Clinical review of treatment options for major depressive disorder in patients with coronary heart disease

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ABSTRACT

أثبتت دراسات متعددة أن نسبة الإصابة باضطراب الاكتئاب الجسيم تتضاعف لدى مرضى شرايين القلب التاجية، ويزيد وجود الاكتئاب من خطورة الوفاة بجلطات قلبية مميتة. وفي هذه الدراسة المنهجية تم البحث في المراجع العلمية عن الدراسات الكبرى العشوائية المقارنة حول علاج هذا النوع من الاكتئاب وذلك خلال الفترة من 1980م إلى 2011م. وقد شمل هذا البحث ما مجموعه 8 من الدراسات. وأوضحت هذه الدراسات على قلتها أن علاجات السيرترالين، والسيتالوبرام، والميرتازابين آمنة بشكل عام لمرضى القلب؛ لكن فقط علاجا السيرترالين والسيتالوبرام أثبتا فعاليتهما لعلاج الاكتئاب الجسيم من النوع المتوسط والشديد وخصوصاً إذا ما كان من النوع المتكرر النوبات وبدأت أعراض نوبته الحالية قبل النوبة القلبية. ولم يؤدي السيرترالين المزود بأوميغا– 3 إلى نتائج مؤثرة على هذا المرض. أما العلاجات الغير دوائية كالعلاج المعرفي السلوكي والعلاج البين شخصي فقد أثبتا فعالية محدودة لبعض فئات هؤلاء المرضى. وقد تفيد ممارسة الرياضة المنتظمة مرضى الاكتئاب من النوع الخفيف.

It is established that the prevalence of major depressive disorder (MDD) in coronary heart disease (CHD) populations is high and is associated with increased mortality. In this systematic review, we examined the evidence for the effective treatment of MDD in CHD patients by reviewing randomized control trials (RCTs) between 1980 and 2011 and then assessing whether these treatments were clinically meaningful. A total of 8 RCTs were retrieved. Sertraline, citalopram, and mirtazapine were safe from a cardiac perspective, but only sertraline and citalopram were clearly more effective than placebo in CHD patients with moderate-to-severe type, recurrent MDD, or MDD episode onset before the CHD event. Augmenting sertraline with omega-3 fatty acids did not result in superior depression outcomes. Cognitive-behavioral therapy was equivocally superior to usual care. Interpersonal psychotherapy was only superior to clinical management in patients with high baseline functional status. Exercise is a potential treatment for those with mild depression.

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Major depressive disorder (MDD) and coronary heart disease (CHD) are common conditions that are associated with considerable morbidity and mortality. In 2004, MDD was found to be the third and CHD the fourth cause of the defined 'global burden of disease.[1] Currently, MDD is the third, leading cause of disability while CHD is the leading cause of death worldwide.[1] According to the World Health Organization projection, by 2020, depression will be the second leading contributor to the global burden of disease only after CHD.[2-4] Major depression is common among patients with CHD with prevalence estimates at 14% or higher, and an additional 20% of patients have subclinical or minor depression.[5] The prevalence of major depression is approximately 3 times higher in the hospitalized patient with coronary artery disease than in the general adult population, whereas rates of minor depression may be even higher. Several studies have examined the relationship between major depression and the development of CHD; they revealed that depression is a significant and independent risk factor for CHD morbidity and mortality.[6] Depression substantially undermines quality-of-life among patients with CHD.[7] It promotes noncompliance to cardiac medications, as well as to cardiac rehabilitation.[8,9] Depression is associated with up to 50% increase in 5-year cardiovascular direct costs (hospitalizations, office visits, procedures, and medications) and indirect

costs (out-of-pocket, lost productivity, and travel).[10] Depression is also associated with a three-fold risk of one-year re-hospitalization among cardiac patients.[11] Moreover, concomitant depression was related in several meta-analysis studies to a 2- to 2.5-fold increase in risk of cardiac or all-cause mortality.[12,13] Despite its consequences for prognosis and quality-of-life, MDD is under recognized and undertreated in cardiac patients.[14,15] Although various pharmacologic and non-pharmacological treatments for depression exist, treatment of MDD is often a challenging task for the treating physician. The cardio toxic effect of the older group of antidepressants (tricyclic antidepressants (TCAs) and monoamine-oxidase inhibitors (MAOIs) medications), drug interactions, and patient's resistance to start medications are some of these challenges.[14,16] Furthermore, the feasibility and availability of standard psychotherapeutic approach is an issue as well. The purpose of this study is to examine the evidence for the effective treatments of MDD among CHD patients by reviewing randomized control trials for differences in effect between active treatment and placebo or usual care and then assessing whether these treatments were clinically effective.

Literature search. We did a literature search between October and November 2011 of the electronic databases including PubMed, MEDLINE, Cochrane Database, EMBASE, and Ovid using these keywords; acute coronary syndrome, coronary artery disease, myocardial infarction (MI), antidepressants, selective serotonin reuptake inhibitors (SSRIs), psychotherapy, non-pharmacological therapy, and MDD. Studies examining the use of various antidepressants modalities of MDD in patients with CHD were limited to randomized controlled trials (RCTs) and systematic reviews in the English language, with human subjects, with adult populations, and published over the last 3 decades (between 1980 and 2011). The RCT had to have an intervention group and a placebo or usual care. The reference lists of all retrieved articles were checked to retrieve any additional RCTs. Both authors reviewed the articles independently. Agreement as to whether an article should be included was settled by consensus after independent review.

Description of the conditions. The CHD is defined as ischemic symptoms leading to coronary angiographic evidence of a 50% or more blockage in at least one major coronary artery, previous hospitalization for an acute coronary syndrome such as MI, or previous revascularization such as percutaneous coronary intervention and coronary artery bypass grafting.[17] The MDD is defined as major depression episode fulfilling the criteria of the Diagnostic and Statistical Manual of Mental Disorders,[18] or the International Statistical Classification of Diseases and Related Health Problems in use at the time of the trial.[19]

Findings of RCTs. Both authors reviewed the chosen RCTs and related secondary analysis manuscripts. The following study criteria were actively retrieved; study design, geographic location, duration of recruitment, sample size, type of population, intervention and placebo/usual care arms, dose and duration of antidepressants, CHD and MDD diagnosis criteria, the onset of MDD in relation to CHD, predefined outcome measures, the outcome in intervention and placebo/usual arms, the study findings, statistical significance, limitations and other comments.

Designs of the studies selected. A total of 8 RCTs were selected as shown in **Table 1**. According to the year of publication, these include Strik and colleagues,[20] McFarlane and colleagues,[21] The Sertraline Antidepressant Heart Attack Trial (SADHART),[22-24] The Enhancing Recovery in CHD Patients (ENRICHD) trial,[25-27] The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial,[28,29] The MI and Depression Intervention Trial (MIND-IT),[30] Carney and colleagues,[31] and Freedland and colleagues.[32] We excluded some studies because of mixing depression and non-depression samples,[33,34] or non-English language.[35,36] Both the ENRICHD[25-27] & MIND-IT[30] trials enrolled patients with either major or minor depression. In the ENRICHD trial,[25-27] treatments with cognitive behavior therapy (CBT) were supplemented with SSRI (usually sertraline) only in those patients who failed to respond to CBT. Most RCTs were multi-center studies with few single-center studies.[21,31,32] Three RCTs were conducted in the USA, 2 in Canada, 2 in the Netherlands, and one in multiple countries including USA, Europe, Canada, and Australia. With exception of ENRICHD that had a large sample size (2481), the rest of the RCTs recruited between 38 and 369 patients. Analysis was carried out using intention-to-treat design in all but one RCT.[21]

The CHD and MDD diagnosis. Myocardial infarction with or without unstable angina, revascularization, or angioplasty was used in diagnosing CHD in all RCTs.

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The time between randomization and the diagnosis of CHD was specified as one month in 2 RCTs,[22,25] within the last 12 months in 3 RCTs,[20,30,32] and was not clearly specified in 3 RCTs.[21,29,31] The Hamilton Depression Rating Scale (HAM-D) was used as primary MDD endpoint measure in 6 RCTs. Other scales used include; the Beck Depression Inventory (BDI), Composite International Diagnostic Interview, Clinical Global Impression (CGI) Improvement scale, SCID, the Inventory to Diagnose Depression questionnaire, and Depression subscale of the Symptom Check List 90 items (dSCL-90). Recurrent depression at baseline was specified in 2 RCTs between 48-66%.[29,31] The relation of MDD diagnosis to CHD diagnosis was specified in only one RCT with 53% of depression developed before index CHD.[22]

Intervention. Sertraline, the most commonly examined antidepressant, was evaluated in 4

Table 1 - Comparisons of the study design and intervention used among selected randomized controlled trials.

Study name	Design	Participants	N	Intervention	Doses & duration	CAD criteria	Depression assessment	Depression onset
Strik et al[20] 2000	Double-blind, multi-center, randomized, placebo-controlled trial (2-arm parallel design)	Patients with MDD from 2 hospitals in Netherlands (70.4% males, mean age 56.4 years) during 1994-1997	T=54 I=27 P=27	Treatment with either SSRI (Fluoxetine) or placebo	Fluoxetine 40-60 mg/day for 9 weeks (with optional 16 weeks additional)	Acute MI within the last 12 months	Patients fulfilling DSM-III-R criteria for a major depressive episode and having a HAM-D score of >17 were included	No patients were taking antidepressant or antipsychotic drugs before the study
McFarlane et al[21] 2001	Double-blind, single-center, randomized, placebo-controlled trial (2-arm parallel design)	Patients from one Canadian hospital with MDD (59.3% male; mean age 56 years) between 1996 and 1999	T=38, I=12, P=15	Treatment with either SSRI or placebo. A third non-depressed non-randomized reference group (n=11)	Sertraline 50 mg/day for 22 weeks	Acute MI	Score >15 on the IDD questionnaire	Unclear
SADHART Glassman et al[22] 2002 Swenson et al[23] 2003	Double-blind, multi-center, randomized, placebo-controlled trial (2-arm parallel design)	Patients from USA, Europe, Canada, Australia with MDD (64% male; mean age 57.1 years) between 1997 and 2001	T=369, I=186, P=183	Treatment with either SSRI (Sertraline) or placebo	Sertraline 50-200 mg/ day for 24 weeks	MI (74%) or unstable angina (26%) within last month	1-Depression: HAM-D scores & CGI-I scale scores. 2- Quality-of-life: QLES-Q	Approximately 53% of depression developed before index CAD and 47% after CAD
ENRICHD Berkman et al[25] 2003 Taylor et al[26] 2005 Cowan et al[27] 2008	Multicenter, randomized clinical trial (2-arm parallel design)	Patients from 8 US centers (56.3% males, mean age 61.0 years) during 1996-2001. Patients had major or minor depression (39.4%), low perceived social support (LPSS, 26.1%), or both (34.5%)	T=2481 I=1238 P=1243	Treatment with CBT supplemented with SSRI (usually Sertraline) or routine care	Sertraline 50-200 mg/day for up to 12 months	Acute MI within the last 4 weeks	1-Depression: 17-item HAM-D & BDI scales 2-LPSS: the ESSI and PSSS	Unclear
CREATE Lespérance et al[29] 2007 Habra et al[28] 2010	Double-blind, multi-center, randomized, placebo-controlled trial (2 by 2 factorial design)	Patients from 9 Canadian academic centers with MDD (75% male; mean age, 58.2 years) between 2002 and 2006	T=284 I=142 P=142	1- IPT plus clinical management or only clinical management 2-Treatment with either SSRI (Citalopram) or placebo	Citalopram 20-40 mg/ day for 12 weeks	MI (65%), revascularization (45%), or angioplasty (58%)	SCID & HAM-D scale	Approximately 47.9% of the patients had recurrent depression at baseline
MIND-IT Honig et al[30] 2007	Double-blind, multi-center, randomized, placebo-controlled trial (nested, 2-arm parallel design)	Patients with major or minor depressive disorders from 8 hospitals in Netherlands (86.9% males, mean age 59.2 years) between 1999 and 2002.	T=91 I=47 P=44	Treatment with either SSRI (Mirtazapine) or placebo; patients who did not respond and patients with relapse were offered open treatment with citalopram	Mirtazapine 30-45 mg/ day for 24 weeks	Acute MI within the last 12 months	Patients with a score ≥10 on BDI were interviewed with the CIDI for major or minor depression diagnosis	Unclear. Patients were screened for depressive symptoms 0, 3, 6, 9, and 12 months after MI
Carney et al[31] 2009	Double-blind, single-center, randomized, placebo-controlled trial (2-arm parallel design)	Patients from one US hospital with MDD (66.4% male; mean age 58.3 years) between 2005 and 2008	T=122 I=62 P=60	Treatment with SSRI (Sertraline) with omega-3 fatty acid or Sertraline only (placebo)	Sertraline 50 mg/ day with or without omega-3 fatty acid 2g/ day for 10 weeks	CHD: stenosis, revascularization, or acute coronary syndrome	Scores on BDI-II and HAM-D	66.4% had history of depression and 62.3% had depression medication at baseline
Freedland et al[32] 2009	Single-blind, single-center, randomized, placebo-controlled trial (3-arm parallel design)	Patients with major or minor depressive disorder from one US (50.4% males, age about 60 years) between 2001 and 2005	T1=41 T2=42 P=40	Treatment with 12-weeks of CBT, SSM, or usual care	50% were taking non-study antidepressant medications	CABG within the last year	HAM-D score, BDI score, Beck Anxiety Inventory, Beck Hopelessness Scale, Perceived Stress Scale, SF-36 and others	Patients had major or minor depression within one year after surgery

MDD - major depressive disorder, MI - myocardial infarction, HAM-D - Hamilton Rating Scale for Depression, SSRI - selective serotonin reuptake inhibitors, IDD - Inventory to Diagnose Depression, CGI-I - Clinical global impression improvement, QLES-Q - Quality of Life Enjoyment and Satisfaction scale, CBT - Cognitive Behavior Therapy, BDI - Beck Depression Inventory, ESSI - ENRICHD Social Support Instrument, PSSS - Perceived Social Support Scale, IPT - Interpersonal therapy, SCID - Structured clinical interview for depression, CIDI - Composite international diagnostic interview, CABG - Coronary artery bypass surgery, SSM - supportive stress management, CAD - coronary artery disease, MI - myocardial infarction, CHD - coronary heart disease, I - intervention, T - total, P - placebo, DSM-III-R - Diagnostic And Statistical Manual Of Mental Disorders, third edition, revised, LPSS - low perceived social support

Table 2 - Comparisons of the study findings among selected randomized controlled trials.

Study name	Outcome measures	Intervention	Placebo	Findings	Limitations and other comments
Strik et al[20] 2000	**1-Change in depression scores at 25 weeks:**-HAM-D	-9.7±7.2	-6.9±6.9	Compared to placebo, Fluoxetine group had similar reduction of HAM-D (p=0.08). HAM-D scale was significantly reduced in Fluoxetine group compared to placebo among those with mild depression	1-The study is under-powered to detect the observed small depression score changes limiting the validity of the findings
	2-Fluoxetine safety: Death or cardiac hospitalization	1 (3.7%)	6 (22.2%)	No significant safety differences between both groups (p=0.13)	2- Selection bias: the response rate among patients receiving Fluoxetine was significantly greater than that among patients receiving placebo at week 25 (48 vs. 26%, p=0.05)
McFarlane et al[21] 2001	**1-Change in depression score at 22 weeks:** IDD score	-5.75 points	+4.0 points	Sertraline group but not placebo had significant drop of IDD score (p<0.05)	1-Significant attrition bias due to drop of 11 participants after randomization
	2- HRV: heart rate, SDNN	5% increase	9% decrease	Increase (recovery) in SDNN in the sertraline-treated group in contrast to the steady decline in SDNN in the placebo group	
SADHART Glassman et al[24] 2002	**Safety of Sertraline:** 1-More than 5-point decrease in left ventricular ejection fraction (LVEF)	6 (4.4%)	5 (4.0%)	No significant change in LVEF or adverse cardiac events between both groups	1-Underpowered to detect combined mortality and hospitalization which was less but not significant in Sertraline group compared to placebo (RR: 0.77, 95% CI 0.51-1.16). However, mortality was not different between both groups (20.8% vs 21.0%) in later analysis after 6.7 years of follow-up[24]
	2-Incidences of adverse cardiac events.	27 (14.5%)	41 (22.4%)	No significant change in HAM-D between both groups. However, significant decrease in Sertraline group than placebo in recurrent (by average 2.2 points) and severe MDD (by average 3.4 points)	
	Depression scores: 1-HAM-D change	–8.4±0.41	–7.6±0.41		
	2-CGI-I responder	125 (67%)	97 (53%)	CGI-I responder was significantly higher in Sertraline group than placebo (p=0.01)	2-Results are generalized only to patients with recent MI or unstable angina and without other life-threatening medical conditions
SADHART Swenson et al[23] 2003	**Change in Quality-of-life and functional status:** A-Quality of Life Enjoyment and Satisfaction scale (QLES-Q)			Sertraline was associated with significant clinical improvement in QLES-Q in recurrent depression (p=0.034) but not the total sample (p=0.290)	1-The small sample sizes in the recurrent depression group did not provide sufficient protection against a type II error
	1-Total sample	9.0	7.7		
	2-Recurrent depression	14.5	9.1		2-Results are generalized only to patients with recent MI or unstable angina and without other life-threatening medical conditions
	B-Medical Outcomes Study Short-Form 36 (SF-36)	Mental component had 17.4-point increase in total and 24.9-point increase in recurrent depression	Mental component had 15.2-point increase in total and 15.1-point increase in recurrent depression	Sertraline was associated with significant clinical improvement in the mental component summary score of SF-36 in recurrent depression (p=0.010) but not the total sample	
ENRICHD Berkman et al[25] 2003 Cowan et al[27] 2008	**Primary endpoints (6 month):** 1-All-cause mortality	168 (13.6%)	172 (13.8%)	No significant difference between the CBT (without SSRI) and usual care groups as regards all-cause mortality (HR=0.98), cardiovascular mortality (HR=0.83), or recurrent non-fatal MI (HR=0.90).	1-Using both psychosocial interventions and SSRI in the study group complicates the impact of either on the outcome.
	2-Cardiovascular mortality	96 (7.8%)	115 (9.3%)		
	3-Recurrent non-fatal MI	168 (13.6%)	170 (13.7%)		
	Change in depression scores (6 month): 1-BDI	–8.6 ±9.2	–5.8 ±8.9	The CBT supplemented with SSRI group had significant (p<0.001) but modest (2 points) reduction in depression scores (BDI and HRSD) among patients with depression at 6 months. Between group differences in BDI diminished over time	2-Sertraline was given to the intervention group only if deemed necessary, thus diluting the pharmacologic effect
	2-HAM-D	–10.1 ±7.8	–8.4 ±7.7		3-Inclusion of minor depression and LPSS may affect the generalizability of the study findings
	Change in social support scores (6 months): 1-ESSI	5.1 (5.9)	3.4 (6)	The CBT supplemented with SSRI group had significant higher (2-4 points) increase in social support scores (ESSI & PSSS) among patients with LPSS at 6 months. Between group differences in ESSI diminished over time	4-Both participants and interventionists were unmasked which may increase detection bias
	2-PSSS	9.0 (14.9)	4.5 (14.9)		

Table 2 Continued - Comparisons of the study findings among selected randomized controlled trials.

Study name	Outcome measures	Intervention	Placebo	Findings	Limitations and other comments
ENRICHD Taylor et al[26] 2005	**Secondary analysis of the ENRICHD trial over 29 months:**			The risk of death (adjusted HR=0.59, 95% CI 0.37-0.96) or recurrent MI (adjusted HR=0.53, 95% CI 0.32-0.90) was significantly lower in patients receiving CBT supplemented with SSRI (usually Sertraline) than usual care	1-The findings represent unplanned post hoc analyses & the sampling to Sertraline was not randomized.
	1-All-cause mortality	21 (7%)	222 (16.0%)		
	3-Recurrent non-fatal MI	45 (15%)	205 (14.8%)		
CREATE Lespérance et al[29] 2007 Habra et al[28] 2010	**Change in depression scores: A-Citalopram vs placebo**			Citalopram was superior to placebo in reducing 12-week HAM-D scores by 3.3 points (p=0.005). Greater reduction was observed in recurrent depressed (-5.7 points). Citalopram was superior to placebo in reducing 12-week BDI-II scores by 3.6 points (p=0.005).	Underpowered to detect adverse cardiac events (total 12 events)
	1-24-item HAM-D score	14.9±10.0	11.6±10.0		
	2-Self-reported BDI-II score	14.7 ±10.7	11.1±10.7		
	B-IPT versus clinical management				
	1-24-item HAM-D score	12.1 (9.97)	14.4 (9.97)	There was no evidence of a benefit of IPT over clinical management using both depression scores except in patients with high baseline functional status.	
	2-Self-reported BDI-II score	13.5 (10.69)	12.4 (10.69)		
	Cardiac Safety: Incidences of adverse cardiac events	1 (1.3%)	2 (3.0%)	There were no safety differences between citalopram and placebo groups	
MIND-IT Honig et al[30] 2007	**Change in depression scores at 24 weeks:**			At 24-week, there was significant difference favoring mirtazapine to placebo on the HAM-D (p=0.003), BDI (p=0.05), and CGI (p=0.007), but not the dSCL-90 (p=0.11). Over the acute treatment phase of 8 weeks mirtazapine did not show to be superior to placebo on the Ham-D, but did on the BDI, dSCL-90, and CGI scale	1-The study is under-powered to detect the observed modest depression score changes. 2-Less than half of the sample completed the 24-week assessment which may further affect the power 3-Inclusion of minor with major depression may affect the generalizability of the study findings 4-Between site variability in interpreting 17 HAM-D was observed introducing detection bias
	1-17 HAM-D	1.60	1.40		
	2-BDI	0.73	0.15		
	3-dSCL-90	1.08	0.73		
	4-CGI-I scale	1.45	0.90		
	Adverse cardiac events: such as heart failure and angina	3 (6.4%)	1 (2.3%)	No significant group differences (p=0.339) in adverse cardiac events	
Carney et al[31] 2009	**Change in depression scores at 10 weeks:**				Underpowered to detect adverse cardiac events (total 4 events)
	BDI-II	-12.0	-14.2	No significant group differences in depression score improvement or adverse cardiac events	
	HAM-D	-11.5	-10.1		
	Adverse cardiac events:	2 (3.2%)	2 (3.3%)		
Freedland et al[32] 2009	**Primary:** Depression remission at 3,6, & 9 months using HAM-D and BDI	Example: 71% in CBT and 57% in SSM at 3-month	Example: 33% at 3-months	CBT and SSM were superior to usual care in contributing to depression remission at most points as measured by HAM-D and BDI	1-Insufficient power for comparisons of the 2 active treatments 2-As in most behavioral trials, double-blinding was not possible
	Secondary: Beck Anxiety Inventory, Beck Hopelessness Scale, Perceived Stress Scale, SF-36 and others			CBT was superior to usual care at most points on secondary measures of depression, anxiety, hopelessness, stress, and quality of life. SSM was superior to usual care only on some of the measures	

HAM-D - Hamilton Rating Scale for Depression, SSRI - selective serotonin reuptake inhibitors, CGI-I - Clinical global impression improvement, QLES-Q - Quality of Life Enjoyment and Satisfaction scale, CBT - Cognitive Behavior Therapy, BDI - Beck Depression Inventory, ESSI - ENRICHD Social Support Instrument, PSSS - Perceived Social Support Scale, IPT- Interpersonal therapy, SCID - Structured clinical interview for depression, SSM - supportive stress management, IDD - Inventory to Diagnose Depression, HRV - heart rate variability, SDNN - SD of all 24-hour N-N intervals, CGI - Clinical global impression, MDD - major depressive disorder, HR - hazard ratio, SSRI - selective serotonin reuptake inhibitors, RR - relative risk, CI - confidence interval, dSCL-90 - depression subscale of the symptom check list 90 items

RCTs.[21,22,25,31] Other examined antidepressants included mirtazapine, citalopram, and fluoxetine. Non-pharmacologic interventions were used in 3 RCTs.[25,29,32]

Outcome measures. Change in depression score and medication safety were the primary or the secondary outcome in all RCTs (**Table 2**). Change in social support was examined in the ENRICHD trial.[26] Change in quality-of-life and functional status was an additional outcome in SADHART.[23] All-cause mortality was examined after 29 months of follow-up in the ENRICHD trial[26] and 6.7 years follow-up in after 29 months in SADHART.[24] At least 5 studies did not have the power or the follow-up time needed to detect adverse cardiac events.[19,21,29,31,32]

Antidepressant efficacy. In more than one RCT, sertraline was safe and effective in treating depression symptoms in CHD patients.[21,25,37] This was especially evident among severe and recurrent depression.[37] Adding omega-3 fatty acids to sertraline did not result in superior depression outcomes.[31] Sertraline was also associated with significant clinical improvement of quality-of-life and functional status only in recurrent

depression.[23] Secondary analysis of sertraline-associated mortality reduction over 2-7 years of follow-up did show consistent results.[24,26] Similar to sertraline, citalopram administered in conjunction with weekly clinical management was effective and safe in treating MDD among patients with CHD.[29] Similar to the findings with sertraline, those patients with recurrent MDD were more likely to respond to citalopram than patients with a first-time MDD episode. Mirtazapine was better than placebo in treating depression among post-MI patients as measured by HAM-D (p=0.003), BDI (p=0.05), and CGI (p=0.007), but not the dSCL-90 (p=0.11).[30] However, the high rate of drop outs and inclusion of patients with either minor or major depression may affect the generalizability of the study findings. Although safe, fluoxetine was not superior to placebo in treating depression symptoms among post-MI patients.[20]

Antidepressant safety. An increased risk of cardiac events was not found with sertraline, citalopram and mirtazapine, but these antidepressants were associated with higher rates of some adverse non-cardiac symptoms compared to placebo. These include dizziness, diarrhoea, somnolence, sweating, palpitations, libido reduction or sexual difficulties with citalopram,[28] fatigue, appetite changes and weight gain with mirtazapine,[30] and nausea and diarrhoea with sertraline.[31]

Non-pharmacologic therapies. Cognitive-behavioral therapy was superior to usual care with regard to depression and social support, but the differences were not obviously clinically meaningful and diminished overtime.[25] Better depression outcomes (measured by the HAM-D) were found among patients who had received a high number of the social communication and assertiveness components of the intervention, and completed a high proportion of homework assignments.[27] Both CBT and supportive stress management (SSM) were superior to usual care in treating depression.[32] With the exception of patients with high functional status, there was no clear evidence of a benefit of interpersonal psychotherapy (IPT) over clinical management.[29]

We reviewed 8 RCTs that used antidepressant medications and/or non-pharmacologic therapies in treating MDD among patients with evidence of concurrent CHD. This review shows that the use of sertraline and citalopram was effective in treating these patients. On the other hand, the results with mirtazapine were mixed and a superior effect of fluoxetine could not be proven. In the meta-analyses[38,39] that reviewed RCTs among patients with CHD, a small but statistically significant reduction in depressive symptoms was observed with antidepressants compared with placebo. On the other hand, a review of mainly observational studies showed uncertain effectiveness of antidepressants on health outcomes in CHD patients.[40] Based on the limited studies to date, the conclusions are that the magnitude of benefit of antidepressants increases with severity of depression and may be minimal or nonexistent in patients with mild symptoms.[41,42]

In both the SADHART and the CREATE study, those with recurrent MDD (namely a history of a past episode) responded better to the antidepressant as compared to those with first episode MDD. This suggests that patients with recurrent MDD have a more typical type of depression, whereas those with first episode MDD in CHD may have a different type of disorder, possibly vascular in origin; however, the evidence for this so far is limited.

A potential motivation for treating depressed CHD patients is the possibility that the cardiovascular outcomes could be improved, given the demonstrated association between depression and mortality in CHD patients. However, the evidence for this is mixed and also limited. Treatment with SSRIs in depressed patients with CHD has been reported to reduce platelet/endothelial activation as well as inflammatory markers.[43,44] This may explain the reduced all-cause mortality and recurrent MI observed among patients taking SSRI (usually sertraline) than placebo.[26] The failure of SADHART to prove the early non-significant reduced mortality on sertraline after 7 years of follow-up could be due to limiting the SSRI therapy to the first 6 months of the study,[22,24] but there was some evidence from SADHART that response to placebo or sertraline conferred protection. Although the above trials have generally found SSRIs to be safe in cardiac patients, interactions with other medications such as hypotensive reactions to beta blockers have occasionally been reported. Furthermore, there has recently been an advisory on the potential of citalopram over 40 mg to cause dose-dependent QT interval prolongation.[45] Also, it is has been found that nonsteroidal antiinflammatory drugs and other analgesics can mitigate the effect of citalopram.[46] Given that most CHD patients are on medications such as acetylsalicylic acid, there is the possibility of a reduced drug effect in many cardiac patients.

Unlike SSRIs, the use of TCAs and MAOIs has been associated with cardio toxic side effects making them less appropriate for cardiac populations.[47] The TCAs for example were associated with independent higher risk of CHD events.[16] This could be due to their direct cardiac effects, such as QT-prolongation

with ventricular arrhythmias, orthostatic hypotension, and less frequently, myocardial dysfunction.[48] Non-SSRIs second-generation antidepressants have variable cardiovascular safety. Venlafaxine has a dose-dependent effect on blood pressure that is clinically significant at high dosages,[49] can produce orthostatic hypotension, and can be associated with potential cardiac rhythm abnormalities, which is a concern especially with elderly patients.[50] Both Duloxetine and Bupropion can cause a mild increase in blood pressure initially; however, they are safe and well tolerated in patients with MDD.[51,52] Bupropion was shown to help short-term smoking cessation among hospitalized smokers with acute cardiovascular disease.[53] Although sometimes under-powered,[20,21,29,31] the reviewed RCTs in this study did not find any increase in cardiac events associated with different antidepressants use. However, the treating physician should weigh the possibility of adverse non-cardiac side effects against the benefits of antidepressant use among CHD patients.

Few RCTs studied non-pharmacological treatments among patients with MDD and CHD. The standard psychotherapeutic modalities examined included CBT, SSM, and IPT. Both CBT and SSM were superior while IPT was equivalent to usual care in treating depression.[25,29,32] There is little evidence so far that such treatments would also improve CHD risk factors.[54] Subgroups may be more amenable to psychotherapeutic interventions, for example, those higher functioning individuals with mild MDD especially with first episode MDD following CHD diagnosis may benefit from IPT, given that patients with higher functional performance in the CREATE study did better on IPT than clinical management.

A combination of treatments over time may be efficacious. Enhanced depression care involving initial individual problem-solving therapy and/or pharmacotherapy followed by a stepped-care approach was evaluated among patients with persistent depression and CHD.[55] It was associated with greater satisfaction, a greater reduction in depressive symptoms, and a promising improvement in prognosis. However, including persistent rather than major depression, taking patient choice in intervention, small sample size, short follow-up duration, and single-blinding may affect the generalizability of such findings especially to those CHD patients with MDD.

Exercise therapy, already an established preventive measure for CHD, has potential efficacy as a treatment for depression in cardiac disease patients.[56] Additionally, exercise has been shown to reduce mortality by around 40% among patients surviving MI.[57] Cardiac rehabilitation, involving even mild improvement in fitness, was associated with both reductions in depressive symptoms (by >60%) and the excess mortality associated with it (by >70%).[58] This beneficial effect could be mediated by improving exercise, education, socialization, dietary changes and bonding with other patients.[58] The contribution of exercise in the treatment of depression is questionable because this review is confined to CHD patients with MDD and not to those with mild depression who potentially may benefit from this intervention. Moreover, there is no single RCT that found robust efficacy of exercise training on major or minor depression in CHD patients. It is presumed that patients with moderate to severe MDD would be less liable to benefit from exercise as motivation to exercise and compliance generally would be diminished, but patients with mild MDD may benefit from regular exercise recommendation, especially in the context of an active cardiac rehabilitation program and considering the lesser effect of interventions on milder forms of MDD.

Several limitations were observed in the reviewed studies, complicating the interpretation of their findings. The inclusion of minor depression patients with patients with MDD is one example.[25,30] The variability in time of diagnosis of both CHD and MDD in relation to randomization as well as to each other is another example. Additionally, the small size and the short follow-up time observed in some of these studies limit their power to detect adverse cardiac events.[20,21,29,31] Moreover, the possibility of selection,[20] detection,[25,30] and attrition[21] biases that were observed in some of these studies may limit the validity of their findings. Future studies on antidepressant and non-pharmacologic therapies among patients with CHD need to address the above limitations. Additionally, they need to stratify the study outcome by the disease severity, the onset of CHD and MDD, and the degree of adherence and duration of therapy. Possible positive effects of antidepressants and non-pharmacologic therapies on CHD risk may warrant conducting studies that are focused on changes of traditional and subclinical cardiovascular risk factors.

Although there is a paucity of data from RCTs on pharmacologic and non-pharmacologic therapies among patients with CHD, 2 noticeable guidelines have emerged in the last few years from the American Academy of Family Physicians[59] and the American Psychiatric Association-endorsed American Heart Association.[60] Both guidelines strongly recommended routine screening for and treatment of depression in patients with CHD. Pharmacologic and non-pharmacologic treatments are known to improve depressive symptoms in patients with CHD, but their

effects on outcomes such as mortality and hospital admissions remain controversial.[61] Current evidence shows that SSRIs especially sertraline and citalopram are both efficacious and safe for the treatment of depression especially severe or recurrent depression with onset preceding the CHD event. Treated patients should be regularly monitored for adherence to their medical care as well as medication efficacy and safety.[59,60] Psychotherapy especially CBT may be beneficial for treatment of depression in post-MI patients.

When selecting an appropriate therapy, clinicians should consider the severity of depression and comorbid conditions among patients with CHD. Starting SSRIs in severe depression and encouraging exercise and cardiac rehabilitation in mild depression is one example. Choosing CBT in patients who can complete a high proportion of homework assignments and IPT in patient with high baseline levels of functional performance is another example. Bupropion may be a good choice if both treating depression and smoking cessation are required.

In conclusion, knowledge on the treatment of MDD in patients with CHD is limited. All such patients should be carefully assessed. Treatment for those with moderate to severe and/or recurrent MDD must be initiated. Available evidence suggests that treatment modalities that may be effective include SSRIs such as sertraline or citalopram, with or without cognitive behavioral therapy. Exercise alone or preferably in the context of a cardiac rehabilitation program should be considered for the CHD patient with mild MDD.

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Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.