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Major Adverse Cognitive Events (MACE-Cog): A New "MACE" Framework for Cognitive Outcomes in Cardiovascular Diseases and Stroke

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ABSTRACT: Cardiovascular diseases, particularly stroke, are leading causes of dementia. Several common cardiac interventions such as coronary artery bypass grafting and transcatheter aortic valve implantation are also associated with cognitive decline. However, cognitive outcomes continue to be poorly collected in clinical trials of cardiovascular diseases. In this article, we review the limitations of current approaches to cognitive assessment in cardiovascular disease studies. When assessed, there is wide variation in cognitive tasks used, and tasks have limited population-specific validation, are subject to floor and ceiling effects, and may suffer from sociocultural and linguistic biases. Many tasks are not available in multilingual formats and often rely on face-to-face testing with trained coordinators. All conventional cognitive outcomes in cardiovascular trials are associated with substantial incompletion, especially among older and more impaired individuals, the very people most important to capture. This nonrandom missingness generates survivor and attrition biases, an unacceptable situation for any trial outcome. Last, the meaning of measured cognitive outcomes is often unclear for patients, caregivers, clinicians, and regulators. To help address these limitations, we propose a new framework, major adverse cognitive events (MACE-Cog), to better capture cognitive outcomes in stroke and other cardiovascular populations. As an inclusive construct reflecting the multidimensional nature of cognitive decline, major adverse cognitive events do not rely solely on performance on cognitive testing but also consider inability to complete cognitive testing due to cognitive-behavioral factors, reported symptoms of cognitive decline, impairment in activities of daily living as a result of cognitive impairment, new clinical diagnoses of dementia, and care home admission. We hope that the proposed composite outcome and multiple use cases presented spark progress in cardiovascular research toward more inclusive approaches to the study of cognitive outcomes that move beyond the confines of cognitive tests alone.

Key Words: cardiovascular diseases ■ cognition ■ randomized controlled trial ■ stroke

Cognitive impairment is a leading contributor to the global burden of disease, affecting >57 million people worldwide.[1] Cognitive impairment refers to deterioration in ≥1 cognitive abilities, including memory, executive function, language, visuospatial function, and social cognition.[2] These changes can arise from a variety of processes that damage brain tissue, including neurodegenerative disorders (the most common one being Alzheimer disease), cerebrovascular disorders, and other pathologies, both chronic and acute (eg, anesthesia impact in postsurgical patients).[3] Cognitive function exists along a spectrum. This spectrum ranges from normal cognition to mild cognitive impairment/mild neurocognitive disorder (characterized by evidence of cognitive decline with preserved independence in activities of daily living [ADLs]), to dementia/major neurocognitive

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Nonstandard Abbreviations and Acronyms

ADL	activities of daily living
CDR-SB	Clinical Dementia Rating Scale Sum of Boxes
CVD	cardiovascular disease
IADL	instrumental activities of daily living
LACI-2	Lacunar Intervention Trial-2
MACE	major adverse cardiac event
MACE-Cog	major adverse cognitive events
MCID	minimal clinically important difference
MoCA	Montreal Cognitive Assessment
mRS	modified Rankin Scale
OXCASC	Oxford Vascular Study
R4VaD	Rates, Risks and Routes to Reduce Vascular Dementia
VasCog	International Society of Vascular Behavioural and Cognitive Disorders
VCID	vascular cognitive impairment and dementia

disorder (characterized by cognitive decline accompanied by a loss of independence in ADLs; Figure 1).[4]

Cardiovascular diseases (CVDs), particularly stroke, are a leading cause of cognitive decline and dementia. For example, cognitive impairment is a well-recognized short- and long-term complication of stroke that progresses to dementia in up to one-third of patients within 1 year of a moderate to severe stroke.[5–7] Incident stroke is associated with a >2-fold risk of dementia, suggesting that it is a strong, independent, and potentially modifiable risk factor for all-cause dementia.[8–10] Even strokes that do not cause detectable physical deficits (covert strokes) are associated with cognitive decline.[11]

Cardiac diseases such as heart failure, atrial fibrillation, and myocardial infarction are also associated with cognitive decline,[3] and up to 50% of cardiac arrest survivors have cognitive impairment at the 3-month follow-up.[12] Several common cardiac interventions are also associated with cognitive decline.[13,14] For example, cognitive impairment is seen in about one-third of patients undergoing transcatheter aortic valve implantation[15] and up to 40% of patients after coronary artery bypass graft.[16]

MECHANISMS AND ASSESSMENT OF COGNITIVE ISSUES IN CARDIOVASCULAR DISEASES

Overt cerebrovascular events, covert events, brain injuries from CVDs, and even vascular risk factors such as hypertension and diabetes can cause cognitive deficits or dementia through multiple mechanisms.[3] They can cause direct injury to strategic brain areas with immediate cognitive consequences. They can undermine fragile brain

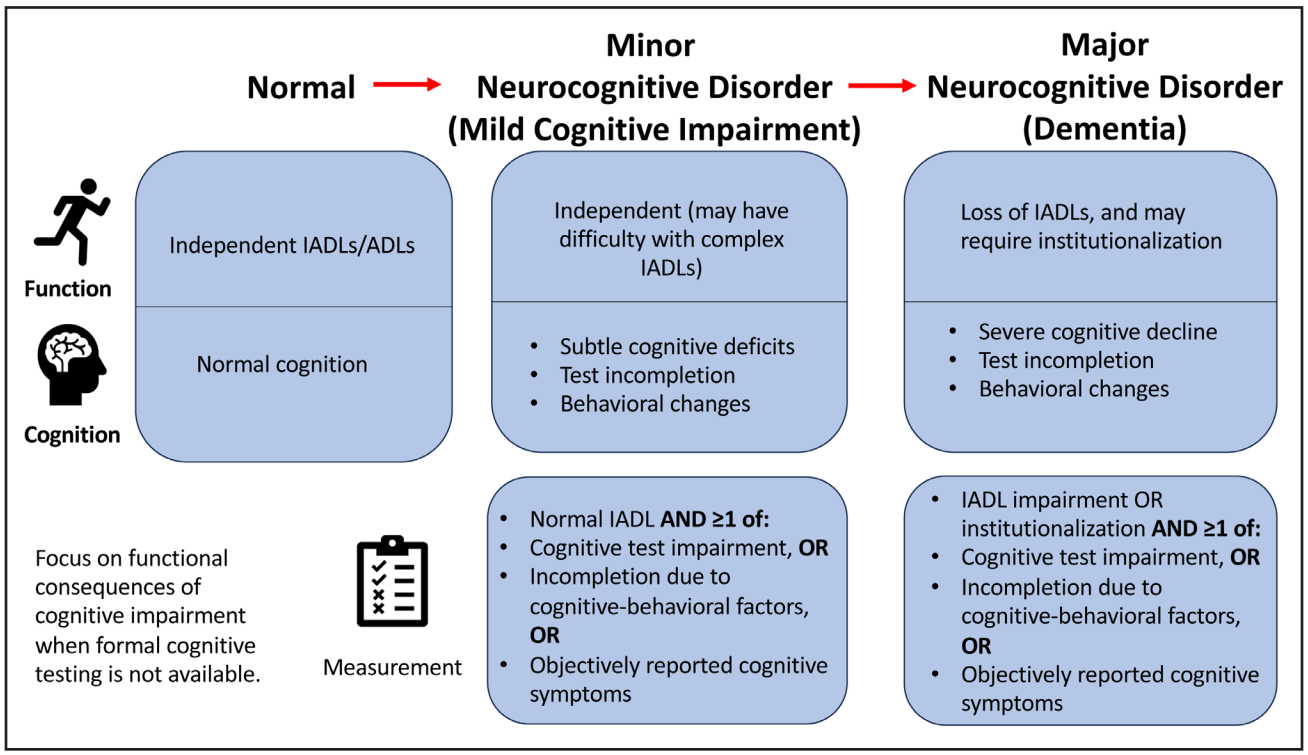

Figure 1. The spectrum of neurocognition and cognitive decline ranging from normal cognition to mild cognitive impairment (mild neurocognitive disorder) to dementia (major neurocognitive disorder).
ADL indicates activities of daily living; and IADL, instrumental activities of daily living.

networks, unmasking or accelerating cognitive changes related to preexisting neurodegenerative diseases.[17] They can also indirectly accelerate neurodegeneration through multiple mechanisms, including neuroinflammation, hypoperfusion with altered cerebral circulation and collateral flow, and white matter injury.[18] Thus, the onset of cognitive decline may become apparent immediately after a cardiovascular event/procedure, or there may be a delay.[19] Regardless, the consequences can be dire; for instance, poststroke dementia is a major contributor to poststroke dependency[20,21] and mortality.[22] Indeed, cognitive impairment and dementia are among the most feared outcomes among individuals with CVD and their families, as highlighted in research priority-setting exercises.[23,24]

It is essential to note that ascertainment of cognitive outcomes in a clinical trial setting (ie, determining whether someone has developed an adverse cognitive outcome such as cognitive impairment or dementia) is fundamentally different from determining the underlying cause of the outcome in question. However, a few etiological considerations bear mentioning. The VasCog group (International Society of Vascular Behavioural and Cognitive Disorders) recently published a second iteration (VasCog-2–World Stroke Organization) of criteria for diagnosing the clinicopathological entity of vascular cognitive impairment and dementia (VCID) as a successor to the original version from 2014, providing operationalization and guidance on potential neuroimaging and fluid biomarkers to facilitate diagnostic consistency among clinicians and researchers.[25] Those criteria describe preclinical, mild, and major dementia levels of VCID, reflecting the spectrum of cognitive outcomes as we have outlined here and in Figure 1. It is important to note that that version also acknowledges that there is no standard cognitive testing profile that is diagnostic of vascular disease, a crucial point for CVD trials.[26,27] Of course, when a patient presents with abrupt and persistent onset of cognitive impairment in the immediate aftermath of a clinical stroke or cardiovascular event/procedure, there is little controversy about CVD as a main underlying cause, but cases are often not so clear-cut in practice. Even that situation may have underlying neurodegenerative disease pathology that is unmasked by the event. Ultimately, we must acknowledge that in a CVD trial, an adverse cognitive outcome itself is important to capture, regardless of our ability to specifically attribute it to VCID, neurodegenerative disease, mixed disease, or other causes. From a participant perspective, the outcome (eg, disabling cognitive impairment) has an immediate impact on their life, whereas the cause, although potentially relevant for devising future prevention strategies, is of secondary importance.[23] This is similar to how we think about other well-established outcomes such as all-cause mortality, major adverse cardiac events (MACE), physical function (modified Rankin Scale [mRS] score), or health-related quality of life in CVD trials. In these instances, their importance is universally understood, but for the most part, ascertainment of these outcomes does not presume that the outcome is always due to a particular cause. In fact, overthinking the etiologic underpinning of outcomes can lead to bias, as has been noted in oncological trials in which all-cause mortality may be less vulnerable to clinician biases that can affect which events are categorized as "cancer-specific" mortality.[28] In practice, cognitive impairment is also often multifactorial in nature, and disentangling VCID from non-VCID contributors can be a challenging endeavour for both clinical research personnel and expert cognitive specialists. Therefore, it is important for ascertainment of cognitive outcomes in CVD trials to be etiologically agnostic, unconstrained by black-and-white categorical diagnoses of CVD-related cognitive impairments.[29]

Regardless of mechanism, cognitive function has received insufficient attention as a clinically relevant outcome in cardiovascular trials, which have traditionally prioritized cardiovascular events (MACEs), physical function (mRS score), quality of life, and mortality.[30,31] These outcomes are widely used because they are well validated, clinically interpretable, and feasible to collect in a large trials: (1) MACEs (with or without mortality) are objective and impactful and can be ascertained from routinely collected clinical data; (2) the mRS score is recommended by regulators as a primary end point in stroke trials; and (3) quality-of-life measures support health economic analyses.[32] However, these commonly used outcomes do not capture cognitive status. In particular, the mRS, which is heavily relied on in most acute stroke trials, measures global functional disability and does not assess cognition, particularly when cognitive impairment occurs in the absence of overt physical disability. As a result, individuals with identical mRS scores may differ substantially in independence and quality of life because of cognitive deficits.[33,34] Conversely, patients with severe motor impairment may score poorly on the mRS despite intact cognition and good quality of life. Even among people with "excellent" outcomes (mRS score 0–1), 54% of people have some degree of cognitive impairment, 32% endorse symptoms of depression, and 52% are not fully reintegrated to their prestroke activities.[35] These limitations underscore the need for cognitive outcome measures that are clinically meaningful, grounded in routine clinical data, and feasible to apply at a large scale within cardiovascular trials.

In this article, we discuss the challenges and limitations of current approaches to cognitive assessment in CVD, discuss how those issues impede progress, and propose a new construct, which we call major adverse cognitive events (MACE-Cog), to help better capture cognitive outcomes after stroke, cardiac events (eg, cardiac arrest), cardiovascular procedures, and other

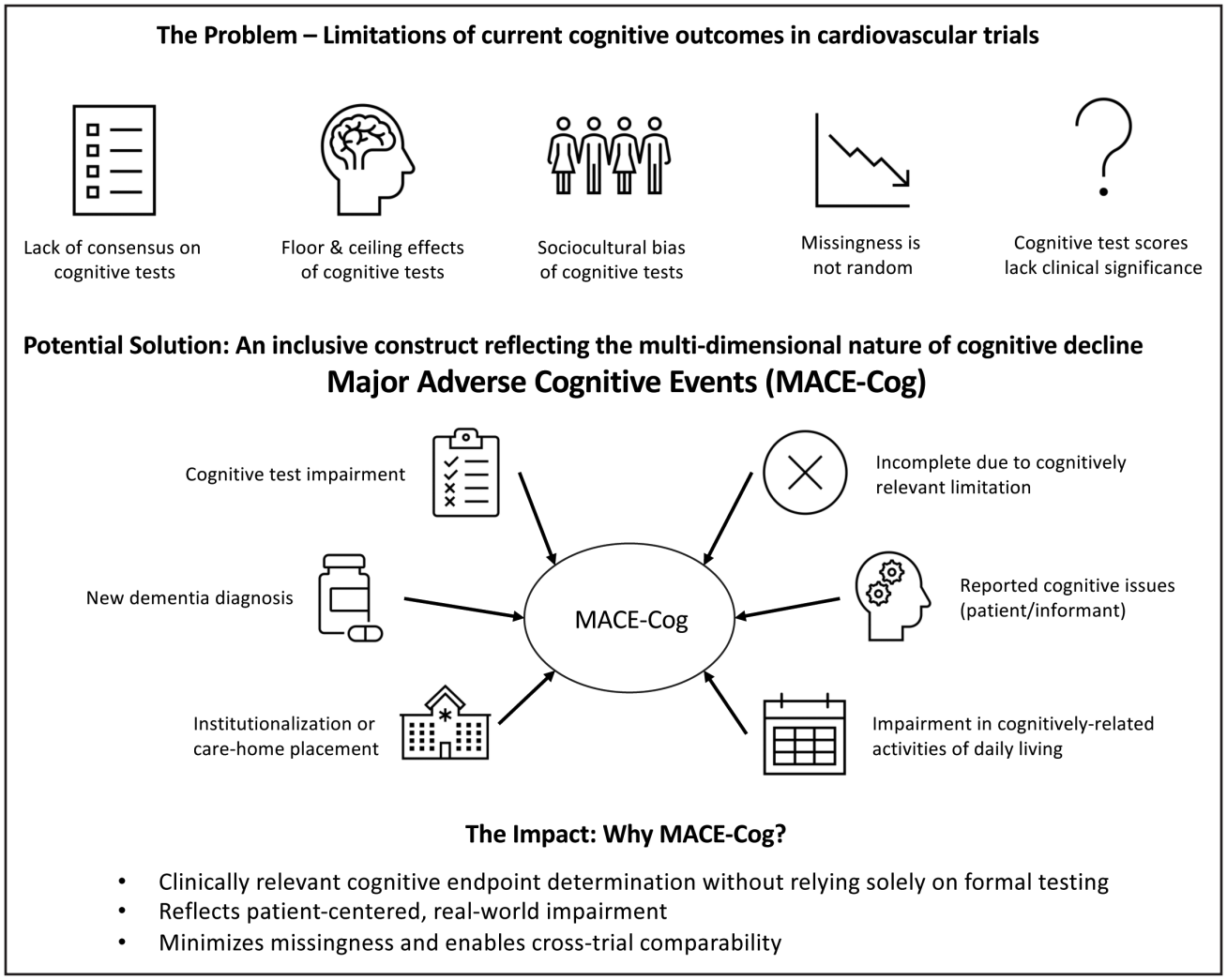

Figure 2. Summary of the problems with current approaches to cognitive outcome evaluation in stroke and other cardiovascular diseases and of the proposed concept of MACE-Cog.
MACE-Cog indicates major adverse cognitive events.

cardiovascular populations (Figure 2). This work is intended to be conceptual; future work will be required to operationalize and validate these concepts.

CHALLENGES WITH CURRENT APPROACHES TO POSTSTROKE COGNITIVE ASSESSMENT IN CARDIOVASCULAR TRIALS

Current Approaches

The main approach to assessing cognitive function in CVD trials has focused on cognitive screening tests or neuropsychological assessments.[31] Screening tests such as the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination, or Oxford Cognitive Screen aim to briefly evaluate global cognition.[36,37] Domain-specific tasks focus on individual cognitive functions (eg, processing speed or verbal memory). Formal neuropsychological assessments and research batteries[38] consist of combinations of validated tasks assessing multiple cognitive domains administered by a trained neuropsychologist. However, they are infrequently used in CVD research,[30] and there is substantial variation in the tasks used and the definition of cognitive impairment.[31] Although online assessments have gained significant attention since the COVID-19 pandemic, they have not been routinely used, and their incorporation within stroke randomized controlled trials has been limited[31] and may introduce their own biases due to technology access or usability.[39] Studies also vary greatly in terms of the setting and thus the time and staff available for cognitive testing (eg, emergency treatment versus prevention versus recovery), evaluation of pre-event cognitive impairment (and inclusion/exclusion of such patients), whether first-ever or recurrent strokes were included, rates of missing cognitive outcomes on follow-up, heterogeneity in timing

of assessment of postevent cognitive impairment or dementia, and method by which they were diagnosed.[31,40–42]

Challenges With Cognitive Tasks

Even when used, cognitive assessments after cardiovascular events/procedures have significant limitations as a trial outcome measure. Some commonly used tests are not validated or well suited for use in multicenter CVD trials given the higher prevalence of language, physical, and cognitive impairments, as well as medical instability in the acute phase, compared with non-CVD survivors.[43] In addition, many brief screening assessments are specific but not sensitive to subtle but important cognitive issues and suffer from both floor and ceiling effects.[44] Many tools are not available or validated in multiple languages. There have been efforts to develop consensus-based cognitive test batteries for poststroke cognitive decline, most notably the National Institutes of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards, which proposed neuropsychological test batteries of various lengths (60, 30, and 5 minutes) using various cognitive tests validated for stroke patients, and the consensus recommendations for neurological outcomes in CVD trials by the Neurologic Academic Research Consortium (Table S1).[38,45] The 60- and 30-minute National Institutes of Neurological Disorders and Stroke–Canadian Stroke Network batteries are too long for the pressures of typical CVD trial visits, whereas the 5-minute battery consists of components of the MoCA and thus is limited by floor and ceiling effects and does not have the responsiveness to change required for a trial outcome.[46] Commonly used global cognitive tests for identifying cognitive impairment in the setting of stroke and CVD include the full MoCA,[47] the Addenbrooke Cognitive Examination-Revised,[48] and the Mini-Mental State Examination.[49] The MoCA and Addenbrooke Cognitive Examination-Revised have been shown to achieve good sensitivity and specificity for detecting cognitive impairment compared with the 60-minute National Institutes of Neurological Disorders and Stroke–Canadian Stroke Network battery in patients evaluated ≥1 year after stroke or transient ischemic attack, whereas the Mini-Mental State Examination has been found to be less sensitive for nonmemory impairments.[47,50] Both detailed testing and especially cognitive screens have significant intraperson and interperson variability. This variability, whether person based (eg, years of education, baseline intellectual functioning, practice effects, recent sleep quality, distractions) or disease based (eg, impacts of acute hospitalizations, anesthetics, and recovery over time), dramatically increases the noise in the measure, making identification of meaningful differences challenging.[46]

In multicultural settings or multicenter studies, administering assessments in a participant's nonnative (even if fluent) language[51] or using assessments that include culturally specific items can influence performance and affect test scores.[51–53] Translating cognitive tests can improve their accessibility, but translations must be validated, sociocultural biases can remain,[54] and application of translated tests is still often limited by availability of trained study personnel able to speak the translated language.

Relevance of Cognitive Scores

The meaning of cognitive test scores for patients or clinicians is often unclear. For example, if an intervention reduced Trails B completion times by 10 seconds or improved a composite outcome by 0.5 SD, would this be enough to motivate doctors, patients, or regulators to change practice? There have been some studies of minimal clinically important differences (MCIDs) to define the smallest amount that a test or scale must change to be meaningful to patient, but this remains unclear for many cognitive tests.[55] Although the literature has shown that MCIDs for cognitive scales are sensitive to severity in major neurocognitive disorders (dementia), they have not been widely studied in CVD-specific contexts.[56] For instance, what may be relevant for community-dwelling aging may not apply equally to stroke or cardiac arrest survivors.

Survivor Biases and Nonrandom Missingness

Many commonly used cognitive measures cannot be completed by patients with severe motor, visual, or language impairments. How missing data are handled is thus a major challenge; relying solely on patients who can complete follow-up assessments can grossly distort the cognitive outcomes in CVD studies.[57] Data are unlikely to be missing completely at random because the very presence of cognitive decline can interfere with completing the outcome. Bias is inevitable if trial participants have missing outcomes after randomization for reasons related to the trial intervention (eg, severity of CVD). Severe functional and behavioral decline (ie, dementia) from the cognitive impact of CVD can prevent patients from participating meaningfully in testing. Dementia or severe CVD outcomes can result in a participant being admitted to a nursing home or other long-term care facility or moving to live with a relative, interfering with follow-up and increasing the risk of bias. This is particularly problematic when cognitive outcomes rely on face-to-face clinic assessment because cognitive impairment is strongly associated with increased morbidity and mortality, with a consequent substantial loss to conventional methods of follow-up.[41] Providing telephone, home-based, or web-based methods of cognitive assessment may potentially increase the number of patients who are able to contribute to

cognitive outcomes. For example, in OXVASC (Oxford Vascular Study), the 5-year cumulative incidence of postevent dementia after stroke/transient ischemic attack was 29% overall but was only 17% in clinic-assessed patients compared with 45% in patients who were captured with the use of other follow-up methods (home visits or telephone calls).[41] However, such alternative methods will not overcome the intrinsic limitations of testing in CVD survivors who are unable to meaningful engage in cognitive tasks.[39]

CVD Trials Differ From Conventional Dementia Studies

The biases and limitations for CVD trials differ from trials of dementia, which more routinely use cognitive measures as part of primary or secondary end points and are designed to capture cognitive decline over a longer period.[58] Dementia trials are typically conducted in stable outpatient settings where patients can be carefully screened and selected for baseline ability to complete testing, informants are often available, and time-intensive assessments can be feasibly administered. In contrast, CVD trials, especially those with a focus on hyperacute interventions (eg, cardiac arrest, stroke), operate under conditions of extreme time pressure without the opportunity to assess the pre-enrollment cognitive status of participants. In these settings, participants may be incapacitated, and informants may not be immediately available, making the collection of high-quality baseline cognitive data much more difficult. In outpatient secondary prevention trials, a staged approach to cognitive assessment, with pre-enrollment screening followed by more comprehensive assessments for mild cognitive impairment or dementia, may be more feasible.

Why This Matters For Clinical Trials: The Need for a New Approach

In clinical trial design, any outcome that is missing in a significant portion of participants, especially in a nonrandom manner, cannot be relied on as a primary, or even secondary, outcome. The issues of survivor bias, missingness, and loss to follow-up become far too important. In addition, to change clinical practice, interventions[58] must affect cognition in a manner that is meaningful to regulatory agencies, funders, CVD survivors, caregivers, and clinicians. The facts that there is no agreement on tasks and that even those recommended by consensus panels are often not included in trials highlight this profound gap. Therefore, cognitive tasks alone, whether through screening tests, in-person batteries, or online assessments, clearly cannot be relied on as outcome measures for CVD clinical trials.

RETHINKING APPROACHES TO COGNITIVE OUTCOMES

Cognitive Outcomes Should Emphasize Change From Baseline and Impact on Daily Activities

The limitations of pen-and-paper cognitive tests are only partially addressed by currently available solutions (as summarized in Table 1). Although cognitive tests certainly have a place in this field, it is essential to avoid relying solely on them for evaluating cognitive outcomes in CVD trials. In fact, it must be emphasized that even the *Diagnostic and Statistical Manual of Mental Disorders* (currently in its Fifth Edition, Text Revision) does not actually require cognitive testing for the diagnosis of major neurocognitive disorder or dementia.[59] Rather, it requires evidence of cognitive decline and difficulties with ADLs, which can be established through patient and caregiver reports.

Questionnaires Can Incorporate Patient and Caregiver Reports

Cognitive decline in specific domains can be assessed with standardized questionnaires that can be completed by informants or patients. For example, the Informant Questionnaire on Cognitive Decline in the Elderly, the short form of which has 16 items, has been validated for identifying both prestroke and poststroke cognitive impairment. The briefer 8-item Interview to Differentiate Aging and Dementia (AD8[60]) has also been validated for identifying prestroke and poststroke cognitive impairment and can be administered either to an informant or the participant.[61–63] In addition, evidence of decline on cognitively relevant daily activities can be provided by completion of instrumental ADL (IADL) questionnaires such as the 20-item Bristol ADL Scale or the considerably briefer 8-item Lawton IADL Scale, which can also be completed by either informants or patients.[64–66] The Standard Assessment of Global Everyday Activities collects information on both cognitive symptoms and ADLs.[67] Having a valid outcome that can be reliably obtained from either an informant or participant reduces missing outcomes and the resulting need to classify missingness as attributable to cognitive or physical limitations. Combining a cognitive symptom assessment with a cognitively relevant IADL scale may allow greater inference as to whether IADL impairments reflect at least some underlying cognitive contributors rather than solely physical impairments.

Seeking data from informants can help mitigate the problem of missing cognitive outcome data. Moreover, cognitive decline can have several important functional and behavioral manifestations in the patient's daily life that are observed by family members, caregivers, or other individuals close to the patient. Their input has clear value

Table 1. Limitations to Current Approaches to Poststroke Cognitive Outcome Collection, Partial Solutions in Use, and Proposed Paradigm Shifts to Better Capture These Outcomes

Current limitations	Partial solutions in use	Proposed paradigm shift
Variation in cognitive tests used	Use NINDS-CSN VCI battery components: 30- and 60-min batteries are too long for typical trials, 5-min protocol has elements of the MoCA but may be too insensitive	Rethink reliance on cognitive testing; capture cognitive symptoms and impact on daily life in addition to or instead of cognitive tests
Cognitive tests used are often not validated for stroke or CVD		
Cognitive tests used are insensitive and have both floor and ceiling effects		
Reliance on face-to-face testing, with trained coordinators	Offer web or telephone-based testing; still suffers from high rates of incompletion	Consider the use of informant assessments when possible
Substantial incompletion rates, high rates of missing data	Statistical imputation; however, because data are not missing at random, this approach is statistically limited. Categorize as impaired anyone with aphasia (National Institutes of Health Stroke Scale item 9 score 2 or 3) or severe neglect (item 11 score 2), or death (as the ultimately poor cognitive outcome)	Consider cognitively relevant reasons (eg, inattention, memory, aphasia) for incompletion as themselves being adverse cognitive outcomes; noncognitive reasons for incompletion (eg, refusal, hemiplegia) would not be considered an adverse cognitive outcome.
Survivor and attrition biases; patients with severe cognitive impairment cannot complete testing	Imputation techniques as above	In addition to above, consider institutionalization as an outcome; although hard to establish that the reason is cognitive decline
Sociocultural and linguistic biases of tests	Offer translated versions of cognitive tests; still does not overcome sociocultural bias because tests were developed primarily in Western countries	Capture an individual's pre-event cognitively relevant activities and compare with post-event activities to account for sociocultural differences
Unclear meaning of cognitive outcomes for patients, caregivers, providers and regulators	Studies of MCIDs to infer relevance of changes on tests or scales	Combined outcome with components that reflect DSM definitions of neurocognitive disorders and incorporate clear change in cognitive symptoms with functional relevance

DSM indicates *Diagnostic and Statistical Manual of Mental Disorders*; MCID, minimal clinically important difference; MoCA, Montreal Cognitive Assessment; NINDS-CSN, National Institutes of Neurological Disorders and Stroke–Canadian Stroke Network; and VCI, vascular cognitive impairment.

in identifying an adverse cognitive outcome for patients, be it symptoms of cognitive decline[63,68,69] or their impact on IADLs.[64,70] However, the availability of informants is imperfect. For example, in 1 study screening for cognitive impairment using informant-based questions in acute care, only ≈50% of participants had a suitable informant within 24 hours.[71] Although this may improve with a longer assessment window, it highlights the practical challenges of relying soley on informant data in acute clinical trials. This does not diminish the value of informant-based information but does suggest the need for careful interpretation when incorporating informant data into clinical trials.

Considering these needs, one consideration that uses informants and captures daily functioning is the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB). The CDR-SB is a widely used outcome measure in dementia intervention trials. It was the main outcome measure in the CLARITY-AD trial (Clarity Alzheimer's Disease) evaluating the efficacy of lecanemab for those with early Alzheimer disease–related cognitive impairment and mild dementia.[72] The CDR-SB is a patient- and informant-rated scale reflecting the severity of cognitive and functional impairment in day-to-day life in the domains of memory, orientation, judgment, and problem solving; in functions in community affairs; in home; and with hobbies and with personal care. It does not require cognitive testing to assess the severity of impairment; it captures granularity in increasing degrees of severity and it can be administered by trained clinical personnel over the telephone. Thus, it is less vulnerable to noncompletion. However, it is not validated in those with CVD. Increasing CDR-SB severity may not distinguish difficulties caused by physical CVD-related deficits from those due to cognitive impacts. CDR-SB is also a long battery (≈30 minutes), which may limit feasibility in large CVD trials.

Administrative and Medication Data May Be Informative

A clinical diagnosis of dementia is a relevant outcome that can be obtained from health care records or administrative data in many regions with high specificity but moderate sensitivity.[73,74] In those without a documented diagnosis, a diagnosis can also be ascertained from prescription records for dementia medications such as cholinesterase inhibitors or memantine.[10] Indeed, diagnostic algorithms have been developed and validated for ascertaining a dementia diagnosis from recorded diagnoses, prescriptions, and physician claims; for example, such an algorithm was recently used for quantifying the magnitude and time course of poststroke dementia in an entire Canadian province.[10] However, that method is not applicable in many jurisdictions and has lower sensitivity for mild dementia, which is underdiagnosed in the community.[75] Direct patient or informant reporting of new medications for or diagnosis of dementia/mild cognitive impairment can also be a specific if not fully sensitive outcome.

Institutionalization for Cognitive/Behavioral Changes Is a Meaningful but Complex End Point

Another outcome component to consider is institutionalization from dementia, which can also often be captured well in some jurisdictions through administrative or electronic health records and represents a clinically relevant, "end-stage" indicator of cognitive decline.[76,77] However, establishing the reason why a given patient ended up at a long-term care facility can be challenging, particularly in the aftermath of an event such as stroke, which can lead to institutionalization because of physical disability alone. Institutionalization derived from routine administrative data may be a valid outcome in European, North American, and Australasian sites, but the definitions of care home/institutional care and the case mix/severity of residents may vary considerably globally.[78] Indeed, institutionalization is also influenced by numerous socioeconomic and sociocultural factors such as cultural views of institutions, marital status, health of caregivers, extent of family or other social supports, public/private or insurance supports available to the patient/family, and financial resources. With these social constructs in mind, the potential outcome of institutionalization, if considered in isolation, would have to be closely adjudicated because many variables beyond cognitive impairment may contribute to institutionalization. This is one reason to have multiple contributors to the definition of adverse cognitive outcomes rather than relying on a single construct. At a group level, particularly after adjustment for confounding comorbidities and baseline stroke severity, institutionalization can still play an important role in distinguishing patients likely to have fared poorly from a neurocognitive standpoint.

Finding Meaning in the Missingness

In rethinking the approach to cognitive outcomes, it must be acknowledged that being unable to perform a cognitive test, particularly when this is attributable to ≥1 cognitively relevant neurological impairments such as aphasia or neglect, is itself an adverse neurocognitive outcome and not missing data. Prospectively capturing the context for incompletion on study case record forms can help improve the ascertainment of adverse cognitive outcomes. If noncompletion can be systematically captured and imputed as an adverse outcome, much of the missing data in CVD trials can be reclassified as interpretable and clinically meaningful. For example, assessors could be encouraged to document standardized reasons for test incompletion or factors that limited their assessment. Some factors such as the participant having moved to a new city may have little to do with cognitive impairment, but others such as severe aphasia or speech disturbance, inappropriate or inconsistent responses, behavioral agitation, neglect, severe apathy, or amotivation could indeed be counted toward adverse cognitive outcomes. A similar approach was used in a secondary analysis of the ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) of thrombectomy for acute ischemic stroke, which examined cognitive outcomes at 90 days. In that study, when data were missing due to severe aphasia (National Institutes of Health Stroke Scale item 9 score 2–3) or severe neglect (National Institutes of Health Stroke Scale item 11 score 2), those patients were assigned to the unfavorable performance group in sensitivity analyses.[79] When doing so, thrombectomy was associated with better cognitive outcome on all five cognitive tests. In sensitivity analyses that included only patients who completed the cognitive testing, the effect of treatment was significant in only 3 of the 5 cognitive tests across all sensitivity analyses with imputed values. This illustrates how reframing missing data can reduce attrition and survivor bias by moving away from analyzing only the skewed subset of survivors able to complete the tests. It may be challenging for nonclinical research personnel to accurately attribute reasons for noncompletion based on neurocognitive context. Clear operational guidance, structured questions or checklists, and training would be essential to support consistent and valid classification. Such an approach has been used in the APPLE study (Assessing Post-Stroke Psychology Longitudinal Evaluation).[80]

In summary, we must consider a different approach to defining cognitive outcomes in CVD trials to support their use as a reliable and valid primary clinical trial end point. To do so, the approach to cognitive outcomes must (1) reflect the multiple different potential manifestations of cognitive impairment; (2) appreciate the value of multiple potential sources of information regarding a patient's cognitive functioning; (3) permit a more inclusive, data-informed approach to outcome capture that does not disproportionately exclude patients with the most severe cognitive decline; and (4) be inclusive of and sensitive to diverse ethnocultural perspectives and languages spoken.

MAJOR ADVERSE COGNITIVE EVENTS

MACEs have become very well accepted as primary outcomes in CVD such that specific guidance has been provided by the U.S. Food and Drugs Administration and the European Medicines Agency on using a 3-point MACE outcome, which includes acute myocardial infarction, stroke, and cardiovascular mortality, in all trials evaluating the cardiovascular safety of diabetic agents.[81] Applying this concept to the problem of evaluating cognitive outcomes after stroke, cardiac arrest, or other cardiovascular events or procedures, which could also be extrapolated to other cardiovascular or neurological diseases, we propose a composite definition of adverse neurocognitive outcomes that we call MACE-Cog.

A proposed framework for such a composite outcome, building on the conceptual shifts we have discussed, is presented in Table 2. The components of the MACE-Cog framework are envisioned to be flexible; not all components must be collected in a every study, depending on study design and available resources. Components could include (1) cognitive screen or task performance below a cutoff or meeting MCID thresholds, (2) symptoms of impairment on validated informant/participant questionnaires, (3) inability to complete cognitive testing because of cognitive/behavioral limitations, (4) impairment in cognitively relevant activities of daily living, (5) new diagnosis of dementia, and (6) institutionalization or care home admission related to cognitive impairment. Although including more options to define a MACE-Cog will improve sensitivity, it is also important to maintain some specificity. An overarching motivation for these definitions is that they should include cognitively relevant events that most people would agree are clearly adverse.

In a study that is using objective cognitive testing, 1 component of MACE-Cog is evidence of impairment on ≥1 completed cognitive tests (acknowledging expected missingness of this outcome). What counts as impaired performance on the tests can be flexibly considered according to the trial design and defined in the statistical analysis plan. For example, acute intervention trials (eg, myocardial infarction, stroke, cardiac arrest) would have only a single time point of cognitive testing (ie, at 90 days) in which case impaired performance could be defined according to published normative data for the tests, ideally against age/sex/education–standardized norms. This approach would require large enough trials to ensure that random differences in baseline cognition between treatment groups are unlikely to be attributable to chance. On the other hand, CVD prevention or recovery studies may often have longitudinal participant testing, in which case the change in the patient's score from baseline (before randomization) to follow-up could be considered, with impairment defined on the basis of a validated MCID.[56,84]

The second proposed component of MACE-Cog is the presence of informant- or patient-reported symptoms of cognitive decline as captured with a standardized questionnaire such as the Informant Questionnaire on Cognitive Decline in the Elderly or 8-item Interview to Differentiate Aging and Dementia. Given that patients with severe deficits, neglect, or anosognosia may have reduced insight into their cognitive decline, it is ideal to have an option for an assessment that can be completed by an informant who knows the patient well. In the absence of such an informant, patient input could also be obtained, as permitted by instruments such as the 8-item Interview to Differentiate Aging and Dementia. For trials and participants who can support more detailed and time-consuming assessments, the CDR-SB could also be used. Adopting the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* definition, the presence of either informant or participant concerns should be considered a positive fulfillment of this component. In trials with a single time point of assessment, published cutoffs could be used, whereas with multiple time points, one could look for a decline from baseline to follow-up. The latter approach, especially for a prevention/longitudinal trial, is preferable because a substantial minority of patients with CVD are expected to have preexisting cognitive impairment.[8] Hyperacute trials may be limited to asking about symptoms or changes in function since the CVD event compared with just before the event.

Table 2. Proposed Framework for MACE-Cog in the Setting of Stroke or Other CVDs

Dichotomous framework	Ordinal framework (example)
"No MACE-Cog" or "Normal cognitive outcome" if all components are absent.	"No MACE-Cog" or "Normal cognitive outcome" if all components are absent.
A MACE-Cog event is "positive" if any one of the following is present: Impairment (based on standardized cut-off or MCID) on ≥1 cognitive test (or domain), if performed as part of the study protocol, OR Incompletion or limitation of cognitive testing due to ≥1 cognitive-behavioural factors (Table 4), OR Reported symptoms of cognitive decline on standardized informant (ideal) or participant questionnaires, OR Impairment in cognitively-relevant instrumental activities of daily living or basic activities of daily living, OR New diagnosis of dementia based on clinic or health records, or prescription of dementia medications, OR Institutionalization or care home admission related to cognitive impairment or dementia	"Mild MACE-Cog" or "Mild cognitive impairment" if only impaired cognitive testing and/or symptoms of decline are present, *or* there are one or more cognitive-behavioural factors identified as limiting/preventing testing Single domain or multiple domain impairment could be distinguished based on number of cognitive domains affected on testing or more simply the number of components (1–3) that are positive
	"Severe MACE-Cog" or "Dementia" if there is impairment in cognitively-relevant IADLs *or* institutionalization, AND either impaired cognitive testing, cognitive symptoms, or cognitively-relevant reason for test incompletion. Additional gradations could be added based on extent of IADL loss or by weighting institutionalization higher*

CVD indicates cardiovascular disease; IADL, instrumental activities of daily living; MACE-Cog, major adverse cognitive events; and MCID, minimal clinically important difference.

*Note that additional gradations for cognitive outcomes have been used in the R4VaD (Rates, Risks and Routes to Reduce Vascular Dementia) and LACI-2 (Lacunar Intervention Trial-2) studies.[82,83] With respect to gradations for the MACE-Cog outcome, adding more categories may make it harder to standardize implementation and may require more intensive data acquisition (eg, multiple cognitive tests or a trial involving both activities of daily living and IADL outcomes).

Table 3. Suggested Reasons for Incompletion or Limited Completion of Cognitive Testing to Track in Clinical Trials That Would and Would Not Count Toward MACE-Cog

Reasons that would count toward MACE-Cog	Reasons that would not count toward MACE-Cog
Severe aphasia or speech disturbance	Impaired hearing or vision limiting data collection
Inappropriate or inconsistent responses	Patient refuses to participate for reasons of scheduling, convenience, etc. If there is not a clear reason (when in doubt), it would not count toward MACE-Cog.
Patient prematurely terminated testing for reasons of poor performance, frustration with testing, or inability to understand instructions	Patient prematurely terminated testing for reasons other than poor performance, test frustration, or inability to learn instructions.
Behavioral agitation	Severe tremor, incoordination, or weakness interfering with a written test
Impaired level of consciousness, prohibiting assessment	
Severe apathy or lack of motivation	

MACE-Cog indicates major adverse cognitive events.

The third proposed component of MACE-Cog is the inability to complete cognitive testing because of a relevant cognitive-behavioral factor as noted previously. For this component to be considered, a study would need to consistently track the reasons for incompletion or limited completion of cognitive testing, ideally with a standardized case report form with adequate training of study personnel. We have included suggestions in Table 3 for what factors might contribute to a MACE-Cog outcome and what factors would not. For instance, we argue that severe apathy/amotivation is a major neurobehavioral manifestation that is well justified as an adverse neurocognitive outcome given that loss of goal-directed behavior or cognitive activity is a key element.[85] In contrast, hearing loss that renders a participant unable to answer telephone questions would not count as a MACE-Cog event. This judgment relies on consistent assessment, but subjective biases could be introduced. As with other outcome scales with potential for subjectivity (eg, the mRS), we propose multiple mitigation strategies, including brief assessor training and certification modules, use of standardized case record forms with prompts focused on observable context rather than inference, and optional blinded adjudication for ambiguous cases. Although some degree of subjectivity in this rating may remain, as long as it is applied consistently across trial groups, we feel strongly that any modest increase in subjectivity is preferable to the inevitable bias created when impaired cognitive outcomes are classified simply as missingness.

The fourth MACE-Cog component is impairment in IADLs on validated scales such as the Lawton or Bristol scales. Such functional impacts of cognition are often prioritized over cognitive task scores by patients, families, and cognitive experts alike.[86] Furthermore, regulators such as the US Food and Drug Administration approve treatments based on change in function; change in a neuropsychological test alone is not sufficient for a US Food and Drug Administration indication.[87] Cognitively relevant IADL impairment could be defined either using cutoffs on a relevant scale if there is a single assessment or by looking for decline from baseline (before the event or study start, depending on the trial design). The latter approach is particularly valuable for IADL evaluation because of sociocultural

Table 4. Examples of Efficient Methods of Evaluating Each MACE-Cog Component

MACE-Cog components	Exemplar method of evaluation	Anticipated time required in a study visit*
Impairment (based on standardized cutoff or MCID) on ≥1 cognitive test (or domain), if performed as part of the study protocol	Face-to-face or telephone/remote cognitive testing with a validated test or test battery (Table S1)	<10 min if brief batteries are used (Table S1). Of course, this time will be reduced if the patient is unable to complete testing.
Incompletion or limitation of cognitive testing due to ≥1 cognitive-behavioral factors	Assessors document reasons for test incompletion or factors that limited their assessment in a standardized manner (Table 3).	No additional time because it is based on outcome assessor's observations of patient behavior during testing above
Reported symptoms of cognitive decline on standardized informant or participant questionnaires	Completion of a structured questionnaire, a brief example being the 8-item Interview to Differentiate Aging and Dementia[60]	5 min if administered by the outcome assessor, but could also be filled out separately by informant
Impairment in cognitively relevant IADL or basic activities of daily living	Completion of a structured questionnaire, a brief example being the 8-item Lawton IADL Scale, which can be completed by either informants or patients[64]	<5 min if administered by the outcome assessor but could also be filled out separately by informant
New diagnosis of dementia based on clinic or health records or prescription of dementia medications	Review of diagnoses and medications in the patient's medical records or linkage with any regional administrative records or registries tracking dementia diagnoses	<1 min to ask about a new dementia diagnosis or related medications. No additional time if passive linkage to health or administrative records is used
Institutionalization or care home admission related to cognitive impairment and dementia	Review of living situation with the patient/informant or tracking with health or administrative records	<1 min to ask about current living situation. No additional time if passive linkage to health or administrative records is used

IADL indicates instrumental activities of daily living; MACE-Cog, major adverse cognitive events; and MCID, minimal clinically important difference.
*Based on internally conducted timed trials with trained clinical research staff.

variations in the extent to which different individuals perform different IADLs; for example, gender disparities remain in such activities as cooking or driving, and patients should not be penalized for preexisting differences in function.[88] Because the participant is used as their own baseline, sociocultural or gender role assumptions are minimized, and change in the individual's own function is emphasized. Using a close observer (ie, informant) as the source of information for the assessment adds further objectivity. Standardized instruments used to assess symptoms and functioning (eg, the Lawton and Bristol scales) are not based on a simple point assessments; instead, they ask respondents to think about the past few weeks for context. This is an important way in which they differ from quality-of-life assessments, which can vary greatly according to how the patient is feeling at the specific moment of the assessment.

The fifth MACE-Cog component is a new clinical diagnosis of dementia, not present at study enrollment, determined from the patient's medical records or from reliable administrative health data or prescription records of dementia-specific medications.[10]

The final MACE-Cog component can consider institutionalization or care home admission related to cognitive impairment or loss of function in cognitively determined ADLs. Similar mitigation strategies (standardized case record forms, training and certification for adjudicators) can reduce subjectivity, and it may be possible to identify purely physical or social reasons for admission. If assessment of cognitive symptoms and ADL changes is available, this can also support whether institutionalization is related to cognitive challenges. However, purely administratively defined outcomes will not be able to disentangle cognitive from other causes of functional decline.

For trialists, our proposed absolute minimum data that should be collected to get a MACE-Cog outcome would include the following: (1) cognitive symptoms (participant or informant reported) and (2) impact on IADLs (participant or informant reported). When robust data are available, through clinical follow-up, administrative records, or other sources, a new diagnosis of dementia and new institutionalization are recommended to be included. Last, if trial resources permit, cognitive screening or assessment (at minimum a brief telephone assessment like the Telephone Montreal Cognitive Assessment or the Modified Telephone Interview for Cognitive Status) that can be performed in the language of all participants is recommended, along with reasons for incompletion.

In this manner, the MACE-Cog framework can help ensure that cognitive outcome ascertainment in CVD trials does not rely exclusively on the patient's ability to complete cognitive testing. Our proposed approach, particularly with its consideration of patient/informant-reported cognitive symptoms and functional decline, is much better aligned with how neurocognition is evaluated in clinical practice because neurocognitive disorders are never diagnosed solely with cognitive testing, which in turn is interpreted only in the context of reported complaints and changes in daily functioning. The additional components of MACE-Cog can be incorporated efficiently into CVD trials with minimal added effort for outcome evaluators, particularly if trials facilitate form completion by informants/patients and linkage or review of administrative or health records as shown in Table 4.

STATISTICAL ANALYSIS CONSIDERATIONS FOR MACE-COG

The MACE-Cog outcome as proposed offers useful versatility for analytical approaches in clinical trials because it can be considered in dichotomous, ordinal, or hierarchical fashions. Any of the following statistical approaches will benefit from the MACE-Cog framework by supporting successful outcome ascertainment in most, if not all, participants.

Binary approaches

Binary approaches would simply consider MACE-Cog as a dichotomous outcome that is present or absent. When MACE-Cog is evaluated at a single time point such as 90 days after stroke or 1 year after cardiac surgery, binary analytical approaches could use binary logistic regressions for multivariable analyses or the χ^2 test or Fisher exact for univariable analyses (Figure 3A). With this approach, fulfillment of any one of the MACE-Cog components would count as a MACE-Cog event. Much as the original MACE construct does, this equates all components (see the following discussion for hierarchical approaches as alternatives). However, when the outcome is evaluated longitudinally at multiple time points, as might be done in a preventive trial, both the occurrence and timing of attainment of MACE-Cog could be analyzed with survival curves (eg, Kaplan-Meier curves) and models such as Cox or Poisson regressions.

Ordinal Approaches

As previously shown with ordinal analyses of measures like the mRS, there can be value in considering a spectrum of cognitive outcomes from both statistical and clinical standpoints.[89] In this regard, the first 3 components of the MACE-Cog framework may be seen as helping distinguish normal cognitive outcome (no MACE-Cog) from mild cognitive impairment (or mild MACE-Cog), whereas the last 3 diagnosis- and

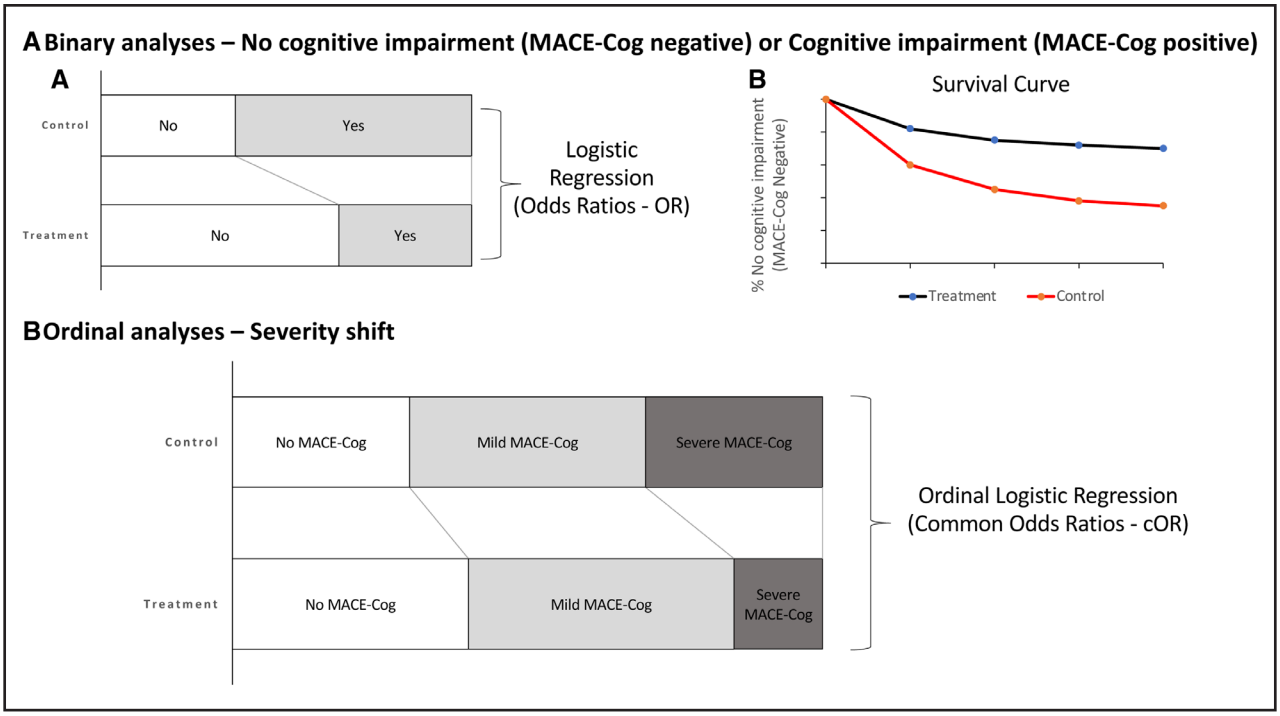

Figure 3. Examples of how MACE-Cog outcomes can be analyzed with (A) binary and (B) ordinal approaches.
MACE-Cog indicates major adverse cognitive events.

function-related components may be seen as distinguishing mild cognitive impairment from dementia (or severe MACE-Cog; Figure 3B).

One might also consider additional gradations, similar to what has been pursued recently by trials. R4VaD (Rates, Risks and Routes to Reduce Vascular Dementia) and LACI-2 (Lacunar Intervention Trial-2) studies used a 7-point ordinal classification of cognitive decline similar to the mRS (normal, minor: single domain, minor: multi domain, major: mild, major: moderate, major: severe, and death),[82,83] designed to reflect *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* criteria for neurocognitive impairment.[83] Each category was operationalized with a combination of Telephone Montreal Cognitive Assessment and the Modified Telephone Interview for Cognitive Status (*T* scores, plus mRS or Barthel functional measures). In LACI-2, 86% of people completed either a Telephone Montreal Cognitive Assessment or Modified Telephone Interview for Cognitive Status and a functional outcome and could thus generate an ordinal cognitive outcome. Although the scale minimized attrition (data were missing in 14% of participants), the scale has some limitations; for example, application for individuals with discrepant cognitive and functional status, given that the mRS is not focused on cognitively relevant activities (eg, mild functional disability with severe cognitive scores or severe functional disability with mild cognitive impairment), may be inconsistent. Furthermore, unlike MACE-Cog, these ordinal approaches could not account for all participants unable to complete testing. Nevertheless, it is an important attempt to create an ordinal scale that captures cognitive function, is available in majority of the participants, and provides a helpful precedent for how ordinal analyses of a MACE-Cog type outcome may be performed. Last, as mentioned, trials with both resources and participants able to complete a CDR-SB could use an ordinal ranking of scores, potentially along with other aspects of MACE-Cog. Ordinal analyses of MACE-Cog could be undertaken with approaches such as ordinal logistic regression (using proportional odds or partial proportional odds models) for multivariable analyses or the Wilcoxon rank-sum or Mann-Whitney *U* test for univariable analyses.[90]

Hierarchical Approaches

The various MACE-Cog components can also be ordered in a hierarchical manner for analysis. Although individual trialists can define the most relevant hierarchy for their trial with appropriate justification and the choice of ranking may differ by population, an exemplar hierarchy ordered to prioritize diagnostically or functionally worse outcomes could include (1) institutionalization or care home admission; (2) new diagnosis of dementia by a physician or prescription of dementia medications; (3) impairment in cognitively relevant IADLs; (4) reported symptoms of cognitive decline on standardized informant or participant questionnaires; (5) impairment (based on standardized cutoff or MCID) on ≥1 cognitive tests (or

domain); and (6) incompletion or limitation of cognitive testing due to ≥1 cognitive-behavioral factors. Such a hierarchy could be analyzed with an approach such as a win ratio, which has gained popularity in recent CVD trials (Figure 4).[91] A win ratio approach, one method for presenting and analyzing data from a Desirability Of Outcome Ranking), would involve comparing the outcome of all possible pairs of participants, one assigned to intervention and one to control, starting at the first hierarchical outcome, and declaring a win for the participant with a better outcome within the pair or a tie if neither participant in the pair had a better outcome. If tied at the first level of the hierarchy, the pair would proceed to the next level of the hierarchy to decide which participant fared better, and so on. The Win Ratio then ends up being the ratio of wins to losses in the treatment group compared with the control group, ignoring ties. This valuable analytical approach gives trialists the ability to assign priority to more clinically important events within the MACE-Cog framework.

The MACE-Cog framework also supports integrating cognitive outcomes into broader cardiovascular outcomes in a larger hierarchical analysis, for example, one that includes being alive, being discharged home, physical function, and cognition. Further work is required to determine how cardiovascular survivors prioritize these various aspects along with MACE-Cog events to generate meaningful hierarchies.

Consideration of Mortality

Death poses an additional complex challenge when seeking to define and analyze an adverse cognitive outcome. As noted, conventional cognitive assessments inevitably result in missing data for patients who have died. This problem will be particularly amplified in diseases with high mortality such as cardiac arrest and intracranial hemorrhage, for which ≥50% of admitted patients do not survive to discharge.[92,93] If deaths inevitably mean missing cognitive data, this can lead to misleading conclusions when the treatment itself (eg, thrombectomy for stroke) has an effect on mortality and survivors report cognitive symptoms.[79] Death is undoubtedly an adverse cognitive event because it represents the cessation of all cognition. However, can a patient who died without contributing cognitive test results truly be considered to have had an adverse cognitive event? The answer is perhaps not, but although death does not necessarily mean that a MACE-Cog event has occurred, a trial in a condition with substantial expected mortality such as stroke or cardiac arrest or in which there is a potential treatment effect on mortality should analyze MACE-Cog in combination with mortality as a MACE-Cog or death outcome to avoid the bias of penalizing survivors or rewarding mortality. In a hierarchical analysis, death could be included as the most severe event, whereas in an ordinal analysis it could be included as the most severe outcome on the ordinal

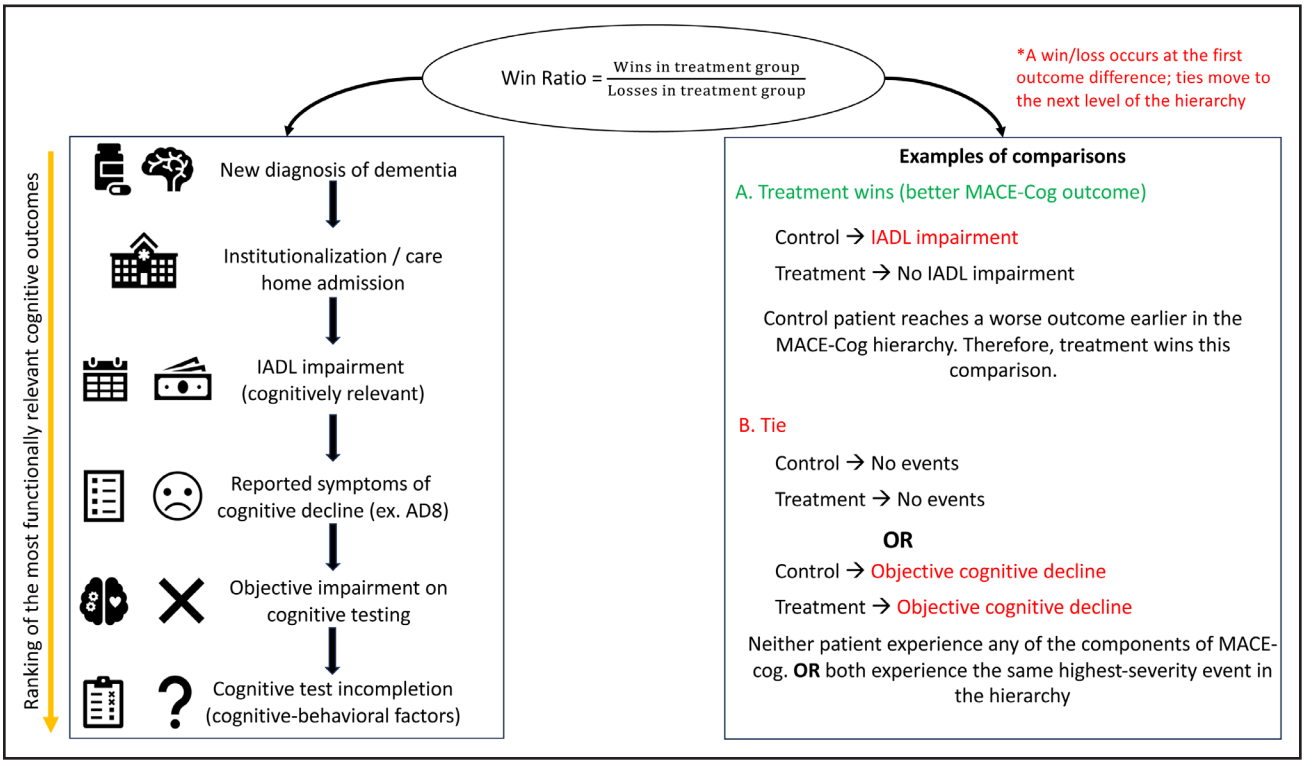

Figure 4. Example of how MACE-Cog outcomes can be analyzed with hierarchical approaches, specifically in this case with a win ratio approach.

IADL indicates instrumental activities of daily living; and MACE-Cog, major adverse cognitive events.

scale. With this approach, deaths will no longer equate to missing data or be paradoxically classified as a favorable outcome. In keeping with this philosophy, death itself was included in the 7-point cognitive ordinal outcome in R4VaD and LACI-2.[82,83] Sensitivity analyses could then separately examine intervention effects on the MACE-Cog component in survivors (ie, when deaths are excluded from the sample).

FUTURE DIRECTIONS

One of the benefits of the MACE definition in CVD has been its standardization by the US Food and Drug Administration and the European Medicines Agency. For a construct like MACE-Cog to gain widespread adoption, a well-justified application of the composite outcome across different studies and settings would be the most desirable way forward. We plan to conduct an expert consensus conference to standardize the more challenging components of the proposed MACE-Cog definition such as what factors for cognitive test incompletion should or should not count toward this outcome. Generation of real-world data on the MACE-Cog outcome from completed or ongoing clinical trials would help bring clarity by demonstrating the feasibility and reliability of its different components. It will be particularly illuminating to examine the agreement among MACE-Cog assessments made with various different combinations of these components.

Validation studies of the MACE-Cog outcome should be conducted in parallel across multiple CVD settings, including cardiac arrest, heart failure, stroke, and post-surgical populations. Studies must verify the extent to which our proposed approach mitigates missingness of cognitive outcomes compared with conventional cognitive test–reliant strategies. The concurrent validity of MACE-Cog should be compared with conventional cognitive approaches and with other useful outcome measures such as health-related quality of life, health and social care use, and caregiver burden—at least for those participants who are able to complete cognitive tasks and patient-reported outcomes. Stronger observed correlations with MACE-Cog would strengthen our confidence that it is clinically valuable. Similarly, the predictive validity of MACE-Cog should be verified in relation to robust, long-term clinical and health economic outcomes, for example, examining how MACE-Cog at 3 months predicts quality of life, health care use, or mortality at 1 year compared with purely cognitive test-based methods. Such efforts are already underway, and collectively, these data will help facilitate the acceptance and adoption of MACE-Cog in CVD trials.

Although the work is motivated by CVD trials, the challenges we have discussed—nonrandom missingness, test incompletion, and survivor biases—are not unique to these populations and clearly extend to other conditions such as Alzheimer disease, multiple sclerosis, and critical illness, among others.[94–96] Although further validations are required, this work advances a more inclusive, functionally relevant, and scalable framework for cognitive outcome ascertainment. MACE-Cog facilitates outcome capture across the full spectrum of survivors, including those unable to complete formal testing.

We hope that the proposed composite outcome sparks important discussions about more inclusive approaches to improve the measurement of adverse cognitive outcomes in CVD trials and beyond. Ultimately, we hope that this approach can support trials and interventions to reduce the burden of cognitive impairment in multiple populations.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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