ESC European Society of Cardiology

ESC GUIDELINES

Questions and answers on the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes by the Task Force

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Q&A by the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Updated on 2 December 2019

1) What is the role of aspirin in patients without revascularization or myocardial infarction (MI)? In earlier guidelines, aspirin was recommended in all patients with coronary artery disease (CAD).

In the 2019 guideline, it is stated that “Aspirin 75-100 mg daily is recommended in patients with a previous MI or revascularization (I A)” and “Aspirin 75-100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging (IIb C)”.

Previous studies strongly supporting the use of aspirin have been in patients with MI or revascularisation. Recent studies of aspirin in diabetes patients (ASCEND) or those with high risk of cardiovascular disease have shown little or no net benefit of aspirin, so the assumption that anyone with evidence of atherosclerotic disease should be on aspirin has been challenged.

Furthermore, there has been accumulation of evidence supporting intensive lipid-lowering and blood pressure management that makes the role of aspirin even more uncertain in patients with asymptomatic CAD, hence the lower recommendation for aspirin in these patients. Please note that recommendation IIb means that aspirin can still be used in selected patients (low bleeding risk, diffuse atherosclerosis, etc…).

2) In antithrombotic therapy in post-PCI patients with atrial fibrillation or another indication for oral anticoagulants (OAC), 20 mg of rivaroxaban was indicated even though the PIONEER-AF PCI study used a 15 mg dose. Why do the guidelines recommend 20 mg instead of 15 mg?

The guideline states that "in post-PCI patients with AF or another indication for OAC […] who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.) is used in preference to a VKA in combination with antiplatelet therapy” and “When rivaroxaban is used and concerns about high bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke, rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or dual antiplatelet therapy."

The dosing of rivaroxaban was extensively discussed by the Task Force. PIONEER-AF was not powered to demonstrate efficacy of rivaroxaban 15 mg o.d. in stroke prevention. Subsequently AUGUSTUS has provided clearer evidence on the value of full-dose NOAC vs VKA, as well as aspirin vs. no aspirin. The Task Force therefore felt it is appropriate to

recommend the proven doses of NOAC for stroke prevention except in cases where bleeding risk prevails, as indicated by the recommendations.

The guideline also states clearly that the dose could be reduced to 15 mg in patients with high bleeding risk and lesser risk of stent thrombosis or ischemic stroke.

3) In patients with high heart rate the combination of beta blockers and non-DHP CCB is a possible second step option, see Figure 8 summarising the anti-ischemic medication. Is this combination safe, as we have been taught that beta blockers and non-DHP CCBs should not be combined?

The guideline states: "A stepwise strategy for anti-ischaemic drug therapy in CCS is proposed, depending on some baseline patient characteristics. Incomplete responses or poor tolerance at each step justify moving to the next step. The strategy must be adapted to each patient's characteristics and preferences and does not necessarily follow the steps indicated in the figure."

Further, the guideline states: "In some selected patients, non-DHP agents may be combined with beta blockers for the treatment of angina. However, on such occasions they must be used under close monitoring of patients' tolerance regarding excessive bradycardia or signs of HF. Use of non-DHP CCBs in patients with LV dysfunction is not advised."

As emphasised in the guideline text, this suggested stepwise strategy requires adaptation at each step depending on individual patient's tolerance and therapeutic response, not necessarily following the steps indicated in the figure. Moving to the next step may only be considered if the condition in the upper row (e.g. high heart rate) persists together with angina symptoms.

The combination of BB and non-DHP-CCB (possible at step 2) should initially use low doses of each drug, under close monitoring of tolerance, particularly heart rate and blood pressure.

To make sure these issues are clear, we have added footnotes to this figure which has been slightly clarified from its initial version in the main document, pocket guidelines, app and guideline slide set.

4) In Figure 8 summarising the anti-ischemic medication, ivabradine was mentioned as a third step option in patients with high heart rate and in patients with low blood pressure. Is the combination with all beta blockers and non-DHP CCBs safe?

As emphasised in the guideline text, a stepwise strategy is suggested requiring adaptation at each step depending on individual patient's tolerance and therapeutic response. Moving to the next step should only be considered if the condition in the upper row (e.g. high heart rate) persists together with anginal symptoms. The addition of ivabradine after combined beta-blocker should only be considered if a patient remains symptomatic and with a HR> 80 bpm.

Ivabradine exposure is significantly increased when combined with verapamil or diltiazem, which are moderate CYP3A4 inhibitors. Therefore, the combination of ivabradine with non-DHP CCBs is not recommended.

Management of patients with low blood pressure is particularly difficult. Low dose β-blocker or low dose non-DHP-CCB can first be tested under close monitoring of tolerance. The addition of LAN was initially suggested at step 2 but was changed to using ivabradine, ranolazine or trimetazidine, either alone or in combination to the drug used at step 1. However, combination of ivabradine with non-DHP CCBs is not recommended.

To make sure these issues are clear, we have added footnotes to this figure which has been slightly clarified from its initial version in the main document, pocket guidelines, app and guideline slide set.

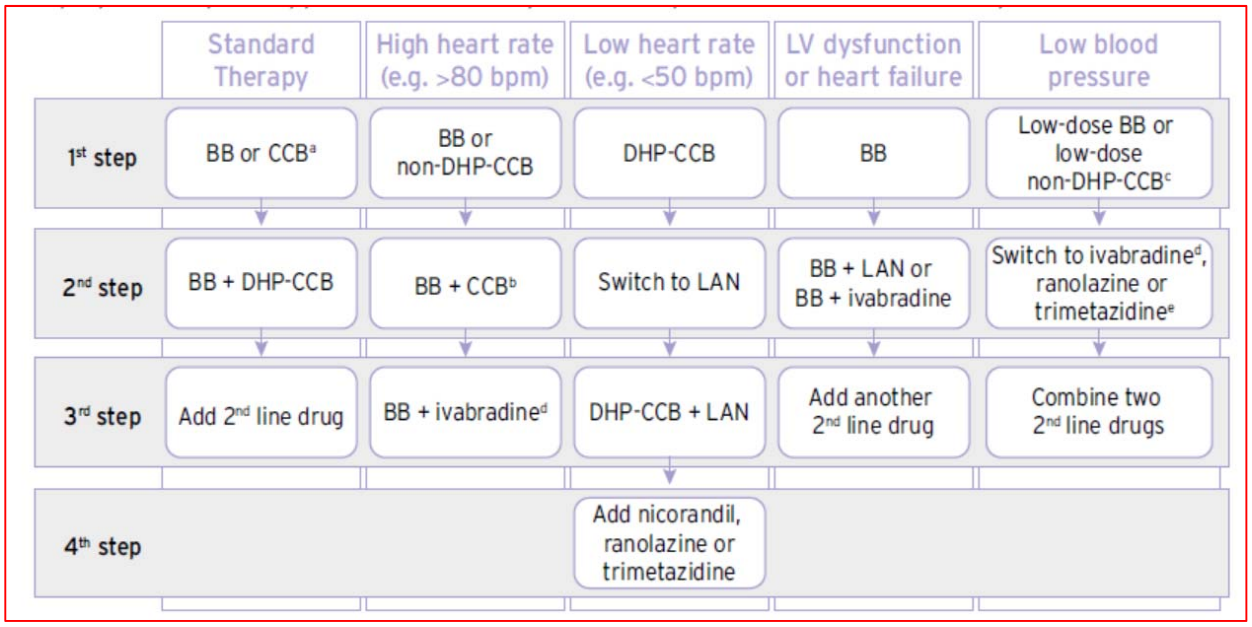

Figure 8 Suggested stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient's characteristics and preferences. Given the limited evidence on various combinations of drugs in different clinical conditions, the proposed options are only indicative of potential combinations and do not represent formal recommendations. BB = beta-blocker; bpm = beats per minute; CCB = [any class of] calcium channel blocker; DHP-CCB = dihydropyridine calcium channel blocker; HF = heart failure; LAN = long-acting nitrate; LV = left ventricular; non-DHP-CCB = non-dihydropyridine calcium channel blocker. [a]Combination of a BB with a DHP-CCB should be considered as first step; combination of a BB or a CCB with a second-line drug may be considered as a first step; [b]The combination of a BB and non-DHP-CCB should initially use low doses of each drug under close monitoring of tolerance, particularly heart rate and blood pressure; [c]Low-dose BB or low-dose non-DHP-CCB should be used under close monitoring of tolerance, particularly heart rate and blood pressure; [d]Ivabradine should not be combined with non-DHP-CCB; [e]Consider adding the drug chosen at step 2 to the drug tested at step 1 if blood pressure remains unchanged.

5) Why was the ORBITA trial not considered in the CCS Guidelines?

The ORBITA study findings were carefully considered during the guideline development and writing process. The main question is whether its results should lead to changes in the clinical guideline recommendations.

The Task Force did not think that a parameter such as exercise time obtained in a population of patients with single-vessel coronary disease and with six weeks of follow-up should change clinical guideline recommendations to perform PCI or not.

The ORBITA trial is an important study and the findings are interesting, but considering the evidence available at the time of writing, it was considered to be premature to make conclusive statements based on this single study.

As the authors themselves stated, ORBITA's findings show that placebo-controlled randomised trials remain necessary. Furthermore, they wrote, "*the findings of ORBITA do not mean that patients should never undergo PCI for stable angina. Not all patients would be satisfied with taking multiple antianginal agents forever. They might prefer an invasive procedure with a small procedural risk for the potential to need fewer medications*."

In the ORBITA trial, the patients who had the placebo procedure had the opportunity to choose to undergo PCI after consultation with their physician. The majority (85%) of sham-arm patients opted for PCI at the end of the 6-week trial period.