Stroke

TOPICAL REVIEW

Role of Cardiac Biomarkers in Stroke and Cognitive Impairment

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ABSTRACT: This topical review assesses the growing role of cardiac biomarkers beyond cardiovascular health and focuses on their importance in stroke and dementia. The first part describes blood-based cardiac biomarkers in patients with stroke and highlights applications in the setting of early diagnosis, poststroke complications, outcome prediction as well as secondary prevention. Among other applications, natriuretic peptides can be helpful in differentiating stroke subtypes. They are also currently being investigated to guide prolonged ECG monitoring and secondary prevention in patients with stroke. Elevated cardiac troponin after ischemic stroke can provide information about various poststroke complications recently termed the stroke-heart syndrome. The second part focuses on the role of cardiac biomarkers in vascular cognitive impairment and dementia, emphasizing their association with structural brain lesions. These lesions such as silent brain infarcts and white matter hyperintensities often co-occur with cardiac disease and may be important mediators between cardiovascular disease and subsequent cognitive decline. ECG and echocardiogram measurements, in addition to blood-based biomarkers, show consistent associations with vascular brain changes and incident dementia, suggesting a role in indicating risk for cognitive decline. Together, the current evidence suggests that cardiac blood-based, electrophysiological, and imaging biomarkers can be used to better understand the heart and brain connection in the setting of not only stroke but also dementia.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: biomarker ■ cardiovascular disease ■ dementia ■ troponin ■ white matter

Cardiac biomarkers can indicate overt cardiac pathology, such as myocardial infarction (MI), but they can also point toward asymptomatic disease states, like atrial fibrillation (AF). They play a role in identifying cardiac etiologies of stroke, estimating the risk of poststroke cardiac complications, and even stroke recurrence rates, as well as indicating risk for cognitive decline.

Electrophysiological, imaging, and blood-based biomarkers reflecting different cardiac diseases at different stages could be useful in various clinical scenarios. Our first objective is to discuss the use of cardiac biomarkers in patients with stroke, such as for prehospital triage, prediction of in-hospital complications poststroke, etiologic workup, and guidance of secondary prevention, with a special focus on blood-based biomarkers (Figure).

Concurrent with the use of cardiac biomarkers in the stroke setting, different cardiac disease entities have also been associated with the presence of subclinical brain lesions, for example, white matter hyperintensities (WMHs) or brain infarcts, which are known to contribute to cognitive decline. Our second objective is therefore to discuss the potential for cardiac biomarkers, either electrophysiological, imaging or blood-based, to provide insight into vascular cognitive impairment or dementia, even apart from clinical stroke (Figure).

Stroke Diagnosis and Triage

Blood-based cardiac biomarkers could play a role in initial stroke diagnostics and triage in the emergency department. The measurement of a panel of biomarkers reflecting different pathways involved in stroke-pathogenesis could help in distinguishing stroke from stroke-mimics, or ischemic from hemorrhagic strokes.

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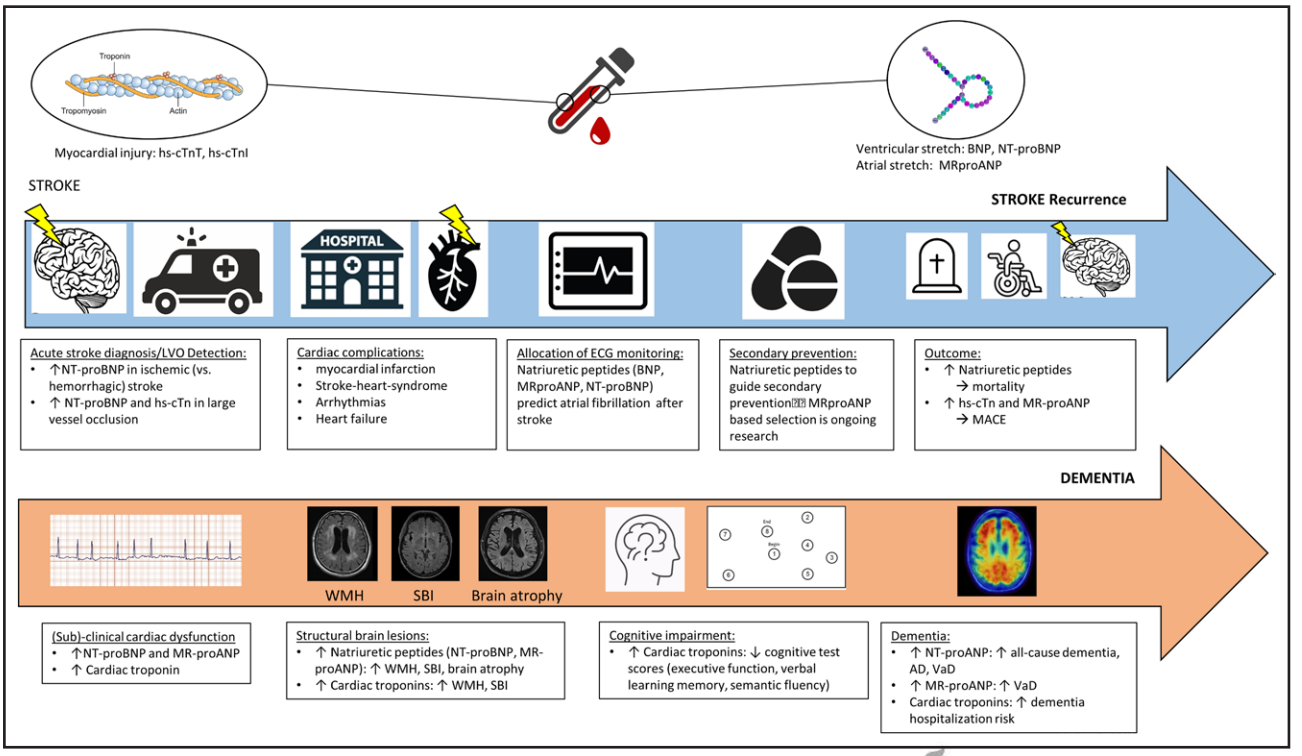

Figure. The use of cardiac biomarkers in stroke and dementia.
A graphical display of the potential points in time at which cardiac biomarkers could provide insight along the diagnostic, and prognostic pathway of disease for both stroke and dementia. BNP indicates B-type natriuretic peptide; hs-cTN, high-sensitivity cardiac troponin; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and WMH, white matter hyperintensities.

While a diagnosis of stroke based on a blood-based biomarker (a troponin of stroke) is still far from being clinically implemented,[1] some studies have tested the combination of several biomarkers in a panel that include cardiac biomarkers for acute stroke diagnosis. For example, the active form of BNP (B-type natriuretic peptide), NT-proBNP (N-terminal pro-B-type natriuretic peptide), a marker of myocardial stretch, was found to distinguish ischemic from hemorrhagic stroke subtypes. However, the discriminative value of this biomarker was considered insufficient for its application in clinical practice.[1] In another study, a 3-biomarker panel (NT-proBNP, GFAP [glial fibrillary acid protein], and RBP-4 [retinol binding protein 4], which is associated with diabetes and insulin resistance) measured within 4.5 hours after stroke symptom onset, provided a non-negligible specificity (>50%) and a high sensitivity (at 100%) for ischemic stroke compared with hemorrhagic stroke.[2] These results, if replicated at the prehospital level, might allow for identification of >1/2 of patients with ischemic stroke, who then could begin thrombolysis prehospital, without obtaining a head CT.[3] However, this is not without controversy, given the important additional information that neuroimaging can offer acutely (such as infarct demarcation) and the fact that portable imaging systems are increasingly available.

Another way cardiac biomarkers could be used is in prediction of large-vessel occlusion (LVO). Since cardiac biomarkers are associated with cardioembolic stroke, and cardioembolism is a common cause of LVO,[4] elevated cardiac biomarkers may suggest an LVO is present. In a secondary analysis of the Stroke-Chip study,[1] NT-proBNP levels were higher among those with LVO, but the association was not statistically significant after adjusting for stroke severity, vascular risk factors, and other blood-based biomarkers.[5] hs-cTn (high-sensitivity cardiac troponin) elevation has also been associated with LVO.[6] A panel of cardiac biomarkers might add to the precision of prehospital scales used to identify LVO patients before vessel imaging. The BIOFAST (Biomarkers for Initiating Onsite and Faster Ambulance Stroke Therapies, http://biofast.technology/biofast/) and the ProGrEss-Bio studies[7] are evaluating the feasibility of measuring biomarkers in the prehospital phase using point-of-care testing,[4] potentially accelerating their integration into clinical practice.

An overview of the above-discussed studies is provided in Table S1.

Acute Poststroke Complications

Up to 60% of patients with ischemic stroke have elevated levels of hs-cTn above the upper reference limit in the acute phase.[8] Patient characteristics that are associated with higher levels of hs-cTn after acute ischemic stroke include older age, impaired renal function, a history of

cardiac comorbidities and higher stroke severity.[9,10] By performing serial hs-cTn measurements, one can distinguish between acute and chronic myocardial injury, both of which occur in patients with ischemic stroke. Usually, the levels of hs-cTn observed during the first days after ischemic stroke are relatively stable, thus indicating chronic (versus acute) myocardial injury.[11,12] About 5% to 20% of patients with stroke, however, will have a rise and fall pattern of hs-cTn, indicating acute myocardial injury.[8] The mechanisms that lead to (acute) elevation of cardiac biomarkers can vary widely, and most cardiac biomarkers are not specific to the underlying pathophysiological mechanism. A coronary culprit lesion that is indicative of a type 1 MI is found in 20% to 25% of patients with stroke with hs-cTn elevation.[12] How to identify patients with stroke with hs-cTn elevation that would benefit from coronary angiography and stent angioplasty is still unclear and is the topic of ongoing research.[13] Clinical symptoms, ECG and echocardiography should be considered in the assessment of signs of myocardial ischemia.[14]

hs-cTn elevation after stroke may also be caused by type 2 MI, which occurs due to a mismatch between coronary oxygen supply and demand.[14,15] Potential triggers of type 2 MI in patients with stroke include tachyarrhythmia, hypertensive emergency, severe anemia, or respiratory failure.[14] Patients with stroke with hs-cTn elevation should therefore also be assessed regarding potential triggers of type 2 MI.

Previous studies have shown an association between stroke localization, stroke severity, and elevation of hs-cTn.[9,10] One study found that patients with ischemic stroke with elevated hs-cTn levels are more likely to have a lesion involving the insular cortex (odds ratio [OR], 2.7 [95% CI, 1.6–4.5]).[9] Using voxel-based lesion symptom mapping, acute myocardial injury was associated with lesions located in the right anterior insular lobe.[16] This supports the notion that acute myocardial injury may actually be induced by the ischemic stroke itself.[15] The insular region is part of the central autonomic network and particularly lesions in the right insula can lead to an increased sympathetic activation and activation of the hypothalamus-pituitary-adrenal axis.[15]

Possible consequences of the increase in catecholamine and cortisol levels include cardiac arrhythmias, myocardial contraction band necrosis as well as takotsubo-like myocardial stunning.[15] hs-cTn elevation can indicate arrhythmias, such as prolonged QTc time, and has been associated with systolic dysfunction on echocardiography and acute heart failure in stroke.[17,18] These observations have led to the development of the term stroke-heart syndrome.[15] To date, there are no evidence-based treatment recommendations for patients with stroke-heart syndrome. However, patients may benefit from prolonged cardiac monitoring to detect arrhythmias as well as a noninvasive workup including echocardiography or cardiac magnetic resonance imaging (MRI) to assess possible heart failure.[14] In addition, it may be beneficial to avoid QTc prolonging drugs (eg, antidepressants or antipsychotics).[19]

An overview of the above-discussed studies is provided in Table S2.

Mortality, Stroke Recurrence, and Functional Outcome

Poststroke mortality is the outcome that has been associated most consistently with elevated levels of several cardiac biomarkers. Higher levels of different natriuretic peptides (MR-proANP [midregional proatrial natriuretic peptide], BNP, and NT-proBNP) have been associated with higher mortality rates after stroke[20–22]: 1 study including 788 patients with ischemic stroke found that levels of MR-proANP were significantly associated with mortality up to 90 days poststroke (adjusted hazard ratio [HR], 6.1 [95% CI, 2.4–15.8]).[21] Another study found that BNP levels were associated with higher mortality up to 1 year after stroke (HR, 1.2 [95% CI, 1.1–1.4]).[22]

Concerning prediction of long-term mortality rates after stroke, 1 study found that higher levels of NT-proBNP were associated with higher mortality up to 5 years poststroke (OR, 5.1 [95% CI, 2.0–13.1]).[23] The cutoff of 794 pg/mL predicted long-term mortality after stroke with a sensitivity of 90% and specificity of 67.5%.[23] Several studies also compared the predictive value of natriuretic peptides on poststroke mortality to clinical predictors alone.[20–22] The addition of MR-proANP, BNP, and NT-proBNP led to a significantly improved prediction of poststroke mortality compared with clinical variables alone.[20–22]

Elevation of hs-cTn has also been linked to higher rates of poststroke mortality across several studies after adjustment for age, stroke severity, and cardiovascular comorbidities but with some conflicting results.[8,24,25] When compared with clinical parameters alone, 1 study found that addition of hs-cTn leads to a moderately improved prediction of mortality after stroke (*C*-index, 0.819 versus 0.834),[26] while another study found that prediction of mortality was not improved by hs-cTn.[22]

Elevation of hs-cTn has been linked to a higher risk of major recurrent cardiovascular events for up to 3 years after an ischemic stroke and transient ischemic attack.[24,27,28] After categorization of patients into quartiles based on hs-cTn levels, a dose-response effect with regard to recurrent cardiovascular events could be observed (15.2 versus 1.8 events per 100 person-years; HR, 4.8 [95% CI, 1.9–11.8]).[27] Also, MR-proANP was independently associated with major recurrent cardiovascular events within 1 year after stroke even after taking into account competing risks (subdistributional HR, 2.0 [95% CI, 1.3–3.1]). The association was more pronounced among patients with cryptogenic stroke (HR, 15.9 [95% CI, 2.9–27.4]).[29]

The link between cardiac biomarkers and functional outcomes apart from mortality after stroke is less clear. Several studies found an independent association

between BNP, NT-proBNP, or MR-proANP and functional outcome assessed by the modified Rankin Scale after 90 days.[23,24,30] In most studies, poor functional outcome was, however, defined as an modified Rankin Scale score of >2, including mortality. Moreover, when compared with clinical parameters alone, adding natriuretic peptides or hs-cTn did not improve the prediction of functional outcome after stroke in other studies.[20,21,31]

An overview of the above-discussed studies is provided in Table S3.

Guidance in Prolonged ECG Monitoring

Elevated levels of natriuretic peptides co-occur with paroxysmal AF[29–31] and thus may represent a potential complementary strategy by which to determine who receives prolonged ECG monitoring poststroke. This is particularly important in low-resource settings and could therefore help to distribute resources more appropriately.[29] Limitations of current research in this area include heterogeneous inclusion criteria (eg, all patients with ischemic stroke versus embolic stroke of undetermined source only), duration of monitoring, the time point of measurement of the biomarker with respect to symptom onset and even the definition of clinically significant AF on follow-up.[32]

For example, while several studies suggest that BNP performs better than NT-proBNP at predicting AF,[33,34] the NOR-FIB study (The Nordic Atrial Fibrillation and Stroke Study) suggested that NT-proBNP performed better than BNP and was actually the only independent biomarker associated with AF diagnosed after stroke after adjustment for potential confounders.[35] In the studies that showed superiority for BNP, biomarker measurement was performed earlier (within 72 and 24 hours, respectively), while in the NOR-FIB study, samples were taken up to 14 days after stroke onset. These conflicting results might reflect different optimal time points for the measurement of different natriuretic peptides to predict AF diagnosed after stroke. Thus, the latest ESO guideline (2022) did not yet recommend using blood-based biomarkers as exclusive parameters for AF screening after stroke.[36] MR-proANP has been associated with cardioembolic stroke etiology, history of AF as well as AF diagnosed after stroke up to 1-year poststroke.[20,29,30] MR-proANP currently provides the only external validated biomarker using the same assay and time point of measurement for the prediction of AF diagnosed after stroke in all ischemic stroke subtypes.[20,29] New cardiac biomarkers such as angiopoietin 2, an endothelial growth factor, and Dickkopf-related protein 3, involved in heart development and found overexpressed in atrial appendages of patients with AF,[37] have been described in recent years, as well as other analytes such as microRNAs.[38] Moreover, echocardiographic and ECG markers have also been described as useful to predict AF. Although an additional description of these markers is beyond the scope of the present review, the combination of several multimodal markers from different pathophysiological pathways might be helpful to develop algorithms that will lead to clinical decision-making in the near future.

An overview of the above-discussed studies is provided in Table S4.

Guidance of Secondary Prevention

Unless AF is diagnosed, patients with underlying paroxysmal AF do not receive the type of antithrombotic drug that best prevents them from having another stroke (ie, oral anticoagulation). However, recent research indicates that embolization from the heart can occur when there are abnormal changes to atrial tissue and function before AF is diagnosed, or even separate from AF.[39,40] Blood-based biomarkers may provide additional insight into the identification of underlying atrial cardiopathy or preclinical AF and thus risk for left atrial (LA) thromboembolism.

The ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) was the first study to specifically define atrial cardiopathy using a cardiac biomarker, NT-proBNP, as well as ECG and echo markers to try to identify patients who might benefit from oral anticoagulation versus aspirin in the absence of AF.[41] Patients with recent embolic stroke of undetermined source and at least 1 marker of atrial cardiopathy were eligible. The study failed to detect a significant difference in stroke recurrence among those on apixaban versus aspirin.[41]

There could be several reasons why no difference was detected and one might be the threshold chosen for NT-proBNP (>250 pl/mL). In a post hoc analysis of the WARSS trial (Warfarin-Aspirin Recurrent Stroke Study), only NT-proBNP levels >750 pg/mL showed a difference in 2-year probability of stroke or death among patients randomized to warfarin versus aspirin.[42] The question remains how best to identify patients at high risk for cardiac embolism resulting in stroke recurrence who have not yet been diagnosed with AF at the time of the index stroke. The MOSES trial (Midregional Proatrial Natriuretic Peptide to Guide Secondary Stroke Prevention) is an ongoing biomarker-guided secondary prevention trial, which aims to select exactly these high-risk patients using MR-proANP, which was also implicated as a causal factor in AF development[43,44] with the cutoff being highly associated with AF.[20,29,45] The design of the study differs from ARCADIA in that it is not restricted to patients with embolic stroke of undetermined source. As a result, this study might offer new insights concerning patient selection for different secondary stroke prevention strategies.

STRUCTURAL BRAIN LESIONS AND COGNITIVE END POINTS

We now transition to a second important potential use of cardiac biomarkers and that is in predicting risk of cognitive decline. Cardiac biomarkers could help us understand

the cognitive trajectory of individuals with cardiovascular disease (CVD) risk factors, or clinical CVD, even apart from clinical stroke.[46] Besides blood-based cardiac biomarkers, we also include a discussion of cardiac imaging biomarkers.

Cerebrovascular pathology is a common finding in all types of dementia and a synergistic effect between Alzheimer disease (AD) and cerebrovascular pathology has been demonstrated.[47] Although a full review of this is outside the scope of this article, it is important to acknowledge that structural brain lesions such as WMHs and cerebral microbleeds often co-occur with cardiac disease[48,49] and represent a key mediator between the existing cardiac disease state and subsequent cognitive decline and dementia.[49] It is plausible that either a cardiac condition could directly contribute to the imaging-based brain pathology, or shared CVD risk factors may affect both the heart and the brain, independently from each other.[50] We think blood-based cardiac biomarkers could be a valuable tool in suggesting the presence of these important cerebral imaging markers,[51] as well as predicting cognitive trajectories over time.

Natriuretic Peptides

Several population-based studies have explored the association of elevated natriuretic peptide levels with neurodegenerative and vascular brain changes. In cross-sectional analyses, higher levels of NT-proBNP were associated with lower total brain, gray matter, and white matter volume independent of cardiovascular risk factors[52,53] In a longitudinal analysis, each unit of higher NT-proBNP was associated with 3.6 mL (95% CI, −6.0 to −1.1) decline in total brain volume and 3.5 mL (95% CI, −5.7 to −1.3) decline in gray matter volume over a period of 5 years.[54]

Among 1920 participants of the ARIC (Atherosclerosis Risk in Communities) study, individuals in the highest NT-proBNP quartile had significantly more infarcts (OR, 3.5 [95% CI, 2.0–6.2]), and WMH (β-coefficient, 0.09; SE, 0.03) on the baseline MRI and more incident infarcts (OR, 2.2 [95% CI, 1.4–3.5]) and WMH progression (β-coefficient, 0.22; SE, 0.10) on the follow-up MRI.[55]

MR-proANP is another natriuretic peptide for which an association with structural brain lesions was found. In 1178 subjects from the Northern Manhattan Study, elevated MR-proANP was associated with a higher frequency of infarcts and greater volume of WMH.[56]

There is evidence for an association of natriuretic peptides with both prevalent and incident dementia. In a longitudinal analysis of 6040 individuals, NT-proBNP was associated with a higher risk of dementia, even after adjusting for cardiovascular risk factors (HR per SD, 1.3 [95% CI, 1.1–1.4]). Associations were particularly strong for vascular dementia (HR per SD, 2.0 [95% CI, 1.2–3.6]).[57] There are less data on the association of MR-proANP with cognitive function, but the data published showed that elevated MR-proANP was associated with all-cause dementia and vascular dementia (not AD).[58] However, further studies are needed to investigate possible differential associations between different natriuretic peptides.

An overview of the above-discussed studies is provided in Table S5.

Cardiac Troponins

There is already a well-established association between prevalent CVD or stroke and hs-cTn, but an important future role for hs-cTn is defining its importance relative to cognition among those without these prevalent disease states. Among 1920 participants of the ARIC study, individuals in the highest hs-cTnT category had more infarcts (OR, 3.0 [95% CI, 1.6–5.8]) and WMH (β-coefficient, 0.11; SE, 0.04) on the initial MRI and more WMH progression (β-coefficient, 0.43; SE, 0.17) compared with individuals in the lowest category.[55] Another study including 3011 individuals assessed whether associations of cardiac biomarkers with structural brain changes and different cognitive domains were modified by age (<60 versus ≥60 years)[59]

Higher hs-cTnT was associated with greater WMH in both age groups, independent of educational level, CVD risk, and lifestyle factors.[59] While the data are strong concerning hs-cTn and vascular brain lesions, there are limited data on its association with more classical MRI-defined markers of neurodegeneration (eg, brain volume, cortical thickness). Whether there is a differential association between hs-cTn and vascular markers of brain damage versus neurodegenerative markers needs further evaluation. There are several studies investigating the link between hs-cTn and cognitive impairment and dementia. A population-based study including 9472 participants demonstrated an association between higher hs-cTnT with lower cognitive test scores and with an increased risk for hospitalization with dementia overall and with vascular dementia but not with AD.[60] In 7114 individuals of the population-based FINRISK study, hs-cTnI was associated with incident dementia (HR, 1.1 [95% CI, 1.0–1.2]), but not independent of NT-proBNP (HR, 1.1 [95% CI, 1.0–1.2]).[61] These results suggest that the different cardiac biomarkers, which capture distinct underlying cardiac pathologies may also be associated with cognitive impairment to varying degrees.

An overview of the above-discussed studies is provided in Table S6.

Electrical and Anatomic Measures of Cardiac Structure and Function

Two methods used to assess cardiovascular health are the ECG and the echocardiogram. These tests of cardiac

function have also been leveraged as biomarkers in research focusing on incident dementia, as well as defining associations between specific measures of cardiac anatomy and changes in cognition overtime.

Perhaps one of the easiest tools to use at the bedside to determine rhythm abnormalities is the ECG.[62] P wave morphology has been a key measure by which AF has been predicted,[63] and has been shown to improve prediction of ischemic stroke when added to the CHADS-VASc score. In a large prospective cohort study of older adults, markers of abnormal P wave morphology, such as an abnormal P wave axis and a prolonged P wave duration, were found to be associated with an increased risk of dementia, even after adjusting for both stroke, and incident AF.[64] A systematic review of 14 eligible studies identified rapid heart rate and p-wave morphology as potential risk factors for dementia,[65] in addition to left ventricular hypertrophy. In 5153 participants living in rural China, prolonged QT and QTc intervals were associated with all-cause dementia, as well as AD and vascular dementia, using DSM-IV criteria. Perhaps, more interestingly, there was a subset of individuals in the same study with plasma AD biomarkers (N=1281), and the investigators found that prolonged QT intervals were significantly associated with a lower $A\beta_{42}/A\beta_{40}$ ratio.[66] Although the exact mechanisms behind these associations are yet to be determined, and some of this data is limited as it reflects a single point in time, it is likely that ECG parameters reflect subclinical cardiac dysfunction, which may lead to either silent infarction or lobar shrinkage through hypoperfusion, as has been suggested in studies examining associations with p-wave parameters and cerebral imaging.[67]

An overview of the above-discussed studies is provided in Table S7.

Echocardiography is another low-risk test that can be used to characterize cardiac structure and function. In a recent publication including nearly 5000 participants followed for a median of 6 years for incident dementia, the investigators used echo with strain to assess measures of stretch in the left atrium. For all LA measures included, the incidence of all-cause dementia was the highest when the parameter was in the lowest quintile (among participants) suggesting that the risk of poorer cognition was highest among those with a worse functioning LA.[68]

An overview of the above-discussed studies is provided in Table S8.

Specific Cardiac Disease States

Finally, diagnosed cardiac diseases have also been shown to be associated with both incident dementia and cognitive decline overtime.[69] One important way by which cardiac disease, such as AF or MI could lead to dementia is through clinically diagnosed stroke.[70] However, even apart from clinically apparent stroke, there is evidence to support a link between cardiac disease and cognitive change overtime.

Atrial cardiopathy has been defined as a state of LA dysfunction and has been implicated as a risk factor of ischemic stroke, even apart from the development of AF, and likely serves as a potential source of stasis, and thereby embolism.[40] Among 5078 participants (mean age, 75 years old) in a prospective cohort study, investigators classified 763 as having atrial cardiopathy using cardiac biomarkers (abnormal p-wave terminal force, elevated NT-proBNP, and enlarged LA volume index by transthoracic echo). A study defined atrial cardiopathy was associated with incident dementia, even after excluding those with AF or stroke. The possible pathophysiology behind atrial cardiopathy–related cognitive impairment is multifactorial. It may include LA thrombogenicity leading to micro embolism[69] or there might be a direct association with underlying dementia pathology, such as beta-amyloid. This is supported by data that demonstrated higher odds of an elevated florbetapir standardized uptake value ratio (an imaging marker of cerebral amyloid) among those with atrial cardiopathy, even after controlling for age and vascular risk factors.[70] Although at the current time it is impossible to tell if the link between atrial cardiopathy and dementia is simply due to vascular risk factors that cannot be captured with adjustment, versus atrial cardiopathy itself being causal, it is at the least, an important indicator of elevated risk.

AF is perhaps one of the most discussed cardiac disease states with regard to cognitive decline and dementia, with research in this area ongoing. Prior systematic reviews have shown higher odds of dementia[71] in stroke-free patients with AF compared with stroke-free patients without AF. Hypothesized mechanisms include AF-induced decreased brain volume through a chronic state of hypoperfusion, systemic inflammation, cerebral microbleed, and possible adverse side effects of medications, such as anticoagulation. However, the data on whether or not anticoagulation is protective or harmful for brain health is still controversial.[72] Infarcts are likely an important contributor to cognitive decline in patients with AF: among 935 stroke-free patients, declines in verbal fluency and executive functioning were only associated with AF if there were infarcts on cerebral imaging.[73] There are several ongoing clinical trials with cognitive end points that will be helpful in the coming years to answer different aspects of this AF-cognition relationship, such as a sub-study of the ARTESiA trial (Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical AF), which will seek to answer (1) the minimal amount of AF burden associated with cognitive decline/dementia and (2) whether or not anticoagulation impacts the cognitive trajectory.[72]

MI is another disease with important public health implications with an estimated 1 person in the United States having an MI every 40 seconds.[74] The annual

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reported death rate secondary to coronary heart disease declined by 25.2% in the last decade, which is good news. However, it also means that those with incident MI are more likely to survive (increasing prevalence).[74] The ability of these patients to survive may increase the risk of post-MI complications and thus the development of cognitive decline. A meta-analysis of 24 801 participants found that the presence of coronary heart disease increased future risk of dementia or cognitive impairment nearly 2 times (OR, 1.5 [95% CI, 1.2–1.7]).[75] In a recent harmonized analysis of cognitive tests of over 30 000 participants from 6 different longitudinal cohort studies, the 1033 individuals who had an acute MI had a steeper annual cognitive decline after the MI than those without MI, even after carefully accounting for shared vascular risk factors, censoring those with prevalent stroke and adjustment for AF.[76]

CONCLUSIONS

The evidence to date suggests that cardiac biomarkers, either blood-based or electrophysiological and cardiac imaging markers, can play an important role in identifying undiagnosed cardiac causes of stroke, estimating the risk of cardiac complications after stroke, and stroke recurrence rates. Cardiac biomarkers may help in improving clinical decision-making by answering specific clinical questions at different time points along a disease process (Figure).

In addition, the same biomarkers can be used to better understand the association between cardiac disease and cognitive decline or incident dementia, potentially mediated by structural brain changes.[77]

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S8
References 78,79

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