is indicated to investigate cardiac disease and in patients who present with exercise induced syncope (131). It is not always possible in older patients who may alternatively require angiography to investigate cardiac status.

Electrophysiological Study

Electrophysiological Study is indicated in the older non-frail patient with syncope when a cardiac arrhythmia is suspected (176). Diagnosis is based on confirmation of an inducible arrhythmia or conduction disturbance (177). The benefit is dependent on pre-test probability based on the presence of organic heart disease or an abnormal ECG (178).

Electrophysiological Study has the advantage of providing both diagnosis and treatment in the same session (transcatheter ablation) (176). It is most

effective for identification of sinus node dysfunction in the presence of significant sinus bradycardia of 50bpm or less; prediction of impending high degree AV block in patients with bifascicular block; inducible monomorphic VT (in patients with previous MI) and inducible SVT with hypotension in patients with palpitations (176).

SUMMARY and controversies in syncope

The prevalence of syncope rises with age and is challenging because of atypical presentation, overlap with falls and poor recall of events. Elders are less likely to have a prodrome, may have amnesia for loss of consciousness and unwitnessed events. Cardiac causes and dual pathology are more common and compliance with newer monitoring technologies is inadequate. Consequent morbidity and mortality is higher than in younger patients. A high index of suspicion for cardiovascular causes of falls and dual pathology will increase diagnosis and early target intervention.

A systematic approach to syncope is needed with the goal being to identify either a single likely cause or multiple treatable contributing factors. Management is then based on removing or reducing the predisposing or precipitating factors through various combinations of medication adjustments, behavioural strategies, and more invasive interventions in select cases such as cardiac pacing, cardiac stenting and intracardiac defibrillators. It is often not possible to clearly attribute a cause of syncope in older persons who frequently have more than one possible cause and pragmatic management of each diagnosis is recommended.

Table 45-3: Causes of Syncope

Reflex syncopal syndromes

- Vasovagal faint (common faint)
- Carotid sinus syncope
- Situational faint
    - acute hemorrhage
    - cough, sneeze
    - gastrointestinal stimulation (swallow, defecation, visceral pain)
- micturition (post-micturition)
- post-exercise
- pain, anxiety
- *Glossopharyngeal and trigeminal neuralgia*

Orthostatic

- Aging
- Antihypertensives
- Autonomic Failure

- Primary autonomic failure syndromes (e.g., pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure)

- Secondary autonomic failure syndromes (e.g., diabetic neuropathy, amyloid neuropathy)

- Medications (see Table 57-1)

- *Volume depletion*
  - Haemorrhage, diarrhoea, Addison's disease, diuretics, febrile illness, hot weather

Cardiac Arrhythmias

- Sinus node dysfunction (including bradycardia/tachycardia syndrome)
- Atrioventricular conduction system disease
- Paroxysmal supraventricular and ventricular tachycardia
- Implanted device (pacemaker, ICD) malfunction

drug-induced proarrhythmias

Structural cardiac or cardiopulmonary disease

- Cardiac valvular disease
- Acute myocardial infarction / ischemia
- Obstructive cardiomyopathy
- Atrial myxoma
- Acute aortic dissection
- Pericardial disease/tamponade
- Pulmonary embolus / pulmonary hypertension

Cerebrovascular

- Vascular steal syndromes

Multifactorial

Chapter 4: Epidemiology of Syncope/Collapse in Younger and Older Western Patient Populations

Professor Rose Anne Kenny, Dr Jaspreet Bhangu, Dr. Bellinda King-Kallimanis

Syncope is a common problem in the population, but its true incidence is difficult to estimate because of lack of definition, differences in population prevalence and under reporting in the general population. For this review, we have focused on western populations and have chosen papers from Pubmed and Medline databases in the English language that examined aspects of the epidemiology of syncope. Given that it is a condition that can occur at any time during ones' lifetime, we have chosen incidence at different times in the lifespan and in different settings.

Syncope and the Framingham studies

The Framingham series illustrates this difficulty of comparisons for the epidemiology of syncope visa vi variations in definitions and methodologies. For example, in the first Framingham cohort of 1985 the authors reported a first syncope episode in 3% of men and 3.5% of women over a *26 year* follow up

period (mean age of cohort was 46 ranging from 30 to 62years). Of these the majority had isolated syncope (179).

The cumulative incidence of syncope during a 4 year follow up in the next Framingham Offspring study was 3% over a *4 year* period (1991 to 1995) much higher than the first report. The age range in this instance was much broader 26 to 84 years (180).

In the latest report of the Framingham Offspring study (147) syncope was defined differently from the previous studies and included subjects with seizures, strokes and transient ischaemic episodes evaluated over a 17 year follow up period. Ten percent of 7,814 participants (mean age 51 range 20 to 96 years) reported at least one episode of syncope. The median peak of first syncope was 15 years. The incidence rate of first syncope was 6.2 per 1,000 person years. There was a sharp increase in incidence after 70 years from 5.7 events per 1,000 person years in men aged 60 to 69 to 11.1 in men aged 70 to 79 – equivalent to an estimated 10 year cumulative incidence of 6%. Reflex syncope - labelled vasovagal – was the most common identifiable cause of syncope responsible for 21.2% of all episodes followed by cardiac syncope (9.5%) and orthostatic hypotension (9.4%). Overall 44% of participants with a syncopal episode reported that they did not see a doctor or visit a hospital for evaluation. Syncope remained unexplained in 37% despite detailed history, physical examination and electrocardiogram (147). Survival of patients with vasovagal syncope was equivalent to those who had not suffered syncope.

The cumulative incidence of syncope in the Framingham Study (all participants were older than 20 years and episodes of syncope were prospectively detailed) was 5% in females aged 20 to 29 and rose to 50% and 48% respectively in females and males aged 80 *(Figure 1 Soteriades 2002 NEJM, Figure 2 Ganzeboom et al).*

Syncope in the young.

The Framingham data is in sharp contrast with the Dutch series of Ganzeboom et al - in 377 medical students the cumulative incidence of at least one syncopal episode rose from 8% before the age of 10 years to 47% in females and 24% in male students at the age of 24 years (181). At least one third of medical students, mean age of 21 years, reported at least one syncopal episode in their lifetime. The majority of triggers involved stresses or conditions that affect orthostatic blood pressure regulation and therefore syncope was most likely reflex in the majority, if not all. The median age for the first episode of syncope was 15 years. The lifetime cumulative incidence of syncope in women was almost twice that of men.

Circumstances or triggers ranged from (i) warm environment (31%), (ii) prolonged standing 27%, (iii) pain (25%), (iv) illness (18%), (v) alcohol (13%), (vi) emotion (11%), (vii) venous puncture (10%), (viii) standing (8%), (ix) fasting (6%), (x) fatigue (5%), (xi) drugs (5%), (xii) menstruation (6%). Alcohol and drugs were significantly more common triggers in men, otherwise there was no gender difference (Table 1).

Syncope in Older Populations

Syncope, is a major cause of morbidity and mortality in older patients, with enormous personal and wider health economy costs. In addition to injury and increasing dependency, quality of life studies consistently show functional impairment similar to other chronic diseases including rheumatoid arthritis and epilepsy (182-184).

Increased susceptibility to syncope with advancing age is accounted for by age-related physiological impairments of heart rate and blood pressure and alterations in cerebral blood flow combined with co-morbidities and polypharmacy (133). The prevalence peaks at 15 and 70 years as evidenced from a number of series Figure 1 and 2). Less recent studies indicate that the prevalence of syncope in an elderly institutionalised population is 23%; with a 1 year incidence of 7% and a 30% 2-year recurrence rate (185). The U.S. National Hospital Ambulatory Medical Centre Survey (1992–2000) reported 6.7 million attendances with syncope to the emergency department over this time period, which accounted for 0.77% of all attendances. There was a disproportionate burden on older patients in terms of hospitalisations, with 58% of sufferers over 80 years being admitted to hospital (186).

Prevalence and incidence figures in older individuals may be a significant underestimate because of the overlap with presentations classified as falls. Patients with or without cognitive impairment have difficultly remembering having fallen (135, 187) while the phenomenon of amnesia for loss of consciousness during syncope- vasovagal or carotid sinus - well

documented (132, 134, 188). The incidence of syncope in older patients is thus likely to be considerably higher than current estimates, with attendant cost implications. Because of the overlap with falls, the true incidence and therefore true costs of syncope to the health and social care systems and to labour market participation is unknown but likely to be considerably high. One recent population study has incorporated three syncope related questions.

Syncope and hospital attendance

A recent study from Denmark (189) identified syncope and collapse from a large register of residents with a first-time admission to hospital. Syncope was classified as a primary discharge diagnosis. The methodologies were well validated in a sub study and syncope patients were matched with five random controls from the Danish population. During the study period, between 1997 and 2009, a total of 127,508 patients were seen in ER (45.3%), in outpatients (11.7%) or in hospital (43%). 52.6% of the population were female. The age distribution of the sample showed 3 peaks, which is a new observation compared to previous studies. The first peak was represented by females around 20 years of age, a second and quite smaller peak in patients around 60 years of age and a third peak around 80 years of age. The largest proportion of syncope occurred in the age group 50 to 79 (35.7%) (Figure 1 & 2).

Syncope accounted for 0.9% of total admissions, 0.6% of total ER visits. Of interest during the study period there was an overall increase in the incident rates of syncope of 13.8 to 19.4 per 1,000 person years.

Syncope was associated with marked cardiovascular co-morbidity and use of cardiovascular pharmacotherapy across all age groups when compared with the control population. 28% of the overall population had cardiovascular disease compared with 14% of the control population. Nearly half (48%) of the syncope population were medicated with one or more types of cardiovascular specific medication as compared to 38% of the control population. This difference was even more pronounced in the 50 to 79 year old age group (66% versus 51%). This reinforces the importance of cardiovascular co-morbidity and pharmacotherapy when evaluating a patient with syncope (190).

Syncope in general practice.

Data from a large general practitioner database in the Netherlands revealed that 2 to 9 per thousand encounters were due to blackouts or fainting. Reflex syncope is the most likely underlying condition. The age distribution of these patients showed a peak in females around 15 years and a second peak in older patients over the age of 65. General practitioners in the Netherlands refer only 10% of patients with reflex syncope to specialists for further evaluation. In most cases, referrals are made to a neurologist or to a cardiologist (191). The reasons for referral are atypical fainting. A very small fraction of patients with syncope in the general population present in any clinical setting. If we take syncope – per 1,000 patient years – the prevalence is anything from 18.1 to 39.7 in the general population of whom 9.3 attend general practice because of the event and 0.7 present to the ER (181).

Syncope in the ER

The prevalence of syncope referrals to emergency departments range from 0.9% to 3.4% (192). Reflex syncope is the most common cause (up to 40%), orthostatic hypotension occurs in 6 to 24%, cardiac syncope 10 to 20%, psychogenic syncope 1 to 5%. Cardiac causes and orthostatic hypotension are more common in the older patient. Although cardiac syncope and orthostatic hypotension are more common causes of syncope in older persons, reflex syncope is also common and is being diagnosed with increasing frequency in this age group (191). Vasovagal syncope may not necessarily follow the benign course however, commonly observed in young patients (193). Older patients are more likely to have concurred co-morbidity and be taking concurrent medications (REF)

Prevalence and causes of syncope.

The prevalence and causes of syncope are different depending on the clinical setting in which the patient is evaluated and the age of patients. Furthermore, there will also be differences in diagnostic definitions, geographical factors, local care pathways, making a comparison between different studies very difficult. The European Cardiac Society (194) has in this context provided a number of general comments with respect to prevalence of causes of syncope.

Reflex syncope is the most frequent cause in any age group.

Syncope secondary to cardiovascular disease is the second most common cause. The number of the patients with cardiovascular causes varies widely between

studies with higher frequencies in the emergency setting in older subjects and in settings orientated towards cardiology.

In patients under 40, orthostatic hypotension is a rare cause of syncope, whereas it is frequent in very old patients.

Non-syncopal conditions are more frequent in emergency referrals and reflect multifactorial complexity of these patients

High unexplained syncope rate in all settings justifies new strategies for evaluation and diagnosis.

Whilst in the young reflex syncope is by far the most frequent cause of TLOC, in older patients multiple causes are often present and the medical history may be less reliable than in the young (133, 146, 195, 196). Table 3.

In conclusion, syncope is a common problem in the general population. Its age distribution is bi-modal or tri-modal according to recent studies, peaking in teenagers and the elderly. Although several studies have been performed in young subjects, the incidents of syncope in the elderly in the general population are less well studied. The lifetime cumulative incidence of syncope is much higher in women than in men. Reflex syncope is much more frequent than any other cause of syncope, although cardiac syncope, orthostatic and post prandial hypotension and the effects of medications are more common causes of syncope in the elderly. Carotid sinus syndrome is also uniquely a cause of syncope in older subjects. Reflex syncope is in general benign. Although again, this has been poorly studied in elderly populations. A recent Danish study has

emphasised a significant association between cardiovascular co-morbidity, pharmacotherapy and syncope in patients who present to hospital emphasising the importance of detailed evaluation of the patient for more serious underlying co-morbidity.

Table 1.

Details of the triggers for syncope from the two large studies in young adults

	Ganzeboom (am j card 2003)	Providencia int j card 2011	O'Dwyer 2012	Graham clin aut research 2001 (Vasovagal)	O'Dwyer 2012
Number with syncope Mean age	N=154/394; mean age 21 yrs	N=598/2011; mean age 22yrs	N=219/219 Mean age 36yrs	N=62/62 Mean age 50yrs	N= 92/92 Mean age 71yrs
Warm environment	31	22.3	52 (23.6%)	37	(23.9%)
Prolonged Stand	27	11.9	119 (54.9%)	27	(51.1%)
Pain	25	11.8	6 (2.7%)		1 (1.1%)
Illness	18	4.5	3 (1.4%)		
Alcohol	13	7.9	22 (10.1%)	10	2 (2.2%)
Emotion	11	13.4	47 (21.7%)	21	7 (7.6%)
Venipuncture	10	13.2	33 (15.1%)	11	3 (3.3%)
Standing	8		174 (79.8%)		68 (73.9%)
Fasting	6	20.8		23	
Fatigue	5				

Drugs	5	1.5		10	
menstruation	6		2 (0.9%)		
Other	10	3.9	8 (3.7%)		
unknown	3	2.5			
Epileptic seizures		1.5	12 (5.5%)		1 (1.1%)
Trauma		2.4			
Early mornings				16	
accident		3.3			
Post prandial			17 (7.8%)		13 (14.1%)
Fall		1.9			
Sitting			80 (36.7%)	19	40 (43.5%)
During physical exercise		7.4	20 (9.2%)		3 (3.3%)
After physical exercise		8.9	24 (11%)		1 (1.1%)
Multiple triggers	55	33			
Head movement					

Table 2. Syncope Frequency Depends on the Setting in Which the Measurement Is Made.

Setting	Incident (per 1,000 patient-years)	Ratio
General population	18 – 40	1
Seeking medical evaluation	9.3 - 9.5	1:2 – 1:4
Referred for specialty evaluation	3.6	1:5 – 1:10
Referred to emergency department	0.7 - 1.8	1:10 – 1:50

Figure 1.

Incidence Rates of Syncope According to Age and Sex

Soteriades ES, Evans JC, Larson MG, et al.: Incidence and Prognosis of Syncope.

N. Engl. J. Med. 2002; 347(12): 878-885.

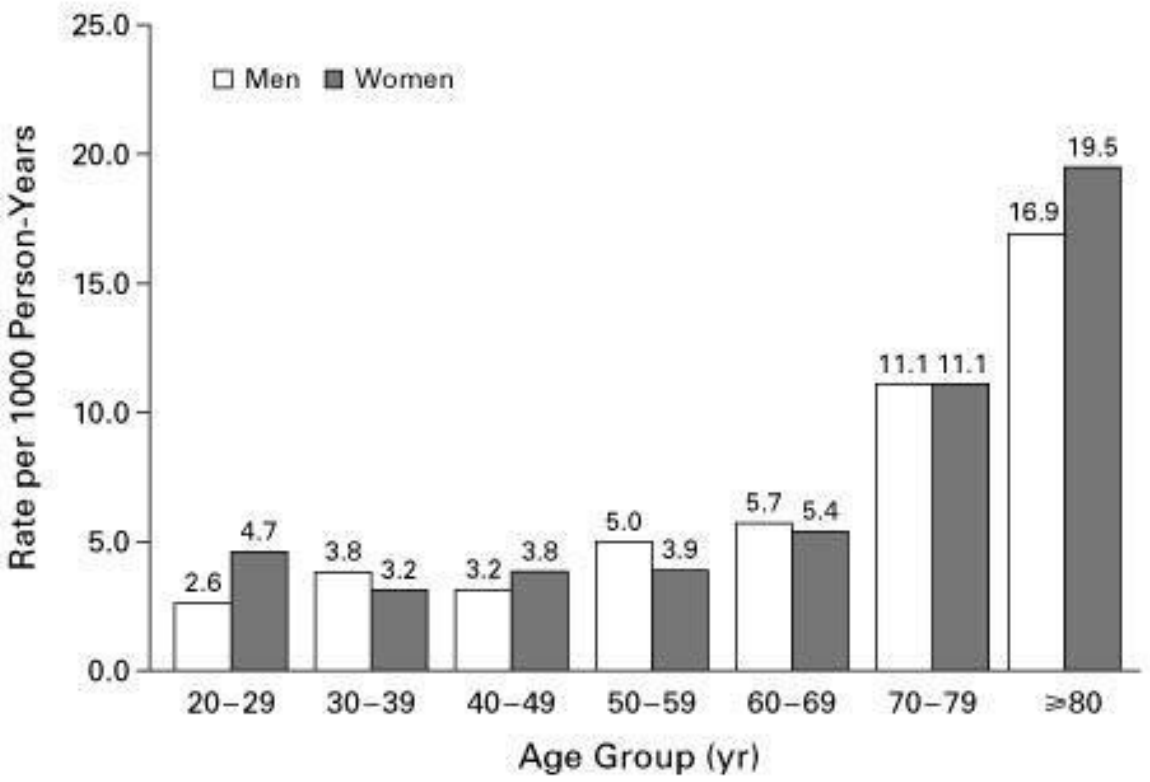


Figure 1. Incidence Rates of Syncope According to Age and Sex

Figure 2.

Age-specific lifetime prevalence of syncope

Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W: Prevalence and triggers of syncope in medical students.

Am J Cardiol 2003; 91(8): 1006-8, A8.

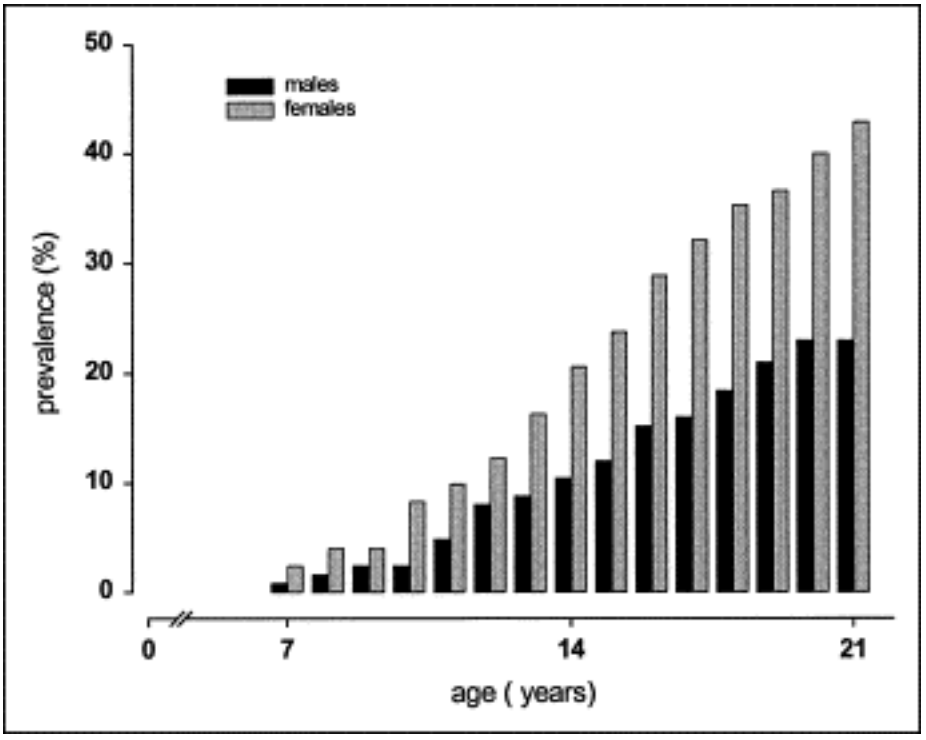


Figure 2. Age-specific lifetime prevalence of syncope

Summary of the literature review and research questions

1. The prevalence of both syncope and falls increases with advancing age in the community dwelling older population
2. Syncope and falls share common associations and risk factors in older adults.
3. Strong associations between cardiovascular morbidity, falls and syncope have been identified in the literature to date. This is especially true of conditions which lead to low blood pressure such as intermittent arrhythmia.
4. Unexplained falls are a common presentation of syncope in the elderly and may often point towards underlying cardiovascular disease
5. There is a strong interaction between psychological symptoms and syncope especially with regards to depressive symptoms.
6. Studies examining the associations between falls, syncope and cardiovascular disease in older adults are limited by a lack of standard definitions, differences in populations studied and differences in the settings used for studies

This thesis will attempt to address these issues in a more succinct manner. The four main papers in this thesis have been designed in order to answer some of the questions above. The methods used for each paper as well as the statistical analysis for each paper are described in detail within each paper. I will provide a summary of the objectives, hypothesis and methods used for each paper below.

Paper 1- Unexplained falls are common with advancing age - implications for cardiovascular assessment in older patients with falls

Objectives: To calculate the prevalence of falls, unexplained falls and syncope in an older, community dwelling population and characterize risk factor profiles.

Design: Prospective, longitudinal cohort study.

Setting: The first two waves of data from the Irish Longitudinal Study on Ageing (TILDA).

Participants: 8172 community-dwelling adults aged 50 years and older resident in the Republic of Ireland.

Measurements: Self-reported history of falls, unexplained falls and syncope in the year preceding the first two waves of data collection. Self-reported health conditions were used to characterize risk factor profiles.

Paper 2 – Transient Loss Of Consciousness (T-LOC) In The Emergency Department – Implications For Resource Use In Older Adults

Objectives: To calculate the prevalence of falls, unexplained falls and syncope presenting to an emergency department and estimate resource use.

Design: Prospective, observational study

Setting: Emergency department in a large urban centre.

Participants: Non-institutional dwelling adults over the age of 50 years who had presented with a fall, collapse episode or syncopal event over a six-month period.

Measurements: Categorization as a fall, unexplained fall or syncope were based on triage reports obtained within the emergency department. Electronic records were reviewed to examine the resources utilised.

Paper 3-Long-term cardiac monitoring in older adults with unexplained falls and syncope

Objectives: To detect the prevalence of arrhythmogenic causes of unexplained falls in older patients.

Design: A single centre, prospective, observational cohort study.

Setting: Emergency department of tertiary referral centre.

Participants: Recurrent fallers (community dwelling) over the age of 50years with two or more unexplained falls.

Measurements: Insertion of an ILR (Reveal®, Medtronic Inc. Minnesota, USA) was used to detect arrhythmia. The primary outcome was detection of cardiac arrhythmia associated with a fall or syncope. The secondary outcome was detection of cardiac arrhythmia independent of falls or syncope, and falls or syncope without associated arrhythmia.

Paper 4- The relationship between syncope, depression and anti-depressant use in older adults

Objectives: To examine the rates of depression in older patients reporting syncope and the effect of anti-depressants on the rates of syncope

Design: Epidemiological, point-prevalence study.

Setting and Participants: Data came from the Irish Longitudinal Study on

Ageing (TILDA), which includes 8,175adults aged 50 and older, living in the community in Ireland.

Measurements: The Centre for Epidemiological Studies Depression scale *(CES-D)* was used to assess levels of depression. Multinomial regression was used to analyse the data with a p value of <0.05 determining significance.

Chapter 5: Unexplained falls are common with advancing age - implications for cardiovascular assessment in older patients with falls

Falls and syncope are common in older adults. Currently, falls account for 4% of the healthcare budget while syncope accounts for 1-2% of all emergency department (ED) presentations per year in the United States (25, 198). Given projected changes in global demographics and advancing age, the management of falls and syncope and their consequences will become even more pertinent in the near future (1).

Falls occur most frequently due to the environment or accidental events such as trips or slips (3). These accidental falls become more common with advancing age and are often due to age and disease associated reductions in physical, sensory and cognitive function which make an individual more susceptible to environmental hazards (3).

However, some falls are not accidental but rather are due to drops in blood pressure which may lead to either balance instability or, in some cases, loss of consciousness i.e. syncope (199). Similar to syncope, these unexplained falls (UF) have been linked to cardiovascular disorders with a possible common causal pathway and overlap (200). Despite the overlap, falls, UF and syncope are generally reported separately, therefore studies which distinguish between them and examine them in more depth are required.

We hypothesize that the prevalence of all falls, UF and syncope increase with age and share common risk factors. In order to show this, we calculated the prevalence of all reported falls, UF and syncope in a population study of community-dwelling adults aged 50 years and over and examined the demographic and health variables associated with all falls, UF and syncope.

Methods

Sample

This study utilised the first two waves of data from the Irish Longitudinal Study on Ageing (TILDA). TILDA is a prospective cohort study of the social, economic and health circumstances of community-dwelling adults aged 50 years and older resident in the Republic of Ireland. The sampling frame was the Irish Geodirectory, a listing of all residential addresses in the Republic of Ireland. Random sampling of geographical clusters was used to select households and all household residents aged 50 years or older and their spouse/partner (of any age) were invited to participate in the study. Institutionalised persons or persons with cognitive impairment or dementia at baseline were excluded from the study and all eligible participants provided informed consent. The household response rate was 62%, leading to a final wave one sample of 8,172 adults aged 50 and older who completed an in-home interview between October 2009 and February 2011. Follow-up data for wave two were collected between March 2012 and March 2013. Attrition accounted for a 12% sample reduction and death a further 2.5%.

The sampling procedure and the study design have been described in detail previously (201,202) . Briefly, data collection involved an in-home interview, a self-completion questionnaire and a health assessment. This study used data

obtained during the in-home interview. Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin.

Measures

Syncope – Participants were asked if they had experienced a faint or blackout in the past twelve months (yes/no). Syncope was defined as at least one syncopal event in the past year.

All falls - Participants were asked if they had fallen in the past year (yes/no). A fall was defined as at least one reported fall in the last year.

Unexplained Falls (UF) - Participants were asked if any of the falls they had experienced in the last year were unexplained, i.e. with no apparent or obvious reason (yes/no). A UF was defined as at least one reported UF in the last year.

Demographic and Health Status variables – In addition to demographic variables (age and sex), participants were asked to self-report any doctor diagnosed cardiovascular conditions including: hypertension, angina, a heart attack, congestive heart failure, diabetes or high blood sugar, a stroke (cerebral vascular disease), mini-stroke or transient ischaemic attack, high cholesterol, a heart murmur, an abnormal heart rhythm (arrhythmia). They also reported chronic conditions including: chronic lung disease such as chronic bronchitis or emphysema, asthma, arthritis (including osteoarthritis, or rheumatism), osteoporosis, cancer or a malignant tumour (including leukaemia or lymphoma but excluding minor skin cancers), any emotional, nervous or psychiatric problems such as depression or anxiety, alcohol or substance abuse, stomach ulcers, varicose ulcers, cirrhosis. Two indicator variables for cardiovascular and chronic conditions were created by summing the number of conditions and are each reported as 0-2, 3-4, or 5+ conditions.

All medications taken regularly were coded using the World Health Organisation Anatomical Therapeutic Chemical (ATC) Classification system (203). Anti-

hypertensives were identified by ATC codes beginning with C02, C03, C07, C08 or C09. Depressive symptoms were assessed using the 20-item Centre for Epidemiological Studies Depression scale (CES-D) (204) where scores of < 16 indicated insignificant symptoms for depression; >16 and < 26 indicated moderate to severe depressive symptoms and > 26 indicated severe depressive symptoms. All demographic and health variables were obtained at wave one.

Statistical Analysis

Prevalence estimates were weighted with respect to age, sex and education to the Quarterly National Household Survey (2010) to ensure that data were nationally representative.

Incidence was calculated using the sub-sample who did not report a syncopal event or fall in wave one. An attrition weight was used to adjust for loss to follow-up through participant refusal, loss of contact or death between waves. Cross tabulation was used to estimate prevalence and 95% confidence intervals. Inferential statistics (design-based F statistic, $p<0.01$) were computed for age and sex estimates using analysis of variance.

To better understand the relationships between basic demographic variables and general health with respect to all falls, UF and syncope, logistic regression was used, without survey weights with univariate odds ratios calculated. Further adjusted odds ratios were then calculated incorporating confounders including age, sex, depressive symptoms, anti- hypertensive drugs, number of self-reported chronic conditions and number of self-reported cardiovascular conditions. Both univariate and multivariate logistic regression models for All falls, UF, and syncopal events were then built based on these results. Odds

ratios, *p*-values and 95% confidence intervals were used to assess the association with potential risk factors.A *p*-value <0.05 represented statistical significance. All analyses were conducted using Stata

12.1 ©Statacorp LP.

Results

The total number of participants aged 50 years and over included in the study was 8,172 (mean age 63.7 years (SD 9.7); 55.6% (n=4,724) female).

Prevalence of All Falls, UF and Syncope in the Irish Population

Baseline descriptives for groups reporting all falls, UF and syncope are provided in Table 1.

The overall prevalence of all falls in the past year was 19.2% or 192 per thousand persons and increased with age (50 – 64 years 17.5%; 65 – 74 years 19.4%; 75+ years 24.4%) (F (2,1240.7) = 15.92, p<0.001) (Figure 1). Falls were more prevalent in females (20.1%) compared to males (18.2%).

UF had an estimated prevalence of 5.1% or 51 falls per thousand persons and accounted for 26.5% of all falls reported. Again, the prevalence increased with age (50 – 64 years 4.0%; 65- 74 years 5.5%; 75+ years 8.0%) (F (2,1247.3) = 15.15, p<0.001) (Figure 1).

The prevalence for syncope was estimated to be 4.4% or 44 per thousand persons (Figure 1). Prevalence was similar for males (4.4%) and females (4.5%) and did not differ when stratified by age in wave one (F (2,1235.8) = 0.87, p 0.10) (Figure 1).

Incidence

The estimated incidence of all falls was 17.5% while UF was 5%. In both cases, incidence was highest for those aged 75 and older (all falls 24.8%; UF 8%) (Figure 1). Overall, the estimated incidence of syncope was 4.2% in wave 1. There was an age-related increase in incidence reported in wave 2, with those over 75 years demonstrating a higher incidence of syncope (50 – 64 years 3.5%; 65-74 years 4.1%; 75+ years 7%) ($F(2,1228.8) = 12.56$, $p < 0.05$). The estimated incidence for males aged 75 and older was 5.2% compared to 8.3% in females of the same age.

Clinical Characteristics

Table 2 summarizes the clinical characteristics associated with all falls, UF and syncope and demonstrates univariate and multivariate associations between cardiovascular conditions and chronic diseases. In univariate analysis, cardiovascular conditions including angina, heart failure, stroke, TIA, diabetes and arrhythmia displayed an association with all three outcomes. However, when adjusted for potential confounders only stroke showed an individual association with all three outcomes. In univariate analysis asthma, arthritis and stomach ulcers displayed an association with all three but these did not reach statistical significance when adjusted.

Table 3 presents the results of multivariate analysis. Participants with at least 5 cardiovascular conditions were more likely to report any falls (OR=2.07, 95% CI 1.18-3.64) and UF (OR=2.89, 95% CI 1.28-6.52). Having three to four cardiovascular conditions was associated with increased odds of reporting

syncope (OR=2.74, 95% CI 1.73-4.35, $p<0.05$) as was being on anti-hypertensive medications (OR=1.45, 95% CI 1.17-1.81). Moderate and severe depressive symptoms were associated with up to three times greater likelihood of reporting any falls, UF and syncope in the past year (Table 3).

Discussion

This paper describes the prevalence of all falls (19.2%), UF (4.4%) and syncope (5.1%) in the past year in a community-dwelling population aged 50 years and older. The prevalence and incidence of all falls and UF increases with age but the same pattern was not consistently observed for syncope. There is an increased odds of reporting all three conditions with increasing number of self-reported cardiovascular conditions.

We have reported a consistent prevalence and incidence rate of all falls of 19.2%. Other community-based studies have reported higher falls rates of 25-30% when measured retrospectively and 35-40% when measured prospectively (2, 4-6, 136, 205). The younger average age profile in the first wave of TILDA may account for the lower reported yearly prevalence. Consistent with previous studies, the over 75 year age group represents over 20% of falls reported.

UF, defined as a fall without any obvious slip or trip accounted for about one quarter of all falls, with those over the age of 75 years twice as likely to report UF as adults aged 50-64 years (8% versus 4%). This study remains the largest community-based cohort to report on the prevalence of UF and is consistent with a previously reported prevalence of 5% in community-dwelling older adults in New Zealand. (129, 136, 206). In contrast, between 20- 50% of all falls presenting to emergency departments are unexplained (206), perhaps indicating a high morbidity associated with UF.

We have been able to show unique prevalence and incidence estimates for syncope in the same population. Our cohort has a similar prevalence of syncope

as the Olmstead community cohort (which also focused on older adults) with 16.9% reported overall and no significant variation seen between age groups (207). Additionally, we have demonstrated a consistent rate of syncope occurrence at 4 per 1000 person years in our cohort. The Framingham cohort studies had reported higher cumulative incidence rate of 5.7 per 1000 person years in men aged 60-69 years and had a sharp rise to 11.1% per 1000 person years in men aged 70 years and older (31). They used a definition of syncope that included transient ischaemic attack, stroke and seizures making it difficult to make direct comparison to our cohort. Although at wave two, we reported an increase in syncope incidence in the over 75 age group, it does not demonstrate the same degree of change as reported in the Framingham cohort. This lack of age variation is also in contrast to falls and UF and may represent an under-reporting of syncope in older age groups; or the presentation of syncope as a fall.

Low blood pressure, intermittent arrhythmia and heart failure have all shown associations with falls risk in epidemiological studies (208). Additionally, disorders which are known to cause syncope in the elderly including vaso-vagal syncope and carotid sinus syndrome occur in up to 25% of UF (111, 209) (72, 210, 211). Observational studies also support the link between cardiovascular disease and UF with higher rates of cardiac arrhythmia and carotid sinus syndrome in participants who report UF (52, 212). We have demonstrated that anti- hypertensive medication and increasing cardiovascular co-morbidity were associated with an increase in reporting UF adding to the evidence linking cardiovascular disease to UF. With increasing evidence for aggressive blood pressure control in older adults, a standardised falls risk assessment is important to ensure judicious use of blood pressure lowering medications (213).

Cardiovascular assessment has been enshrined in the original American Geriatrics Society/British Geriatrics Society guidelines for falls prevention and our data would suggest a continued emphasis on the use of a structured cardiovascular assessment as part of a falls prevention work-up (28). Given the similarities between UF and syncope, it is recommended that UF are managed in the same way as syncope in order to realize beneficial responses to intervention (49, 214).

Both depressive symptoms and stroke demonstrated an association with all falls, UF and syncope. There are a number of possible explanations. Falls, UF and syncope are all known to have associations with low blood pressure (211). Older patients who suffer stroke have higher rates of cognitive impairment, gait/balance impairments and slow protective reflexes, all of which are risk factors for subsequent falls (215). With up to 60% of falls in older adults being unwitnessed and up to 50% demonstrating amnesia for loss of consciousness, it is entirely plausible that an older adult with gait instability, who had a momentary drop in blood pressure, could present as a fall (216) (217). Further work is needed to uncover the exact interplay between low blood pressure, neural damage and subsequent gait instability. Similarly, depression has previously been linked with both falls and syncope (218). The underlying aetiology of this is less well defined but depressive symptoms and/or treatment with anti-depressant therapy have been associated with impaired heart rate variability (219), blood pressure control (220) and gait deficits (221). Further work uncovering the link between mood, cardiovascular function and gait is also warranted.

Strengths and Limitations

TILDA provides an opportunity to distinguish between and characterize falls, UF and syncope in a large, community-dwelling cohort. Few studies present these together despite the strong overlap between all three. However, there are also some limitations, mainly the use of self-reported falls and syncope over the past year which relies on a participant's ability to recall past events. This may lead to inaccurate reporting of these events when compared to cohorts in which falls are recorded prospectively, for example with falls diaries. Despite this limitation, the cohort is well characterised and will continue to be followed at regular intervals providing a rich source of information as to the exact incidence and associations between falls and syncope in older adults. This cohort was a community dwelling, cognitively intact cohort so results may not pertain to frailer, institutional dwelling older adults.

Conclusions

We have shown that the prevalence of all falls and UF is 19.2% and 5.1% respectively in the community-dwelling middle-aged and older population in Ireland. Prevalence of falls and unexplained falls in particular are higher in the older age groups. Syncope has yearly occurrence rates of 4.4% and a less consistent age gradient. We have demonstrated that falls, UF and syncope have common associations; particularly with increasing cardio-vascular co-morbidity, depressive symptoms and stroke. TILDA represents the largest community-dwelling cohort to present data on falls, UF and syncope and allows researchers to focus efforts on untangling the associations between these conditions in order to focus appropriate clinical management strategies and future prevention.

Table 1 Baseline variables for all participants reporting all falls (n=1,579), unexplained falls (UF) (n=406) and syncope (n=363) in wave one of TILDA.

Variable	**Falls**	**UF**	**Syncope**
	N (%)	**N (%)**	**N (%)**
Age (years)			
50-65	882 (56)	234 (58)	186 (51)
65-75	433 (27)	105 (26)	107 (29)
75+	264 (17)	67 (17)	70 (19)
Gender (female)	919 (58)	238 (59)	177 (49)
Anti-hypertensive medications[1]	634 (40)	198 (49)	169 (47)
Number of chronic conditions[2]			
0	10 (1)	6 (1)	2 (1)
1	1197 (76)	263 (65)	254 (70)
2	227 (14)	75 (18)	68 (19)
3	104 (7)	44 (11)	21 (6)
>3	41 (3)	18 (4)	18 (5)
Number of cardiovascular conditions[3]			
0	346 (22)	70 (17)	54 (15)
1	901 (57)	236 (58)	213 (59)

2	209 (13)	63 (16)	51 (14)
3	74 (5)	15 (4)	25(7)
>3	49 (3)	22 (5)	20 (6)
Depressive symptoms°			
None/insignificant	1006 (64)	212 (52)	197 (54)
Moderate	323 (20)	106 (26)	82 (23)
Severe	219 (14)	78 (19)	75 (21)

[1] As coded by the WHO Anatomic Therapeutic Chemical (ATC) Classification System; anti-hypertensive medication with ATC code C02, C03, C07, C08, C09

[2] Self- reported chronic conditions including chronic lung disease, asthma, arthritis, osteoporosis, cancer, any emotional, nervous or psychiatric problems, such as depression or anxiety, alcohol or substance abuse, stomach ulcers, varicose ulcers or cirrhosis

[3]Self- reported cardiovascular conditions including angina, hypertension, congestive cardiac failure, diabetes, stroke, transient ischemic attack, high cholesterol, cardiac murmurs and cardiac arrhythmia

°As measured by Centre for Epidemiological Studies Depression Scale (CES-D); scores of < 16 indicated insignificant symptoms for depression; >16 and < 26 indicated moderate to severe depressive symptoms and > 26 indicated severe depressive symptoms

Table 2 Univariate and adjusted (OR) odds ratios for all falls, unexplained falls (UF) and syncope in the 12 months prior to wave 1 based on self-reported health variables for all TILDA participants (n=8172)

ConditionsΨ	Falls OR (95% CI)	Adjusted Falls OR (95%CI)	UF OR (95%CI)	Adjusted UF OR (95% CI)	Syncope OR (95% CI)	Adjusted syncope OR[i] (95% CI)
Hypertension	1.08 (0.96-1.29)	0.96 (0.82-1.14)	1.50*(1.23-1.83)	1.09 (0.81-1.45)	1.48*(1.20-1.82)	1.18 (0.87-1.60)
Angina	1.41*(1.13-1.75)	1.01 (0.77-1.32)	1.97*(1.40-2.77)	1.21 (0.80-1.83)	2.22*(1.58-3.13)	1.39 (0.92-2.10)
Heart attack	0.98 (0.75-1.27)	0.78 (0.58-1.05)	1.2 (0.77-1.87)	0.84 (0.51-1.37)	1.78*(1.19-2.65)	1.17 (0.74-1.85)
Heart failure	1.64* (1.03-2.62)	1.13 (0.69-1.87)	2.47* (1.27-4.81)	1.44 (0.70-2.96)	2.15*(1.03-4.49)	1.28 (0.59-2.80)
Stroke	1.87*(1.29-2.71)	1.59*(1.06-2.38)	3.50*(2.15-5.69)	2.35*(1.35-4.09)	3.94*(2.42-6.41)	2.79*(1.61-4.82)
Diabetes	1.36*(1.12-1.64)	1.23*(1.00-1.52)	1.40*(1.01-1.94)	1.07 (0.74-1.55)	1.48*(1.06-2.08)	1.08 (0.74-1.58)
TIA	1.82* (1.31-2.52)	1.56* (1.09-2.21)	2.68*(1.68-4.28)	1.92*(1.14-3.22)	2.35*(1.41-3.92)	1.72 (0.98-3.00)
High Cholesterol	1.11*(1.00-1.24)	1.06 (0.93-1.21)	1.21 (0.99-1.48)	1.04 (0.83-1.31)	1.20 (0.98-1.49)	0.97 (0.76-1.24)
Heart murmur	1.56*(1.25-1.96)	1.35*(1.06-1.72)	1.45 (0.98-2.16)	1.18 (0.70-1.61)	1.98*(1.37-2.88)	1.50*(1.00-2.40)
Arrhythmia	1.49*(1.23-1.81)	1.30*(1.05-1.62)	1.42*(1.01-1.99)	0.88 (0.59-1.31)	2.05*(1.51-2.81)	1.39 (0.97-2.00)

Asthma	**1.35*(1.14-1.61)**	**1.06 (0.87-1.29)**	**1.65* (1.24-2.20)**	**1.10 (0.79-1.53)**	**1.37*(1.00-1.89)**	**1.07 (0.74-1.54)**
Lung Disease	**1.08 (0.82-1.42)**	**0.72 (0.53-0.98)**	**1.37 (0.88-2.12)**	**0.73 (0.44-1.21)**	**1.95*(1.29-2.92)**	**1.28 (0.80-2.06)**
Arthritis	**1.53*(1.36-1.71)**	**1.40*(1.23-1.59)**	**2.30*(1.88-2.80)**	**1.88*(1.50-2.35)**	**1.47*(1.19-1.83)**	**1.17 (0.91-1.49)**
Osteoporosis	**1.33*(1.12-1.58)**	**1.07 (0.88-1.30)**	**2.01*(1.53-2.63)**	**1.38*(1.01-1.89)**	**1.34(0.97-1.84)**	**1.07 (0.75-1.53)**
Stomach ulcers	**1.37*(1.12-1.67)**	**1.02 (0.82-1.28)**	**1.45*(1.04-2.04)**	**0.89 (0.61-1.32)**	**2.05*(1.50-2.81)**	**1.81*(1.27-2.57)**

Ψ Based on logistic regression controlling for age, sex, antihypertensives (coded by the Anatomic Therapeutic Chemical (ATC) anti-hypertensive medication with ATC code C02, C03, C07, C08, C09), depressive symptoms (as measured by CES-D scale with scores of < 16 indicating insignificant symptoms for depression; >16 and < 26 indicating moderate to severe depressive symptoms and > 26 indicating severe depressive symptoms.), composite number of self- reported cardiac conditions including angina, hypertension, diabetes, stroke, TIA (transient ischemic attack), high cholesterol and cardiac arrhythmia and composite number of self-reported chronic conditions including lung disease such as chronic bronchitis or emphysema, asthma, arthritis (including osteoarthritis, or rheumatism), osteoporosis, cancer or a malignant tumour (including leukaemia or lymphoma but excluding minor skin cancers), any emotional, nervous or psychiatric problems such as depression or anxiety, alcohol or substance abuse, stomach ulcers, varicose ulcers, cirrhosis.

*Denotes statistical significance at p<0.05

Table 3 Multi-variate analysis of participants reporting all falls (n=1,579), unexplained falls (UF) (n= 406) and syncope (n= 363) in wave one of TILDA (n = 8,172)

	All falls	**Unexplained falls**	**Syncope**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Sex (female)	1.04 (0.93-1.16)	1.06 (0.86-1.29)	0.67 (0.54-0.83)
Age group (years)			
50-64 years	0.98 (0.73-1.32)	1.32 (0.73-2.37)	0.75 (0.42-1.34)
65-74 years	1.09 (0.80-1.48)	1.27 (0.70-2.30)	0.97 (0.54-1.74)
75+ years	1.09 (0.79-1.49)	1.28 (0.69-2.36)	1.03 (0.57-1.88)
Anti-hypertensive medications[ii]	1.07 (0.94-1.21)	1.45* (1.17-1.81)	1.17 (0.92-1.47)
Depressive symptoms (CES-D)			
None /Insignificant	ref	ref	ref
Moderate	1.45* (1.26-1.66)	2.08* (1.64-2.64)	1.74* (1.34-2.26)
Severe	1.85* (1.57-2.19)	2.99* (2.29-3.91)	2.78* (2.11-3.67)
Cardiovascular conditions			
0 – 2	0.92 (0.79-1.07)	1.16 (0.86-1.57)	1.22 (0.88-1.70)
3 – 4	1.20 (0.91-1.58)	1.17 (0.72-1.91)	2.74* (1.73-4.35)
5+	2.07* (1.18-3.64)	2.89* (1.28-6.52)	1.52 (0.45-5.11)

As coded by the World Health Organisation Anatomic Therapeutic Chemical (ATC) anti-hypertensive medication with ATC code C02, C03, C07, C08, C09

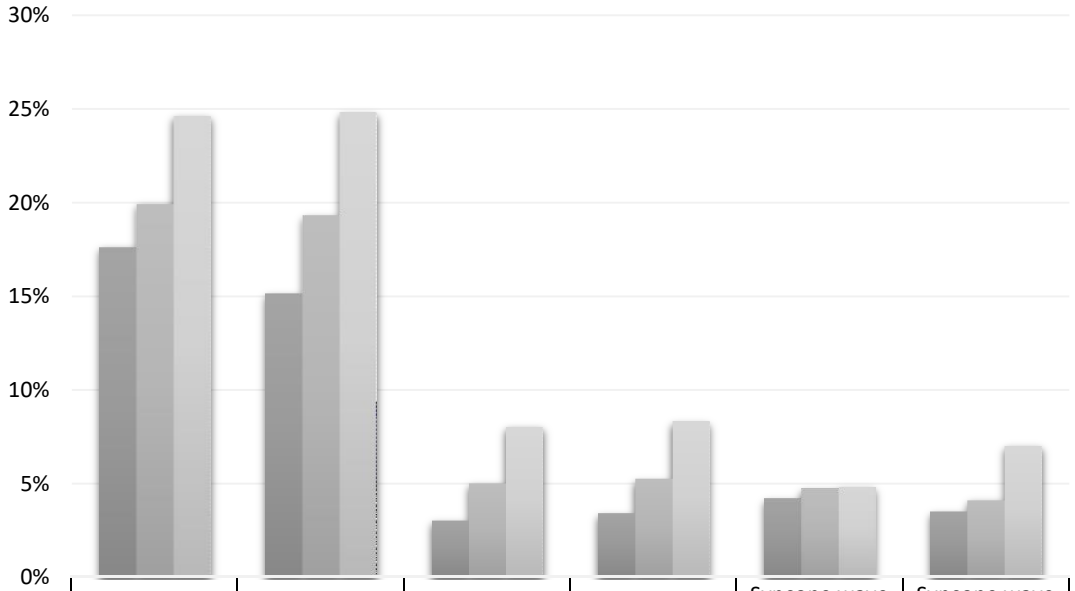
As measured by Centre for Epidemiological Studies Depression Scale (CES-D); scores of < 16 indicated insignificant symptoms for depression; >16 and < 26 indicated moderate to severe depressive symptoms and > 26 indicated severe depressive symptoms.

Self- reported cardiovascular conditions including angina, hypertension, diabetes, stroke, transient ischemic attack, high cholesterol and cardiac arrhythmia

CI = confidence interval

*denotes statistical significance with p-value <0.05

Figure 1 Prevalence (wave one) and incidence (wave two) of all falls, unexplained falls (UF) and syncope based on self-reported data from TILDA participants (n= 8504).



	Falls wave 1	Falls wave 2	UF wave 1	UF wave2	Syncope wave 1	Syncope wave 2
50-64 years	17.60%	15.10%	3%	3%	4%	4%
65-74 years	19.90%	19.30%	5%	5%	5%	4%
>=75 years	24.60%	24.80%	8%	8%	5%	7%

Chapter 6: Transient Loss of Consciousness (T-LOC) In The Emergency Department – Implications For Resource Use In Older Adults

Bhangu J, Hall P, Devaney N, Bennett K, Carroll L, Kenny RA, Mc Mahon CG

Introduction

The world is undergoing enormous demographic changes and by 2030 the older population is predicted to represent approximately 25% of Western populations (222). This is reflected in an increased prevalence of older patients (>65 year age group) presenting to Emergency Departments (EDs) (14, 223). Falls and syncope are common presentations to EDs in this age group and are associated with a substantial healthcare resource utilisation with high rates of hospital admission (49, 186)' (198).

Furthermore, there is a strong overlap between falls and syncope in older people. Amnesia for loss of consciousness complicates up to 60% of cases of syncope resulting from carotid sinus syndrome (CSS) and 20% of syncopal episodes resulting from orthostatic hypotension (224). In the absence of a witness account of the event, which is the case in over 70%(51), it can be difficult to differentiate between these two conditions (225).

Syncope is a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion (49). The aetiology of syncope includes vasovagal syncope, orthostatic hypotension (OH), cardiac arrhythmia and CSS (32), with cardiac syncope becoming more common with age (31). The prevalence of syncope also increases with advancing years, from 6.2 per 100,000 person years in adults aged 50 to 70 years, to 20 in the over 80s (31).

The diagnosis of syncope relies primarily on recognition of T-LOC in a patient with a fall or collapse. However, older patients who suffer from T- LOC are more likely to present atypically with unexplained falls; resulting in critical underlying cardiovascular contributory causes being overlooked (199). Syncope has serious consequences for older adults including depression, hip fracture and increased rates of institutionalization (226). Recognition of T-LOC presenting as unexplained falls is therefore critical to ensure appropriate cardiovascular assessment and intervention.

The aim of this study was to examine the prevalence of T-LOC in older patients presenting to the ED with a fall or collapse and secondly, to examine the resource utilisation associated with ED T-LOC presentations.

Methods

A single centre, prospective, observational study was conducted over a six-month period. Consecutive patients over 50 years who presented to

the ED because of a fall, collapse or syncope were included. The primary presenting complaint was captured from the Hospital Patient Administration System [PAS] (iSOFT Plc). The research team examined the clinical details of all patients who presented with a fall, collapse or syncope using the methodology outlined by Kaji (227). Patients were categorized as an explained fall; unexplained fall or suspected T-LOC. *Explained falls* (EF) Falls which resulted in a person coming to rest on a lower level from an identifiable mechanism based on history. *Unexplained falls* (UEF) patient had no recollection of a trip or mechanism to account for the fall. *Suspected T-LOC* was defined as transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous complete recovery (49). Patients with a fall or collapse episode secondary to underlying medical illness including, but not limited to, stroke/transient ischaemic attack, witnessed seizure in a patient with known seizure disorder, sepsis, anaemia, acute blood loss and alcohol intoxication were also included.

Patients in an unconscious or comatose state (Glasgow Coma Scale under 12/15) on arrival), who died in the ED or who self-discharged following triage prior to medical evaluation were excluded.

Demographic variables including age and sex were recorded on an internal database. Pre-specified resource variables were recorded and included: plain film x-ray imaging, brain imaging (computerised

tomography or magnetic resonance imaging) ordered within the ED and performed within 24 hours of presentation; the requirement for admission from the ED and the average length of stay (ALOS) for that admission; and presentations to the ED in the six months prior to the index presentation. Additionally, any injuries suffered as a result of the fall and a recurrent fall (defined as 2 or more self-reported falls within the previous calendar year) was recorded as well. Institutional ethics committee approval was obtained.

Statistical Analysis

To examine the prevalence of T-LOC in older adults presenting to the ED descriptive statistics are presented as percentages, means (SD, 95% confidence intervals (CI) and medians (IQR) where appropriate. Only those patients for whom all data was available were included in the analysis.

A hypothesis driven logistic regression model was generated using an a priori hypothesis that patients who suffered an explained fall utilized lower amounts of resources than other types of falls. The type of fall was used as the dependent variable and the five pre-specified resource variables as independent variables with unadjusted odds ratios calculated from this. Each odds ratio was adjusted for both age and sex to assess for potential confounding using multi-variable logistic regression analysis. This same model was used to examine the association between type of fall and the odds ratio of suffering injury from the fall or having a recurrent fall. Lastly a regression analyses was performed to examine the association of age and average length of stay. A p value<0.05 was considered statistically significant. Stata 12.1□ Statacorp LP was used for all statistical analysis.

Results

In total 751 presentations to ED were identified over a six months period; 29 were excluded because of duplicate number, 6 were brought in unconscious to ED, 155 patients had incomplete charts or did not wait long enough in the ED to be seen by a doctor. 561 records were subsequently included for analysis (Figure 1).

Primary Outcome

561 patients presented to the ED over a 6-month period with a fall or collapse episode. The mean age of the cohort was 75 years of age (range 50-100 years) with a female predominance at 61.1% (95% CI 59.2- 63.1). Explained falls were the most common presentation occurring in 56.7% (95% CI 54.7-58.7); Unexplained falls in 14.3% (95%CI 13.3- 15.3); Syncope in 12.7% (95% CI 11.7-13.6); T-LOC from underlying medical cause in 16.4% (95% CI 13.4-15.5); Table 1 summaries the baseline characteristics of patients included in the analysis.

There were 148 (26.3%, 95% CI 24.8-28.0) patients who re-presented because of recurrent falls episodes (See table 2). Patients with unexplained falls were the most likely to have suffered a recurrent fall within the year of their index presentation (Adj OR 4.97, 95% CI 2.898.56). Both unexplained falls (Adj OR 0.99, 95% CI 0.60-1.66) and syncope (Adj OR 0.58, 95% CI 0.33-1.01) were less likely than explained falls to have suffered an injury at the time of their fall.

Secondary Analysis

50% (95% CI 48.20-52.34) of included patients required admission to hospital. Those that were admitted were older (mean 77.87 years, SD ± 10.7) compared

to those not admitted (mean age 72.51, SD ±11.56, p< 0.001) (Figure 2). Patients over 80 years of age had a longer average length of stay (aLOS) than those in younger age groups (Figure 2). Following adjustments for age and gender, patients with syncope, unexplained falls and T-LOC from medical causes had a higher odds ratio of admission from ED than those with an explained fall (Table 2).

In total 29.2% (95% CI 27.5-30.6) of the cohort, presented in the six months prior to the index event; The majority of patients who presented had plain film x-rays carried out in ED (89% , 95% CI 86.2-88.1). Brain imaging was performed within 24 hours of presentation to ED in (43.9%, 95%CI 41.8-45.9). Logistic regression showed those with unexplained falls and syncope had a higher odds ratio of admission, undergoing brain scanning as well as re-presentation to the ED within six months when compared to explained falls (Table 2).

Discussion

12.7% of over 50s presenting with a fall or collapse had a diagnosis of syncope while a further 14.3% had an unexplained fall. Patients who had syncope and unexplained falls had higher odds of admission, brain scanning and recurrent falls. Furthermore, 50% of older adults who present with a fall or collapse to ED were admitted; with advancing age strongly predicting admission.

Understanding the true incidence of syncope in older adults presenting to ED is challenging and is compounded by the differences in definitions of syncope, lack of recognition of T-LOC in an older patient who has fallen, and overlap with other conditions which may mimic syncope (32). We have shown that more than 1 in 10 older adults who present with a fall or collapse episode have symptoms of T-LOC, and a further 14.3% have falls for which no obvious explanation can be found on history. This is consistent with similar studies conducted in EDs, demonstrating syncope as the cause of unexplained falls in 25-30% of older patients (209). Recognizing T-LOC in older patients is vitally important as there are successful treatments available. In one series, up to 50% of patients who had presented to the ED because of an unexplained fall, had underlying carotid sinus hypersensitivity, which was successfully treated with a pacemaker (52). Other observational studies have found that 20% of older adults who present with an unexplained fall have an underlying arrhythmia requiring intervention (212). This study adds to previous evidence that 1 in every 5 patients over the age of 50 presenting to the ED with a fall or collapse have symptoms suggestive of T-LOC on history which would benefit from further investigation.

Hospital admission costs account for a large portion of the costs of syncope and in the US the estimated annual healthcare costs for this condition are

approximately 2.4 billion dollars (228)' We have shown a high rate of admission and investigations with patients with syncope and unexplained falls significantly more likely to be admitted and undergo investigations when compared to those who had presented with an explained fall. Moreover, we have shown that those over the age of 80 years were the most likely to be admitted overall with a significantly higher average length of stay. A previous study in our institution in 2010 showed an admission rate of 51% for patients diagnosed with syncope (229). Estimates from the US show that syncope has an overall admission rate of 32% across all ages that almost doubles to 58% in those over the age of 80 years (186). Systematic approaches to the diagnosis of syncope result in reduced admission rates, hospital length of stay and unnecessary diagnostic tests (138)' (230). The European Society of Cardiology has proposed that syncope units be created in an effort to ensure that patients with T-LOC get appropriate directed investigations (214). Syncope units present an opportunity to provide standardised care and further studies are needed to see if this would result in lower admission rates and resource use for elderly patients with T-LOC.

With advancing age, cardiovascular morbidity plays an important role in the aetiology of syncope and unexplained falls (231). Most patients who present with falls alone never realise cardiovascular assessment because it is assumed that falls are due to locomotor or other traditional causes, rather than underlying cardiovascular disease. (206) This is despite evidence showing a link between cardiovascular conditions including cardiac arrhythmia, heart failure and falls in older adults (208) The prevalence of orthostatic hypotension three times higher in those over the age of 80 compared to those in younger age groups (44). This has significant biological consequences for older patients with greater rates of

cognitive decline, gait and mobility disturbances, depression, falls and frailty (35). Structured cardiovascular assessment remains an essential part of recurrent falls work-up and its importance in older adults presenting to ED cannot be underestimated.

Limitations

This study was designed as a prospective cohort study that relied on clinical history obtained by individual physicians. Therefore, it is subject to the heterogeneity inherent in clinical history taking. This also differentiates this study from other large databases sets that focus solely on discharge diagnosis and may reflect more of the real-life scenarios encountered in an undifferentiated presentation to the ED. The variables chosen are not comprehensive and are likely an underestimate of the true resource use arising from a T-LOC episode. There is the potential for ascertainment bias in this study as we focused only patients who had presented to the ED. As such these patients are more likely to have suffered serious outcomes thus affecting the overall admission rates.

Implications for clinical practice

As older adults are more likely to describe T-LOC in an atypical fashion a high degree of suspicion is needed in order to establish those who truly may have syncope and those who do not (217). Recent meta- analysis has demonstrated both the lack of data on screening tools for older adults who have recurrent falls in ED as well as the lack of accurate prediction tools for patients with undifferentiated collapse episodes (232). Early comprehensive geriatric approaches to complex conditions in older patients such as those used in dementia care and hip fracture care have shown improvements in outcomes (233). Similarly, a comprehensive approach to older adults who present to the

ED secondary to a fall, have shown evidence for improvement in outcomes (234). EDs provide a place to not only identify older patients with T-LOC who may benefit from targeted interventions but also to implement and study the effectiveness of those interventions (235).

We have shown that 1-in 4 patients presenting to an ED have symptoms suggestive of T-LOC or an unexplained fall, with higher rates of admission and investigations carried out in this group. Further work on the identification of symptoms suggestive of T-LOC in older adults combined with structured cardiovascular assessment and diagnostics may provide a
template for targeted treatments in the future.

Table 1 – Baseline characteristics of adult patients presenting to the emergency department (ED) following a fall or T-LOC episode

Patient characteristics	**Explained Falls n (%) (95% CI)**	**Unexplained falls n (%) (95% CI)**	**Syncope n (%) (95% CI)**	**Medical causes n (%) (95% CI)**	**Totals n (%) (95% CI)**
Totals	318 (56.7) (54.7-58.7)	80 (14.3) (13.3-15.3)	71(12.7) (11.7-13.6)	92(16.4) (15.3-17.5)	561 (100)
Breakdown by Age category					
50 – 59 years	45 (14.2) (12.8-15.5)	10 (12.5) (10.1-14.9)	14(19.7) (16.0-23.4)	9 (9.8) (7.9-11.6)	78 (13.9) (12.9-14.9)
60– 69 years	55 (17.3) (15.7-18.9)	8 (10.0) (8.0-12.0)	12 (16.9) (13.6-20.2)	9 (9.8) (7.9-11.6)	84 (15.0) (13.9-16.0)
70-79 years	92 (28.9) (26.7-31.2)	22 (27.5) (23.1-31.9)	23 (32.4) (27.3- 37.5)	26(28.2) (24.1-32.4)	164 (29.2) (27.5-30.9)
80-89 years	100(31.5) (29.1-33.8)	31 (38.7) (33.6- 44.0)	19 (26.8) (22.2-31.3)	38(41.3) (36.4-46.3)	187 (33.4) (31.5-35.2)
90-100 years	26 (8.2) (7.35-9.00)	9 (11.3) (9.1-13.4)	3 (4.23) (3.28-5.2)	10(10.9) (8.9-12.9)	48 (8.5) (7.9-9.2)
Sex (female)	215 (67.6) (65.2-70.0)	34 (42.5) (37.1-47.9)	39 (54.9) (49.2-60.7)	55 (59.8) (54.9-64.7)	343 (61.1) (59.1-63.1)
Secondary Outcomes					
Admissions	130 (40.9) (38.2-43.5)	52 (65.0) (60.1-70.0)	41 (57.8) (52.1-63.4)	59 (64.1) (59.4-68.8)	282 (50.3) (48.2-52.3)
X ray	285 (89.6) (88.6-90.6)	71 (89.8) (86.6-90.9)	57 (80.3) (76.6-83.9)	85 (92.4) (91.0-93.8)	498 (89.0) (88.0-89.6)
Brain scanning[1]	104 (32.7) (30.3-35.1)	46 (57.5) (52.1-62.9)	45 (63.4) (57.9-68.9)	52(56.5) (51.5-61.5)	246 (43.9) (41.8-45.9)
Medical Referrals	202 (63.5) (60.9-66.1)	56 (70.1) (65.4-74.6)	51(71.3) (67.1-76.5)	75(81.5) (78.4-84.6)	384 (68.5) (66.7-70.2)
Prior ED attendance	79 (24.8) (22.8-26.9)	32 (40.0) (34.7-45.3)	21 (29.6) (24.7-34.4)	32 (34.8) (30.2-39.4)	164 (29.2) (27.5-31.0)
Injury from fall	141 (44.3) (41.6-47.1)	34 (42.5) (37.1-47.9)	22 (30.1) (26.0-36.0)	28 (30.4) (26.1-34.8)	225 (40.1)

[1]Brain scanning denotes MRI or CT scan

Table 2- Logistic regression analysis demonstrating the crude and adjusted odds ratio for investigation required and injuries sustained based on sub-classification of fall at index

Variables	Unadjusted Odds ratio	95% CI (p value)*	Adjusted Odds Ratio[5]	95% CI† (p value)[1]
Admission[2]				
Gender (F vs M)			0.88	0.61-1.27 (0.49)
Age			1.04	1.03-1.06 (<0.01)
Explained Falls	REF	REF	REF	REF
Unexplained Falls	2.66*	1.61-4.48 (<0.01)	2.48	1.45-4.23 (<0.01)
Syncope	1.98*	1.17-3.33 (<0.01)	2.36	1.37-4.08 (<0.01)
Medical causes	2.59*	1.60-4.18 (<0.01)	2.4	1.46-3.94 (<0.01)
X-ray[1]				
Gender (F vs M)			1	0.57-1.75 (0.99)
Age			1	0.98-1.03 (0.60)
Explained Falls	REF	REF	REF	REF
Unexplained Falls	1.03	0.45-2.32 -0.95	1.01	0.44-2.32 (0.98)
Syncope	0.47	0.24-0.94 -0.03	0.52	0.25-1.05 (0.07)
Medical Causes	1.41	0.60-3.29 -0.43	1.36	0.58-3.20 (0.48)
Brain imaging°				
Gender			0.96	0.66-1.39 (0.83)
Age			1.03	1.02-1.05 (<0.01)
Explained Falls	REF	REF	REF	REF
Unexplained Falls	2.78*	1.69-4.60 (<0.01)	2.63	1.56- 4.43 (<0.01)
Syncope	3.56*	2.08-6.09 (<0.01)	4.25	2.43-7.44 (<0.01)
Medical causes	2.68*	1.66-4.30 (<0.01)	2.52	1.55-4.10 (<0.01)
Recurrent Falls[3]				

Gender			0.92	0.61-1.38 (0.68)
Age			1.02	1.00-1.04 (0.04)
Explained Falls	REF	REF	REF	REF
Unexplained Falls	5.23*	3.08-8.90 (<0.01)	4.97	2.89-8.56 (<0.01)
Syncope	3.22*	1.83-5.65 (<0.01)	3.46	1.95-6.15 (<0.01)
Medical causes	2.67*	1.57-4.50 (<0.01)	2.55	1.50-4.34 (<0.01)
Injuries suffered[æ]				
Gender			1.25	0.87-1.80 (0.22)
Age			1	0.98-1.01 (0.39)
Explained Falls	REF	REF	REF	REF
Unexplained Falls	0.93	0.57-1.52 -0.77	0.99	0.60-1.66 (0.99)
Syncope	0.56	0.33-0.98 -0.04	0.58	0.33-1.01 (0.05)
Medical Causes	0.55*	0.33-0.90 -0.02	0.58	0.35-0.96 (0.03)
Re-presentation to ED[δ]				
Gender			0.64	0.98- 1.01 (0.56)
Age			1	0.44-0.94 (0.02)
Explained Falls	REF	REF	REF	REF
Unexplained Falls	2.02	1.21-3.37 -0.01	1.84	1.08-3.11 (0.02)
Syncope	1.27	0.72-2.25 -0.41	1.22	0.68-2.16 (0.51)
Medical causes	1.61	0.98-2.66 -0.06	1.54	0.92- 2.56 (0.10)

Note: Outcome defined as either x-ray, blood testing, CT scan or MRI scan within 24 hours of presentation to the emergency department or injury sustained at time of index fall

† CI = 95% confidence interval for the adjusted odds ratio

*denotes statistically significant p value at <0.05

[5]Adjusted for both age and sex

[δ] presentations to the ED in the six months prior to the index presentation

[æ] any injuries suffered as a result of the fall

[3] recurrent fall (defined as 2 or more self-reported falls within the previous calendar year)

[1] plain film x-ray imaging

[2]; the requirement for admission from the ED

°computerised tomography or magnetic resonance imaging ordered within the ED and performed within 24 hours of presentation

Figure 1- Flow sheet of recruitment, exclusion numbers and subsequent analysis

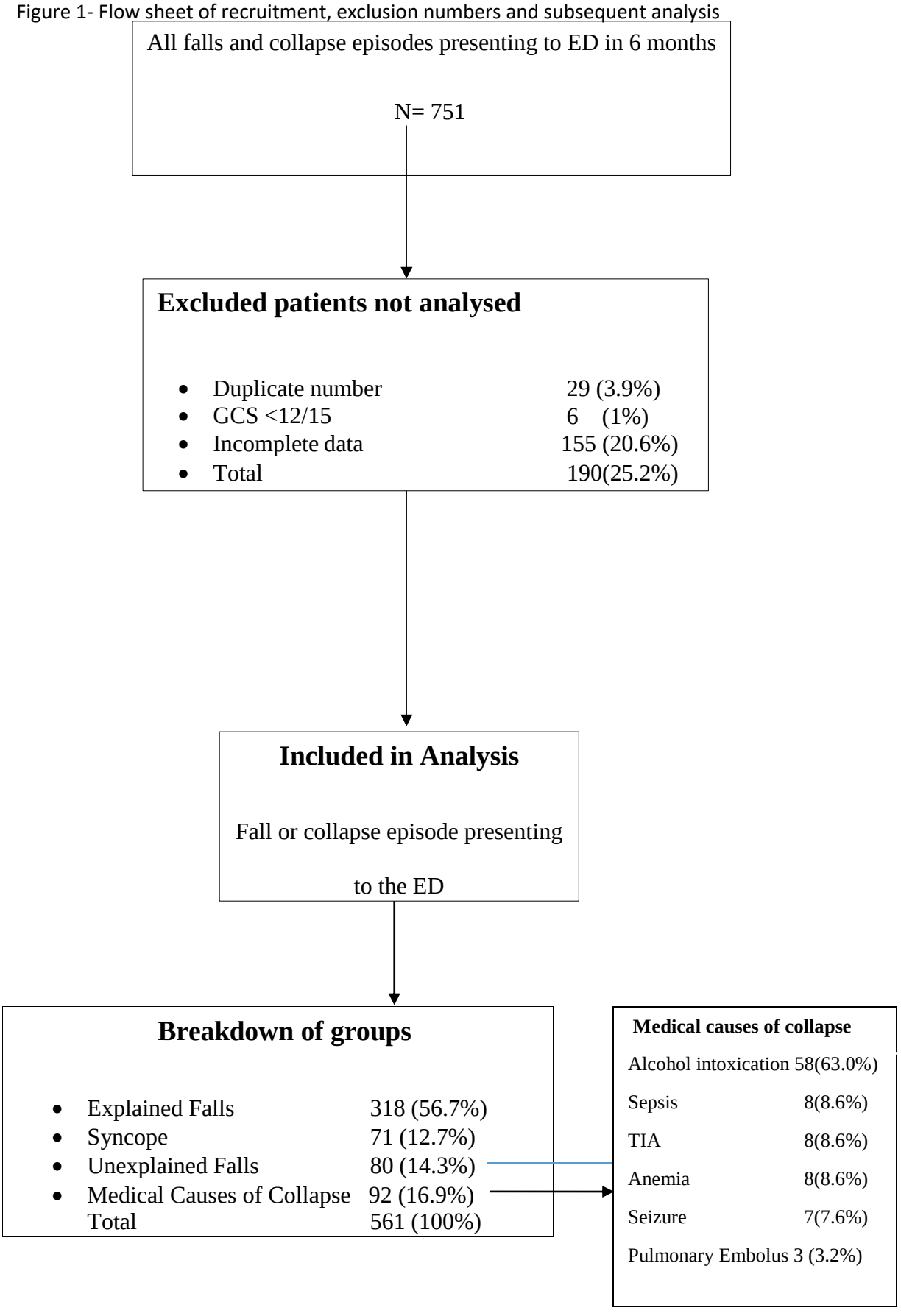
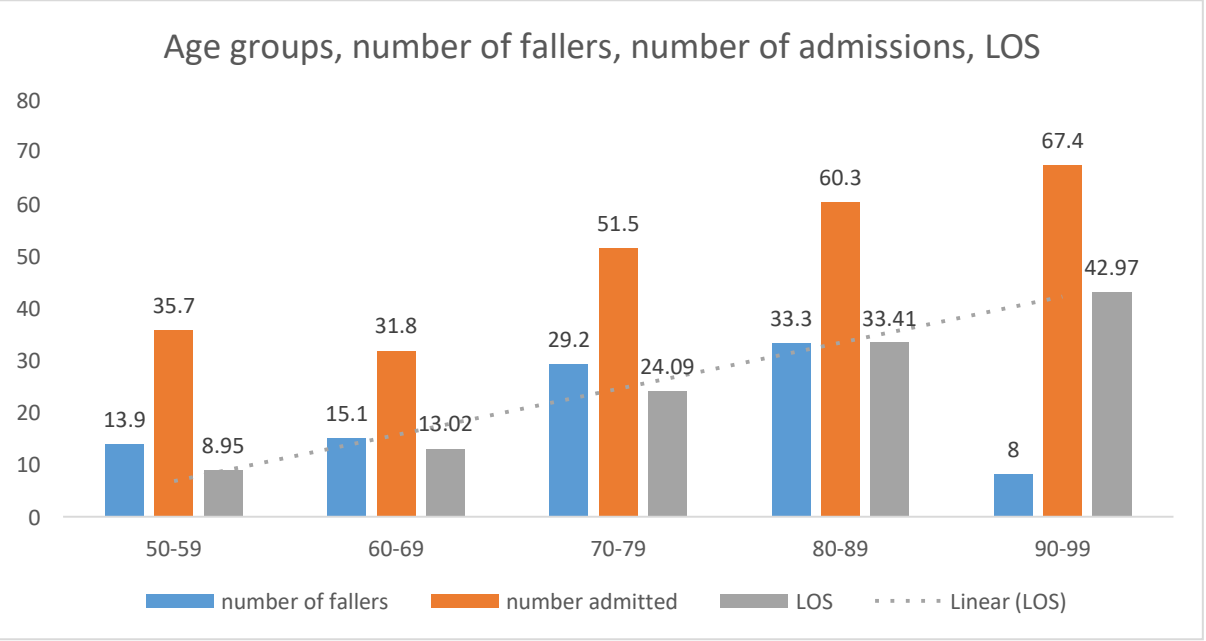


Figure 2- Age breakdown of patients over the age of 50 who had presented the emergency department (ED) in a six month period. Numbers represent percentages of patients in each category who presented to ED, numbers admitted from ED and mean length of stay (LOS) with regression line



Chapter 7- Falls And Syncope In The Emergency Department (FUSE) – Benefits Of Long-Term Cardiac Monitoring

Introduction

Falls are the most common cause of injury and associated morbidity and mortality in older people (25). 35% of community dwelling individuals aged over 65 years will fall once a year. 10% of these falls result in significant injury and morbidity (136, 236). Due to accelerated growth of the global ageing demographic, the number of fall-related presentations to the emergency department (ED) has increased by more than 50% in the last two decades (104). Falls are the single most common reason for older patients to attend the ED, accounting for one third of all adult attendances (25, 57). Falls in older adults are more likely to be associated with significant injury, including hip fractures, and more likely to lead to hospital admission (136, 237). Direct and indirect costs of falls are more than 2 billion pounds per year in the UK and 30 billion dollars in the USA per year (24, 25). Up to one fifth of older fallers have no obvious cause for their fall event and are classified as 'unexplained' or 'non-accidental' falls (52, 200, 206). Furthermore, in one third of patients presenting with a hip fracture, the cause of the fall is 'unexplained' (238). In the emergency setting the injury sustained following a fall is very often the primary focus of medical attention and important risk modification opportunities may be overlooked.

With advancing age cardiovascular morbidity plays an important role in the aetiology of syncope and unexplained falls. There is strong evidence of an overlap between syncope and unexplained falls in older people. Syncope is defined as transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion characterised by rapid onset, short duration, and spontaneous complete recovery (49). Up to 40% of older fallers have amnesia for loss of consciousness, and 60% of community dwelling older people have no witness to a fall event (51, 187, 216). Thus "syncope" is likely to present as a fall in the absence of a witness account, coupled with amnesia for loss of consciousness. These patients are also more likely to sustain a serious injury (239).

Falls have been associated with orthostatic hypotension (OH), vasovagal syncope (VVS), carotid sinus syndrome (CSS) and cardiac arrhythmias, but attributing a single cause for syncope and unexplained falls is challenging and diagnostic clarity can be elusive (92) (209). Recently, implantable loop recorders (ILRs) have greatly contributed to the diagnosis of arrhythmia as a cause of syncope (240). The most recent European Society of Cardiology (ESC) Syncope guidelines recommend that ILR monitoring should be considered in patients with recurrent, unexplained syncope or falls after conventional work-up (241), although the evidence for the use of ILR monitoring in patients with unexplained falls is lacking.

We hypothesize that cardiac arrhythmias are an under-diagnosed cause of unexplained falls. The objective of this study is to determine the diagnostic utility of cardiac loop recorders in detection of arrhythmogenic causes for unexplained falls in older patients.

Methods

A single centre, prospective, observational cohort study of recurrent fallers (defined as 2 or more falls in the previous year) was undertaken. All patients over 50 years who presented to the ED as a result of an unexplained fall were screened during a six-month period. A 'fall' was defined as an event which resulted in a person coming to rest inadvertently on the ground or floor or other lower level (1); an 'unexplained fall', as an event for which a cause was not apparent, either intrinsic (e.g. stroke, myocardial infarction, gastro-intestinal haemorrhage or other medical diagnosis) or extrinsic (e.g. trip over carpet) (242). Institutional ethics committee approval was obtained.

Between the hours of 09.00 and 17.00, a research doctor and nurse screened all patients presenting to ED. ED records of patients presenting outside these hours were screened daily and eligible patients were contacted by telephone and invited to participate in the study. Patients with a life expectancy of less than 12-months, cognitive impairment (defined as a Mini Mental State Exam (MMSE)<24) (243), a pacemaker insitu or prior diagnosis of a syncope syndrome were excluded. Patients with no access to a telephone landline were also excluded.

A comprehensive geriatric assessment was performed on all patients detailing falls history, fear of falling using the Falls Efficacy Scale (FES) (maximum score 0/100) (15), medications history (classified according to the British National Formulary), polypharmacy (defined as five or more drugs (244)), timed up and go test (TUG) (abnormal score 13.5 seconds) (245), (246), balance and mobility assessment (POMA) (maximum score
56) (247), (248), mental health scores (CES-D) (Maximum score 60),(204) and medical history (self-report, doctor diagnosed). Where risk factors for falls were detected, falls prevention interventions were delivered in keeping with current

guidelines (28).

Cardiovascular assessment was undertaken in line with ESC guidelines (49), and included a 12-lead electrocardiogram (ECG), phasic blood pressure (BP) and heart rate (HR) measurement during orthostatic change from supine (10 minute resting period) to upright over a 3 minute period (active stand) with ECG and phasic BP recordings (Beatscope Finometer data®). Carotid sinus massage (supine left and right and upright position at 70 degrees), (249) and head up tilt table test were performed when indicated (250). Patients with OH, vasodepressor carotid sinus hypersensitivity (CSH) and suspected VVS had appropriate interventions. Patients diagnosed with cardio-inhibitory carotid sinus syndrome (CICSS), sinus bradycardia, first, second or third degree atrio-ventricular block (AVB), supraventricular tachycardia (SVT) were withdrawn from the study and appropriate treatment instituted.

Implantable Loop Recorder.

Remaining consented patients underwent ILR (Reveal,® Medtronic Inc. Minnesota, USA) implantation (Figure 2.) The ILR device was implanted in the left parasternal region, under aseptic conditions. It is capable of storing ECG data automatically in response to a significant bradyarrhythmia or tachyarrhythmia and in response to patient activation. The ILR DX model was used in the initial stage of the study and the ILR XT model in the latter stage when it became available, as it is a superior model for detection of atrial fibrillation. ECG data was downloaded and interpreted remotely on a daily basis using the CARELINK system (Medtronic Minnesota®) with all patient activations as well as pre- programmed alerts reviewed. Patients were instructed to activate the device after syncope, presyncope or fall.

Participants returned weekly symptom diaries, with regular telephone prompting (bi-weekly) to optimize compliance. Details on the circumstance of each fall or syncopal event together with prodromal symptoms, consequences (i.e. fracture, head injury) and hospital and ED attendances were recorded. Patients attended for clinical review at 6 monthly intervals or when indicated. The minimum follow up was 6 months.The primary outcome measure was detection of cardiac arrhythmia associated with a fall or syncope during follow up. Cardiac arrhythmias detected by the ILR were defined according to ISSUE classification (251). The secondary outcome measure was a) detection of cardiac arrhythmia independent of falls or syncope, b) falls or syncope without associated arrhythmia.

SAS software (version 9.3) was used for the calculation of sample size requirements with the Clopper-Pearson Exact Binomial method using a two-sided 95% confidence interval. The expected proportion of patients, who have an arrhythmia within 1 year, was 0.33. This estimate was based on previous studies that used a sample size of 200 to detect an 18% improvement in ECG diagnosis (252). Under these assumptions, a sample size of 45 subjects with 1-year follow-up was required for the evaluation of this objective. Assuming an attrition rate of 10%, a minimum sample size of 50 subjects was required.

Means and standard deviations, or number and percentages were calculated for patients' baseline characteristics. Comparison of patient characteristics, including the number and percentage use of medicines, and polypharmacy between the arrhythmia and non-arrhythmia group was examined using Fisher's exact test, with significance at $p<0.05$ assumed. Student's t-test was used for continuous variables.

Results

Screening

970 ED fallers were screened over the study period. 886 were excluded on the basis of fulfilling pre-specified exclusion criteria in 438 (49.3%) patients, other medical illness which contributed to the fall in 171 (19.6%), pacemaker already in situ and/or known diagnosis of syncopal syndrome 40 (4.5%), patient unable to download information on a daily basis 72 (8.2%), declined or unable to contact 144 (18.6%) (Figure 1).

84 patients were eligible for study inclusion as they had presented to ED because of an unexplained fall, had at least two falls in previous year and an MMSE >24 (figure 1). Of these a cardiac arrhythmia or conduction disorder was diagnosed at initial cardiovascular assessment in 9 patients and therefore did not proceed to ILR implantation. Arrhythmias detected at this assessment included 5 CICSS, one VVS, 2 trifasicular block, one second degree AVB. A further 5 patients declined an ILR.

Baseline characteristics

70 patients underwent ILR implantation (83%), mean age 70 years (SD +/- 10.02; range 50-82 years), 45 females (63%), median MMSE of 28 (range 24-30). The mean number of falls in the last year was 4.17 (range 2-12) per patient. The mean follow-up period was 9 months (range 6 – 12months) (Table 1).

Arrhythmia

50 patients (71.4%) had a cardiac arrhythmia detected by ILR at a mean of 47.3 days (SD 48.25, range 1-190 days) post implantation. Fourteen

(28 %) met the primary end point of simultaneous fall or syncope together with a cardiac arrhythmia. Cardiac pacing for bradycardia or asystole was required in 10 (20%) and treatment of SVT in 4 (8%). The mean time to event in these patients was 43 days (SD 36.28); Patients who had an arrhythmia detected were more likely to have a history of co- morbid diagnoses including cardiovascular disease, hypertension, depression, arthritis and hypercholesterolemia. They were also more likely to be on five or more medications and to have suffered injurious events in their index fall. (Table 1)

Secondary end points

Cardiac arrhythmia independent of falls or syncope was detected in 36 (51%) patients. These included atrial fibrillation, SVT, and sinus bradycardia of < 50 bpm which were detected in 4 (8%), 8 (16%) and 24(48%) patients respectively independent of falls or syncope (Table 2).

36 (51%) patients had a fall or T-LOC during follow up which was not associated with an arrhythmia. Time to first falls or T-LOC was 93.33 days (SD 72.15) days after implant. This group had a mean TUG of 11.39 (± 1.56), MMSE of 28.27 (± 0.60), CES-D of 12.47 (± 2.18), POMA score of 24.41 (±1.604), FES score of 25.5 (±8.19). These values did not differ significantly between groups. Patients who had a cardiac arrhythmia were

5 times more likely to fall during follow up (p= 0.0012) (Table 3). One patient had a witnessed seizure and was subsequently diagnosed with epilepsy. One patient had a fall that resulted in a hip fracture.

Discussion

A major finding in this study is that two thirds of older patients with unexplained falls who attend the ED have a cardiac arrhythmia that is not apparent at the time of presentation, but detected within 9 months of continuous monitoring using ILR. In 20% of these patients, events were directly attributable to a modifiable cardiac arrhythmia. A further 11% have an arrhythmia detected during the initial detailed cardiovascular assessment. Furthermore, falls were 5 times more likely to recur in patients who had cardiac arrhythmias.

We have recently demonstrated in a large population study, the Irish longitudinal study of ageing (TILDA), that cardiovascular diseases, including cardiac arrhythmias such as atrial fibrillation, are retrospectively and prospectively associated with falls risk (211) (253). The association was strongest for syncope and cardiac arrhythmia in younger cohorts but more likely to be related to falls rather than syncope in older cohorts (199). Additionally, previous studies of ED cohorts support an association between falls and cardiovascular disorders such OH, VVS and CSS and to a lesser extent cardiac arrhythmias (206) This study has demonstrated that cardiac arrhythmias occurred with a large frequency in this cohort; with 2/3rd of patients having an arrhythmia detected. 1 in 5 of these were major arrhythmias occurring at the time of the fall and required invasive intervention. Previous observational studies have shown a prevalence of between 1-25% for detection of cardiac arrhythmia in older fallers. They differed significantly in their methods, definitions of cardiac arrhythmia and the ways in which they had captured arrhythmia. This is the first study to look at prolonged cardiac monitoring in a large group with prospective falls diaries coupled with capture of abnormal cardiac rhythms. We have provided evidence which

strengthens the association between cardiac arrhythmias and falls and demonstrated that cardiac arrhythmias are a casual, modifiable risk factor in falls prevention.

Previous studies using prolonged monitoring for detection of cardiac arrhythmias has focused on syncope as a primary outcome and have supported the use of ILR in older adults. Brignole et al. previously compared the use of ILR in patients over the age of 65 to those under the age of 65, referred for investigation of unexplained syncope. Syncope recurrence was 2.7 times higher and modifiable cardiac arrhythmias were 3.1 times more frequent in those over 65 years (254, 255). The diagnostic yield of ILR is higher in older patients; use of an ILR in older fallers achieved a diagnostic yield similar to that reported for syncope at 20%. Furthermore, cardiac data was obtained as a result of ILR monitoring which resulted in detection of asymptomatic cardiac arrhythmias which did not require an invasive procedure but resulted in guided treatment interventions. For example, 4 patients had new atrial fibrillation detected requiring the initiation of anti-coagulation and a further 24 patients had medication dosages adjusted because of the detection of cardiac arrhythmia. Our data support not only an initial detailed cardiovascular assessment in patients with unexplained falls but also continuous prolonged cardiac monitoring using ILR to detect underlying cardiac arrhythmias.

This study has demonstrated that those patients with cardiovascular disease, hypertension and hypercholesterolemia were most likely to have cardiac arrhythmia detected by ILR. In addition those with higher depression scores as well as arthritis had a higher risk of detection of cardiac arrhythmia demonstrating the multi-factorial nature of falls in older adults. Our results

support the AGS/BGS and NICE guidelines, which recommend standardised cardiovascular investigations as well as a multi-factorial assessment in all patients with recurrent falls in order to detect and adequately prevent future falls (28) (103). Overall 51% of the cohort had a subsequent fall during follow up despite application of guideline based falls assessment and intervention emphasising that these are high risk patients for whom new interventions are needed (28). Randomised control trials, which include multifactorial intervention for traditional falls risk factors, coupled with targeted treatment of cardiovascular disorders show benefit for falls prevention in cognitively intact older patients (29, 50, 52). In one study, dual chamber cardiac pacing reduced falls by 70% during a 12-month follow up period in patients with unexplained falls and CSS (52). Despite this and other evidence, cardiovascular assessments are not consistently performed in ED. (256) (257). Further randomised studies are needed to discern if targeted intervention of arrhythmia is of benefit for falls reduction in older adults.

One explanation for the overlap between syncope and falls is amnesia for loss of consciousness (51, 216). If patients with cardiac arrhythmia have amnesia for T-LOC and if events are not witnessed, the patient will present with an unexplained 'fall' rather than 'syncope'. Although amnesia for T-LOC is not exclusive to older persons (occurring in 20% of adults under 40 years with VVS) it is five times more prevalent in older patients (51, 187, 216). In this study, the detection of asymptomatic arrhythmia was a common finding with the majority of arrhythmias detected not occurring at the time of a fall or collapse episode. Furthermore, bradycardia detected under 50 beats per minute but over 40 beats

per minute was the most common type of arrhythmia described. Although these heart rates are often considered a normal variant; patients with this arrhythmia were more likely to have suffered subsequent fall than those who maintained a normal sinus rhythm. In addition, commonly measured variables predictive of gait imbalance and falls risk such as TUG and POMA scores were not significantly higher in the falls group. In the absence of concomitant BP measurement, it is difficult to ascertain the exact clinical consequences of intermittent arrhythmia. One explanation is that modest reductions in cerebral perfusion are caused by hypotension secondary to arrhythmia, resulting in balance instability and consequent falls without necessarily causing loss of consciousness (49). Another plausible explanation is that repeated episodes of arrhythmia are sufficient to result in cerebral hypoperfusion and vascular damage to neural pathways which govern balance (258). Further research looking at the effect of intermittent arrhythmia on blood pressure and cerebral perfusion may provide insight into optimal heart rate management in older patients with falls.

Limitations

This is a single site prospective observational cohort study. In this series, 10% of patients over 50 years who attended ED because of a fall were classified as 'unexplained'. This is likely to be an underestimation of the true prevalence of this condition. We excluded patients who were cognitively impaired or who were in an institution and did not have access to a landline. The prevalence of cardiac arrhythmia in these cohorts has not been studied. The implication of our findings in other settings i.e. community falls without injury, requires separate study. It may be that injurious falls are more likely to be associated with arrhythmias. A multi- centre trial to determine whether the findings can be generalised and whether ILR guided intervention prevents falls is now warranted.

Conclusion

A better understanding of causal factors for unexplained falls is critical in order to develop more effective prevention strategies and improve successful ageing in our changing population demographic. Further studies are now required to determine whether ILR guided intervention coupled with traditional risk factor modification will prevent falls in older patients.

Table 1- Baseline characteristics of patients with ILR inserted

Variable	Patients with ILR inserted n=70	Patients with arrhythmia detected n= 50	Patients with no arrhythmia detected n=20
Sex (female)	45 (63%)	29(58%)	16 (80 %)
Mean age ± SD (years)	69.4 ± 10.0	67.9 ± 10.24	72.4 ± 8.38
MMSE score[1] (Mean ± SD)	28.18 ±1.746	28.28 ±1.71	27.94 ± 1.82
TUG score [2] (Mean ± SD)	14.1 ± 4.47	13.3 ± 3.92	15.13 ± 4.935
CES-D score[3] (Mean ± SD)	9 ± 8.001	11.08 ± 8.02	8.167 ± 7.53
POMA [4] (Mean ± SD)	24.76 ± 4.02	25.10 ± 3.908	26 ± 4.11
Falls efficacy scale[5] (Mean ± SD)	22.39 ± 22.65	22 ±21.85	25.71 ± 24.5
Warning symptoms prior to index fall[6]	21(30%)	16 (32%)	5 (25%)
Head injury during index fall	18 (26%)	10(14%)	8 (40%)
Fracture during index fall[7]	24 (34%)	16(23%)	8 (40%)
History of cardiovascular disease[8]	31(44%)	27(39%)	2 (10%)
Hypertension	41(59%)	32 (46%)	9 (45%)
Diabetes	8(11%)	7 (10%)	1 (5%)
Hypercholesterolemia	32(46%)	27 (39%)	5 (25%)
Chronic Obstructive Pulmonary Disease (COPD)	11(16%)	9 (13%)	2 (10%)
Depression	20(29%)	18 (36%)	2 (10%)
Osteoporosis	15(21%)	9 (18%)	6 (30%)
Polypharmacy (> 5 medications)	41(59%)	28 (56%)	13(65%)
Anti-hypertensive	44(63%)	32 (64%)	12 (60%)
Anti- arrhythmic	7(10%)	7 (14%)	0 (0%)
Beta-blockers	15(21%)	12 (24%)	3 (15%)
Hypnotic/anxiolytic	16(23%)	12 (24%)	4 (20%)
Anti-depressant	22(31%)	16 (32%)	6 (30%)
non-opioid analgesia	15(21%)	11 (22%)	4 (20%)

Diuretic	12(17%)	10 (20%)	2 (10%)
Anti-platelet	25(36%)	18 (36%)	7 (35%)
Bisphosphonate	10(14%)	5(10%)	5(25%)

Denotes significance at $p < 0.05$

[1] MMSE – Mini mental state examination. Maximum score out of

30 [2]Timed Up and Go test (TUG) (abnormal score 13.5 seconds)

[3]Centre For Epidemiologic Studies Depression Scale (CES-D) (Maximum score 60)

[4]Performance Oriented Mobility Assessment (POMA) (maximum score 56)

[5]Falls Efficacy Scale (FES) (maximum score 0/100)

[6]Warning symptoms included those typically reported preceding a syncopal event including light-headedness, dizziness, palpitations or visual disturbance

[7] Self- reported fracture of any bone

[8] Cardiovascular disease included doctor diagnosed history of myocardial infarction, angina, stroke

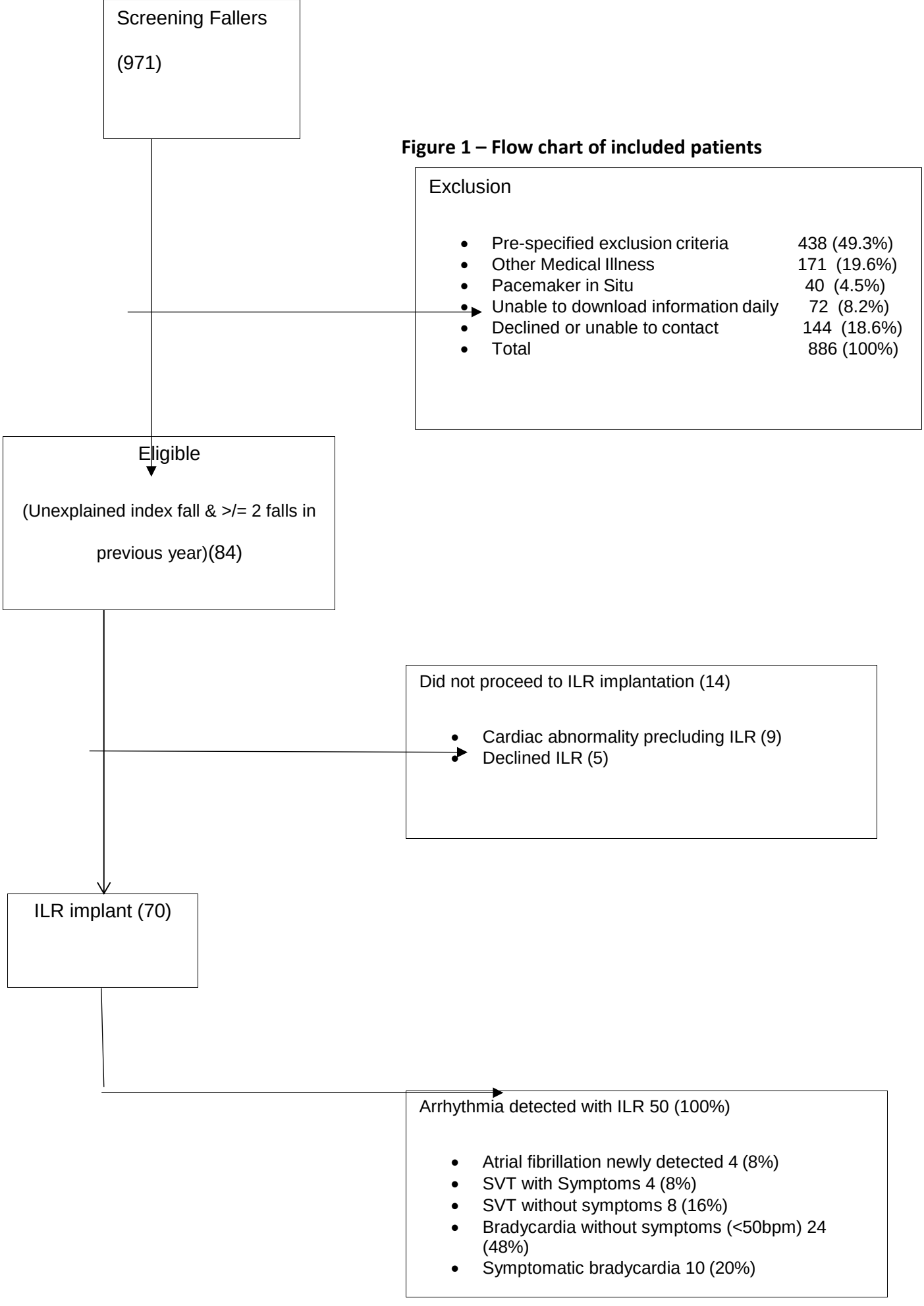


Figure 1 – Flow chart of included patients

Table 2 - Description and classification of arrhythmias detected in patients with ILR inserted at a mean of 9 months

Number of patients 50 (100%)	Mean age ± SD	Description of arrhythmia	ISSUE classification
9 (18%)	73 +/- 9.04	Asystole (RR interval pause >/= 3 seconds)	1
4 (8%)	73+/- 9.30	Bradycardia (Heart rate < 40 beats per minute for > than 10 seconds)	2
22 (44%)	67.45+/-10.23	Bradycardia (Heart rate > 40 beats per minute and <60 beats per minute for > than 10 seconds)	3
15 (30%)	65.26+/- 10.38	SVT (> 140 beats per minute for more than 15 seconds)	4

Table 3 – Univariate analysis of patients with an ILR inserted who experienced further falls during a mean follow-up of 9 months

Fall risk factor at baseline	Fall during follow-up N= 36	No fall during follow-up N=34	p value
Age	68.2 (10.80)	70.2 (8.86)	0.40
TUG (Mean ± SD)	11.39 ± 1.56	10.60 ±1.24	0.42
MMSE (Mean ± SD)	28.27± 0.60	28.08 ± 0.60	0.65
CES-D (Mean ± SD)	12.47 ± 2.18	8.79 ± 2.58	0.06
POMA (Mean ± SD)	24.41 ±1.604	25.09 ± 1.12	0.49
FES (Mean ± SD)	25.5 ± 8.19	19.35 ± 6.85	0.25
Arrhythmia detected during follow-up 36 (100%)	30(83%)	6 (18%)	0.001*

*Denotes significance at $p<0.05$

Chapter 8 –The relationship between syncope, depression and anti-depressant use in older adults

Introduction

Syncope is defined as a sudden loss of consciousness associated with the inability to maintain postural tone, followed by spontaneous recovery (Moya et al., 2009b). The true incidence of syncope in the general population is difficult to estimate due to the lack of definition, differences in population prevalence and under reporting in the general population (259). Large population studies have shown a rise in the incidence of syncope as people age. The Framingham cohort estimates that the cumulative incidence of syncope is approximately 50% in men and women aged over 80 years (31). In tandem with the observed rise in incidence , there is an increase in both hospital admissions, as well as morbidity and mortality in older patients who present with syncope (260) (261). Syncope recurrence rates are also higher in older age groups (176). In older patients multiple causes of syncope are often present and the medical history may be less reliable than in the young (196). For example, polypharmacy and cognitive impairment are known risk factors which can increase susceptibility to syncope in older populations (262)

Depressive symptoms have been described in patients with recurrent vasovagal syncope, as well as unexplained syncope (263, 264). Despite the higher rates of depression seen in patients who experience syncope the exact relationship between the two has not been fully established. In older cohorts there have been links observed between depressive symptoms and rates of syncope. In older patients who have been hospitalized for syncope, there were higher rates of depression diagnosed after two years of follow-up (226). However, in community dwelling cohorts, the prevalence of depression and its role in susceptibility to syncope remains unknown. With an estimated prevalence of between 2 and 5%, depression is a significant co-morbid condition in community dwelling older cohorts (265, 266). Anti-depressant (AD) medications are also increasingly being prescribed for older patients with studies showing a prevalence of AD prescriptions to be between 10 and 13.7 % of prescriptions for community dwelling older people (267, 268).

To date no population based study has investigated the prevalence of syncope in community dwelling elderly populations and its relationship to depression. We aim to estimate the prevalence of depression in older patients reporting syncope and the effect that treatment of depression with commonly prescribed ADs has on rates of syncopal attacks.

Methods

Data

The data come from Wave 1 of The Irish Longitudinal Study on Ageing (TILDA), which includes 8,175 adults aged 50 and older living in the community in Ireland. TILDA is a nationally representative survey of people aged 50 and over. The household response rate was 62% and those who participated provided informed consent. Participants were interviewed in their homes and were invited to attend a comprehensive physical health assessment. Further study details have been described in detail previously (201). In this study we use data from the in-home assessment.

Study procedures

Computer Assisted Personal Interview

Structured interviews were undertaken in the respondents' homes by trained professional social interviewers using computer-aided personal interviewing (CAPI). During the interview, information on the health and well-being of participants, including demographics, socioeconomic status, medical history, personal health behaviours, physical functioning and medication use was collected.

Ethics

Ethical approval for the study was obtained from the Trinity College Research Ethics committee. All participants provided written informed consent prior to participating in the study.

Measures

Syncope – all participants were asked whether they had fainted at any point during their lifetime. Those who responded positively were for asked further details that included whether they were a frequent fainter in youth (yes/no), had fainted in the past 12 months (yes/no) and how many faints they had experienced in the past 12 months. Center for Epidemiological Studies Depression scale (CES-D) was used to assess depression (204). This is a 20 item scale that asks respondents to evaluate how often ("rarely or none of the time" to "most or all of the time") in the last week they have experienced a symptom. Higher scores indicate increased depression. Cut-off values were applied, where 0– 15 indicates no or mild depression, 16 – 26 indicates moderate depression and 27 and higher indicates severe depression (204). Anti-depressant use

– all medications were coded using the World Health Organizations Anatomical Therapeutic Chemical index (203). All ADs have the same first 4 digit code (N06A), once ADs were identified, these were broken into classes. In this paper we only make the distinction between selective serotonin reuptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs) and other ADs (serotonin–norepinephrine reuptake inhibitors, serotonin antagonist and reuptake inhibitors, tetracyclic and monoamine oxidase inhibitors) due to small number of other ADs prescribed. Comorbidity – A number of self-reported conditions were controlled for in the analysis, these included: high blood pressure, angina, heart attack, heart failure, diabetes, stroke, transient ischemic attack, lung disease and dementia.

These were all dichotomously coded (absent/present). Antihypertensive

Medications – Participants were asked "Are you currently taking any tablets or pills for high blood pressure?" (Yes/no). Substance Abuse – Participants were asked "Has a doctor ever told you that you have any of the following conditions?" where alcohol or substance abuse was listed as one of the conditions (yes/no). Demographic Information – Age, sex, level of education achieved (primary/none, secondary and tertiary) and marital status (married, never married, widowed or separated/divorced) were controlled for in the analysis.

Statistical Analysis

Descriptive statistics were used to explore the relationships between syncope, depression and AD usage. To calculate the prevalence of syncope, survey weights, cluster and stratum were set and tabulation and cross tabulation was used. The standard errors were calculated using the Taylor series linearization method, and differences assessed using the design-based F statistic. The outcome, number of syncopal episodes in the past 12 months, is a count variable and was over dispersed (standard deviation larger than the mean [mean = 0.09, SD =0.78]).

We therefore chose to categorize our outcome into three categories; no episodes, one syncopal episode, and multiple syncopal episodes. As a result of this categorization we use bivariate multinomial regression to investigate the relationships between recent syncopal episodes with depression and AD use. Subsequently, we fitted a multivariate multinomial regression model using survey weights where we adjusted for

age, sex, education, marital status, health conditions, antihypertensive medications and substance abuse. Relative risk ratios (RRR) were produced and represented the chance that an observation fell into the comparison category rather than the baseline category (no syncopal events). Finally, we investigated interaction terms between medication type and depression. All analyses are conducted in Stata (v12.1). 162

Results

8,175 participants, aged 50 and older were enrolled in this study, and 152 were excluded due to incomplete data. An additional 30 participants were removed with a self-reported physician diagnosis of dementia or a Mini Mental State Exam result less than 18, due to potential recall bias. This resulted in a final sample of 7,993 participants. Descriptive statistics can be seen in Table 1. The age of the patients ranged from 50-99 years was an interquartile range of 56-71 (SD 0.2) Of all the participants, 225 reported one syncopal episode in the last year and 124 reported two or more syncopal episodes. The sample had an evenly split gender distribution. Females reported higher rates of recurrent syncope when compared to their male counterparts (59.1% vs. 40.9%) but this failed to reach statistical significance. Compared to participants with no episodes, participants with syncopal episodes reported higher rates of all health conditions. There were statistically significantly higher rates of hypertension, heart attack, stroke and anti-hypertensive use in the group who reported syncope. In relation to AD medication usage, the most

frequently prescribed AD was the SSRI class, with 3.9% of the total sample taking an SSRI.

Prevalence

The overall prevalence of syncope in the TILDA population was 4.4% (overall) and 2.8% (SE = 0.2) for one syncopal event and 1.6% (SE = 0.1) for multiple syncopal events. The prevalence rates of syncope differed for AD medication type and depression. Patients who were taking SSRIs, TCAs and other ADs had a higher prevalence of syncope (for both a single and multiple syncopal event) while there was a non-significant trend of an increase for those on other ADs. (Table 2). This difference in prevalence was significant only in regards to SSRIs and TCAs. Participants with symptoms of depression (CES-D categories) or a diagnosis of depression by a physician had a significantly higher prevalence of syncope than those without symptoms or a diagnosis of depression. There was an age gradient apparent in the prevalence of syncope and being on any AD, having depressive symptoms or having both (Figure 1). Older adults (75+ years) taking an AD or having depressive symptoms had a higher prevalence of syncope than younger adults (50-64 years) taking an AD or with depressive symptoms. The reverse was seen for the prevalence for those both on an AD and with depressive symptoms, this however may have been due to very small numbers in this group.

Covariates of Syncopal

Events Effect of depression

Participants who reported moderate or severe symptoms of depression as evidenced by CES-D testing were more likely to have experienced at least one syncopal episode on the past year. This is evidenced by the prevalence rates (Table 2) and the results from both the bivariate (Table
3) and multivariate (Table 4) multinomial regression analyses.
Participants who reported being told by their doctor that they had depression were also more likely to have experienced multiple syncopal episodes within the last year. After controlling for demographic characteristics, health conditions and AD use these relationships were less pronounced (Table 4). Participants with severe depression (CES-D) were at an increased risk of either a single syncopal episode (RRR = 2.8) (CI - 1.48-5.25) or multiple syncopal episodes (RRR = 2.9) (CI- 1.27-6.45), when compared with those with none or mild symptoms of depression.
Participants with moderate depression were at an increased risk only of a single syncopal episode (RRR = 2.0) (CI-1.29-3.01). Finally, participants who reported being told by a doctor that they had depression had a higher risk of experiencing multiple syncopal episodes (RRR =2.7) (CI- 1.36-5.19).

Effect of anti-depressants

Before adjusting for participant characteristics, health conditions and depression, participants taking either SSRIs or TCAs were at greater risk of having experienced a single or multiple syncopal episodes (Table 3). All relationships were significant aside from the relationship between SSRIs and a single syncopal episode, which approached significance.

After controlling for participant characteristics, health conditions and depression (CES-D or doctor diagnosis), SSRIs were no longer significantly associated with syncopal events in the past 12 months. In regards to participants on TCAs, there remained significantly increased risk of multiple syncopal events (RRR = 3.0) (CI 1.15-7.94). The relationship to a single syncopal event was not statistically significant, however there was a trend suggesting increased risk of a single syncopal episode (RRR = 2.3) (CI 0.97-5.63).

Discussion

In this representative population sample of community dwelling adults aged 50 and older we investigated the prevalence of syncopal events. This is the largest, to our knowledge, investigation of the prevalence of syncopal events in a population based community-dwelling sample of older people. Participants in this study with depression or using TCA ADs were at increased risk of syncopal events.

Syncope and Depression

In this study, participants with depression were more likely to have reported syncope in the last year. Furthermore, participants who were

classified with moderate or severe depression according to the CES-D scale were more likely to have reported a syncopal event in the last year and were also more likely to have reported multiple syncopal events in the last year. This effect appears to be independent of common co- morbidities including cardiovascular disease. This study has added to the observations made previously of the link between depressive symptoms and syncope. Previous studies have focused on groups presenting to specialized syncope clinics as well as patients who were hospitalized for syncope (226, 263, 264, 269), therefore, it is difficult to extrapolate the observations previously made in these studies to a general population.

This study was performed on a representative sample and is more likely to reflect the true incidence and prevalence of syncope rates in patients reporting symptoms of depression. The data show that depression is a significant co-morbid condition in older people with syncope. Previous work by our group has highlighted the link between depression and falls in older people.

Effects of anti-depressant medications

The prevalence of a syncopal event was higher for participants who were taking either an SSRI or TCA AD. However, once we adjusted for demographic characteristics, health conditions and depression, we found that the increased risk of a syncopal event was only for participants prescribed TCAs. Taking a TCA increased the odds of experiencing multiple syncopal events. There was a trend towards higher rates of

syncope in those taking SSRIs but this failed to reach statistical significance. This again was the first paper to fully explore the effects of commonly prescribed ADs on syncope. Previous studies investigating AD medication use in older people have highlighted increasing concerns regarding the safety of these medications (270). Cohort studies have shown a higher risk of adverse events in older people on AD medication with increasing rates of gastrointestinal bleeding, myocardial infarction, stroke, falls and overall mortality reported (271). SSRIs have previously been shown to be beneficial for recurrent syncope in younger cohorts (272, 273). Patients in these studies demonstrated a longer time between syncopal episodes and a reduction in pre-syncopal symptoms when treated with SSRIs. These studies, however, were unable to separate out the effect that mood had on the rates of recurrent syncope. The authors did comment on the positive effects on mood in the SSRI group, which they felt may have been therapeutically beneficial (274). This study differs in that we were able to correct for the effect of depression on syncope. When depression score was corrected for, SSRIs usage was associated with an increased risk of syncope but this failed to reach statistical significance. There was also a trend towards recurrent syncope in this group. This study was designed as an epidemiological, point prevalence study and was therefore unable to draw any firm causation for the observed effects of TCAs. Previous studies have focused on the cardiovascular side effects of TCAs on older people. The most commonly reported cardiovascular side effect due to TCAs was hypotension, but also

included bradycardia and tachycardia (275) (276). Other studies have shown significant blood pressure alterations causing orthostatic hypotension (277). A previous study with community dwelling older people found an increase in falls and hip fractures but did not specifically mention rates of syncope (278). However further work in this area is needed to help individualize patient risk and guide clinicians when prescribing TCAD.

The strength of this study is that it is population representative of community dwelling older Irish adults. However, we had to rely solely on self- reported syncope and depression. The CES-D has been shown to be correlated with clinical ratings of depression; however, the CES-D is not considered a tool for the formal diagnosis of depression. Also, depression symptoms (CES-D) were assessed as occurring in the past week only, whereas syncope was assessed in the past 12 months. It is possible that we are underestimating the relationship between depression and syncope. A series of single items were used to assess syncope. Reporting syncopal episodes within the last year has previously been shown to have a good predictive value for future syncope risk (279). However, this method is liable to recall bias and may be influenced by an individual's understanding of what fainting is. It may, for example, underestimate other conditions which are similar to syncope such as seizure disorders. An MMSE cut-off score of 18 was used to exclude patients from the final analysis. A further analysis of subgroups based on MMSE score showed no statistically significant difference (chi-square 5.45, p= 0.244) between faints in the past 12 months and MMSE score.

There are also very few respondents in the older age groups who are taking ADs and have depressive symptoms, limiting our conclusions about this older group.

Finally, the data used in this study are cross-sectional. These limitations in the study reduce our ability to fully understand the associations between depression, AD use and syncope. To achieve this, a prospective longitudinal study is required. As a longitudinal study, however, there are further opportunities to examine this effect in future waves of the TILDA study and observe the association over time.

In summary there is a clear association between depressive symptoms and the prevalence of syncope. Clinicians should be aware of this, as depression is a potentially modifiable co-morbidity in older patients who present with syncope. The choice of treatment should also be given careful consideration as increased rates of syncope have been observed with commonly used anti-depressants. Further studies are needed to focus on the causes for the observed association found in this study.

Table 1. Demographic and Clinical Characteristics of Participants (n = 7,993)

	No episode - past 12 months		One syncopal episode - past 12 months		Multiple syncopal episodes - past 12 months			Total	
	N=7,664	Weighted prevalence, % (SE)	N=225	Weighted prevalence, % (SE)	N=124	Weighted prevalence, % (SE)	Test Statistic	N	Weighted prevalence, % (SE)
Sex									
Male	3,507	48.1 (0.5)	114	51.7 (3.5)	48	40.9 (4.8)	*F(2,1245.6)* = 1.64	3,669	48.1 (0.5)
Female	4,137	51.9 (0.5)	111	48.3 (3.5)	76	59.1 (4.8)		4,324	51.9 (0.5)
Age(non –weighted)		63.7 (SD- 9.69)		64.6 (SD-10.49)		63.5(SD-10.06)			63.7 (SD-10.06)
Age (mean & SD)	7,644	63.8 (0.2)	225	64.4 (0.8)	124	63.9 (1.0)	*F(2, 624)* = 0.29	7,993	63.8 (0.2)
Education									
Primary/none	2,310	37.7 (0.8)	69	37.8 (3.5)	44	45.3 (4.8)		2,423	37.8 (0.8)
Secondary	3,077	43.7 (0.7)	95	45.0 (3.3)	39	34.0 (4.3)	*F(4,2381.2)* = 1.31	3,211	43.6 (0.7)
Third/higher	2,257	18.6 (0.5)	61	17.2 (2.1)	41	20.7 (3.3)		2,359	18.6 (0.5)
Marital Status									
Married	5,327	68.7 (0.7)	144	61.6 (3.5)	69	54.0 (4.6)		5,540	68.2 (0.7)
Never married	730	9.5 (0.4)	26	12.1 (2.2)	18	13.8 (3.1)	*F(6,3681.8)* = 3.74**	774	9.7 (0.4)
Separated/Divorced	499	6.3 (0.3)	21	9.8 (2.1)	16	14.0 (3.3)		536	6.5 (0.3)
Widowed	1,088	15.5 (0.5)	34	16.5 (0.7)	21	18.2 (3.6)		1,143	15.6 (0.5)
Comorbidity									
High blood pressure	2,803	37.2 (0.6)	106	49.1 (3.4)	57	46.8 (4.8)	*F(2,1242.6)* = 7.81***	2,966	37.7 (0.6)
Angina	392	5.3 (0.3)	17	8.5 (2.0)	19	17.9 (3.7)	*F(2,1248.5)* = 18.46***	428	5.6 (0.3)
Heart Attack	344	4.6 (0.3)	19	9.1 (2.1)	7	5.9 (2.3)	*F(2,1246.2)* = 4.38*	370	4.7 (0.3)
Heart failure	79	1.1 (0.1)	3	1.5 (0.9)	3	3.2 (1.8)	*F(2,1246.7)* =2.21	85	1.1 (0.1)
Diabetes	582	7.9 (0.3)	21	9.1 (2.0)	16	13.0 (3.1)	*F(2,1245.7)* = 2.15	619	8.0 (0.3)
Stroke	104	1.4 (0.1)	8	4.1 (1.4)	9	6.8 (2.3)	*F(2,1245.3)* = 15.41***	121	1.5 (0.1)
TIA	153	2.0 (0.2)	11	4.8 (1.5)	6	4.6 (1.9)	F(2,1241.7) = 5.26**	170	2.1 (0.2)
Lung Disease	297	4.0 (0.3)	15	7.4 (1.9)	10	7.9 (2.5)	*F(2,1234.5)* = 4.68**	322	7.9 (0.3)
Substance Abuse	121	1.6 (0.2)	5	2.3 (1.0)	3	3.0 (1.8)	*F(2,1239.1)* = 0.89	129	1.7 (0.2)
Antihypertensive Medication	2,398	32.1 (0.6)	86	39.1 (3.3)	51	41.7 (4.7)	*F(2,1243.8)* = 4.59**	2,535	32.4 (0.6)
SSRI	271	3.7 (0.2)	12	6.3 (1.8)	13	10.7 (2.9)	*F(2,1237.2)* = 8.57***	296	3.9 (0.2)
Tricyclic	94	1.3 (0.1)	7	3.1 (1.2)	8	6.32 (2.3)	*F(2,1249.8)* = 12.68***	109	1.4 (0.1)
Other	139	1.8 (0.2)	7	2.6 (1.0)	3	2.4 (1.5)	*F(2,1244.6)* = *0.44*	149	1.9 (0.2)

Dr ever told you: depression	384	4.8 (0.3)	16	7.3 (1.8)	23	19.2 (3.9)	*F(2,1248.1) = 22.65***	423	5.1 (0.3)
CES-D Score									
None/mild	6,950	90.6 (0.4)	183	79.9 (2.7)	94	74.4 (4.2)		7,227	90.1(0.4)
Moderate	528	7.1 (0.4)	29	13.8 (2.4)	19	15.1 (3.2)	*F(4,2473.5) = 17.37****	579	7.4 (0.4)
Severe	166	2.3 (0.2)	13	6.3 (1.7)	11	10.5 (3.0)		190	2.5 (0.2)

Note: * p < .050; ** p < .010; *** p <.001

Table 2. Weighted Prevalence and Standard Errors of Syncope by Medication and Depression

	One syncopal episode in past 12 months		Multiple syncopal episodes in past 12 months		
	N	Weighted prevalence, % (SE)	N	Weighted prevalence, % (SE)	*F* Statistic
SSRI (N=296)					
Yes	12	4.6 (1.3)	13	4.20 (1.16)	$F_{(2,1237.2)} = 8.57$***
	213	2.8 (0.2)	111	1.41 (0.15)	
Tricyclic (N=109)					
Yes	7	6.3 (2.4)	8	6.89 (2.49)	$F_{(2,1249.8)} = 12.68$***
No	218	2.8 (0.2)	116	1.44 (0.14)	
Other (N=149)					
Yes	7	3.92 (1.5)	3	1.97 (1.17)	$F_{(2,1244.8)} = 0.44$
No	218	2.82 (0.20)	121	1.51 (0.15)	
Dr ever told you: depression					
Yes	16	4.06 (1.04)	23	5.69 (1.26)	$F_{(2,1248.1)} = 22.65$***
No	209	2.78 (0.20)	101	1.29 (0.14)	
CES-D					
None/mild	183	2.52 (0.20)	94	1.25 (0.13)	
Moderate	29	5.30 (0.95)	19	3.10 (0.72)	$F_{(4,2473.8)} = 17.37$***
Severe	13	7.07 (1.83)	11	6.25 (1.87)	

Note: * p < .050; ** p < .010; *** p <.001

Table 3. Bivariate Multinomial Regression Results Comparing a Single and Multiple Syncopal Episode to No Syncopal Episode in the Past 12 Months (n = 7,993)

	No episode vs. One syncopal episode		No episode vs. Multiple syncopal episodes	
	RRR (95% CI)	p Value	RRR (95% CI)	p Value
SSRI	1.75 (0.96-3.22)	0.069	3.13 (1.71-5.76)	<0.001
Tricyclic	2.50 (1.11-5.61)	0.027	5.28 (2.40-11.60)	<0.001
Other	1.41 (0.63-3.17)	0.405	1.33 (0.40-4.41)	0.639
Dr ever told you: depression	1.55 (0.89-2.70)	0.118	4.68 (2.82-7.76)	<0.001
CES-D				
None/mild	Ref		Ref	
Moderate	2.21 (1.48-3.30)	<0.001	2.60 (1.57-4.32)	<0.001
Severe	3.11 (1.76-5.49)	<0.001	5.54 (2.86-10.74)	<0.001

RRR – Relative risk ratio

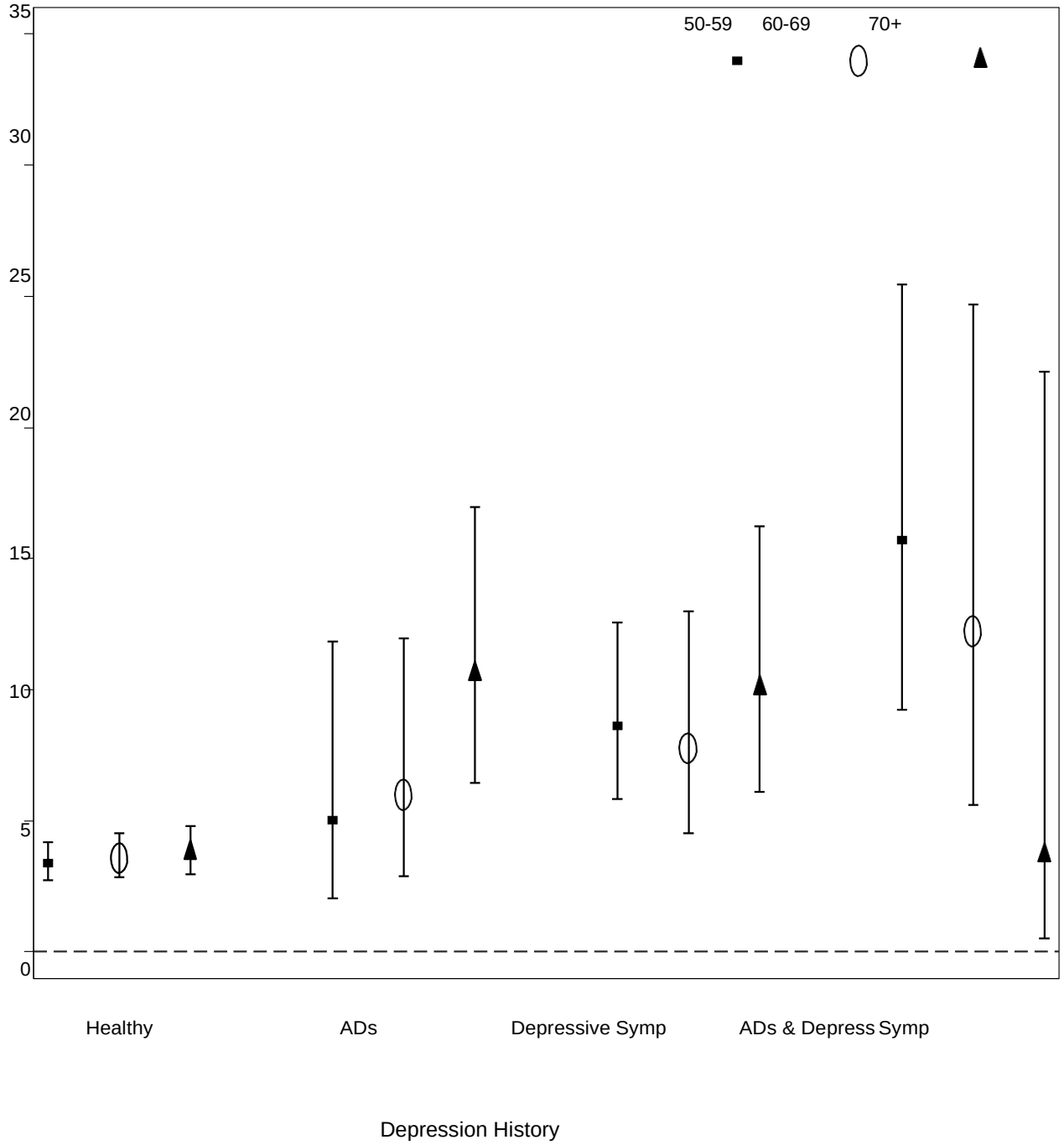
Table 4. Multivariate Multinomial Regression Results Comparing a Single and Multiple Syncopal Episode to No Syncopal Episode in the Past 12 Months (n = 7,993)

	No episode vs. One syncopal episode		No episode vs. Multiple syncopal episodes	
Variable	RRR (95% CI)	p Value	RRR (95% CI)	p Value
Sex – female	0.79 (0.60-1.05)	0.600	1.18 (0.76-1.83)	0.460
Age	1.00 (0.99-1.02)	0.110	0.99 (0.96-1.02)	0.432
Education				
Primary/none	Ref		Ref	
Secondary	1.23 (0.89-1.70)	0.203	0.76 (0.48-1.22)	0.259
Third/higher	1.12 (0.77-1.63)	0.556	1.17 (0.72-1.90)	0.534
Marital Status				
Married	Ref		Ref	

Never married	1.31 (0.85-2.01)	0.216	1.81 (1.03-3.18)	0.038
Separated/Divorced				
Widowed	1.59 (0.98-2.57)	0.060	2.10 (1.14-3.85)	0.017
	1.05 (0.68-1.63)	0.807	1.30 (0.66-2.56)	0.442
SSRI AD	1.25 (0.68-2.31)	0.467	1.29 (0.57-2.92)	0.546
Tricyclic AD	2.33 (0.97-5.63)	0.060	3.02 (1.15-7.94)	0.025
Other AD	0.98 (0.41-2.36)	0.973	0.46 (0.10-2.02)	0.300
Hypertensive Medication	0.62 (0.37-1.04)	0.073	1.13 (0.47- 2.72)	0.787
Dr ever told you that you have				
Depression	0.99 (0.52-1.88)	0.980	2.66 (1.36-5.19)	0.004
CES-D				
None/mild	Ref		Ref	
Moderate				
Severe	1.97 (1.29-3.01)	0.002	1.65 (0.96-2.84)	0.069
	2.79 (1.48-5.25)	0.002	2.86 (1.27-6.45)	0.011
Comorbidity				
High blood pressure	2.19 (1.34-3.59)	0.002	1.03 (0.43-2.49)	0.943
Angina	1.10 (0.59-2.04)	0.770	3.68 (2.00-6.76)	<0.001
Heart Attack	1.60 (0.89-2.87)	0.117	0.51 (0.21-1.23)	0.135
Heart failure	0.85 (0.23-3.09)	0.808	1.91 (0.56-6.48)	0.298
Diabetes	0.96 (0.59-1.57)	0.870	1.28 (0.70-2.35)	0.422
Stroke	2.22 (1.03-4.75)	0.041	4.20 (1.90-9.26)	<0.001
TIA	1.75 (0.82-3.73)	0.147	1.52 (0.54-4.26)	0.421
Lung Disease	1.57 (0.89-2.76)	0.120	1.42 (0.68-3.00)	0.350
Substance Abuse	0.81 (0.33-2.03)	0.660	0.72 (0.19-2.75)	0.636

RRR – Relative risk ratio

Figure 1. Prevalence of Syncope by age and history of depression



Chapter 9 - Conclusions

In conclusion I have shown that there is an overlap in the epidemiology of falls, unexplained falls and syncope. The importance of cardiovascular co- morbidity in older adults who suffer falls has been further established both within the TILDA sample and within the cohort who were in the observational trial. Similarly the interplay between depression and syncope has been further explored within this thesis. Lastly I have proven cardiac arrhythmia as a significant cause of unexplained falls in older adults and one that is potentially modifiable.

1. Prevalence of syncope, falls and unexplained falls in a community dwelling sample

Paper 1 had demonstrated that the prevalence of all falls in the past year was 19.2% or 192 per thousand persons and increased with age (50 – 64 years 17.5%; 65 – 74 years 19.4%; 75+ years 24.4%). Unexplained falls had an estimated prevalence of 5.1% or 51 falls per thousand persons and accounted for 26.5% of all falls reported and also increased with age (50 – 64 years 4.0%; 65-74 years 5.5%; 75+ years 8.0%). The prevalence for syncope was estimated to be 4.4% or 44 per thousand persons but did not show a similar age gradient. From this I have concluded that the prevalence and incidence of falls and unexplained falls increases with age but the same pattern was not consistently observed

for syncope. I have shown a relatively constant incidence in reporting of falls and unexplained falls over the two waves of TILDA. This was true whether incidence or prevalence measurements were used. I did note a slight rise in the incidence of syncope reported in the second wave in the over 75 years age group.

My hypothesis that syncope incidence would increase with age was not supported by the figures. One explanation for this is that as people age they do not recognize the classical symptoms of syncope. Therefore they may report an unexplained fall event rather than syncope. This may partially explain the rise in incidence observed in patients who reported unexplained falls in the over 75 years age category. Alternatively low syncope incidence in the TILDA cohort may point towards a healthier population with less cardiovascular co-morbidity. Further data on the next waves of TILDA will reveal if this trend continues as the population included in TILDA ages.

This paper also continues to highlight the difficulties in comparison between different studies. TILDA is the first study that had asked specifically about unexplained falls and syncope in the same population. The Framingham cohort has significant methodological differences to ours including a different definition of syncope and a different way of measuring and reporting syncope. For instance they had included stroke and seizures in their definition which was not the case in TILDA. This may have contributed to the large rise in incidence that they had reported in

older age groups as both stroke and seizure incidence is known to rise with age. Other studies have used discharge diagnosis or relied on emergency department data for syncope incidence. These studies showed a rise in incidence of syncope in older age groups but they included older adults who had sought medical advice making them prone to selection bias. In TILDA we only asked if the patient had experienced a faint or unexplained fall in the past year without a specific stipulation about the need to seek medical advice as a result of the episode. This may mean that the estimate from TILDA is a more accurate portrayal of the incidence of syncope or that patients who do not experience injury in relation to syncope will under-report the incidence. Further work on this cohort may help to answer this important epidemiological question.

Paper 2- Prevalence of syncope, falls and unexplained falls in the emergency department

Paper 2 had demonstrated that 12.7% of over 50s presenting with a fall or collapse had a diagnosis of syncope while a further 14.3% had an unexplained fall. Patients who had syncope and unexplained falls had higher odds of admission, investigations and recurrent falls. Furthermore, 50% of older adults who present with a falls or collapse to ED were admitted; with advancing age strongly predicting admission.

From this I concluded that 1-in 4 patients presenting to an ED have symptoms suggestive of T-LOC or an unexplained fall, with higher rates of admission and investigations carried out in this group. It is not possible to directly compare this study to the TILDA cohort above as there was a difference in the time period (six months as compared to one year) , methods of reporting (self-reported vs. chart review) and populations studied (community dwelling as opposed to ED presenters). However, there is a strikingly high prevalence of patients who had presented with an unexplained fall or syncope episode to the ED over six months. This is in contrast to the relatively low incidence of syncope and unexplained falls reported in the community dwelling sample. What is apparent is that unexplained falls are more common as people age and that they account for up to 20% of falls reported in the TILDA cohort as well as within the ED.

This study mirrors other studies done in EDs which suggest that up to one quarter of falls which present to an ED are unexplained. It also highlights the morbidity surrounding these types of falls as they have longer stays, can be recurrent and have increased admission rates. Interestingly, we did not show a higher odds ratio of injury in patients who had suffered a T-LOC episode or an unexplained fall. This may have been because patients only presented to ED with an explained fall due to an injury suffered in association with the fall.

The higher rates of unexplained falls and T-LOC in ED may also be accounted for by other risk factors for falls in older adults such as cognitive impairment. Patients with cognitive impairment frequently present to the ED without a witnessed history of the fall and will not be able to give an accurate history themselves. Further work on the identification of symptoms suggestive of T-LOC in older adults combined with structured cardiovascular assessment and diagnostics may provide a template for targeted treatments in the future.

Cardiovascular co-morbidity and falls:

In Paper 1 I had found that participants with at least 5 cardiovascular conditions were more likely to report any falls (OR=2.07, 95% CI 1.18- 3.64) and unexplained falls (OR=2.89, 95% CI 1.28-6.52). There is an increased odds of reporting syncope, falls and unexplained falls with an increasing number of self-reported cardiovascular conditions. In univariate analysis, cardiovascular conditions including angina, heart failure, stroke, TIA, diabetes and arrhythmia displayed an association with all three outcomes. However when adjusted for potential confounders only stroke showed an individual association with all three outcomes. The explanations may be related to gait disorders secondary to neurological disability as a result of the stroke. Alternatively it may point to an increased susceptibility to sudden changes in cerebral perfusion pressure causing subsequent falls. As was hypothesized in the literature review those conditions which lead to low blood pressure were the most likely to

be associated with falls. In this thesis I have shown that overall cardiovascular morbidity may be more important than individual cardio- vascular diseases in a predisposition to falls. This may point to an association between cardiovascular morbidity and frailty or may be a result of multiple treatment modalities making an older person more susceptible to falls.

Arrhythmia as a cause of falls

In Paper 3 I had found that in 70% of patients cardiac arrhythmias were detected at a mean time of 47.3 days (SD 48.25). In 20%, falls were attributable to a modifiable cardiac arrhythmia; 10 (14%) received a cardiac pacemaker, 4 (6%) had treatment for SVT. Patients who had a cardiac arrhythmia detected were 5 times more likely to experience a further fall.

From this I concluded that 1in 5 patients demonstrate an arrhythmia which is attributable as the cause of their fall. Patients who have cardiac arrhythmia are significantly more likely to experience future falls. This paper highlighted one possible causative association in older adults with falls. As highlighted in the literature review cardiac arrhythmia has previously been associated with falls. However this study was able to demonstrate that even short bursts of arrhythmia could be sufficient to cause gait instability. The likely underlying mechanism is a drop in blood

pressure for a sufficient period of time to cause a decrease in cerebral perfusion pressure. However, as will be elaborated on in the section on future directions the exact mechanisms of this need to be better explored. What this does provide is evidence that cardiac arrhythmia may be more common in older age groups than previously thought and that even small bursts of arrhythmia may be enough to cause clinical symptoms.

It also showed a trend that those patients who had bradycardia (heart rate under 60 beats per minute) were more likely to experience a future fall. Cardiac arrhythmia is a description of a condition and not a disease itself. It can be caused by many different underlying disease mechanisms and the population included in this study did have a significant amount of cardiovascular co-morbidity. Overall this continues to add to the hypothesis that cardiovascular co-morbidity is a significant factor in falls in older adults.

The importance of psychological symptoms in syncope.

In Paper 4 I had found that after controlling for participant characteristics and general health, those with severe depression had a greater risk of single and multiple syncopal events (RRR 2.78 and 2.84, respectively p <.050) and participants treated with tricyclic anti-depressants were also at greater risk for single and multiple syncopal episode in the last year (RRR 2.31, p=.062; RRR 2.95 p<0.05). I concluded that this study demonstrated an increased risk of syncope in patients with depression,
with higher rates of syncope reported with increasing severity of

depression. Treatment with tricyclic antidepressants increased both the risk and frequency of syncope in the community.

The effect of depression on falls and unexplained falls was also similarly seen in Paper 1 and paper 3 with patients who had an increasing number of depressive symptoms reported more likely to report a fall or unexplained fall. Physiological explanations for these observations are not obvious and the effect observed may be due to reverse causality; patients who have falls and syncope are more likely to develop depressive symptoms. I had attempted to filter out the possible effects that anti- depressant medication may have had on these rates by studying them separately. What I did find was that tricyclic agents were associated with increased risk of syncope. My explanation for that was a direct cardiovascular effect from the anti-cholinergic properties of tricyclic anti-depressants. This is unlikely to be the same for SSRIs or other anti- depressant medication as they do not have the same anti-cholinergic properties. This remains to be solved but depression is a potentially modifiable risk factor for syncope and treatment options need to be tailored in the older patient population.

Limitations

Using the TILDA longitudinal registry has allowed for prospective characterisation of an Irish ageing cohort. Therefore, observations which have been made within these studies may not have applicability outside of Ireland. Having said that this cohort represents a relatively stable population which is well defined both from a demographic and geographic stand-point.

As the categorisation of exposure status is based on self-report, these data may

be prone to recall bias. Case ascertainment may also bias toward a younger, more educated patient. Those with cognitive impairment may be less likely to accurately recall an event. Equally, patients with disability may differentially recall syncopal events compared to other groups or depending on injuries sustained. The TILDA cohort does represent patients over the age of 50 years but again because of the nature of a longitudinal study we have a cognitively intact population with a younger age profile at wave one. This has greatly limited the ability of this thesis to examine the impact of dementia on falls. These patients will be followed longitudinally so the true relevance of the outcomes and associations may become clearer over time.

Another limitation of longitudinal studies is the difficulty maintaining follow-up. In this cohort a small number of individuals were lost to follow- up between the two waves. If these individual differ systematically to those who remain within the study selection bias may occur. We attempted to correct for this using statistical measures for the drop out of patients in TILDA between wave one and wave two. Although this drop out was relatively small it may result in bias despite statistical corrections and the results from the second wave of TILDA when compared to the first wave should be interpreted in this context. Lastly due to the observational nature of these studies causal inference is prohibited and further controlled trial are warranted to decipher the causality.

In my second paper I relied primarily on health record based data which can be prone to misclassification bias. When conducting research in an emergency department this is often a major problem as it is difficult to control and prospectively measure all variables recorded in an emergency visit without

significant resources. Also the classification of patients into outcome groups relied on observations documented by other physicians and health staff. Therefore there is an inherent subjective bias with the interpretation and recording of symptoms. To have undertaken a study which eliminated these potential confounders we would have required a significant increase in the resources used for this study.

In paper 3 we used a clear definition of unexplained falls with clear exclusion and exclusion criteria. The main limitations within this study however related to the lack of a control group. The study was set up as a prospective observational study which meant we were looking for signal from the data which may allow for a larger study with a control group included. However the rates of significant arrhythmia found (20%) may be the result of a selection bias. The group which we had examined appear to represent a group with a large number of co-morbid conditions and the fact that they presented to either a tertiary referral clinic or the emergency department sets them out as patients who differ from other populations. Therefore until a control study, preferably with a randomised selection at the outset, is performed we cannot say with certainty that 20% of older patients with unexplained falls have an arrhythmia. Notwithstanding that we do have a strong signal which is showing a large number of significant arrhythmia which can now be measured in a meaningful way and can allow for a randomised control study in the future.
As mentioned in the literature review, frailty is a known association with both falls and syncope. This thesis has been limited by not including frailty scores within the analysis. This limits conslusions that can be drawn about the

potential cofounding and interaction between frailty states and cardiovascular causes of falls. This is an area that would be important to further explore in future studies.

Future directions

Clinical

This thesis has established several clinical questions which deserve future consideration. Firstly, a theme which has been apparent throughout the thesis has related to how we measure and report falls and syncope. Indeed, even the nomenclature of the terms can be confusing for clinicians and may have difficulties with clinical applicability. In my second paper, we attempted to explore the more clinically useful concept of transient loss of consciousness (T-LOC). We felt that this would apply to those patients who have an undifferentiated cause of falls and would allow clinicians to identify these patients more easily. The difficulty with the current definition of syncope as was used in this thesis is that it depends on diagnostic accuracy and this can be difficult in syncope and falls in the elderly. As highlighted by the paper the first challenge is to establish that T-LOC has indeed occurred and then to triage the episode appropriately. With many possible aetiologies which underlie the clinical presentation of T-LOC the clinician is often forced to decide on admission for the patient and the ordering of multiple tests which accompany that. Future research should be directed at a more clinical level. Firstly, focusing on the clinical and operational diagnosis of syncope may allow clinicians to use the concept of T-

LOC to appropriately triage those older patients who would benefit most from in-patient work-up and investigations. Secondly research into screening tools which are more applicable to older patients will allow physicians to risk stratify patients with greater clarity. This has already been identified as a research priority by emergency physicians and the output from this thesis would support this as an area of need.

My third paper has established a very important clinical conundrum in the use of technologies for the detection of abnormalities of physiology. As technology advances we can detect multiple abnormalities in normal human physiology. As my work has shown even small momentary abnormalities or deviations in normal physiological responses can produce significant clinical consequences for older patients. The clinical challenge lies in the interpretation of these abnormalities. Even slight changes in the definitions that were used for heart rate abnormalities may have produced significantly different results. For instance, the definition of a heat rate under 60 beats per minute as bradycardia lead to much larger numbers of patients being classified as having bradycardia. As technology advances it is imperative that clinicians attempt to define what the threshold for abnormality is for each specific recent technology. In our paper, we used a largely clinical diagnosis of symptoms matched with cardiac arrhythmia to make the diagnosis. Future work should be directed at attempting to re-produce this on a larger scale.

Biological

There are some important biological considerations which may be looked at further into the future. The first of these was postulated in my first paper and that was with regards to the interaction between blood pressure, cerebral

hypoperfusion and gait abnormalities. Specifically, future work could be generated which examines in greater detail the exact cut-off points in which cerebral oxygen delivery falls below perfusion requirements and results in ischemic damage. Although we have shown evidence for epidemiological overlap in our papers we have not shown any evidence of causality and possible mechanisms for the overlap. Further work using biological models may help to delineate this further.

At the moment, we do not have a non-invasive way of measuring blood pressure which is commercially available. This thesis is based mainly on

the premise that intermittent drops in blood pressure can be enough to cause gait instability which results in a fall. Until we can develop a device which is able to monitor ambulatory blood pressure in an accurate way this premise is likely to remain hypothetical. As stated above the main finding from my third paper pertains to intermittent arrhythmia causing drops in blood pressure. Although we have evidence of this process in patients who have a prolonged arrhythmia, the evidence of blood pressure fluctuations in short lived arrhythmias in ambulatory humans are currently lacking. The signals from this thesis are that intermittent drops in blood pressure are significant enough to cause gait disturbance. This could be used to assist future projects to develop the tools which could measure these blood pressure drops in real time and allow us to better advice patients on specific risks.

References

1. WHO | Falls. WHO. 2014.
2. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988;319(26):1701-7.
3. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing. 2006;35 Suppl 2:ii37-ii41.
4. Prudham D, Evans JG. Factors associated with falls in the elderly: a community study. Age & Ageing. 1981;10(3):141-6.
5. Rapp K, Freiberger E, Todd C, Klenk J, Becker C, Denkinger M, et al. Fall incidence in Germany: results of two population-based studies, and comparison of retrospective and prospective falls data collection methods. BMC Geriatr. 2014;14:105.
6. Campbell AJ, Reinken J, Allan BC, Martinez GS. Falls in old age: a study of frequency and related clinical factors. Age & Ageing. 1981;10(4):264-70.
7. Dyer SM, Crotty M, Fairhall N, Magaziner J, Beaupre LA, Cameron ID, et al. A critical review of the long-term disability outcomes following hip fracture. BMC Geriatr. 2016;16:158.
8. Hartholt KA, Polinder S, Van der Cammen TJM, Panneman MJM, Van der Velde N, Van Lieshout EMM, et al. Costs of falls in an ageing population: A nationwide study from the Netherlands (2007–2009). Injury. 2012;43(7):1199-203.
9. Magaziner J, Fredman L, Hawkes W, Hebel JR, Zimmerman S, Orwig DL, et al. Changes in functional status attributable to hip fracture: a comparison of hip fracture patients to community-dwelling aged. Am J Epidemiol. 2003;157(11):1023-31.
10. Bertram M, Norman R, Kemp L, Vos T. Review of the long-term disability associated with hip fractures. Inj Prev. 2011;17(6):365-70.
11. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. Jama. 2009;302(14):1573-9.
12. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci. 2007;62(7):744-51.
13. van den Bergh JP, van Geel TA, Geusens PP. Osteoporosis, frailty and fracture: implications for case finding and therapy. Nat Rev Rheumatol. 2012;8(3):163-72.
14. McMahon CG, Kenny RA, Bennett K, Bouamra O, Lecky F. Diurnal variation in mortality in older nocturnal fallers. Age Ageing. 2012;41(1):29-35.
15. Tinetti ME, Richman D, Powell L. Falls Efficacy as a Measure of Fear of Falling. 1990.
16. Scheffer AC, Schuurmans MJ, Dijk Nv, Hooft Tvd, Rooij SEd. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. 2008.
17. Cumming RG, Salkeld G, Thomas M, Szonyi G. Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores, and nursing home admission. J Gerontol A Biol Sci Med Sci. 2000;55(5):M299-305.
18. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med. 1997;337(18):1279-84.

19. Close JC, Lord SR, Antonova EJ, Martin M, Lensberg B, Taylor M, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. Emerg Med J. 2012;29(9):742-7.
20. Sterling DA, O'Connor JA, Bonadies J. Geriatric falls: injury severity is high and disproportionate to mechanism. J Trauma. 2001;50(1):116-9.
21. Centers for Disease Control and Prevention NCfIPaC. Web–based Injury Statistics Query and Reporting System (WISQARS) 2013 [Available from: http://www.cdc.gov/injury/wisqars/.
22. Wallace SP. More than half a million older Californians fell repeatedly in the past year. Policy Brief UCLA Cent Health Policy Res. 2014(Pb2014-8):1-7.
23. Gannon B, O'Shea E, Hudson E. Economic consequences of falls and fractures among older people. Ir Med J. 2008;101(6):170-3.
24. Tian Y, Thompson J, Buck D. The cost of falls. http://dxdoiorg/101108/JICA-04-2014-0012. 2014.
25. CDC - Older Adult Falls - Falls Among Older Adults: An Overview - Home and Recreational Safety - Injury Center 2014 [Available from: http://www.cdc.gov/homeandrecreationalsafety/falls/adultfalls.html.
26. Tinetti ME. Clinical practice. Preventing falls in elderly persons. N Engl J Med. 2003;348(1):42-9.
27. Kenny RA, O'Shea D. Falls and syncope in elderly patients. Clin Geriatr Med. 2002;18(2):xiii-xiv.
28. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;59(1):148-57.
29. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med. 1994;331(13):821-7.
30. Tinetti ME, Speechley M. Prevention of falls among the elderly. N Engl J Med. 1989;320(16):1055-9.
31. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. N Engl J Med. 2002;347(12):878-85.
32. Kenny RA, Bhangu J, King-Kallimanis BL. Epidemiology of syncope/collapse in younger and older Western patient populations. Prog Cardiovasc Dis. 2013;55(4):357-63.
33. McCarthy F, Fan CW, Kearney PM, Walsh C, Kenny RA. What is the evidence for cardiovascular disorders as a risk factor for non-syncopal falls? Scope for future research. European Geriatric Medicine.1(4):244-51.
34. Shaw BH, Claydon VE. The relationship between orthostatic hypotension and falling in older adults. Clin Auton Res. 2014;24(1):3-13.
35. Angelousi A, Girerd N, Benetos A, Frimat L, Gautier S, Weryha G, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. J Hypertens. 2014;32(8):1562-71; discussion 71.
36. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
37. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
38. Kennelly S, Collins O. Walking the cognitive "minefield" between high and low blood pressure. J Alzheimers Dis. 2012;32(3):609-21.
39. Ryan DJ, Kenny RA, Christensen S, Meaney JF, Fagan AJ, Harbison J. Ischaemic stroke or TIA in older subjects associated with impaired dynamic blood pressure control in the absence of severe large artery stenosis. Age Ageing. 2015.

40. Ryan DJ, Harbison JA, Meaney JF, Rice CP, King-Kallimanis B, Kenny RA. Syncope causes transient focal neurological symptoms. QJM. 2015.
41. Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, et al. Effects of Low Blood Pressure in Cognitively Impaired Elderly Patients Treated With Antihypertensive Drugs. JAMA Intern Med. 2015.
42. Muller M, Sigurdsson S, Kjartansson O, Aspelund T, Lopez OL, Jonnson PV, et al. Joint effect of mid- and late-life blood pressure on the brain: the AGES-Reykjavik study. Neurology. 2014;82(24):2187-95.
43. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of hypertension in the oldest old: a critical role for frailty? Hypertension. 2014;63(3):433-41.
44. Finucane C, O'Connell MD, Fan CW, Savva GM, Soraghan CJ, Nolan H, et al. Age-related normative changes in phasic orthostatic blood pressure in a large population study: findings from The Irish Longitudinal Study on Ageing (TILDA). Circulation. 2014;130(20):1780-9.
45. Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. Eur Heart J. 2014;35(26):1726-31.
46. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc. 2014;62(12):2261-72.
47. van der Velde N, Stricker BHC, Pols HAP, van der Cammen TJM. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. Br J Clin Pharmacol. 2007;63(2):232-7.
48. van der Velde N, van den Meiracker AH, Pols HA, Stricker BH, van der Cammen TJ. Withdrawal of fall-risk-increasing drugs in older persons: effect on tilt-table test outcomes. J Am Geriatr Soc. 55. United States2007. p. 734-9.
49. Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30(21):2631-71.
50. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;9:Cd007146.
51. Parry SW, Steen IN, Baptist M, Kenny RA. Amnesia for loss of consciousness in carotid sinus syndrome: implications for presentation with falls. J Am Coll Cardiol. 2005;45(11):1840-3.
52. Kenny RA, Richardson DA, Steen N, Bexton RS, Shaw FE, Bond J. Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). J Am Coll Cardiol. 2001;38(5):1491-6.
53. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, et al. Clinical context and outcome of carotid sinus syndrome diagnosed by means of the 'method of symptoms'. Europace. 2014;16(6):928-34.
54. Alamgir H, Wong NJ, Hu Y, Yu M, Marshall A, Yu S. Epidemiology of falls in older adults in Texas. South Med J. 2015;108(2):119-24.
55. Downton JH, Andrews K. Prevalence, characteristics and factors associated with falls among the elderly living at home. Aging-Clinical & Experimental Research. 1991;3(3):219-28.
56. Ekici AB, Hackenbeck T, Moriniere V, Pannes A, Buettner M, Uebe S, et al. Renal fibrosis is the common feature of Autosomal Dominant Tubulointerstitial Kidney Diseases caused by mutations in mucin 1 or uromodulin. Kidney Int. 2014.
57. Albert M, McCaig LF, Ashman JJ. Emergency department visits by persons aged 65 and over: United States, 2009-2010. NCHS Data Brief. 2013(130):1-8.
58. Assantachai P, Chatthanawaree W, Thamlikitkul V, Praditsuwan R, Pisalsarakij D. Risk factors for falls in the Thai elderly in an urban community. Journal of the Medical Association of Thailand. 2003;86(2):124-30.
59. Davison J, Brady S, Kenny RA. 24-hour ambulatory electrocardiographic monitoring is unhelpful in the investigation of older persons with recurrent falls. Age & Ageing. 2005;34(4):382-6.

60. Campbell AJ, Reinken J, Allan BC, Martinez GS. Falls in old age: a study of frequency and related clinical factors. Age & Ageing. 1981;10(4):264-70.
61. Yardley L, Beyer N, Hauer K, Kempen G, Piot-Ziegler C, Todd C. Development and initial validation of the Falls Efficacy Scale-International (FES-I). 2005.
62. Satko SG, Freedman BI. The importance of family history on the development of renal disease. Curr Opin Nephrol Hypertens. 2004;13(3):337-41.
63. Rafanelli M, Ruffolo E, Chisciotti VM, Brunetti MA, Ceccofiglio A, Tesi F, et al. Clinical aspects and diagnostic relevance of neuroautonomic evaluation in patients with unexplained falls. Aging-Clinical & Experimental Research. 2014;26(1):33-7.
64. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: the health and retirement study. Journal of the American Geriatrics Society. 2009;57(3):511-6.
65. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. Journal of Gerontology. 1989;44(4):M112-7.
66. Gangavati A, Hajjar I, Quach L, Jones RN, Kiely DK, Gagnon P, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study.[Erratum appears in J Am Geriatr Soc. 2011 May;59(5):960]. Journal of the American Geriatrics Society. 2011;59(3):383-9.
67. Parry SW, Steen IN, Baptist M, Kenny RA. Amnesia for loss of consciousness in carotid sinus syndrome: Implications for presentation with falls. Journal of the American College of Cardiology. 2005;45(11):1840-3.
68. Stengel B, Billon S, van Dijk PCW, Jager KJ, Dekker FW, Simpson K, et al. Trends in the incidence of renal replacement therapy for end-stage renal disease in Europe, 1990–1999. Nephrology Dialysis Transplantation. 2003;18(9):1824-33.
69. Hung CY, Wu TJ, Wang KY, Huang JL, Loh EW, Chen YM, et al. Falls and atrial fibrillation in elderly patients. Acta Cardiologica Sinica. 2013;29(5):436-43.
70. Mader SL, Josephson KR, Rubenstein LZ. Low prevalence of postural hypotension among community-dwelling elderly. JAMA. 1987;258(11):1511-4.
71. Sorond FA, Galica A, Serrador JM, Kiely DK, Iloputaife I, Cupples LA, et al. Cerebrovascular hemodynamics, gait, and falls in an elderly population: MOBILIZE Boston Study. Neurology. 2010;74(20):1627-33.
72. Jansen S, Frewen J, Finucane C, de Rooij SE, van der Velde N, Kenny RA. AF is associated with self-reported syncope and falls in a general population cohort. Age Ageing. 2015.
73. Sarasin FP, Louis-Simonet M, Carballo D, Slama S, Rajeswaran A, Metzger JT, et al. Prospective evaluation of patients with syncope: a population-based study. Am J Med. 2001;111(3):177-84.
74. Venkat-Raman G, Tomson CRV, Gao Y, Cornet R, Stengel B, Gronhagen-Riska C, et al. New primary renal diagnosis codes for the ERA-EDTA. Nephrology Dialysis Transplantation. 2012;27(12):4414-9.
75. Freitas J, Santos R, Azevedo E, Carvalho M. Carotid sinus syndrome in an unselected population of eight hundred consecutive patients with syncope. Prevalence and clinical profile. Revista Portuguesa de Cardiologia. 2004;23(6):835-40.
76. Murphy AL, Rowbotham BJ, Boyle RS, Thew CM, Fardoulys JA, Wilson K. Carotid sinus hypersensitivity in elderly nursing home patients. Australian & New Zealand Journal of Medicine. 1986;16(1):24-7.
77. Liu BA, Topper AK, Reeves RA, Gryfe C, Maki BE. Falls among older people: relationship to medication use and orthostatic hypotension. Journal of the American Geriatrics Society. 1995;43(10):1141-5.
78. Schoon Y, Olde Rikkert MGM, Rongen S, Lagro J, Schalk B, Claassen JAHR. Head Turning-Induced Hypotension in Elderly People. PLoS ONE. 2013;8(8).

79. Lagro J, Laurenssen NC, Schalk BW, Schoon Y, Claassen JA, Olde Rikkert MG. Diastolic blood pressure drop after standing as a clinical sign for increased mortality in older falls clinic patients. Journal of Hypertension. 2012;30(6):1195-202.
80. Jansen S, Kenny RA, de Rooij SE, van der Velde N. Self-reported cardiovascular conditions are associated with falls and syncope in community-dwelling older adults. Age Ageing. 2015;44(3):525-9.
81. Le Couteur DG, Fisher AA, Davis MW, McLean AJ. Postprandial systolic blood pressure responses of older people in residential care: association with risk of falling. Gerontology. 2003;49(4):260-4.
82. Puisieux F, Bulckaen H, Fauchais AL, Drumez S, Salomez-Granier F, Dewailly P. Ambulatory blood pressure monitoring and postprandial hypotension in elderly persons with falls or syncopes. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2000;55(9):M535-40.
83. Romero-Ortuno R, Cogan L, Foran T, Kenny RA, Fan CW. Continuous noninvasive orthostatic blood pressure measurements and their relationship with orthostatic intolerance, falls, and frailty in older people. Journal of the American Geriatrics Society. 2011;59(4):655-65.
84. Sibley KM, Voth J, Munce SE, Straus SE, Jaglal SB. Chronic disease and falls in community-dwelling Canadians over 65 years old: a population-based study exploring associations with number and pattern of chronic conditions. BMC Geriatrics. 2014;14:22.
85. Kenny RA, Traynor G. Carotid sinus syndrome--clinical characteristics in elderly patients. Age & Ageing. 1991;20(6):449-54.
86. Klein D, Nagel G, Kleiner A, Ulmer H, Rehberger B, Concin H, et al. Blood pressure and falls in community-dwelling people aged 60 years and older in the VHM&PP cohort. BMC Geriatrics. 2013;13:50.
87. Kumar NP, Thomas A, Mudd P, Morris RO, Masud T. The usefulness of carotid sinus massage in different patient groups. Age & Ageing. 2003;32(6):666-9.
88. Lacerda Gde C, Pedrosa RC, Lacerda RC, Santos MC, Perez Mde A, Teixeira AB, et al. Cardioinhibitory carotid sinus hypersensitivity: prevalence and predictors in 502 outpatients. Arquivos Brasileiros de Cardiologia. 2008;90(3):148-55.
89. Martinez P, Pilar Saez M, Rubio JA, Canovas E, Esteban E, Botas J. [Experience with the use of an implantable loop recorder in a series of older people with falls and suspected arrhythmic syncopes]. Revista Espanola de Geriatria y Gerontologia. 2014;49(3):121-4.
90. Joint Formulary C. British national formulary: Pharmaceutical Press; 2013.
91. Sanders NA, Ganguly JA, Jetter TL, Daccarett M, Wasmund SL, Brignole M, et al. Atrial fibrillation: an independent risk factor for nonaccidental falls in older patients. Pacing & Clinical Electrophysiology. 2012;35(8):973-9.
92. Sutton R, Brignole M, Benditt DG. Key challenges in the current management of syncope. Nat Rev Cardiol. 2012;9(10):590-8.
93. Kumar NP, Thomas A, Mudd P, Morris RO, Masud T. The usefulness of carotid sinus massage in different patient groups. Age & Ageing. 2003;32(6):666-9.
94. Luukinen H, Koski K, Kivela SL, Laippala P. Social status, life changes, housing conditions, health, functional abilities and life-style as risk factors for recurrent falls among the home-dwelling elderly. Public Health. 1996;110(2):115-8.
95. Richardson DA, Bexton RS, Shaw FE, Kenny RA. Prevalence of cardioinhibitory carotid sinus hypersensitivity in patients 50 years or over presenting to the accident and emergency department with "unexplained" or "recurrent" falls. Pacing & Clinical Electrophysiology. 1997;20(3 Pt 2):820-3.
96. Boddaert J, Tamim H, Verny M, Belmin J. Arterial stiffness is associated with orthostatic hypotension in elderly subjects with history of falls. Journal of the American Geriatrics Society. 2004;52(4):568-72.
97. Chang NT, Yang NP, Chou P. Incidence, risk factors and consequences of falling injuries among the community-dwelling elderly in Shihpai, Taiwan. Aging-Clinical & Experimental Research. 2010;22(1):70-7.

98. Damian J, Pastor-Barriuso R, Valderrama-Gama E, de Pedro-Cuesta J. Factors associated with falls among older adults living in institutions. BMC Geriatrics. 2013;13:6.
99. Davies AJ, Kenny RA. Falls presenting to the accident and emergency department: types of presentation and risk factor profile. Age & Ageing. 1996;25(5):362-6.
100. Chen YM, Hwang SJ, Chen LK, Chen DY, Lan CF. Risk factors for falls among elderly men in a veterans home. Journal of the Chinese Medical Association: JCMA. 2008;71(4):180-5.
101. McIntosh S, Da Costa D, Kenny RA. Outcome of an integrated approach to the investigation of dizziness, falls and syncope in elderly patients referred to a 'syncope' clinic. Age & Ageing. 1993;22(1):53-8.
102. Murphy AL, Rowbotham BJ, Boyle RS, Thew CM, Fardoulys JA, Wilson K. Carotid sinus hypersensitivity in elderly nursing home patients. Australian & New Zealand Journal of Medicine. 1986;16(1):24-7.
103. Centre for Clinical Practice at N. National Institute for Health and Clinical Excellence: Guidance. Falls: Assessment and Prevention of Falls in Older People. London: National Institute for Health and Care Excellence (UK)Copyright (c) National Institute for Health and Care Excellence, 2013.; 2013.
104. Hartholt KA, van der Velde N, Looman CW, van Lieshout EM, Panneman MJ, van Beeck EF, et al. Trends in fall-related hospital admissions in older persons in the Netherlands. Arch Intern Med. 2010;170(10):905-11.
105. Office CS, Office CS. Population and Migration Estimates April 2014. Central Statistics Office; 2015.
106. Lei HH, Perneger TV, Klag MJ, Whelton PK, Coresh J. Familial aggregation of renal disease in a population-based case-control study. J Am Soc Nephrol. 1998;9(7):1270-6.
107. Jitapunkul S, Songkhla MN, Chayovan N, Chirawatkul A, Choprapawon C, Kachondham Y, et al. Falls and their associated factors: a national survey of the Thai elderly. Journal of the Medical Association of Thailand. 1998;81(4):233-42.
108. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. Jama. 1995;273(17):1348-53.
109. Benchimol M, Oliveira-Souza R. Diagnostic relevance of the carotid sinus massage during a head up tilt table test (HUTT). Arquivos Brasileiros de Cardiologia. 2008;90(4):264-7.
110. Lipsitz LA, Jonsson PV, Kelley MM, Koestner JS. Causes and correlates of recurrent falls in ambulatory frail elderly. Journal of Gerontology. 1991;46(4):M114-22.
111. Richardson DA, Bexton RS, Shaw FE, Kenny RA. Prevalence of cardioinhibitory carotid sinus hypersensitivity in patients 50 years or over presenting to the accident and emergency department with "unexplained" or "recurrent" falls. Pacing & Clinical Electrophysiology. 1997;20(3 Pt2):820-3.
112. Bumin G, Uyanik M, Aki E, Kayihan H. An investigation of risk factors for falls in elderly people in a Turkish rest home: A pilot study. Aging - Clinical and Experimental Research. 2002;14(3):192-6.
113. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, et al. Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders. New England Journal of Medicine.0(0):null.
114. Tan MP, Newton JL, Reeve P, Murray A, Chadwick TJ, Parry SW. Results of carotid sinus massage in a tertiary referral unit - Is carotid sinus syndrome still relevant? Age and Ageing. 2009;38(6):680-6.
115. Maurer MS, Burcham J, Cheng H. Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2005;60(9):1157-62.
116. Aronow WS, Ahn C. Association of postprandial hypotension with incidence of falls, syncope, coronary events, stroke, and total mortality at 29-month follow-up in 499 older nursing home residents. Journal of the American Geriatrics Society. 1997;45(9):1051-3.

117. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. Hypertension. 1992;19(6 Pt 1):508-19.
118. Tan MP, Newton JL, Chadwick TJ, Parry SW. The relationship between carotid sinus hypersensitivity, orthostatic hypotension, and vasovagal syncope: A case-control study. Europace. 2008;10(12):1400-5.
119. Kario K, Tobin JN, Wolfson LI, Whipple R, Derby CA, Singh D, et al. Lower standing systolic blood pressure as a predictor of falls in the elderly: a community-based prospective study. Journal of the American College of Cardiology. 2001;38(1):246-52.
120. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. 2006.
121. Rosado JA, Rubenstein LZ, Robbins AS, Heng MK, Schulman BL, Josephson KR. The value of Holter monitoring in evaluating the elderly patient who falls. Journal of the American Geriatrics Society. 1989;37(5):430-4.
122. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. 1995.
123. Midttun M. Diagnosis effectiveness of arrhythmia with R-test electrocardiogram in old fallers. European Geriatric Medicine. 2011;2(5):270-2.
124. Allcock LM, O'Shea D. Diagnostic yield and development of a neurocardiovascular investigation unit for older adults in a district hospital. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2000;55(8):M458-62.
125. Dey AB, Stout NR, Kenny RA. Cardiovascular syncope is the most common cause of drop attacks in the elderly. Pacing & Clinical Electrophysiology. 1997;20(3 Pt 2):818-9.
126. Eltrafi A, King D, Silas JH, Currie P, Lye M. Role of carotid sinus syndrome and neurocardiogenic syncope in recurrent syncope and falls in patients referred to an outpatient clinic in a district general hospital. Postgraduate Medical Journal. 2000;76(897):405-8.
127. Milton JC, Lee TC, Jackson SHD. Determinants of a positive response to carotid sinus massage and head-up tilt testing. European Journal of Internal Medicine. 2009;20(7):709-11.
128. Paling D, Vilches-Moraga A, Akram Q, Atkinson O, Staniland J, Paredes-Galan E. Carotid sinus syndrome is common in very elderly patients undergoing tilt table testing and carotid sinus massage because of syncope or unexplained falls. Aging-Clinical & Experimental Research. 2011;23(4):304-8.
129. Rafanelli M, Ruffolo E, Chisciotti VM, Brunetti MA, Ceccofiglio A, Tesi F, et al. Clinical aspects and diagnostic relevance of neuroautonomic evaluation in patients with unexplained falls. Aging-Clinical & Experimental Research. 2014;26(1):33-7.
130. Smebye KL, Granum S, Wyller TB, Mellingsaeter M. Medical findings in an interdisciplinary geriatric outpatient clinic specialising in falls. Tidsskrift for Den Norske Laegeforening. 2014;134(7):705-9.
131. Moya A, Sutton R, Ammirati F, Blanc J-J, Brignole M, Dahm JB, et al. Guidelines for the diagnosis and management of syncope (version 2009): The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). European Heart Journal. 2009;30(21):2631-71.
132. O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA. Amnesia for loss of consciousness is common in vasovagal syncope. Europace. 2011;13(7):1040-5.
133. Kenny RA. Syncope in the elderly: diagnosis, evaluation, and treatment. J Cardiovasc Electrophysiol. 2003;14(9 Suppl):S74-7.
134. Parry SW, Steen IN, Baptist M, Kenny RA. Amnesia for Loss of Consciousness in Carotid Sinus Syndrome: Implications for Presentation With Falls. J Am Coll Cardiol 2005;45(11):1840-3.
135. Shaw FE, Kenny RA. The overlap between syncope and falls in the elderly. Postgrad Med J. 1997;73(864):635-9.
136. Campbell AJ, Borrie MJ, Spears GF, Jackson SL, Brown JS, Fitzgerald JL. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. Age Ageing. 1990;19(2):136-41.

137. Galizia G, Abete P, Mussi C, Noro G, Morrione A, Langellotto A, et al. Role of early symptoms in assessment of syncope in elderly people: results from the italian group for the study of syncope in the elderly. J Am Geriatr Soc. 2009;57(1):18-23.
138. Parry SW, Kenny RA. Drop attacks in older adults: systematic assessment has a high diagnostic yield. J Am Geriatr Soc. 2005;53(1):74-8.
139. Benditt DG, van Dijk JG, Sutton R, Wieling W, Lin JC, Sakaguchi S, et al. Syncope. Curr Probl Cardiol. 2004;29(4):152-229.
140. Blanc JJ, Janousek J. Specific causes of syncope: their evaluation and treatment strategies. In: Blenditt D, Blanc JJ, Brignole M, Sutton R, editor. The Evaluation and Treatment of Syncope: a handbook for clinical practice (European Society of Cardiology). 2nd edition ed: Blackwell Publishing.; 2006. p. 205-15.
141. The Consensus Committee of the American Autonomic S, the American Academy of N. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. Neurology. 1996;46(5):1470-.
142. Parry SW, Gray JC, Newton JL, Reeve P, O'Shea D, Kenny RA. 'Front-loaded' head-up tilt table testing: validation of a rapid first line nitrate-provoked tilt protocol for the diagnosis of vasovagal syncope. Age Ageing 2008;37(4):411-5.
143. Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. Lancet. 1986;1(8494):1352-5.
144. Task Force on Syncope ESoC, Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, et al. Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J 2001;22(15):1256-306.
145. Parry SW, Richardson DA, O'Shea D, Sen B, Kenny RA. Diagnosis of carotid sinus hypersensitivity in older adults: carotid sinus massage in the upright position is essential. Heart. 2000;83(1):22-3.
146. Del Rosso A, Alboni P, Brignole M, Menozzi C, Raviele A. Relation of clinical presentation of syncope to the age of patients. Am J Cardiol. 2005;96(10):1431-5.
147. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and Prognosis of Syncope. N Engl J Med 2002;347(12):878-85.
148. Kapoor WN, Karpf M, Wieand S, Peterson JR, Levey GS. A prospective evaluation and follow-up of patients with syncope. N Engl J Med. 1983;309(4):197-204.
149. Marrison VK, Fletcher A, Parry SW. The older patient with syncope: practicalities and controversies. Int J Cardiol. 2012;155(1):9-13.
150. Alboni P, Brignole M, Menozzi C, Raviele A, Del Rosso A, Dinelli M, et al. Diagnostic value of history in patients with syncope with or without heart disease. J Am Coll Cardiol. 2001;37(7):1921-8.
151. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics--2013 Update: A Report From the American Heart Association. Circulation. 2013;127(1):e6-245.
152. Parry SW, Tan MP. An approach to the evaluation and management of syncope in adults. Bmj. 2010;340:c880.
153. Aronow WS, Ahn C, Mercando AD, Epstein S. Correlation of atrial fibrillation, paroxysmal supraventricular tachycardia, and sinus rhythm with incidences of new coronary events in 1,359 patients, mean age 81 years, with heart disease. Am J Cardiol. 1995;75(2):182-4.
154. Krahn AD, Klein GJ, Yee R, Skanes AC. Detection of asymptomatic arrhythmias in unexplained syncope. Am Heart J. 2004;148(2):326-32.
155. Ermis C, Zhu AX, Pham S, Li JM, Guerrero M, Vrudney A, et al. Comparison of automatic and patient-activated arrhythmia recordings by implantable loop recorders in the evaluation of syncope. Am J Cardiol. 2003;92(7):815-9.
156. Moya A, Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Wieling W, et al. Reproducibility of electrocardiographic findings in patients with suspected reflex neurally-mediated syncope. Am J Cardiol. 2008;102(11):1518-23.

157. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, et al. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. Eur Heart J 2006;27(9):1085-92.
158. Moya A, Brignole M, Menozzi C, Garcia-Civera R, Tognarini S, Mont L, et al. Mechanism of Syncope in Patients With Isolated Syncope and in Patients With Tilt-Positive Syncope. Circulation. 2001;104(11):1261-7.
159. Solano A, Menozzi C, Maggi R, Donateo P, Bottoni N, Lolli G, et al. Incidence, diagnostic yield and safety of the implantable loop-recorder to detect the mechanism of syncope in patients with and without structural heart disease. Eur Heart J. 2004;25(13):1116-9.
160. Pezawas T, Stix G, Kastner J, Schneider B, Wolzt M, Schmidinger H. Implantable loop recorder in unexplained syncope: classification, mechanism, transient loss of consciousness and role of major depressive disorder in patients with and without structural heart disease. Heart. 2008;94(4):e17-.
161. Mendu ML, McAvay G, Lampert R, Stoehr J, Tinetti ME. Yield of diagnostic tests in evaluating syncopal episodes in older patients. Arch Intern Med. 2009;169(14):1299-305.
162. Frewen J, Finucane C, Cronin H, Rice C, Kearney PM, Harbison J, et al. Factors that influence awareness and treatment of atrial fibrillation in older adults. QJM. 2013;106(5):415-24.
163. Sivakumaran S, Krahn AD, Klein GJ, Finan J, Yee R, Renner S, et al. A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope. Am J Med. 2003;115(1):1-5.
164. Rockx MA, Hoch JS, Klein GJ, Yee R, Skanes AC, Gula LJ, et al. Is ambulatory monitoring for "community-acquired" syncope economically attractive? A cost-effectiveness analysis of a randomized trial of external loop recorders versus Holter monitoring. Am Heart J. 2005;150(5):1065.
165. Balmelli N, Naegeli B, Bertel O. Diagnostic yield of automatic and patient-triggered ambulatory cardiac event recording in the evaluation of patients with palpitations, dizziness, or syncope. Clin Cardiol. 2003;26(4):173-6.
166. Farwell DJ, Sulke AN. Does the use of a syncope diagnostic protocol improve the investigation and management of syncope? Heart 2004;90(1):52-8.
167. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an Extended Monitoring Strategy in Patients With Problematic Syncope. Circulation. 1999;99(3):406-10.
168. Brignole M, Menozzi C, Maggi R, Solano A, Donateo P, Bottoni N, et al. The usage and diagnostic yield of the implantable loop-recorder in detection of the mechanism of syncope and in guiding effective antiarrhythmic therapy in older people. Europace. 2005;7(3):273-9.
169. Armstrong VL, Lawson J, Kamper AM, Newton J, Kenny RA. The use of an implantable loop recorder in the investigation of unexplained syncope in older people. Age Ageing. 2003;32(2):185-8.
170. Ruwald MH ZW. ECG monitoring in syncope. Prog Cardiovasc Dis. 2013;56(2):203-10.
171. Benditt DG, Ermis C, Pham S, Hiltner L, Vrudney A, Lurie KG, et al. Implantable diagnostic monitoring devices for evaluation of syncope, and tachy- and brady-arrhythmias. J Interv Card Electrophysiol. 2003;9(2):137-44.
172. Krahn AD, Klein GJ, Yee R, Hoch JS, Skanes AC. Cost implications of testing strategy in patients with syncope: Randomized assessment of syncope trial. J Am Coll Cardiol. 2003;42(3):495-501.
173. Parry SW, Matthews I. The implantable loop recorder in older patients with syncope: is sooner better? Age Ageing. 2010;39(3):284-5.
174. Omran H, Fehske W, Rabahieh R, Hagendorff A, Luderitz B. Relation between symptoms and profiles of coronary artery blood flow velocities in patients with aortic valve stenosis: a study using transoesophageal Doppler echocardiography. Heart. 1996;75(4):377-83.
175. Sarasin FP, Junod AF, Carballo D, Slama S, Unger PF, Louis-Simonet M. Role of echocardiography in the evaluation of syncope: a prospective study. Heart. 2002;88(4):363-7.
176. Tan MP, Kenny RA. Cardiovascular assessment of falls in older people. Clin Interv Aging. 2006;1(1):57-66.

177. Lu J, Lu Z, Voss F, Schoels W. Results of invasive electrophysiologic evaluation in 268 patients with unexplained syncope. J Huazhong Univ Sci Technolog Med Sci. 2003;23(3):278-9.
178. Linzer M, Yang EH, Estes NA, 3rd, Wang P, Vorperian VR, Kapoor WN. Diagnosing syncope. Part 2: Unexplained syncope. Clinical Efficacy Assessment Project of the American College of Physicians. Annals of internal medicine. 1997;127(1):76-86.
179. Savage DD, Corwin L, McGee DL, Kannel WB, Wolf PA. Epidemiologic features of isolated syncope: the Framingham Study. Stroke. 1985;16(4):626-9.
180. Freed LA, Levy D, Levine RA, Larson MG, Evans JC, Fuller DL, et al. Prevalence and clinical outcome of mitral-valve prolapse. N Engl J Med. 1999;341(1):1-7.
181. Ganzeboom KS, Colman N, Reitsma JB, Shen WK, Wieling W. Prevalence and triggers of syncope in medical students. Am J Cardiol. 2003;91(8):1006-8, A8.
182. Linzer M, Pontinen M, Gold DT, Divine GW, Felder A, Brooks WB. Impairment of physical and psychosocial function in recurrent syncope. J Clin Epidemiol. 1991;44(10):1037-43.
183. Santhouse J, Carrier C, Arya S, Fowler H, Duncan S. A comparison of self-reported quality of life between patients with epilepsy and neurocardiogenic syncope. Epilepsia. 2007;48(5):1019-22.
184. van Dijk N, Sprangers MA, Colman N, Boer KR, Wieling W, Linzer M. Clinical factors associated with quality of life in patients with transient loss of consciousness. J Cardiovasc Electrophysiol. 2006;17(9):998-1003.
185. Lipsitz LA, Wei JY, Rowe JW. Syncope in an elderly, institutionalised population: prevalence, incidence, and associated risk. Q J Med. 1985;55(216):45-54.
186. Sun BC, Emond JA, Camargo CA. Characteristics and admission patterns of patients presenting with syncope to U.S. emergency departments, 1992-2000. Acad Emerg Med. 2004;11(10):1029-34.
187. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. J Am Geriatr Soc. 1988;36(7):613-6.
188. McIntosh S, Costa DD, Kenny RA. Outcome of an Integrated Approach to the Investigation of Dizziness, Falls and Syncope, in Elderly Patients Referred to a 'Syncope' Clinic. Age Ageing 1993;22(1):53-8.
189. Ruwald MH, Hansen ML, Lamberts M, Hansen CM, Hojgaard MV, Kober L, et al. The relation between age, sex, comorbidity, and pharmacotherapy and the risk of syncope: a Danish nationwide study. Europace. 2012;14(10):1506-14.
190. Kapoor WN, Hanusa BH. Is syncope a risk factor for poor outcomes? Comparison of patients with and without syncope. Am J Med. 1996;100(6):646-55.
191. Colman N, Nahm K, Ganzeboom KS, Shen WK, Reitsma J, Linzer M, et al. Epidemiology of reflex syncope. Clin Auton Res. 2004;14 Suppl 1:9-17.
192. Casini-Raggi V, Bandinelli G, Lagi A. Vasovagal syncope in emergency room patients: analysis of a metropolitan area registry. Neuroepidemiology. 2002;21(6):287-91.
193. Alboni P, Brignole M, degli Uberti EC. Is vasovagal syncope a disease? Europace. 2007;9(2):83-7.
194. Developed in collaboration w, European Heart Rhythm A, Heart Failure A, and Heart Rhythm S, Endorsed by the following s, European Society of Emergency M, et al. Guidelines for the diagnosis and management of syncope (version 2009): The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Eur Heart J. 2009;30(21):2631-71.
195. Chen LY, Gersh BJ, Hodge DO, Wieling W, Hammill SC, Shen WK. Prevalence and clinical outcomes of patients with multiple potential causes of syncope. Mayo Clin Proc. 2003;78(4):414-20.
196. Romme JJ, van Dijk N, Boer KR, Dekker LR, Stam J, Reitsma JB, et al. Influence of age and gender on the occurrence and presentation of reflex syncope. Clin Auton Res. 2008;18(3):127-33.
197. Providencia R, Silva J, Mota P, Nascimento J, Leitao-Marques A. Transient loss of consciousness in young adults. Int J Cardiol. 2011;152(1):139-43.
198. Probst MA, Kanzaria HK, Gbedemah M, Richardson LD, Sun BC. National trends in resource utilization associated with ED visits for syncope. Am J Emerg Med. 2015;33(8):998-1001.

199. Cronin H, Kenny RA. Cardiac causes for falls and their treatment. Clin Geriatr Med. 2010;26(4):539-67.
200. Shaw FE, Kenny RA. The overlap between syncope and falls in the elderly. Postgrad Med J. 1997;73(864):635-9.
201. Kearney PM, Cronin H, O'Regan C, Kamiya Y, Savva GM, Whelan B, et al. Cohort profile: the Irish Longitudinal Study on Ageing. Int J Epidemiol. 2011;40(4):877-84.
202. Whelan BJ, Savva GM. Design and methodology of the Irish Longitudinal Study on Ageing. J Am Geriatr Soc. 2013;61 Suppl 2:S265-8.
203. Health NIoP. ATC/DDD Index 2016. In: Methodology WCCfDS, editor. Oslo2016.
204. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. Am J Epidemiol. 1977;106(3):203-14.
205. Downton JH, Andrews K. Prevalence, characteristics and factors associated with falls among the elderly living at home. Aging-Clinical & Experimental Research. 1991;3(3):219-28.
206. Davies AJ, Kenny RA. Falls presenting to the accident and emergency department: types of presentation and risk factor profile. Age Ageing. 1996;25(5):362-6.
207. Chen LY, Shen WK, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Prevalence of syncope in a population aged more than 45 years. Am J Med. 2006;119(12):1088 e1-7.
208. Jansen S, Bhangu J, de Rooij S, Daams J, Kenny RA, van der Velde N. The Association of Cardiovascular Disorders and Falls: A Systematic Review. J Am Med Dir Assoc. 2015.
209. Anpalahan M, Gibson S. The prevalence of Neurally Mediated Syncope in older patients presenting with unexplained falls. Eur J Intern Med. 2012;23(2):e48-52.
210. Parry SW, Frearson R, Steen N, Newton JL, Tryambake P, Kenny RA. Evidence-based algorithms and the management of falls and syncope presenting to acute medical services. Clin Med. 2008;8(2):157-62.
211. Jansen S, Kenny RA, de Rooij SE, van der Velde N. Self-reported cardiovascular conditions are associated with falls and syncope in community-dwelling older adults. Age Ageing. 2014.
212. Bhangu J, McMahon CG, Hall P, Bennett K, Rice C, Crean P, et al. Long-term cardiac monitoring in older adults with unexplained falls and syncope. Heart. 2016.
213. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. Jama. 2016.
214. Kenny RA, Brignole M, Dan GA, Deharo JC, van Dijk JG, Doherty C, et al. Syncope Unit: rationale and requirement - the European Heart Rhythm Association position statement endorsed by the Heart Rhythm Society. Europace. 2015;17(9):1325-40.
215. Minet LR, Peterson E, von Koch L, Ytterberg C. Occurrence and Predictors of Falls in People With Stroke: Six-Year Prospective Study. Stroke. 2015;46(9):2688-90.
216. O'Dwyer C, Bennett K, Langan Y, Fan CW, Kenny RA. Amnesia for loss of consciousness is common in vasovagal syncope. Europace. 2011;13(7):1040-5.
217. Duncan GW, Tan MP, Newton JL, Reeve P, Parry SW. Vasovagal syncope in the older person: differences in presentation between older and younger patients. Age Ageing. 2010;39(4):465-70.
218. Bhangu JS, King-Kallimanis B, Cunningham C, Kenny RA. The relationship between syncope, depression and anti-depressant use in older adults. Age Ageing. 2014.
219. O'Regan C, Kenny RA, Cronin H, Finucane C, Kearney PM. Antidepressants strongly influence the relationship between depression and heart rate variability: findings from The Irish Longitudinal Study on Ageing (TILDA). Psychol Med. 2015;45(3):623-36.
220. Regan CO, Kearney PM, Cronin H, Savva GM, Lawlor BA, Kenny R. Oscillometric measure of blood pressure detects association between orthostatic hypotension and depression in population based study of older adults. BMC Psychiatry. 2013;13(1):1.
221. Donoghue OA, odonogh@tcd.ie, O'Hare C, King-Kallimanis B, Kenny RA. Antidepressants are Independently Associated with Gait Deficits in Single and Dual Task Conditions. The American Journal of Geriatric Psychiatry. 2015;23(2):189-99.

222. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. New England Journal of Medicine. 1997;337(18):1279-84.
223. Jacobs DG, Plaisier BR, Barie PS, Hammond JS, Holevar MR, Sinclair KE, et al. Practice management guidelines for geriatric trauma: the EAST Practice Management Guidelines Work Group. J Trauma. 2003;54(2):391-416.
224. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. Journal of the American Geriatrics Society. 1988;36(7):613-6.
225. McIntosh SJ, Lawson J, Kenny RA. Clinical characteristics of vasodepressor, cardioinhibitory, and mixed carotid sinus syndrome in the elderly. Am J Med. 1993;95(2):203-8.
226. Ungar A, Galizia G, Morrione A, Mussi C, Noro G, Ghirelli L, et al. Two-year morbidity and mortality in elderly patients with syncope. Age Ageing. 2011;40(6):696-702.
227. Kaji AH, Schriger D, Green S. Looking through the retrospectoscope: reducing bias in emergency medicine chart review studies. Ann Emerg Med. 2014;64(3):292-8.
228. Sun BC, Emond JA, Camargo CA, Jr. Direct medical costs of syncope-related hospitalizations in the United States. Am J Cardiol. 2005;95(5):668-71.
229. McCarthy F, De Bhladraithe S, Rice C, McMahon CG, Geary U, Plunkett PK, et al. Resource utilisation for syncope presenting to an acute hospital Emergency Department. Ir J Med Sci. 2010;179(4):551-5.
230. Sun BC, McCreath H, Liang LJ, Bohan S, Baugh C, Ragsdale L, et al. Randomized Clinical Trial of an Emergency Department Observation Syncope Protocol Versus Routine Inpatient Admission. Ann Emerg Med. 2013.
231. Duncan GW, Tan MP, Newton JL, Reeve P, Parry SW. Vasovagal syncope in the older person: differences in presentation between older and younger patients. Age Ageing. 2010;39(4):465-70.
232. Carpenter CR, Shelton E, Fowler S, Suffoletto B, Platts-Mills TF, Rothman RE, et al. Risk factors and screening instruments to predict adverse outcomes for undifferentiated older emergency department patients: a systematic review and meta-analysis. Acad Emerg Med. 2015;22(1):1-21.
233. Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev. 2011(7):Cd006211.
234. Costa AP, Hirdes JP, Heckman GA, Dey AB, Jonsson PV, Lakhan P, et al. Geriatric syndromes predict postdischarge outcomes among older emergency department patients: findings from the interRAI Multinational Emergency Department Study. Acad Emerg Med. 2014;21(4):422-33.
235. Costantino G, Sun BC, Barbic F, Bossi I, Casazza G, Dipaola F, et al. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department. Eur Heart J. 2016;37(19):1493-8.
236. Blake AJ, Morgan K, Bendall MJ, Dallosso H, Ebrahim SB, Arie TH, et al. Falls by elderly people at home: prevalence and associated factors. Age Ageing. 1988;17(6):365-72.
237. Close JCT, Lord SR, Antonova EJ, Martin M, Lensberg B, Taylor M, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. 2012.
238. Chiara M, Gianluigi G, Pasquale A, Alessandro M, Alice M, Gabriele N, et al. Unexplained Falls Are Frequent in Patients with Fall-Related Injury Admitted to Orthopaedic Wards: The UFO Study (Unexplained Falls in Older Patients). Current gerontology and geriatrics research. 2013;2013:928603.
239. Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. J Gerontol. 1991;46(5):M164-70.
240. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. Europace. 2009;11(5):671-87.
241. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC).

Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013;15(8):1070-118.
242. Parry SW, Steen N, Bexton RS, Tynan M, Kenny RA. Pacing in elderly recurrent fallers with carotid sinus hypersensitivity: a randomised, double-blind, placebo controlled crossover trial. Heart. 2009;95(5):405-9.
243. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. Arch Gen Psychiatry. 1983;40(7):812.
244. Richardson K, Kenny RA, Bennett K. The effect of free health care on polypharmacy: a comparison of propensity score methods and multivariable regression to account for confounding. Pharmacoepidemiol Drug Saf. 2014;23(6):656-65.
245. Okuyan E, Uslu A, Ozan Levent M. Cardiac effects of "mad honey": a case series. Clin Toxicol (Phila). 2010;48(6):528-32.
246. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-8.
247. Carhuapoma JR, Williams MA. Endotracheal suctioning and cerebral ischemia in traumatic brain injury: the "phantom menace?" [editorial; comment]. Critical Care Medicine. 1999;27(12):2843-4.
248. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc. 1986;34(2):119-26.
249. O'Shea D, Parry SW, Kenny RA. The Newcastle protocol for carotid sinus massage. J Am Geriatr Soc. 2001;49(2):236-7.
250. Bartoletti A, Alboni P, Ammirati F, Brignole M, Del Rosso A, Foglia Manzillo G, et al. 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. Europace. 2000;2(4):339-42.
251. Brignole M, Moya A, Menozzi C, Garcia-Civera R, Sutton R. Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder. Europace. 2005;7(1):14-8.
252. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. Eur Heart J. 2006;27(3):351-6.
253. Donoghue OA, Jansen S, Dooley C, De Rooij S, Van Der Velde N, Kenny RA. Atrial Fibrillation Is Associated With Impaired Mobility in Community-Dwelling Older Adults. J Am Med Dir Assoc. 2014.
254. Brignole M, Menozzi C, Maggi R, Solano A, Donateo P, Bottoni N, et al. The usage and diagnostic yield of the implantable loop-recorder in detection of the mechanism of syncope and in guiding effective antiarrhythmic therapy in older people. 2005.
255. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, et al. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. Eur Heart J. 2006;27(9):1085-92.
256. Daccarett M, Brignole M, Malasana GR, Sherwood RP, Jetter TL, Hamdan MH. Underevaluation of cardiovascular risk factors in patients with nonaccidental falls. J Prim Care Community Health. 2011;2(3):173-80.
257. McMahon CG, Cahir CA, Kenny RA, Bennett K. Inappropriate prescribing in older fallers presenting to an Irish emergency department. Age Ageing. 2014;43(1):44-50.
258. Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, et al. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. J Cereb Blood Flow Metab. 2014;34(2):228-34.
259. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. J Cardiovasc Electrophysiol. 2006;17(11):1172-6.
260. Kapoor W, Snustad D, Peterson J, Wieand HS, Cha R, Karpf M. Syncope in the elderly. Am J Med. 1986;80(3):419-28.

261. Getchell WS, Larsen GC, Morris CD, McAnulty JH. Epidemiology of syncope in hospitalized patients. J Gen Intern Med. 1999;14(11):677-87.
262. Colman N, Nahm K, van Dijk JG, Reitsma JB, Wieling W, Kaufmann H. Diagnostic value of history taking in reflex syncope. Clin Auton Res. 2004;14 Suppl 1:37-44.
263. D'Antono B, Dupuis G, St-Jean K, Levesque K, Nadeau R, Guerra P, et al. Prospective evaluation of psychological distress and psychiatric morbidity in recurrent vasovagal and unexplained syncope. J Psychosom Res. 2009;67(3):213-22.
264. Kouakam C, Lacroix D, Klug D, Baux P, Marquie C, Kacet S. Prevalence and prognostic significance of psychiatric disorders in patients evaluated for recurrent unexplained syncope. Am J Cardiol. 2002;89(5):530-5.
265. Gum AM, King-Kallimanis B, Kohn R. Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. Am J Geriatr Psychiatry. 2009;17(9):769-81.
266. Moore M, Yuen HM, Dunn N, Mullee MA, Maskell J, Kendrick T. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. Bmj. 2009;339:b3999.
267. Petty DR, House A, Knapp P, Raynor T, Zermansky A. Prevalence, duration and indications for prescribing of antidepressants in primary care. Age Ageing. 2006;35(5):523-6.
268. Harris T, Carey IM, Shah SM, DeWilde S, Cook DG. Antidepressant prescribing in older primary care patients in community and care home settings in England and Wales. J Am Med Dir Assoc. 2012;13(1):41-7.
269. Linzer M, Varia I, Pontinen M, Divine GW, Grubb BP, Estes NA, 3rd. Medically unexplained syncope: relationship to psychiatric illness. Am J Med. 1992;92(1a):18s-25s.
270. Kerse N, Flicker L, Pfaff JJ, Draper B, Lautenschlager NT, Sim M, et al. Falls, depression and antidepressants in later life: a large primary care appraisal. PLoS One. 2008;3(6):e2423.
271. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. Bmj. 2011;343:d4551.
272. Grubb BP, Wolfe DA, Samoil D, Temesy-Armos P, Hahn H, Elliott L. Usefulness of fluoxetine hydrochloride for prevention of resistant upright tilt induced syncope. Pacing Clin Electrophysiol. 1993;16(3 Pt 1):458-64.
273. Di Girolamo E, Di Iorio C, Sabatini P, Leonzio L, Barbone C, Barsotti A. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 1999;33(5):1227-30.
274. Kremastinos DT. Cardiogenic syncope and serotonin reuptake inhibitors. Hellenic J Cardiol. 2008;49(5):375-6.
275. Vieweg WV, Wood MA, Fernandez A, Beatty-Brooks M, Hasnain M, Pandurangi AK. Proarrhythmic risk with antipsychotic and antidepressant drugs: implications in the elderly. Drugs Aging. 2009;26(12):997-1012.
276. Pacher P, Ungvari Z, Kecskemeti V, Furst S. Review of cardiovascular effects of fluoxetine, a selective serotonin reuptake inhibitor, compared to tricyclic antidepressants. Curr Med Chem. 1998;5(5):381-90.
277. Pacher P, Ungvari Z, Nanasi PP, Furst S, Kecskemeti V. Speculations on difference between tricyclic and selective serotonin reuptake inhibitor antidepressants on their cardiac effects. Is there any? Curr Med Chem. 1999;6(6):469-80.
278. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. Lancet. 1998;351(9112):1303-7.
279. Sumner GL, Rose MS, Koshman ML, Ritchie D, Sheldon RS. Recent history of vasovagal syncope in a young, referral-based population is a stronger predictor of recurrent syncope than lifetime syncope burden. J Cardiovasc Electrophysiol. 2010;21(12):1375-80.