

# Heart disease as a risk factor for dementia

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**Abstract:** As life expectancy lengthens, dementia is becoming a significant human condition in terms of its prevalence and cost to society worldwide. It is important in that context to understand the preventable and treatable causes of dementia. This article exposes the link between dementia and heart disease in all its forms, including coronary artery disease, myocardial infarction, atrial fibrillation, valvular disease, and heart failure. This article also explores the cardiovascular risk factors and emphasizes that several of them are preventable and treatable. In addition to medical therapies, the lifestyle changes that may be useful in retarding the onset of dementia are also summarized.

**Keywords:** Alzheimer's disease, coronary artery disease, myocardial infarction, atrial fibrillation, valvular disease, heart failure, cardiovascular risk factors, prevention

## Introduction

Dementia is a common neurological disorder and is an increasingly prevalent problem, especially among the elderly population. It is estimated there are upwards of 24.3 million cases of dementia presently, with that number expected to double every 20 years, resulting in 81.1 million cases in 2040.<sup>1</sup> The frequency of dementia is compounded by the growing worldwide population of the elderly (>65 years old), which is estimated to increase (from 606 million in 2000) to nearly 2 billion in 2050.<sup>2</sup>

Dementia is a loss of brain function and overall global cognitive ability. It is the result of progressive impairment in more than one cognitive domain, leading to an eventual loss of the ability to perform all tasks of daily living.<sup>3</sup> Types of dementia include Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia, dementia with Lewy body, Parkinson's disease-related dementia, and dementia as a result of disease (for example AIDS or multiple sclerosis).<sup>4</sup> Cognitive impairment is a broad term that generally describes a decline in cognitive functions, and the severity of the impairment ranges from mild cognitive impairment (MCI) to dementia.

When investigating the effects of cognitive decline, many studies use MCI as the main outcome, instead of dementia. It is very important to note that while MCI is only considered an intermediate stage between a normal cognitive state and dementia, individuals with MCI are at an increased risk of progression to dementia, especially in the elderly.<sup>5,6</sup> Multi-domain MCI, amnesic MCI (aMCI), and non-amnesic MCI (naMCI) all progress to different types of dementia, with the estimated annual progression rates of 12.2%, 11.7%, and 4.1%, respectively.<sup>7</sup> Therefore, even though dementia may evolve from MCI, the increased risk of progression means that it is still important to discuss studies whose main outcome is MCI, as we have done here. By contrast, while the

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presence of the APOE e4 allele is strongly associated with cardiovascular disease as well as cognitive impairment and dementia, it will not be discussed in detail in this review.

Heart disease is defined as any condition that impairs cardiac function regardless of the specific modality that is affected. Heart disease is a growing problem, and the resultant vascular insufficiency has the potential to impair function in other organs, including the brain.<sup>8</sup> There is an expanding body of literature implicating heart disease as a risk factor for dementia. In addition, a number of studies suggest that cardiovascular risk factors are independently associated with the development of dementia. These risk factors include hypertension, hypercholesterolemia, diabetes, obesity, and smoking. Even though there are many types of dementias and a wide spectrum of vascular cognitive impairment, this review will focus mainly on the two most common, AD and VaD,<sup>9,10</sup> as well as the most common variety, mixed dementia that is characterized by multiple cerebral pathologies with prominent vascular involvement.<sup>11</sup> The purpose of this review is to present the current knowledge base regarding heart disease and its associated risk factors in relation to dementia.

## Dementia

While it may not be surprising that heart disease is a significant cause of VaD, it is perhaps unexpected that more studies are also linking it to AD. VaD and AD have very different underlying pathologies. The pathology of AD is defined by the accumulation of neuritic plaques ( $\beta$ -amyloid ( $A\beta$ )) in the extracellular neuropil and neurofibrillary tangles (composed of tau protein) in neurons,<sup>12</sup> while VaD is characterized by a cerebrovascular pathology, exhibiting white matter hyperintensities, lacunar infarctions, and ischemic periventricular leukoencephalopathy.<sup>13,14</sup> There is a large overlap between AD and VaD in regard to clinical features and neuropathological changes.<sup>15</sup> More specifically, both dementias can occur in tandem and share common cardiovascular risk factors which when clustered together can increase the likelihood of dementia independently or through the increased risk of heart disease.<sup>16–20</sup> For these reasons, a review by Bowler and Hachinski defined AD as a vascular disorder more than a decade ago.<sup>21</sup>

## Heart disease as a risk factor for dementia

Reduced cerebral blood flow (CBF) due to heart disease of any kind worsens the vascular homeostasis of the brain, and magnifies any cognitive problems caused by the buildup

of tau and  $A\beta$  proteins. A recent study has shown that dementia patients with a prior history of heart disease are more likely to have structural and functional cardiac abnormalities compared with controls.<sup>22</sup> Using cardiac magnetic resonance imaging (MRI) as a method to measure cardiac function, this study has also shown that cardiac index, as a marker of overall cardiac function, is positively related to total brain volume and processing speed.<sup>23</sup> Positive associations have been shown between ischemic heart disease and cognitive impairment on the one hand, and between atherosclerotic cardiovascular disease and cognitive decline on the other.<sup>24–26</sup> As well, an association between the degeneration of myocardial post-ganglionic sympathetic nerves and the Lewy body variant in Parkinson's disease has been reported.<sup>27</sup> It is important, however, to focus on more specific types of heart disease and dementia in order to clarify the relative contribution of each entity to cognitive impairment.

## Coronary artery disease

The association between coronary artery disease and cognitive decline, including dementia, is strong. Atherosclerosis plays a major role in the development of both coronary artery disease and dementia. In the Cardiovascular Health Study cohort, the incidence of dementia was higher in those with prevalent coronary artery disease,<sup>28</sup> and several studies have confirmed that coronary artery disease is associated with cognitive impairment,<sup>29–31</sup> reduced hippocampal volume,<sup>32</sup> dementia due to platelet hyperactivity,<sup>33</sup> and increased senile plaque formation in cortical areas of the brain.<sup>34</sup> A recent study by Graban and colleagues showed that coronary artery disease was observed more frequently in VaD patients.<sup>35</sup> Cross-section analysis of the AGES-Reykjavik Study by Vidal and colleagues showed that lower scores on each cognitive domain were strongly related to atherosclerotic burden, indirectly estimated by coronary artery calcium (CAC) load. The percentage of dementia significantly increased with quartiles of CAC (Q1 10.3%, Q2 21.8%, Q3 29.1%, Q4 38.8%), while gray matter, white matter, and total brain tissue volumes decreased.<sup>36</sup>

Coronary artery disease may lead to dementia through its association with brain small vessel disease.<sup>37,38</sup> Small vessel disease in turn disturbs CBF regulation and perfusion, disrupts the blood–brain barrier, and leads to an increased susceptibility to neurological insults.<sup>39</sup> In addition, the failure in small vessel disease to clear excess  $A\beta$  produced by cortical neurons contributes to cerebral hemorrhaging and AD pathology.<sup>40,41</sup>

## Atrial fibrillation (AF)

AF, the most common cardiac arrhythmia, is an important and modifiable cause of ischemic stroke and results in considerable physical and cognitive disability. While there is still some uncertainty regarding the relationship between AF and dementia in the absence of stroke,<sup>42,43</sup> it is clear that AF can be considered a contributor to the onset of dementia.<sup>44–47</sup> Moreover, there is growing evidence supporting AF as a risk factor for dementia without stroke.<sup>48–50</sup>

Recent data also show an association between AF and AD progression.<sup>51</sup> In a study of 37,025 patients, 10,161 (27%) developed AF and 1535 (4.1%) developed dementia, and AF was independently significantly associated with senile, vascular, and AD dementia.<sup>52</sup> The cross-sectional analysis in the Rotterdam study reported that AF exerts its effects only partly through stroke and showed a significant association between AF and both dementia and cognitive decline, where dementia was twice as common among AF patients than controls.<sup>53</sup> The strongest association was for AD with cerebrovascular disease, rather than VaD.<sup>53</sup> In a recent analysis of the ONTARGET and TRANSCEND studies by Marzona and colleagues, it was determined that AF was associated with an increased risk of cognitive decline (hazard ratio [HR] 1.14, 95% confidence interval [CI] 1.03–1.26) and new dementia (HR 1.14, 95% CI 1.14–1.49).<sup>54</sup> In another longitudinal, community-based cohort study by Miyasaka and colleagues, 299 AF subjects were diagnosed with dementia, with an estimated overall incidence rate of 22.5 per 1000 person-years, suggesting a risk of dementia following the development of AF.<sup>55</sup> Finally, studies show that AF is associated with brain abnormalities, more specifically, a smaller hippocampal volume and left ventricular hypertrophy.<sup>56</sup> In addition, in individuals suffering from AF, learning, memory, attention, and executive functions are poorer,<sup>57</sup> consistent with other studies showing decreased scores on cognitive domain tests in patients with AF.<sup>58,59</sup>

Several mechanisms have been suggested linking AF and dementia. In AF, irregular rapid ventricular rates could lead to decreased cerebral perfusion due to low cardiac output.<sup>60–62</sup> Another suggested mechanism is the increase in risk of covert cerebral infarction and transient ischemic attacks.<sup>63–65</sup> AF also leads to a hypercoagulable state, which may give rise to subclinical cerebral embolism.<sup>66,67</sup> Finally, experimental data suggest that cerebrovascular disease may precipitate neurodegenerative changes seen as white matter hyperintensities on MRI.<sup>68,69</sup>

## Myocardial infarction (MI)

There are a limited number of studies associating MI with dementia. Men with unrecognized MI have an increased risk of stroke.<sup>70</sup> Those with MI also share a genetic background with AD, involving abnormalities in cholesterol metabolism and an upregulation in inflammation. Some studies have reported that there is a higher risk of cognitive impairment after MI due to brain hypoperfusion,<sup>71</sup> and a cross-sectional evaluation in the Rotterdam study showed a positive association between cognitive impairment and prior MI.<sup>72</sup> In addition, the Bronx Aging Study showed that women with a history of MI had a fivefold increase in the risk of dementia.<sup>73</sup> Ghara-cholou and colleagues showed that older subjects with prior MI had measurable cognitive impairment prior to dementia.<sup>74</sup> Finally, using the results from the Rotterdam and Rotterdam Scan Study, Ikram and colleagues demonstrated that in men, unrecognized MI was associated with an increased risk of dementia (HR 2.14, 95% CI 1.37–3.35), increased white matter lesion load, and brain infarctions,<sup>75</sup> supporting the possibility that small vessel disease may be one mechanism by which the risk of dementia increases in MI patients.

However, the impact of MI on dementia remains controversial, and findings lack consistency.<sup>76</sup> Studies such as the Honolulu-Asia Aging Study found no association between MI and later cognitive impairment.<sup>77</sup> In a population-based study by Bursi and colleagues, the frequency of MI preceding dementia was identical in the index cases and the control subjects, thus showing no significant evidence of a positive association between MI and dementia.<sup>78</sup> Therefore, further research is needed to enhance our understanding of the influence of MI on subsequent dementia.

## Valve disease

Studies have reported significant aortic and mitral valve disease in AD subjects compared with a non-demented control group at autopsy.<sup>79</sup> Boudoulas and colleagues concluded that left atrial dysfunction increased with chronic mitral valve disease, contributing to AF, thereby increasing risk of dementia.<sup>80</sup> This is supported by work done by Rodriguez and colleagues in a community-based study of 2680 participants from the Cardiovascular Health Study who underwent MRI analysis. Participants, without prior history of stroke, with left-sided annular or valvular calcification had a 33% greater risk of covert brain infarcts.<sup>81</sup> Coupled with other studies demonstrating the presence of brain infarcts in association with calcification of the aortic valve, this supports the association between valve disease and a higher risk of both stroke and cognitive decline.<sup>82–84</sup> Thus, evaluation of patients

for aortic and mitral valve disease may be important in the work-up of dementia and its prevention.

## Heart failure (HF)

HF is defined as insufficient cardiac pump function to provide adequate perfusion to body organs. HF is a growing problem with significant prevalence and mortality rates. In the elderly (>65 years of age), 6%–10% of the population has a diagnosis of HF.<sup>85</sup> Any number of underlying heart conditions and diseases can lead to HF, including those mentioned in previous sections. According to the Heart-Mind Study, participants with both HF and coronary artery disease were found to experience similar declines in cognitive function versus non-controls with HF but not coronary artery disease.<sup>86</sup>

Studies have reported that HF is associated with both cognitive impairment and dementia.<sup>87–92</sup> In a recent pilot case-control study, HF patients had lower scores on a neuropsychological battery designed to assess cognitive functions for dementia than controls in visuospatial, executive function, visual memory, and verbal learning tasks, and showed structural brain changes including right medial temporal lobe atrophy.<sup>93</sup>

The pathophysiological mechanisms that underlie the association between HF and cognitive impairment and dementia are still being investigated. Reduced CBF seems to worsen cognitive impairment associated with HF, and those with heart transplantation had a restoration of CBF and improved cognitive performance.<sup>94–96</sup> In HF, low cardiac output combined with impaired cerebral autoregulatory mechanisms, may result in decreased CBF leading to the association with cognitive impairment and dementia.<sup>23,97,98</sup> HF is also a risk factor for multiple cerebral emboli, which could lead to cognitive impairment.<sup>99</sup>

## Cardiovascular risk factors

Not only is heart disease a risk factor for dementia, but more studies are implicating cardiovascular risk factors as both increasing the risk of dementia through risk of heart diseases and stroke,<sup>100</sup> and as independent risk factors for dementia.<sup>101</sup> Etorre and colleagues reported that in a group of MCI patients, 60% of them eventually developed dementia, and all subgroups with cardiovascular risk factors had a higher conversion rate to AD.<sup>102</sup> In addition, many cardiovascular risk factors occur in conjunction with each other, compounding the risk of subtle gray matter changes and subclinical cerebrovascular abnormalities in the brain, as well as dementia.<sup>103–106</sup> When combined with the presence

of the APOE  $\epsilon$ 4 allele and stroke, vascular risk factors lead to both vascular and AD pathology.<sup>107,108</sup>

## Hypertension and hypotension

High blood pressure (BP) is a major risk factor for cerebrovascular disorders, including stroke, ischemic white matter lesions, and cerebral infarcts. It is well known that these disorders increase the risk of dementia.<sup>64,109,110</sup> Less known is that hypertension is an independent risk factor for dementia. The association between hypertension and risk of dementia is prominent, and while a rare study has failed to show this relationship,<sup>111</sup> the overwhelming majority show a positive association. The high prevalence of hypertension, especially between the age of 30 and 50 years, shows that insight into this relationship is important due to the potential it offers for prevention of cognitive impairment, as we discuss below.

Studies have shown that hypertension is associated with both VaD and AD.<sup>112</sup> In a review from the *American Journal of Hypertension* by Nagai and colleagues, out of seven cited studies, only one did not report that high systolic BP (SBP) and/or diastolic BP (DBP) were risk factors for dementia incidence.<sup>113</sup> Yamada and colleagues showed that elderly individuals with increased hypertension and SBP had increased risk of VaD.<sup>114</sup> The Cache County study by Mielke and colleagues further showed that SBP > 160 mmHg at baseline was associated with higher rates of cognitive decline in the elderly, compared with those with lower SBP. A study by Shah and colleagues showed a significant interaction between DBP and plasma A $\beta$  levels, indicating that the A $\beta$ -related risk for AD was higher when BP was higher.<sup>115</sup>

Hypertension is also associated with an increased pulse pressure. In the Kungsholmen Project, patients aged  $\geq$  75 years with higher pulse pressure had a greater chance of developing dementia than controls. In comparison with the median tertile of pulse pressure (70–84 mmHg), those with higher pulse pressure had relative risk of 1.4 (95% CI 1.0–2.0;  $P = 0.04$ ) for AD and 1.3 (95% CI 0.9–1.7) for dementia.<sup>116</sup> Midlife BP has been reported to have greater effect on the development of AD than late-life hypertension.<sup>117</sup>

Different hypotheses have been offered to elucidate the pathophysiological links between hypertension and dementia. These include hypertension causing vascular alterations leading to lacunar and cortical infarcts and leukoariosis, hypertension being responsible for cerebrovascular disease, and hypertension leading to neurobiologic alterations, such as the accumulation of  $\beta$ -amyloid, causing the onset of dementia. More specifically, hypertension may lead to

hypoperfusion, or hypoxia of the brain, which can lead to AD pathology.<sup>110,118</sup> Individuals who underwent antihypertensive treatment had lower neuritic plaques and neurofibrillary tangles than controls.<sup>119</sup> Hypertension also has an effect on the blood–brain barrier, leading to inflammation or the accumulation of  $\beta$ -amyloid, causing the development of AD. Brain imaging studies, such as the Honolulu-Asia Aging Study, reported that elevated levels of BP are associated with declines in gray matter volumes in the hippocampus and lateral temporal lobe.<sup>120</sup>

Interestingly, hypotension has also been implicated in the development of dementia. Several longitudinal studies report that hypotension is a risk factor for dementia, but the studies are generally limited to the very elderly.<sup>121</sup> Most recently, in a study of 599 patients, Nilsson and colleagues reported that low SBP was associated with cognitive decline, dementia, and AD.<sup>122</sup>

## Diabetes mellitus

Diabetes is one of the strongest risk factors for dementia. Diabetes has also been associated with an increased prevalence of cognitive impairment.<sup>24</sup> In the Rotterdam study of 1999, diabetes mellitus was found to almost double the risk of dementia (relative risk [RR] 1.9 [1.3–2.8]) and AD (RR 1.9 [1.2–3.1]).<sup>123</sup> The Honolulu-Asia Aging study reinforced this association, showing that type 2 diabetes was associated with total dementia, AD, and VaD.<sup>124</sup> Another study from 2004 suggests that type 2 diabetes might be present in up to 80% of patients with AD.<sup>125</sup> A recent review by Beeri and colleagues reported an association between diabetes and risk of dementia and cognitive decline in most but not all epidemiological studies cited.<sup>126</sup> Brain imaging studies such as the CASCADE Study reported that diabetes is associated with cortical brain atrophy.<sup>127</sup> Much like other cardiovascular risk factors, the aggregation of diabetes and other risk factors leads to an acceleration in dementia risk. In this setting, the risk of AD is increased threefold.<sup>16</sup>

There are several potential biological mechanisms underlying the association between diabetes mellitus and dementia including the impact of diabetes on cerebral microvessel dysfunction and oxidative stress.<sup>128</sup> In addition, the role of insulin itself may be important in the potential development of dementia and AD. Insulin degrading enzyme also degrades  $A\beta$ ,<sup>129</sup> and in AD patients, insulin degrading enzyme levels are reduced,<sup>130</sup> which could contribute to the accumulation of  $A\beta$  in AD patients. Additionally, brain insulin signaling may be altered in AD, leading to pathological interactions

between the receptor for advanced glycation end products and  $A\beta$  peptides.<sup>131</sup>

## Hypercholesterolemia, smoking, and obesity

The association between hypercholesterolemia and risk of dementia is still controversial. The accumulation of  $\beta$ -amyloid plaques and the loss of neurons, particularly in the hippocampus, are thought to be central events in the development of AD. Consequently, either overproduction or impaired clearance of  $\beta$ -amyloid, or both, may be causative in AD. It should be pointed out however that no direct causal relationship has been established between AD and the dysregulation of cholesterol metabolism. In particular, it is not clear whether the modification of cholesterol homeostasis in AD brains is a cause or a consequence of the disease.<sup>132</sup> For this reason, some have cautioned against inappropriate treatments.<sup>133</sup>

There are a very limited number of studies on the association between smoking and risk of dementia. A recent meta-analysis of 19 prospective studies by Anstey and colleagues showed that smoking is a risk factor for cognitive decline and dementia.<sup>134</sup> More importantly smoking is a strong, independent risk factor for stroke,<sup>135</sup> which is a well established risk factor for dementia. A recent study reported that smoking showed the most consistent inverse association of all cardiovascular risk factors tested with cognitive test results.<sup>136</sup> As well, neuroimaging studies have associated smoking with reduced gray matter in the prefrontal cortex, anterior cingulate cortex, and temporal lobe in adults, and decreased frontal cortex, posterior cingulum, precuneus, and thalamus in the elderly.<sup>137</sup> Atrophy in these structures may contribute to the cognitive impairment.

Obesity is a growing problem in modern society and has been linked with the risk of dementia and cognitive impairment. Worldwide, low education is responsible for the largest contribution to dementia, but in the US, this is replaced by physical inactivity.<sup>138</sup> Body mass index (BMI) is associated with heart disease, in addition to its association with dementia. A recent cardiovascular health study reported that high BMI at midlife (obese, BMI > 30) is associated with higher dementia risk compared with normal weight individuals (HR 1.39, 95% CI 1.03–1.87).<sup>139</sup> These results are supported by previous studies by Kivipelto and colleagues and Whitmer and colleagues who also reported an association between midlife obesity and higher dementia risk.<sup>140,141</sup> Diet is an important, and preventable, risk factor for the development of obesity and subsequently dementia. In particular, the

consumption of a higher calorie diet rich in unsaturated fatty acids and cholesterol is associated with the development of AD and cognitive impairment through increased amyloidosis and altered synaptic plasticity.<sup>142,143</sup>

## Treatment/prevention

Since the development of heart disease may be modifiable, the prevention of heart disease through the regulation and moderation of its risk factors is of the utmost importance.

## Diet and exercise

A healthy diet is one modality for prevention of heart disease, but studies have shown very mixed results for diet as an effective method for slowing cognitive decline and dementia. A recent study by Vercambre and colleagues reported that an adherence to a Mediterranean-style diet was not associated with cognitive change in women at higher risk of cognitive decline due to vascular disease or risk factors.<sup>144</sup> Other studies testing the effects of omega-3 fatty acids, such as those found in dietary fish or fish oil, on cognitive decline found no effect of dietary doses of omega-3 fatty acids on the prevention of cognitive decline.<sup>145,146</sup>

Nevertheless, a healthy diet may indirectly reduce the likelihood of dementia. A prospective observational study of 36,019 subjects by Levitan and colleagues reported that those with diets consistent with the DASH (Dietary Approaches to Stop Hypertension) had a 37% lower rate of developing HF,<sup>147</sup> which has been shown previously to be a major risk factor for dementia. As well, multiple studies by Scarmeas and colleagues reported that more optimal adherence to the Mediterranean diet was associated with a reduced risk for AD as well as conversion to AD in MCI patients.<sup>148–150</sup> Salt reduction as recommended in the DASH diet is a major tool for reducing hypertension and its vascular consequences including dementia.

Exercise has been implicated in the prevention of cognitive decline and dementia. While studies on the exact relationship are still limited, a recent review by Román and colleagues highlights several studies showing physical activity and exercise as being strongly associated with improved cognition and a lower risk of cognitive decline.<sup>151</sup> A similar benefit of exercise in reducing AD risk has been reported.<sup>152</sup> Another systematic review by Aarsland and colleagues demonstrated a significant association between physical exercise and reduced risk of developing VaD.<sup>153</sup> Finally, a randomized controlled trial by Vreugdenhil and colleagues reported that AD patients who were in the exercise program had increased

Mini-Mental State Examination scores and Instrumental Activities of Daily Living scores compared with those without exercise.<sup>154</sup>

## Treatment options

Since heart disease and cardiovascular risk factors have been associated with dementia, many studies have been conducted to determine whether there is a positive association between lowering such risk factors and lowering the risk of dementia. Antihypertensive medications have been tested extensively. Data from the Cache County Study demonstrated that the use of antihypertensives at baseline was associated with lower incidence of AD.<sup>155</sup> Also, a meta-analysis of randomized controlled trials by Feigin and colleagues supported the hypothesis that BP lowering may prevent dementia in those with vascular disease.<sup>156</sup> The cited studies include the Systolic Hypertension in Europe (Syst-Eur) trial, which showed that treating hypertension with an antihypertensive protocol, specifically the calcium channel blocker nitrendipine, resulted in a 50% reduction in incident cases of dementia.<sup>157</sup> A post-hoc analysis in the PROGRESS trial showed that dementia incidence in patients with recurring stroke was reduced by 34% when treated with antihypertensives.<sup>158</sup> The Kungsholmen Study reported that antihypertensive treatment was more effective in reducing dementia among those carrying the APOE ε4 allele.<sup>159</sup> These findings are consistent with those of the Honolulu-Asia Aging Study, which demonstrated that the association between high midlife BP and the development of AD was strongest among those who were never treated for hypertension.<sup>160</sup>

Despite the growing number of positive studies, the Syst-Eur study remains the only recent study with a direct association between antihypertensive use and a decrease in the incidence of dementia.<sup>161</sup> The Hypertension in the very Elderly Trial Cognitive Function Assessment (HYVET-COG) study, which was a double-blind, placebo-controlled trial, reported that antihypertensive treatment in the elderly did not statistically reduce the incidence of dementia.<sup>162</sup> A meta-analysis of three randomized, double-blind, placebo controlled trials by McGuinness and colleagues reported that there was no convincing evidence from the trials that BP lowering in hypertensive patients prevented the development of dementia or cognitive impairment.<sup>163</sup> Despite these mixed results, the use of antihypertensive drugs for lowering midlife BP remains an important treatment option that may prevent the onset of dementia.

How far should BP be lowered? Studies by Lee and colleagues showed that BP in the range of SBP of

130–139 mmHg and DBP of 85–89 mmHg was associated with a substantial increase in stroke risk.<sup>164</sup> The SPS-3 trial should clarify this important issue, since prehypertension with SBP under 140 mmHg is frequently not treated aggressively.<sup>165</sup>

Data for an association between statins and the prevention of AD neurodegeneration are mixed. Statins are used to lower cholesterol levels. A recent review highlights the controversial nature of statin use, reporting that statin users have a lower prevalence of AD, while also showing that there is no or only a modest decreased risk of AD.<sup>166</sup> Another review by Wolozin and colleagues confirms this finding.<sup>167</sup>

Treatment of evident heart disease could also prove beneficial for the prevention of dementia. For example, Stanek and colleagues showed that when treated, HF patients improved their performance on cognitive tests.<sup>168</sup> Puccio and colleagues reported that AF patients treated with an anticoagulant, warfarin, showed better scores at the Clinical Dementia Rating Scale, the Geriatric Depression Scale, and the Global Deterioration Scale, suggesting a neuroprotective role.<sup>169</sup> Long-term warfarin is protective against the development of dementia in subjects with AF.<sup>170</sup>

Another drug, donepezil, an acetylcholinesterase inhibitor, has shown promise as an anti-AD drug. In studies on mice, donepezil prevents cardiac rupture during the acute phase of MI through its inhibition of the enzymatic matrix metalloproteinase-9 (MMP-9), as well as through its prevention of pumping failure and cardiac remodeling.<sup>171</sup> Inhibiting the enzymatic activity of MMP-9 can be an effective treatment for AD.<sup>172</sup>

In the Cardiovascular Health Study, Sink and colleagues reported that angiotensin converting enzyme (ACE) inhibitors might protect against dementia beyond control of BP. Centrally active ACE inhibitors that cross the blood–brain barrier were associated with 65% less decline on the mini-mental state exam when compared with other antihypertensive drugs.<sup>173</sup> In another study, the use of ACE inhibitors in HF patients was associated with an improvement in cognitive performance, and the probability of improvement increased with increasing dosage and longer treatment duration.<sup>71</sup>

## Conclusion

Heart disease as well as cardiovascular risk factors, particularly if they manifest in midlife, are associated with the eventual development of dementia later in life. Early prevention and treatment could potentially mitigate the onset of dementia. However, further research is still needed to find the

most effective methods of dementia prevention and to better elucidate the vascular mechanisms of this disorder.

## Disclosure

The authors report no conflicts of interest in this work.

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