Effect of oral β-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis

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Aims	Guidelines concerning β-blocker treatment following acute myocardial infarction (AMI) are based on studies undertaken before the implementation of reperfusion and secondary prevention therapies. We aimed to estimate the effect of oral β-blockers on mortality in contemporary post-AMI patients with low prevalence of heart failure and/or reduced left ventricular ejection fraction.
Methods and results	A random effects model was used to synthetize results of 16 observational studies published between 1 January 2000 and 30 October 2017. Publication bias was evaluated, and heterogeneity between studies examined by subgroup and random effects meta-regression analyses considering patient-related and study-level variables. The pooled estimate showed that β-blocker treatment [among 164 408 (86.8%) patients, with median follow-up time of 2.7 years] was associated with a 26% reduction in all-cause mortality [rate ratio (RR) 0.74, 95% confidence interval (CI) 0.64–0.85] with moderate heterogeneity ($I^2 = 67.4\%$). The patient-level variable mean age of the cohort explained 31.5% of between study heterogeneity. There was presence of publication bias, or small study effect, and when controlling for bias by the *trim and fill* simulation method, the effect disappeared (adjusted RR 0.90, 95% CI 0.77–1.04). Also, small study effect was demonstrated by a cumulative meta-analysis starting with the largest study showing no effect, with increasing effect as the smaller studies were accumulated.
Conclusion	Evidence from this study suggests that there is no association between β-blockers and all-cause mortality. A possible beneficial effect in AMI survivors needs to be tested by large randomized clinical trials.
Keywords	Beta-blocker • Mortality • Myocardial infarction • PCI • Secondary prevention

Introduction

Oral β-blockers have been a central component of secondary prevention pharmacotherapy following acute myocardial infarction (AMI) irrespective of its severity for decades. Recent international guidelines on the management of coronary disease, however, call into question the efficacy of β-blockers.[1–4] The foremost reason for this is because studies of β-blockers among patients following AMI were conducted prior to the implementation of acute coronary revascularization and the use of modern secondary preventive treatments.

Moreover, landmark studies which established the rationale for the routine use of long-term oral β-blockade after AMI were published in the early 1980s.[5,6] The only randomized large-scale β-blocker trial conducted in patients following AMI in recent years,[7] found no prognostic benefit of early intravenous metoprolol followed by 4 weeks of oral treatment compared with placebo. A meta-analysis of

randomized, controlled trials did not find a mortality effect associated with β-blockers in studies from the reperfusion era, as opposed to a significant reduction in mortality for studies published in the pre-reperfusion era.[8]

The incidence of AMI remains high and many patients with AMI who do not have reduced left ventricular systolic ejection fraction (LVEF) and/or heart failure (HF) receive oral β-blockers. Whilst β-blockers are considered relatively safe and inexpensive, they do have well-known side effects, and adherence to other (potentially more efficacious) secondary preventive medications may wane as a result of concomitant use of β-blockers.[9] Given the absence of randomized controlled trials to test the efficacy of β-blockers in contemporary AMI patients without reduced left ventricular function or HF are lacking, meta-analyses of population-based studies are potentially of value for guiding β-blocker treatment in clinical practice.

We hypothesized that the survival benefit of β-blockers observed in historical trials may not be present in the contemporary post-AMI population. As such, we aimed to estimate the effect of oral β-blockers on mortality in patients with both ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) where the majority of patients did not have reduced LVEF and/or no clinical signs of HF.

Methods

The review protocol is registered at https://www.crd.york.ac.uk/PROSPERO/, ID: CRD42017079199.

Eligibility criteria

All study types and sizes published after 1 January 2000 concerning patients following AMI were eligible for inclusion. Studies where none or only a minority of patients had a history of HF, were in Killip class ≥III or had LVEF <40% at baseline, were included. It was anticipated that not all studies would have complete data on these three categories reflecting HF and/or left ventricular (LV) systolic dysfunction. Studies that did not provide estimates between the β-blocker group and the no β-blocker group were excluded.

Study selection and search

The literature search strategy is presented in Supplementary material online, Tables S1 and S2. We searched the electronic bibliographic databases Embase and Medline(r) for studies written in English from inception until 18 July 2017, with an additional search undertaken per 30 October 2017. After removal of duplicate references, two members of the review team undertook initial screening of article titles and abstracts. Potentially, relevant articles were obtained in full-text and read independently by three review team members. Conflicts were resolved by consensus. Reference lists were scrutinized to identify articles not included in the original search.

Quality assessment

The Newcastle–Ottawa Scale (NOS) for cohort studies[10] was used to assess the quality of the included studies according to (i) methods for study participant selection, (ii) appropriate control for confounding (comparability), and (iii) methods for assessing the outcome. We further assessed the timing of the study (prospective vs. retrospective), and methods used to control for confounding (propensity score analysis vs. multivariate analysis).

Data abstraction

The primary endpoint considered was all-cause mortality.

Publication status, study design, patient-related characteristics, and results were extracted on a standardized form according to an a priori protocol. Investigators were contacted for additional data. Patient-related variables were mean age of the cohort, frequency of male sex, diabetes mellitus, hypertension, smoking, previous myocardial infarction (MI); treatment with acetylsalicylic acid (ASA), statins, angiotensin receptor blockers (ARBs)/angiotensin-converting enzyme inhibitors (ACEI), in addition to LVEF, Killip class, history of HF, STEMI/NSTEMI, and percutaneous coronary intervention (PCI).

Quantitative data synthesis

Statistical pooling

The method used to combine results from individual studies, was based on the adjusted risk estimate and its 95% confidence intervals (CIs) obtained from each study. To obtain summary measures, a random effects model according to the DerSimonian Laird method[11] was used because of the heterogeneity among studies.

Sources of heterogeneity, evaluation and quantification

Statistical heterogeneity was assessed with the Cochran's Q test and its magnitude evaluated by the I^2 statistics (I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively).[12] A series of sensitivity analyses were undertaken, including subgroup analyses and meta-regression to investigate potential sources of heterogeneity in the association between β-blocker treatment and mortality. Data were stratified according to the following study level variables; prospective vs. retrospective study design, statistical methods used to control for confounding (propensity score vs. multivariable analysis), and the following patient-level variables; country (Asia vs. US/Europe), AMI type (STEMI vs. STEMI/NSTEMI or unclear), and revascularization (only PCI treated patients vs. mixed or unclear). Subgroup analyses were extended by a random-effect meta-regression analysis that allowed the effect of the continuous covariates to be investigated (such as in years; median follow-up time and mean age, and in percent; LVEF, male sex, diabetes mellitus, hypertension, and smoking) as well as the categorical covariates used in the subgroup analysis. Meta-regression was performed to explore the influence of each covariate on the effect of β-blockers. If the covariate decreased the between-study variance, the source of heterogeneity was considered important. The estimate of τ^2 in the presence of a covariate in comparison to that when the covariate is omitted allowed the proportion of the heterogeneity variance explained by the covariate to be calculated.[13]

Finally, a sensitivity analysis was undertaken to investigate the influence of each study by omitting each in turn from the meta-analysis and assessing the degree to which the magnitude and significance of the exposure effect changed.[14]

Evaluation of publication bias or small-study effect

Publication bias is known to occur in meta-analyses, as studies that show a statistically significant effect of treatment are more likely to be published. Such selective publication of studies may lead to biased estimates that appear to be precise in meta-analysis based on literature search. In order to assess potential publication bias or small-study effect, we used the funnel-plot, which is a good visual evaluation of sampling bias. Funnel plot asymmetry raises the possibility of bias, and leads to a questioning of the interpretation of the overall effect when studies are combined in a meta-analysis. Sterne et al.[15] have suggested that the funnel plot should be seen as a generic means of examining small study effect, which is the

Table I   Characteristics of the 16 cohort studies included in the meta-analysis

First author (Publication year)	Country	Inclusion period	β-Blocker	Total cohort	Control for confounding	Timing of the study	Follow-up (years), median	Age (years), mean	Men (%)	STEMI (%)	PCI[a] (%)	LVEF (%)	History of HF (%)	Killip ≤2 (%)	Diabetes (%)	Hypertension (%)	Smoking (%)	Prior MI (%)	ASA (%)	Statins (%)	ARB/ ACEi (%)
Kernis (2004)[19]	USA/ Europe	1991–1999	1661	2442	PS adjusted	Retrospective	0.5	60.6	73.7	100	100	48.9	2.3	98.7	16.6	44.9	66.2	13.8	—	—	—
Yamada (2006)[20]	Japan	1994–2001	400	546	Multivariate	Prospective	2.0	63.0	75.5	82.5[b]	61.1	54.0	—	87.7	37.4	41.3	64.3	0	92.1	31.9	51.6
Ozasa (2010)[21]	Japan	2004–2006	349	910	PS adjusted	Retrospective	3.0	67.4	76.0	100	100	52.3	17.0	—	38.0	68.0	38.0	8	99.1	54.6	76.2
Bangalore[c] (2012)[22]	USA/ Europe	2003–2004	3379	6758	PS matched	Retrospective	3.6	68.6	75.1	—	—	—	22.3	—	37.3	73.6	9.7	—	75.8	74.5	69.4
Bao (2013)[23]	Japan	2005–2007	1614	3692	Multivariate	Retrospective	2.6	67.1	74.6	100	100	53.5	27.3	—	31.4	78.7	41.6	8.6	99.5	56.6	75.7
Nakatani (2013)[24]	Japan	1998–2011	2880	5628	PS adjusted	Retrospective	3.9	64.7	77.3	100	100	—	—	85.4[d]	32.8	59.5	65.9	10.9	94.6	44.3	77.1
Bangalore[c] (2014)[25]	USA/ Europe	2002–2003	981	1962	PS matched	Retrospective	2.3	64.5	79.4	—	—	—	0	—	35.4	69.7	18.2	—	98.0	80.4	17.7
Choo (2014)[26]	Korea	2004–2009	2424	3019	PS adjusted	Retrospective	3.0	61.3	73.2	58.1	100	60.4	—	93.8	40.6	50.0	44.0	3.3	99.7	90.4	81.8
Yang (2014)[27]	Korea	2005–2010	2650	3975	PS matched	Retrospective	1.0	65.7	73.0	100	100	50.0	0.9	85.3	25.3	43.6	45.7	6.5	98.6	80.8	75.9
Lee (2015)[28]	Korea	2003–2009	598	901	Multivariate	Retrospective	4.5	57.7	79.5	100	100	51.7	—	87.9	21.9	40.1	64.8	3.2	99.2	66.3	93.2
Raposeiras-Roubin (2015)[29]	Spain	2003–2012	555	1110	PS matched	Retrospective	5.2	66.1	69.0	28.0	65.2	—[e]	10.8	—	25.9	56.7	27.6	9	87.2	82.8	58.9
Hioki (2016)[30]	Japan	2008–2010	251	444	PS adjusted	Retrospective	2.9	65.7	81.8	81.8	100	56.1	—	100	24.1	22.7	65.1	—	—	100	85.1
Konishi (2016)[31]	Japan	1997–2011	103	206	PS matched	Retrospective	4.7	64.6	80.6	100	100	56.4	0	—	41.3	61.7	35.9	0	99.0	51.5	80.1
Lee[f] (2016)[32]	Korea	2009–2013	3683	7261	Multivariate	Retrospective	2.4	62.5	75.1	—	100	—	2.9	—	27.1	30.1	—	0	88.0	93.1	0
Puymirat[g] (2016)[33]	France	2005	1783	2217	Multivariate	Prospective	1.0	64.4	72.0	56.0	48.7	55.0	0	100	31.8	54.8	32.5	14.5	—	32.2	37.5
Dondo (2017)[34]	UK	2007–2013	141 097	148 314	PS adjusted	Retrospective	1.0	63.5	71.0	53.0	45.9[h]	—	0	—	11.4	33.6	62.3	0	96.7	96.3	88.3

[a]At index AMI.

[b]Q-wave MI.

[c]Subgroup of patients with known prior myocardial infarction.

[d]Killip >1.

[e]All patients had LVEF ≥ 50%.

[f]Subgroup of patients who received β-blocker only vs. no drug.

[g]One-year population.

[h]In total, 68 095/148 314 (45.9%) had in-hospital coronary intervention (PCI/CABG) and 49 087/68 095 (72.1%) was treated with primary PCI for STEMI.

HF, heart failure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PS, propensity score; STEMI, ST-elevation myocardial infarction; UK, United Kingdom; USA, United States of America.

Table 2 Subgroup analysis performed according to patient and study characteristics considered as potential sources of heterogeneity for outcome all-cause mortality

Subdivision	N	RR (95% CI)	RR = 1, Z	P-value	Variation in RR due to heterogeneity, I^2 (%)
All studies	16	0.74 (0.64–0.85)	4.20	<0.001	67.4
ST-elevation myocardial infarction					
All patients	7	0.70 (0.52–0.93)	2.44	0.015	70.3
Mixed/unclear	9	0.78 (0.67–0.91)	3.16	0.002	61.9
PCI					
All patients	10	0.68 (0.54–0.86)	3.29	0.001	65.9
Mixed/unclear	6	0.83 (0.71–0.97)	2.39	0.017	57.8
Follow-up by quartiles					
0.5–1.5 years	4	0.64 (0.41–1.01)	1.90	0.057	82.0
1.5–2.7 years	4	0.85 (0.70–1.03)	1.67	0.095	19.9
2.7–3.8 years	4	0.75 (0.51–1.10)	1.48	0.138	68.6
3.8–5.2 years	4	0.68 (0.51–0.91)	2.64	0.008	61.3
Timing of the study					
Prospective	2	0.65 (0.44–0.98)	2.08	0.038	0.0
Retrospective	14	0.75 (0.65–0.87)	3.86	<0.001	69.8
Control for confounding					
Propensity score analysis	11	0.74 (0.62–0.78)	3.48	0.001	70.0
Multivariate analysis	5	0.74 (0.56–0.97)	2.19	0.029	61.4

CI, confidence interval; RR, rate ratio.

tendency for smaller studies in a meta-analysis to show larger treatment effects. To avoid evaluating publication bias only according to visually judgement, this was complemented by Egger's test of asymmetry applied on the funnel plot.[16]

We used the *trim and fill* simulation method to detect and control for bias.[17] In the presence of publication bias, the trim and fill method could help reduce bias in pooled estimates. Even though the performance is not ideal, this method is a kind of sensitivity analysis to assess the potential impact of missing studies. This then allows an adjusted overall estimate with CI to be calculated. A test of the presence of bias could be derived from this method based on the estimated number of missing studies. The estimated effect of the missing studies provides an indication of whether the imputed missing studies affect the overall result of the meta-analysis.

We followed the PRISMA guidelines for meta-analyses and systematic reviews of observational studies in reporting the present study.[18] All statistical analyses were performed with Stata version 15 (Stata Corporation, College Station, TX, USA) or R Package-meta (Guido Schwarzer, R News 2007).
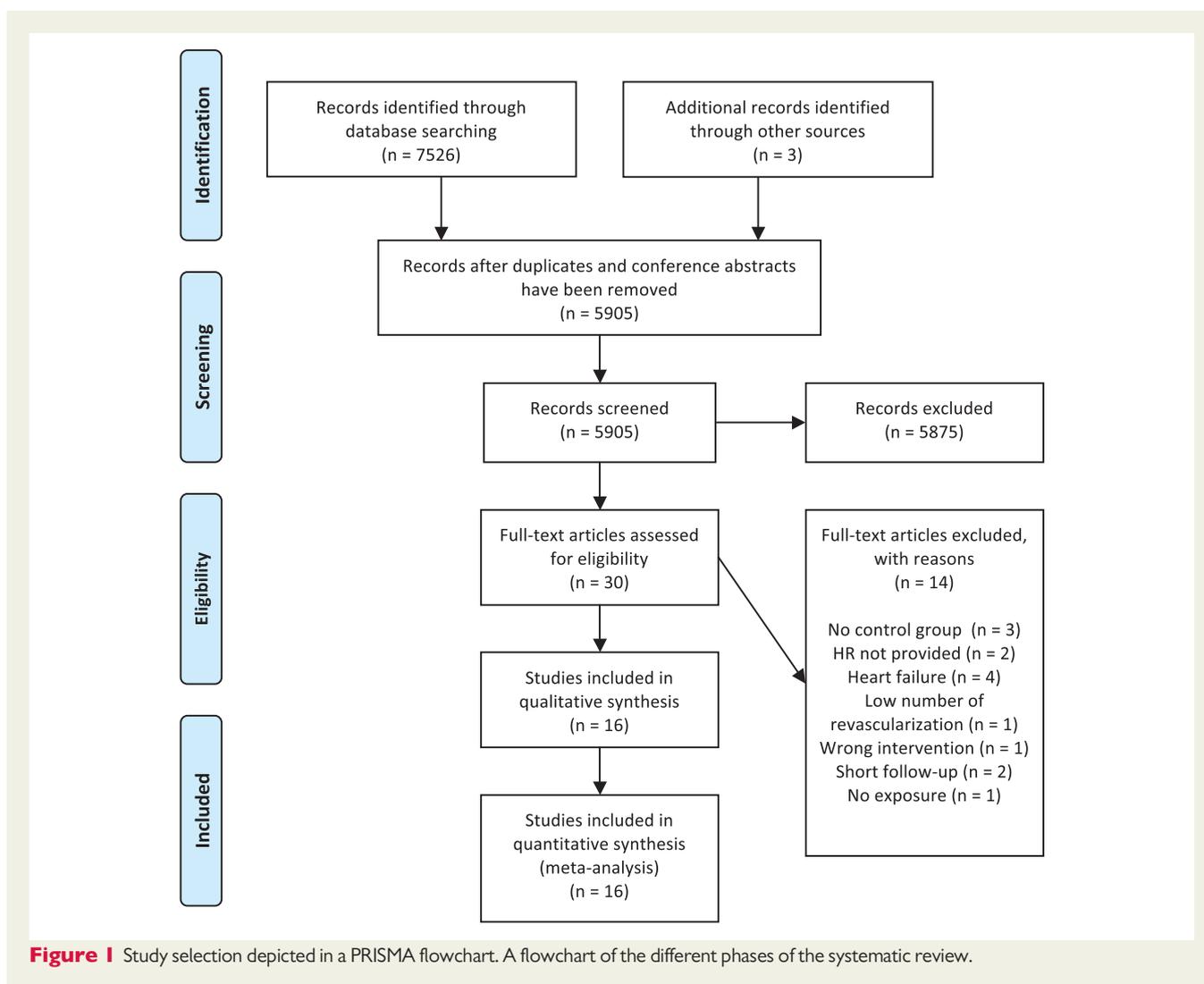
Results

Study selection

After identifying 7529 references, 7499 were excluded due to irrelevant content and duplicate publications, leaving 30 potentially eligible studies. Fourteen of these did not fulfil the inclusion criteria (see Supplementary material online, *Table S3*) and 16 studies[19–34] were thus included in the meta-analysis (*Figure 1*). Additional data were obtained for three studies.[23,29,34]

Study characteristics

Study characteristics are shown in *Table 1*. The pooled cohort comprised 189 385 patients with AMI. The median age was 64.6 years (range 57.7–68.6 years), 75% was men (range 69.0–81.8%), and median follow-up was 2.7 years (range 0.5–5.2 years). Of ten studies providing information, median LVEF was 53.7% (range 48.9–60.4%). Only four studies used a predefined LVEF cut-off value for inclusion, being >40% in two studies[31,33] and ≥ 50% in two.[26,29] Eleven studies provided information about history of HF, with a median prevalence of 1.8% (range 0–27.3%). Eight studies provided information about Killip class ≤2 with a median prevalence of 90.6% (range 85.3–100%). On average, 30% of patients had diabetes, 52% hypertension, 6% previous MI, and 45% were smokers when included. Average percentages for concomitant treatments were 94% with aspirin, 69% with statins, and 64% with ARBs/ACEIs. Ten studies were on Asian populations, and six on North American or European populations.

In total, 86.8% (*n* = 164 408) of the pooled cohort received β-blockers. Information about β-blocker type and dose was provided in two studies,[23,33] five studies reported only the type prescribed at hospital discharge,[24,26,28,30,32] and for the remaining nine studies no information was provided (see Supplementary material online, *Table S4* for further information about study β-blocker types and doses). Follow-up information concerning dose changes, discontinuation or new β-blocker prescriptions was not available for any of the included studies.

Two studies[22,25] included subpopulations with prior MI eligible for inclusion in the meta-analysis. All studies were cohort by design, of which 14 were retrospective. For 11 studies, confounding was controlled for on multiple clinically relevant variables by propensity score

Figure 1 Study selection depicted in a PRISMA flowchart. A flowchart of the different phases of the systematic review.

analysis, and multivariable analysis in five studies (see Supplementary material online, *Tables S5 and S6*). The quality of studies according to the NOS was excellent, with seven studies achieving 9/9 and nine achieving 8/9 stars (see Supplementary material online, *Table S7*).

Quantitative data synthesis

The pooled estimate from the 16 studies (*Figure 2*) found that oral β-blockers compared with no oral β-blockers were associated with a 26% reduction in the risk of all-cause mortality [rate ratio (RR) 0.74, 95% CI 0.64–0.85] with moderate between study heterogeneity ($I^2 = 67.4\%$). The funnel plot visually showed the possibility of bias or small-study effect (*Figure 3*) confirmed by the Egger's test ($P = 0.001$). The trim and fill simulation method suggested seven studies as missing, and the imputed point estimate was altered (adjusted RR 0.90, 95% CI 0.77–1.04). This indicates a change in magnitude and significance of the pooled effect after correction for publication bias or small-study effect. The cumulative meta-analysis starting with the largest study showed no effect, with increasing effect as the smaller studies were accumulated (*Figure 4*).

According to the pre-specified subgroup analysis (*Table 2*), the stratified pooled meta-analyses demonstrated no substantial differences in effect of oral β-blockers on all-cause mortality.

We extended the analyses with meta-regression, and the results are presented in *Table 3*. One covariate was associated with mortality risk; the patient related variable 'mean age of the cohort' showing decreasing effect of β-blockers on mortality with increasing age of the patients accounting for 31.5% of between study heterogeneity. Of note is that neither subtype of AMI, LVEF, history of HF, length of follow-up, concomitant medical therapy, or ethnicity of the cohort was significantly associated with mortality.

The robustness of the primary result obtained from the 16 studies was supported in the influential analysis. When omitting one study at a time from the meta-analysis a stable pooled estimate was shown (see Supplementary material online, *Table S8*).

Discussion

This meta-analysis of 16 cohort studies comprising 189 385 patients following AMI of whom only a minority had reduced LVEF and/or

Table 3 Meta-regression model between risk of all-cause mortality and the different patient-and study-level variables

Covariates	N	Level	β-Coefficient	Standard error	t	P-value	$^a\tau^2$	^{b}Heterogeneity (%)
None	16	—	-0.3105	0.0794	-3.91	0.001	0.05396	—
ST-elevation myocardial infarction	16	1/0	-0.0649	0.1674	-0.39	0.704	0.05861	-8.63
PCI	16	1/0	-0.1325	0.1625	-0.82	0.429	0.05621	-4.16
Median follow-up time	16	Years	0.0064	0.0597	0.11	0.917	0.06240	-15.65
Mean left ventricular ejection fraction	10	Percent	0.0133	0.0379	0.35	0.734	0.08332	-18.63
Mean age of patients in the cohort	16	Years	0.0530	0.0245	2.16	0.049	0.03697	31.48
Frequency in cohort								
Men	16	Percent	-0.0130	0.0252	-0.52	0.614	0.06012	-11.42
Diabetes mellitus	16	Percent	0.0051	0.0094	0.54	0.596	0.06396	-18.53
Hypertension	16	Percent	0.0081	0.0050	1.63	0.125	0.05842	-8.27
Smokers	15	Percent	-0.0052	0.0045	-1.15	0.270	0.06757	-11.18
Previous MI	13	Percent	-0.0037	0.0184	-0.20	0.843	0.06657	-13.04
Heart failure	11	Percent	0.0109	0.0080	1.35	0.209	0.04209	-14.71
ASA	13	Percent	-0.0077	0.0102	-0.76	0.463	0.04577	-12.21
Statin	15	Percent	-0.0011	0.0039	-0.30	0.772	0.04979	-18.09
ARB/ACEi	15	Percent	-0.0014	0.0029	-0.49	0.633	0.05040	-19.55
Country (Asia vs. USA/Europe)	16	1/0	-0.0789	0.1651	-0.48	0.640	0.05978	-10.79
Prospective timing of the study	16	1/0	-0.1415	0.2901	-0.49	0.633	0.05640	-4.52
Propensity score analysis	16	1/0	-0.0160	0.1778	-0.09	0.930	0.06191	-14.73

$^a\tau^2$ = between study variance.
^{b}The heterogeneity accounted by the covariate included in the random effect meta-regression.

clinical HF found that the use of oral β-blockers was associated with a reduction in the risk of all-cause mortality. However, publication bias or small-study effect was found to influence the result with diluted effect seen after correction of small-study effect. Heterogeneity could be explained by the patient related variable mean age of the cohort.

β-Blockers have long since been a pharmacotherapy for the management of AMI, but currently their role in the treatment of AMI could be called into question. In the 1980's, after a series of randomized controlled trials showed improved outcomes and reduced mortality, β-blockers were approved for the treatment of AMI.[5,6,35] However, these trials preceded the reperfusion era and enrolled mainly patients with large infarcts and/or HF. Meta-analyses of recent observational studies of the impact of β-blockers after AMI on mortality suggest a beneficial effect.[36,37] Misumida et al.[36] included six subgroups of patients with preserved LVEF, treated with primary PCI for STEMI (n = 10 857). In this selected population, oral β-blockers compared with no oral β-blockers were associated with a 21% reduction in all-cause mortality. Huang et al.[37] included ten studies of whom the majority had STEMI, and eight with early revascularization to find that β-blockers were associated with a reduced risk of all-cause mortality for all subgroups, except those with sample size ≤1000 and those with preserved LVEF. Our study contrasts from Misumida et al. and Huang et al. by including larger studies, and with both STEMI and NSTEMI patients. Therefore, as opposed to the two other studies, this meta-analysis represents a more general post-AMI population with both subtypes of MI where the majority of patients are treated with an oral β-blocker, even in the absence of HF or reduced LVEF.

Our results based upon the largest studies are further supported by a recent registry study of 90 869 Medicare beneficiaries aged ≥65 years who had prescriptions for ACE-inhibitors, ARBs, β-blockers, or statins and survived AMI ≥180 days.[9] Only those patients who were adherent to ACE-inhibitors/ARBs and statins had similar mortality rates to those adherent to all therapies, including β-blockers—suggesting limited additional mortality benefit from β-blockers. The problem with non-adherence to a medication may have been an important confounder. If sicker patients discontinue a medication more commonly than their healthy peers, the benefits of adherence to that medication will be exaggerated. In contrast, the directionality of bias may be the opposite for β-blockers. Those with disease progression and recurrent events may be more adherent to their β-blockers, whereas younger, healthier individuals may be more susceptible to real or perceived β-blocker side effects, and thus less adherent.[38]

The use of β-blockers following AMI is based upon historical evidence and nowadays applied to a different treatment and population landscape. Moreover, international advances in the management of AMI have resulted in a decline in deaths,[39,40] and it is possible that in this context β-blockers may have lost some of their effectiveness.

Limitations

The lack of international consensus about the effectiveness of β-blockers following AMI among patients without HF is, in part, a reflection of the lack of contemporary randomized evidence. Consequently, inferences are left to be drawn from observational data, which have inherent bias. Beyond smaller cohort studies, which (as seen in this study) may impact upon the direction of pooled estimates, cohort studies of the effectiveness of pharmacotherapies are
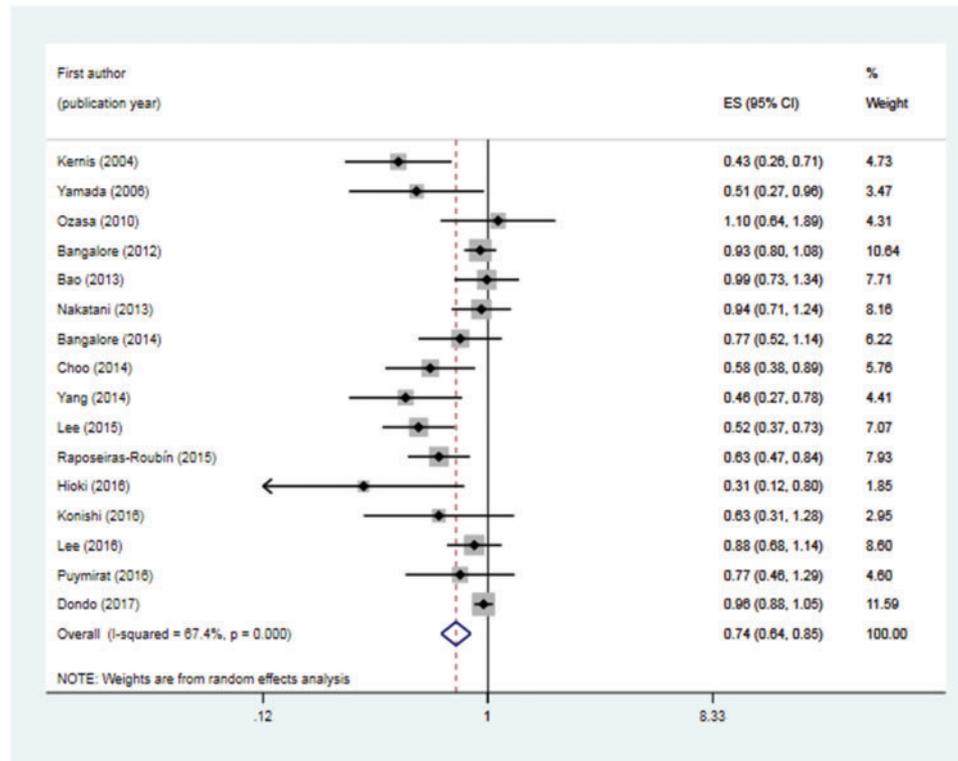
Figure 2 Forest plot for meta-analysis of 16 cohort studies comparing β-blocker therapy with no β-blocker in post-AMI patients on all-cause mortality during follow-up. Weights are from random effects analysis. CI, confidence interval; ES, effect size.
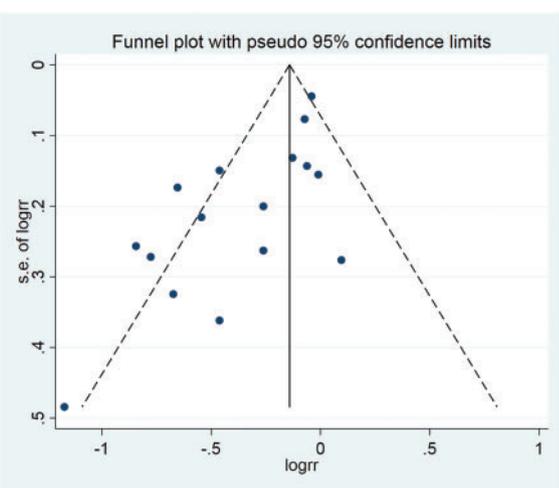

Figure 3 Funnel plot of the 16 cohort studies included in the meta-analysis. logrr, log rate ratio; se, standard error.

weakened by selection and confounding bias as well as missing data. Even though some of the studies included in our meta-analysis used propensity score methods, residual confounding may remain at play.

Our investigation is further limited by publication bias, or small-study effect, which may lead to biased estimates which appear precise.[13]

Compromises were made in this meta-analysis regarding the number of patients with HF in each study. A small percentage of patients had a history of HF (albeit between 20% and 30% in two studies), were in Killip class ≥3 and were assumed to have LVEF <40%. Based upon these, in part incomplete data, we have not been able to express a more clear cut-off for the definition of HF than the statement of a majority of patients being without HF and/or LV systolic dysfunction. In the meta-regression model presented in *Table 3*, neither a history of HF nor mean LVEF was significantly associated with mortality.

We did not have information from the included studies about the type, dose, persistence, and new prescription of β-blockers, which may have skewed their impact on mortality. In the study of Puymirat *et al.*[33] neither type of β-blockers at discharge nor dose was related to mortality after adjustment for age and GRACE score. Similar findings were reported by Goldberger *et al.*[41] who could not demonstrate increased survival in patients treated with β-blockers in doses approximating those used in prior randomized trials compared with lower doses. The authors state, however, that an important caveat for their findings is that they do not represent randomized clinical trial results.
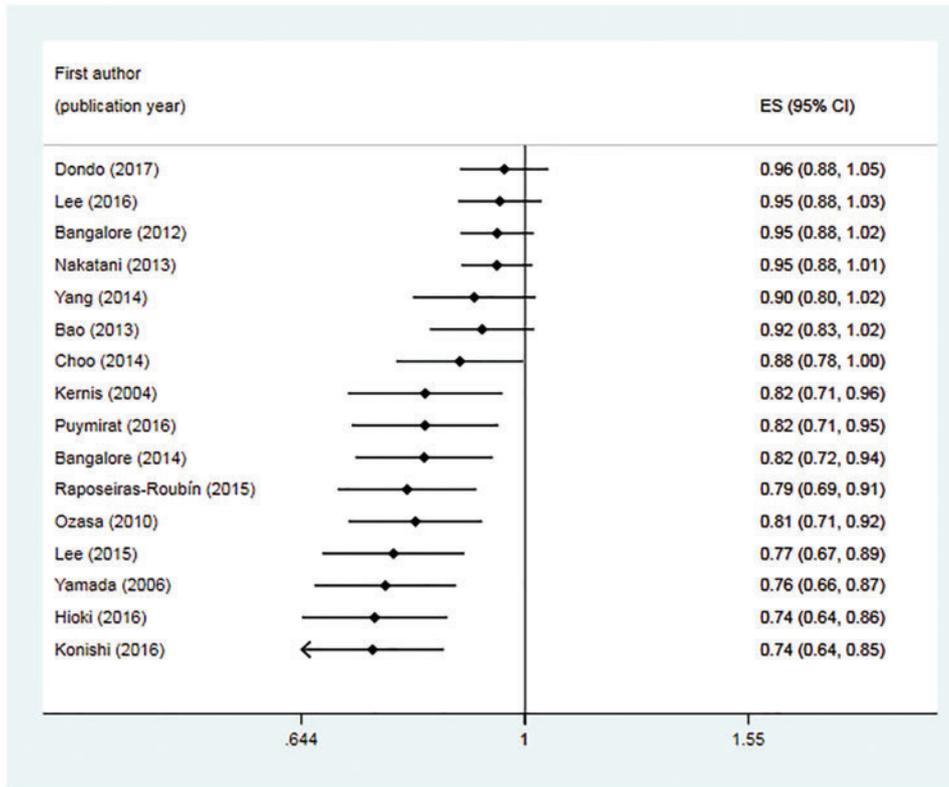
Figure 4 Forest plot for cumulative random effects meta-analysis of 16 cohort studies comparing β-blocker therapy with no β-blocker in post-AMI patients on all-cause mortality during follow-up. The studies are sorted by study size, starting with the largest sized. CI, confidence interval; ES, effect size.

Conclusions

The results from this meta-analysis of nearly 200 000 patients following AMI of whom only a minority had reduced LVEF and/or clinical signs of HF, provides evidence that the association between β-blockers and long-term survival is due to small study effect, and that there might not be a significant reduction in the risk of all-cause mortality when controlling for bias. To be conclusive as for the efficacy of β-blockers on mortality in patients without HF following AMI, randomized controlled trials are a necessary next step.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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