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Hypertension and Aging

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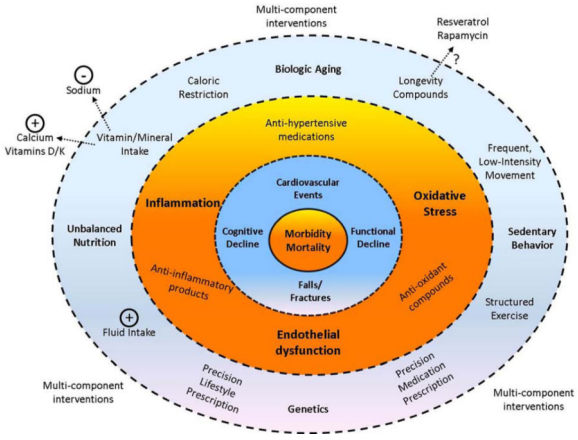
Abstract

Hypertension is a highly prevalent condition with numerous health risks, and the incidence of hypertension is greatest among older adults. Traditional discussions of hypertension have largely focused on the risks for cardiovascular disease and associated events. However, there are a number of collateral effects, including risks for dementia, physical disability, and falls/fractures which are increasingly garnering attention in the hypertension literature. Several key mechanisms – including inflammation, oxidative stress, and endothelial dysfunction – are common to biologic aging and hypertension development and appear to have key mechanistic roles in the development of the cardiovascular and collateral risks of late-life hypertension. The objective of the present review is to highlight the multi-dimensional risks of hypertension among older adults and discuss potential strategies for treatment and future areas of research for improving overall care for older adults with hypertension.

Graphical Abstract



Keywords

Cardiovascular; Falls; Disability; Cognition; Blood Pressure; Antihypertensive

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> "Our great struggle in medicine these days is not just with ignorance and uncertainty. It's also with complexity: how much you have to make sure you have in your head and think about. There are a thousand ways things can go wrong."
>
> Atul Gawande(Gawande, 2009)

1. Introduction

Life expectancy continues to increase in developed countries worldwide (Roberts, 2011), leading to ever-increasing representation of older adults (i.e. persons over 65 years of age) within the population. In fact, life expectancy worldwide has increased by 20 years since 1950. In the United States, the number of older adults is expected to double to approximately 80 million in the next three decades (Federal Interagency Forum on Aging-Related Statistics, 2009). Given the dramatically disproportionate utilization of health care resources by older adults – e.g. nearly three quarters of cardiovascular disease (CVD)-related expenditures (Hodgson and Cohen, 1999) – the maintenance of health and well-being among older adults is a critical scientific and public health priority (Institute of Medicine, 2008; National Institute on Aging, 2007).

Among the potential targets for improving health among older adults, hypertension represents one of the most prevalent and potentially modifiable. Hypertension causes over 7 million premature deaths per year and contributes to 4.5% of the total disease burden worldwide (Bramlage and Hasford, 2009). Notably, older adults account for the bulk of hypertension-related morbidity and mortality – due largely to dramatically greater prevalence among the elderly (Mozaffarian et al., 2015). In fact, recent data from the National Health and Nutrition Examination Survey indicate that 70% of older adults have hypertension, compared to only 32% for adults aged 40-59 years (Figure 1) (Mozaffarian et al., 2015). Despite the well-documented pervasiveness of late-life hypertension among older adults, many challenges remain. A 2010 report from the Institute of Medicine (IOM) called hypertension a neglected disease that is often ignored by the general public and underappreciated by the medical community (Institute of Medicine, 2010). "Although hypertension is relatively easy to prevent, simple to diagnose, and relatively inexpensive to treat, it remains the second leading cause of death among Americans, and as such should rightly be called a neglected disease", said David W. Fleming, MD, chair of the committee that prepared the report (Mitka, 2010). Proper screening and adherence to treatment guidelines was particularly emphasized for elderly patients.

Since the release of the IOM report, a number of large clinical trials, systematic reviews, and meta-analyses have been published focusing on proper treatment for patients with hypertension. However, relatively few of these have focused on the treatment of hypertension among older adults (Goeres et al., 2014). This relative paucity of data in this area may be related to the common practice of excluding older adults from randomized controlled trials (RCTs) due to concerns about safety and/or confounding effects of co-morbid conditions (Pahor and Cesari, 2012; Van Spall et al., 2007). Indeed, numerous challenges exist in the treatment of hypertension among older adults – including and altered drug metabolism (Belmin et al., 2000), multiple concomitant medications and co-morbidities

(Benetos et al., 2015), as well as increased blood pressure variability and orthostatic hypotension (Sera and McPherson, 2012) – that make it difficult to obtain definitive evidence of proper treatment guidelines. Still, it is these challenges which make it critical to conduct studies which will improve medical decision making related to the treatment of hypertension among older adults.

Furthermore, RCTs have primarily focused on cardiovascular effects of hypertension treatment despite well-documented links between late-life hypertension and other health outcomes relevant to older adults including physical function, bone health, and cognition. It is critical that we improve our understanding of how hypertension treatment influences such geriatric outcomes as they, like cardiovascular disease, dramatically influence risks for hospitalization, morbidity, and mortality (Ray et al., 1997; Sachs et al., 2011; Studenski et al., 2011). Decision making in treating hypertensive older adults is further convoluted by the fact that these varied health outcomes are not independent but often have similar etiologies and may interact to exacerbate the progression of one another. It is this complexity that makes it necessary to view geriatric hypertension decision making not from the perspective of a single outcome (e.g. CVD, dementia) but rather using a holistic approach that incorporates the individual characteristics of each patient and uses a broad lens to assess health. The objective of this review is to therefore synthesize hypertension literature from several fields into a framework which integrates these distinct but overlapping fields.

2. Common Mechanisms of Aging and Hypertension – The Vascular Health Triad

In humans, aging is a continual and progressive process that results in decreased physiologic function across all organ systems (Franceschi et al., 2008). These physiologic decrements result in an increased vulnerability to infection and disease which dramatically elevate mortality risk (Candore et al., 2006; Troen, 2003). In fact, compared to persons 25-44 years of age, mortality risk among older adults is elevated by 100-fold for stroke and chronic lung disease, roughly 90-fold for heart disease, pneumonia and influenza, and over 40-fold for cancer (Troen, 2003). As diverse as the etiologies of age-related diseases are, significant evidence implicates two interconnected mechanisms among the most common biologic contributors to age-related disease: 1) chronic, low-grade inflammation (Cevenini et al., 2010; Chung et al., 2009; Singh and Newman, 2011; Vasto et al., 2007) and 2) increased cellular oxidative stress (Chen et al., 2007; Harman, 1956; Valko et al., 2007; Yu and Yang, 1996).

Inflammation is a localized response to tissue injury or infection which aids in the repair of damaged tissue and/or destruction of the harmful agent. Classically characterized by pain, heat, redness, swelling, and loss of function – acute inflammation is typically resolved in relatively short order to promote the restoration of tissue function. However, during advanced age, the ability to resolve inflammation becomes impaired leading to sustained tissue infiltration of leukocytes and the chronic release of pro-inflammatory cytokines and chemokines (Sarkar and Fisher, 2006). As a result, the initial local event has long-term systemic consequences. Though factors such as obesity and insulin resistance, smoking, and changes in circulating sex hormone concentrations are associated with age-related

inflammation (Krabbe et al., 2004), increases in inflammatory mediators are thought to derive most directly from decreases in the efficiency of the immune system (i.e. immuno-senescence) (Chung et al., 2009; Vasto et al., 2007). Immuno-senescence is characterized by thymus atrophy, reductions in neutrophil function, naïve T cell number, and the cytotoxic capacity of natural killer cells, and lowered B-cell antibody production in response to antigen (Hawkley and Cacioppo, 2004; Phillips et al., 2007). The most widely held belief regarding the cause of immune-senescence is that chronic antigen burden over the course of a lifetime exhausts a finite capacity of the immune system (Buford and Willoughby, 2008; De Martinis et al., 2007). As a result, we trade the long-term risk of chronic inflammation and disease for life-long protection against infection and injury (Wick et al., 2003).

Inflammation is the most consistently documented biological feature of aging, though it remains unknown whether inflammatory mediators directly cause adverse health outcomes. The inflammatory biomarkers most consistently associated with aging are elevated circulating concentrations of interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α) (Singh and Newman, 2011). Notably, these markers increase during aging even in the absence of acute infection (Ershler et al., 1993; Fagiolo et al., 1993; Wei et al., 1992) and have been associated with the prevalence of a wide-range of age-related co-morbidities – cardiovascular disease (Cesari et al., 2003; Cesari et al., 2003; Tracy et al., 1997), insulin resistance and diabetes (Bertoni et al., 2010; Pickup et al., 2000; Pradhan et al., 2001), osteoporosis (Ding et al., 2008; Khosla et al., 1994; Zheng et al., 1997), cognitive decline and dementia (Engelhart et al., 2004; Weaver et al., 2002; Yaffe et al., 2003), frailty and disability (Ershler and Keller, 2000; Ferrucci et al., 2002; Walston et al., 2002), and cancer (Aggarwal et al., 2006; Il'yasova et al., 2005; Lu et al., 2006) – as well as mortality (Harris et al., 1999; Newman et al., 2009; Roubenoff et al., 2003).

Though a conclusive causal relationship between inflammation and age-related conditions has not been firmly established, one potential supportive link is the contribution of inflammation to intracellular oxidative stress. In addition to producing pro-inflammatory cytokines, tissue-infiltrating leukocytes such as neutrophils and macrophages produce reactive oxygen species (ROS) [e.g. superoxide (O_2^-) and hydrogen peroxide (H_2O_2)] to kill pathogens (Crowley, 2014). Under homeostatic conditions, ROS and other free radicals (i.e. reactive nitrogen species; RNS) are necessary intracellular signaling molecules involved in ongoing reduction-oxidation (redox) reactions that occur as a part of normal metabolic processes (Brown and Griendling, 2009; Gillespie et al., 2009). However, chronic elevations in inflammatory mediators during late life contribute to a deleterious chronic overproduction of ROS (Dinh et al., 2014). Coupled with aged-related declines in nitric oxide (NO) production and bioavailability (Torregrossa et al., 2011), these increases in ROS formation contribute to an imbalance between the production and breakdown of ROS (i.e. oxidative stress) which leads to damage of cellular proteins and organelles. It is this chronic cellular damage and dysfunction that is thought to at least partially contribute to physiologic dysfunction and the development of age-related disease.

Notably, though chronic inflammation is a driver of oxidative stress, several other age-related changes – including mitochondrial dysfunction (Kujoth et al., 2005; Pang et al., 2008) and decrease in the efficiency of various endogenous antioxidant defense systems (Ji

et al., 1998; Pinzani et al., 1997) – contribute to the development of oxidative stress in late life. Moreover, chronic oxidative stress also reflexively stimulates inflammation at least partially through the induction of the transcription factor nuclear factor kappa B (NF-kB) and the subsequent biosynthesis of prostaglandins via cyclooxygenase (COX) activity (Baek et al., 2001; Chung et al., 1999). Thus, though elevations in inflammation and oxidative stress stem at least partially from distinct age-related physiologic changes, they are also intricately linked as elevations in one induce concordant increases in the other (Kim et al., 2006; Sarkar and Fisher, 2006) – sometimes referred to as a "vicious cycle" (Chung et al., 2009).

In addition to their role in the aging process, inflammation and oxidative stress have also each been associated with hypertension. Several studies have demonstrated higher plasma levels of CRP (Bautista et al., 2004; Stuveling et al., 2004; Sung et al., 2003), IL-6 (Bautista et al., 2005; Chae et al., 2001; Fernandez-Real et al., 2001), TNF-α (Bautista et al., 2005; Furumoto et al., 2002; Yu et al., 2010), and IL-1β (Dalekos et al., 1997; Zhao et al., 2004) in hypertensive patients compared to normotensive peers. The association between oxidative stress and hypertension is less substantiated but this could be partially due to challenges in measuring in vivo oxidative stress in humans. However, clinical and pre-clinical evidence also indicates that vascular O_2^- production and systemic oxidative stress are present prior to substantial elevations in blood pressure and may contribute to the transition from prehypertension to hypertension (Lacy et al., 1998; Lacy et al., 2000; Nabha et al., 2005). Animal studies have documented increased production of vascular, renal, cardiac, and neural production of O_2^- and H_2O_2 production in Ang II-induced hypertension(Briones and Touyz, 2010) and oxidative stress in salt-sensitive forms of hypertension (Callera et al., 2003; Lassegue and Clempus, 2003). Meanwhile, clinical evidence previously indicated elevations in nonspecific markers of oxidative injury in plasma and urine from middle-aged, hypertensive patients (Ward et al., 2004) and elevated O_2^- and H_2O_2 concentrations in vascular smooth muscle cells from patients with essential hypertension (Touyz and Schiffrin, 2001).

Notably, with evidence suggesting potential bi-directional relationship whereby these mechanisms both contribute to and are exacerbated by hypertension (Briones and Touyz, 2010; Dinh et al., 2014; Rubio-Ruiz et al., 2014; Wadley et al., 2013). For example, common secondary causes of hypertension such as obstructive sleep apnea, chronic kidney disease, and renal artery stenosis are all associated with inflammation and highly prevalent in the elderly (Rafey, 2009). These conditions are thought to stem at least partially from sympathetic nervous system (SNS) activation – a common feature of hypertension (Guyenet, 2006). Increased sympathetic drive to the kidneys causes the release of renin and subsequently raises blood pressure (Bunag et al., 1966). Such increases in SNS activity have been demonstrated in response to elevations in both central (Zhang et al., 2010) and systemic (Yu et al., 2010) inflammation. Meanwhile, most immune cells express catecholamine receptors (Nance and Sanders, 2007) – facilitating the reciprocal stimulation of inflammation by the SNS demonstrated in pre-clinical studies (Lob et al., 2010; Veelken et al., 2008).

Presently, the strongest link between inflammation/oxidative stress and hypertension appears to be vascular dysfunction (Briones and Touyz, 2010; Dinh et al., 2014; Rubio-Ruiz et al., 2014; Wadley et al., 2013). In fact, the relationships among these three biological mechanisms have been termed the "Vascular Health Triad" (Figure 2) which has been implicated separately in both aging (Wadley et al., 2013) and hypertension (Dinh et al., 2014). Indeed, inflammation and oxidative stress have been consistently documented as contributors to endothelial dysfunction (Brinkley et al., 2009; Donato et al., 2007; Pierce et al., 2009; Rodriguez-Manas et al., 2009). For example, increases in free radical formation cause deterioration of the NO cascade, alter and activate prostaglandin metabolism, and promotes novel oxidative posttranslational protein modifications that interfere with vascular and cell signaling pathways (Rubio-Ruiz et al., 2014). Endothelial dysfunction develops in response these changes and contributes directly to increased systemic vascular resistance, and therefore increased blood pressure, due to an imbalance between vasodilatory and vasocontrictory substances (Chrissobolis et al., 2011). Thus, endothelial dysfunction contributes directly to the pathogenesis of hypertension and associated health effects. However, endothelial dysfunction also contributes to further exacerbating inflammation and oxidative stress, creating an even larger vicious cycle (Dinh et al., 2014; Wadley et al., 2013). Healthy endothelium exerts anti-inflammatory effects such as NO-dependent inhibition of leukocyte adhesion (Kubes et al., 1991). When NO is released it also causes smooth muscle relaxation and subsequent vasodilation (Chrissobolis et al., 2011). However, in response to aging and hypertension, the endothelium also releases other vasoactive substances such as endothelin-1 (ET-1), angiotensin II (Ang II), and COX-derived prostanoid and superoxide anions which contribute to impaired endothelium-dependent vasodilation (Rubio-Ruiz et al., 2014). Moreover, NO also tends to react with oxidants, particularly O_2^- to form the potent free radical peroxynitrite ($ONOO^-$) which removes NO from the endothelium thereby reducing the vasodilatory capacity of the vessel (Squadrito and Pryor, 1995). Thus, because of chronic elevations in O_2^-, NO-dependent vasodilation is impaired – further exacerbating the vicious cycle.

3. Collateral Health Risks among Older Adults with Hypertension

Traditional discussions of the Vascular Health Triad and hypertension have largely focused on the risks for cardiovascular disease and associated events. Indeed, it is well established that cardiovascular events are a critical risk for older adults with hypertension and reviews on this topic can be found elsewhere (Goeres et al., 2014; Rubio-Ruiz et al., 2014; Sun, 2015). However, there are a number of "collateral effects" (e.g. cognitive, musculoskeletal) which are increasingly garnering attention in the hypertension literature. These effects are particularly relevant to older adults given the independent effects of age on these outcomes. The following section outlines the evidence regarding the joint contributions of hypertension and aging to three such collateral effects including 1) declines in cognition and the development of dementia, 2) declining physical abilities ("functional decline") and disablement, and 3) the incidence of falls and injurious fractures (Figure 3). It should be noted, however, that these collateral effects are not independent of one another as numerous cross-relationships exist. For example, cardiovascular burden is key predictor of both dementia (Duron and Hanon, 2008; Ihle-Hansen et al., 2015; Launer et al., 2000; Peters et

al., 2013) and physical disability (Bootsma-van der Wiel et al., 2002; Hajjar et al., 2007; Iritani et al., 2014; Newman et al., 2006). Declining cognitive function is also strongly associated with both functional decline/disability (Carlson et al., 1999; Hajjar et al., 2009; Mielke et al., 2013; Watson et al., 2010) and the incidence of falls (Rubenstein, 2006; Segev-Jacubovski et al., 2011; Springer et al., 2006; Tinetti et al., 1988). Additionally, functional decline and falls share several etiological features and can reciprocally exacerbate risk for the other (Abellan van Kan et al., 2009; Gill et al., 2013; Tinetti et al., 1988; Tinetti and Williams, 1998). Thus, though we discuss each of the conditions separately here, the interdependence of these conditions highlights the tremendous health risks and importance of managing hypertension in the elderly.

3.1 Cognitive Decline and Dementia

Among age-related conditions, perhaps none are more concerning or disheartening to both the individual and loved ones than the loss of memory and (in some cases) subsequent onset of dementia (Riley et al., 2014; Wikler et al., 2013). Dementia, of which Alzheimer's disease (AD) is the most common form, is a potentially debilitating condition which negatively impacts quality of life for both affected patients and caregivers and has tremendous associated healthcare costs (Boustani et al., 2007). Because of the increases in life expectancy, the number of people with dementia worldwide is expected to increase to over 80 million by the year 2040 (Duron and Hanon, 2008). Despite the tremendous public health burden expected from dementia incidence, these statistics underestimate the potential consequences of age-related declines in cognition. Mild cognitive impairment (MCI), an intermediate stage between normal cognitive function and dementia (Petersen et al., 2001), is about four-times as prevalent as dementia (DeCarli, 2003). MCI is typically associated with either memory impairments or deficits in cognitive and/or motor performance (Gauthier et al., 2006; Kluger et al., 2008; Petersen et al., 1999). Importantly, MCI is associated with an increased risk of dementia (DeCarli, 2003; Gauthier et al., 2006; Ward et al., 2012) and is a strong predictor of excess mortality (i.e. premature death)(Bennett et al., 2002; Contador et al., 2014; Sachs et al., 2011). Recognition of these consequences has led to a growing awareness of the need to treat MCI among older adults (Eshkoor et al., 2015; Langa and Levine, 2014).

In recent years, hypertension has become increasingly recognized as an important risk factor for the development of MCI and dementia (Cherubini et al., 2010; DeCarli, 2015; Hanon and Forette, 2005; Power et al., 2011). Though cognition may be affected by hypertension through increased risk for stroke and subsequent post-stroke cognitive decline (Ihle-Hansen et al., 2015), hypertension appears to also have a distinct association with cognitive decline independent of stroke incidence. For example, Haring et al.(Haring et al., 2015) recently reported findings from over 6,000 women aged 65-79 indicating that hypertension was associated with an increased risk of MCI or probable dementia (HR = 1.20) and risk was highest among those with blood pressure ≥ 140/90 (HR = 1.30; Figure 4). Though the biologic source of such associations has not been completely refined, the relationship is thought by many to center around the development of “vascular dementia” whereby age- and hypertension-related changes in the cerebral vasculature impair cerebral perfusion and induce tissue damage – particularly in the white matter (Kim et al., 2015; McEvoy et al.,

2015). Excellent reviews on this specific topic are available elsewhere (Cherubini et al., 2010; Ritter and Pillai, 2015; Venkat et al., 2015).

To date, mid-life hypertension appears to be even more strongly associated with the development of MCI/dementia than late-life hypertension (Freitag et al., 2006; Kivipelto et al., 2001; Launer et al., 1995; Launer et al., 2000). In a recent study from the Atherosclerosis Risk in Communities cohort, Gottesman et al.(Gottesman et al., 2014) reported findings more than 15,000 individuals (mean age of 56 years old at baseline) followed for 20 years indicating a modest but significant association between systolic blood pressure (SBP) at baseline and rate of cognitive decline (Figure 4). When adjusted for mortality, hypertension increased risk of cognitive decline by nearly 70%. Interestingly, this study reported greater cognitive declines with higher midlife blood pressure among Caucasians than African Americans. This observation is in contrast to recent reports from the National Health and Nutrition Examination Survey (NHANES) indicating a higher burden of cognitive limitations among hypertensive African Americans than Caucasians (Hajjar et al., 2015). These differences may be due to the fact that the latter study included a wider range of participants (20 years and older) and utilized subjective reports of cognitive limitations rather than objective measures of cognition. Future studies are likely needed to tease out potential racial differences in the effects of hypertension on age-related cognition and the development of MCI/dementia.

In recent years, appreciation has increased for the role of lifestyle-related factors relevant to the progression of hypertension (e.g. diet and exercise) in the prevention of onset and progression of dementia. For instance, a high-fat diet and commonly associated consequences (e.g. obesity, insulin resistance) are thought to contribute to dementia development largely through the processes of the Vascular Health Triad (Freeman et al., 2014) possibly resulting in disruption of the blood-brain barrier (Hsu and Kanoski, 2014). Other studies have proposed potential roles for intake of dietary sodium (Fiocco et al., 2012; Haring et al., 2015) and antioxidants (Crichton et al., 2013), though these links are yet to be firmly substantiated. Still, several studies have reported that diets commonly recommended for hypertensive individuals – including a Mediterranean-style diet and the Dietary Approach to Stop Hypertension (DASH) diet – are associated with improved cognition and potential reductions in the incidences of MCI and dementia (Alles et al., 2012; Singh et al., 2014; Wengreen et al., 2013). The lack of physical regular exercise has also been associated with increased risk for cognitive decline (Vassilaki et al., 2015), and though not definitive, several studies suggest that exercise may aid in the maintenance of cognitive function and prevention of dementia (Aarsland et al., 2010; Hamer and Chida, 2009; Hindin and Zelinski, 2012; Kelly et al., 2014). Thus, though much remains to be evaluated in this area, it appears as if lifestyle behaviors typically recommended for the treatment of hypertension hold promise for not only cardiovascular benefits but possibly cognitive benefits as well.

3.2 Functional Decline and Physical Disability

The maintenance of one's physical capabilities during older age is an essential part of healthy aging. The capacity to perform basic physical functions is a central aspect of health-related quality of life (Muszalik et al., 2011) and a key predictor of hospitalization, surgical

outcomes, and mortality (Afilalo et al., 2010; Dumurgier et al., 2009; Penninx et al., 2000; Studenski et al., 2011). Declines in basic physical functions such as walking are also strong predictors of future cardiovascular events. In fact, declines in walking speed are associated with incident stroke (McGinn et al., 2008), adverse outcomes following cardiac surgery (Afilalo et al., 2010), as well as cardiovascular mortality (Dumurgier et al., 2009; Newman et al., 2006; Studenski et al., 2011). Accordingly, maintenance of independent functioning is a critical factor in preserving the health and well-being of older adults. In the U.S., nearly half of the 37.3 million persons aged ≥ 65 years report having one or more physical limitations in performing essential daily tasks (Seeman et al., 2010). The physical disablement of older adults is also a central contributor to rising healthcare costs, accounting for a significant portion of the U.S.'s annual $300 billion in disability-related medical costs (US Department of Health and Human Services, 2005). This burden is also expected to dramatically rise in coming years given rising healthcare costs and the fact that older adults represent the fastest growing segment of the population (Federal Interagency Forum on Aging-Related Statistics, 2009; U.S. Census Bureau,).

Compared to normotensive counterparts, older adults with hypertension experience accelerated declines in physical function and increased incidence of disability (Balzi et al., 2010; Dumurgier et al., 2010; Hajjar et al., 2007; Rosano et al., 2011). Among 999 older adults (68.5 ± SE = 0.2 years) enrolled in the Charleston Heart Study and evaluated between 1984 and 1993, higher systolic blood pressure was associated with increased risk of developing new disability.(Hajjar et al., 2007) According to three validated scales of disability, participants with hypertension had elevated risk of disablement (HR = 1.3) and those with uncontrolled hypertension were at greatest risk compared with normotensive participants (Figure 5). Similar results were observed among 897 older adults in the InCHIANTI study, an Italian population based study (Balzi et al., 2010). Over 3 years of follow up, hypertension was significantly associated (HR = 1.91) with worsening disability in the performance of activities of daily living (ADLs). Hypertension has also been strongly associated with accelerated declines in walking speed, a key indicator of functional status and recommended indicator of health and well-being among seniors (Abellan van Kan et al., 2009; Hall, 2006). Among 3604 older adults (65-85 years) enrolled in the Three-City study conducted in France, baseline walking speed was lower among hypertensive (1.51 ± 0.31 m/s) than non-hypertensive (1.59 ± 0.30 m/s) – a difference that is clinically meaningful based on established minimal clinically-meaningful difference of 0.05 m/s (Dumurgier et al., 2010). Moreover, during a mean follow-up of 7.0 ± 0.05 years, annual decline in walking speed was significantly greater among hypertensive (−2.30 ± 3.4 cm/s) than non-hypertensive (−1.87 ± 3.3 cm/s) individuals. Similar results were observed among 2,733 participants in the U.S.-based Cardiovascular Health Study as rates of decline in walking speed over 18 years were significantly greater among those with hypertension (~ Δ = 0.4 cm/s/yr) even after adjustment or numerous potentially confounding factors (Rosano et al., 2011).

Taken together, these data from large-scale cohort studies appear to indicate that hypertension is involved in accelerated functional decline and the development of physical disability. However, the mechanisms by which these changes occur are yet to be fully elucidated. Sarcopenia, the age-related decline in muscle mass and strength, may represent

one possible mechanism through which hypertension accelerates functional declines – though this potential is presently speculative given the limited evidence in this area. Several studies from Asian populations have recently demonstrated a cross-sectional link between hypertension and sarcopenia (Han et al., 2014; Park et al., 2013; Wu et al., 2014), while a longitudinal cohort study in Finish individuals reported hypertension as a significant predictor of muscle strength decline over 22 years of follow-up (Stenholm et al., 2012). This potential acceleration of sarcopenia could result in response to hypertension-mediated increases in inflammation and oxidative stress (as discussed above) – key molecular contributors to the development and progression of sarcopenia (Buford et al., 2010; Marzetti et al., 2013; Roubenoff, 2003). Such changes may also be partly attributable to the common concomitant prevalence of insulin resistance and diabetes as these conditions are also associated with increased inflammation and oxidative stress (Liu et al., 2007; Monnier et al., 2006) as well as accelerated sarcopenia progression (O'Neill et al., 2010; Park et al., 2006; Sakkas et al., 2006).

Notably, altered function of the renin-angiotensin system (RAS) is a common identifying characteristic of both insulin resistance and hypertension (Henriksen and Prasannarong, 2013). Thus, RAS activity may be a key mechanistic contributor to functional decline in this population. Moreover, in addition to effects in mitigating hypertension, several antihypertensive drugs are also thought to have pleiotropic physiologic effects that extend beyond lowering blood pressure (Sica, 2011; Zoccali and Mallamaci, 2014). For instance, prior work has demonstrated the effects of angiotensin converting enzyme (ACE) inhibitors in endocrine signaling, regulation to tissue-specific oxidative stress and inflammation, and in the regulation of body composition (Carter et al., 2011; Giovannini et al., 2010; Marzetti et al., 2012). Epidemiological studies have also suggested that use of ACE inhibitors may indeed slow functional decline among seniors (Gambassi et al., 2000; Onder et al., 2002), though subsequent evidence suggests that these benefits may only exist when combined with physical exercise (Buford et al., 2012; Carter et al., 2012). However, future research is needed to fully elucidate the true role of ACE inhibitors and other antihypertensive medications in functional decline of hypertensive older adults.

3.3 Falls and Fractures

Among older adults, falls are the leading cause of both fatal and non-fatal injuries (Centers for Disease Control and Prevention). In fact, about 30% of community-living older persons fall each year and 20-30% of those who fall suffer moderate to severe injuries such as lacerations, fractures, or head trauma (Centers for Disease Control and Prevention, 2008; Nevitt et al., 1991; O'Loughlin et al., 1993; Sattin et al., 1990; Tinetti et al., 1995). In 2010, over 2.3 million nonfatal fall injuries were treated in U.S. emergency departments and over 662,000 of these patients were hospitalized (Centers for Disease Control and Prevention) – contributing to an estimated $28.2 billion annual healthcare burden related to falls (Centers for Disease Control and Prevention). The clinical burden on the patient is also quite significant as falls, particularly those causing injury, are independently associated with a subsequent decline in the ability to carry out important daily functions including bathing, dressing, shopping and housekeeping (Tinetti and Williams, 1997; Tinetti and Williams, 1998). Injurious falls also significantly increase risk of long-term nursing home admission

(Gill et al., 2013; Tinetti and Williams, 1997; Tinetti and Williams, 1998), further adding to the tremendous importance fall prevention among older adults.

Hypertension – or more commonly the use of antihypertensive drugs to control hypertension – has been commonly proposed as a risk factor for falls and fractures. The acute administration of antihypertensive medications can produce significant hypotension in older adults which may threaten cerebral perfusion thereby causing dizziness, syncope, and falls (Pepersack et al., 2013; Rutan et al., 1992; Shannon et al., 1986; Slavachevsky et al., 2000). This mechanism may explain recent findings indicating from hundreds of thousands of Canadian older adults indicating that initiation of antihypertensive treatment significantly increases risk of both falls (Incident Risk Ratio [IRR] = 1.69] and hip fractures [IRR = 1.43] within the first 45 days of treatment (Butt et al., 2012; Butt et al., 2013). To our knowledge these are the strongest data indicating the risks of early antihypertensive treatment on falls and fractures in the elderly. However, these negative effects on cerebral perfusion are thought to be short-term and wane after prolonged drug administration (Pepersack et al., 2013; Rutan et al., 1992; Shannon et al., 1986; Slavachevsky et al., 2000). As a result, Lai and Laio reiterated the importance of a key principle for medication prescription for older adults: “start low and go slow” (Lai and Liao, 2013).

Rather than hypotension and syncope, the longer-term risk for falls and fractures among older adults may be more related to the development of osteoporosis (El-Bikai et al., 2015; Vestergaard et al., 2009). Prior studies have demonstrated that bone loss is positively associated with both systolic and diastolic blood pressure (Metz et al., 1999; Rejnmark et al., 2006). Persons with hypertension have increased urinary calcium excretion and increased mobilization of calcium from the bones (Cappuccio et al., 1999; Metz et al., 1999; Perez-Castrillon et al., 2005). These changes are thought to occur either as a result of increased blood volume (as sodium intake is also positively associated with calcium excretion (Cappuccio et al., 1999)) or as a result of a disorder within the kidney tubule (Ilic et al., 2013). Diminished intake of vitamins D and K, which are each important to calcium absorption (Ilic et al., 2013), may also play a role. In either case, decreased serum calcium stimulates parathyroid hormone which further increases bone turnover (Perez-Castrillon et al., 2005). Meanwhile, angiotensin II activity has also been reported to contribute to osteoporosis by activating osteoclasts while impairing osteoblast activity (Asaba et al., 2009; Li et al., 2014; Shimizu et al., 2008). These findings are thus in line with two studies indicating the benefits of angiotensin receptor II antagonists (ARBs) and ACE inhibitors in the preservation of bone mass among mice and rats (Shimizu et al., 2009; Zhao et al., 2014).

However, such a finding of a benefit to these drugs remains inconclusive among humans. In fact, the only firm conclusion regarding the effect of individual drug classes appears to be the contraindication of loop diuretics as they increase risks of both orthostatic hypotension and osteoporosis (Arnold and Shibao, 2013; Ghosh and Majumdar, 2014; Ilic et al., 2013). Moreover, the overall association of antihypertensive use with older adults’ risk of falls and fractures remains hotly debated. Numerous studies exist to both support (Butt et al., 2012; Butt et al., 2013; Choi et al., 2015; Tinetti et al., 2014) and refute (Gribbin et al., 2010; Lipsitz et al., 2015; Margolis et al., 2014; Peters et al., 2010; Thorell et al., 2014; Wong et al., 2013; Zang, 2013) the notion that antihypertensive use increases the risk of falls and

fractures among older adults (Table 1). Numerous issues, including disparities between individuals included in observational studies versus clinical trials, treatment dose and duration, and patient age at time of medication initiation remain to be fully investigated to potentially reconcile the differences between these studies.

4. Future Directions – Potential Points of Intervention

Given the multi-dimensional health risks of hypertension in late life, treatment strategies to fully mitigate each of these risks among hypertensive older adults may be quite diverse (Figure 6). Development of such a treatment approach may also require different considerations for older adults than for younger populations (Lee et al., 2013; Schwartz, 2015). Moreover, rather than simply treating blood pressure, therapies designed to treat the underlying biologic mechanisms (i.e. inflammation, oxidative stress, endothelial dysfunction) may aid in the prevention of adverse clinical outcomes among this population. Notably, because of the underlying contributions of aging to changes in these biologic functions, interventions thought to promote longevity and/or healthy aging may also have utility for older adults with hypertension. A number of potential “longevity interventions” have been investigated to date, with varying degrees of promise (de Cabo et al., 2014). Though more study is certainly needed related to the use of these interventions in the context of aging per se, future studies might consider hypertension as a potential model to investigate their potential utility for promoting healthy aging.

Treatment strategies for late-life hypertension may also need to increasingly encompass lifestyle-related factors. For instance, the benefits of exercise and physical activity are well known and include contributions to improved cardiovascular fitness, bone health, as well as physical and cognitive functions (Fiuza-Luces et al., 2013). Yet despite the well-known benefits of exercise and the fact that a clinical recommendation doubles the likelihood of meeting exercise guidelines, nearly one in five hypertensive patients do not receive such a recommendation from their healthcare provider (Mu et al., 2015). Moreover, many healthcare teams do not involve consultation with a dietician despite the fact that diet plays an important role in maintaining blood pressure and maintaining overall health. These areas may represent opportunities for improvement through the creation of more comprehensive healthcare teams.

Increasing evidence also indicates that consideration of a hypertensive patient's genetic profile could improve care. In 2007, the U.S. Congress passed the Genomic and Personalized Medicine Act with the intent of advancing this new field of medicine (Obama, 2007). The importance of this area was later reiterated by the Institute of Medicine (Institute of Medicine, 2009) and the NIH Director (Hamburg and Collins, 2010). In light of this mandate, scientists have increasingly elucidated genetic factors which influence patients’ responsiveness to antihypertensive and other cardiovascular medications (Cavallari et al., 2011; Cooper et al., 2008; Hindorff et al., 2008; Johnson et al., 2009; McDonough et al., 2013; Shuldiner et al., 2009; Thompson et al., 2005). Though the application of findings from pharmacogenomics studies in hypertension are yet to be widely implemented clinically, this possibility may exist in the not too distant future as such program have already launched within academic healthcare settings (Johnson et al., 2013; Shuldiner et al.,

2013; Weitzel et al., 2014). Interestingly, genetics may also play a vital role in the efficacy of lifestyle-based interventions (e.g. diet and exercise) as well. For instance, a number of studies have reported that extreme variability exists in individual responses to exercise even under well-controlled, experimental conditions (Bouchard, 1995; Bouchard and Rankinen, 2001; Kohrt et al., 1991) and genetics appears to play an important role in determining the extent of these differences (An et al., 2003; Bouchard et al., 2011; Buford et al., 2014; Giaccaglia et al., 2008; Rankinen et al., 2012; Rice et al., 2002; Thompson et al., 2004). Similarly, several large-scale clinical trials (e.g. LOOK AHEAD, DASH, and VISP) have also identified genetic factors which contribute to determining responsiveness to dietary interventions (Hsu et al., 2011; McCaffery et al., 2012; Svetkey et al., 2011). Accordingly, though extensive research remains to be conducted in this area, genetic profiling may at some point aid in the prescription of both pharmaceutical and lifestyle-based interventions for the treatment of hypertension, even in late-life.

Despite the potential utility of each of the aforementioned approaches, the most promising interventions for treating the multiple risks of late-life hypertension may be those which incorporate multiple components. Increasing evidence indicates that clinicians and scientists should focus not only on drug-drug interactions (Hines and Murphy, 2011) but may also consider other potential interactions between treatments. For instance, exercise and prescription medications exhibit a variety of biologic interactions whereby one intervention can be critical to the proper prescription of the other (Lenz et al., 2004). In one direction, exercise has the ability to alter drug pharmacokinetics by altering hemodynamic and metabolic parameters (Lenz et al., 2004; Lenz, 2011). Conversely, many drug therapies have the ability to impact exercise performance – e.g. the attenuated heart rate response and decreased cellular oxygen intake induced by β-blockers (Kaiser et al., 1985; Tesch, 1985) or skeletal muscle weakness associated with statin use (Baer and Wortmann, 2007; Thompson et al., 2003). While these treatments may have negative interactions that must be considered, they may also prove to be beneficial as well – as evidenced by the earlier reference to potentially beneficial effects of antihypertensive medications and physical exercise on physical function (Buford et al., 2012). Thus, it will be important to continue to develop our collective understanding of interactions between not only medications and exercise but other combinations of interventions as well.

Finally, as with genetics, an increased consideration of biologic sex in intervention development may contribute to improved health outcomes among hypertensive older adults. As depicted in Figure 1, rates of hypertension among younger women are much lower than age-matched men but dramatically increase in late middle-age (Kearney et al., 2005; Wiinberg et al., 1995). This age-related increase in the prevalence of hypertension among women is attributable at least partially to the rapid decrease in sex hormones (e.g. estrogen) accompanying menopause (Maranon and Reckelhoff, 2013; Maric-Bilkan et al., 2014; Staessen et al., 1997). While the influence of menopause on increases in blood pressure is well-recognized, the mechanisms which underlie this change are still being elucidated. Presently, sex differences in several physiologic mechanisms including sympathetic nerve activity, cardiovascular hemodynamics, and immunomodulation/inflammation have been implicated as potential causal factors (Hart et al., 2012; Hay, 2016; Sandberg et al., 2015). Moreover, sex differences are also known to influence a variety of age-related physiologic

changes in several tissues (e.g. brain, skeletal muscle, bone) which are relevant to collateral health outcomes among hypertensive older adults (Hay, 2016; Pendergrass et al., 2008; Puntus et al., 2011). Continued investigation is needed to fully elucidate the mechanisms which influence differential rates of hypertension among older adults and to determine if sex influences rates of dementia, physical disability, and falls/fractures among this population. Once these questions are answered, it may be necessary to develop differential treatment strategies for older men and women with hypertension. At minimum, sex may be at least more carefully considered as a relevant variable in the clinical decision making process for this population.

5. Conclusion

In conclusion, hypertension is a highly prevalent condition that dramatically rises in incidence with increasing age. Several key mechanisms, represented by the Vascular Health Triad, influence the development of cardiovascular and other “collateral” risks among older adults. Targeting these mechanisms, in addition to blood pressure control, may represent important points of intervention for preventing adverse health events in this growing population. Future research is needed to identify efficacious methods to prevent the variety of potential health events posed by hypertension in late life. The use of multi-component interventions and individual health characteristics appears to hold tremendous promise for substantially advancing treatment options according to the principles of precision medicine. Yet further research is still needed to evaluate the influence of relevant biologic characteristics – including genetics and biologic sex – on the efficacy of potential interventions. I look forward to witnessing continued advances in this area to hopefully reduce the number of older adults with hypertension and the overall health burden among those with the condition.

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Highlights

- Hypertension is a highly prevalent condition with numerous health risks, and the incidence of hypertension is greatest among older adults.
- In addition to cardiovascular risk, there are a number of collateral risks of hypertension among older adults including dementia, physical disability, and falls/fractures.
- Several key mechanisms – including inflammation, oxidative stress, and endothelial dysfunction – are common to biologic aging and hypertension development and appear to have key mechanistic roles in the development of the cardiovascular and collateral risks of late-life hypertension.
- This review highlights the multi-dimensional risks of hypertension among older adults and discuss potential strategies for treatment and future areas of research for improving overall care for older adults with hypertension.

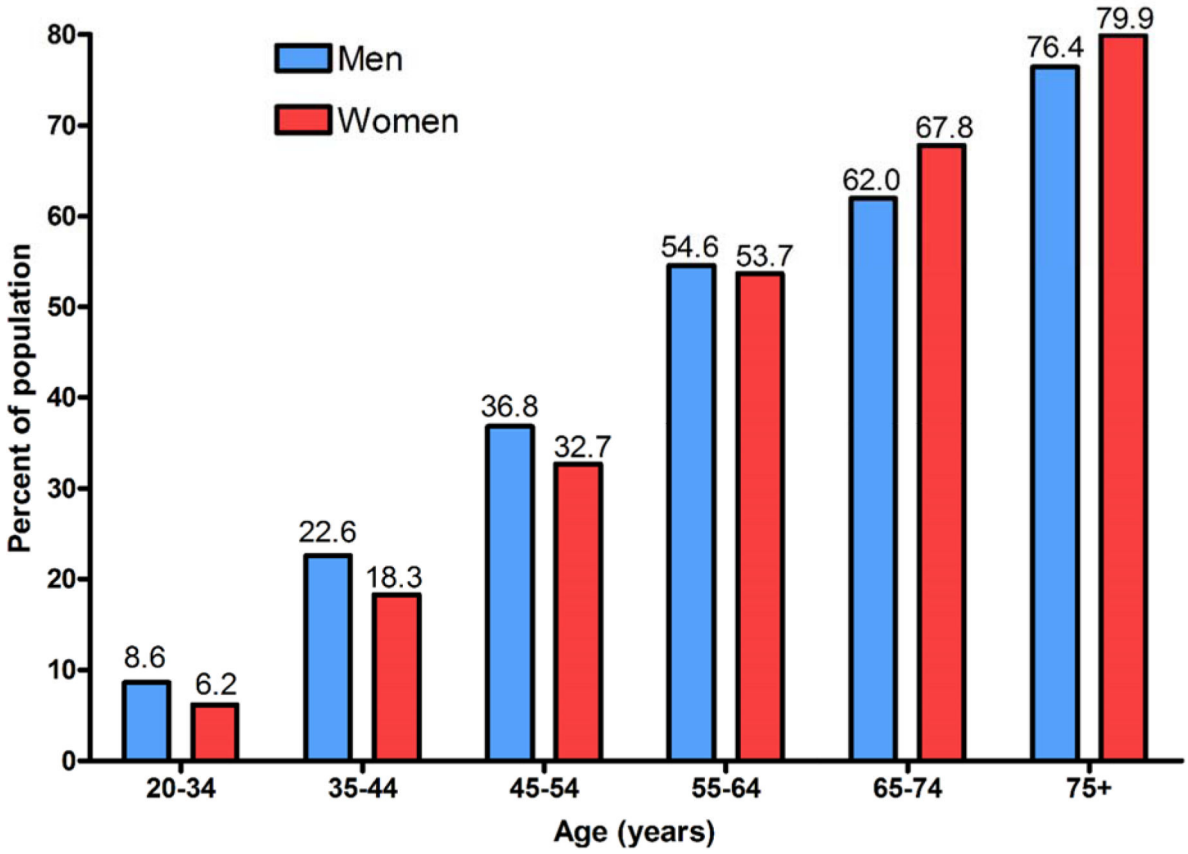

Figure 1.

Prevalence of hypertension among adults by age and sex according to the National Health and Nutrition Examination Survey: 2007-2012. Re-created from Chart 9.1 in Mozaffarian et al.(Mozaffarian et al., 2015)

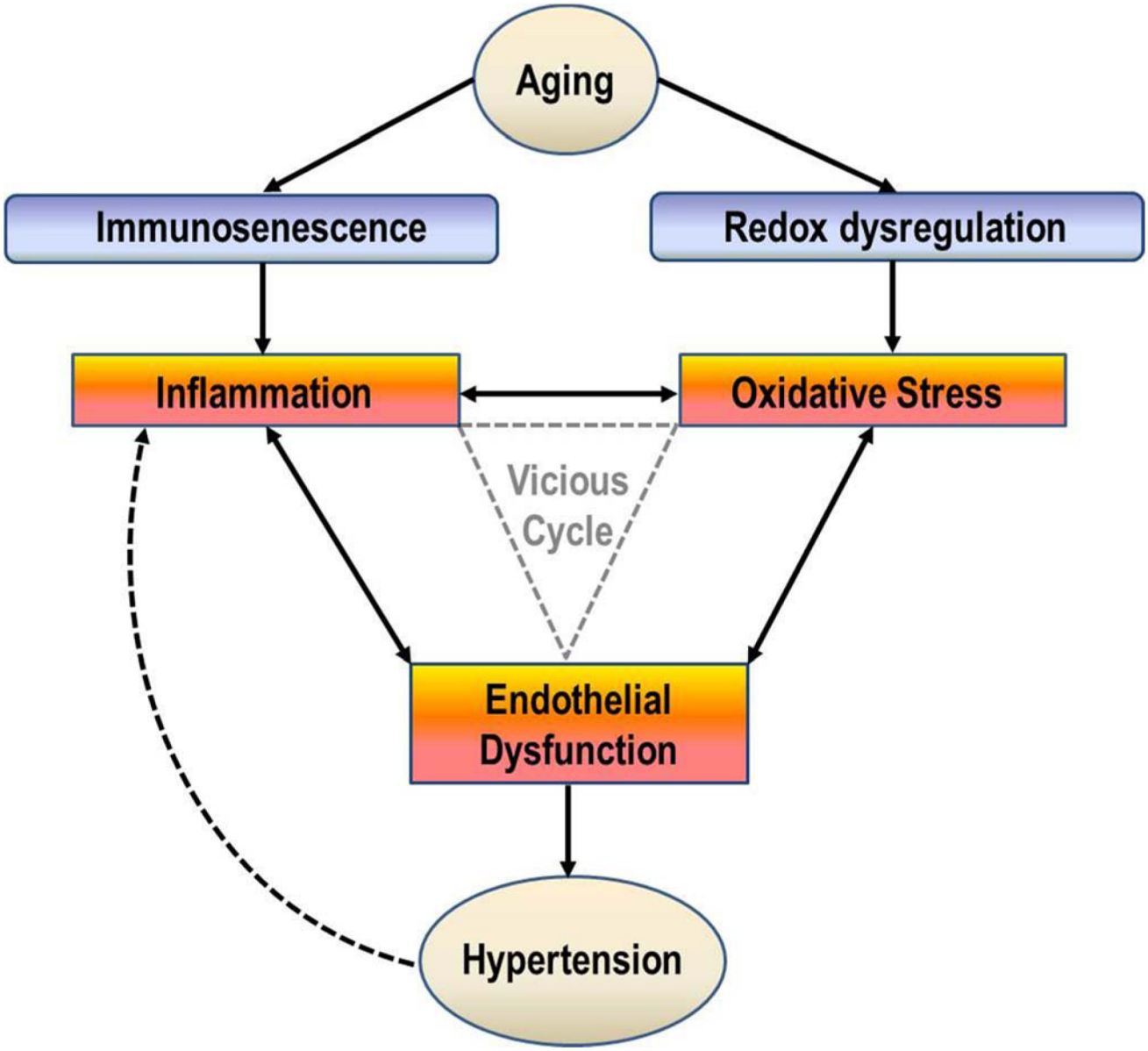

Figure 2.
Simplified schematic illustrating common relationships of aging and hypertension with inflammation, oxidative stress, and vascular dysfunction – i.e. Vascular Health Triad. Modified from Figure 2 in Wadley et al.(Wadley et al., 2013) (Figure 2) and Figure 1 in Dinh et al.(Dinh et al., 2014)

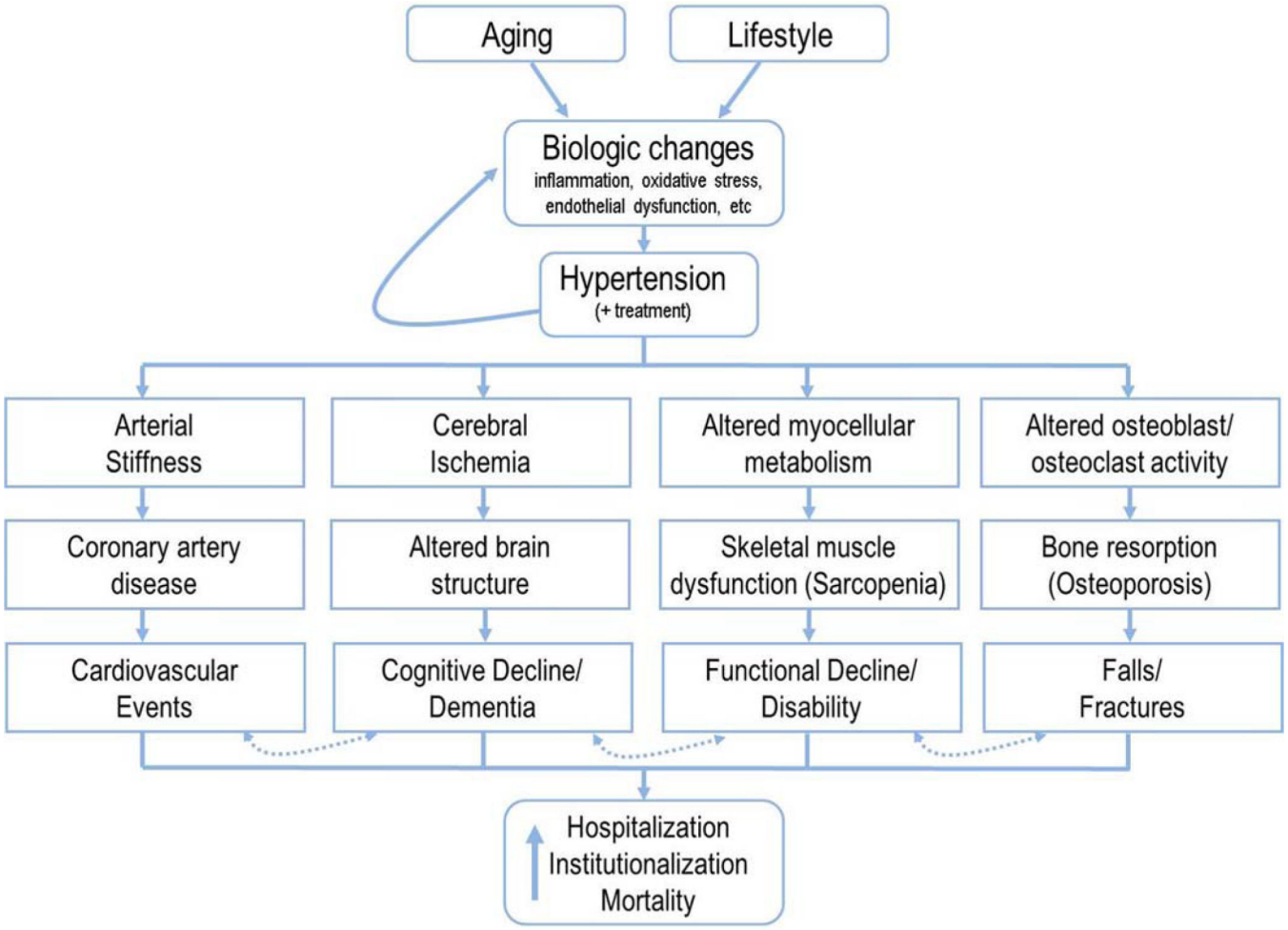

Figure 3.

Simplified schematic of the multi-dimensional health risks for older adults with hypertension. Note the dashed arrows indicating the inter-related nature of health outcomes whereby the presence of one condition tends to increase risk of one or more of the others.

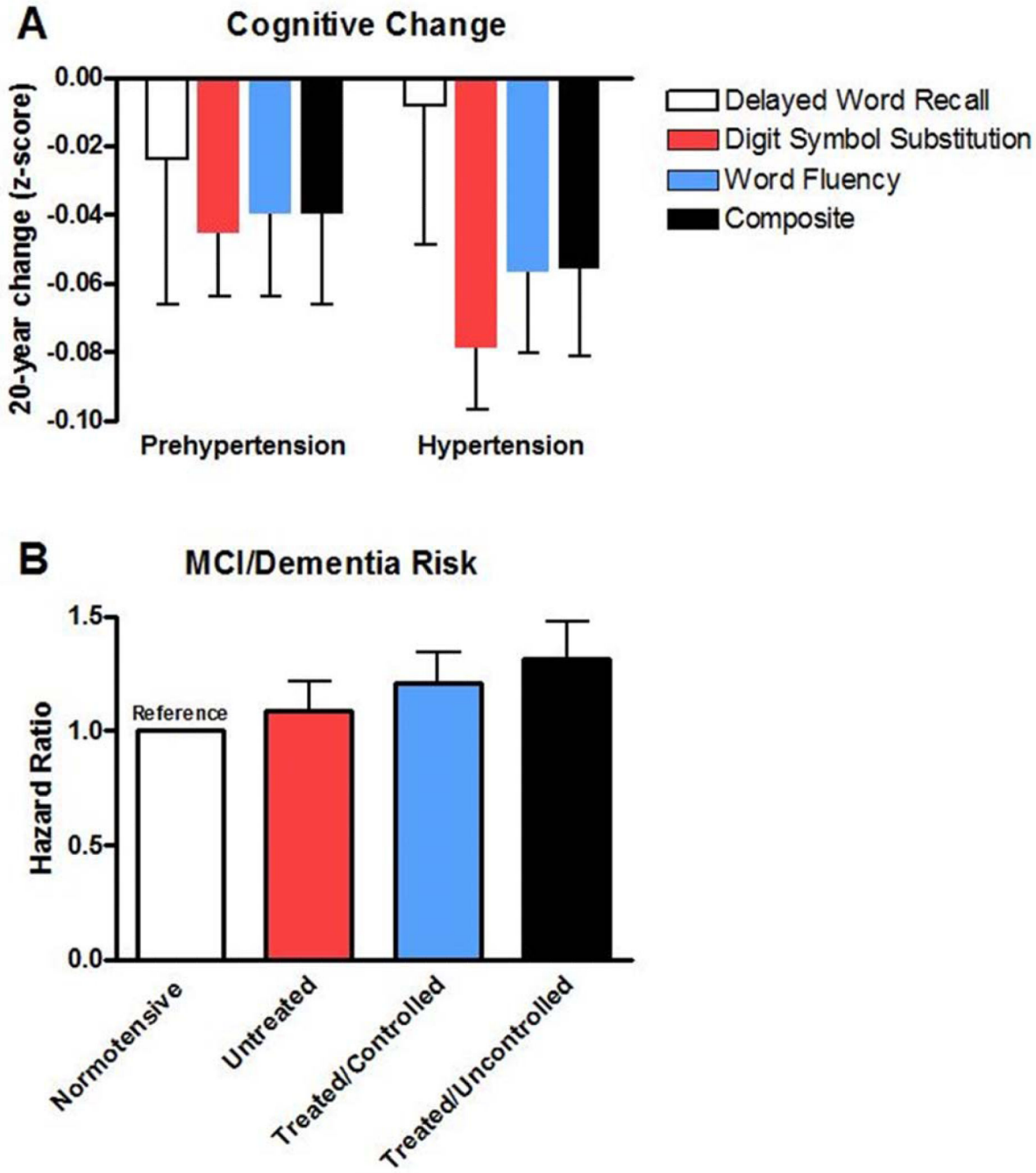

Figure 4.

Risks of cognitive decline and development of mild cognitive impairment (MCI)/dementia among hypertensive older adults. Panel A): Change in objective measures of cognition over 20 years among pre-hypertensive and hypertensive persons aged 48-67 years at baseline. Created from data in Table 2 of Gottesman et al.(Gottesman et al., 2014) (N = 13, 476) and indicate z-score changes relative to normotensive individuals. A z-score change of 0 indicates similar changes to normotensive individuals. Panel B): Risk of developing MCI or dementia over a mean follow-up of 9.1 years among 6,426 women aged 65-79 years.

Created from data in Table 1 of Haring et al.(Haring et al., 2015). Hazard ratio (HR) indicates risk of experiencing MCI/dementia compared to normotensive individuals where each 0.1 increase in HR indicates a 10% increase in risk.

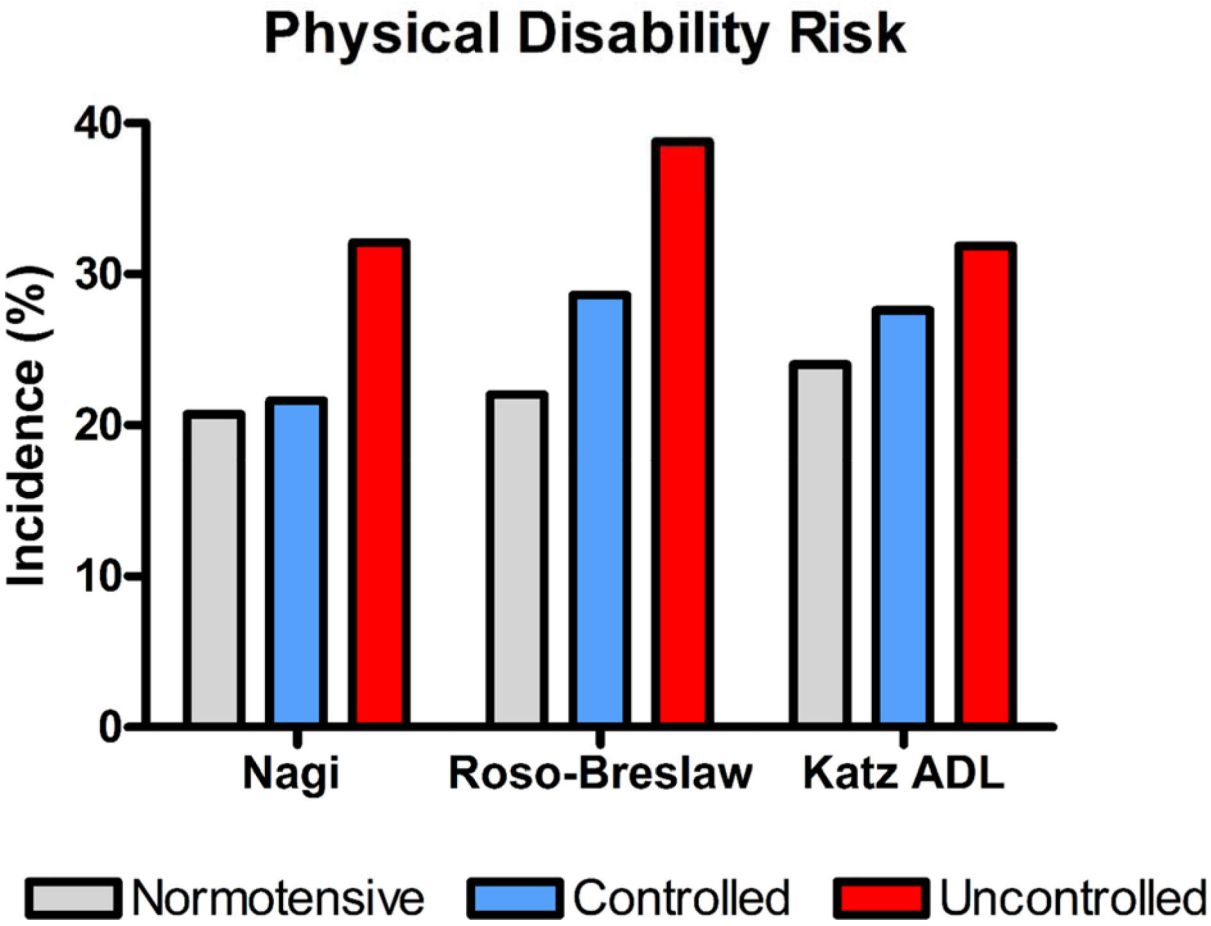

Figure 5.

Risk of developing physical disability among older adults according to hypertension status, i.e. normotensive, controlled hypertension, or uncontrolled hypertension. Created from data in Table 3 of Hajjar et al.(Hajjar et al., 2007) Data reflect rates of disability based on three validated disability scales: the Nagi Scale, Rosow-Breslaw Scale, and Katz Activities of Daily Living (ADL) Scale.

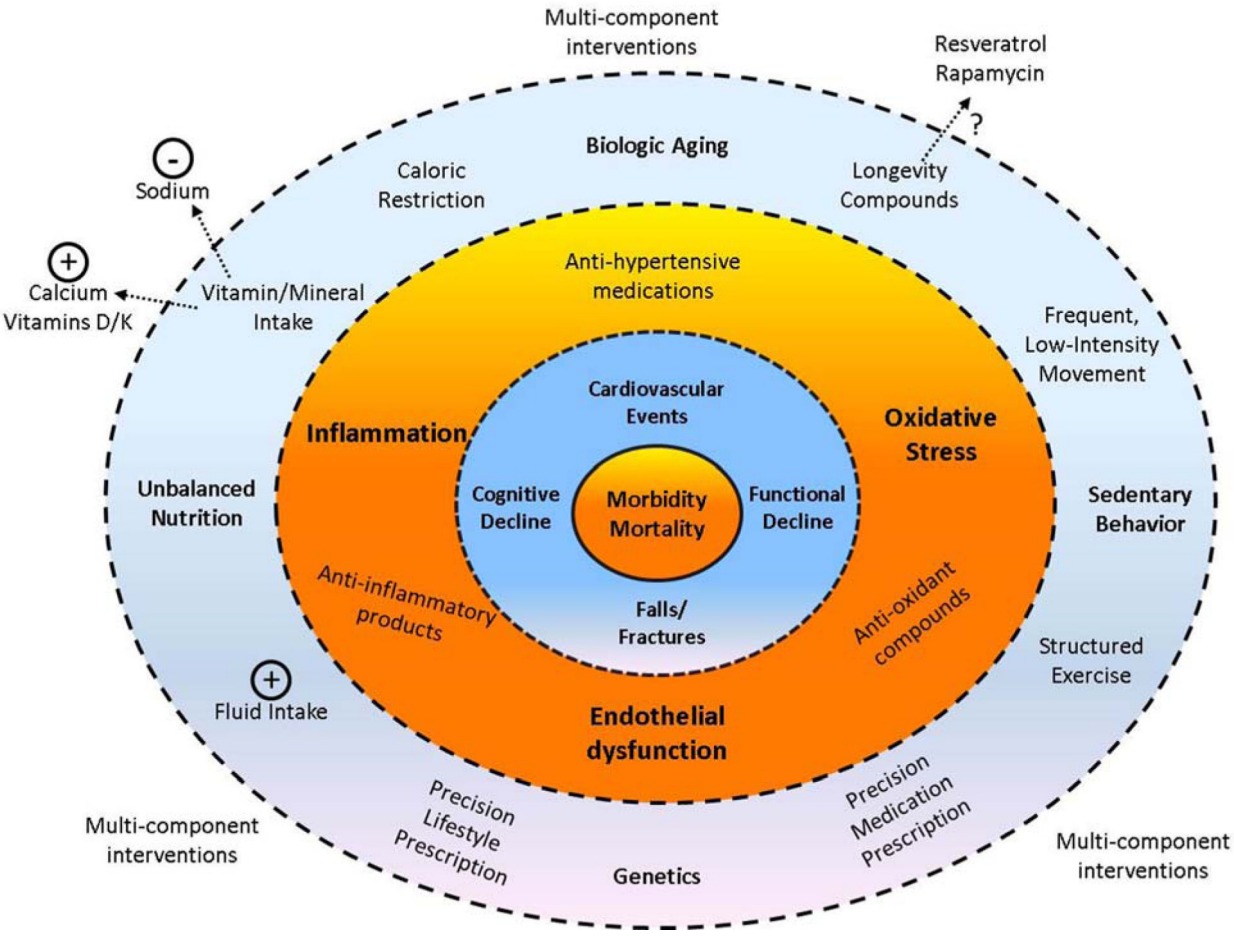

Figure 6.

Conceptual figure illustrating the potential points of intervention for the multi-dimensional risks of hypertension among older adults. Inner rings indicate the potential health risks of late-life hypertension; middle ring indicates mechanistic risk factors exacerbated by hypertension (bold) and potential interventions to combat these risks (non-bold); outer ring indicates concomitant risk factors which contribute to both hypertension and associated health outcomes (bold) as well as potential interventions to combat these risks (non-bold).

Table 1

Selected studies of antihypertensive treatment and fall/fracture risk among hypertensive older adults

Study	Study type	Sample size	Study Dates	Participants	Outcome	Results	Overall Effect on Fall/ Fracture Risk
Gribbin et al. 2010(Gribbin et al., 2010)	Retrospective, matched case-control study	Cases = 9,682 Controls = 52,100	2003-2006	British patients ≥ 60 yr: Cases = those with first recorded fall	Falls	Increased risk with thiazide diuretic prescription (aOR = 1.28) Decreased risk with BB prescription (aOR = 0.90) No other classes significantly associated	↔
Peters et al. 2010(Peters et al., 2010)	Randomized controlled trial	N = 3,845	2000-2007 (mean follow-up = 2.1 yr)	Hypertensive older adults 80+ yr (Multi-national)	Fracture	Treatment with a thiazide diuretic and ACEi did not increase and trended toward decreasing fracture risk (HR = 0.69)	↔
Butt et al. 2012(Butt et al., 2012)	Population-based, self-controlled case series	N = 310,591	2000-2009	Community-dwelling, hypertensive Canadian elderly: 80.8 ± 7.3 yr	Fracture	43% increased risk of hip fracture in first 45 days of treatment. Results consistent across drug classes but highest risk with ACEi (IRR = 1.54) and BB (IRR = 2.08) use.	↑
Butt et al. 2013(Butt et al., 2013)	Population-based, self-controlled case series	N = 543, 572	2000-2009	Community-dwelling, hypertensive Canadian elderly: 80.8 ± 7.3 yr	Falls	94% increased risk of fall during first 14 days of treatment; 69% increased risk in first 45 days. Generally consistent across drug classes.	↑
Wong et al. 2013(Wong et al., 2013)	Prospective cohort study	N = 520	2008-2009; 1-yr follow-up	Community-dwelling older adults from Sydney (AUS): 79.4 ± 4.4 yr	Falls	Antihypertensive drugs overall not associated with falls, though trend toward risk reduction (aOR = 0.69) Reduced risk of falls with ARB use (aOR = 0.68)	↔
Zang et al. 2013(Zang, 2013)	Systematic review and meta-analysis	62 articles	1975-2012	Cohort and case-control studies: patient age 60+ years	Fall injuries	No significant association between antihypertensive use and fall injuries	↔
Thorell et al. 2014(Thorell et al., 2014)	Retrospective cohort study	N = 38, 407	2006-2007	Swedish older adults (75+ year)	Fracture	No class of antihypertensive drug was associated with increased risk of hip fracture	↔
Tinetti et al. 2014(Tinetti et al., 2014)	Retrospective nationwide medical claim study	N = 4, 961	2004-2007	Community-dwelling, hypertensive	Serious fall injuries	Increased risk with both moderate (aHR = 1.40) and	↑

Study	Study type	Sample size	Study Dates	Participants	Outcome	Results	Overall Effect on Fall/ Fracture Risk
				American elderly: 80.2 ± 6.8 yr American elderly: 80.2 ± 6.8 yr		high (aHR = 1.28) levels of AHT use. No specific class associated with increased risk.	
Margolis et al. 2014(Margolis et al., 2014)	Randomized controlled trial	N = 3,099	2006+ (mean follow-up = 4.9 years)	Hypertensive adults (Mean = 62 years) with Type 2 diabetes (USA/ Canada)	Falls/fractures	Intensive BP control not significantly different from standard control for risk of falls (RR = 0.84) and non-spine fractures (HR = 0.79)	↔
Choi et al. 2015(Choi et al., 2015)	Retrospective nationwide medical claim study	N = 528, 522	2007-2011	Middle- and older-aged (50+ year), hypertensive Koreans	Fracture	Increased risk with all classes expect ARBs Highest fracture rate among AB (aHR = 2.26) and ACEi (aHR = 1.68)	↑
Lipsitz et al. 2015(Lipsitz et al., 2015)	Prospective observational study	N = 598	Dates NR: 1-yr follow-up	Hypertensive older adults from Boston, MA (USA): 78.4 ± 5.4 yr	Falls	Overall AHT use not significantly associated with falls. CCB use associated with reduced risk of falls (aOR = 0.62). ACEi use associated with reduced risk of injurious falls (aOR = 0.62).	↔

Abbreviations: aOR= adjusted odds ratio; HR = hazard ratio; IRR = incidence rate ratio; RR = relative risk; AB = alpha-blocker; BB = beta-blocker; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; NR = not reported