Surveillance report 2017 – Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013) NICE guideline CG172

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SurvSurveillance decision

We will plan an update of the guideline on myocardial infarction: secondary prevention (CG172). The update will focus on:

- Beta-blocker treatment for patients without left ventricular dysfunction.

We will also amend the guideline to replace recommendations on alcohol consumption and antiplatelet therapy for people without an indication for anticoagulation. The following amendments will be made:

- Recommendation 1.2.8 will be replaced with a cross referral to the most recent guidance from the Department of Health on how to keep health risks from drinking alcohol to a low level.

- Recommendations 1.3.12–1.3.21 about antiplatelet therapy for people without an indication for anticoagulation will be stood down. The NICE guideline on unstable angina and NSTEMI: early management published in 2010, is currently undergoing update and a cross referral to this guideline will be made after publication.

During surveillance editorial or factual corrections were identified. Details are included in appendix A: summary of evidence from surveillance.

Reason for the decision

Assessing the evidence

We found 55 studies through surveillance of this guideline.

Evidence that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated:

Lifestyle changes after myocardial infarction

- What is the effectiveness of low/moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after myocardial infarction (MI)?

- What is the effectiveness of no/low/moderate alcohol consumption versus high alcohol consumption to improve outcome in patients after MI?
Although no new evidence was identified during the surveillance review, a topic expert highlighted that the current recommendation (1.2.8) is not in line with the latest guidance from the Department of Health. Topic experts were in agreement that recommendation 1.2.8 should be replaced with a cross referral to this guidance.

**Decision:** Recommendations under these questions should be removed. They will be replaced with a cross referral to the most recent guidance from the Department of Health on how to keep health risks from drinking alcohol to a low level.

**Drug therapy – beta-blockers**

- What is the clinical and cost effectiveness of adding a beta-blocker versus placebo to improve outcome in people after an MI i) with and ii) without left ventricular dysfunction and is there an optimal duration?

The 4-year surveillance review identified new evidence on the use of beta-blockers in people without left ventricular dysfunction which may have an impact on current recommendations. The new evidence suggests that long term treatment with beta-blockers in this group of patients may increase the risk of heart failure, cardiogenic shock and drug discontinuation. Furthermore, there may be no mortality benefit of continuing beta-blockers beyond one year. NICE guideline CG172 currently recommends continuing a beta-blocker for at least 12 months after an MI in people without left ventricular systolic dysfunction or heart failure. 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 (1.3.32) may need updating in light of the new evidence.

**Decision:** This question should be updated.

**Drug therapy – antiplatelet therapy for people without an indication for anticoagulation**

- In people with a proven MI in the past who were not initiated on dual antiplatelet therapy (clopidogrel, prasugrel or ticagrelor in combination with aspirin), should this be initiated?
- What is the optimal duration that clopidogrel should be continued in patients after an MI?

Any recommendations relating to antiplatelet therapy for patients without an indication for anticoagulation will potentially overlap with recommendations in NICE guideline CG94, which is currently undergoing update. Topic experts were in agreement that recommendations in this section of the guideline should therefore be stood down and replaced with a link to the updated NICE guideline CG94 once it is published.
Decision: should be removed. The NICE guideline on unstable angina and NSTEMI: early management published in 2010, is currently undergoing update and a cross referral will be made after publication.

**Other clinical areas**

We also found evidence that supports current recommendations on:

- Comprehensive cardiac rehabilitation.
- Factors associated with a person's uptake and adherence to cardiac rehabilitation programmes.
- Interventions to increase engagement and/or adherence to cardiac rehabilitation programmes.
- Health education and information needs.
- Use of ACE inhibitors in people after an MI.
- Use of ACE inhibitors with ARBs in people after an MI.
- Use of antiplatelet therapy in combination with anticoagulant therapy.
- The optimal time for a beta-blocker to be initiated in people who have had an MI.

We found evidence on the off-label use of colchicine and L-carnitine, which are not covered in the guideline. However, the evidence was insufficient to add new recommendations in these areas at this time.

We found evidence on a range of specific psychological interventions to address depression and anxiety in patients with MI, which are not currently advised in the guideline. We also found evidence on omega-3 fatty acids, which the guideline does not currently recommend. However for both of these areas, the evidence was insufficient to impact the recommendations at this time.

We did not find any evidence related to:

- sexual activity
- changing diet
- oily fish consumption
- advice on regular physical activity
- smoking cessation
- weight management
- the optimal time for ACE inhibitors to be initiated in people who have had an MI
- calcium channel blockers
- potassium channel blockers
- aldosterone antagonists in patients with heart failure and left ventricular dysfunction
- coronary revascularisation after an MI
- patients with hypertension.

For any evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision. This included Vorapaxar for reducing atherothrombotic events after a myocardial infarction or in peripheral vascular disease.

**Equalities**

No equalities issues were identified during the surveillance process.

**Overall decision**

After considering all the evidence and views of topic experts, it was decided that a partial update is necessary for this guideline.

See [how we made the decision](#) for further information.
Commentary on selected evidence

With advice from topic experts we selected 2 studies for further commentary.

**Drug therapy – Beta-blockers**

We selected a meta-analysis by Bangalore et al. (2014) and a prospective cohort study by Puymirat et al. (2016) for a full commentary. Both studies add useful data which could impact on current recommendations on beta-blocker treatment after MI in people without left ventricular dysfunction. They are also relevant to research recommendation 2.2, which calls for more evidence on the balance of risks and benefits of long-term beta-blocker use in people without left ventricular dysfunction, particularly in the context of modern acute treatment of MI.

**What the guideline recommends**

NICE guideline CG172 recommends that people without left ventricular dysfunction or heart failure should continue beta-blocker for at least 12 months after an MI. However, if they have had an MI more than 12 months ago, it is not recommended that beta-blockers be offered unless there is an additional clinical indication for a beta-blocker. See the guideline for full details (recommendations 1.3.32–1.3.35).

**Methods**

Bangalore et al. (2014) reported a meta-analysis which compared beta-blockers with controls (placebo/no treatment/other active treatment) in MI patients without left ventricular dysfunction. Four databases were searched without language restrictions and two authors independently reviewed trial eligibility. The quality of the trials was assessed using the Cochrane Collaboration risk of bias criteria, which has 6 components: 1) sequence generation of allocation, 2) allocation concealment, 3) blinding of participants, staff, and outcome assessors, 4) incomplete outcome reporting, 5) selective outcome reporting, 6) and other sources of bias. The primary outcome was all-cause mortality and the secondary outcomes were cardiovascular mortality, sudden death, recurrent MI, angina pectoris, heart failure, cardiogenic shock, stroke, and drug discontinuation.

Trials were classified according to two 'eras' representing different approaches to managing MI. 'Reperfusion era' trials were defined as those that included more than 50% of patients receiving reperfusion either with thrombolitics or with revascularisation or aspirin/statin, otherwise trials were defined as 'pre-reperfusion era' trials. Trials were also classified as acute MI or post-MI. Acute MI trials were defined as those that included patients randomised within 48 hours of symptom onset whilst post-MI trials were those with more than 48 hours after symptom onset.
After stratifying for reperfusion era status, the analysis was performed for the acute MI trials and the post-MI trials separately. A landmark analysis was also performed at 3 time points to investigate the duration of benefit of beta-blocker treatment.

**Results**

There were 60 randomised trials (n=102,003) included in this meta-analysis.

**All-cause mortality**

For the acute MI trials (no. of studies=41, n=79,285), there was a significant interaction for reperfusion era status (p=0.02) where beta-blockers reduced all-cause mortality in the pre-reperfusion era trials (incident rate ratio [IRR] 0.86, 95% confidence interval [CI] 0.79 to 0.94; 48 studies) but not the reperfusion era trials (IRR 0.98, 95% CI 0.92 to 1.05; 12 studies).

A sensitivity analyses was performed to account for the potentially confounding influence of the large COMMIT trial (n=45,852). Results showed the same absence of effect of beta-blockers in the reperfusion era trials when the COMMIT trial was excluded.

Another sensitivity analyses accounted for variation in quality of trials. When the low-quality trials were pooled, results showed that beta-blockers reduced all-cause mortality (IRR 0.82, 95% CI 0.72 to 0.94, p=0.005). However, the pooled results of the high-quality trials showed no effect of beta-blocker on all-cause mortality (IRR 0.96, 95% CI 0.91 to 1.02, p=0.18). The number of studies and the reperfusion status of the trials within this analysis is not reported.

For the post-MI trials (no. of studies=20, n=21,847), beta-blockers were found to significantly reduce all-cause mortality in both the pre-reperfusion era (IRR 0.79, 95% CI 0.71 to 0.86) and the reperfusion era (IRR 0.79, 95% CI 0.72 to 0.87).

**Secondary outcomes**

For the acute MI trials in the pre-reperfusion era, beta-blockers were associated with the following results for the different secondary outcomes:

- Reduction in cardiovascular mortality (IRR 0.87, 95% CI 0.78 to 0.98).
- Reduction in MI (IRR 0.78, 95% CI 0.62 to 0.97).
- Reduction in angina (IRR 0.88, 95% CI 0.82 to 0.95).
• No difference in sudden death, heart failure, cardiogenic shock, or stroke.

For the reperfusion era trials, beta-blockers were associated with the following results for the different secondary outcomes:

• Reduction in MI (IRR 0.72, 95% CI 0.62 to 0.83).
• Reduction in angina (IRR 0.80, 95% CI 0.65 to 0.98).
• Increase in heart failure (IRR 1.10, 95% CI 1.05 to 1.16).
• Increase in cardiogenic shock (IRR 1.29, 95% CI 1.18 to 1.41).
• Increase in drug discontinuation (IRR 1.64, 95% CI 1.55 to 1.73).
• No difference in cardiovascular mortality, sudden death, or stroke.

Results for the post-MI trials were only partially reported. Similar effects were found for the outcome of MI and drug discontinuation, however there were some differences in results for the outcome of heart failure. For post-MI trials, beta-blockers were associated with a significant increase in heart failure in both the pre-reperfusion era (IRR 1.16, 95% CI 1.04 to 1.30) and the reperfusion era (IRR 1.18, 95% CI 1.06 to 1.32).

Landmark analysis: required duration of beta-blockers

For the pre-reperfusion era trials, beta-blockers were associated with a decrease in all-cause mortality at the following time points:

• 30 days (IRR 0.87, 95% CI 0.79 to 0.96).
• Between 30 days and 1 year (IRR 0.79, 95% CI 0.71 to 0.88).
• After 1 year (IRR 0.81, 95% CI 0.66 to 0.98).

The same analysis showed that beta-blockers were also associated with reduced MI between 30 days and 1 year (IRR 0.77, 95% CI 0.64 to 0.91) but no effect was found after 1 year.

For the reperfusion era trials, there was no significant effect of beta-blockers on all-cause mortality at any time point. However, they were found to significantly reduce MI at 30 days (IRR 0.72, 95% CI 0.62 to 0.84).
In summary, pre-reperfusion era trials appear to show a benefit of beta-blockers on all-cause mortality and recurrent MI for a long duration. Whereas the reperfusion era trials indicate that beta-blockers only seem to have a benefit on recurrent MI in the short term. It is not clear whether these trials are acute MI or post-MI.

**Strengths and limitations**

**Strengths**

This is a large study that used Cochrane methodology and had an overall low risk of bias. The primary outcome in this study was all-cause mortality which is directly relevant to the guideline.

**Limitations**

The majority of results were from trials of patients in the acute phase of MI, which is not covered in the scope of this guideline. However, the sensitivity analysis combining acute and post-MI trials yielded largely similar results (full details not reported).

Additionally, the results from the reperfusion era trials were heavily weighted by a single large trial (COMMIT) which used fibrinolysis as the reperfusion strategy. However, the results of the sensitivity analysis indicate similar results when this trial is excluded.

Finally, the majority of the trials included in this meta-analysis had a high risk of bias. A sensitivity analysis was performed to account for this, indicating that the beneficial effect of beta-blockers on all-cause mortality in the acute MI cohort was driven by trials with a high risk of bias. No benefit was observed in trials with low risk of bias.

**Impact on guideline**

This meta-analysis provides further insight into the effect of beta-blockers in patients with and without revascularisation. Trials from the 'pre-reperfusion era' are compared to those in the 'reperfusion era', with results suggesting that patients undergoing reperfusion treated with beta-blockers saw a short term reduction in myocardial infarction and angina, but an increase in heart failure, cardiogenic shock, and drug discontinuation.

NICE guideline CG172 does not currently take into account the pre-reperfusion era status of the evidence when recommending beta-blocker treatment in patients after MI. Given that it is now common practice for patients to undergo some form of revascularisation after MI and other secondary prevention interventions are common, the recommendations may need updating in light
of the results of this study. The results of the landmark analysis provide some further clarification on the optimum treatment duration of beta-blockers in people without left ventricular dysfunction, indicating that any benefits found in this group were short term (30 days). This is applicable to recommendation 1.3.32 and the research recommendation 2.2 and could have the potential to impact this guidance.

Methods

Puymirat et al. conducted a multicentre prospective cohort study (n=2,679) assessing the association between early and prolonged beta-blocker treatment and mortality after acute MI. Data from consecutive patients with acute MI but without heart failure or left ventricular function were taken from a nationwide French registry that covered 223 centres. The registry included details such as cardiovascular history, drug treatment at the time of admission, risk factors, discharge drugs, type and dose of beta-blocker.

The primary outcome was mortality, which was assessed at different time points for consideration in three comparisons: 30 days in relation to early use of beta-blockers (≤48 hours of admission); at one year in relation to discharge prescription; and at five years in relation to one year use. Cumulative hazard ratios were calculated for each covariate. Several analyses were performed on different sets of covariates, these were chosen ad hoc and on the basis of their physiological relevance and potential to be associated with short term and long term mortality. Hazard ratios were then adjusted accordingly using multivariate adjustment.

Results

The registry included 2,679 patients, with 2,050 (76.5%) treated with beta-blockers during the first 48 hours after admission. In total, 2,217 patients were discharged from hospital alive (n with beta-blockers=1,783, n without beta-blockers=434). Of the patients discharged from hospital on beta-blockers, 1,383 had their prescription known at one year (n with beta-blockers=1,230, n without beta-blockers=153).

Mortality at the different time points in relation to beta-blocker treatment are described below.

**Beta-blockers in first 48 hours and 30 day mortality**

For patients who received beta-blockers in the first 48 hours, 30 day mortality was 2.3%. For patients that did not receive beta-blockers, mortality was 8.6% (adjusted hazard ratio 0.46, 95% CI 0.26 to 0.82, p=0.008).
Beta-blockers at discharge and one year mortality

For patients who were discharged taking beta-blockers, one year mortality was 3.4%. For patients that were discharged without beta-blockers, one year mortality was 7.8% (adjusted hazard ratio 0.77, 95% CI 0.46 to 1.30, p=0.32).

Continued beta-blocker treatment at one year and five year mortality

For the patients still taking beta-blockers at one year, five year mortality was 7.6%. For the patients who had stopped taking beta-blockers by one year, five year mortality was 9.2% (adjust hazard ratio 1.19, 95% CI 0.65 to 2.18, p=0.57).

In summary, early use of beta-blockers was associated with a significant decrease in 30 day mortality. Whereas further results for later time-points indicate that prolonged beta-blocker treatment beyond one year is unlikely to increase survival.

Strengths and limitations

Strengths

This study investigates the optimum treatment duration of beta-blockers in patients without left ventricular dysfunction or heart failure after an MI. This is an area of the guideline that requires some clarification and is currently the focus of research recommendation 2.2. The population and the primary outcome of mortality in this study directly match the guideline.

Limitations

Given the observational design of this study, the authors highlighted several important limitations. It was identified that during the acute stage of treatment, the most severely ill patients received beta-blockers less often. This could be a confounding factor not completely adjusted for in the analyses, with the potential to drive the favourable association found between early beta-blocker treatment and mortality. It is also not possible to rule out the possibility that unusual or unmeasured confounders were responsible for the patients discontinuing beta-blockers at discharge and at one year. However, the authors state that that registry data was very detailed and it is unlikely that major confounders were missed.

The study had a limited population size, particularly in the groups with no beta-blockers for each population. This increases the risk of type B error and the underestimation of the potential benefit of beta-blockers.
There may have been bias introduced through the natural tendency of more 'health conscious' individuals to be better at adhering to treatment. This could lead to a bias where drug adherence is associated with higher survival, which could have the potential to impact this study. However, the authors point out that patients discontinuing beta-blockers gave considerably different mortality results to those discontinuing statins (results reported in the paper). This indicates that the results are unlikely to be affected by such a bias.

**Impact on guideline**

This prospective cohort study provides further evidence on the required treatment duration of beta-blockers in patients without left ventricular dysfunction after an MI. The findings directly address research recommendation 2.2. Results showed that early beta-blocker use was significantly associated with reduced 30 day mortality whereas prolonged beta-blocker treatment beyond one year is unlikely to improve survival.

Despite the limitations of the study design, the guideline committee members agreed that this was a useful study that addressed an area of the guideline requiring clarification. Currently, recommendation 1.3.32 states 'continue a beta-blocker for at least 12 months after an MI in people without left ventricular systolic dysfunction or heart failure'. As well as addressing the research recommendation in this area, the results of this study would also impact this recommendation as it clarifies the timeframe in which beta-blockers might be beneficial for this group.
How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of NICE's guideline on myocardial infarction: secondary prevention (CG172) in 2013.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence

We found 54 studies in a search for randomised controlled trials and systematic reviews published between 23 March 2013 and 26 October 2016. We also included 1 relevant study identified by a topic expert.

From all sources, we considered 55 studies to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: summary of evidence from surveillance for details of all evidence considered, and references.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 4-year surveillance review, and the decision was to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.
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