

# Sex Differences in Cardiovascular Disease and Cognitive Impairment: Another Health Disparity for Women?

Annabelle Santos Volgman, MD; C. Noel Bairey Merz, MD; Neelum T. Aggarwal, MD; Vera Bittner, MD, MSPH; T. Jared Bunch, MD; Philip B. Gorelick, MD, MPH; Pauline Maki, PhD; Hena N. Patel, MD; Athena Poppas, MD; Jeremy Ruskin, MD; Andrea M. Russo, MD; Shari R. Waldstein, PhD; Nanette K. Wenger, MD; Kristine Yaffe, MD; Carl J. Pepine, MD

**A**lthough the number of Americans dying of cardiovascular disease (CVD) continues to increase since 2010 after decades of decrease, advances in the management of CVD have led to increased longevity among both women and men, with more people, mostly women, now surviving into their 80s and beyond.<sup>1</sup> Paralleling this increased longevity, however, is an increasing prevalence of, and mortality from, neurodegenerative cognitive disorders.<sup>1</sup> These cognitive disorders include dementia, a syndrome that has a multitude of causes and symptoms that ultimately have substantial impact on social and occupational activities and aspects of daily living.<sup>2</sup> Typical symptoms of dementia include changes in memory, problem solving, language, and executive functioning.<sup>2</sup> Although there are often distinct patterns, symptoms, and specific brain

pathology associated with different dementias, multiple autopsy studies are now demonstrating that people with symptoms of a dementia will often have multiple brain pathologies noted at autopsy that were associated with the dementia.<sup>3,4</sup> Multiple reports document that approximately two thirds of those clinically diagnosed with Alzheimer dementia are women.<sup>5</sup> Furthermore, it is estimated that by 2040 the number of Americans with some form of cognitive impairment (CI), including dementia, will be  $\approx 8.3$  million women and  $\approx 3.3$  million men.<sup>5</sup> This sex-related CI disparity is concerning and raises important questions about its possible relation to CVD and CVD-related risk factor conditions.

Although there are multiple types of dementia syndromes with different cognitive, behavioral, and pathological characteristics, the most common types are Alzheimer dementia and vascular cognitive impairment.<sup>6</sup> Alzheimer dementia is characterized by an irreversible, progressive disorder that slowly destroys memory and thinking skills, and eventually the ability to perform simple tasks.<sup>7</sup> Vascular cognitive impairment, a term that encompasses all levels of CI from its mildest form to vascular dementia, is characterized by progressive changes in behavior, function, and cognition caused by vascular injury (eg, strokes [infarcts], microbleeds [cerebral amyloid angiopathy and microhemorrhages]) or disease within the brain and includes deficits in executive functioning, attention, and language. This is in contrast to episodic memory deficits, which are more prominent in Alzheimer dementia. Increasingly, the term “mixed dementia” is used to describe the coexistence of both Alzheimer disease (AD) and vascular neuropathology in people experiencing dementia symptoms.<sup>8</sup>

In 2018, new criteria for AD were established by the National Institute on Aging and Alzheimer’s Association to recognize that the disease occurs across a continuum of pathologic changes that precede its clinical manifestations and culminates with Alzheimer dementia.<sup>9</sup> The clinical syndrome is noted as Alzheimer dementia, and the term dementia caused by AD is used when neuroimaging biomarkers or biofluid markers or autopsy confirm the diagnosis. This distinction continues to highlight the ongoing research that shows that AD begins many years before the symptoms of

*From the Section of Cardiology, Departments of Medicine (A.S.V., H.N.P.) and Neurological Sciences, Rush Alzheimer’s Disease Center (N.T.A.), Rush Medical College, Chicago, IL; Barbra Streisand Women’s Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA (C.N.B.M.); Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, AL (V.B.); Section of Cardiology, Department of Medicine, Stanford University, Palo Alto, California (T.J.B.); Department of Cardiology, Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, UT (T.J.B.); Department of Translational Neuroscience, Michigan State University College of Human Medicine, Grand Rapids, MI (P.B.G.); Department of Psychiatry, Psychology and Obstetrics & Gynecology, University of Illinois at Chicago, IL (P.M.); Section of Cardiology, Department of Medicine, Brown University, School of Medicine, Providence, RI (A.P.); Division of Cardiology, Massachusetts General Hospital, Boston, MA (J.R.); Section of Cardiology, Department of Medicine, Cooper Medical School of Rowan University, Camden, NJ (A.M.R.); Department of Psychology, University of Maryland, Baltimore County, Baltimore, MD (S.R.W.); Section of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA (N.K.W.); Department of Psychiatry, Neurology and Epidemiology, University of California San Francisco, San Francisco, CA (K.Y.); Division of Cardiovascular Medicine, Department of Medicine, University of Florida, Gainesville, FL (C.J.P.).*

**Correspondence to:** Annabelle Santos Volgman, MD, Clinical Cardiology, Rush College of Medicine, Rush Heart Center for Women, Rush University Medical Center, 1725 W Harrison St, Room 1159, Chicago, IL 60612. E-mail: annabelle\_volgman@rush.edu

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Alzheimer dementia are present.<sup>10</sup> The term mild cognitive impairment (MCI) is used in people with demonstrable CI who have not crossed the threshold to dementia. MCI can refer to either a predominantly memory (amnesic) or nonmemory (nonamnesic) cognitive deficit and can be the initial symptom of a dementia syndrome, but it may also be secondary to other conditions or disease processes.<sup>11</sup> A meta-analysis revealed that women have a higher prevalence of nonamnesic MCI but suggested no sex-related differences in the incidence or prevalence of amnesic MCI.<sup>12</sup>

At age 45 years, the lifetime risk for developing Alzheimer dementia is estimated at 1 in 5 for women versus only 1 in 10 for men.<sup>13</sup> Possible reasons for this sex disparity, alone or more likely in combination, include greater longevity of women; their higher incidence of chronic diseases (particularly those CVD linked with CI), genetic predispositions, differences in cognitive testing performance (women outperform men on tests of verbal ability)<sup>14</sup> (thereby potentially “masking” any underlying cognitive deficits, resulting in a later presentation to the healthcare provider for complaints of change in cognitive function), socioeconomic, psychosocial, and biological factors.<sup>15</sup> Education level and occupational attainment (eg employment) can impact cognitive resilience and explain some of the sex disparities noted in dementia.<sup>16,17</sup> Traditionally, older women may not have had as many opportunities for attaining a higher level of education nor an equal period of time in the workforce compared with men, thus possibly putting them at an increased risk for developing cognitive decline and dementia. However, results from studies continue to be mixed, as methodological issues, study design, and comparability across studies remain difficult. Lastly, among the psychosocial factors, caregiving has emerged as a potential risk factor for developing dementia. Sex differences in spousal care are highly prevalent for patients with dementia, with women delivering the majority of the care and spending more time devoted to care.<sup>18</sup> The increased stress of caregiving, coupled with lower levels of social support and poor physical health, are increasingly being examined as strong risk factors for cognitive decline and dementia in female caregivers.

In addition to the aforementioned contributing factors of sex-related differences in the dementia syndromes, this review examines sex differences in CVD and a broad range of CVD risk factors that may contribute to CI to explain, at least in part, the higher prevalence of dementias in women versus men. Potential implications of these sex differences are addressed in context for practitioners, our healthcare system, and related resource consumption. Important knowledge gaps are identified to direct the focus of future research.

The American College of Cardiology CVD in Women Committee identified this topic and invited experts in the fields of CVD and/or CI to contribute sections in their

respective fields. They did their own literature searches and submitted their sections to the chair of the writing committee (ASV), who compiled and summarized the sections to create a cohesive document. Over 300 selected publications were reviewed, and those addressing sex differences or new information were included in this document.

This document is a summary of the topics that include stroke, microvascular or small-vessel disease, and sex-specific issues about differences in CVD that may help explain the increased prevalence of CI and dementia in women.

## Causes of Cerebrovascular Accident/Brain Ischemia, and Infarct

### Hypertension

A substantial literature documents that higher blood pressure (BP), a key risk factor for stroke, as well as myocardial infarction and heart failure (HF), also presage vascular dementia, AD, and earlier forms of vascular CI.<sup>19–22</sup> In addition, higher BP is associated with lower levels of cognitive function before evidence of frank “impairment.”<sup>23</sup> This process occurs over the life span,<sup>20,24</sup> starting in childhood,<sup>25</sup> and exhibits a long and insidious course. Higher childhood systolic BP has been associated with lower levels of cognitive function in midlife,<sup>26</sup> and higher midlife BP predicts less favorable later-life cognitive outcomes.<sup>19,20</sup> However, among the elderly, a reversal of association shows that higher BP often relates to better cognitive outcome.<sup>20</sup> Men have a higher prevalence of hypertension versus women until about age 64 years; however, after that age the prevalence of hypertension in women is higher than in men.<sup>1</sup> Data generally suggest that both high and low BP are associated with reduced cognitive function and greater dementia risk.<sup>19,20</sup>

Impairment in multiple cognitive domains is associated with higher BP, although the preponderance of evidence suggests that executive functions, perceptual motor speed, and learning and memory may be most affected.<sup>20</sup> However, patterns of affected cognitive domains (including null findings) vary greatly by study. This is not surprising given pronounced methodological differences among studies, variations in BP measurement and risk factors, heterogeneity among hypertension patients, and as discussed later, the likelihood of multiple underlying brain mechanisms with potentially differing impacts on cognitive function. This striking admixture of results may also reflect the influence of vulnerability and resilience factors.<sup>24,27</sup> In that regard, studies of effect modification suggest more pronounced BP-related risk is conferred at younger ages, lower levels of education, presence of APOE ε4 alleles, and in conjunction with other CVD risk factors.<sup>19,20,24,27</sup> Those receiving antihypertensive medication appear to fare better longitudinally.<sup>28</sup> A review of

randomized trials of antihypertensive agents for prevention of either cognitive decline or dementia suggests that risk reduction can be achieved with some select drug classes.<sup>28</sup>

Proposed mechanistic pathways linking elevated BP to cognitive decline and dementia are numerous and include structural and functional brain mechanisms that promote both ischemic injury and expression of AD neuropathology.<sup>19–22</sup> With standard neuroimaging procedures, higher BP has been associated with decreased global and regional cerebral blood flow and metabolism, brain atrophy, white matter lesions, subclinical brain infarction, lesser white matter microstructural integrity, and altered functional connectivity and activation patterns. Studies in predominantly animal models suggest mechanistic pathways that include structural changes to cerebral vessels, atherosclerosis, vascular remodeling and stiffening, small-vessel disease, microvascular rarefaction, endothelial dysfunction, diminished neurovascular coupling and autoregulatory function, and alterations in the blood–brain barrier. Higher BP has also been associated with increased expression of AD neuropathology, which includes brain  $\beta$ -amyloid levels, neuritic plaques, and neurofibrillary tangles.<sup>19–22</sup>

The SPRINT (Memory and Cognition in Decreased Hypertension) MIND study is the first randomized trial to investigate the cognitive effects of intensive BP lowering (<120 mm Hg systolic BP goal) versus a traditional goal of <140/90 mm Hg. In adults  $\geq 50$  years old without diabetes mellitus or prior stroke, intensive BP lowering significantly reduced the rate of MCI (14.6 versus 18.3 cases per 1000 person-years; hazard ratio [HR], 0.81; 95% CI, 0.69–0.95) and the combined rate of MCI or probable dementia (20.2 versus 24.1 cases per 1000 person-years; HR, 0.85; 95% CI, 0.74–0.97).<sup>29</sup> Furthermore, a preliminary report of their brain magnetic resonance imaging (MRI) substudy documented significantly reduced development of white matter lesions,<sup>29,30</sup> supporting the hypothesis of a microvascular mechanism. These are remarkable findings considering that the population enrolled in SPRINT was at low risk for CI, as patients with diabetes mellitus or prior stroke were excluded, and follow-up was terminated early (only 3.26 years, median) because of significant 27% reduction in all-cause mortality with the lower BP goal. However, the Alzheimer's Association awarded support for SPRINT MIND 2.0 that will extend follow-up for 2 additional years to determine effects on “probable dementia” alone. Whether significant sex differences in development of MCI, dementia, or white matter hyperintensity lesions will emerge in subsequent analyses would be very important.

These studies reveal biologically plausible pathways to vascular dementia, Alzheimer dementia, and mixed forms of dementia among those with higher BP and may help explain varying patterns of cognitive correlates noted across investigations. Although several investigations suggest sex

differences, findings are mixed regarding the relative vulnerability of women versus men.<sup>31,32</sup> Variation in the course of CVD among women and men suggests that interactions of sex and age are important considerations relative to CI. An interaction between hypertension and menopausal status indicated that cognitive performance was worse in hypertensive, versus normotensive, postmenopausal women. Notably, this finding was not present in premenopausal women,<sup>33</sup> suggesting the importance of examining hormonal and other influences that may be operative within different samples of women.

## Atherosclerosis

### Intracranial large artery disease

Severe atherosclerosis is recognized as a potent risk factor for CI.<sup>34</sup> Large-artery intracranial occlusive disease remains the most common stroke subtype.<sup>35</sup> This subtype may occur more frequently in women than men<sup>36</sup> and progresses rapidly after menopause.<sup>37</sup> Among women, hypertension and diabetes mellitus are predictors of intracranial internal carotid artery calcification or intracranial atherosclerosis,<sup>38</sup> and women with severe large-artery intracranial occlusive disease, defined as  $\geq 70\%$  stenosis, appear to have a higher risk of recurrent stroke than men.<sup>39</sup> To our knowledge, no large-scale studies have examined sex differences in cognitive function among people with large-artery intracranial occlusive disease.

### Cerebrovascular small-vessel disease

While hypertension, hyperlipidemia, and diabetes mellitus have long been recognized as risk factors for stroke and vascular dementia, epidemiological data suggest that they are also associated with increased incidence of cognitive decline<sup>40</sup> and clinically diagnosed Alzheimer dementia.<sup>41</sup> Vascular disease risk factors are thought to accelerate the development of AD neuropathology (eg, accumulation of  $\beta$ -amyloid and neurofibrillary degeneration). Alternatively, CVD-related brain injury may interact additively (or synergistically) with AD neuropathology to cause earlier expression of dementia.

Neuropathology studies note that most people with dementia who die have substantial cerebrovascular disease (small-vessel disease, cerebral microbleeds, and microinfarcts)<sup>42,43</sup> and axonal damage.<sup>44</sup> MRI imaging documents damage from small-vessel disease such as white matter lesions and lacunar infarcts. Atherosclerotic calcification is strongly associated with these MRI-markers of subclinical vascular brain disease.<sup>45</sup> Although no studies report on sex differences in intracranial small-vessel disease, it well known that women are more likely than men to have nonobstructive multivessel disease and more microvascular dysfunction.<sup>46</sup> There is considerable overlap between risk factors for vascular disease and for cognitive decline.<sup>40,42,43</sup> The shared

risk factors for CVD and the clinical development of Alzheimer dementia are associated with reduced cerebral glucose uptake and reductions in blood flow, which together are thought to be associated with increased accumulation of cerebral  $\beta$ -amyloid over time.

Recent advances in MRI have shown that “breakdown” of the blood–brain barrier is a core mechanism in cerebral small-vessel disease and dementia.<sup>47</sup> It is unclear whether the biological mechanisms involved in disrupting the blood–brain barrier are similar to those associated with coronary or other organ microvascular dysfunction. Establishing whether these relationships exist may be an important research direction to better understand links between CVD and CI/dementia.

### ***Coronary atherosclerosis–nonobstructive (coronary artery disease)/coronary microvascular disease***

Coronary artery calcification scores have been associated with dementia and cognitive decline. A population-based study of 5764 men and women aged 66 to 86 years born between 1907 and 1935 found that an increasing coronary artery calcification score was associated with higher rates of dementia and lower executive function scores. Brain volumes (ie, gray matter, white matter, and total brain tissue volumes by MRI) were decreased with increasing coronary artery calcification.<sup>48</sup>

On the contrary, the Rotterdam Study followed 7983 people to evaluate determinants of disease in those  $\geq 55$  years old.<sup>49</sup> Nonenhanced computed tomography chest imaging, including proximal vessels of the head, was performed in 1847 subjects. Non–coronary artery calcifications, but not coronary artery calcification, were significantly associated with increased rates of dementia: extracranial carotid arteries (HR 1.39; 95% CI 1.09; 1.77); aortic arch (HR 1.38; 95% CI 1.02; 1.86); and intracranial carotid arteries (HR 1.31; 95% CI 1.01; 1.70). The authors postulated that more coronary artery calcification caused increased CVD events, including death, so those subjects may not have survived long enough to develop dementia.

Women more frequently have nonobstructive coronary artery disease (CAD), coronary spasm, and microvascular or small-vessel disease than men.<sup>46,50</sup> Both nonobstructive CAD and microvascular disease may contribute to increased risk of CI and dementias in women.<sup>51</sup> Most diseases caused by microvascular dysfunction/disease have no evidence-based treatments documented to be effective, but potential treatments are being investigated.

An association between CAD and CI has been observed in men, but not in women<sup>52</sup>; however, this sex difference was no longer statistically significant with increasing age ( $n=1969$ ; aged 70–89 years).<sup>53</sup> Although no sex interaction was reported, after acute myocardial infarction, CI was associated with less invasive care, less referral and participation in cardiac rehabilitation, and worse risk-adjusted 1-year survival.<sup>54</sup>

## **Atrial Fibrillation**

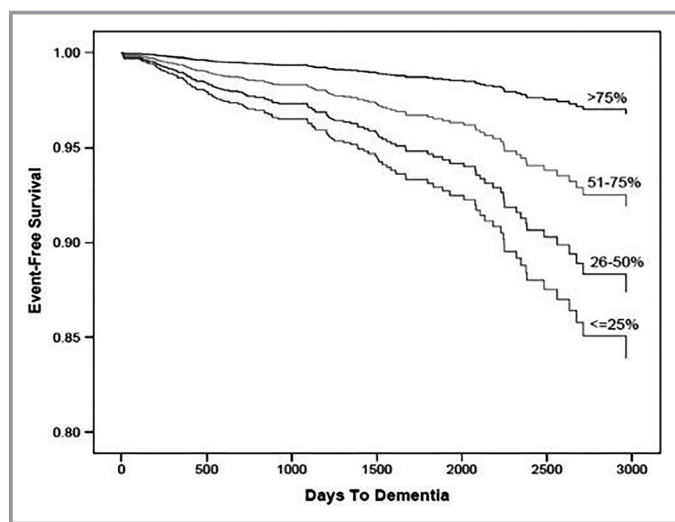
In an observational analysis of 35 608 patients without either atrial fibrillation (AF) or dementia, the 5-year rate of AF in men was 14.0% versus 11.9% in women ( $P<0.0001$ ).<sup>55</sup> Despite higher rates of AF in men, it appeared that women may have slightly higher 5-year rates of dementia (1.1% versus 0.9%,  $P=0.09$ ).<sup>55</sup> Among patients who developed AF, women appeared to have a slightly higher incidence of dementia compared with men (3.7% versus 3.0%,  $P=0.11$ ). In this analysis, older age, diabetes mellitus, prior stroke, and kidney disease predicted dementia in women without AF, and greater age, prior stroke, and CAD predicted dementia in women with AF.<sup>55</sup> In meta-analyses of AF patients with stroke, risk ratios for CI or dementia range from 2.43<sup>56</sup> to 2.70.<sup>57</sup> After a stroke, women have worse long-term functional outcomes with reduced quality of life, compared with men.<sup>58</sup> Although sex-specific data regarding long-term risk of CI after a stroke are lacking, a stroke registry showed that women had significantly lower cognitive function scores than men on a stroke-specific quality-of-life scale; (2.8 versus 3.4,  $P<0.001$ ).<sup>59</sup>

Observational studies in AF patients indicate that “time in therapeutic range” of anticoagulation is inversely associated with dementia risk (Figure 1).<sup>60</sup> Interestingly, increased dementia risk was observed with both under- and overanticoagulation.<sup>60</sup> Although direct oral anticoagulants have not been studied in randomized controlled trials versus warfarin to study the effect of anticoagulation on CI and dementia, observational data (41% women) suggest a lower long-term risk of stroke and dementia with these agents.<sup>61</sup> Underuse of anticoagulation remains a problem in AF and is more frequent in women versus men,<sup>62</sup> despite observational data indicating that warfarin lowers stroke risk more in women.<sup>63</sup> Improving prompt anticoagulant use in women with AF is critical, as delays in initiation incrementally increase dementia risk.<sup>64</sup> Although sex differences were not evaluated, AF was associated with a  $>2$ -fold increased risk of developing silent cerebral infarction, detected by MRIs.<sup>65</sup> These subclinical cerebral ischemic events are associated with CI despite use of oral anticoagulants in up to 88% of AF patients.<sup>66</sup>

In a retrospective registry study of almost half a million AF patients, those treated with anticoagulants at baseline had a 29% lower risk of dementia versus patients without anticoagulant treatment (HR 0.71, 95% CI 0.68–0.74). When analyzed “on anticoagulant treatment,” there was a 48% lower risk (HR 0.52, 95% CI 0.50–0.55), and no sex-related differences or differences between new oral anticoagulants and warfarin were observed.<sup>67</sup>

Sleep apnea and sleep-disordered breathing can increase the risk of AF.<sup>68</sup> Whether sleep apnea causes CI has been investigated; a pooled analysis of 7 cross-sectional studies





**Figure 1.** Event-free survival estimates for dementia incidence among categories of percent time anticoagulation with vitamin K antagonists is in the therapeutic range. Reprinted from Jacobs et al<sup>60</sup> with permission. Copyright ©2014, Elsevier.

suggested that those with sleep-disordered breathing had slightly worse executive function (standard mean difference,  $-0.05$ ; 95% CI  $-0.09$  to  $0.00$ ) but was not associated with global cognition or memory.<sup>69</sup> No sex differences were analyzed in this report. However, a nationwide survey confirmed sex differences in the association between various self-reported sleep disturbances and CI in people aged 65 years and older. They found that there was a significant interaction between sex and difficulty breathing during sleep on CI. In men, difficulty breathing during sleep, habitual snoring, and prolonged sleep duration ( $>8.5$  hours) correlated significantly with CI. In women, only prolonged sleep duration ( $>8.5$  hours) was associated with higher likelihood of CI.<sup>70</sup>

## Heart Failure

About 30% to 80% of HF patients experience some degree of CI, depending on study design, HF severity, patient age, sample size, and diagnostic criteria.<sup>71</sup> Most HF patients have MCI, a quarter may have moderate-to-severe CI,<sup>72</sup> and severity may fluctuate over time, either improving with effective HF treatment or progressing to dementia.<sup>71</sup> The role of sex in CI development among HF patients, however, is unclear. In a cross-sectional analysis of Medicare claims data for individuals  $\geq 67$  years (58% women), sex did not predict moderate-to-severe CI.<sup>73</sup>

HF with preserved ejection fraction (HFpEF) was the most prevalent form of HF in older women, and these patients had higher risk of subclinical cerebral infarction, even without AF, than those without HFpEF.<sup>74</sup> In patients with HFpEF but no AF, only male sex (odds ratio 2.26, 95% CI 1.12–4.58) and a

larger left atrium (odds ratio 1.41, 95% CI 1.00–2.00) were associated with increased odds of having subclinical cerebral infarction after multivariable adjustment. Those with HFpEF and subclinical cerebral infarction had lower cognitive scores, noted in tests for executive functioning and episodic memory, than the reference (no HFpEF/no subclinical cerebral infarction) and HFpEF/no subclinical cerebral infarction groups.<sup>75</sup> Cognitive performance by sex was not reported.

Multiple studies in HF patients document a strong, independent association between CI and increased mortality and hospital readmissions. Intact executive function and memory are needed to identify worsening symptoms, adhere to self-care practices such as medication regimens and lifestyle modifications, maintain clinic visits, and comply with dietary recommendations. No clear association has been identified between sex and medication adherence among HF patients with CI.<sup>76</sup>

## Cardiovascular Interventional Procedures

Sex differences in cardiac interventions such as catheter-based procedures and surgeries were evaluated for sources of cerebral microinfarcts and strokes that can contribute to CI.

### Cardiac procedures

Cardioembolic strokes are a well-recognized complication of many invasive cardiovascular procedures. Invasive cerebral and coronary angiography, coronary artery bypass graft surgery (CABG), surgical aortic valve replacement, and transcatheter aortic valve replacement (TAVR) may cause both acute and, even more frequently, subacute, “subclinical” microinfarcts (Table 1).<sup>77</sup> For TAVR, women generally have higher Society of Thoracic Surgeons risk scores, more bleeding, and more vascular complications but similar stroke rates with improved 1-year, all-cause mortality.<sup>78</sup> With surgical aortic valve replacement, women appear to have similar stroke rates, but higher in-hospital mortality.<sup>79</sup>

With TAVR, the increase in overt (4%) and silent (70%)<sup>80</sup> stroke risk may be offset by the increase in forward blood flow, with significant and sustained improved executive functioning in most patients.<sup>81</sup> However, female sex was a predictor of increased clinical neurologic events after TAVR.<sup>81</sup> A review of TAVR in women concluded that, although women had better long-term survival versus men, women had increased stroke risk.<sup>82</sup>

### Implantable cardioverter defibrillator implantation procedures

There are several potential central nervous system risks associated with defibrillation testing during implantation of implantable cardioverter defibrillators (ICDs). These include

**Table 1.** Estimated Annual US Patients With New Brain Lesions After Vascular Procedures

Procedures	No. of Annual US Patients	Incidence of New Brain Lesions, %	No. of Annual Patients With New Brain Lesions
Coronary angiography	1 072 000	11–17	118 000–182 000
Percutaneous coronary intervention	596 000	11–17	66 000–101 000
CABG	242 000	16–51	39 000–123 000
Surgical aortic valve replacement	90 000	38–47	34 000–42 000
AF ablation	72 000	8–18	6000–13 000
Transcatheter aortic valve implantation	10 000	68–91	7000–9000
Carotid endarterectomy	93 000	4–34	4000–32 000
Carotid artery stenting	70 000	15–67	11 000–47 000
Cerebral angiography	300 000	11–20	33 000–60 000
Endovascular aneurysm	30 000	10–64	3000–19 000
Total	2 600 000	13–24	321 000–628 000

AF indicates atrial fibrillation; CABG, coronary artery bypass graft.  
Reprinted from Gress<sup>77</sup> with permission. Copyright ©2012, Elsevier.

risks related to ventricular fibrillation itself, which may lead to circulatory arrest and hypoperfusion, and thromboembolic events resulting from shock therapy. In addition, adverse effects related to anesthetic drugs required during implantation or testing undoubtedly contribute to adverse neurological effects. However, data on sex-specific differences of these risks are lacking.

After repeated ventricular fibrillation episodes, cumulative quantitative electroencephalographic depression (a sign of cerebral ischemia) was associated with ICD testing.<sup>83</sup> However, others found a negative correlation between the number of tests and recovery time.<sup>84</sup> The mean reperfusion time interval between episodes of ventricular fibrillation induction was shorter in patients with CI versus those without, and there was correlation between circulatory arrest time and electroencephalographic recovery time.<sup>84</sup> However, the small number of patients in these studies (9–37) precludes evaluation of sex differences and definitive conclusions. Nevertheless, it is now standard to wait at least 5 minutes between ventricular fibrillation inductions.

Cognitive assessments were done in patients receiving ICDs for primary prevention to evaluate CI after appropriate ICD events for ventricular fibrillation. Over 26-month follow-up, 15 appropriate shocks were observed in 7 patients, and among those with appropriate shocks, defibrillation was an independent predictor of poor cognitive function, along with age and education.<sup>85</sup> However, this association does not prove a “cause–effect” relationship as factors other than those examined may contribute. Psychocognitive improvement has been noted following ICD implantation with cardiac resynchronization devices, presumably related to improved cardiac function.<sup>86</sup>

Thromboembolic complications may also be associated with defibrillation testing. Shocks, with restoration of sinus rhythm in the presence of intracardiac thrombi, may result in thromboembolic complications such as stroke, microinfarcts, and associated CI. If defibrillation testing at the time of ICD implantation is planned for persistent AF patients not adequately anticoagulated, preoperative transesophageal echocardiography is indicated to exclude pre-existing thrombus. To avoid cerebral hypoperfusion, induction of ventricular fibrillation for ICD testing is no longer done with contemporary ICD technologies.

### *Surgical procedures requiring cardiopulmonary bypass*

Earlier studies showed that sex is an independent predictor of operative mortality after CABG,<sup>87</sup> but women are often referred for surgery later in the course of their disease, or for more urgent CABG, which may partially explain the higher mortality risk.<sup>88</sup> More recent studies such as the STICH Trial (Surgical Treatment for Ischemic Heart Failure) showed no sex differences in mortality.<sup>89</sup> However, women undergoing CABG or valve surgery were more likely than men to have postoperative neurological events after 30 days (HR 1.21, 95% CI 1.14, 1.28) that were not explained by known risk factors.<sup>90</sup>

While stroke is reported in 2% to 4% of patients following cardiac surgery, postoperative CI is much more frequent, with a variable incidence depending on definition and time after surgery.<sup>90</sup> After CABG, CI incidence was 53% at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years; importantly, CI at discharge predicted long-term CI in both women and men.<sup>91</sup>

A meta-analysis of 13 randomized trials (2405 patients) found no significant differences between on- and off-pump

surgery in postoperative psychometric tests, suggesting that cardiopulmonary bypass may not be a major cause of postoperative CI.<sup>92</sup> Advanced age, longer aortic cross-clamp duration, and pre-existing CI are risk factors for postcardiac surgery CI.<sup>93</sup> After CABG, overall CI frequency was not different between women and men in a study using several cognitive domains and neuropsychological tools; however, women had poorer performance postoperatively on visual-spatial tasks.<sup>94</sup>

## Sex-Specific Risks

### Preeclampsia

A meta-analysis of 13 studies (1314 women with prior preeclampsia and 289 080 women with prior normotensive pregnancy) evaluated the relationship of preeclampsia and CI; however, the median time since pregnancy was only 6 years. Pooling of cognitive outcome measures for studies assessing brain imaging or a clinical diagnosis of dementia were limited by differences in reporting and marked heterogeneity between studies. It was concluded that although preeclampsia is associated with subjective cognitive symptoms, the review did not clearly demonstrate an association with preeclampsia and CI on standard neurocognitive tests.<sup>95</sup>

### Hormone replacement therapy and dementia: role of cardiovascular risk factors

The WHIMS (Women Health Initiative Memory Study) of women  $\geq 65$  years old is the only randomized, placebo-controlled trial of menopausal hormone therapy for primary prevention of dementia.<sup>96</sup> Women with a uterus ( $n=2947$ ) were randomized to receive oral conjugated equine estrogen (CEE; 0.625 mg/d) plus medroxyprogesterone acetate (MPA; 2.5 mg/d CEE/MPA) or placebo. Women without a uterus ( $n=4532$ ) were randomized to receive oral CEE (0.625 mg/day) or placebo. Compared with placebo, CEE/MPA doubled the risk for all-cause dementia, but CEE alone had no effect and these outcomes were not modified by smoking, CVD, stroke, diabetes mellitus, hypertension, or statin or aspirin use.<sup>96</sup> Similar to dementia findings, CVD risk factors did not modify effects of hormone therapy on global cognitive function.

In a subgroup of WHIMS ( $n=1424$ ) who underwent brain MRI, ischemic brain volume (a measure of subclinical cerebrovascular disease) did not differ between hormone therapy and placebo groups, suggesting that ischemic changes were not the main mechanism underlying the observed increase in all-cause dementia risk.<sup>97</sup> However, consistent with the stroke risk associated with hormone therapy found in the Women's Health Initiative,<sup>98</sup> rates of accumulation in white matter lesion volume and total brain lesion volume were higher among women with a history of CVD treated with hormone therapy versus placebo.<sup>97</sup>

In contrast to the WHIMS, an 18-year observational follow-up study of 27 347 women in the Women's Health Initiative found a lower risk of mortality from Alzheimer dementia or dementia with CEE versus placebo, but no effect of CEE/MPA.<sup>99</sup> Mortality findings should be interpreted with caution due to the nonrandomized study design, and because the cause of death was determined by National Death Index search, or in some cases contacting next of kin, whereas 48% to 55% of dementia cases were prospectively adjudicated in WHIMS. Given that hormone therapy reduces diabetes mellitus risk, and diabetes mellitus is associated with increased risk of Alzheimer dementia and dementia,<sup>100</sup> additional investigation is needed to determine whether hormone therapy-associated reductions in mortality from dementia are related to menopausal hormone therapy-associated reductions in diabetes mellitus.

Overall, there is limited evidence from the Women's Health Initiative to support the view that CVD risk factors or CVD history mediate effects of hormone therapy on dementia or cognition.

## Cardiac Medications and Anti-Inflammatory Drugs

Many medications can affect cognition, either directly by altering neural processes or indirectly by reducing perfusion pressure or inducing hypoglycemia or hyponatremia. Older individuals are particularly susceptible, in part because of polypharmacy and age-related alterations in drug metabolism. Older women may be more susceptible than men because of smaller stature, because less muscle mass may mask the severity of renal impairment.

A detailed review of all cardiovascular medications is beyond the scope of this review, but available data show that aspirin, statins and other lipid-lowering agents,  $\beta$ -blockers, modulators of the renin-angiotensin system, calcium channel blockers, etc, have no significant effect on cognitive function. Of note, women were managed less aggressively with evidence-based treatments for ischemic heart disease but sex differences were not examined.<sup>101</sup>

Noncardiac medications, such as drugs for depression, anxiety, and sleep disorders, can have significant effects on CI in both women and men, although women have smaller hippocampi and nonhippocampal brain volumes. Medications for depression, anxiety, and sleep disorders may have worse effects on CI in women.<sup>102</sup>

The role for endothelial dysfunction and inflammation causing accelerated atherosclerosis in collagen vascular diseases has been studied. Certain anti-inflammatory drugs have been shown to reduce major adverse cardiovascular events.<sup>103</sup> Future studies of these drugs are warranted to assess their role in CVD and CI, as well as possible sex-related differences.

## CVD, Dementia, and Genetics

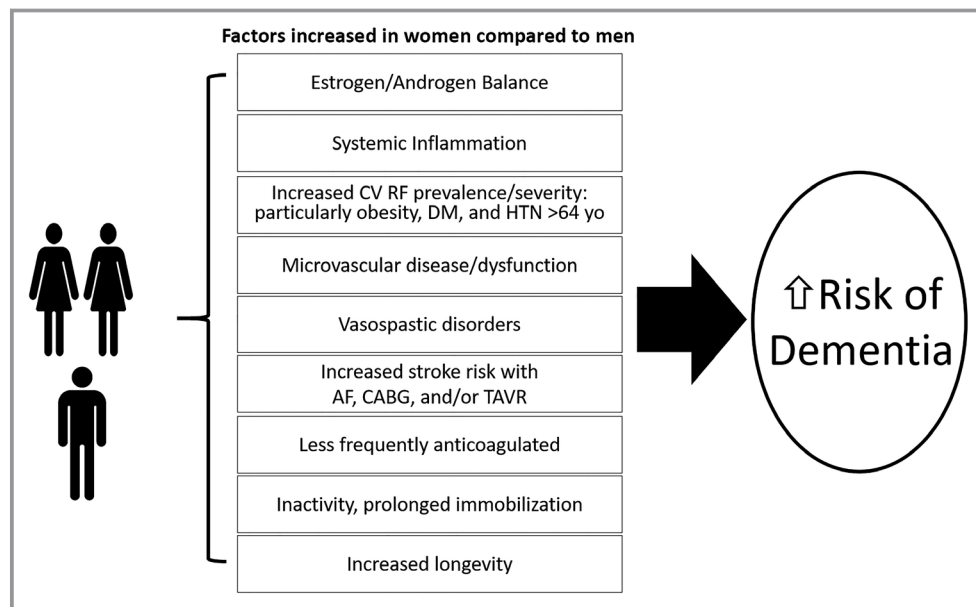
CVD and Alzheimer dementia are multifactorial diseases that also share common disease mechanisms because of an overlap in genetic<sup>104</sup> and biological risk factors, which together increase the risk for CI and dementia.<sup>105</sup> The APOE gene is polymorphic and encoded by 3 major alleles: APOE- $\epsilon$ 2, APOE- $\epsilon$ 3, and APOE- $\epsilon$ 4. The APOE- $\epsilon$ 4 gene is one of the most studied risk factors for CVD. Not only is the APOE protein integral to lipid metabolism and other physiological processes,<sup>106</sup> but also homozygosity of the APOE  $\epsilon$ 4 allele increases CAD risk by  $\approx 40\%$ .<sup>104,106–109</sup>

The APOE  $\epsilon$ 4 allele has also been associated with increased risk of developing CI and Alzheimer dementia by lowering the age of onset for both CI and dementia.<sup>107</sup> Those with the APOE  $\epsilon$ 4/ $\epsilon$ 4 genotype appear to have more senile plaque density and amyloid burden than those with the APOE  $\epsilon$ 2/ $\epsilon$ 4,  $\epsilon$ 3/ $\epsilon$ 3, or  $\epsilon$ 3/ $\epsilon$ 4 genotypes.<sup>108</sup> The APOE genotype also appears to differentially interact with Alzheimer dementia biomarkers in older women versus men.<sup>109</sup> Lastly, there may be a stronger association of the APOE  $\epsilon$ 4 genotype with cognitive function and CI in women compared with men, suggesting a strong sex-APOE  $\epsilon$ 4 interaction in women for risk of converting to MCI and Alzheimer dementia.<sup>110</sup> Women with APOE  $\epsilon$ 3/ $\epsilon$ 4 versus men with APOE  $\epsilon$ 3/ $\epsilon$ 4 had an elevated risk, but only between the ages of 65 and 75 years.

## Summary and Conclusions

The higher prevalence of CI and dementia in women may be explained in part by sex-related differences in CVD risk factors, CVD and its sequelae, and CVD treatment or lack thereof. Figure 2 illustrates other factors that affect women more than men that contribute to women having a higher proportion of the population with dementia. Women have greater longevity compared with men and thus longer exposure to CVD risk factors and CVD. We summarize sex-specific critical knowledge gaps that should be addressed in future research in Table 2. The higher prevalence of MCI in women compared with men may be ameliorated by improvements in the following: (1) stroke prevention in those with AF and hypertension; (2) appropriate treatment to prevent or reduce atherosclerosis progression; (3) better understanding of links between menopause and hypertension control; (4) work to reduce neurological complications associated with cardiac procedures; (5) avoiding menopausal hormone replacement therapy with CEE/MPA; (6) avoidance of potentially harmful medications that affect memory and cognition; and (7) understanding of the mechanistic role of APOE  $\epsilon$ 4 genotype in dementia to develop treatment targets. Analyses of sex-specific differences in future trials are critical to improve our understanding of how CVD affects CI in women and men.

Importantly for both women and men, prevention of cognitive impairment and dementia must be viewed as a lifelong process. Therefore, to help maintain optimal brain



**Figure 2.** Factors that contribute to the findings that women have a higher proportion of the population with dementia. AD indicates Alzheimer disease; AF, atrial fibrillation; CABG, coronary artery bypass graft surgery; CV RF, cardiovascular risk factors; DM, diabetes mellitus; HTN, hypertension; TAVR, transcatheter aortic valve replacement.



**Table 2.** Sex-Specific Critical Knowledge Gaps

Actionable Items
Studies can be retrospectively analyzed and ongoing and future studies of cognitive function should provide sex-specific data
Establishing whether relationships exist between coronary and cerebrovascular dysfunction to better understand links between CVD and CI/dementia
Cardiac intervention studies can be augmented to detect sex differences in detrimental effects on cognitive function
Treatment for stroke prevention such as antihypertensive medications, cholesterol-lowering medication, and anticoagulants for AF can be assessed for their effect on sex differences in CI
Various treatments of AF can be analyzed to determine sex differences in CI
Determine whether aortic or mitral valve calcification contributes to stroke risk or a marker of increased risk and whether there are sex differences in risk of stroke
Sex differences in potential cognitive deficits with implantation of contemporary ICDs using intravenous conscious sedation and limited or no ventricular fibrillation inductions can be analyzed
Determine whether there are sex differences in interventions with therapeutic lifestyle changes to decrease cognitive impairment

AF indicates atrial fibrillation; CI, cognitive impairment; CVD, cardiovascular disease; ICD, implantable cardioverter defibrillator.

health we endorse recommendations from national organizations such as the American Heart Association and others for promotion of cardiovascular health as a means of maintaining brain health.<sup>111</sup>

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## Disclosures

Dr Volgman is a consultant of the American Heart Association and a speaker for Aptus Health. Dr Aggarwal has contracts between Rush University and trial sponsors to allow her to serve as a member of the Steering Committee or as site PI for the following trials: Eli Lilly: A4 Study Novartis, Amgen: Generation Study. Dr Bunch has an Institutional grant from Boehringer Ingelheim for the Cognitive Atrial Fibrillation (CAF) trial. Dr Bittner has contracts between University of Alabama and trial sponsors to allow her to serve as member of executive steering committee or as national coordinator for the following trials: Sanofi/Regeneron: ODYSSEY OUTCOMES TRIAL (Steering Committee); Astra Zeneca: STRENGTH Trial (National Coordinator); Esperion: CLEAR Trial (National Coordinator); Dalcor: Dalgene Trial (National Coordinator). She also has contracts between University of Alabama and trial

sponsors to allow her to serve as a site principal investigator for the following trials: Astra Zeneca: ARTEMIS Trial, Bayer Healthcare: COMPASS Trial. She has received honoraria for attending Advisory Board meetings for Sanofi. Dr Gorelick serves on a Novartis Data Safety and Monitoring Board committee for a study of cognition in patients with heart failure utilizing the drug LCZ 696. Dr Maki is a speaker for Mylan Pharmaceutical. Dr Poppas has GE stock worth > \$10 000.00. Dr Ruskin is a consultant for Acesion Pharma, Advanced Medical Education, Apple Inc., InCarda Therapeutics, Janssen, and Cala Health. He is a consultant with equity for Portola Pharmaceuticals. He is on the Scientific Advisory Board with equity options for Element Science, InfoBionic, and NewPace Medical. He is on the Scientific Advisory Board for Lantheus Medical. He is on the Steering Committee of Medtronic Pfizer. He is on the Data Monitoring Committee for Gilead Sciences. Dr Russo conducts clinical research trials for Boston Scientific, Boehringer Ingelheim, and Medtronic. She has received honoraria for consulting for Biotronik, Boston Scientific, Medtronic, and St. Jude, Zoll. She receives honorarium from Up-to-Date and Fellowship support from Medtronic. The remaining authors have no disclosures to report.

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**Key Words:** Alzheimer disease • APOE • cardiac procedures • complication • dementia • ischemic heart disease • strokes