VIA MEDICA

REVIEW ARTICLE

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2024 ESC Guidelines on the treatment of chronic coronary syndrome — unanswered questions regarding antianginal medical therapy recommendations. A position paper of the ELECTRA-SIRIO 2 investigators

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Medical Research Journal 2024;
Volume 9, Number 4, 426–430
DOI: 10.5603/mrj.103601

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

According to the 2024 ESC guidelines for the management of chronic coronary syndrome antianginal medical therapy aims to control symptoms while ensuring acceptable tolerability and patient adherence. The guidelines specify the indications for particular groups of antianginal drugs, defining the class of indications and the level of evidence based on the results of expert opinions, registries, clinical studies, and meta-analyses. This very important document has a great impact on clinical practice as it constitutes the basis for therapeutic decisions. Therefore, it is worth understanding the assumptions that guided the authors when formulating specific recommendations. As the investigators of the ELCTRA -SIRIO 2 trial*, we are monitoring new scientific evidence and new guidelines that may impact our study protocol.

Key words: chronic coronary syndrome, antianginal medication

Med Res J 2024; 9 (4): 426–430

According to the 2024 ESC guidelines for the management of chronic coronary syndrome (CCS), antianginal medical therapy aims to control symptoms while ensuring acceptable tolerability and patient adherence [1]. The history of antianginal medications is long and dates back to the 19th century when amyl nitrate (1867) and nitroglycerine (1879) were described [2]. The next therapeutic options — beta-blockers (BBs) and calcium channel blockers (CCBs) — appeared almost 100 years later. The exploration of different pathophysiological mechanisms has led to the introduction of further groups of antianginal drugs: modulators of myocardial metabolism (trimetazidine), ATP-dependent potassium channel openers (nicorandil), If channel inhibitors (ivabradine) and late inward sodium channel inhibitors (ranolazine) [2]. The ESC guidelines specify the indications for particular groups of antianginal drugs, defining the class of indications and the level of evidence based on expert opinions and results of registries, clinical studies, and meta-analyses [1]. However, it has been emphasized that the evidence directly comparing antianginal drugs is limited, in particular there are no large randomized trials directly comparing the first approved antianginal drugs [i.e. BBs or CCBs] with the newer agents (ivabradine, nicorandil, ranolazine, trimetazidine) [1].

This very important document has a great impact on clinical practice as it constitutes the basis for therapeutic decisions. Understanding the assumptions that guided the authors when formulating specific recommendations may be further helpful in deliberate clinical decision-making. The structure of the 2024 ESC guidelines is intended to make it easier for the readers to spot provisions that are new and those that have been revised [1, 3]. The guidelines end with a list of gaps in evidence. Adopting this concept of structure, we decided to analyze the content of all cited documents that became the basis for the current guidelines. As investigators of the ELCTRA-SIRIO 2 trial*, we are monitoring new scientific evidence and new guidelines that may impact our study protocol [4–10]. The study was designed to assess two de-escalation strategies based on ticagrelor dose reduction with or without continuation of ASA versus DAPT with standard dose ticagrelor in reducing clinically relevant bleeding and maintaining anti-ischemic efficacy in ACS patients [11–14].

The current ESC guidelines are an update of the 2019 guidelines [3]. There is a new consensus of experts in the 2024 ESC guidelines to tailor the selection of antianginal drugs according to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost (Class I, Level C). Based on the results of subanalyses of the BEAUTIFUL study, the authors of the 2024 guidelines were consistent that ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF < 40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients (Class IIa, Level B) [1, 15, 16]. Indeed, this study confirmed the benefits of ivabradine far beyond its antianginal effects in patients with coronary artery disease and left ventricular systolic dysfunction. While it is difficult to have any reservations regarding the content of this recommendation, it should be noted that the source publications origin from 2008 and 2009, respectively. Another new recommendation concerning the use of ivabradine was supported by the results of the SIGNIFY study [1, 17, 18]: Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF > 40%, and no clinical heart failure (Class III, Level B); Combination of ivabradine with non-dihydropyridine-CCB or other strong CYP3A4 inhibitors is not recommended (Class III, Level B) [1]. The source publications for this recommendation come from 2014 and 2015.

Two more recommendations have been revised.

First: Long-acting nitrates or ranolazine should be considered as add-on therapy for patients with inadequate control of symptoms while on treatment with BBs and/or CCBs, or as part of initial treatment in properly selected patients (Class IIa, Level B). This recommendation replaces a previous one: nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are inadequately controlled by BBs, CCBs, and long-acting nitrates (Class IIa, Level B). In support of this change the expert consensus by Ferrari et al. (available since 2017) [19] and meta-analysis by Wei et al. (published in 2010) [20] were cited.

Second: Nicorandil or trimetazidine may be considered as add-on therapy for patients with inadequate symptom control despite treatment with BBs and/or CCBs, or as part of initial treatment in properly selected patients (Class IIb, Level B). This recommendation replaces an earlier one from 2019, which stated that in selected patients, the combination of a BB or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment based on heart rate, blood pressure, and tolerance (Class IIb, Level B). The revised recommendation is supported by citations of several reports providing results of clinical studies showing antianginal efficacy of nicorandil [21–26] and trimetazidine [27, 28].

The new guidelines maintain the previously introduced division of antianginal medications into first and second-choice agents, while introducing a preference for long-acting nitrates and ranolazine over nicorandil and trimetazidine in second-choice treatment [1, 3]. This division is difficult to justify substantively, as no direct comparisons between first-choice and second-choice treatments have demonstrated the superiority of one group over the other [29]. Similarly, the results of meta-analyses do not justify the proposed levels of recommendation for antianginal drugs [30]. Moreover, the newer, second-choice agents have more evidence-based and more contemporary clinical data than the traditional first-choice antianginal drugs [2, 19]. Surprisingly, both publications cited in the new guidelines in support of the first recommendation change had been also cited in the previous guidelines in support of the old version of recommendations [19, 20]. Could it be that the experts interpreted the conclusions of these papers differently after 5 years? We undoubtedly deserve an answer to this question. While waiting for the answer, it is worth analyzing what the evidence says. Strangely, the cited publications do not provide any substantive arguments for such changes. Ferrari et al. [19] commenting on the 2019 ESC guidelines conclude: "The little available evidence shows that no antianginal drug is superior to another. (…) Guidelines draw conclusions not from evidence but from clinical beliefs." On the other hand, the meta-analysis by Wei J et al. [20] does not address the content of this recommendation at all, as it only deals with the use of nitrates.

The recommendations that have remained unchanged do not raise any doubts in our opinion, so we list them without comment.

- Short-acting nitrates are recommended for immediate relief of angina (Class I, Level B).
- Initial treatment with BBs and/or CCBs to control heart rate and symptoms is recommended for most patients with CCS (Class I, Level B).
- If anginal symptoms are not successfully controlled by initial treatment with a BB or a CCB alone, the combination of a BB and a dihydropyridine CCB should be considered, unless contraindicated (Class IIa, Level B).
- When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance (Class IIa, Level B).
- Nitrates are not recommended in patients with hypertrophic cardiomyopathy or in co-administration with phosphodiesterase inhibitors (Class III, Level B) [1].

It should be emphasized that in the "gaps in evidence" section the authors of the guidelines state "Because of how evidence has accrued over time, there is no clear evidence about the existence of first- and second-line antianginal therapy. It is unclear whether long-acting nitrates, ranolazine, nicorandil, ivabradine, trimetazidine, or any of their combinations improve anginal symptoms more than BBs or CCBs" [1]. We agree with this statement without reservation. However, we ask ourselves how to relate this statement to the recommendations discussed above.

We also agree that the pathophysiological processes responsible for myocardial ischemia are diverse and usually complex [1]. Therefore, it should be assumed that the efficacy of antianginal medication for reducing symptoms may profoundly depend on the underlying mechanism of the angina [31]. Conversely, it is often difficult to assess which of the ischemic mechanisms is dominant in a specific case. Hence, it seems that the trial-and-error method may prove to be the most effective way of selecting an individual antianginal treatment.

Creating guidelines is certainly a huge challenge for the authors. Questions and even criticism from clinical practitioners like us, who seek not only to know, but also understand the guidelines are inevitable. That is why discussing what we do not understand, and even more, trying to explain it to us, would be particularly valuable. We are pleased to invite those involved in the development of the ESC Guidelines to express their opinions on our position.

*The study was designed as a phase III, randomized, multicenter, double-blind, investigator-initiated clinical study with a 12-month follow-up (ClinicalTrials.gov Identifier: NCT04718025; EudraCT number: 2020-005130-15). This research received financial support from the Medical Research Agency, Poland, Project no. 2019/ABM/01/00009.

Article information

Author contributions: *Jacek Kubica — conceptualization, investigation, writing — original draft preparation; Piotr Adamski — data curation, investigation, writing — original draft preparation; Piotr Buszman — data curation, investigation; Jakub Foryś — data curation, investigation; Robert Gajda — conceptualization, methodology, writing — review & editing; Mariusz Gąsior — methodology, project administration; Marek Gierlotka — methodology, project administration, supervision; Robert Gil — project administration, supervision; Tomasz Hajdukiewicz — resources; Miłosz Jaguszewski*

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Funding: *None.*

Acknowledgments: *None.*

Conflict of interest: *None.*

Supplementary material: *None.*

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