### Additional file 2: Overview of meta-analyses regarding beta-blocker therapy after myocardial infarction

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| Title, author, year | Inclusion criteria*Type of studies**Sample size**STEMI/NSTEMI/MI**Follow up duration* *Reperfusion status**Other inclusion criteria* | Characteristics of meta-analysis*Type and number of studies included**Number of patients* *STEMI/NSTEMI/MI**Reperfusion status**Follow up duration (mean/median, range)**Other characteristics of interest* | Outcomes*Primary outcome**-Results**Secondary outcomes* | Subgroup analyses*LVEF**Long term follow up**Subgroup analysis of particular interest* | Conclusion |
| *Title:* Beta-blockade after myocardial infarction: a systematic review and meta regression analysis*Author*: Freemantle et al*Year*: 1999 | *Type of studies included:* RCT’s*Sample size:* NA*STEMI/NSTEMI/MI:* MI*Follow up duration:* >1 day*Reperfusion status:* NA*Other inclusion criteria:* NA | *Type and number of studies:* 82 RCT’s*Number of patients:* 54,234 *STEMI/NSTEMI/MI:* MI *Reperfusion status:* No reperfusion*Follow up duration:* *-Mean/Median*: NA-*Range*: In hospital - 3 years *Other characteristics:* NA | *Primary outcome:* All-cause mortality *-Results:* 23% odds of death in long term trials (95% CI 15% - 31%). 4% reduction in the odds of death in short term trials ( -8% - 15%).*Secondary outcomes:* -Non­fatal reinfarction -Withdrawal from treatment | *LVEF*: No subgroup analysis for preserved LVEF*Long term follow up*: Long term treatment was defined as 6-48 months. Pooled odds ratio of long-term treatment was 0.77, 95% CI 0.69-0.85.  | Beta-blockers are effective in long term secondary prevention after myocardial infarction.  |
| *Title:* Clinical Outcomes with beta-blockers for Myocardial Infarction: A Meta-analysis of Randomized Trials*Author*: Bangalore et al*Year*: 2014 | *Type of studies included:* RCT’s*Sample size:* >100 *STEMI/NSTEMI/MI:* MI*Follow up duration:* NA*Reperfusion status:* NA*Other inclusion criteria:* NA | *Type and number of studies:* 60 RCT’s*Number of patients:* 102,003*STEMI/NSTEMI/MI:* MI*Reperfusion status:* -48 pre-reperfusion studies-12 reperfusion studies (50% of patients received reperfusion (trombolytics, aspirin, statin)) *Follow up duration:* -*Mean*: 10 months -*Range*: In-hospital - 4 years *Other characteristics:* NA | *Primary outcome:* All-cause mortality*-Results:* Overall mortality incidence ratio 0.98, 95% CI 0.92-1.05*Secondary outcomes:* Cardiovascular mortality, sudden death, recurrent myocardial infarction, angina pectoris, heart failure, cardiogenic shock, stroke, and drug discontinuation | *LVEF*: No subgroup analysis for preserved LVEF*Long term follow up*: Long-term efficacy (>1year) were not investigated in the reperfusion era. *Subgroup analysis of particular interest:* Cardiovascular mortality, sudden death, recurrent myocardial infarction, angina pectoris, heart failure, cardiogenic shock, stroke, and drug discontinuation in acute and post-MI trials. Analysis stratified by reperfusion status | Beta-blockers have no mortality benefit but reduce recurrent MI and angina (short-term) at the expense of increase in HF, cardiogenic shock, and drug discontinuation in the reperfusion era. |
| *Title:* Meta-Analysis of Relation Between Oral β-Blocker Therapy and Outcomes in Patients with Acute Myocardial Infarction Who Underwent Percutaneous Coronary Intervention. *Author*: Huang et al*Year*: 2015 | *Type of studies included:* NA*Sample size:* >100 *STEMI/NSTEMI/MI:* MI*Follow up duration:* >3 months*Reperfusion status:* Treated with PCI*Other inclusion criteria:* Oral beta-blocker treatment | *Type and number of studies:* 10 observational studies *Number of patients:* 40,873*STEMI/NSTEMI/MI:* MI*Reperfusion status:* PCI*Follow up duration:* NA -*Mean/Median*: NA *-Range*: 1/2 - 4 years*Other characteristics:* NA | *Primary outcome:* All-cause mortality*-Results:* Adjusted hazard ratio for all-cause mortality 0.76, 95% CI 0.62-0.94*Secondary outcomes:* -Cardiac death -Myocardial infarction -Heart failure admission | *LVEF*: All-cause mortality in patients with preserved LVEF: relative risk 0.76, 95% CI 0.59-1.07.*Long term follow up*: Subgroup analysis with follow-up <1 and >1 year. Efficacy of beta-blocker treatment >1 year after incident MI: relative risk 0.76, 95% CI 0.59-0.98. | The potential benefit of beta-blockers in preventing all-cause death was not similar in all population but was restricted to those with reduced ejection fraction, with low use proportion of other secondary prevention drugs or with none ST-segment elevation myocardial infarction. The association between the use of beta-blockers and improved survival rate was significant in <1-year follow-up duration. Rates of cardiac death, myocardial infarction, and heart failure readmission in patients using beta-blockers were not significantly different from those in patients without beta-blocker therapy. In conclusion, there is lack of evidence to support routine use of b-blockers in all patients with AMI who underwent PCI.  |
| *Title:* Does Oral Beta-Blocker Therapy Improve Long-Term Survival in ST-Segment Elevation Myocardial Infarction with Preserved Systolic Function? A Meta-Analysis*Author*: Misumida et al*Year*: 2016 | *Type of studies included:* RCT’s/observational studies*Sample size:* NA *STEMI/NSTEMI/MI:* STEMI*Follow up duration:* >6 months*Reperfusion status:* Treated with PCI*Other inclusion criteria:* -Preserved LVEF-Available adjusted HR for observational studies or HR in propensity score-matched patients | *Type and number of studies:* 7 observational studies*Number of patients:* 10,857*STEMI/NSTEMI/MI:* STEMI*Reperfusion status:* PCI*Follow up duration:**-Mean/median:* NA*-Range:* 6 months - 5.2 years*Other characteristics:* NA  | *Primary outcome:* All-cause mortality*-Results:* Combined hazard ratio for all-cause mortality 0.79, 95% CI 0.65-0.97 | *LVEF*: Primary analysis of LVEF>40%*Long term follow up*: Primary analysis with follow up duration >6 months | In patients with STEMI undergoing primary PCI, who have preserved LVEF oral beta-blocker treatment was associated with decreased all-cause mortality.  |
| *Title:* Meta-Analysis Comparing Metoprolol and Carvedilol on Mortality Benefits in Patients with Acute Myocardial Infarction*Author*: Li et al*Year*: 2017 | *Type of studies included:* RCT’s*Sample size:* NA *STEMI/NSTEMI/MI:* MI*Follow up duration:* NA*Reperfusion status:* NA*Other inclusion criteria:* Comparison of carvedilol or metoprolol with placebo or RCTs directly comparing carvedilol with metoprolol.  | *Type and number of studies:* 12 RCT’s*Number of patients:* 61,081*STEMI/NSTEMI/MI:* MI*Reperfusion status:* Except for 5 trials not reporting the baseline treatments,all trials adopted guideline-recommended standard therapies for MI, with only 1 trial adopting primary PCI*Follow up duration:**-Mean/median*: NA*-Range:* 0,5 - 40 months*Other characteristics:* NA | *Primary outcome:* All-cause death*-Results:* Carvedilol vs placebo: Risk ratio for all-cause death was 0.73, 95% credible interval 0.47-1.10Metoprolol vs placebo: Risk ratio 0.86, 95% credible interval 0.70-1.00*Secondary outcomes:* A composite cardiovascular events (cardiovascular death, nonfatal re-infarction, and nonfatal stroke), sudden death, cardiovascular death, re-infarction, revascularization, rehospitalization, ventricular arrhythmia, drug discontinuation for all reasons except for death. | *LVEF*: No subgroup analysis for preserved LVEF.*Long term follow up*: No subgroup analysis of long-term efficacy*Other subgroup analysis of particular interest*: Compared with placebo, carvedilol and metoprolol reduced composite cardiovascular events in patients with MI (risk ratio 0.63, 95% credible interval 0.41-0.85 for carvedilol; risk ratio 0.78; 95% credible interval 0.65-0.93 for metoprolol). | Pooled results showed that compared with placebo, carvedilol and metoprolol significantly reduced composite cardiovascular events and re-infarction in patients with MI. However, neither carvedilol nor metoprolol showed significant benefits on all-cause death, cardiovascular death, revascularization, and rehospitalization. Also, no obvious difference was found when comparing carvedilol and metoprolol on primary or secondary outcomes. |
| *Title:* Effect of oral beta-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis*Author:* Dahl Aarvik et al*Year:* 2018 | *Type of studies included:* All study types and sizes*Sample size:* NA *STEMI/NSTEMI/MI:* MI*Follow up duration:* NA*Reperfusion status:* NA*Other inclusion criteria:* -None or only a minority with HF, Killip class over 3 or LVEF<40%.-Studies published after 1. January 2000 | *Type and number of studies:* 16 observational studies *Number of patients:* 164,408 *STEMI/NSTEMI/MI:* MI*Reperfusion status:* 45.9% had PCI/CABG and 72.1% were treated with primary PCI for STEMI.*Follow up duration:**-Median:* 2.7 years*-Range:* 0.5 - 5.2 years*Other characteristics:* NA | *Primary outcome:* All-cause mortality*-Results:* Rate ratio for all-cause mortality was 0.74, 95% CI 0.64–0.85. After controlling for bias the rate ratio was 0.90, 95% CI 0.77–1.04 | *LVEF*: Primary analysis of none or only a minority with HF, Killip class over 3 or LVEF<40%.*Long term follow up*: Primary analysis with a median follow up of 2.7 years | The results from the 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 beta-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. After controlling for bias no mortality effect of beta-blocker therapy was found. |
| *Title:* Beta-blocker therapy reduces mortality in patients with coronary artery disease treated with percutaneous revascularization: a meta-analysis of adjusted results*Author*: Peyracchia et al*Year*: 2018 | *Type of studies included:* Studies with multivariate adjustment*Sample size:* NA *STEMI/NSTEMI/MI:* NA*Follow up duration:* >1 year*Reperfusion status:* Treated with PCI*Other inclusion criteria:* MI or stable angina | *Type and number of studies:* 26 observational studies *Number of patients:* 863,335 *STEMI/NSTEMI/MI:* MI*Reperfusion status:* PCI*Follow up duration:**-Median:* 3 years*-Range:* 1 - 4.3 years*Other characteristics:* Patients suffering from MI or stable angina | *Primary outcome:* All-cause death *-Results:* Risk of all-cause death in patients on beta-blockers after 3 years: odds ratio 0.69, 95% CI 0.66–0.72*Secondary outcomes:* -A composite endpoint of all-cause death or MI-Myocardial infarction  | *LVEF*: Subgroup analysis for all cause death in patients with LVEF>40%, odds ratio 0.79, 95% CI 0.69–0.91*Long term follow up*: After 3 years: odds ratio for all-cause death for patients with MI and stabile angina 0.69, 95% CI 0.66–0.72*Other subgroup analysis of particular interest*: Subgroup analysis for all cause death in patients with MI (odds ratio 0.60, 95% CI 0.56–0.65) and stable angina patients (odds ratio 0.84, 95% CI 0.78–0.91) | After 3 years, long-term risk of all-cause death was lower in patients on beta-blockers, both for acute coronary syndrome and stable angina patients, independently from ejection fraction. The risk of long-term MACE was lower but not significant for acute coronary syndrome patients treated with beta-blockers as in stable angina. Similarly, risk of myocardial infarction did not differ between patients treated with beta-blockers or without beta-blockers. |
| *Title:* Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials*Author*: Cleland et al*Year*: 2018 | *Type of studies included:* RCT’s*Sample size:* Sample > 300 *STEMI/NSTEMI/MI:* NA*Follow up duration:* > 6 months*Reperfusion status:* NA*Other inclusion criteria:* Patients suffering from heart failure | *Type and number of studies:* 11 RCT’s*Number of patients:* 18,637 (819 patients with LVEF$\geq $40%)*STEMI/NSTEMI/MI:* 71.8% and 36.1% of patients with 40–49% and $\geq $ 50% had suffered from a prior MI.*Reperfusion status:* NA*Follow up duration:* -*Median*: 1.3 years-*Interquartile range:* 0.8–1.9 years*Other characteristics:* Patients with heart-failure | *Primary outcomes:* All-cause mortality and cardiovascular death*-Results:* Patients with LVEF<40% in sinus rhythm: -Kaplan Meier plots for unadjusted all-cause mortality (log rank p<0.001) cardiovascular mortality (log rank p<0.001)Patients with LVEF40–49% in sinus rhythm: -All-cause mortality: adjusted HR 0.59, 95% CI 0.34–1.03-Cardiovascular death: adjusted HR 0.48, 95% CI 0.24–0.97-Kaplan Meier plots for unadjusted all-cause mortality (log rank p = 0.042) cardiovascular mortality (log rank p = 0.022)Patients with LVEF$\geq $50% in sinus rhythm: -All-cause mortality: HR 1.79, 95% CI 0.78–4.10-Cardiovascular death: 1.77, 95% CI 0.61–5.14-Kaplan Meier plots for unadjusted all-cause mortality (log rank p = 0.51) cardiovascular mortality (log rank p = 0.57)*Secondary outcomes:* First cardiovascular hospitalization and the composite of cardiovascular death and cardiovascular hospitalization | *LVEF*: Primary analysis stratified by LVEF<40%, LVEF40–49% and LVEF$\geq $50%*Long term follow up*: Kaplan Meyer plot performed with treatment duration up to 3 years.  | For patients with heart failure in sinus rhythm and LVEF <40%, beta-blockers improve left ventricular systolic function and reduce cardiovascular morbidity and mortality. These benefits also apply to patients with LVEF 40–49%. No benefit was seen in patients with LVEF$\geq $50%, but too few patients have been studied in double-blind RCTs to draw firm conclusions on the efficacy or safety of beta-blockers for HFpEF. |
| Systematic reviews of particular interest |
| *Title:* Long-term beta-blocker therapy after myocardial infarction in the reperfusion era: A systematic review*Author*: Hong and Berry*Year*: 2018 | *Type of studies included:* RCT’s, regression cohort or propensity score matched studies*Sample size:* NA*STEMI/NSTEMI/MI:* MI*Follow up duration:* > 1 year*Reperfusion status:* NA*Other inclusion criteria:*-LVEF > 30%-Studies based on data from 1. January 2000 onward | *Type and number of studies:* 8 cohort studies*Number of patients:* 31,501 *STEMI/NSTEMI/MI:* MI*Reperfusion status:* NA*Follow up duration:* -*Median*: 3 years-*Range*: 1-5.2 years*Other characteristics:* NA | Outcomes of interest included all-cause and cardiovascular mortality, nonfatal MI, and nonfatal stroke. | *LVEF*: Primary analysis with LVEF>30%*Long term duration*: Primary analysis with follow up > 1 year | The majority of the included studies in the systemic review failed to demonstrate a benefit in survival or cardiovascular events with long-term beta-blockers (>1 year) in post-MI patients with normal left ventricular function.  |