

# Antidepressant treatment in patients following acute coronary syndromes: a systematic review and Bayesian meta-analysis

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## Abstract

**Aims** The aim of this study is to investigate the effect of antidepressant therapy on mortality and cardiovascular outcomes in patients with acute coronary syndrome (ACS).

**Methods and results** We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials and performed a Bayesian random-effects meta-analysis of randomized controlled trials that investigated antidepressant pharmacotherapy in patients following ACS. The primary outcome was all-cause mortality. Secondary outcomes were repeat hospitalizations and recurrent myocardial infarctions (MIs). Ten randomized controlled trials with a total of 1935 patients qualified for inclusion. Selective serotonin reuptake inhibitors were investigated in six, bupropion in three, and mirtazapine in one trial. Placebo was used as control in eight trials. There was no difference in all-cause mortality [odds ratio (OR) 0.97, 95% credible interval (CrI) 0.66–1.42] and recurrent MI (OR 0.64, 95% CrI 0.40–1.02) between patients receiving antidepressants compared with controls, whereas antidepressant therapy was associated with less repeat hospitalizations (OR 0.62, 95% CrI 0.40–0.94). In patients with ACS and concomitant depression, antidepressants reduced the odds of recurrent MI compared with usual care/placebo (OR 0.45, 95% CrI 0.25–0.81). Extended funnel plots suggest robustness of the observations.

**Conclusions** Antidepressants in patients following ACS have no effect on mortality but reduce repeat hospitalizations; in patients with depression, there is a reduced risk of recurrent MI with antidepressant therapy.

**Keywords** Acute coronary syndrome; Myocardial infarction; Depression; Mental health; Antidepressants; Meta-analysis

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## Introduction

Acute coronary syndromes (ACS) and major depressive disorders are frequently intertwined and recognized to catalyze the development and aggravate the clinical course of each other.<sup>1,2</sup> The prevalence of post-myocardial infarction depression is estimated to range between 10% and 40%, with some reports describing clinical signs of depression in up to two-thirds of ACS survivors.<sup>3–6</sup> Detection and treatment of major depression in patients with cardiovascular disorders has been demonstrated to improve therapy adherence, functional ability, and quality of life.<sup>7–9</sup> The optimal therapeutic approach and the use, safety, and efficacy of antidepressant

pharmacotherapy in this population remain controversial, however. Tricyclic antidepressants are well known for their cardiovascular side effects. The newer selective serotonin (SSRIs) and noradrenalin reuptake inhibitors are generally considered safe in patients with cardiac co-morbidities,<sup>10–12</sup> although clinical and preclinical studies have shown that also these drugs may interfere with myocardial ion channels, influence heart rate and blood pressure, and possibly exert adverse effects by interacting with commonly used cardiac medications, such as clopidogrel or beta-blockers.<sup>12–17</sup> Accordingly, ACS patients taking SSRIs were found to have higher bleeding rates; moreover, an increased incidence of sudden death in new generation antidepressant users has

raised concerns about potential pro-arrhythmic effects.<sup>15,18–21</sup> The objective of the present analysis was to summarize the available evidence regarding the effects of antidepressants on clinical outcomes in patients following ACS.

## Methods

The study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement<sup>22</sup> and was prospectively registered at the PROSPERO international register of systematic reviews (CRD42018110818).

### Search strategy and study selection

We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from the date of their inception up to 24 July 2019 for randomized controlled trials (RCTs) that investigated the effect of one or more pharmacological antidepressants compared with a control (placebo or usual care) in patients following ACS with respect to the outcomes of interest as described in the succeeding text. The search algorithm applied to each database is provided in Supporting Information, *Table S1*. Following the initial search, we also scrutinized the reference lists of eligible articles for additional relevant entries. To be included, antidepressant treatment had to be initiated within 1 year after the index ACS and continued for a minimum of 30 days. ACS includes both ST-elevation and non-ST-elevation myocardial infarction and unstable angina pectoris. Studies investigating patients with stable coronary artery disease (CAD), chronic heart failure, and other cardiac or non-cardiac conditions were excluded. Also, non-randomized studies, studies without primarily pharmacological intervention and without quantitative information on the outcomes of interest, were excluded. Language was restricted to English or German articles. In case of overlapping study populations (according to participating institutions and recruitment periods), we included the most recent results with the longest available follow-up and available data of interest. Search results were screened on title and abstract level, and potentially eligible reports were subsequently scrutinized in full text according to the aforementioned inclusion criteria by two investigators independently. In case of discrepancies at either the screening or inclusion level, consensus was found by common review and discussion between investigators.

### Data collection and outcomes of interest

For all eligible trials, we extracted the following items from full-text articles and any supplementary material into an

electronic data reporting form: study characteristics (first author, study title, study ID, year of publication, study design, recruitment region and period of inclusion, sample size, arms of randomization, and follow-up duration); population characteristics (age, sex, body mass index, smoking status, co-morbidities/past medical history, and left ventricular ejection fraction); and characteristics of the interventions (treatment arms, treatment initiation and duration, and drug dosage).

The primary outcome was all-cause mortality. Secondary outcomes were myocardial infarction (MI) and rehospitalizations. For all outcomes, the longest available follow-up for each individual trial was considered. We extracted the respective numbers and percentages of events as well as applicable effect sizes with respective adjustment factors.

### Risk of bias

We used the Cochrane risk of bias tool<sup>23</sup> to categorize the risk of bias for each trial across the following domains: random sequence generation, allocation concealment, blinding (participants/personnel and outcomes), incomplete outcome data, and selective outcome reporting. We evaluated the risk of bias in each study as low, moderate, or high risk of bias, based on our judgements for allocation concealment and blinding of outcome assessment. A trial was considered to be of low risk of bias, when both items were judged to be low risk. When at least one of these two individual domains was judged to be of unclear risk, we considered the random sequence generation and incomplete outcome data domains. A judgement of high risk of bias in one of these two domains resulted in an overall high risk of bias; otherwise, the trial was judged to be of moderate risk.

### Sensitivity analyses

Sensitivity analyses were performed with regard to control arm (trials in which placebo arm was tested), population (ACS with or without concomitant depression), treatment initiation (after 30 days following the index cardiac event), and treatment duration (>12 weeks).

### Data synthesis and analysis

We synthesized the studies using a random-effects meta-analysis model. Because of the limited number of the included trials, meta-analysis models were fitted in a Bayesian framework. A Bayesian random-effects meta-analysis is advantageous in such scenarios, because it incorporates external evidence on the likely extent of between-study heterogeneity in a particular research setting and facilitates prediction of effects in future studies and flexibility in

modelling.<sup>24–26</sup> We presented the results by calculating the odds ratio (OR) together with 95% credible intervals (CrIs). We assumed a normal prior distribution with mean 0 and standard deviation 1.52 for treatment effects [lower and upper 95% limits (0.05, 20)]. We used informative priors for heterogeneity, as derived from relevant empirical distributions assuming an objective outcome for all-cause mortality and a semi-objective outcome for recurrent MI and rehospitalizations and a ‘pharmacological vs. placebo’ intervention comparison type.<sup>27,28</sup> The magnitude of the heterogeneity variance parameter ( $\tau$ ) was used to assess statistically the presence of heterogeneity. To provide useful additional information in decision-making process, we calculated the prediction intervals under the Bayesian random-effects meta-analyses for each research question.<sup>26,29,30</sup> The prediction interval gives a range for the predicted true effect size in an individual (future) trial of similar setting.

We also investigated whether hypothetical future studies are likely to alter the meta-analysis results using extended funnel plots.<sup>31</sup> A colour code appended in conventional funnel plots illustrates where the result of an updated meta-analysis would lie, depending on the effect estimate and the standard error of a hypothetical new study to be added to the evidence base. Heterogeneity was imputed to equal the posterior value from the Bayesian meta-analysis (with the first prior), and contours of statistical significance were drawn to represent a *P*-value of 0.005.<sup>32,33</sup> We considered a more conservative level of statistical significance (0.5%) to avoid spuriously concluding over the benefit of one of the two interventions. Statistical analyses were performed using Stata 16.0 (StataCorp 2019, Stata Statistical Software: Release 16, StataCorp LLC, College Station, TX) and R (R Development Core Team, Vienna, Austria).

## Results

### Trial selection and characteristics

Our search yielded 2098 citations, from which 12 reports of 10 RCTs with a total of 1935 participants (68% male) fulfilled our inclusion criteria (*Figure 1*). A few landmark trials in the field were excluded because of ineligible comparisons, study populations, and/or outcomes as provided in Supporting Information, *Table S2* together with the reasons for exclusion. Characteristics of included trials and enrolled participants are summarized in *Tables 1* and *2*. Six trials (eight reports)<sup>8,9,34–37,42,43</sup> included patients with ACS and a concomitant diagnosis of depression, one trial<sup>40</sup> was performed in patients with ACS without depression, and three trials<sup>38,39,41</sup> investigated the use of bupropion for smoking cessation after ACS. Other tested drugs apart from bupropion

were SSRIs in six<sup>9,34–37,40,42,43</sup> and the noradrenergic and specific serotonergic antidepressant mirtazapine in one RCT.<sup>8</sup> In four trials, antidepressant pharmacotherapy was initiated in-hospital up to 1 month after the index cardiac event,<sup>38,39,41,42</sup> whereas in the other five trials, drug therapy was started up to 12 months thereafter<sup>8,9,34–36,40,43</sup>; in one trial, the timing of antidepressant initiation was not reported.<sup>37</sup> Treatment duration ranged from 8 to 52 weeks. The median follow-up time was 12 months with a range from 2 months to 8 years (*Table 1*).

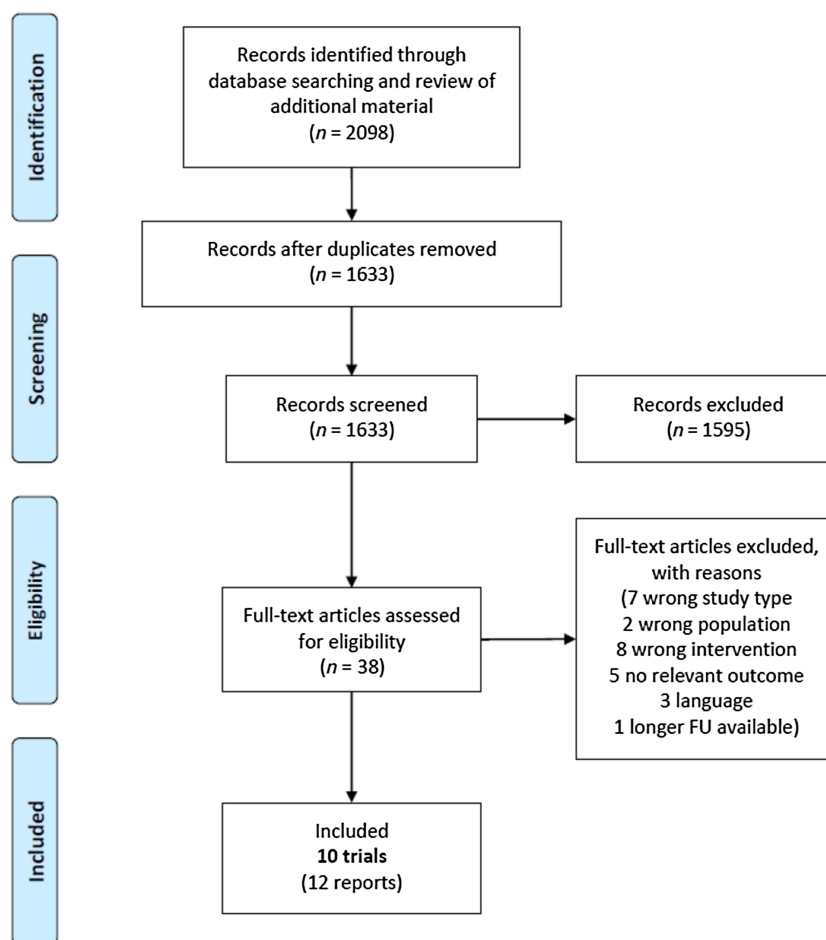
### Primary outcome

Six trials involving 1572 patients provided adequate data on all-cause mortality.<sup>9,35–38,40,41,43</sup> During a median follow-up period of 12 months, 171 events were reported. The summary effect estimate showed no difference between patients receiving antidepressant pharmacotherapy compared with those under placebo/usual care (OR 0.97, 95% CrI 0.66–1.42), with low heterogeneity across the trials ( $\tau = 0.12$ , prediction interval OR 0.97, 95% CrI 0.58–1.63, *Figure 2A*). Also, sensitivity analyses considering only trials with placebo control, trials in patients with major depression and ACS, treatment initiation after 30 days, and treatment duration beyond 12 weeks revealed no differences between groups (Supporting Information, *Figures S1A–S4A*).

### Secondary outcomes

Data on recurrent MI were available in seven trials with a total of 1536 randomized patients and 98 events during a median follow-up period of 12 months.<sup>9,35–37,39–43</sup> As shown in *Figure 2B*, there was no difference between the treatment arms (OR 0.64, 95% CrI 0.40–1.02) in the main analysis neither in the sensitivity analyses based on type of control arm, treatment initiation, and treatment duration (Supporting Information, *Figures S1B, S3B, and S4B*, respectively). Restricting the analysis to trials enrolling patients with ACS and a concomitant diagnosis of depression,<sup>8,9,34–37,41–43</sup> antidepressant therapy was associated with reduction in odds of recurrent MI compared with usual care/placebo (OR 0.45, 95% CrI 0.25–0.81), with a 95% prediction interval of 0.21–0.97 (Supporting Information, *Figure S2B*).

Repeat hospitalizations were assessed in five trials including 682 participants and 220 events during a median follow-up period of 12 months.<sup>8,9,34–37,39</sup> Antidepressants decreased the odds of the participants having repeat hospitalizations compared with placebo/usual care (OR 0.62, 95% CrI 0.40–0.94) (95% prediction interval of 0.33–1.13) (*Figure 2C*). The results were consistent also in sensitivity analyses (Supporting Information, *Figures S1C–S4C*).

**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of literature search and study selection. FU, follow-up.

## Extended funnel plots

Figure 3 shows extended funnel plots for all outcomes. Shaded regions depict where the effect size/standard error combination of a hypothetical novel study must lie in order to alter the conclusion of the present analysis in favour of treatment (medium grey) or placebo/usual care (dark grey). Extended funnel plots point towards robustness of the current analysis as any additional trial of similar effect size/standard error combination in the range of existing trials will not considerably alter the results.

## Risk of bias

Results of the risk of bias assessment are summarized in Figure 4. The overall risk of bias was deemed low, intermediate, and high in four, two, and four trials, respectively, although insufficient reporting resulted in many domains being rated as unclear risk of bias. Incomplete outcome reporting was the domain with the highest risk of bias, as half

of the included trials suffered from high rates of follow-up losses.

## Discussion

In this systematic review and meta-analysis of 10 RCTs comparing antidepressants to placebo/usual care in patients following ACS, we found no difference in mortality, while antidepressant therapy reduced the risk of repeat hospitalizations. In patients with concomitant depression, antidepressants additionally decreased the odds of patients having recurrent MIs compared with placebo/usual care.

Approximately one in eight patients with an ACS takes an antidepressant agent.<sup>10,44,45</sup> The efficacy of antidepressants to ameliorate depression and functional scores is well established, whereas their impact on cardiovascular outcomes remains a topic of ongoing discussion.<sup>16,17,46</sup> In a meta-analysis on the effect of SSRIs in patients with acute or stable CAD, Mazza and colleagues found that the

**Table 1** Characteristics of randomized controlled trials comparing antidepressants vs. placebo/usual care in patients following ACS

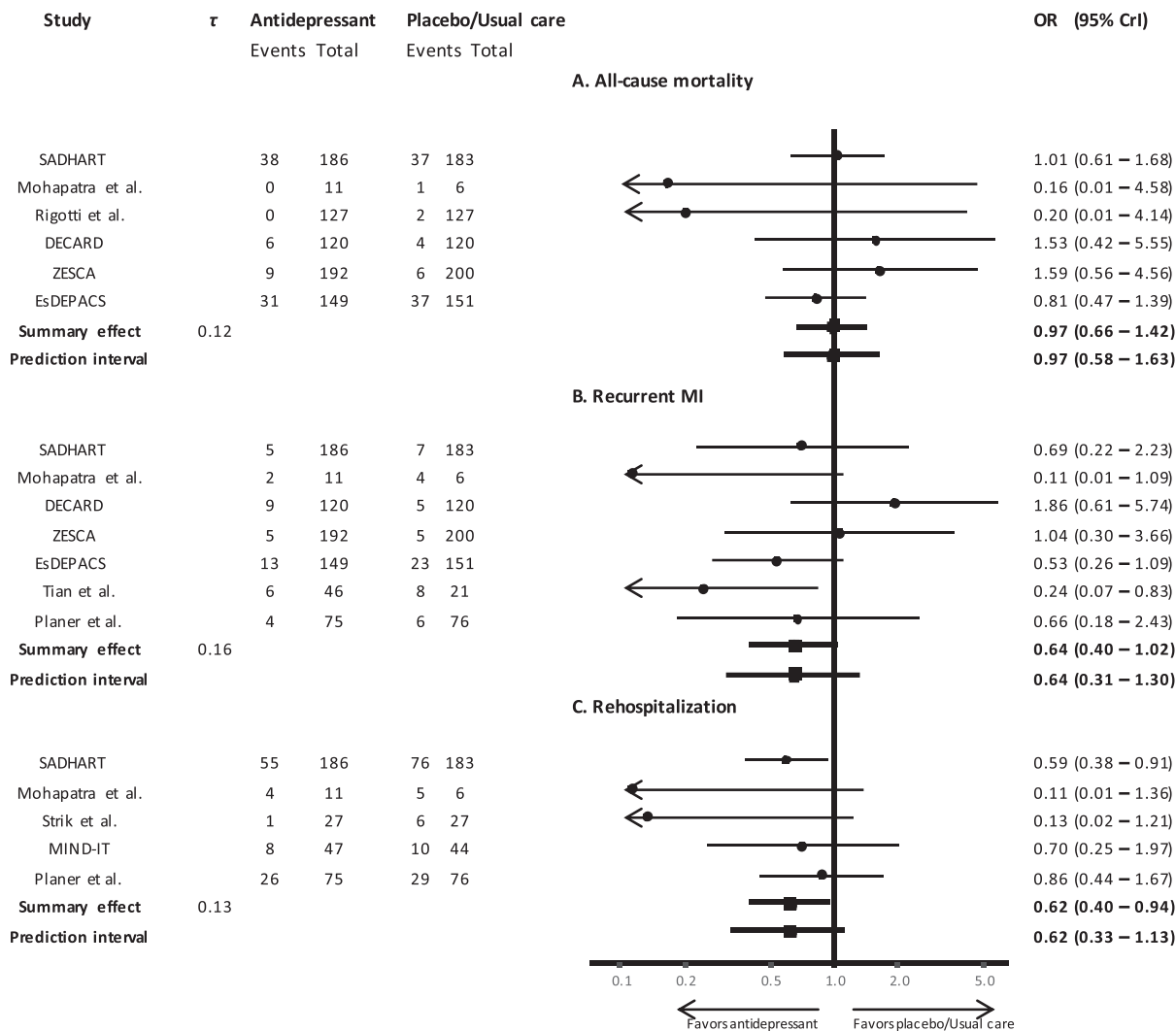
	Strik et al. <sup>34</sup>	SADHART <sup>9,35,36</sup>	Mohapatra et al. <sup>37</sup>	Rigotti et al. <sup>38</sup>	MIND-IT <sup>8</sup>	Planger et al. <sup>39</sup>	DECARD <sup>40</sup>	ZESCA <sup>41</sup>	Tian et al. <sup>42</sup>	EsDEPACS <sup>43</sup>
Publication year	2000	2002	2005	2006	2007	2011	2012	2013	2016	2018
Region	The Netherlands	Europe, USA, Canada, Australia	India	USA	The Netherlands	Israel	Denmark	Canada, USA, India, Iran, Pakistan, Tunisia	China	South Korea
Diagnosis	ACS + D	ACS + D	ACS + D	ACS + S	ACS + D	ACS + S	ACS	ACS + S	ACS + D	ACS + D
Comparison	Fluoxetine/placebo	Sertraline/placebo	Sertraline/usual care	Bupropion/placebo	Mirtazapine/placebo	Bupropion/placebo	Escitalopram/placebo	Bupropion/placebo	Paroxetine/fluoxetine/usual care	Escitalopram/placebo
Patient total (ITT)	54	369	17	254	91	151	240	392	67	300
Patients (treatment <sup>a</sup> /control)	27/27	186/183	11/6	124/124	47/44	75/76	120/120	192/200	23/23/21	149/151
Treatment dose	20–60 mg	50–200 mg	50–200 mg	150 mg	15 mg	150 mg	10 mg	150 mg	10–20 mg	5–20 mg
Treatment initiation	>3 months	33 (10) days <sup>b</sup>	na	In-hospital	>3 months	In-hospital	8 weeks	In-hospital	In-hospital	3 months
Treatment duration	25 weeks	24 weeks	24 weeks	12 weeks	24 weeks	8 weeks	52 weeks	9 weeks	8 weeks	24 weeks
Follow-up duration	12 months	6 months	6 months	12 months	27 months	12 months	12 months	12 months	2 months	8 years

ACS, acute coronary syndromes; D, depression; ITT, intention to treat; na, not available; S, smoking.

<sup>a</sup>In Tian et al., values represent Treatment Arm 1/Treatment Arm 2/control.

<sup>b</sup>Values represent mean (standard deviation).

**Figure 2** Forest plot of the primary and secondary endpoints. The figure shows the results of Bayesian random-effects meta-analysis of antidepressant therapy vs. placebo/usual care on (A) all-cause mortality, (B) recurrent myocardial infarction (MI), and (C) rehospitalization. CrI, credible interval; OR, odds ratio.

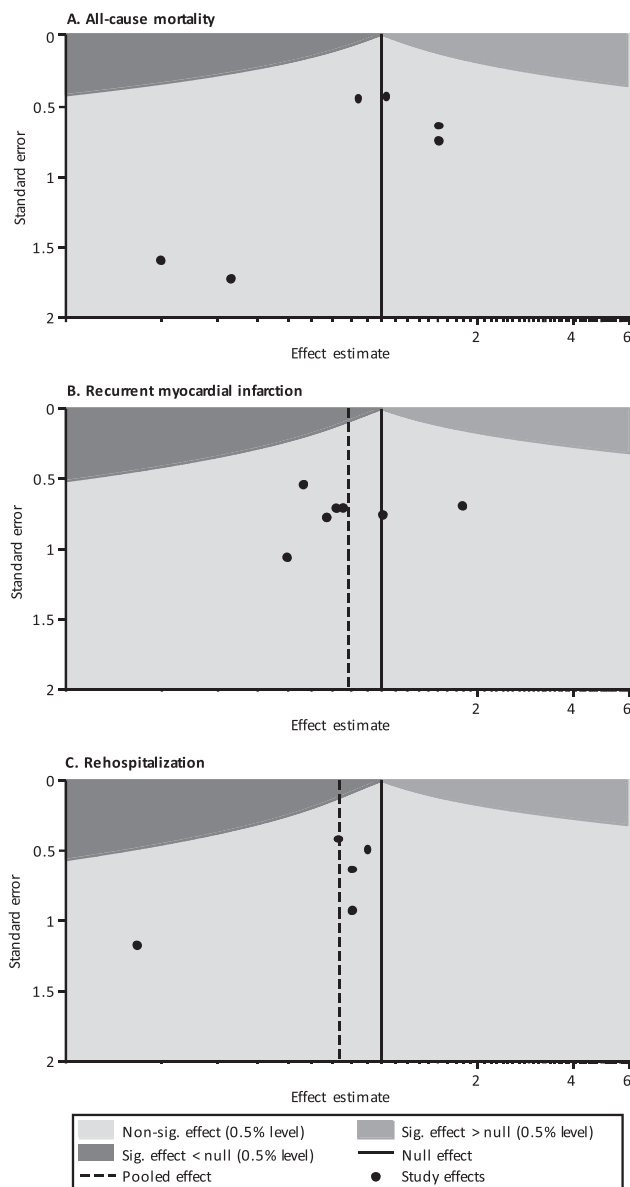


treatment lowered readmission rates without affecting major cardiovascular adverse events, MIs, repeat revascularizations or mortality.<sup>10</sup> Our study differs from the former by the exclusive inclusion of patients with ACS. Moreover, we considered also non-SSRI antidepressants and identified eight additional studies that were not included in the previous meta-analysis that was published nearly 10 years ago.<sup>8,36,38–43</sup> While the findings of our updated meta-analysis are largely consistent with the study by Mazza and colleagues, we found a lower rate of recurrent MIs in ACS patients with major depression under treatment with antidepressants. Another meta-analysis on the impact of SSRIs in patients recovering from interventions for stable or acute CAD was performed by Pizzi and colleagues.<sup>11</sup> The authors considered both randomized trials (three of which were included also in our

analysis<sup>34,37,43</sup>) as well as non-randomized studies. Consistent with the findings of Mazza and colleagues and our study, the authors reported a reduction of rehospitalizations by SSRI treatment in patients with CAD and major depression. Additionally, Pizzi and colleagues found that SSRI treatment reduced mortality rates, which was mainly driven by the inclusion of a *post hoc* analysis of the ENRICH trial that showed that depressed and/or socially isolated patients with recent ACS taking SSRIs had a significantly lower risk of recurrent MI and all-cause mortality over a mean follow-up period of 29 months compared with controls.<sup>47</sup> In our study, in which only RCTs were included, we found no difference in mortality rates between active treatment and control arms. Nevertheless, our results strengthen the accumulating evidence that antidepressant therapy might have a favourable



**Figure 3** Extended funnel plots for all outcomes. The funnel plots show the conclusions of an updated meta-analysis including a hypothetical new trial with certain combinations of treatment effect (odds ratio) and standard error. Solid line represents the line of no effect, and the dotted line represents the summary odds ratio. Dots indicate the odds ratio and the standard error of the existing studies. An updated meta-analysis including a new study lying in the light grey area will remain non-statistically significant; an updated meta-analysis including a new study lying in the dark grey area will become statistically significant favouring usual care; an updated meta-analysis including a new study lying in the medium grey area will become statistically significant favouring experimental. Statistical significance was judged on the 0.005 level. (A) All-cause mortality, (B) recurrent myocardial infarction, and (C) rehospitalization.



risk/benefit ratio in CAD patients with major depression and suggest a proactive approach in this population, although the optimal strategy to identify and deal with the

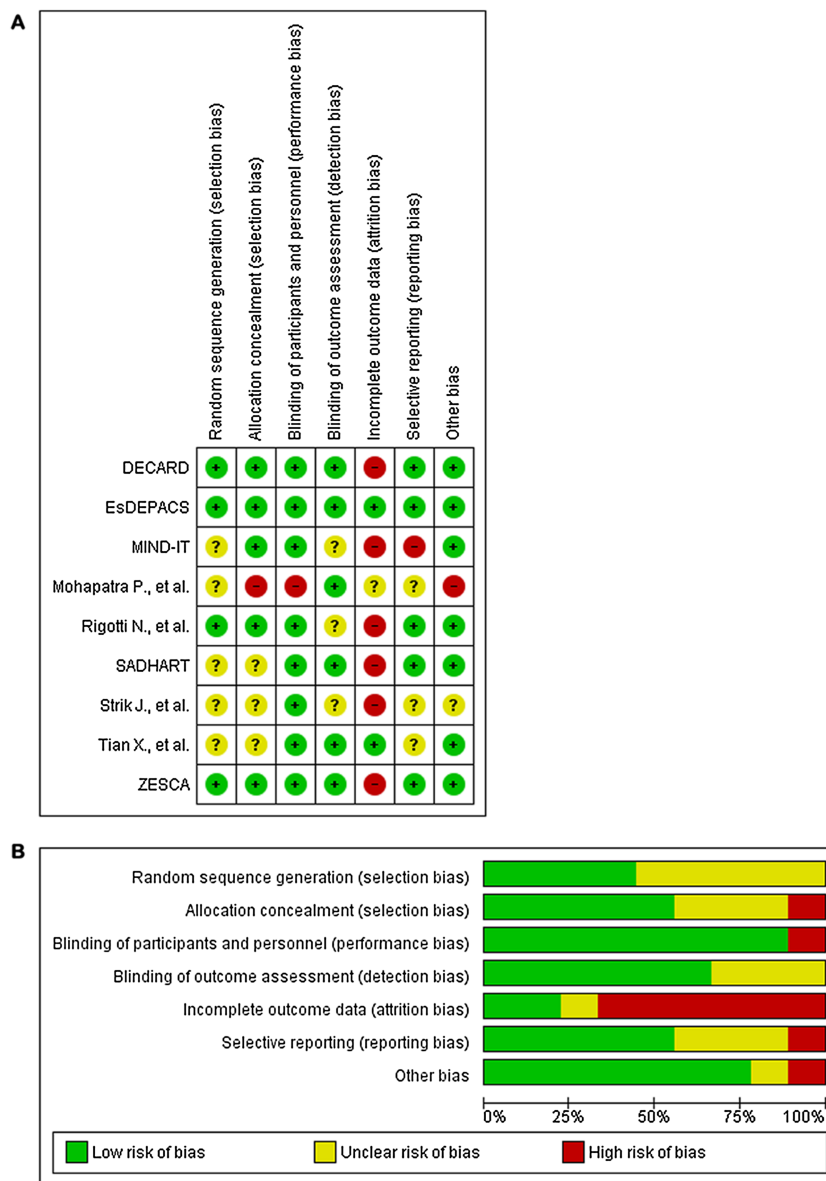
unfavourable combination of depression and CAD remains to be determined.<sup>48</sup>

The mechanisms by which depression negatively affects the cardiovascular system and by which therapeutic interventions exert positive effects are not well understood. Hypotheses for an adverse impact of depression include a dysregulation of autonomic control, up-regulation of pro-inflammatory molecules, and increased platelet activation in depressed patients.<sup>49–52</sup> Pharmacological antidepressant therapy on the other hand has been demonstrated to reduce systemic sympathetic nervous activity, improve therapy adherence, and encourage health behaviours.<sup>49–52</sup> Our finding that antidepressants reduce the rate of recurrent MIs in patients with major depression but not in the overall population supports these concepts. Another particularly intriguing observation is the recently described inhibitory effect of the SSRI paroxetine on the G protein-coupled receptor kinase GRK2, which plays a major role in the development of cardiovascular disease.<sup>53–55</sup> Inhibition of the protein in various preclinical studies was shown to improve myocardial contractility, reverse cardiac remodelling, and attenuate heart failure progression.<sup>55–58</sup> Whether these preclinical observations translate into a measurable effect in humans remains to be determined. From the trials included in this meta-analysis, only one specifically investigated paroxetine.<sup>42</sup> In this study, Tian and colleagues found that GRK2 expression was higher in patients with ACS and concomitant depression and that paroxetine treatment reduced the levels of GRK2, led to a normalization of the autonomic nervous system function, improved cardiac performance, and lowered the rate of recurrent infarctions.<sup>42</sup> Potentially beneficial effects of paroxetine in patients with ACS irrespective of depression are currently being tested in a double-blinded RCT (NCT03274752), which will hopefully shed further light on the therapeutic potential of this drug for reversal of the adverse sequelae following myocardial ischaemia.

## Limitations

The results of our analysis have to be interpreted in view of several limitations. First, we did not have any access to patient-level data, and all analyses were performed on a population level, with insufficient data to identify potentially relevant subgroups. Second, although we identified 10 eligible trials, the cumulative number of participants and events was low. In specific, for the primary outcome of all-cause mortality, the majority of events occurred within two trials, while the others contributed only little to the derived estimate. Third, the included trials varied in a number of relevant characteristics. Apart from differences in eligible populations (including both depressed and not depressed patients), treatment regimens, and follow-up durations, also the inclusion

**Figure 4** Risk of bias for each study (A) and for each item presented as percentage across all included studies (B).



period extends over a long time span during which standards of care have changed. Especially on the cardiological side, both interventional and post-interventional therapies have experienced a remarkable evolution over the last decade, which is important to keep in mind with regard to potential drug interactions as a driving factor of adverse events. Even though we observed no signal for the overall treatment strategy, we cannot exclude relevant effects for individual agents. Conversely, higher adverse event rates due to side effects are expected to occur around the time of drug ingestion, whereas beneficial effects may take years to become

apparent. Consistent with this, the recently reported long-term results of the double-blind randomized EsDEPACS trial showed that patients with post-ACS depression that were allocated to a 24 week treatment with escitalopram had a significantly lower rate of major adverse cardiac events compared with the placebo arm after 8 years of follow-up, while this was not observed at an earlier time point.<sup>43,59</sup> In our analysis, the median follow-up duration was 1 year, and only three of the 10 trials reported long-term outcomes. Finally, patients recruited in RCTs are well selected and might not represent the general population. However, we decided



**Table 2** Study population characteristics in individual trials

	Strik et al. <sup>34</sup>	SADHART <sup>9,35,36</sup>	Mohapatra et al. <sup>37</sup>	Rigotti et al. <sup>38</sup>	MIND-IT <sup>8</sup>	Planer et al. <sup>39</sup>	DECARD <sup>40</sup>	ZESCA <sup>41</sup>	Tian et al. <sup>42</sup>	EsDEPACS <sup>43</sup>
Age, years (mean ± SD)	54 ± 11/59 ± 10 63/78	57 ± 10/58 ± 10 63/64	55 ± 12/57 ± 11 46/67	57 ± 10/55 ± 10 69/69	57 ± 11/58 ± 10 87/82	52 ± 11/52 ± 9 76/83	65 ± 12/64 ± 12 63/63	55 ± 10/53 ± 10 84/83	63 ± 11/62 ± 10 10/62 ± 10 57/52/57	60 ± 11/60 ± 11 59/62 na
Male (%)	na	30 ± 7/29 ± 7	na	28 ± 6/30 ± 7	na	28 ± 5/28 ± 6	27 ± 5/28 ± 4	na	na	na
BMI, kg/m <sup>2</sup> (mean ± SD)	na	61/69	36/67	61/46	na	45/39	38/43	42/37	57/54/57	60/62
Art. hypertension (%)	na	31/30	46/17	18/22	na	26/25	9/17	23/12	29/29/26	30/27
Diabetes mellitus (%)	na	70/67	na	87/80	na	60/63	na	52/48	na	49/47
Dyslipidaemia (%)	na	27/28	27/50	100/100	na	100/100	16/13	100/100	54/48/50	29/28
Smoking (%)	HAMD 22 ± 4	HAMD 20 ± 5	HDRS 15 ± 7	BDI 9 ± 9	HAMD 19 ± 4	na	HAMD 3	na	HAMD 27 ± 5/27	BDI 16 [13–22]/17 [14–23]
Depression score (mean ± SD or median [IQR])	4/21 ± 4	5/20 ± 5	5/17 ± 7	8/10 ± 9	5/17 ± 4	na	[1–6]/3 [1–5]	na	± 4/27 ± 5	na

Art., arterial; BDI, Beck Depression Index; BMI, body mass index; HAMD, Hamilton Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; IQR, inter-quartile range; na, not available; SD, standard deviation.

Values represent treatment/control arm, respectively, except for Tian et al., where values represent Treatment Arm 1/Treatment Arm 2/control.

not to include non-randomized studies of similar interventions, because multiple sources of biases could not have been accounted for in our analysis.

## Conclusions

Current evidence suggests that antidepressants in patients following ACS have no effect on mortality but reduce repeat hospitalizations; in patients with depression, there is a reduced risk of recurrent MI with antidepressant therapy.

## Conflict of interest

S.W. reports having received research and educational grants to the institution by Abbott, Amgen, Bayer, BMS, Boston Scientific, Biotronik, CSL Behring, Edwards Lifesciences, Medtronic, Polares, and SINOMED. T.P. reports having received research grants to the institution and speaker fees from Biotronik and Boston Scientific, and consultancy from HgihLife SAS (as a paid clinical event committee member).

## Funding

No funding was obtained for this study.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Search strategy.

**Table S2.** Selected not included trials with exclusion reasons  
**Figure S1.** Forest plot showing the results of Bayesian random-effects meta-analysis of antidepressant therapy vs. placebo on all-cause mortality (A), recurrent myocardial infarction (B) and rehospitalization (C) including only trials with placebo arm.

**Figure S2.** Forest plot showing the results of Bayesian random-effects meta-analysis of antidepressant therapy vs. placebo/usual care on all-cause mortality (A), recurrent myocardial infarction (B) and rehospitalization (C) including only trials with patients diagnosed with ACS and depression.

**Figure S3.** Forest plot showing the results of Bayesian random-effects meta-analysis of antidepressant therapy vs. placebo/usual care on all-cause mortality (A), recurrent myocardial infarction (B) and rehospitalization (C) including only trials with antidepressant treatment initiation after the first 30 days following the index event.

**Figure S4.** Forest plot showing the results of Bayesian random-effects meta-analysis of antidepressant therapy vs. placebo/usual care on all-cause mortality (A), recurrent myocardial infarction (B) and rehospitalization (C) including only trials with treatment duration of more than 12 weeks.

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