

Management of brain–heart multimorbidity: a clinical practice guideline

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Abstract

Background: Although brain and heart conditions share overlapping risk factors and commonly co-occur, current cardiac and neurologic clinical guidelines are typically produced within specialty silos. The objective of this guideline from a Canadian Cardiovascular Harmonized National Guideline Endeavour (C-CHANGE) panel is to expand on current cardiovascular guidelines to include evidence from the neurologic and mental health literature, with specific recommendations for providers managing comorbid brain and heart conditions.

Methods: The guideline development panel comprised an Executive Steering Committee; 10 expert subgroups to develop research questions and draft recommendations for specific brain–heart conditions; an Evidence Review Team to ensure the rigour and consistent application of the methodology; and

an Implementation Committee to facilitate uptake of the recommendations by clinicians and into electronic medical records. The McMaster Evidence Review and Synthesis Team supported the literature searches and critical appraisal. A panel of people with lived experience of specific conditions and caregivers provided input on patient values and perspectives throughout the guideline development process. Our consensus process followed the Appraisal of Guidelines for Research and Evaluation II framework. We used an established evidence appraisal approach to determine the level of evidence and strength of each recommendation, and adhered to the Guidelines International Network's principles for managing competing interests.

Recommendations: We developed 11 recommendations for the manage-

ment of joint brain and heart diseases. Key recommendations include screening for cognitive decline in atrial fibrillation and depression in coronary artery disease; treatment of depression in coronary artery disease, cognitive impairment in hypertension, and dyslipidemia in stroke; and vaccination to prevent stroke, myocardial infarction, and dementia. We also recommend shared decision-making, including the use of evidence-based decision aids, to support patients with heart–brain diseases.

Interpretation: We sought to produce an implementable and actionable guideline for patients with brain and heart comorbidity. It is primarily targeted to primary care providers, but also relevant to help address and individualize subspecialty care and for interprofessional teams caring for patients with joint brain and heart diseases.

Diseases of the brain and heart affect millions and are the leading causes of mortality and morbidity globally. Ischemic heart disease accounts for an estimated 16% of global deaths,^{1,2} and stroke and dementia are leading drivers of healthy life-years lost and disability, with these conditions costing health systems billions annually.^{3,4} Although brain and heart diseases share overlapping risk factors and commonly co-occur,^{5,6} current cardiac, neurologic, and mental health clinical guidelines are typically produced within specialty silos.⁷⁻⁹

The Canadian Cardiovascular Harmonized National Guideline Endeavour (C-CHANGE) initiative, established in 2008,¹⁰ was designed to provide health care providers in Canada with a harmonized set of cardiovascular guideline recommendations, drawn from the major Canadian cardiovascular guideline groups, to help care teams formulate comprehensive treatment plans for patients with multimorbid disease.¹¹

This extension of the C-CHANGE process was motivated by the growing recognition of the important connections between brain and heart diseases as a critical source of multimorbidity in aging populations. A close interplay between heart and brain diseases exists, with many comorbidities sharing overlapping risk factors,¹² pathophysiological processes, and potential genetic and phenotypic connections.^{13,14} As a result, heart and brain conditions frequently co-occur and confer reciprocal increased risks. This clinical practice guideline expands beyond the current cardiovascular guidelines to include evidence from the neurologic and mental health literature.

The C-CHANGE process uses the SMART (Specific, Measurable, Achievable, Relevant, and Time-bound) framework¹⁵ (Appendix 1, Supplemental Table 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.251137/tab-related-content) to develop recommendations that are easily measurable and readily implementable, including incorporation into electronic medical records, and actionable for clinicians in primary care settings within specified time frames. Recommendations are organized to address and individualize the diagnosis and management of patients with multiple comorbidities. Guidelines from C-CHANGE follow a patient-centred approach and include patient-identified values and preferences.¹⁶

The objective of this clinical practice guideline is to expand on current cardiovascular guidelines to include evidence from the neurologic and mental health literature, with specific recommendations for providers caring for patients with joint brain and heart conditions.

Scope

The purpose of this guideline is to provide up-to-date, evidence-based, and patient-centred recommendations for the prevention and management of brain and heart conditions, incorporating the principles of shared decision-making, social determinants of health, and patient engagement. The guideline is designed for primary care providers and will also be useful and relevant to subspecialists in cardiology, neurology, and mental health, and members of interprofessional teams managing brain and heart diseases.

Although many potential clinical presentations of comorbid brain–heart disease exist, for this clinical practice guideline, we focused on comorbid conditions that we considered had the most established evidence base and were of high priority to our panel of people with lived experience (PWLE) and caregivers. These topics include the relationships between cognitive impairment and atrial fibrillation (AF) and with hypertension, coronary artery disease (CAD) with depression, and dyslipidemia with stroke and with overall cardiovascular disease (CVD) risk, along with vaccination to prevent stroke, myocardial infarction (MI), and dementia.

Most recommendations will be most relevant to providers caring for middle-aged and older adults with CVD risk factors, with certain recommendations (e.g., depression) potentially extending to broader populations. We also include specific reference to sex and gender considerations for each recommendation, where sex refers to biological sex and gender refers to the social, psychological, and cultural construct of gender identity. However, most studies collected or reported data by sex, with few reporting information on gender identity.

Recommendations

Recommendations were developed by 10 expert subgroups (Appendix 2, Supplemental Figure 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.251137/tab-related-content), reviewed in parallel by our PWLE panel, and approved by the guideline development panel, with the consensus process (described in Methods and in Appendix 2, Supplemental Figure 2) resulting in a total of 11 discrete recommendations for joint brain and heart diseases. Recommendations are organized into screening and treatment recommendations (Table 1). A final recommendation reflects current evidence for shared decision-making and the use of patient decision aids, relevant across all brain and heart recommendations.

Following Woolf and colleagues,¹⁷ for each recommendation, we provide an evidence summary and an assessment of evidence quality, which was the basis for our decision-making. We provide supporting information for each recommendation for providers to facilitate implementation into their practices (Appendix 3, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.251137/tab-related-content). We also developed 2 clinical considerations addressing heart failure and cognitive impairment, and screening for social determinants of health (Appendix 3).

In Appendix 4 (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.251137/tab-related-content), sex and gender considerations for the recommendations and clinical considerations are found in Supplemental Table 2, patient values and preferences from PWLE panel input in Supplemental Table 3, and benefits and harms and resource and cost implications (although we did not conduct a formal benefit–harm analysis), in Supplemental Table 4.

Table 2 outlines the grading scheme we used for our recommendations. Strong recommendations (A) are those based directly on level 1 evidence and, as such, are stated as “we recommend,” and weaker recommendations (B to D) are those based on level 2

Table 1: Recommendations for screening and treatment and shared decision-making for joint brain and heart diseases

Topic	Recommendation	Evidence grading; recommendation strength
Screening		
Atrial fibrillation and risk of cognitive impairment	We suggest that individuals with atrial fibrillation be screened using a validated screening tool to identify those at risk for cognitive impairment.	Level of evidence 2A; strength of recommendation B
Coronary artery disease and depression	We suggest that individuals with coronary artery disease be screened for depression using a validated screening tool.	Level of evidence 1B; strength of recommendation B
Treatment		
Coronary artery disease and depression	In individuals with coronary artery disease, if a depression diagnosis is confirmed, we recommend treatment be initiated with an SSRI; or We suggest treatment with other evidence-based therapies, such as cognitive behavioural therapy, based on disease severity.	Level of evidence 1A; strength of recommendation A Level of evidence 1B; strength of recommendation C
Hypertension and risk for cognitive impairment	We recommend that individuals who have a systolic blood pressure between 130 mm Hg and 180 mm Hg and an increased cardiovascular risk (defined as having clinical or subclinical cardiovascular disease, chronic kidney disease, a Framingham Risk Score of $\geq 15\%$, or age ≥ 75 yr) undergo intensive blood pressure lowering to < 120 mm Hg to reduce the risk for cognitive impairment.	Level of evidence 1B; strength of recommendation A
<i>Dyslipidemia and risk of stroke or cardiovascular disease</i>		
Dyslipidemia and risk of stroke or cardiovascular disease	We recommend that individuals with coronary artery disease with LDL-C levels above the threshold of 1.8 mmol/L undergo intensification of therapy to bring the LDL-C below target, to prevent stroke and reduce cardiovascular risk.	Level of evidence 1A; strength of recommendation A
	We suggest that individuals with stroke with LDL-C levels above the threshold of 1.8 mmol/L undergo intensification of therapy to bring the LDL-C below target, to reduce the risk of major cardiovascular events.	Level of evidence 1B; strength of recommendation B
<i>Vaccination and risk of stroke, cardiovascular death, myocardial infarction, or dementia</i>		
Influenza vaccination	We suggest routinely offering all individuals, particularly those older than 65 years, vaccination against influenza to reduce the risk of cardiovascular death and stroke and possibly dementia.	Cardiovascular death and stroke: Level of evidence 2A; strength of recommendation C Dementia: Level of evidence 3; strength of recommendation C
Pneumococcal vaccination	We suggest routinely offering all individuals, particularly those older than 65 years, the pneumococcal vaccine to reduce the risk of MI and stroke.	Level of evidence 2A; strength of recommendation B
Herpes zoster vaccination	We suggest routinely offering all individuals, particularly those older than 65 years, vaccination against herpes zoster to reduce the risk of MI and stroke, and possibly dementia.	MI and stroke: Level of evidence 2A; strength of recommendation B Dementia: Level of evidence 3; strength of recommendation C
Shared decision-making		
Shared decision-making and heart–brain health	We recommend that clinicians support individuals with or at risk of brain and heart conditions to actively participate in decision-making about their care by using evidence-based decision aids in preparation for and during consultations, to facilitate the shared decision-making process.	Level of evidence 1A; strength of recommendation B
Note: LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, SSRI = selective serotonin reuptake inhibitor.		

Table 2: Classification of evidence and strengths of recommendation for treatment or prevention¹⁷

Classification of evidence	Criteria
Level 1A	Systematic review or meta-analysis of high-quality RCTs • Comprehensive search for evidence • Low risk of bias in selecting articles for inclusion • Each included article individually assessed • Clear conclusions that are supported by the data and appropriate analyses
Level 1B	Appropriately designed RCTs with adequate power to answer the research question • Patients were randomly allocated to treatment groups • At least 80% follow-up • Patients and investigators were blinded to the treatment allocation • Patients were analyzed in the treatment groups to which they were assigned • The sample size was large enough to detect the outcome of interest
Level 2A	Evidence from at least 1 controlled study without randomization
Level 2B	Evidence from at least 1 other type of quasi-experimental study
Level 3	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
Level 4	Evidence from expert committee reports, opinions or clinical experience of respected authorities, or both
Strength and wording of recommendation	
A — recommend	Directly based on level 1 evidence
B — suggest	Directly based on level 2 evidence or extrapolated recommendation from level 1 evidence
C — suggest	Directly based on level 3 evidence or extrapolated recommendation from level 1 or 2 evidence
D — suggest	Directly based on level 4 evidence or extrapolated recommendation from level 1, 2, or 3 evidence
Note: RCT = randomized controlled trial.	

to 4 evidence or that required extrapolation from related higher-level literature and are stated as “we suggest.” As most of the available evidence was not explicitly designed to test joint brain and heart outcomes directly, the evidence level for most recommendations was downgraded because of lack of directness of evidence.¹⁸

Screening

Atrial fibrillation and risk of cognitive impairment

We suggest that individuals with atrial fibrillation be screened using a validated screening tool to identify those at risk for cognitive impairment (level of evidence 2A, strength of recommendation B).

Numerous prospective and retrospective studies have examined the relationship between AF and cognitive impairment and dementia.^{19–22} In a systematic review and meta-analysis of prospective studies (15 studies; 2822974 patients), AF was associated with a 39% increased risk of cognitive impairment in the general population (at follow-up 3.8 to 25 yr: hazard ratio [HR] 1.39, 95% confidence interval [CI] 1.25 to 1.53; $I^2=90.3\%$), and a 2.70-fold increased risk of cognitive impairment (at follow-up 0.25 to 3.78 yr: adjusted odds ratio [OR] 2.70, 95% CI 1.66 to 3.74; $I^2=0.0\%$) in a poststroke cohort (6 studies; 2009 patients), adjusting for CVD risk factors in multivariable analysis.²¹

Data suggest an association between AF and vascular cognitive impairment of all types (all-cause, Alzheimer, and vascular

dementia).²³ Importantly, AF may increase the risk of early-onset dementia. A pooled analysis of 6 studies showed an increased risk of developing early-onset dementia in individuals with AF, with a summary relative risk (RR) of 1.50 (95% CI 1.00 to 2.26; $I^2=57\%$) in patients younger than 70 years, and 1.06 (95% CI 0.55 to 2.06; $I^2=99.6\%$) in those younger than 65 years.²³ In a prospective, population-based cohort study using data from the UK Biobank, younger age at AF onset was associated with higher risks of developing all-cause dementia (adjusted HR per 10-year decrease 1.23, 95% CI 1.16 to 1.32), Alzheimer dementia (adjusted HR per 10-year decrease 1.27, 95% CI 1.13 to 1.42), and vascular dementia (adjusted HR per 10-year decrease 1.35, 95% CI 1.20 to 1.51).²⁴ After propensity score matching, individuals with AF diagnosed at younger than 65 years had the highest risk of developing all-cause dementia (adjusted HR 1.82, 95% CI 1.54 to 2.15), followed by those with AF diagnosed at age 65 to 74 years (adjusted HR 1.47, 95% CI 1.31 to 1.65), and those diagnosed at 75 years or older (adjusted HR 1.11, 95% CI 0.96 to 1.28). Similar results were found for Alzheimer and vascular dementia.

The quality of evidence for this recommendation was moderate to high. Findings were consistent across large prospective cohort studies and meta-analyses, with minimal bias. In the meta-analysis of 2.8 million people,²¹ the authors reported that all included studies fulfilled the Newcastle–Ottawa Score for being representative of the relevant cohort with adequate sample size, and all studies showed low risk of detection and information biases. Further, funnel plots and an Egger test found no

significant publication bias in any of the statistical analyses. However, in the pooled analysis of risk of developing early-onset dementia in individuals with AF,²³ authors reported high heterogeneity among studies. Limitations of existing data included widely different methods and definitions of ascertainment for AF and cognitive impairment. Despite this, the expert subgroup highlighted the strong, independent link between AF and cognitive impairment,^{19–22} including shared vascular risks and stroke.^{25,26} There are also important sex differences in AF risk and treatment²⁷ (Appendix 4, Supplemental Table 2).

Screening offers a simple, safe way to identify patients at higher risk, but cognitive screening is valued differently by patients (Table 1 and Appendix 4, Supplemental Table 3).^{28,29} Risks of screening include stigma,^{28,29} and screening tools validated for heart–brain comorbidity are lacking.

Even though randomized controlled trials (RCTs) demonstrating that screening improves outcomes are lacking, the guideline development panel considered that the strength and consistency of observational data justified recommending routine cognitive screening in patients with AF, particularly to enable early behavioural and medical intervention. There are currently insufficient data to indicate whether AF guideline–recommended therapies reduce the risk of cognitive decline. The long follow-up and large sample size required may make it unlikely that RCTs of some therapies (e.g., rhythm control medications) will be conducted to demonstrate effects on cognitive decline in patients with AF.

Coronary artery disease and depression

We suggest that individuals with coronary artery disease be screened for depression using a validated screening tool (level of evidence 1B, strength of recommendation B).

Several observational studies have examined the accuracy of screening tools for depression in individuals with CAD. A systematic review of 6 observational studies with a total of 1755 patients after acute coronary syndrome (ACS) showed high sensitivity and specificity for screening across different instruments.³⁰ Studies examining the Beck Depression Inventory-II (BDI-II), using a cut-off score of 14 or greater, reported estimates of sensitivity ranging from 83% to 91%, and specificity from 74% to 88%. A meta-analysis of 4 of these studies using this traditional cut-off reported an overall sensitivity of 90% (95% CI 86% to 92%) and specificity of 80% (95% CI 68% to 88%), with positive predictive values ranging from 28% to 46%, and negative predictive values from 98% to 99%.³⁰ Studies that evaluated the Hospital Anxiety and Depression Scale (HADS) and its subscales at traditional and optimal cut-offs reported lower accuracy, with sensitivity estimates ranging from 41% to 86%, specificity from 62% to 90%, positive predictive values from 23% to 34%, and negative predictive values from 93% to 98%. However, there was heterogeneity in the use of this instrument, with only 1 study using the full HADS. A final study examined the Patient Health Questionnaire (PHQ) — evaluating the 2-item (threshold > 0 point), 9-item (threshold > 4 points), and 10-item (threshold > 5 points) versions — and reported excellent sensitivity (96% to 97%) and specificity (71% to 78%).

A scoping review of 51 studies, including 21 790 participants, showed that the HADS, BDI-II, and PHQ were the most common instruments used to screen for depression, but reported a lack of consistency in how these screening tools were integrated into cardiac models of care and clinical pathways, and across ACS guidelines for screening for depression or anxiety, and in identifying the best screening tool. This review was downgraded, as it was a scoping review and narrative synthesis.³¹

Moderate-to-high quality of evidence supports the use of depression screening tools. Studies in the ACS systematic review³⁰ showed an overall low risk of bias and demonstrated high accuracy for depression screening. Whereas the PHQ showed the highest sensitivity and specificity, the BDI-II had the most evidence for screening accuracy. Although mental health is an important component of cardiovascular rehabilitation, the guideline development panel acknowledged that evidence from RCTs demonstrating that screening improves outcomes is lacking. The PWLE panel stressed the importance of communication among health care providers to ensure mental health support is timely. The Lancet Women and Cardiovascular Disease Commission includes depression and anxiety as under-recognized risk factors for CVD in females (Appendix 4, Supplemental Table 2).³² Screening for depression is feasible, is effective, and aligns with patient-centred care, but some patients may have concerns about the stigma of being diagnosed with depression and do not want to be screened (Appendix 4, Supplemental Table 3).³³

Treatment

Coronary artery disease and depression

In individuals with coronary artery disease, if a depression diagnosis is confirmed, we recommend treatment be initiated with a selective serotonin reuptake inhibitor (level of evidence 1A, strength of recommendation A), or we suggest treatment with other evidence-based therapies, such as cognitive behavioural therapy, based on disease severity (level of evidence 1B, strength of recommendation C).

Evidence for this recommendation focused primarily on a network meta-analysis of 33 RCTs that compared treatment for depression (pharmacotherapy, psychotherapy, combined pharmacologic and psychotherapy, exercise, collaborative care) with no care or usual care among people with CAD and depressive symptoms, with 24 studies available with estimates for depression efficacy at 8 to 26 weeks.³⁴ Most included trials involved combination interventions of pharmacotherapy paired with psychotherapy (i.e., interpersonal therapy, counselling, cognitive behavioural therapy) or exercise-focused interventions. Among those with pharmacotherapeutic interventions, the most common medication class tested was selective serotonin reuptake inhibitors (SSRIs) (14 studies, 70%); 10 trials with 1935 patients compared pharmacotherapy to placebo alone.³⁵ With negative standardized mean differences (SMDs) indicating better treatment effects, the network meta-analysis found the best evidence for efficacy at 8 weeks for antidepressants (mostly SSRIs) compared with placebo (SMD –0.28, 95% CI –0.52 to –0.03) and usual care (SMD –0.78, 95% CI –1.27 to –0.29), and possibly

compared with a composite of active and inactive treatment controls (SMD -0.33 , 95% CI -0.69 to 0.40). At 26 weeks, the study found efficacy for antidepressants compared with placebo (SMD -0.50 , 95% CI -0.69 to -0.32), usual care (SMD -1.57 , 95% CI -2.57 to -0.58), and treatment controls (SMD -1.43 , 95% CI -2.48 to -0.39). Results of the network meta-analysis showed that cognitive behavioural therapy reduced depression scores (SMD -0.48 , 95% CI -0.73 to -0.23). For secondary outcomes (change in between-group differences in depressive symptoms, mortality), the results also predominantly favoured antidepressant therapy.

In other systematic reviews of trials testing various combination therapies, SSRIs were reported to be safe in patients with cardiac disease and to have beneficial effects on depression, with some suggestion of cardiac benefit in patients with CAD. In a systematic review of 8 RCTs with 1148 patients,³⁶ SSRIs were associated with a significantly lower risk of MI in patients with CAD and depression (RR 0.54, 95% CI 0.34 to 0.86), and in patients post-ACS with depression (RR 0.56, 95% CI 0.35 to 0.90), but there was no statistically significant difference in all-cause mortality, cardiovascular mortality, hospital admissions, angina, congestive heart failure, or stroke incidence. A scoping review reported no difference in cardiovascular events with a flexible 6-month management of depression with mirtazapine-citalopram, or psychiatrist-recommended management at 18 months (OR 1.07, 95% CI 0.57 to 2.00).³⁷

There is moderate-to-strong evidence for SSRIs improving depressive symptoms and moderate evidence for the use of cognitive behavioural therapy; however, the evidence for direct cardiovascular outcome improvements from treatment of depression is less robust. In the network meta-analysis, the modal risk of bias assessments were low for most comparisons.³⁴ Comparisons between individual modes of psychotherapy versus usual care were rated as “some concerns,” whereas antidepressant-treatment control comparisons were rated as having a high risk of bias. The authors noted substantial heterogeneity for 8-week efficacy for psychotherapy versus usual care. There are also important sex differences in SSRI use and efficacy (Appendix 4, Supplemental Table 2).

Reviews assessing direct cardiac benefits were downgraded for narrative synthesis of results and a lack of critical appraisal. The expert subgroup emphasized the importance of mental health as part of cardiac rehabilitation. Although direct cardiovascular outcome benefits from treating depression are less clear, given the compelling improvements in quality of life with treatment of depression, combined with trends toward fewer adverse cardiac events, the guideline development panel considered that strong recommendations for screening and treating depression after ACS were justified. It is noted that patients often differ in the value assigned to different types of treatment for depression (Appendix 4, Supplemental Table 3).³⁸

Hypertension and risk of cognitive impairment

We recommend that individuals who have a systolic blood pressure between 130 mm Hg and 180 mm Hg and an increased cardiovascular risk (defined as having clinical or subclinical cardiovascular disease, chronic kidney disease, a Framingham Risk Score of $\geq 15\%$, or age ≥ 75 yr) undergo intensive blood pressure lowering to less than 120 mm Hg to reduce the risk for cognitive impairment (level of evidence 1B, strength of recommendation A).

Evidence for this recommendation was based on several meta-analyses, large high-quality RCTs, and prospective cohort studies. The strongest evidence was reported in a pooled individual participant analysis of 5 RCTs from the Dementia Risk Reduction (DIRECT) collaboration,³⁹ which included 28 008 adults with a systolic blood pressure greater than 160 mm Hg or a risk factor (i.e., type 2 diabetes, stroke), from 20 countries. Multilevel logistic regression showed an adjusted OR of 0.87 (95% CI 0.75 to 0.99) in favour of blood pressure-lowering treatment to reduce the likelihood of incident dementia, with the authors indicating that results support the highest grade of evidence (i.e., level 1) in favour of antihypertensive treatment compared with placebo.

In another recent random-effects meta-analysis⁴⁰ of 14 RCTs with 96 158 adult participants with hypertension (mean baseline blood pressure: systolic 154 mm Hg, standard deviation [SD] 14.9 mm Hg; diastolic 83.3 mm Hg, SD 9.9 mm Hg), 12 studies reported incident dementia and 8 reported cognitive decline; blood pressure lowering with antihypertensive therapy was significantly associated with a reduced likelihood of incident dementia (OR 0.93, 95% CI 0.88 to 0.98; absolute risk reduction 0.39%, 95% CI 0.09% to 0.68%) and cognitive impairment (OR 0.93, 95% CI 0.88 to 0.99; absolute risk reduction 0.71%, 95% CI 0.19% to 1.2%), over a mean follow-up of 4.1 years.

In the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) trial,⁴¹ 9361 adult participants with elevated blood pressure were randomized to a systolic blood pressure target of either less than 120 mm Hg (intensive) or less than 140 mm Hg (standard) treatment for a primary outcome of adjudicated probable dementia. Over the median follow-up period (5.11 yr), results showed no increases in the risk of probable dementia between the 2 groups (HR 0.83, 95% CI 0.67 to 1.04); however, they did show that intensive blood pressure control significantly reduced the risk of the secondary outcome of mild cognitive impairment (HR 0.81, 95% CI 0.69 to 0.95) and the combined rate of mild cognitive impairment or probable dementia (HR 0.85, 95% CI 0.74 to 0.97). New data from the China Rural Hypertension Control Project Phase-3 trial (CRHCP-3),⁴² randomizing 14 541 adults with hypertension to a systolic blood pressure target of less than 130 mm Hg and a diastolic blood pressure target of less than 80 mm Hg compared with usual care, also showed reduced risks of the primary outcome (all-cause dementia), over a mean of 48 months of follow-up (RR 0.85, 95% CI 0.76 to 0.95; number needed to treat 123) (data not considered in recommendation).

In the Women's Health Initiative Memory (WHIMS) study,⁴³ involving a large prospective cohort of 7207 females aged 65 to 79 years, the primary outcome of cognitive loss (mild or probable dementia) was assessed over a median of 9 years of follow-up, where the incidence of the primary outcome was 20.3 (95% CI 19.3 to 21.3) per 1000 person-years. Results showed that females with hypertension taking antihypertensive treatment were at an increased hazard of cognitive loss (HR 1.27, 95% CI 1.09 to 1.48) and mild cognitive impairment (HR 1.35, 95% CI 1.13 to 1.62) compared with those with normal blood pressure, with significant tests for HR trends ($p < 0.01$).

Moderate-to-strong evidence supports reduced risk of cognitive impairment among those taking antihypertensive treatment.

Although network meta-analyses showed strong (level 1) evidence, the SPRINT MIND trial was stopped prematurely, and meta-analytic effects sizes were consistent but small. The guideline development panel considered the moderate but consistent evidence base, strong patient preference for brain health preservation, and the low absolute risk increase of serious harms. Given the dual cardiovascular and cognitive benefits, the panel considered that targeting a systolic blood pressure of less than 120 mmHg is justified in older adults with elevated cardiovascular risk.

Dyslipidemia and risk of stroke or cardiovascular disease

We recommend that individuals with coronary artery disease with low-density lipoprotein cholesterol (LDL-C) levels above the threshold of 1.8 mmol/L undergo intensification of therapy to bring the LDL-C below target, to prevent stroke and reduce cardiovascular risk (level of evidence 1A, strength of recommendation A); and we suggest that individuals with stroke with LDL-C levels above the threshold of 1.8 mmol/L undergo intensification of therapy to bring the LDL-C below target, to reduce the risk of major cardiovascular events (level of evidence 1B, strength of recommendation B).

Several high-quality meta-analyses of large RCTs formed a strong evidence base for this recommendation.^{44,45} With respect to stroke risk reduction in CVD, a meta-analysis of 5 RCTs evaluating the effect of intensive versus standard lipid-lowering pharmacotherapy with statins on the risk of stroke in 39 612 patients with ACS found a 14% reduction in stroke risk in patients receiving intensive compared with standard statin therapy (RR 0.86, 95% CI 0.76 to 0.98), particularly those using atorvastatin.⁴⁴

In a meta-analysis of 11 trials with 24 732 patients that assessed the efficacy and safety of proprotein convertase subtilisin-kexin type 9 inhibitors (PCSK9i) in patients with ACS, PCSK9i was associated with significantly lower risk of stroke (OR 0.71, 95% CI 0.52 to 0.98) in addition to a lower risk of MI (OR 0.87, 95% CI 0.78 to 0.97), resulting in the authors recommending PCSK9i drugs as an optimal treatment strategy.⁴⁵ These drugs decrease the levels of LDL-C, total cholesterol, triglycerides, lipoprotein(a), and apolipoprotein B.

The ODYSSEY OUTCOMES and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trials,^{46,47} 2 of the largest PCSK9i trials, both demonstrated that PCSK9 therapy significantly reduced the risk of stroke in patients with atherosclerotic CVD (FOURIER: HR for stroke 0.79, 95% CI 0.66 to 0.95; ODYSSEY: HR for fatal or nonfatal ischemic stroke 0.73, 95% CI 0.57 to 0.93). A meta-analysis of 11 RCTs including these trials (most were secondary prevention trials in patients with CAD) reported that achieving an LDL-C of less than 1.8 mmol/L was associated with a significantly lower risk of ischemic stroke (RR 0.77, 95% CI 0.69 to 0.85).⁴⁸

With respect to CVD risk reduction in stroke, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial evaluated high-dose atorvastatin in 4731 patients who had experienced a stroke or transient ischemic attack 1 to 6 months earlier, with LDL-C levels of 2.6 to 4.9 mmol/L and no known CAD.⁴⁹ Significant cardiovascular risk reductions were observed, including in the risk of acute coronary events (HR 0.65, 95% CI 0.50 to 0.84),

need for revascularization (HR 0.55, 95% CI 0.43 to 0.72), and non-fatal MI (HR 0.51, 95% CI 0.35 to 0.74). Achieved average LDL-C in the statin-treated group was approximately 1.9 mmol/L. A post hoc analysis of the SPARCL trial demonstrated that patients who achieved an LDL-C of less than 1.8 mmol/L had a significantly lower risk of major coronary events than those who remained at or above a level of 2.6 mmol/L (HR 0.64, 95% CI 0.45 to 0.91).⁵⁰

Finally, the parallel-group Treat Stroke to Target trial randomized 2860 patients with ischemic stroke within 3 months or a transient ischemic attack within 15 days to a target LDL-C level of less than 1.8 mmol/L (lower-target group) or 2.3 to 2.8 mmol/L (higher-target group).⁵¹ The composite primary outcome of major cardiovascular events included ischemic stroke, MI, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes. The mean LDL-C level at baseline was 3.5 mmol/L, and the mean achieved LDL-C level was 1.7 mmol/L in the lower-target group and 2.5 mmol/L in the higher-target group. Patients randomized to the lower LDL-C target of less than 1.8 mmol/L had a lower risk of the composite primary outcome of subsequent major cardiovascular events (HR 0.78, 95% CI 0.61 to 0.98).⁵¹

The quality of evidence for the use of lipid-lowering therapy for the reduction of stroke and CVD risk is high. Large meta-analyses and RCTs support significant risk reductions across diverse patient groups, with another meta-analysis reporting no significant heterogeneity across included trials ($I^2 = 0\%$; $p = 0.74$).⁴⁴ The guideline development panel recognized that lipid-lowering provides clear dual protection against heart and brain events. The strength of randomized data showing stroke and coronary event reductions with LDL-C to less than 1.8 mmol/L justifies harmonizing management for cardiovascular and cerebrovascular disease. The benefit is particularly relevant given the devastating personal and societal consequences of stroke. Notably, across trials included in the meta-analysis by Xie and colleagues,⁴⁴ the percentage of males ranged from 75% to 83%, highlighting a substantial underrepresentation of women overall in lipid-lowering trials and in the evidence used to form this recommendation (Appendix 4, Supplemental Table 2).

Vaccination and risk of stroke, cardiovascular death, myocardial infarction, or dementia

We suggest routinely offering all individuals, particularly those older than 65 years, vaccination against influenza to reduce the risk of cardiovascular death and stroke (level of evidence 2A, strength of recommendation C) and possibly dementia (level of evidence 3, strength of recommendation C); pneumococcal vaccine to reduce the risk of MI and stroke (level of evidence 2A, strength of recommendation B); and vaccination against herpes zoster to reduce the risk of MI and stroke (level of evidence 2A, strength of recommendation B), and possibly dementia (level of evidence 3, strength of recommendation C).

The recommendations for influenza and pneumococcal vaccination were based primarily on meta-analyses of RCT data, with only observational data available for the herpes zoster vaccine and for dementia outcomes, downgrading these recommendations.

A high-quality meta-analysis of 6 RCTs⁵² with a total of 9001 patients (mean age 65.5 yr) showed that influenza vaccination was associated with a reduced risk of composite cardiovascular events (RR 0.66, 95% CI 0.53 to 0.83) and that, for cardiovascular death within 12 months of follow-up, a treatment interaction was present between patients with a recent ACS (RR 0.44, 95% CI 0.23 to 0.85) and without (RR 1.45, 95% CI 0.84 to 2.50). Another recent meta-analysis of 15 trials with a total of 745 001 patients⁵³ reported lower rates of all-cause mortality (OR 0.74, 95% CI 0.64 to 0.86), cardiovascular mortality (OR 0.73, 95% CI 0.59 to 0.92), and stroke (OR 0.71, 95% CI 0.57 to 0.89) in patients who received the influenza vaccine compared with placebo. Finally, the most recent evidence shows that, in vaccinated individuals at high risk for cardiovascular events, the risk of cardiovascular death was significantly reduced by 23% to 47%, major adverse cardiac events by 26% to 37%, MI by 29% to 34%, and stroke by 13% to 19%, compared with unvaccinated individuals.⁵⁴

Two large meta-analyses (2020: 11 studies involving 332 367 patients; 2015: 12 studies involving 716 108 patients)^{55,56} reported benefits of pneumococcal vaccination for the risk of MI and stroke. In the 2015 meta-analysis, the pooled RRs were 0.86 (95% CI 0.76 to 0.97) for cardiovascular events and 0.92 (95% CI 0.86 to 0.98) for cardiovascular mortality, with this protective effect attenuated for both outcomes after 1 year (RR 1.03, 95% CI 0.93 to 1.14).⁵⁶ For MI and stroke specifically, the protective role of pneumococcal vaccination was statistically significant only in adults (8/11 studies, mean age > 60 yr; RR 0.90, 95% CI 0.817 to 0.99 for cardiovascular events; RR 0.86, 95% CI 0.75 to 0.99 for cardiovascular mortality). In the 2020 meta-analysis, vaccination with the pneumococcal polysaccharide vaccine (PPV23) decreased risk of MI (RR 0.88, 95% CI 0.79 to 0.98) and all-cause mortality (RR 0.78, 95% CI 0.68 to 0.88), with significant effects in those aged 65 years or older, but did not significantly reduce the risk of stroke.⁵⁵ Consistent with these meta-analyses of trial data, a large, recent population-based nested case-control study (including 383 781 patients, age ≥ 65 yr)⁵⁷ also reported lower odds of acute MI (OR 0.70, 95% CI 0.62 to 0.80) and stroke (OR 0.81, 95% CI 0.77 to 0.86).

In a meta-analysis of 12 observational studies, with 6 studies evaluating the herpes zoster vaccine, vaccination for herpes zoster was found to be associated with a lower likelihood of stroke (OR 0.78, 95% CI 0.68 to 0.90).⁵⁸ A large, recent retrospective matched case-control study of 27 093 adults with at-risk comorbidities showed reduced odds of stroke and MI with herpes zoster vaccination for adults with diabetes (stroke: OR 0.64, 95% CI 0.58 to 0.71; MI: OR 0.63, 95% CI 0.57 to 0.71), hypertension (stroke: OR 0.75, 95% CI 0.68 to 0.83; MI: OR 0.73, 95% CI 0.65 to 0.81), and chronic obstructive pulmonary disease (stroke: OR 0.75, 95% CI 0.68 to 0.83; MI: OR 0.74, 95% CI 0.66 to 0.83).⁵⁹

In our initial search, dementia outcomes associated with vaccination were based primarily on observational data from the Clinical Practice Research Datalink in the United Kingdom.⁶⁰ This observational study identified 2 matched cohorts of 854 745 people exposed to the herpes zoster vaccine, matched with 8.8 million comparators, and 742 487 people exposed to the influenza vaccine, with 7.12 million comparators, and showed that the herpes

vaccine was associated with a lower risk of diagnosis of dementia (adjusted HR 0.78, 95% CI 0.77 to 0.79) and Alzheimer disease (adjusted HR 0.91, 95% CI 0.89 to 0.92), whereas influenza vaccination reduced the risk of dementia (HR 0.96, 95% CI 0.94 to 0.97). More recent meta-analyses confirm that vaccination against shingles and influenza reduces the risk of dementia.^{61–63} Studies from these meta-analyses also extend this finding to vaccination against pneumococcal disease.

The quality of evidence was moderate to high for both influenza and pneumococcal vaccination for cardiovascular protection and moderate for herpes zoster vaccination, but no trial data were available for herpes zoster vaccination. Evidence for dementia outcomes was also downgraded, with only observational data available. The expert subgroup highlighted that evidence supporting vaccination as a means of preventing cardiovascular and cerebrovascular complications is strong and growing. Given the favourable risk-benefit profile, cost-effectiveness, and broad patient relevance, the guideline development panel considered that systematic offering of these vaccines to older adults and high-risk populations is warranted as part of brain-heart health promotion strategies. We found insufficient data on respiratory syncytial virus and COVID-19 vaccination to make recommendations.

Shared decision-making

We recommend that clinicians support individuals with or at risk of brain and heart conditions to actively participate in decision-making about their care by using evidence-based decision aids in preparation for and during consultations, to facilitate the shared decision-making process (level of evidence 1A, strength of recommendation B).

Evidence-based knowledge translation tools are designed to help patients make specific and deliberate choices from among health care options and are intended to supplement, rather than replace, clinicians' counselling about care options. According to the International Patient Decision Aid Standards Collaboration,⁶⁴ patient decision aids, at a minimum, should include the following elements: explicitly state the decision that must be considered for the target population; provide evidence-based, balanced information about a health condition, the options, associated benefits, and harms; and help patients clarify, either implicitly or explicitly, the value they place on the benefits and harms of each option.

Evidence for this recommendation was based on a high-quality systematic review of 209 RCTs comparing usual care to care with the use of decision aids.⁶⁵ Results of this review showed that decision aids increased patient knowledge (high-certainty evidence), improved accuracy of risk perceptions (high-certainty evidence), increased patient participation in decision-making (high-certainty evidence), enhanced clarity of values (high-certainty evidence), and likely improved the congruence between choices and informed values (moderate-certainty evidence).

The evidence for the benefits of decision aids was high. The expert subgroup prioritized the use of decision aids, given their strong evidence base for improving the decision-making process

without introducing harm. Given the complex trade-offs involved in brain and heart health management (e.g., stroke prevention strategies, vaccination decisions, lifestyle interventions), facilitating informed, values-based choices is critical. Integrating decision aids into clinical care supports empowerment, better alignment with patient preferences, and potentially better long-term adherence to chosen therapies. Work is in progress to identify publicly available patient decision aids.

Methods

The detailed methodology for this guideline is reported in the protocol paper.¹⁸ Briefly, the guideline was developed by a guideline development panel involving a diverse group of experts across multiple disciplines, with at least half from target end-user primary care providers (Appendix 5, Supplemental Table 5, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.251137/tab-related-content). Development of this guideline followed the Appraisal of Guidelines for Research and Evaluation II (AGREE II) framework, a validated framework for developing and reporting clinical practice guideline development.⁶⁶ Appraisal of recommendations was conducted according to the grading criteria reported in Shekelle and colleagues,⁶⁷ which combine expert consensus and context with the available evidence (Table 2).

The guideline development was funded by the University of Ottawa's Brain-Heart Interconnectome (BHI) program (<https://www.uottawa.ca/research-innovation/bhi>), supported by the Canada First Research Excellence Fund.

Composition of participating groups

The Executive Steering Committee (P.L., S.W.T., R.J., J.D.E., D.H.S.) for the guideline was drawn from C-CHANGE members, with the addition of an expert in brain–heart health (J.D.E.), and provided oversight on planning, resource utilization, timelines, committee development, and implementation, as well as ensuring the transparency of competing interests during recommendation development and voting.

Ten expert subgroups (Appendix 2, Supplemental Figure 1 and Appendix 5, Supplemental Table 5) were assembled based on relevant expertise in guideline development and subject matter, and representation of target end-users (Appendix 5, Supplemental Table 5), with each subgroup comprising 1 or 2 chairs and 4 or 5 expert members. The subgroups were brain–heart diseases and diabetes, brain–heart diseases and hypertension, brain–heart diseases and dyslipidemia, heart disease and depression, heart failure and dementia, AF and dementia, vaccination to prevent heart and stroke events, behavioural intervention, shared decision-making and decision support, and social accountability.

The Evidence Review Team consisted of 8 members (2 co-chairs [J.D.E., Z.L.] and 6 experts [M.H., D.H.S., M.R., C.A.G., M.L., S.M.] in epidemiology, biostatistics, research methods, and evidence appraisal) to ensure consistency and rigour throughout the guideline development process, and a member was assigned to each subgroup. Additionally, we engaged the McMaster Evidence Review and Synthesis Team to support the literature searches and critical appraisal.

To ensure that recommendations were grounded in real-world experience and applicable to those directly affected by the guideline, the Executive Steering Committee also engaged PWLE of relevant conditions and their caregivers to join the PWLE panel to contribute to the development from inception. Participants were recruited by the Heart and Stroke Foundation from its PWLE group and from the clinical practices of the Executive Steering Committee. Specifically, as part of our co-development approach, the 12-member PWLE panel provided the steering committee with input and insights from lived experience for the list of selected recommendation topics and questions of interest. During evidence extraction and critical appraisal, the panel members provided feedback on questions brought forward by the expert subgroups. Finally, panel members were invited to be present and participate during the consensus meeting, reviewed and commented on the draft recommendations brought forward from the conference to ratification, reviewed the draft manuscript before submission, and are acknowledged with their permission in this manuscript.

Finally, the Implementation Committee's role (K.K., N.H., P.H.J., S.V.P.) was to facilitate incorporation of practice recommendations into electronic health records, using the SMART framework, and to facilitate uptake by clinicians (Appendix 1, Supplemental Table 1).¹⁸

The guideline development panel (59 members) comprised the Executive Steering Committee, the expert subgroups, the Evidence Review Team, and the Implementation Committee.

Selection of priority topics

The Executive Steering Committee developed a list of potential brain–heart comorbidity topics and, in conjunction with the McMaster Evidence Review and Synthesis Team, conducted the guideline literature searches and did an initial scan of the literature to determine whether there was sufficient evidence on each topic to form a recommendation. Before formation of the expert subgroups, the topics were reviewed by current C-CHANGE guideline members, the Evidence Review Team, the Executive Steering Committee, and the PWLE panel. Any relevant topics that were already addressed in the C-CHANGE¹¹ and Canadian Cardiovascular Society guidelines (<https://ccs.ca/guidelines/>) were removed.

Using a consensus process, we selected the final topics and formed 10 expert subgroups. Note that the final recommendations do not include those from the behavioural intervention and the brain–heart diseases and diabetes subgroups; however, we recognize the importance of health behavioural change to heart and brain health and note other guidelines, specifically for type 2 diabetes, that have focused on behavioural interventions.⁶⁸

Literature review and quality assessment

Each subgroup met virtually to develop an operational PICO (Population, Intervention, Comparison, Outcome) framework for their selected topic. We consulted the McMaster Evidence Review and Synthesis Team to systematically search and review the literature and support critical appraisal for each PICO (Appendix 6, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.251137/tab-related-content). A Cochrane-trained health sciences librarian

conducted a comprehensive literature search of 3 databases (MEDLINE, the Cochrane Library, and Embase). Searches were started in May 2024 and completed in August 2024. Each citation was critically appraised by members of the Evidence Review Team using standardized tools for interventional or observational studies to assess the level of evidence, taking into account relevance to the clinical question, methodologic quality, risk of bias, and generalizability.

The approach used in this guideline (Table 2) to appraise evidence was originally developed by Shekelle and colleagues and has been described previously.^{18,67} This method was specifically selected, as it combines expert consensus and context with the available evidence, which is particularly important when the evidence is limited or there are heterogeneous study designs. The Shekelle approach prioritizes external over internal validity, which is helpful when applied in the context of multimorbidity, similar to other recently published guidelines on multimorbid conditions.⁶⁹ This evidence appraisal system classifies the quality of evidence into 4 levels, where evidence based on systematic reviews or meta-analyses of RCTs, or appropriately designed and well-powered RCTs, is evaluated to be the highest quality evidence.

Specifically, we critically appraised each study based on the design, using valid and reliable methodologic critical appraisal tools (e.g., risk-of-bias tools). However, like Grading of Recommendations Assessment, Development and Evaluation (GRADE),^{70,71} we downgraded the evidence quality for several reasons, including study design limitations or risk of bias and use of non-RCT study designs (Table 2). As is critical to the C-CHANGE process, we prioritized the quality of a body of evidence to determine the strength of a recommendation but recognized that other factors may also contribute to the strength of a recommendation, including patient values and preferences.¹⁶

Development of recommendations

The process timeline for data extraction and development of recommendations is presented in Appendix 2, Supplemental Figure 2, which shows how our process mapped to the relevant domain and recommendation from the AGREE II tool.⁶⁶

Once the critical appraisal assessment was completed in DistillerSR, the Evidence Review Team provided a critical appraisal report to each subgroup to support writing their draft recommendations. Grading of each recommendation depended on the certainty and totality of the evidence in relation to the recommendation and its fidelity based on the evidence cited (Table 1). The PICO for each subgroup, search strategies, and evidence tables are available in Appendix 6, Supplementary Tables 6 to 13).

In November 2024, we held a conference to discuss the draft recommendations from each expert subgroup. We followed the American College of Obstetricians and Gynecologists' Clinical Consensus Methodology⁷² to build consensus. The draft recommendations developed by each subgroup had to be approved by the expert subgroup as a whole and the Evidence Review Team to be discussed at the conference.

The Evidence Review Team member who had worked closely with an expert subgroup presented its draft recommendations,

along with the PICOs, relevant literature, evidence rating, and recommendation, including benefits and harms, patient values, and preferences, and if available, sex and gender considerations and resource implications. This ensured that recommendations were presented consistently and comprehensively.

A quorum of two-thirds of guideline development panel members attending was required to hold a vote, and any member with a conflict of interest that prevented them from voting on the topic was subtracted from the total number of eligible voting participants. After a comprehensive discussion of each recommendation and supporting evidence, we held a vote among attendees to approve the recommendation, with a 70% approval threshold needed to move a recommendation forward.⁷³ Proposed recommendations not meeting this threshold were reconsidered in further discussion and after this discussion, a second vote was held with the same approval threshold.

Over the course of the guideline development process, the evidence presented at the time of the conference was not sufficient to develop a recommendation (behavioural intervention) or to reach the threshold for during voting for inclusion in the final recommendations (brain–heart diseases and diabetes).¹⁸

All proposed recommendations that met the threshold after either the first or second vote were sent forward to the full guideline development panel for a ratification vote 2 weeks after the conference. To ensure that the recommendations would help health care providers facilitate the best possible care, the draft recommendations were provided to the PWLE panel and Implementation Committee, before being ratified by the full guideline panel. The PWLE panel explicitly defined the preferences and values of patient groups and provided additional context inputs to refine and prioritize the recommendations. The Implementation Committee advised on wording to facilitate uptake of the recommendations into electronic health records and use by clinicians.

Management of competing interests

This guideline was informed by the Guidelines International Network principles regarding the disclosure of conflicts of interest,⁷⁴ ensuring that all conflicts were reported and transparent, and that members with conflicts of interest represented a minority of the guideline panel and were recused from voting, where appropriate. Supports included a dashboard web tool to ensure active management of conflicts throughout the guideline process and safeguards so that accidental voting did not occur. Each expert subgroup was chaired by an expert with no or minimal competing interests for that topic, with participation by an Evidence Review Team member with no competing interests. Each panel member was asked to complete the standardized International Committee of Medical Journal Editors form initially (as the expert subgroups submitted their PICOs) to disclose all relationships, activities, and interests related to the guideline development, and to update the form before the consensus conference, as well as before publication.

The funder, BHI, had no influence on the content, development, or recommendations presented in this guideline. Although

several guideline development panel members (P.L., Sm.P, M.H., T.V., K.L., D.S., C.G., M.L.) were researchers and clinical experts affiliated with this program, they were invited to participate based on their expertise and did not represent BHI.

Implementation

Implementation of this guideline will be facilitated through C-CHANGE's knowledge translation arm, CHEP+, a not-for-profit physician organization, and through open-access publication. To promote integration into clinical practice, knowledge translation processes include accredited continuing professional development programs for in-person and online group-learning activities. The guideline will be highlighted at the 2026 national C-CHANGE clinical guideline update conference with plenary speakers and interactive case-based workshops, accredited by the College of Family Physicians of Canada and the Royal College of Physicians and Surgeons of Canada, and designed to help practitioners change their practice behaviours. Accredited individual home learning is also available at CHEP+ Learning Series@Home (www.chepplus.com, www.cchangeguidelines.com, and learningstore.chepplus.com). We are working with the Patient Decision Aids Research Group at the University of Ottawa (<https://decisionaid.ohri.ca/>) to enhance implementation through the use of decision aids.

At the provincial level, C-CHANGE works closely with ministries of health to promote regional programs and propose workshops at national and provincial primary care meetings. This includes application of equity-oriented approaches, such as engagement with Canada's First Nations, Métis, and Inuit communities.

Development of this guideline was sponsored by the federally funded BHI project, which includes support for biannual updates. We will conduct regular updates for this guideline, with the next cycle beginning in 2027. Ongoing monitoring and evaluation will assess uptake, identify barriers to implementation, and inform these updates.

Other guidelines

Although no other guidelines are directly comparable to this guideline, as it incorporates evidence from both the neurology and cardiology literature to inform joint brain–heart multimorbid disease management, other relevant guidelines include recent American Heart Association/American College of Cardiology (ACC) and European Society of Cardiology guidelines for the management of high blood pressure,^{75,76} the 2024 ACC expert consensus pathway for treatment of heart failure,⁷⁷ and the HEARTS 2.0 clinical pathway for integrating hypertension and cardio–renal–metabolic multimorbidity.⁷⁸

Knowledge gaps

Key gaps in the literature that we noted during guideline development related specifically to sex and gender analyses in the literature reviewed. As we have highlighted for several recommendations, sev-

eral trials had under-recruitment of female participants, limiting the generalizability of the recommendations to the female population. There is also insufficient reporting of sex and gender information across studies, and we call on investigators to include sex- and gender-based analyses in their reporting. Another noted gap was that the literature drawn on for this guideline did not explicitly test joint brain and heart outcomes directly, resulting in a downgrading of evidence for most recommendations. Further research is required to develop outcome measures appropriate for multimorbid populations.

Limitations

This guideline was limited by the extent of the published literature for multimorbid conditions. As indicated, much of the included literature was not explicitly designed to test brain and heart outcomes directly, resulting in a downgrading of evidence for most recommendations. Further, this guideline was narrow in scope, and given the broad spectrum of comorbid brain and heart diseases, does not represent a comprehensive set of recommendations for all brain and heart comorbidities. Rather, we focused on joint brain and heart conditions that we thought had the most established evidence base. Additional brain and heart comorbidities will be topics for potential inclusion in our next guideline development cycle.

Conclusion

This guideline was motivated by the growing recognition of the important connections between brain and heart diseases as a critical source of multimorbidity in aging populations. Key recommendations for this guideline include screening for cognitive decline in AF and for depression in CAD; treatment of depression in CAD, cognitive impairment in hypertension, and dyslipidemia in stroke; and for vaccination to prevent stroke, MI, and dementia. We also recommend shared decision-making. We sought to produce an implementable and actionable guideline primarily targeted to primary care providers, but also relevant to help address and individualize subspecialty care and for interprofessional teams managing comorbid brain and heart diseases in their patients.

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