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REVIEW ARTICLE

Effects of antidepressants in cardiovascular disease: Cardiovascular safety and efficacy in randomized trials

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Abstract

Depression commonly coexists with cardiovascular disease (CVD) and worsens prognosis, yet uncertainty persists about the efficacy and cardiovascular safety of antidepressants in cardiac populations. Following PRISMA 2020 guidelines, we systematically reviewed randomized controlled trials (RCTs) in English that contained Food and Drug Administration-approved antidepressant with at least one cardiovascular outcome (primary, secondary, or safety). Dual screening, extraction, and outcome-level risk of bias (RoB 2) were performed, and certainty was graded with GRADE. Heterogeneity in outcomes precluded meta-analysis and was summarized qualitatively. Seven RCTs (N = 3,512; mean age 58–67 years) met criteria. Results showed that selective serotonin reuptake inhibitors (SSRI) were CVD-neutral versus placebo/usual care, no excess in major adverse cardiovascular events (MACE), arrhythmia, QTc prolongation, or mortality. Antidepressant efficacy results were mixed with sertraline not outperforming placebo in heart failure, whereas escitalopram prevented incident depression post-acute coronary syndrome. A head-to-head trial showed that nortriptyline had more cardiac adverse events than paroxetine, supporting avoidance of tricyclics in ischemic heart disease. Integrated models showed dual benefits where older adults markedly improved depression and tripled hypertension control and those without baseline CVD had reduced long-term myocardial infarction or stroke. Overall, GRADE certainty score was higher for SSRI cardiovascular safety than for antidepressant efficacy, limited by modest sample sizes, outcome heterogeneity, and short follow-up. SSRIs appear cardiologically safe in adults with CVD in short term, tricyclics should generally be avoided, and early, collaborative depression care may yield cardiometabolic benefits, especially before overt CVD. Finally, large, longer-term RCTs with prespecified MACE and bleeding/QTc endpoints are needed to refine efficacy estimates.

Keywords: Depression; Cardiovascular disease; Comorbidity; Antidepressants; Selective serotonin reuptake inhibitors; Tricyclic antidepressants; Randomized controlled trials; Collaborative care; Systematic review

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1. Introduction

Depression and cardiovascular disease (CVD) are leading contributors to the global burden of disability and mortality, and their coexistence is both common and clinically consequential. Epidemiologic studies estimate that 20–30% of patients with ischemic heart disease (IHD) or heart failure (HF) meet diagnostic criteria for major depression (MD), a prevalence 2 to 3 times higher than in the general population.[1-3] Depression in CVD is not only a marker of psychological distress but also a prognostic factor. Meta-analyses demonstrate that comorbid depression is associated with a two-fold increase in recurrent CV events and mortality.[1,4,5] This bidirectional association is supported by longitudinal data showing that depression predicts incident CVD in otherwise healthy individuals,[6,7] while new CVD diagnoses frequently precipitate depressive syndromes and are associated with increased mortality.[3] Given the global prevalence of both conditions, clarifying optimal management of depression in cardiac populations is a pressing clinical and public health priority.

The frequent co-occurrence of depression and CVD is underpinned by overlapping biological and behavioral mechanisms that constitute the brain–heart axis. Autonomic dysregulation, characterized by reduced heart rate variability and sympathetic predominance, is common to both depression and adverse cardiac outcomes and contributes to arrhythmogenesis and sudden cardiac death.[8,9]

Chronic inflammation represents another shared pathway, with elevated C-reactive protein, interleukin-6, and tumor necrosis factor-α detected in both depressive disorders and atherosclerosis.[10-12] Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis further links the two conditions: persistent hypercortisolemia promotes insulin resistance, hypertension, and endothelial dysfunction, thereby worsening CVD prognosis.[13,14] Platelet activation also plays a role, as heightened platelet reactivity in depressed patients may increase thrombotic risk.[15] Together, these shared pathophysiological mechanisms explain why depression is associated with worse cardiovascular outcomes and why interventions targeting depression may exert downstream CVD effects.

Pharmacotherapy in these patients have also historically raised safety concerns, often do not have prespecified endpoints which limit interpretability, and have produced heterogeneous findings.[16] Tricyclic antidepressants (TCA), once widely used, are associated with negative inotropic effects, conduction abnormalities, and arrhythmias, making them unsuitable for patients with coronary heart disease (CHD).[16] Selective serotonin reuptake inhibitors (SSRIs) are now the preferred pharmacologic option, having demonstrated safer CVD profiles in both observational studies and clinical trials.[17,18] However, several mechanistic concerns remain. By inhibiting platelet serotonin uptake, SSRIs reduce aggregation and may increase bleeding risk, particularly in patients receiving aspirin or anticoagulants.[19,20] QT interval corrected for heart rate (QTc) prolongation has also been reported with agents such as citalopram and escitalopram, raising the possibility of proarrhythmia in susceptible patients.[21] Furthermore, the frequent use of multiple medications in cardiac populations introduces risks of pharmacokinetic and pharmacodynamic drug-drug interactions. Beyond pharmacotherapy, integrated and collaborative care models incorporating psychosocial support, behavioral modification, and care coordination have emerged as promising strategies. Such interventions may yield dual benefits by simultaneously improving depression and modifying CVD risk factors.[22,23]

Despite the strong rationale for treating depression in CVD, optimal treatment strategies in these populations remain unclear. Clarifying the benefit–risk balance of antidepressant therapy is essential for clinicians managing patients with complex comorbidity, especially as modern collaborative-care models increasingly integrate mental health treatment within cardiology settings. Given the clinical importance of this comorbidity and the potential for antidepressants to influence both psychiatric and CVD trajectories, this systematic review highlights the need for an updated randomized controlled trials (RCT)–only synthesis focused specifically on Food and Drug Administration (FDA)-approved antidepressants and clinically meaningful cardiovascular outcomes, while also considering the contribution of integrated care approaches.

2. Methods

2.1. Protocol and reporting

This review was conducted in accordance with the PRISMA 2020 guidelines.[24] Screening, data extraction, and risk-of-bias assessment were performed using Covidence systematic review software by three reviewers (A.H., A.A., and K.V.).[25]

2.2. Eligibility criteria

This systematic review was based on RCTs, focusing on participants with CVD or at elevated CVD risk. Elevated CVD risk was defined as the presence of established risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking, that increase the likelihood but do not yet meet

criteria for clinical CVD. Interventions included an FDA-approved antidepressant. Eligible comparators included placebo, usual care, or an active antidepressant comparator. Trials were eligible if they reported any cardiovascular outcome as a prespecified primary or secondary outcome, or as a safety endpoint. Exclusions included non-randomized designs, non-English, not peer reviewed, no full text, trials without an FDA-approved antidepressant, or mechanistic studies without clinical outcomes.

2.3. Information sources and search strategy

Online databases including MEDLINE/PubMed, Embase, PsycINFO, Scopus, Web of Science Core Collection, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Library were used from inception to August 15, 2025. A librarian-vetted strategy was applied using the terms: (antidepress* AND comorbi* AND CVD). Reference lists of included studies and relevant reviews were also screened to identify additional eligible articles.

2.4. Screening, data extraction, and risk of bias (ROB) assessment

All records were imported into Covidence, where duplicates were identified both automatically and manually. Screening was conducted in two stages: title and abstract review, followed by full-text review. Conflicts were resolved through consensus or adjudication by the primary reviewer. Reasons for full-text exclusion were documented, and the overall study selection process is summarized in the PRISMA flow diagram (Figure 1).

Data extraction was performed independently by two reviewers using a structured data extraction form. Extracted variables included study design, sample size, mean/median age, trial duration, depression measures, interventions, depression outcomes, cardiovascular outcomes, and type of CVD. Extracted data were then crosschecked by two additional screeners to ensure accuracy.

ROB was assessed at the outcome level using the Cochrane ROB 2 tool.[26] Two reviewers independently rated each domain, and all judgments were subsequently reviewed for accuracy by two additional screeners. The following domains were evaluated: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For each study, the predicted direction of bias was also recorded. Details for each included study are presented in the ROB table (Table 1).

2.5. Methods for synthesis of data

We planned quantitative synthesis following PRISMA 2020 guidelines.[24] For outcomes reported with sufficient consistency (*e.g.*, major adverse cardiovascular events [MACE] and Hamilton Depression Rating Scale [HDRS]), we prespecified random-effects meta-analysis with Hartung–Knapp adjustments. Effect measures would have included risk ratios for outcomes and mean differences or standardized mean differences for continuous outcomes.

However, heterogeneity in outcome definitions, time points, and measurement tools across trials precluded formal pooling. Instead, results were synthesized narratively. Studies were grouped by CVD population and intervention class. Findings were summarized in relation

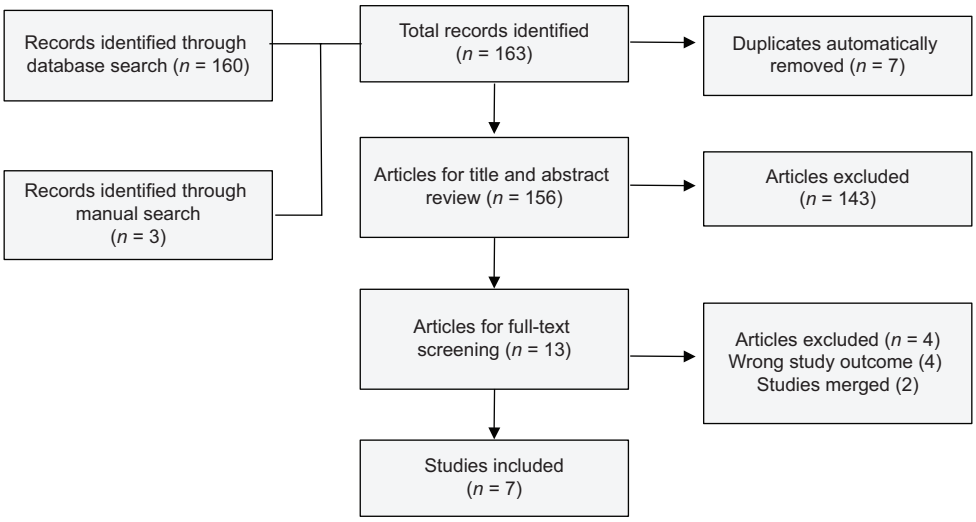

Figure 1. PRISMA flow diagram of study selection. The search yielded 163 records. After removal of duplicates and screening, only seven RCTs met the predefined inclusion criteria.

Table 1. Risk of bias

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result
Roose *et al.*, 1998[16]	Low risk	Low risk	Some concerns. Dropout higher in the nortriptyline group (10/40 vs. 4/41 in paroxetine); discontinuations often due to adverse events (especially cardiac), which could cause bias outcomes.	Low risk	Some concerns. Protocol not referenced.
Chen *et al.*, 2022[23]	Some concerns. Small number of clusters (5 per arm) raises imbalance risk.	Some concerns. Blinding not feasible for participants or PCPs; risk of performance bias. However, structured protocols reduced deviations.	Low risk	Some concerns. HDRS is interviewer-administered and assessors were not blinded to allocation (though blinded to hypotheses); blood pressure was objectively measured.	Some concerns. Antidepressant uptake and subgroup analyses were exploratory.
Hansen *et al.*, 2012, Hansel *et al.*, 2009[28,29]	Low risk	Low risk	Some concerns. About 27% dropouts; ITT mentioned but unclear sensitivity analyses.	Low risk	Low risk
Hanash *et al.*, 2012[30]	Low risk	Low risk	Some concerns. Dropout rate of about 25%, but relatively even between groups; unclear if handled with ITT or sensitivity analyses.	Low risk	Low risk
O'Connor *et al.*, 2010[31]	Low risk	Low risk	Some concerns. 38% non-completion; ITT + mixed models used, but high attrition.	Low risk	Some concerns. Multiple secondary measures raise risk of selective emphasis.
Stewart *et al.*, 2014[32]	Low risk	Some concerns. Participants/ clinicians unblinded; ITT for time-to-event; complex, multi-component care may introduce performance differences.	Low risk	Low risk	Some concerns. CVD endpoints post hoc for this follow-up; not prespecified in original IMPACT protocol.
Carney *et al.*, 2009[33]	Low risk	Low risk	Low risk	Low risk	Some concern. Cardiovascular events were not pre-specified as outcomes.

Notes: Risk of bias assessment of included RCTs, using the Cochrane Risk of Bias 2.0 tool. Judgments were made separately for each section.
Abbreviations: CVD: Cardiovascular disease; HDRS: Hamilton Depression Rating Scale; IMPACT: Improving Mood–Promoting Access to Collaborative Treatment trial; ITT: Intention-to-treat; PCP: Primary care provider.

to direction and strength of effect, with ROB and GRADE certainty incorporated into interpretation.[27]

2.6. Outcomes and synthesis

The primary outcomes of interest were cardiovascular outcomes (*e.g.*, MACE, arrhythmias, QTc prolongation, blood pressure control, mortality, and adverse CVF events) and depression outcomes (*e.g.*, HDRS, Beck Depression Inventory-II [BDI-II], and Hopkins Symptom Checklist-20 [SCL-20]) or diagnostic criteria (*e.g.*, International Classification of Diseases, 10th Revision [ICD-10]). Secondary outcomes would be clearly stated. Safety outcomes included health-related quality of life and adherence, and safety outcomes included treatment discontinuation, tolerability (*e.g.*, nausea and dizziness), and adverse events of special interest such as bleeding

complications, QTc prolongation, and sudden cardiac death were reported.

2.7. Certainty of evidence

The certainty of evidence for each outcome was assessed using the GRADE framework.[27] Evidence was graded as high, moderate, low, or very low, considering ROB, inconsistency, indirectness, imprecision, and publication bias. Certainty ratings for each outcome are summarized in Table 2's GRADE column.

3. Results

3.1. Study selection

Study selection is summarized in Figure 1, which presents the PRISMA flow diagram. A total of 163 records (3 records manually searched) were identified. After removing seven automated duplicates, 156 records were screened for their title and abstract. A total of 133 were excluded due to lack of relevance and 13 full texts were assessed. An additional four records were excluded for wrong study outcome and three studies were merged. A total of seven RCTs were included in Figure 1 with characteristics elaborated on in Table 2.

3.2. Characteristics of included studies

Across seven trials (N = 3,512; mean participant age of 58–67 years), interventions included SSRIs (sertraline, escitalopram, and paroxetine), a tricyclic comparator (nortriptyline), omega-3 augmentation of sertraline, and collaborative/integrated care models in which antidepressants could be offered within stepped care. Two companion depression in patients with coronary artery disease (DECARD) trials were included: (i) escitalopram to prevent incident depression post–acute coronary syndrome (ACS) in non-depressed patients,[28] and (ii) 12-month cardiovascular safety of escitalopram in clinically non-depressed ACS patients.[29] Follow-ups ranged from 6 weeks[16] to 12 months[23] with extended outcomes up to 8–9 years in the IMPACT follow-up.[32] Depression outcomes were measured with validated scales (HDRS, BDI-II, and SCL-20), and CV outcomes included physiological measures (blood pressure, QTc interval, and arrhythmias) as well as clinical endpoints (MACE, MI, stroke, and composite CV status) depending on study design. Study-level details are summarized in Table 2.

3.3. ROB

Risk-of-bias assessments for all included studies are presented in Table 1, which summarizes judgments across all ROB 2 domains. From Table 1, overall ROB was low-to-moderate. Randomization and allocation concealment were generally adequate across pharmacological trials,[16,28,30,31] with the exception of the COACH cluster RCT allocation,[23] where the small number of clusters increased imbalance risk. Blinding was maintained in drug trials through double-dummy or matched placebo procedures,[16,29-31] but was not feasible for collaborative care models.[23,32] Attrition was substantial but balanced by arm in Sertraline Against Depression and Heart disease in Chronic Heart Failure (SADHART-CHF) trial (approximately 38%[31]) and moderate in DECARD trial (approximately 25–27%).[28,30] Outcome measures used validated scales or objective endpoints, though in Chen *et al.*[23] interview-rated depression scores were collected by unblinded assessors, raising potential for detection bias. Finally, selective reporting was a concern in studies where cardiovascular outcomes were exploratory or not pre-specified.[32,33] Publication bias cannot be excluded, as all included trials were relatively small and industry involvement was present in some (*e.g.*, Hanash *et al.*[30]). The full appraisal is provided in Table 1.

3.4. Depression outcomes

Four randomized trials directly tested antidepressant efficacy, spanning populations with IHD,[16] CHD with comorbid depression,[33] HF with depression,[31] and ACS without baseline depression.[28] Beyond drug efficacy, two collaborative or integrated care trials[32,23] provided insight into combined psychosocial and pharmacological approaches in elderly patients with multi-morbidity. One additional trial evaluated cardiovascular safety only.[30]

3.4.1. Sertraline in HF (SADHART-CHF)

In SADHART-CHF, sertraline showed no significant difference from placebo for change in HDRS scores (−7.1 vs. −6.8; p=0.89), remission, or response.[31] Dose–response analyses also showed no interaction between assigned dose (50–200 mg/day) and depression outcomes (p=0.28), and in a subgroup with more severe depression (HDRS >17 at baseline), sertraline conferred no added benefit over placebo. Attrition was high (approximately 38%), and participants were patients with NYHA class II–IV chronic HF, which may limit generalizability. Extended follow-up (approximately 2.2 years) similarly found no difference in depression outcomes between groups.

3.4.2. Omega-3 augmentation of sertraline in CHD

In patients with stable CHD and comorbid MD, augmentation of sertraline with omega-3 fatty acids did not improve depression outcomes.[33] Weekly BDI-II trajectories were nearly identical between groups (interaction p=0.91), and endpoint scores showed no

Table 2. Characteristics of included studies.

Study (country; design; *n*)	Population type and study length	Age (mean years±SD) and sex (female %)	Intervention(s) (name, dose, duration of antidepressant)	Depression outcome(s)	Cardiovascular outcome(s)	Cardiovascular outcome role	GRADE certainty of evidence
Roose *et al.*, 1998[16] (USA; RCT; *n*=81)	Patients with IHD and MD, 6 weeks	58±11, paroxetine; 58±13, nortriptyline 12.2% paroxetine, 22.5% nortriptyline	Paroxetine 20 mg/day (titrated to 30–40 mg if nonresponse; starting 10 mg in patients ≥65 years), versus nortriptyline titrated to plasma 190–570 nmol/L (50–150 ng/mL)	Response (≥50% reduction in HDRS+ ≤esponse (≥50% reduction in HDRS/mL)(25/41) versus 55% nortriptyline (22/40). Completers were 85% nortriptyline versus 68% paroxetine. No statistical difference overall.	Paroxetine arm: Transient HR decrease at week 2 (−4 bpm), slight increase in supine SBP at week 6, 1 cardiac adverse event (unstable angina, 2%) Nortriptyline arm: Increase in HR by 11% (75 to 83 bpm, sustained), decrease in HRV (SDNN, pNN50), transient orthostatic drop at week 2, and 7 cardiac adverse events (tachycardia, angina, proarrhythmia)	Safety	Low
Chen *et al.*, 2022[23] (China; Cluster RCT; *n*=2,365)	≥2,365)er adults with comorbid hypertension and depression, 12 months	74.58±8.34, eCAU; 74.35±8.13, COACH 66.4% eCAU, 66.9% COACH	COACH: PCPs, aging workers, psychiatrists collaborated using depression + hypertension management algorithms; antidepressants prescribed as indicated. Comparator: enhanced care-as-usual (standard hypertension management care + depression guideline info)	Significant reduction in HDRS in COACH versus eCAU (Cohen's $d \approx -1.4$, $p<0.001$)	Hypertension control improved in COACH (25.1% to 71.6%) versus eCAU (20.2% to 40.9%) (OR = 18.24, $p<0.001$)	Primary	Moderate
Hansen *et al.*, 2012, Hansel *et al.*, 2009[28,29] (Denmark; RCT; *n*=240)	Clinically non-depressed post-ACS patients, 12 months	65.2±12.1, escitalopram; 64.2±12.2, placebo 36.7% escitalopram, 37.0% placebo	Escitalopram 10 mg/day versus placebo	Escitalopram significantly reduced new depression incidence (NNT=15). New ICD-10 depressive episode was 2/120 (1.7%) escitalopram versus 10/119 (8.4%) placebo (HR 0.18; 95% CI 0.03–0.82; p=0.02)	No significant differences between groups, not powered for cardiovascular outcomes	Safety	Moderate
Hanash *et al.*, 2012[30] (Denmark; RCT; *n*=240)	Clinically non-depressed post-ACS patients, 12 months	65.2±12.1, escitalopram; 64.2±12.2, placebo 36.7% escitalopram, 37.0% placebo	Escitalopram 10 mg/day versus placebo	Not assessed (patients were non-depressed)	No significant differences between groups in arrhythmia, ST depression, QTc, echo measures, or MACE. Events of MACE were 16/120 (13.3%) in escitalopram versus 13/119 (10.9%) placebo (RR 0.90; 95% CI 0.60–1.28)	Safety	Moderate

(Cont'd)

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Table 2. (*Continued*)

Study (country; design; *n*)	Population type and study length	Age (mean years±SD) and sex (female %)	Intervention(s) (name, dose, duration of antidepressant)	Depression outcome(s)	Cardiovascular outcome(s)	Cardiovascular outcome role	GRADE certainty of evidence
O'Connor *et al.*, 2010[31] (USA; RCT; *n*=469)	≥45 adults with chronic HF and MD, 12 weeks (followed up 2 years afterwards)	62.9±10.5, sertraline; 61.4±11, placebo 43.2% sertraline, 37.9% placebo	Sertraline 50–200 mg/day versus placebo	Mean HDRS change of −7.1 sertraline versus −6.8 placebo (p=0.89), response rates (≥50% reduction in HDRS) were 42.3% versus 40.2%, and remission (HDRS ≤40 occurred in 29.9% versus 32.2%, respectively. None are statistically significance	Composite CV status worsened in 29.9% sertraline versus 31.1% placebo, p=0.78. No differences in death, MI, stroke, arrhythmia, HF hospitalization	Primary	Low
Stewart *et al.*, 2014[32] (USA; RCT secondary analysis; *n*=235)	≥60 older adults with depression, 12 months (followed up 7.5–9.5 years afterwards)	No baseline CVD: 66.8±6.3, IMPACT; 67.8±6.6, usual care With baseline CVD: 67.9±6.9, IMPACT; 67.8±7.8, usual care No baseline CVD: 81.2% IMPACT; 77.1% usual care With baseline CVD: 68.6% IMPACT; 68.8% usual care	Collaborative care of stepped management with antidepressants and/or PST-PC psychotherapy, care management, and psychiatric/geriatric supervision versus usual care	No baseline CVD: 35% versus 10% achieved 50% reduction in SCL-20 (p<0.001) With baseline CVD: no statistical difference. Mean SCL-20 change: −0.4 versus +0.1 (p<0.001)	No baseline CVD arm: Hard cardiovascular events 28% IMPACT versus 47% usual care HR 0.52 (95% CI 0.31–0.86; NNT ≈6 over 5 years). MI HR 0.47 (95% CI 0.24–0.93), stroke HR 0.25 (95% CI 0.08–0.75) With baseline CVD arm: HR 1.19 (95% CI 0.70–2.03) and all-cause mortality, both not significant	Primary	Low
Carney *et al.*, 2009[33] (USA; RCT; *n*=122)	Patients with CHD and MD, 10 weeks	58.6±8.5 placebo; 58.1±9.4 omega-3 31.7% placebo, 27.4% omega-3	All participants: Sertraline 50 mg/day Randomized arms: Omega-3 fatty acids (2 g/d: EPA 930 mg + DHA 750 mg), corn oil placebo, 10 weeks after 2-week sertraline run-in	No significant difference between groups on BDI-II, HDRS, or BAI Response (≥50% reduction BDI-II): 47.7% omega-3 versus 49.0% placebo Remission (BDI-II ≤8): 28.3% omega-3 versus 27.4% placebo	14 serious adverse events requiring hospitalization (7 per group): 1 MI (placebo), 2 angioplasties (omega-3), 1 angioplasty (placebo), 1 syncope hospitalization (omega-3), 1 atrial flutter ablation (placebo), 1 implantable cardioverter-defibrillator implantation (placebo) No between-group difference	Safety	Very low

Notes: *One placebo participant excluded due to protocol violation; modified ITT analysis set to n = 239 (escitalopram 120; placebo 119). Primary outcomes are explicitly designated as primary in trial protocol/publication, secondary outcomes are formally reported secondary outcomes, and safety outcomes are adverse event or tolerability endpoints of study.
Abbreviations: ACS: Acute coronary syndrome; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BDI-II: Beck Depression Inventory-II; BP: Blood pressure; CCS: Canadian Cardiovascular Society; CEC: Clinical Endpoints Committee; CHD: Coronary heart disease; CI: Confidence interval; CGI: Clinical Global Impression; CVD: Cardiovascular disease; *d*: Cohen's *d* effect size; DHA: Docosahexaenoic acid; ECG: Electrocardiogram; Echo: Echocardiography; EF: Ejection fraction; EMR: Electronic medical record; EPA, Eicosapentaenoic acid; HDRS: Hamilton Depression Rating Scale; HF: Heart failure; HR: Hazard ratio; HRV: Heart rate variability; ICD: International Classification of Diseases; ICD-10 DD: International Classification of Diseases, 10th Revision Depressive Episode; ITT: Intention-to-treat; KCQ: Kansas City Cardiomyopathy Questionnaire; MADRS: Montgomery–Åsberg Depression Rating Scale; MACE: Major adverse cardiovascular events; MD: Major depression; MI: Myocardial infarction; NYHA: New York Heart Association; OR: Odds ratio; PHQ-9: Patient Health Questionnaire-9; RCT: Randomized controlled trial; SCL-20: Hopkins Symptom Checklist-20; SDNN: Standard deviation of normal-to-normal intervals; SBP: Systolic blood pressure; pNN50: Percentage of adjacent NN intervals differing by >50 ms; PST-PC: Problem-solving therapy for primary care; SF-36: 36-Item Short Form Health Survey; SSRI: Selective serotonin reuptake inhibitor; UKU: Udvalg for Kliniske Undersøgelser Side Effect Rating Scale; USA: United States of America; 6MWT: 6-Minute Walk Test.

benefit (BDI-II: 14.8 placebo vs. 16.1 omega-3, p=0.44; HDRS: 9.4 vs. 9.3, p=0.90). Response rates (>50% BDI-II reduction) were 49.0% versus 47.7%, and remission rates (BDI-II reduction)versus 28.3%, with no between-group differences. Trial adherence was excellent (>97% confirmed by pill counts and biomarker increases in red blood cell omega-3 index). Omega-3 augmentation did not produce statistically significant differences in antidepressant benefit in CHD cohort compared to placebo.

3.4.3. Collaborative care in hypertension and late-life depression (COACH)

In a large cluster RCT of older adults with comorbid hypertension and depression (n = 2,365), collaborative care produced substantial 12-month improvements in depressive symptoms compared with enhanced usual care.[23] HDRS scores declined from approximately 22.0 to 12.7 in the intervention arm versus 21.8 to 18.8 in controls, with a significant group × time interaction (Cohen's d = −1.43, 95% CI [−1.71, −1.15], p<0.001). Outcomes were greater among participants who accepted antidepressants, and both medicated and non-medicated subgroups showed greater improvement than the usual care group.

3.4.4. Escitalopram for depression prevention after ACS (DECARD trials)

In a double-blind RCT of 239 non-depressed patients with recent ACS, escitalopram significantly reduced the incidence of new-onset depression over 12 months.[28] Only 2 of 120 escitalopram patients (1.6%) developed an ICD-10 depressive episode compared with 10 of 119 on placebo (8.4%), corresponding to an absolute risk reduction of 6.8%, an NNT of approximately 15, and a log-rank p=0.022. In multivariate analysis, placebo assignment and higher baseline HDRS scores independently predicted depression onset, while escitalopram remained protective (HR = 0.18, 95% CI [0.03, 0.82]; p=0.02). Prophylactic SSRI therapy post-ACS significantly reduced incidence of new-onset depression compared with placebo. The related DECARD safety trial[30] enrolled non-depressed ACS population but evaluated only cardiovascular outcomes, not antidepressant efficacy.

3.4.5. SSRIs versus TCAs in IHD

In an RCT of 81 outpatients with IHD and MD, paroxetine and nortriptyline demonstrated comparable antidepressant efficacy.[16] Response rates were 25 of 41 patients (61%) for paroxetine and 22 of 40 patients (55%) for nortriptyline, with final HDRS scores ≤8 achieved at similar frequencies in both groups. Both paroxetine and nortriptyline treatment groups demonstrated similar reductions in depressive symptoms over the trial period. Cardiovascular safety differences are further explained in section 3.5.5.

3.4.6. Collaborative care by baseline CVD (IMPACT)

In a long-term follow-up of the IMPACT trial, collaborative care reduced depressive symptoms in older adults without baseline CVD, with 23 of 67 patients (35%) achieving ≥50% reduction in SCL-20 scores compared with 17 of 168 patients (10%) in usual care (p<0.001). No effect was found among those with established CVD as similar outcomes were seen in both groups with 11 of 67 patients (16%) in collaborative care and 29 of 168 patients (17%) in usual care (p=0.91).[32]

3.5. Cardiovascular outcomes

Across the seven trials, CV outcomes were variably prioritized. Three trials prespecified CV endpoints as primary outcomes, including patients with HF,[31] older adults followed long-term for incident MI and stroke,[32] and blood pressure control in a cluster RCT of older adults with depression and hypertension.[23] The remaining four trials reported CV measures as safety endpoints, including IHD patients treated with SSRIs versus TCAs,[16] omega-3 augmentation of sertraline in CHD,[33] prophylactic escitalopram for post-ACS depression prevention,[28] and escitalopram safety in non-depressed ACS patients.[30]

3.5.1. Sertraline in HF (SADHART-CHF)

Composite cardiovascular status worsened in 29.9% of patients receiving sertraline compared with 31.1% on placebo (p=0.78), with no significant differences in death, MI, stroke, arrhythmia, or hospitalization.[31] Twelve-week mortality was 7% overall with 18 in the sertraline group versus 15 in the placebo group (p=0.58). Long-term follow-up (median of approximately 2.2 years) likewise showed no significant difference in all-cause mortality (29.1% vs. 26%; HR = 1.30, 95% CI [0.66, 2.58]) or in nonfatal cardiovascular events.

However, discontinuations due to drug-related adverse effects were more frequent with sertraline than placebo (11.5% vs. 6.0%, p=0.03), driven primarily by nausea and dizziness, while rates of serious adverse events did not differ between groups.

3.5.2. Collaborative care in late-life depression and CVD risk (IMPACT)

In the IMPACT follow-up, Stewart *et al.*[32] found that among participants without baseline CVD, collaborative care significantly reduced incident major CV events (MI or stroke) over approximately 8 years (HR 0.52, 95% CI [0.31, 0.86]). Event rates were 28% with collaborative care versus 47% with usual care, corresponding to an NNT of 6.1. Cardioprotective effects extended to both enzyme-confirmed MI (HR 0.47, 95% CI [0.24, 0.93])

and stroke (HR 0.25, 95% CI [0.08, 0.75]). In contrast, among participants with established CVD, no benefit was observed (events 86% vs. 81%; HR 1.19, 95% CI [0.70, 2.03]). Subgroup analysis had a stronger reduction in men (HR 0.30, 95% CI [0.10, 0.93]) than women (HR 0.63, 95% CI [0.35, 1.12]).

3.5.3. Collaborative/integrated care and hypertension control (COACH)

Chen *et al.*[23] demonstrated that integrated collaborative care significantly improved both depressive symptoms and hypertension control (OR 18.2, 95% CI [8.40, 39.63], $p<0.001$). Specifically, hypertension control increased from 25.1% to 71.6% in the COACH intervention compared with 20.2% to 40.9% in enhanced usual care. Major adverse cardiovascular events (MACE) were not prespecified outcomes, and cardiovascular risk modification was instead inferred through improved blood pressure control. Notably, only 58% of intervention participants accepted antidepressant prescriptions, with most of the cardiovascular benefit was mediated by non-pharmacologic elements of the collaborative care model.

Adverse-event monitoring documented 40 antidepressant discontinuations due to side effects and 36 deaths (22 intervention and 14 control), all adjudicated as natural causes.

3.5.4. SSRIs versus TCAs in IHD

Roose *et al.*[16] reported that nortriptyline produced a sustained 11% increase in heart rate (75 to 83 bpm, $p<0.001$) and a significant reduction in heart rate variability (SDNN 112 to 96 ms, $p<0.01$). In contrast, paroxetine caused only a transient 4 bpm decrease at week 2 and a modest 4 mmHg rise in systolic blood pressure at week 6, with no lasting cardiovascular effects. Neither agent significantly altered conduction intervals.

Cardiac adverse events were more frequent with nortriptyline (18%) than with paroxetine (2%). Discontinuations in the nortriptyline arm included sinus tachycardia >120 bpm ($n = 4$), severe angina with ST-segment depression ($n = 1$), and proarrhythmic ventricular ectopy ($n = 2$), while in the paroxetine arm, discontinuations occurred for diarrhea ($n = 1$) and unstable angina requiring angioplasty ($n = 1$), the latter safely resumed after resolution.

3.5.5. Omega-3 augmentation of sertraline in CHD

Carney *et al.*[33] reported no significant difference in adverse cardiac events between groups, with seven serious adverse events in each arm, evenly distributed across cardiac and non-cardiac hospitalizations. Isolated events, such as a single MI in the placebo group and two angioplasties in the omega-3 group, showed no consistent pattern.

Overall tolerability was very high, with ≥97% adherence confirmed by pill counts, increased red blood cell omega-3 index in the intervention arm, and only infrequent minor side effects (stomach upset in 3% vs. 10% for placebo). Emergency visits ($n = 3$ per group) and non-cardiac hospitalizations were balanced and non–life-threatening.

3.5.6. Escitalopram after ACS (DECARD trials)

Two companion DECARD trials evaluated escitalopram after ACS in patients without baseline depression. Hanash *et al.*[30] assessed cardiovascular safety over 12 months in 240 participants and found no significant between-group differences across Holter-detected arrhythmias, ST-segment depression, QTc interval, echocardiographic systolic/diastolic indices, N-terminal pro-B-type natriuretic peptide (NT-proBNP), or laboratory measures. Major adverse cardiovascular events (death, recurrent ACS, or urgent revascularization) occurred in 16 escitalopram versus 13 placebo patients (13.3% vs. 10.9%; $p=0.59$). Hansen *et al.*[28,29] primarily tested depression prevention, monitored CV outcomes as safety endpoints, and reported no excess of MACE in the escitalopram group. Adverse-event reporting across both trials showed good tolerability, with adherence >85%, 13 discontinuations due to suspected adverse effects (8 escitalopram vs. 5 placebo; $p=0.61$), and infrequent bleeding (4 vs. 2; $p=0.68$). The only symptom more common with escitalopram was increased dream activity, and no unexpected serious events were observed.

4. Discussion

Across seven RCTs, SSRIs, notably sertraline and escitalopram, were consistently cardiovascularly neutral, with no excess risk of MACE, arrhythmias, QTc prolongation, or mortality versus placebo/usual care in cardiac populations.[30,31] Depression efficacy signals were mixed and appeared to depend on population, context, and timing of treatment. In HF, sertraline did not outperform placebo for depressive symptoms or composite cardiovascular status (worsened status 29.9% vs. 31.1%; $p=0.78$), and discontinuations for adverse effects were more frequent with sertraline (11.5% vs. 6.0%; $p=0.03$).[31]

By contrast, preventive use of escitalopram after ACS reduced incident depression (2/120 vs. 10/120; $p=0.022$; NNT of approximately 15)[28] and was cardiovascularly safe over 12 months (16 vs. 13 MACE; not significant).[30] Interventions embedding antidepressants within collaborative or integrated care showed the clearest dual benefits: in COACH, integrated care strongly improved both depression and hypertension control (blood pressure

control OR 18.24, 95% CI [8.40, 39.63]) despite only 58% initiating antidepressants, implying substantial non-pharmacologic contributions.[23] In IMPACT, collaborative care reduced long-term hard CVD events among older adults without baseline CVD (28% vs. 47%; HR 0.52, 95% CI [0.31, 0.86]; NNT 6.1 over 5 years), with no benefit in those with established CVD.[32]

Head-to-head data emphasize class differences: in IHD, nortriptyline increased adverse cardiac events (18% vs. 2%) and reduced heart-rate variability, whereas paroxetine remained neutral.[16] Overall, SSRIs appear safe across diverse CV disease populations, including prophylactic use post-ACS, while treatment efficacy varies. The strongest signals for cardiovascular risk modification arise when depression care is delivered earlier and within collaborative systems.

4.1. Mechanism considerations

Overall, these studies illustrate that SSRIs have theoretical liabilities related to bleeding and QTc prolongation, but these did not translate into excess adverse cardiovascular events in RCTs. In contrast, TCAs demonstrated electrophysiologic harm consistent with mechanistic expectations. Our findings align with evidence that depression and CVD share pathobiology and may be causally linked, at least in part,[1] which provides a coherent framework for why earlier or system-level depression care (*e.g.*, collaborative models) could influence downstream cardiometabolic risk even when individual SSRI trials are cardiovascular-neutral.

4.1.1. Platelet aggregation and bleeding risk

Platelets rely on serotonin uptake from plasma, and SSRIs deplete platelet serotonin stores by blocking reuptake, impairing aggregation and potentially increasing bleeding risk.[19] Observational studies consistently report higher rates of gastrointestinal bleeding and intracranial hemorrhage, especially with concomitant antiplatelets or anticoagulants.[34] However, none of the included RCTs were large or long enough to detect bleeding complications. In the DECARD escitalopram trials, bleeding events were rare and nonsignificant.[28,30]

4.1.2. Electrophysiology and arrhythmia

SSRIs such as escitalopram and citalopram can block the hERG potassium channel *in vitro*, delaying repolarization and prolonging QTc.[21] Clinically, no significant increase in QTc prolongation, torsade de pointes, or arrhythmia was observed in escitalopram or sertraline RCTs, consistent with prior meta-analyses. By contrast, TCAs exhibit sodium channel blockade, negative inotropy, and autonomic imbalance, predisposing to tachyarrhythmia. In the study by Roose *et al.*,[16] nortriptyline produced sustained tachycardia, reduced heart-rate variability, and a higher incidence of cardiac events. Paroxetine, in contrast, showed only transient and clinically minor changes without sustained effects, reinforcing its cardiovascular neutrality. These findings highlight a mechanistic distinction which is that SSRIs lack clinically significant sodium channel blockade, whereas TCAs carry class I antiarrhythmic–like liabilities that increase myocardial oxygen demand and confer prognostic risk, as reduced heart rate variability is a validated predictor of adverse cardiovascular outcomes.[35]

4.1.3. Vascular tone and cerebrovascular risk

Serotonin also acts as a vasoactive amine, and excess serotonergic signaling has been hypothesized to promote coronary or cerebral vasoconstriction.[36] Observational studies suggest associations between SSRIs and ischemic stroke,[37] though residual confounding by depression severity is likely. None of the included RCTs observed this signal, suggesting that clinical stability and trial monitoring may mitigate risk.

4.1.4. Inflammatory and autonomic modulation

Beyond safety, SSRIs may exert indirect prognostic effects through autonomic tone, stress reactivity, and inflammation. In IMPACT, treating depression before overt CVD onset halved subsequent MI and stroke risk, but no benefit was seen in those with established CVD, consistent with prevention rather than secondary treatment.[32] The preventive signal in DECARD similarly suggests that escitalopram may stabilize affective regulation in the post-ACS period, blunting HPA hyperactivation and neuroinflammation.[28] Although not powered for CV endpoints, decline in both arms without between-group difference and absence of excess arrhythmias reinforce physiological neutrality.

4.1.5. Nutritional augmentation

The negative result of Carney *et al.*[33] indicates that raising membrane EPA+DHA levels alone may be insufficient to augment SSRI efficacy in CHD patients. Baseline DHA deficits are common in depressed ACS cohorts, but the trial's 750 mg/day DHA dose may have been too low. Differential vascular and neurobiological effects of EPA versus DHA may also explain the lack of synergy with sertraline.

4.1.6. COACH mechanistic signal

Although COACH was not designed around pharmacologic antidepressants, it demonstrated that collaborative care improved both depression and hypertension control.

Because only 58% of participants initiated antidepressants, the blood pressure benefit was likely mediated by behavioral adherence support and care coordination rather than SSRI pharmacology.[23]

4.2. Completeness and applicability of the evidence

Trials largely enrolled older adults with HF, ACS, or hypertension, and primarily tested sertraline, paroxetine, escitalopram, or nortriptyline for 6 weeks–12 months. Younger adults, women, multi-morbid, and ethnically diverse groups were underrepresented. Most trials were also in North America, Europe, or China, limiting generalizability. Sample sizes were modest, limiting power for rare outcomes (*e.g.*, sudden cardiac death and major bleeding). In SADHART-CHF, short-term neutral cardiovascular effects persisted at approximately 2.2-year follow-up with no survival difference (HR 1.30, 95% CI [0.66, 2.58]).[31]

DECARD extends applicability to post-ACS prophylaxis with fixed-dose escitalopram (10 mg/day) prevented depression (NNT of approximately 15) and remained cardiovascular-neutral, although precision was limited by total sample size of approximately 240 and dropout of approximately 27% versus 23%.[28,30] External validity also derives from resource-limited settings (COACH), where integrated care delivered by non-specialist teams improved both depression and blood pressure control.[23] IMPACT suggests primary prevention potential when collaborative care precedes clinical CVD.[32] Notably, earlier post-MI data with sertraline in unstable angina/MI cohorts by Glassman *et al.*[17] also demonstrated cardiovascular neutrality under intensive trial monitoring, which is directionally consistent with our synthesis and suggests applicability across different eras of ACS care and background therapies.

Collectively, these trials confirm the short-term cardiovascular safety of SSRIs in older adults with stable CVD while underscoring gaps in generalizability to younger, more diverse, and multi-morbid populations, particularly in low- and middle-income settings.

4.3. Demographic characteristics

Across RCTs, participants were predominantly older adults (mean age 58–75 years) with a modest female representation (approximately 30–45%), reflecting the male preponderance of CHD and HF cohorts.[23,29-31,33] U.S.-based trials largely enrolled Caucasian participants (approximately 55–80%), with African American representation in sertraline/HF studies (≈35–40%) and mixed representation in primary care cohorts.[31] Race and ethnicity were rarely reported outside of U.S. settings, limiting cross-national comparability.[31] The COACH cluster trial in rural China recruited very elderly participants (mean age of approximately 75 years), most of whom were women with limited formal education, highlighting unique contextual constraints.[23] Overall, samples were small to moderate in size (n=81–469), except for COACH (n=2,365), with most studies restricted to high-income settings. This demographic skew toward older, Caucasian, North American, or European populations constrains the generalizability of findings to younger, more diverse, and low- or middle-income populations.

4.4. Agreements and disagreements with prior evidence

The evidence synthesized here is broadly consistent with recent randomized and meta-analytic data supporting that SSRIs remain cardiovascular-neutral across diverse cardiac conditions and support their cardiovascular safety.[1] In a recent systematic review, Kimura *et al.*[21] confirmed that escitalopram was not associated with excess MACE, QTc prolongation, or trial discontinuation in patients with CVD, aligning with SADHART-CHF[31] and the DECARD safety trial.[30] Similarly, Carney *et al.*[33] reported no excess of serious cardiovascular events with omega-3 augmentation of sertraline, reinforcing the conclusion that SSRIs are generally neutral in controlled settings. Observational data also support this neutrality as Coupland *et al.*[38] found no increase in all-cause mortality once confounding was addressed, further validating trial-based evidence.

Moreover, large-scale synthesis continues to affirm both the high burden and potential causal links between depression and CVD. In a 2025 meta-analysis with Mendelian randomization, Zeng *et al.*[1] estimated a pooled depression prevalence of approximately 20.8% among CVD patients (coronary artery disease 19.8% and HF 24.7%) and reported genetic evidence consistent with bidirectional influence between mood disorders and cardiometabolic disease. These data contextualize with our findings that highlight the importance of early intervention and prevention.[28,29] That is to say that earlier identification and treatment of depressive syndromes, particularly before advanced CVD, is biologically plausible and may translate to downstream cardiovascular risk modification, whereas later treatment during overt disease appears less likely to shift hard cardiovascular endpoints.

Trial data outside our inclusion set are also concordant with SSRI cardiovascular neutrality, even among high-risk groups. In SADHART study by Glassman *et al.*,[17] sertraline in recent MI/unstable angina showed no adverse effects on left ventricular ejection fraction (LVEF), QTc, heart rate variability, or arrhythmias versus placebo, and efficacy on depressive symptoms in clinical subgroups. This mirrors our conclusion that SSRIs can be used safely in cardiac

populations with routine monitoring. Bleeding and stroke risks could also be further investigated for their significance when adjustments for baseline vascular burden, depression severity, or polypharmacy are accounted for.

By contrast, observational syntheses have sometimes produced divergent signals. Alamri *et al.*,[37] in a meta-analysis of nonrandomized studies, identified an elevated risk of ischemic and hemorrhagic stroke (particularly intracerebral hemorrhage) among SSRI users. These findings conflict with RCT evidence, which has not shown such risks, and likely reflect confounding by indication, unmeasured vascular burden, and differential prescribing patterns. This highlights the importance of RCT-focused syntheses for adjudicating safety questions that observational designs may distort.

Head-to-head evidence also clarifies class-specific risks. Roose *et al.*[16] demonstrated that while both paroxetine and nortriptyline improved depressive symptoms in IHD, nortriptyline produced tachycardia, reduced heart rate variability, and a significantly higher incidence of adverse cardiac events. These findings reinforce guideline recommendations that SSRIs should be preferred over TCAs in patients with CHD.

Furthermore, the null findings of Carney *et al.*[33] are especially instructive. Despite biochemical confirmation of increased omega-3 indices, augmentation conferred no benefit for depression or cardiovascular outcomes in patients already receiving sertraline. This underscores that encouraging results from smaller or uncontrolled studies of nutritional strategies may not translate into clinically meaningful synergy in cardiac populations, underscoring the need for rigorous randomized testing before nutritional adjuncts are considered for clinical adoption.

Finally, not all effective depression care translates into fewer cardiovascular events. In an ENRICHD study[39] of a large post-MI trial of cognitive-behavioral therapy and support, depressive symptoms and social support improved but the primary endpoint (death/nonfatal MI) did not. Secondary analyses and re-analyses suggest that any survival signal is concentrated among treatment responders, underscoring that cardiovascular benefit likely depends on achieving and sustaining remission rather than treatment assignment alone.

4.5. GRADE certainty of evidence

When appraised with the GRADE score in Table 2, the evidence supports short-term cardiovascular neutrality of SSRIs in patients with CVD, but certainty varies by outcome. Across domains, ROB was generally low, though attrition and non-prespecified outcomes led to downgrades. Imprecision was common due to modest sample sizes (<500 in most pharmacologic trials) and few events. Overall, evidence for safety was stronger than for antidepressant efficacy.

4.6. Clinical translation and implications

The cumulative trial evidence supports SSRIs as the preferred antidepressants for patients with comorbid CVD. In SADHART-CHF, sertraline showed no excess in cardiovascular worsening compared with placebo, although discontinuations for nausea and dizziness were more frequent[31]. Similarly, the DECARD safety trial confirmed that 12 months of escitalopram in non-depressed post-ACS patients was cardiovascularly neutral, with no increase in MACE, arrhythmias, or QTc prolongation.[30] These data support SSRIs as first-line options in cardiac populations, with standard monitoring for QTc, arrhythmia symptoms, drug–drug interactions, and bleeding risk.

When SSRIs are co-prescribed with oral anticoagulants, large population-based analyses show an approximate 33% relative increase in major bleeding (incidence rate ratio 1.33; 95% CI [1.24, 1.42]), peaking in the first 30 days (incidence rate ratio of approximately 1.74), and persisting up to 6 months.[19] This warrants closer surveillance and gastroprotection where appropriate. For QTc, a focused systematic review in CVD cohorts found no significant excess QTc prolongation or MACE with escitalopram versus placebo, though confidence intervals remain wide and further powered trials are needed.[21]

Prophylactic use may also be relevant. In DECARD prevention, escitalopram lowered the incidence of depression after ACS, with a number needed to treat to be approximately 15.[28] Whether this justifies that routine use is debatable, given modest absolute risk reduction and uncertain long-term cardiac impact. Nonetheless, the findings underscore the value of early depression screening and selective preventive pharmacotherapy in high-risk subgroups.

By contrast, TCAs should generally be avoided in IHD. Roose *et al.*[16] demonstrated that although paroxetine and nortriptyline were similarly effective for depression, nortriptyline induced sustained tachycardia, reduced heart rate variability, and caused substantially more cardiac events (18% vs. 2%). This trial remains pivotal in reinforcing guideline recommendations for SSRIs over TCAs in coronary populations.

Adjunctive strategies appear less promising. The Omega-3 Augmentation of Sertraline trial showed no improvement in depressive or cardiovascular outcomes despite excellent adherence and biochemical confirmation of uptake.[33] Omega-3s therefore remain appropriate for general cardiovascular health, but not as antidepressant augmentation in CHD populations.

At the health-system level, integrated care may offer the greatest translational impact. COACH demonstrated that embedding non-specialist health workers into collaborative care frameworks produced large improvements in both depression and hypertension control, with blood pressure control tripling in the intervention arm.[23] Benefits extended even to patients who declined antidepressants, highlighting the primacy of behavioral and adherence support. Similarly, the IMPACT follow-up showed that collaborative care halved the risk of incident MI and stroke in older adults without baseline CVD, with an NNT of approximately 6 over the 8 years.[32] These preventive effects compare favorably with established interventions such as statins, suggesting that upstream depression care may be a valuable component of cardiovascular risk reduction. The absence of benefit in patients with established CVD, however, underscores that timing of intervention is critical.

4.7. Biases and limitations

Several limitations should be acknowledged. First, outcome heterogeneity was substantial: depression was assessed with different tools (*e.g.*, HDRS, BDI-II, and ICD-10), while cardiovascular outcomes ranged from surrogate markers such as blood-pressure control to hard endpoints such as MACE. Many cardiovascular outcomes were exploratory or reported only as safety events rather than prespecified primaries, limiting interpretability and precision.

Second, integrated and collaborative care interventions combined antidepressants with psychotherapy, case management, and adherence support, preventing isolation of antidepressant-specific effects.[32] Methodological concerns were most evident in COACH, where township-level cluster randomization with only five clusters per arm and unblinded assessors raised risk of performance and detection bias despite statistical adjustment.[23]

Third, adverse events were incompletely reported. Gastrointestinal bleeding, an established SSRI risk when combined with antiplatelets or anticoagulants, was not systematically captured, despite consistent observational evidence.[20,34] Likewise, outcomes relevant to torsade de pointes or sudden arrhythmic death were underpowered or absent.

Finally, adherence to antidepressants and key lifestyle behaviors (*e.g.*, diet, exercise, and smoking cessation) were rarely measured, constraining mechanistic inference about how psychiatric interventions may influence downstream cardiovascular outcomes.

4.8. Future research needs

Future research should prioritize adequately powered, longer-term RCTs with prespecified cardiovascular endpoints, including MACE, sudden cardiac death, and major bleeding. Most existing trials were modest in size and rarely extended beyond 12 months, leaving uncertainty about long-term outcomes. Comparative effectiveness studies are also needed to delineate the cardiovascular safety of SSRIs, SNRIs, and newer antidepressant classes in patients with established CVD.

Mechanistic substudies should be embedded in future RCTs to clarify pathways linking antidepressants with cardiovascular outcomes, incorporating autonomic testing, inflammatory biomarkers, platelet function assays, and evaluation of drug–drug interactions. Standardized reporting of adverse events, particularly bleeding, arrhythmias, and QTc prolongation, is critical given the polypharmacy common in cardiology practice.

Stratified and adaptive designs are warranted to test effect modification by baseline depression status, CVD severity, sex, and age, and to better identify subgroups most likely to benefit from treatment or prophylaxis. Finally, targeted evaluation of post-ACS prophylaxis and primary-prevention strategies in underrepresented populations, including women, younger adults, and those in low- and middle-income countries, will be essential to guide clinical decision-making and broaden generalizability.

5. Conclusion

In patients with CVD, SSRIs, particularly sertraline and escitalopram, demonstrate short-term cardiovascular safety, with no consistent signal for increased MACE, arrhythmias, QTc prolongation, or mortality across RCTs. Antidepressant efficacy remains variable, but collaborative and integrated care models consistently improved both depressive symptoms and cardiometabolic risk factors. By contrast, TCAs carry clear cardiovascular liabilities, including tachycardia, reduced heart rate variability, and higher adverse-event rates, and should generally be avoided in IHD.

Mechanistic concerns such as bleeding, QTc prolongation, and altered vascular tone remain biologically plausible but were not substantiated by trial evidence. Taken together, current findings support SSRIs as appropriate first-line therapy for depression in patients with stable CVD, which provided clinicians monitor tolerability and consider individual risk factors (*e.g.*, concurrent antiplatelet or anticoagulant use).

Finally, early and integrated depression care may offer dual benefits, improving mental health while lowering downstream cardiovascular risk, particularly when delivered before clinical disease onset. Future large, long-term trials are needed to confirm cardiovascular safety,

clarify antidepressant efficacy across diverse populations, and better define the role of prophylaxis in post-ACS and primary-prevention contexts.

Taken together, this review provides the first integrated synthesis across randomized trials evaluating both antidepressant efficacy and cardiovascular safety in diverse cardiac populations. By combining pharmacologic and collaborative-care evidence, our findings clarify that SSRIs are consistently cardiovascular-neutral across heart disease populations. This review also uniquely highlights that collaborative and preventive models likely provide benefits independent of medication effects. These contributions address long-standing uncertainty and offer evidence to guide depression treatment decisions in patients with CVD.

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