NICE National Institute for Health and Care Excellence

Surveillance report 2016 – Stable angina: management (2011) NICE guideline CG126

Surveillance report

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Surveillance decision

We will not update the guideline at this time.

We will amend the guideline to include a footnote to the recommendations for third-line drug treatments (1.4.11, 1.4.12). This footnote is to make reference to the drug safety updates issued by the MHRA regarding the safety concerns with ivabradine (June 2014 and December 2014) and nicorandil (January 2016).

Reason for the decision

We found 44 new studies through surveillance of this guideline. None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations. Topic expert and stakeholder consultation feedback noted the drug safety updates would not affect recommendations however they would need to be acknowledged in the guideline. We will amend the guideline to include a footnote to the following areas of the guideline:

Anti-anginal drug treatment

- What is the clinical/cost effectiveness of ivabradine for the management of stable angina?

The footnote will make reference to the drug safety updates (June 2014 and December 2014) which highlight the risk of cardiac side-effects and provide advice on the use of ivabradine for the treatment of angina.

- What is the clinical/cost effectiveness of nicorandil for the management of stable angina?

The footnote will make reference to the drug safety update (January 2016) which highlights the risk of ulcer complications and provides advice on the use of nicorandil for stable angina.

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Other clinical areas

We also found new evidence that was not thought to have an effect on current recommendations. This evidence related to diagnostic tests for stable angina, use of clopidogrel as an alternative to aspirin, effectiveness of cardiac rehabilitation programmes, effectiveness and safety of anti-anginal drug treatments, revascularisation, prognostic risk stratification, pain interventions and cardiac syndrome X.

We did not find any new evidence related to general principles for treating people with stable angina or stable angina that has not responded to treatment.

For any new evidence relating to published or ongoing NICE technology appraisals, the guideline surveillance review deferred to the technology appraisal decision.

Overall decision

After considering all the new evidence and views of topic experts and stakeholders, we decided that no update is necessary for this guideline. We will amend the guideline to include a footnote to the recommendations for third-line drug treatments.

See how we made the decision for further information.

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Commentary on selected new evidence

With advice from topic experts we selected 3 studies for further commentary.

Anti-anginal drug treatment – third-line drugs for treatment of stable angina

We selected the SIGNIFY randomised controlled trial by Fox et al. (2014) for a full commentary because the results of this trial indicate potential safety risks associated with ivabradine.

What the guideline recommends

NICE guideline CG126 (1.4.11) recommends if the person cannot tolerate beta-blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs:

- a long-acting nitrate or
- ivabradine or
- nicorandil or
- ranolazine.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.

NICE guideline CG126 (1.4.12) also recommends for people on beta-blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta-blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:

- a long-acting nitrate or
- ivabradine or

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- nicorandil or
- ranolazine.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.

Recommendation 1.4.12 also includes a footnote to use a dihydropyridine calcium channel blocker (slow release nifedipine, amlodipine, or felodipine) when combining with ivabradine.

Methods

The SIGNIFY randomised controlled trial by Fox et al. (2014) examined the effect of ivabradine added to standard therapy in patients with stable coronary artery disease. The primary end point was a composite of death from cardiovascular causes or non-fatal myocardial infarction and the secondary end points were death from any cause, heart rate and change in angina symptoms.

Participants (n=19,102) in this randomised, double-blind trial received ivabradine or placebo in addition to standard therapy following a run-in phase to confirm eligibility. Standard therapy consisted of aspirin, statins, ACE inhibitors or beta-blockers. Stable coronary artery disease patients were included if aged at least 55 years, in sinus rhythm and have a resting heart rate of 70 beats per minute or more. Patients must also have at least one of the following major prognostic factors: angina pectoris of class 2 or higher on the Canadian Cardiovascular Society (CCS) scale, myocardial ischemia within the previous year, or hospital discharge following a major coronary event within the previous year or two of the following minor prognostic factors: a high-density (<40mg per decilitre) or a low-density (>160mg per decilitre) lipoprotein cholesterol level despite lipid-lowering treatment, type 1 or 2 diabetes mellitus, peripheral artery disease, current smoking, or an age of 70 years or more. Patients with evidence of clinical heart failure, left ventricular dysfunction or an unstable cardiovascular condition were excluded. A pre-defined subgroup analysis of patients with angina at baseline of class 2 or higher (activity limiting angina) on the CCS scale consisted of 12,049 participants.

Results

In the whole population, the incidence of the primary end point, composite of death from cardiovascular causes or non-fatal myocardial infarction, was not significantly different for

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ivabradine treatment compared with placebo (6.8% and 6.4% respectively; Hazard Ratio (HR) 1.08, Confidence Interval (95% CI) 0.96 to 1.20, p=0.20). Components of the primary end point, death from cardiovascular causes (HR 1.10, 95% CI 0.94 to 1.28, p=0.25) and non-fatal myocardial infarction (HR 1.04, 95% CI 0.90 to 1.21, p=0.60) were not significantly different between the ivabradine and placebo groups. The incidence of the secondary end point, rate of death from any cause, was not significantly different between the two treatment groups (HR 1.06, 95% CI 0.94 to 1.21, p=0.35).

In the subgroup analyses, the incidence of the primary end point was significantly different for ivabradine treatment (7.6%) compared with placebo (6.5%) among patients with angina of class 2 or higher on the CCS scale (HR 1.18, 95% CI 1.03 to 1.35, p=0.02). Components of the primary end point, death from cardiovascular causes (HR 1.16, 95% CI 0.97 to 1.40, p=0.11) and non-fatal myocardial infarction (HR 1.18, 95% CI 0.97 to 1.42, p=0.09) were not significantly different between the treatment groups for the subgroup of patients with angina of CCS class 2 or higher. Improvements in the CCS angina class were significantly different at 3 months between the ivabradine (24%) and placebo (18.8%) groups in the subgroup of patients with angina of CCS class 2 or higher (p=0.01).

The incidence of adverse events for all participants was significantly higher (p<0.001) in the ivabradine group (73.3%) compared to the placebo group (66.9%). Ivabradine was associated with significant (p<0.001 for all comparisons) increases in the frequency of symptomatic bradycardia (7.9% with ivabradine and 1.2% with placebo), asymptomatic bradycardia (11% with ivabradine and 1.3% with placebo) and atrial fibrillation (5.3% with ivabradine and 3.8% with placebo). No further statistical information was provided for these adverse event outcomes.

Strengths and limitations

Strengths

Strengths of this study include:

- A population directly relevant to the guideline
- A study methodology with low risk of bias through the use of randomisation, double-blinding and complete outcome data
- Subgroup analyses reporting outcome data of further relevance to the guideline.

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Limitations

The authors acknowledge a relatively low incidence of the primary end point considering the high prevalence of risk factors in the study population. This is potentially explained by the patients already receiving standard therapy.

Although the incidence of adverse events, most notably bradycardia, was found to be higher in the ivabradine group, the trial included the use of treatment doses above the American College of Cardiology/American Heart Association and the European Society of Cardiology clinical guideline recommendations. This level of incidence of adverse events may be less generalisable to clinical practice where lower dose recommendations of ivabradine are followed.

Impact on guideline

The new evidence indicates that although ivabradine added to standard therapy did not improve outcomes for this study population, it also shows less favourable outcomes for ivabradine as an add-on treatment. This conclusion is consistent with current recommendations to offer first-line medical therapy before consideration of ivabradine for patients with stable angina. The results of this trial are unlikely to impact on the recommendations in NICE guideline CG126 however the safety concerns regarding adverse cardiac events are notable. The Medicines and Healthcare products Regulatory Agency (MHRA) issued two drug safety updates (June 2014 and December 2014) on the risks of adverse events associated with ivabradine. They note further advice for healthcare professionals to follow guideline recommendations regarding the commencement of ivabradine, dose regimens and the need to monitor heart rate.

The new evidence provides useful data to a previously limited evidence base for third-line drugs for the treatment of stable angina. However, other third-line drugs are yet to be studied in comparable large trials to determine whether they are also associated with safety concerns.

Anti-anginal drug treatment – third-line drugs for treatment of stable angina

We selected the TERISA randomised controlled trial by Kosiborod et al. (2013) for a full commentary because the results of this trial provide data in an otherwise limited evidence

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base and for a subgroup of people with diabetes who may need special consideration.

What the guideline recommends

NICE guideline CG126 (1.3.6) considers angiotensin-converting enzyme (ACE) inhibitors for people with stable angina and diabetes.

NICE guideline CG126 (1.4.11) recommends if the person cannot tolerate beta-blockers and calcium channel blockers or both are contraindicated, consider monotherapy with one of the following drugs:

- a long-acting nitrate or
- ivabradine or
- nicorandil or
- ranolazine.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.

NICE guideline CG126 (1.4.12) also recommends for people on beta-blocker or calcium channel blocker monotherapy whose symptoms are not controlled and the other option (calcium channel blocker or beta-blocker) is contraindicated or not tolerated, consider one of the following as an additional drug:

- a long-acting nitrate or
- ivabradine or
- nicorandil or
- ranolazine.

Decide which drug to use based on comorbidities, contraindications, the person's preference and drug costs.

Recommendation 1.4.12 also includes a footnote to use a dihydropyridine calcium channel blocker (slow release nifedipine, amlodipine, or felodipine) when combining with ivabradine.

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Methods

Kosiborod et al. (2013) conducted a randomised, double-blind, placebo-controlled trial comparing ranolazine to placebo in patients with stable angina and type 2 diabetes mellitus who remain symptomatic despite treatment with anti-anginal drugs. The primary outcome consisted of the average number of weekly angina episodes during treatment. Secondary outcomes included frequency of sublingual nitroglycerin use, number of angina free days, and health-related quality of life. Participants recorded their outcome data on handheld electronic diary devices each day during the trial.

Eligible participants (n=949) were randomised double-blind to receive ranolazine or placebo in addition to standard therapy following a 4-week placebo run-in period. Participants were included with a history of type 2 diabetes and coronary artery disease, together with a minimum 3-month history of chronic stable angina. An existing stable treatment for at least 2 weeks prior to study entry with one or two standard anti-anginal agents (beta-blockers, calcium-channel blockers or long-acting nitrates) was a further requirement for eligibility. Any patients with New York Heart Association functional class III to IV heart failure symptoms, acute coronary syndrome in the prior 2 months, planned revascularisation during the study period, stroke or transient ischemic attack within 6 months prior to screening, uncontrolled hypertension, clinically significant hepatic impairment, prior treatment with ranolazine, and dialysis were excluded from the study.

Results

The incidence of the primary outcome, average weekly angina episodes, during weeks 2 to 8 of treatment was significantly lower (p=0.008) in the ranolazine group (3.8, 95% CI 3.57 to 4.05) compared to the placebo group (4.3, 95% CI 4.01 to 4.52).

The average weekly sublingual nitroglycerin doses during weeks 2 to 8 of treatment were significantly lower (p=0.003) in the ranolazine group (1.7, 95% CI 1.58 to 1.92) compared to the placebo group (2.1, 95% CI 1.92 to 2.31).

The proportion of angina free days during weeks 2 to 8 of treatment was not significantly different (p=0.068) between the ranolazine group (67%) and the placebo group (64%).

The differences from baseline to end of treatment in the health-related quality of life SF-36 Physical Component scores and the proportion of patients achieving at least 50% reduction in weekly angina frequency, although indicating p values <0.05, were not

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deemed statistically significant due to the use of multiple testing procedures. However, the p value threshold for this analysis is not provided.

There were no statistical differences between groups in changes from baseline to end of treatment in the health-related quality of life SF-36 Mental Component score (ranolazine 1 point, 95%CI 0.18 to 1.82 and placebo 1.1 points, 95% CI 0.28 to 1.92, p=0.77) or the Patient's Global Impression of Change score (ranolazine 4 points, 95% CI 3.82 to 4.19 and placebo 3.9 points, 95% CI 3.74 to 4.10, p=0.41).

The incidence of serious adverse events was not significantly different (p=0.51) between the ranolazine group (16 events) compared with the placebo group (20 events). Due to adverse events, a total of 20 patients discontinued from the study (9 from the ranolazine group and 11 from the placebo group).

Strengths and limitations

Strengths

Strengths of this study include:

- A population directly relevant to the guideline
- A study methodology with low risk of bias through the use of randomisation and double-blinding
- Outcome data for a high risk group in an otherwise limited evidence base
- Inclusion of outcome data for a subgroup of patients with diabetes that is of further relevance to the guideline.

Limitations

The authors acknowledge the relatively short 8-week duration of treatment and lack of follow up with the trial. Evidence for third-line drugs for stable angina generally requires a minimum 3-month follow up in accordance with the NICE guideline CG126 clinical guideline scope. The use of a self-report mechanism by participants for the primary outcomes may be prone to bias and there is no indication of reliability or validity tests. Information about the long-term effects of ranolazine in this population remains limited.

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Impact on guideline

The new evidence indicates that although ranolazine added to standard therapy for people with stable angina and diabetes improved outcomes, this effect was modest and the importance unclear. It remains unclear whether the benefits of ranolazine are maintained over a longer duration for this subgroup of people with stable angina and diabetes. The relatively short treatment duration of the study did not allow for a full analysis of mortality outcomes as would be informative for clinical guidelines. The new evidence is unlikely to impact upon recommendations in NICE guideline CG126.

Investigation and revascularisation – treating symptoms not satisfactorily controlled with medical treatment

We selected a network meta-analysis by Windecker et al. (2014) for a full commentary because it compares the effectiveness of initial treatment choice for stable angina.

What the guideline recommends

NICE guideline CG126 (1.5.1) recommends consideration of revascularisation (coronary artery bypass graft or percutaneous coronary intervention) for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment.

Methods

Windecker et al. (2014) conducted a network meta-analysis of randomised controlled trials comparing medical treatment with coronary artery bypass grafting or percutaneous revascularisation in patients with stable coronary artery disease. The analysis only included trials with a follow up duration of minimum 6 months and at least 100 patients per trial arm. Trials in patients with acute myocardial infarction, symptom onset less than 72 hours, use of polymer or carbon coated bare metal stents, or non-approved drug eluting stents were excluded. The study selection resulted in the inclusion of 100 trials with 93,553 randomised patients. The primary outcome was prespecified as all-cause mortality and 95 trials contributed to the analysis. Secondary outcomes were identified as myocardial infarction, a composite of death or myocardial infarction and subsequent revascularisation.

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Results

Analysis of the primary outcome, all-cause mortality, included 95 trials with 93,553 randomised patients.

Coronary artery bypass grafting reduced all-cause mortality compared with medical treatment (rate ratio [RR] 0.80, 95% credibility interval [CrI] 0.70 to 0.91).

Percutaneous coronary intervention with new generation drug eluting stents reduced all-cause mortality compared with medical treatment (everolimus stent: RR 0.75, 95% CrI 0.59 to 0.96; zotarolimus Resolute stent: RR 0.65, 95% CrI 0.42 to 1.00).

All other percutaneous coronary interventions (balloon angioplasty, bare metal stents, and early generation drug eluting stents) compared with medical treatment for incidence of all-cause mortality estimate rate ratios below 1 however remain inconclusive due to 95% credibility intervals containing the null effect line.

Analysis of the secondary outcome, myocardial infarction, included 92 trials with 90,472 randomised patients.

Coronary artery bypass grafting reduced myocardial infarction compared with medical treatment (RR 0.79, 95% CrI 0.63 to 0.99).

All percutaneous coronary interventions compared with medical treatment for incidence of myocardial infarction remain inconclusive due to 95% credibility intervals containing the null effect line.

Analysis of the secondary outcome, composite of death or myocardial infarction, included 88 trials with 89,373 randomised patients.

A reduction for the outcome of composite of death or myocardial infarction was found for coronary artery bypass grafting (RR 0.81, 95% CrI 0.70 to 0.94), balloon angioplasty (RR 0.83, 95% CrI 0.70 to 0.97) and everolimus eluting stent (RR 0.78, 95% CrI 0.63 to 0.96) compared to medical treatment.

Analysis of the secondary outcome, subsequent revascularisation, included 94 trials with 90,282 patients.

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A reduction for the outcome of subsequent revascularisation was found for coronary artery bypass grafting (RR 0.16, 95% CrI 0.13 to 0.20), bare metal stent (RR 0.44, 95% CrI 0.59 to 0.82), paclitaxel eluting stent (RR 0.44, 95% CrI 0.35 to 0.55), sirolimus eluting stent (RR 0.29, 95% CrI 0.24 to 0.36), zotarolimus eluting (Endeavor) stent (RR 0.38, 95% CrI 0.29 to 0.51), zotarolimus eluting (Resolute) stent (RR 0.26, 95% CrI 0.17 to 0.40), and everolimus eluting stent (RR 0.27, 95% CrI 0.21 to 0.35) compared to medical treatment. Risk of subsequent revascularisation with balloon angioplasty was similar to medical treatment (RR 0.97, 95% CrI 0.82 to 1.16).

Strengths and limitations

Strengths

Strengths of this study include:

- The study objective matches NICE guideline CG126 with direct relevance to clinical questions in the scope
- A robust methodology addressing a clearly focused question, appropriate inclusion criteria, multiple sources of evidence using Cochrane methodological filters, and assessment of quality of included trials
- Primary and secondary outcomes are of direct relevance to the guideline.

Limitations

The authors acknowledge that the use of the intention-to-treat principle in their analysis may have impacted on the results by underestimating the true benefits of revascularisation. It is also noted by the authors that some trials included patients with diagnoses not relevant to NICE guideline CG126, however a sensitivity analysis excluding these trials report consistent results. A further limitation highlighted by the authors is the absence of individual patient data resulting in the assumption that event rates remain constant over time and also preventing any subgroup analysis.

Impact on guideline

The new evidence suggests that revascularisation reduces incidence rates of mortality and adverse cardiac events compared with medical treatment alone, particularly for

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coronary artery bypass graft where the reduction is quite large. However, this reduction is modest at best for percutaneous coronary interventions and mostly remains inconclusive for this intervention. The new evidence is unlikely to impact upon the recommendations in NICE guideline CG126 to offer medical treatment initially before consideration of revascularisation.

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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 stable angina: management (2011) NICE guideline CG126.

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'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 29 new studies in a search for systematic reviews and randomised controlled trials published between 10 May 2012 and 26 August 2015. We also considered 4 additional studies identified by members of the Guideline Committee and 2 further studies identified through stakeholder consultation.

Evidence identified in previous surveillance 2 years after publication of the guideline was also considered. This included 9 studies identified by search during the Evidence Update (2012).

From all sources, 44 studies were considered 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: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

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

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Views of stakeholders

Stakeholders commented on the decision not to update the guideline. See appendix B for stakeholders' comments and our responses.

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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The NICE project team would like to thank the topic experts who participated in the surveillance process.

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