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Clinical benefit of drugs targeting mitochondrial function as an adjunct to reperfusion in ST-segment elevation myocardial infarction: A meta-analysis of randomized clinical trials

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ABSTRACT

Aims: To perform a systematic review and meta-analysis of randomized clinical trials (RCT) comparing the effectiveness of drugs targeting mitochondrial function vs. placebo in patients with ST-segment elevation myocardial infarction (STEMI) undergoing mechanical coronary reperfusion.
Methods: Inclusion criteria: RCTs enrolling STEMI patients treated with primary percutaneous coronary intervention (PCI) and comparing drugs targeting mitochondrial function vs. placebo. Odds ratios (OR) were computed from individual studies and pooled with random-effect meta-analysis.
Results: Fifteen studies were identified involving 5680 patients. When compared with placebo, drugs targeting mitochondrial component/pathway were not associated with significant reduction of cardiovascular and all-cause mortality (OR 0.9, 95% CI 0.7–1.17 and OR 0.92, 95% CI 0.69–1.23, respectively). However, these agents significantly reduced hospital admission for heart failure (HF) (OR 0.64; 95% CI 0.45–0.92) and increased left ventricular ejection fraction (LVEF) (OR 1.44; 95% CI 1.15–1.82). After analysis for subgroups according to the mechanism of action, drugs with direct/selective action did not reduce any outcome. Conversely, those with indirect/unspecific action showed a significant effect on cardiovascular mortality (0.65, 95% CI 0.46–0.92), all-cause mortality (OR 0.69, 95% CI 0.52–0.92), hospital readmission for HF (OR 0.41, 95% CI 0.28–0.6) and LVEF (OR 1.49, 95% CI 1.09–2.05).
Conclusions: Administration of drugs targeting mitochondrial function in STEMI patients undergoing primary PCI appear to have no effect on mortality, but may reduce hospital readmission for HF. The drugs with a broad-spectrum mechanism of action seem to be more effective in reducing adverse events.

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1. Introduction

Despite timely and complete reperfusion by primary percutaneous coronary intervention (PCI), mortality and morbidity are still high in patients with large ST-segment elevation myocardial infarction (STEMI) [1]. Data from animal models suggested that the process of restoring coronary blood flow itself paradoxically induces myocardial injury and contributes to final infarct size (IS) [2–4]. This phenomenon is called "reperfusion injury" (RI) and it is thought to mitigate the full benefit of reperfusion [2–4]. Although several aspects remain obscure and definitive evidence in humans is lacking, experimental studies have established that altered mitochondrial function is strongly involved in the RI genesis [4–5]. As such, several randomized clinical trials (RCT) assessed the effectiveness of novel agents capable of targeting mitochondrial function with the aim to reduce IS and improve outcome [4–19]. These studies have reported conflicting results using surrogate markers and none was individually adequately powered for hard endpoints [6–19]. Systematic reviews employing meta-analytic techniques provide quantitative and objective means to pool and assess available clinical evidence, emphasizing internal validity and homogeneity, while affording increased statistical power for hypothesis testing. Thus, the aim of this study was to perform a systematic review and meta-analysis of RCTs comparing drugs targeting mitochondrial function vs. placebo in patients undergoing primary PCI for STEMI.

2. Methods

We developed a systematic review and meta-analysis following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement [20–23]. The protocol for this study was previously published on an international prospective register for systematic reviews (PROSPERO) with the number: CRD42016033085.

2.1. Search strategy

Two expert cardiologists (RP, SB) independently and systematically searched (MESH strategy) MEDLINE, Cochrane Library, Google Scholar and Biomed Central for RCTs comparing drugs against the RI vs. placebo in patients with STEMI. The terms searched were: (reperfusion injury) AND ((PCI) OR (percutaneous coronary intervention) OR (ST elevation myocardial infarction) OR (STEMI) OR (myocardial infarction)). Details of the search strategy are reported in the appendix online. The research was carried out in December 2015.

2.2. Selection criteria

Shortlisted studies were retrieved as full articles and appraised independently by two unblinded reviewers (GC, FO), with divergences resolved after consensus, according to the following inclusion criteria: i) English language; ii) enrollment of STEMI patients; iii) reperfusion strategy by primary PCI; iv) randomized treatment allocation; v) comparison of agent/drug against RI vs. placebo/gold standard treatment; vi) at least 50 patients. Exclusion criteria were: i) duplicate reports failing to report additional or extended clinical outcomes, ii) lack of outcome data beyond hospitalization; iii) equivocal or non-random treatment allocation. Finally, selected studies were analysed by two independent reviewers (PP, GM) to establish if the experimental drug did or did not have a mechanism of action targeting mitochondrial function (detailed description in the supplemental appendix). They checked the following items for each drug/agent: pharmacological targets, location or not of the targets in mitochondria, activation or not of mitochondrial pathways, selectivity and exclusivity in the action against mitochondria. This adjudication was performed according to a recent overview [5] and after revision of all available information regarding the agent/drug. The studies were classified into three groups: i) direct/selective mechanism of action targeting a mitochondrial component/pathway; ii) indirect/unspecific mechanism of action targeting mitochondrial component/pathway; and iii) mechanism of action not targeting mitochondria. The present study focused its attention on the first two groups.

2.3. Data abstraction, endpoints, contact with authors

The reviewers (RP, SB, GC, FO) independently abstracted data. In the case of incomplete or unclear data, authors were contacted obtaining missing information. In addition, for the studies of Jones et al. and Lønborg et al., a longer follow-up was available (36 vs. 12 months and 12 vs. 1 months, respectively) and it was included in our analysis [16–17]. The primary endpoint of the analysis was the incidence of cardiovascular death. Secondary endpoints were: all-cause death, hospital readmission for heart failure (HF) and left ventricular ejection fraction (LVEF). We performed a pre-hoc stratification of studies according to mechanism of action (direct/selective vs. indirect/unspecific). Additional analyses were performed after stratification of studies according to the following criteria: i) administration of cyclosporine, ii) administration of nicorandil, iii) follow-up length <12 vs. ≥ 12 months, iv) indirect/unspecific drugs after exclusion of the study of Pizarro et al. [15].

2.4. Internal validity and quality appraisal

Two unblinded reviewers (RP, SB) evaluated the quality of included studies using pre-specified electronic forms that were piloted over the first 3 cases. No studies were excluded on the basis of this analysis. The same authors independently verified the eventual exclusion of some studies analyzing references from all the papers. Modifying the MOOSE item list in order to take into account the specific features of included studies, we separately abstracted and appraised study design, setting and data sources. Hence, following the Cochrane Collaboration approach we evaluated for each RCT the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias).

2.5. Data analysis and synthesis

Continuous variables were reported as mean ($\pm$SD) or median [interquartile range]. Categorical variables were expressed as number and percentage. The endpoints were expressed as an odds ratio (OR). Point estimates and standard errors were calculated and combined by the generic inverse variance method [24], computing risk estimates with 95% confidence intervals according to logarithmic transformation of the hazard measures. Considering the high likelihood of between-study variance, we used a random effect model. Statistical heterogeneity was assessed using the Cochran's Q test. This statistic was complemented with the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0 to 25% represents insignificant heterogeneity, 26 to 50% low heterogeneity, 51 to 75% moderate heterogeneity, and >75% high heterogeneity [25]. To test the difference between subgroup analyses the Chi^2 test has been used. Finally, random effect meta-regression analysis was performed to assess the effect of several potential confounding factors (sex, anterior MI, glycoprotein IIb/IIa inhibitor, baseline TIMI flow 0–1, smoking, dyslipidemia, prior MI, stent implantation, thrombus-aspiration, diabetes, hypertension) on results. Publication bias was appraised by graphical valuation of funnel plots and through Begg and Mazumdar rank correlation, Egger's regression intercept, and Duval and Tweedie trim and fill [26]. Prometa (Internovi, Cesena, Italy) and RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) software were used for statistical analyses.

3. Results

3.1. Search results and study selection

The database search yielded 948 citations (Fig. 1). Shortlisted citations were retrieved and checked at the title/abstract level excluding 889 papers (Fig. 1). Complete articles for the remaining 45 studies were checked for compliance to inclusion/exclusion criteria (Fig. 1). Finally, we identified 25 eligible trials meeting our inclusion/exclusion criteria of which 10 were excluded because the experimental drug was not targeting mitochondria. A total of 15 studies were included in qualitative and quantitative meta-analysis (Table 1, Fig. 1). Overall, 8 (53%) studies were double blind [7,9–12,16–18], 4 (27%) single blind [6,13,15] and 3 (20%) open label [8,14,19]. Of note, reviewers largely debated about classification of the study by Lincoff et al. and inclusion of the study by Pizarro et al. [9,15] (see online supplemental for more details). Finally, they decided to classify the first as direct/selective mechanism of action and to include the second, but as indirect/unspecific mechanism of action.

3.2. Baseline characteristics

Overall, 5864 patients were randomized and 5680 (97%) patients were included in the final analysis (Table 1). Six studies randomized 1774 subjects to treatment with an experimental drug with direct/selective mechanism of action against mitochondrial component/pathways (Table 1). Three studies used cyclosporine, whereas in 3 studies other drugs were administered (delcasertib, MTP-131, TRO40303). Conversely, 9 studies randomized 1329 patients to an experimental drug with an indirect/unspecific mechanism of action against mitochondrial component/pathways (metoprolol, atrial natriuretic peptide, nicorandil, exenatide, doxycycline, nitrite). The mean age of the population was 61 ± 1 years old (Table 1). Anterior MI was present in 3802 (66%) patients. Baseline TIMI flow grade was 0–1 in 4693 (82%) patients. The use of glycoprotein IIb/IIIa inhibitors and thromboaspiration was relatively common (37% and 35% of patients, respectively).

3.3. Cardiovascular mortality

Overall, the pooled effect estimate analysis showed a non-significant reduction in cardiovascular mortality (OR 0.9, 95% CI 0.7–1.17, $p = 0.4$, $I^2 = 10\%$) in patients randomly allocated to receive drugs targeting mitochondrial function (Fig. 2). Interestingly, after stratification of studies according to the mechanism of action, we found that indirect/unspecific drugs had a significant effect (OR 0.65, 95% CI 0.46–0.92, $p = 0.02$, $I^2 = 0\%$), whereas the direct/selective ones did not (OR 1.18, 95% CI 0.86–1.61, $p = 0.3$, $I^2 = 3\%$) (Fig. 2). The difference between the two subgroups reached statistical significance ($p = 0.01$) (Fig. 2).

3.4. All-cause mortality

All-cause mortality was not affected by the treatment (OR 0.92, 95% CI 0.69–1.23, $p = 0.58$, $I^2 = 37\%$) (Fig. 2). Limiting the analysis to indirect/unspecific drugs, we observed a statistically significant reduction of all-cause mortality (OR 0.69, 95% CI 0.52–0.92, $p = 0.01$, $I^2 = 0\%$) (Fig. 2).

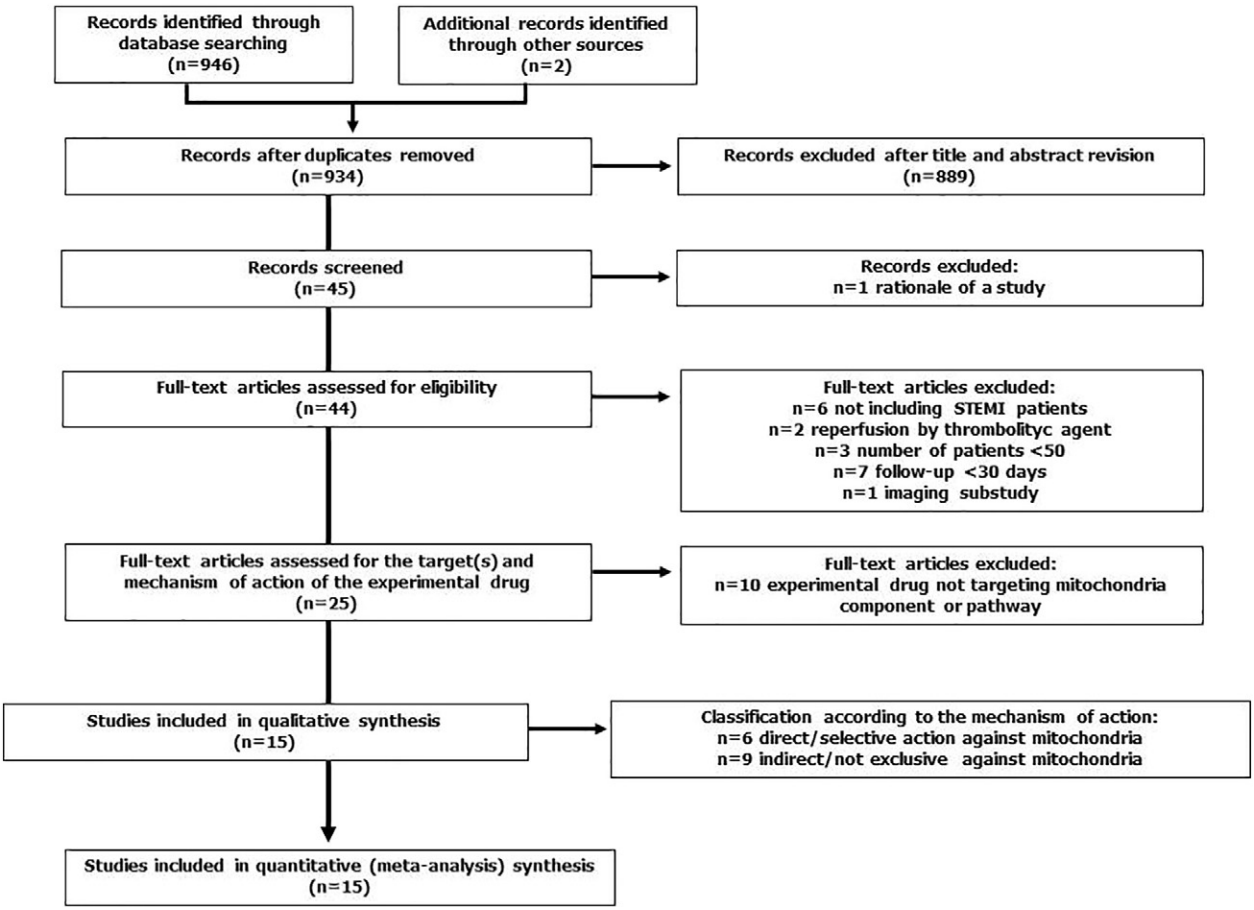

Fig. 1. Flow diagram of the systematic literature search indicating the inclusion and exclusion process. STEMI: ST-segment elevation myocardial infarction.

Table 1
Main characteristics of the randomized clinical trials.

	Direct/selective mechanism of action against mitochondrial component/pathway							Indirect/unspecific mechanism of action against mitochondrial component/pathway								
Study	Piot	Cung	Ottani	Lincoff ANT	Lincoff INF	Atar	Gibson	Ishii	Lee	Kitakaze NIC	Kitakaze ANP	Pizarro	Lønborg	Jones	Siddiqi	Cerisano
Pts randomized	58	970	410	1010	166	167	297	368	73	613	603	270	387	82	280	110
Pts included in the analysis	58	969	410	997	159	165	297	368	73	545	569	270	330	80	280	110
Experimental drug	CYC	CYC	CYC	DEL	DEL	TRO40303	MTP131	NIC	NIC	NIC	ANP	Metoprolol	Exenatide	Nitrite	Nitrite	Doxycycline
Pts receiving experimental drug	30	474	207	748	80	85	150	185	37	276	277	139	174	40	146	55
Only anterior MI	N	Y	N	Y	N	N	Y	N	N	N	N	Y	N	N	N	N
Max symptoms-PCI time (h)	12	12	6	6	6	6	4	24	12	12	12	6	12	6	12	12
Prior MI exclusion criteria	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Follow-up (months)	3	12	6	3	3	1	6	27 ± 15	1	30 ± 13	32 ± 12	24[a]	12	36	6	6
LVEF (method)	TTE	TTE	TTE	TTE	NA	CMR	CMR	LVG	NA	LVG	LVG	CMR	CMR	CMR	CMR	TTE
LVEF timing (months)	3	12	6	3	NA	1	1	6	NA	6	6	6	3	6	6	6
Age (years)	58 ± 2	60 ± 12	63 ± 13	60 ± 8	61 ± 8	62 ± 12	60 ± 11	58 ± 2	63 ± 10	58 ± 12	62 ± 10	63 ± 10	58 ± 11	63 ± 11	57 ± 12	63 ± 13
Male n. (%)	46 (79)	795 (82)	327 (80)	729 (72)	126 (76)	136 (83)	224 (75)	298 (81)	61 (73)	466 (76)	454 (75)	233 (86)	263 (80)	67 (84)	177 (77)	76 (69)
Diabetes n. (%)	8 (14)	123 (13)	58 (14)	146 (14)	25 (15)	12 (7)	35 (14)	119 (32)	23 (31)	186 (30)	167 (28)	55 (20)	27 (8)	6 (8)	33 (14)	23 (21)
Anterior MI n. (%)	24 (41)	969 (99)	203 (49)	997 (99)	0 (0)	62 (38)	282 (98)	174 (47)	40 (55)	269 (44)	206 (34)	222 (82)	137 (42)	21 (26)	87 (38)	101 (92)
Symptom-balloon time (minutes)	302 ± 28	270 ± 180	180 ± 60	180 ± 72	180 ± 72	170 ± 72	180 ± 60	282 ± 180	360 ± 180	210 ± 150	240 ± 180	120 ± 60	180 ± 110	189 ± 72	220 ± 128	224 ± 202
Thromboaspiration n. (%)	0 (0)	736 (76)	275 (67)	NA	NA	NA	138 (48)	128 (35)	0 (0)	0 (0)	0 (0)	208 (77)	185 (56)	64 (80)	127 (45)	69 (63)
GPI IIb/IIIa n. (%)	21 (36)	366 (38)	182 (44)	474 (47)	80 (48)	66 (40)	159 (54)	0 (0)	10 (14)	0 (0)	0 (0)	191 (71)	270 (81)	80 (100)	115 (41)	101 (92)
TIMI pre 0–1 n. (%)	58 (100)	864 (89)	410 (100)	547 (54)	111 (68)	163 (100)	147 (52)	311 (84)	48 (66)	613 (100)	603 (100)	205 (76)	220 (67)	70 (87)	226 (81)	77 (70)

Pts: patients. MI: myocardial infarction. PCI: percutaneous coronary intervention. LVEF: left ventricle ejection fraction. TTE: transthoracic echocardiography. ANT: anterior cohort. INF: inferior cohort. CMR: cardiac magnetic resonance. LVG: left ventricle angiography. ANP: atrial natriuretic peptide. NIC: nicorandil. NA: data not available/not assessed. Y: yes. N: not. GPI: glycoprotein inhibitor. TIMI: thrombolysis in myocardial infarction. CYC: cyclosporine. DEL: delcasertib.

[a] Median follow-up.

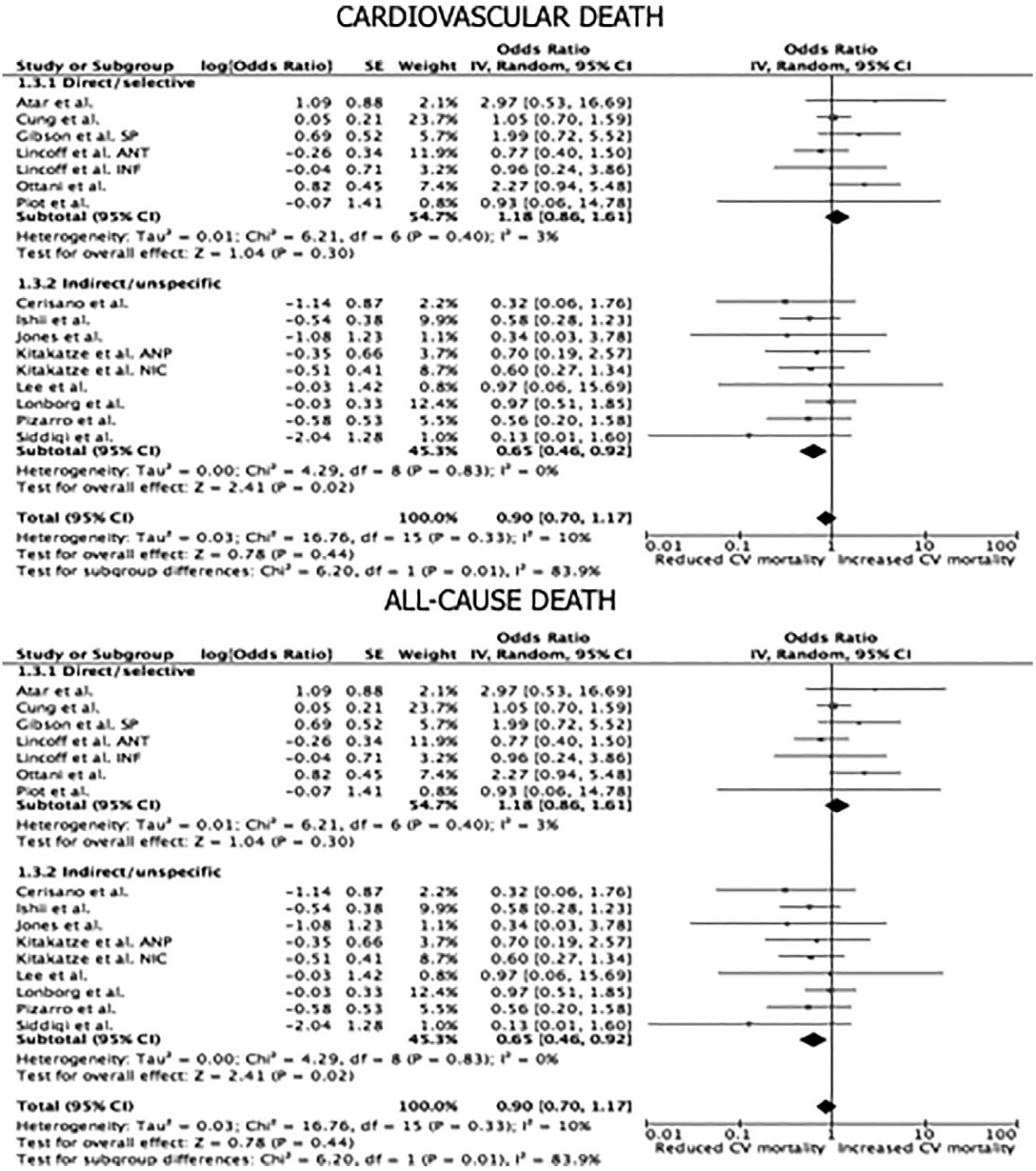

Fig. 2. Forest plots on cardiovascular mortality and all-cause mortality. SF: safety population. ANT: anterior cohort. INF: inferior cohort. ANP: atrial natriuretic peptide. NIC: nicorandil. CV: cardiovascular.

3.5. Hospital readmission for heart failure

Hospital readmissions for HF were significantly reduced (OR 0.64; 95% CI 0.45–0.92, $p = 0.01$, $I^2 = 59\%$) in patients randomly allocated to receive drugs targeting mitochondrial component/pathways (Fig. 3). The overall effect was principally driven by studies of drugs with indirect/unspecific mechanism of action (OR 0.41; 95% CI 0.28–0.60; $p < 0.00001$, $I^2 = 17\%$ vs. OR 1.03, 95% CI 0.77–1.37, $p = 0.85$, $I^2 = 15\%$, Chi^2 test for the difference $p = 0.0002$).

3.6. Left ventricular ejection fraction

The administration of drugs targeting mitochondrial function demonstrated an increase in LVEF as compared to placebo (OR 1.44; 95% CI 1.15–1.82; $p = 0.002$, $I^2 = 80\%$) (Fig. 3). This effect was due to studies randomizing to indirect/unspecific drugs (OR 1.49, 95% CI 1.09–2.05, $p = 0.01$) as compared to the others (OR 1.40, 95% CI 0.96–2.05, $p = 0.08$), although the difference between the two subgroups did not reach statistical significance ($p = 0.8$) (Fig. 3).

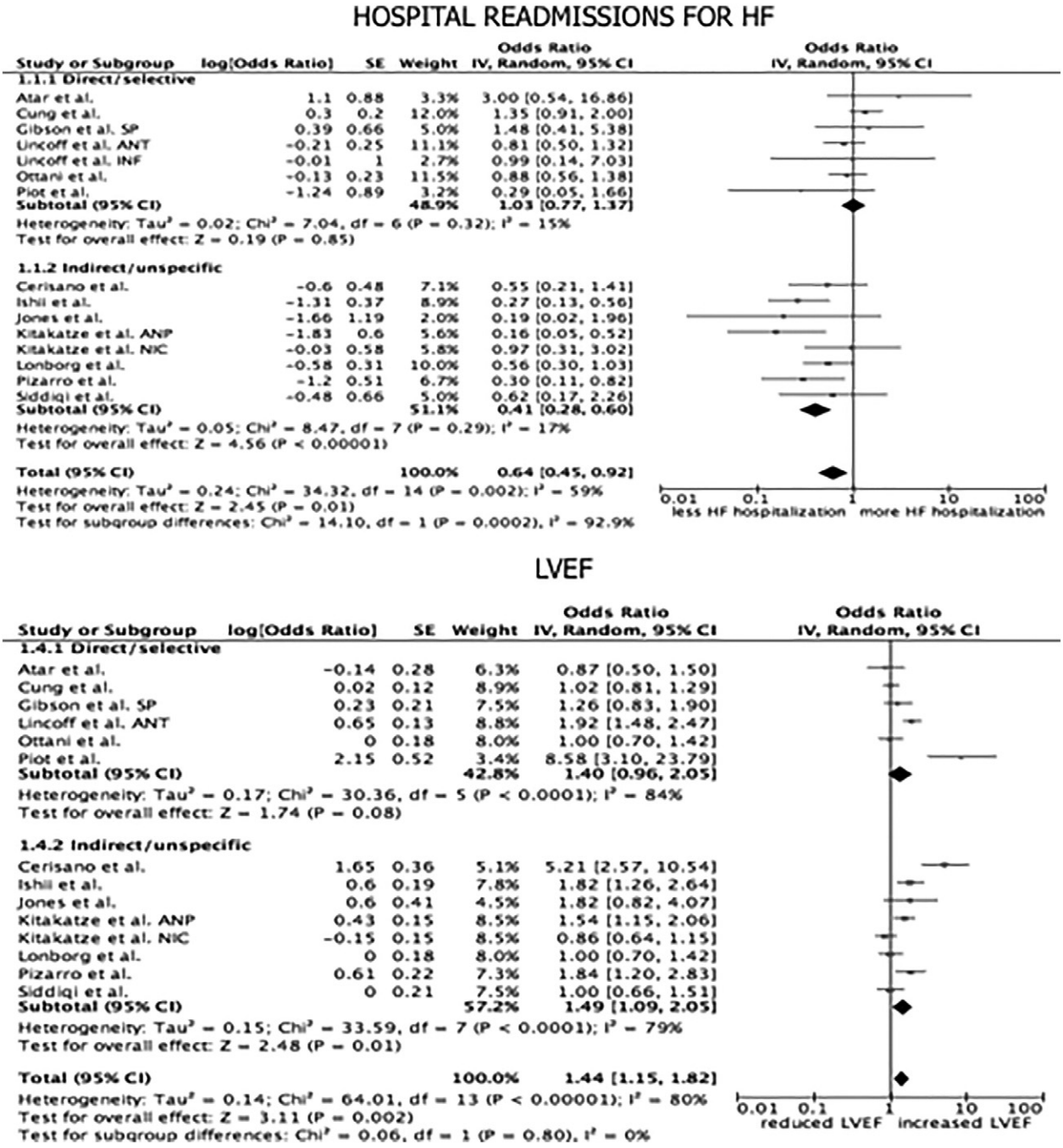

Fig. 3. Forest plots on hospital readmissions for heart failure and left ventricle ejection fraction. SF: safety population. ANT: anterior cohort. INF: inferior cohort. ANP: atrial natriuretic peptide. NIC: nicorandil. HF: heart failure. LVEF: left ventricle ejection fraction.

3.7. Additional analyses

Additional analyses are detailed in the online appendix. Briefly, the administration of cyclosporine or nicorandil vs. placebo did not affect study outcomes (see Figs. 1 and 2 in Ref [27]). A reduction in hospital readmission for HF was more evident in studies with follow-up length ≥12 months (see Figs. 4, 5 and 6 in Ref [27]). Excluding the study by Pizarro et al. (metoprolol) [15], we did not observe significant differences in our results (see Fig. 3 in Ref [27]). Finally, random effects meta-regression disclosed no significant interaction between confounding factors and the administration of drugs targeting mitochondrial function and outcomes (Supplemental Table 3). Especially, baseline TIMI flow >1, thromboaspiration and glycoprotein IIb/IIIa inhibitor did not affect the relationship between experimental drug and outcome.

3.8. Publication bias

There was no evidence of publication bias (supplemental online).

4. Discussion

In the last decades, we observed a significant and progressive mortality reduction in STEMI patients receiving coronary reperfusion by primary PCI [1]. Nevertheless, mortality after STEMI is still not negligible and the number of patients developing HF is increasing [1–3,28]. As such, new treatments are clearly on demand to further reduce IS and preserve LVEF, thereby improving clinical outcome. A field of cardiovascular research pursuing this ambitious aim is termed "cardioprotection", based on the hotly debated concept of lethal RI and on the application of

strategies and/or drugs able to reduce it [2–5]. Although it is still debated by some authors, mitochondrial function is considered the crucial mediator of RI [4–5]. Consequently, it is not surprising that several RCTs with drugs targeting mitochondrial function have been conducted in the recent past [6–19]. The major characteristics of these studies can be summarized as follows: i) selection of agents against mitochondrial component/pathways; ii) positive results of the agent in preclinical investigations; iii) inclusion of selected series of STEMI patients being "proof-of concept" investigations; iv) surrogate markers of left ventricle (LV) salvage or LV function or IS as primary endpoint; v) absence of persuasive results to demonstrate the effectiveness of the experimental treatment. In addition, all of these trials were underpowered for hard clinical endpoints. The reasons for this failure are multiple and not the aim of our study [28]. Surely, discrepancies in the dose of the experimental drug, of the timing of its administration and of the patient's selection (e.g. location of MI, spontaneous coronary reperfusion, time between symptom's onset and reperfusion) played a crucial role in these mixed or neutral results [29].

The purpose of the present meta-analysis was to collect data from each RCT to assess the presence of benefit on hard endpoints deriving from the administration of experimental drug against mitochondrial component/pathways. The strengths of our work are the selection of agents, the adjudication of the mechanism of action by experts in the field of mitochondrial function, the collection of original data from authors, the largest sample size for a study in this topic and the low degree of heterogeneity (expressed as I^2%) in the majority of the analyses. Overall, we did not demonstrate a significant reduction in either cardiovascular or all-cause mortality. The administration of experimental drugs targeting mitochondrial function in STEMI patients did not affect mortality. This neutral effect was observed despite the significant improvement in LVEF and the reduction in HF hospital readmissions. We may speculate that the benefit in terms of LVEF preservation and HF reduction is too small to translate into a mortality advantage or that the study population and/or the number of deaths are not adequate to observe a significant difference. In addition, we have a follow-up length >12 months only in 7 studies and the short follow-up could be limited the benefit in terms of mortality due to HF hospital readmission reduction.

The major novelty of our work is the focus on drugs targeting mitochondrial function. This is the first attempt to classify drugs according the mechanism of action against mitochondria and to investigate their effectiveness. The pathophysiological rationale derives from previous and recent studies suggesting that most critical subcellular signalling of lethal RI are located in mitochondria components and/or pathways [4–5]. Interestingly, we did not observe any benefit from the administration of drugs with a mechanism of action direct and selective for mitochondrial targets. Conversely, drugs with a broad-spectrum mechanism of action reduced all clinical endpoints, including cardiovascular and all-cause mortality. Furthermore, the findings were also confirmed after the exclusion of the study by Pizarro et al. where patients were randomized to metoprolol vs. placebo (questionable effect against mitochondrial targets) [15]. These findings could be interpreted as indirect evidence against RI. We may infer that RI is not important or that it is not a major determinant of prognosis in humans. Nicorandil, exenatide, metoprolol, nitrite, doxycycline and atrial natriuretic peptide have multiple physiological effects which could have improved LVEF or reduced mortality and HF, independently from any effect on RI [12–19]. Alternatively, the results of this study could be viewed as proof against mitochondrial involvement in RI. Nevertheless, we may hypothesize that the targets of drugs with presumed direct/selective mechanisms of action against mitochondria were in fact not directed primarily at key factors in the RI genesis, as recent evidence suggest for cyclosporine and TRO40303 [4,30–31]. Finally, our findings should be also interpreted in context with the results from mechanical strategies of cardioprotection (post and remote conditioning) [32]. We cannot exclude that components and pathways involved in myocardial necrosis during myocardial ischemia and reperfusion are multiple. Accordingly, a broad-spectrum approach (e.g. the recently proposed "combination reperfusion therapy") could be more effective as compared to a single-target approach [5]. Besides such intriguing speculations, further studies are clearly warranted either in pre-clinical and clinical setting [29–34].

4.1. Study limitations

Our results suffer from those limitations which are inherent to all meta-analytic techniques including particularly heterogeneity in patient populations, different study drug regimens, and variable endpoint definitions across studies. This mainly applies to the different criteria employed to assess IS. Due to variable definitions and methods (cardiac magnetic resonance, troponin T or I or creatine kinase release) across studies, we are not able to give a comprehensive estimate of effect on IS. In addition, despite the inclusion of 15 studies, our final study population (5680 STEMI patients) remains underpowered to draw final conclusions on mortality. Consequently, subgroup analyses should be considered hypothesis-generating and require further confirmations. Finally, since non-fatal endpoints were included in the analysis, competing risk should be accounted for in the analysis, but data to calculate them were not available.

5. Conclusions

Administration of drugs targeting mitochondrial function in STEMI patients undergoing primary PCI appear to have no effect on mortality, but may reduce hospital readmission for HF. The drugs with a broad-spectrum mechanism of action seem to be more effective in reducing adverse events.

Funding

None.

Conflict of interest

Lincoff receives research support from Kai Pharmaceuticals; Gibson receives research support from Stealth pharmaceuticals; other authors do not declare conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.06.040.

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