Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Cardiovascular Disease: study questions use of beta-blockers after MI in people without heart failure or ventricular dysfunction

A prospective cohort study of 179,810 UK adults hospitalised with a myocardial infarction (MI) but without heart failure or left ventricular systolic dysfunction (LVSD) found that beta-blocker use was not associated with a lower risk of mortality at any time point up to one year. The study has many limitations and should be interpreted with caution. Clinicians are advised to follow the current NICE guidelines until these are updated in light of any new robust evidence.

Reference: Dondo TB, Hall, M, West RM, *et al.* β-Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction. J Am Coll Cardiol 2017;69:2710–20

What do we know already?

- The NICE guideline myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease recommends that a beta-blocker should be offered to all patients as soon as possible after an MI, when the person is haemodynamically stable. The beta-blocker should be continued indefinitely in people who have LVSD, and continued for at least 12 months for those who do not have LVSD or heart failure. NICE has recently announced that following a review of the evidence in May 2017, the guideline will be updated and will focus on beta-blocker treatment for patients without left ventricular dysfunction. Topic experts agreed that "the optimum duration of beta-blocker treatment in this group is currently an area of uncertainty for practitioners and this recommendation may need updating in light of the new evidence."
- There is good evidence to support the use of beta-blockers in survivors of acute MI with heart failure as well as in hospitalised patients who are haemodynamically stable. However data for use in people with preserved left ventricular ejection fraction following acute MI are more limited. The majority of studies that have assessed this were conducted when currently used secondary prevention drugs, such as statins, were not available and reperfusion therapy (such as fibrinolysis and primary percutaneous coronary intervention [PCI]) was not used. Very little data on the effects of beta-blockers beyond the first month are available from contemporary randomised trials.[1,2]
- A recently published French observational study of 2,679 patients without heart failure or LVSD found that although early beta-blocker use after MI was associated with a reduction in 30-day mortality, continued use was not associated with a statistically significant reduction in mortality at one year. In addition, discontinuation of beta-blockers at one year was not associated with higher five-year mortality.

What does this evidence add?

- This large prospective observational cohort study used data from the UK's Myocardial Ischaemia National Audit Project (MINAP) to assess the effect of beta-blockers on mortality in people hospitalised with acute MI but without heart failure or LVSD. The study found that although the *unadjusted* one-year mortality was significantly lower among those prescribed beta-blockers at discharge compared with those who were not (4.9% *vs.* 11.2%, p < 0.001), after weighting and adjustment for confounding factors, beta-blocker use was *not* associated with a lower risk of mortality. The lack of association of beta-blockers with survival was apparent one month and six months after hospitalisation, as well as in separate analyses of patients with ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI).
- Although this study has many strengths, including its size (the authors report that it is largest analysis to date on this topic), it has some important limitations:
  - Patients prescribed beta-blockers tended to be younger and have less co-morbidity than those not given beta-blockers. The study authors noted that although their analysis adjusted for many confounders, residual confounding due to unmeasured variables is likely.

- Prescription of beta-blockers was recorded only at discharge and rates of discontinuation, adherence, dose changes or new prescriptions during the year after hospital discharge are unknown.
- Heart failure or LVSD was only assessed using data recorded during the hospital stay and some patients may have developed heart failure in the following year that was not reported. There is good evidence that beta-blockers would have been beneficial for these patients.
- Only patients who survived their hospital stay were included, so the role of beta-blockers taken during the hospital stay was not investigated (e.g. for patients with early arrhythmias complicating acute MI).

- An accompanying editorial notes that the results of the study should be interpreted with "extreme caution" because of the general limitations inherent to observational studies. The authors suggest that the study "should be hypothesis generating and shouldn't change clinical practice. However, this important report highlights the need to reboot the system: the role of beta-blockers in post-MI patients without LVSD needs to be evaluated from scratch".

Study details

Participants:

- This prospective cohort study used data from MINAP, a national registry of patients admitted to hospitals in England and Wales with acute coronary syndrome. The analysis included a total of 179,810 people hospitalised between January 2007 and June 2013, with acute MI but without heart failure or LVSD. Heart failure was defined as a history of heart failure, loop diuretic use during hospitalisation, and/or left ventricular ejection fraction < 30% .
- People who died in hospital were excluded. Other exclusion criteria were age over 100 years, absent mortality data, previous acute MI, angina, PCI, and /or coronary artery bypass graft surgery, previous beta-blocker use, contraindication to beta-blockers.

Intervention and comparison:

- The association between beta-blocker use (recorded at discharge from hospital) and mortality was evaluated using survival time inverse probability weighting propensity score analysis and instrumental variable analysis. The primary outcome was all-cause mortality one year after hospitalisation.
- The data were adjusted for a wide range of potential confounders including sex, socioeconomic deprivation (Index of Multiple Deprivation score), diabetes, hypercholesterolaemia, hypertension, smoking status, family history of coronary heart disease, chronic obstructive pulmonary disease (COPD), peripheral or cerebrovascular disease, discharge medications, mini-Global Registry of Acute Coronary Events (GRACE) risk score variables, cardiologist care.

Outcomes and results:

- Of 91,895 patients with STEMI, 96.4% received beta-blockers, and of 87,915 patients with NSTEMI, 93.2% received beta-blockers.
- Patients who did not receive beta-blockers were older than those who did (mean age 68.6 years *vs.* 63.3 years, $p < 0.001$), less likely to be male (61.7% *vs.* 71.4%, $p < 0.001$) and were more likely to have co-morbidities including diabetes (15.4% *vs.* 11.6%, $p < 0.001$), chronic renal failure (3.2% *vs.* 1.6%, $p < 0.001$), asthma or COPD (20.6% *vs.* 7.8%, $p < 0.001$), peripheral vascular disease (3.3% *vs.* 1.9%, $p < 0.001$), cerebrovascular disease (7.0% *vs.* 3.8%, $p < 0.001$) and an intermediate or high GRACE risk score (76.5% *vs.* 69.8%, $p < 0.001$).
- Overall, 9,373 people died within a year of initial hospitalisation. *Unadjusted* 1-year mortality was significantly lower among people who received beta-blockers compared with those who did not (4.9% *vs.* 11.2%, $p < 0.001$).
- After balanced propensity score analysis, there were 16,683 patients (4,932 STEMI and 11,751 NSTEMI) remaining for analysis. Among this cohort, after weighting and adjustment for confounding factors, there was no significant difference in mortality between beta blocker users and non-users:
  - 1 month after initial hospitalisation for acute MI (average treatment effect [ATE] coefficient 0.47, 95% confidence interval [CI] -2.99 to 3.94, $p = 0.785$)
  - 6 months after hospitalisation (ATE coefficient 0.06, 95% CI -0.35 to 0.46, $p = 0.768$)
  - 1 year after hospitalisation (ATE coefficient 0.07, 95% CI -0.60 to 0.75, $p = 0.827$).
- Findings were similar at 1 year for STEMI (ATE coefficient 0.30; 95% CI -0.98 to 1.58, $p = 0.637$) and NSTEMI (ATE coefficient -0.07, 95% CI -0.68 to 0.54, $p = 0.819$).
- The authors also performed an instrumental variable analysis. "Hospital rates of prescription of guideline indicated treatments (aspirin, $P2Y_{12}$ inhibitors, beta-blockers, statins and ACE/ARBs)" was used as the instrument variable to further assess potential selection bias. The analysis included all 179,810 cases and also found no difference in mortality at 1 month, 6 months and 1 year for patients who received beta-blockers compared with those who did not. This result was consistent across cases of STEMI and NSTEMI.

Level of evidence: Level 2 (limited quality patient-oriented evidence) according to the SORT criteria.
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