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Editorial

Commentary: The new ESC guidelines for the diagnosis and management of chronic coronary syndromes

Conflict of interests statement

- Prof. Filippo Crea has received Speaker fees from: Menarini, Boheringher Ingelheim, Astra Zeneca, Novartis, BMS, Pfizer, Amgen, Servier.
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Commentary: The new ESC Guidelines for the diagnosis and management of chronic coronary syndromes

During the annual meeting in Paris, the ESC has released the new 2019 Guidelines for the diagnosis and management of chronic coronary syndromes (CCS) [1] that will replace the 2013 Guidelines on stable coronary artery disease [2]. The new terminology used (CCS) describes more accurately, compared to the previous, the different clinical presentations of the disease and is coherent with the term used to describe the acute coronary syndromes.

The 2019 guidelines contain a number of new very positive issues including the central role of non-invasive testing for myocardial ischemia, the fact the optimal medical therapy remains paramount, the importance of myocardial revascularization in patients non responsive to antianginal treatment etc. However, we have also identified some limitations that will be discussed briefly in this commentary.

1. Symptoms and diagnostic flowchart

The first issue is related to the pathophysiology of CCS. One of the main breakthroughs in the past 3 decades has been the demonstration of the multiplicity of mechanisms that can cause myocardial ischemia [3]. Many patients with symptoms and signs of myocardial ischemia have no evidence of obstructive coronary artery disease (CAD) and ischemia can be due to either epicardial vasospasm or coronary microvascular dysfunction [4]. Nowhere in the new guidelines, there is a description of the different pathophysiologic mechanisms leading to CCS. The lack of pathophysiologic clarity translates into the description of symptoms and the diagnostic flowchart. As opposed to patients with obstructive CAD, that often report symptoms fulfilling the criteria for typical angina, patients with vasospastic or microvascular disease present generally with atypical symptoms (rest pain, prolonged episodes, poor response to nitrates etc.). These different presentations reflect different mechanisms of ischemia. Taking into account the multiplicity of mechanisms of myocardial ischemia and the symptoms, one should design a diagnostic flowchart that helps to distinguish among the different groups of patients with CCS as the one recently proposed by Kaski et al. [5].

2. Antianginal treatment

The second issue is related to pharmacological treatment. The 2019 Guidelines on pharmacological treatment of angina represent a clear step forward relative to the 2013 edition particularly concerning the recommendations on event prevention. Emphasis is on lifestyle modifications (*including practical advice on smoking cessation* – "5As" *and diet*), on the use of proton-pump inhibitors as well as on antithrombotic therapy. This last section, which closely resembles the 2017 update on dual antiplatelet therapy in coronary artery disease (CAD) [6], is well detailed and documented, dealing with patients in sinus rhythm, atrial fibrillation or post PCI and provides useful new indications on the duration of dual antiplatelet therapy as well as on the preference of NOACs over Warfarin.

Unfortunately, the same does not apply to the recommendations on anti-ischemic drugs for patients with CCS. The previous Guidelines were criticised for categorising antianginal drugs in first- and second-line treatment without scientific evidence or relation to the underlying pathophysiology of angina and patients' comorbidities [7–11]. The criticism remains for the 2019 Guidelines, which, may cause even more confusion. Here are just a few examples:

First, Beta Blockers (*BB*) and/or calcium channel blockers (*CCBs*) continue to be first step (*instead of first line!*) treatment supported by the highest level of evidence: 1A, a labelling which requires data from multiple randomised clinical trials (*RCT*). However, the text says, "*no RCT to date has compared BB or CCBs to alternative strategies*". Furthermore, the two cited (*old*) studies supporting the **1A** labelling also suggest no superiority of BB or CCBs over the other anti-ischaemic drugs in agreement with a recent (*and not cited!*) systematic review covering 50 years of medical treatment [12].

Second, long lasting nitrates have been, somehow, upgraded to second line step, when a combination of the first step drugs is contraindicated, poorly tolerated, or inadequate to control angina. Only after having tried long lasting nitrates, should the other more contemporary and better studied anti-ischaemic drugs be considered. It is not clear,

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nor explained anywhere in the text the reason for such an upgrade in absence of any evidence.

Third, the laudable attempt to consider the patient's characteristics (*which was not present in the previous Guidelines*) provides curious suggestions. When angina is associated with left ventricular dysfunction or heart failure, BB are, correctly, indicated as first step followed by long lasting nitrates, or Ivabradine as a second step. Whilst the use of Ivabradine on top of BBs is supported by two large CRT [13–15], there is no evidence at all for long lasting nitrates! Once again, an unjustified upgrade.

Fourth, and more troublesome, is the suggestion in patients with angina and high heart rate (*>80 bpm*) or those with angina and low blood pressure (*unfortunately not defined!*) to add Ivabradine (*as a third step*) to BB and non-dihydropyridines (*Verapamil and Diltiazem*) CCBs which is a clear contraindication from the results of a large (*and cited!*) RCT and is reflected in ivabradine's EMA label.

These are just some of the most obvious examples, which, in our opinion, should be immediately corrected to avoid confusion and, in some cases, even malpractice. It is disappointing that the authors of the 2019 Guidelines didn't decide to consider the previous suggestions to avoid hieratical algorithms for the use of anti-ischaemic drugs. In the absence of evidence that one drug is superior to another, it would have been better, as it was done for the Hypertension Guidelines, to leave the choice of treatment to the practitioner according to the pathophysiology of angina or to the comorbidities of the patient.

3. Myocardial revascularization

The third issue is related to myocardial revascularization. It is surprising that the 2019 Guidelines do not provide any table of recommendations on myocardial revascularization. Although the authors note in the text that "new data support a less restrictive indication for revascularization in CCS as compared to previous Guidelines", in Fig. 9 they simply suggest to "consider revascularization on top of medical therapy", while for the discussion of the best choice between revascularization modalities, PCI or CABG, for individual patients, they refer readers to the 2018 ESC myocardial revascularization Guidelines [16].

On the one hand this is wise as the evidence of a symptomatic and prognostic advantage of myocardial revascularization in patients with stable angina is rather flimsy [17] and we are waiting for the results of long-waited ISCHEMIA trial which will shed new light on this important issue [18]. On the other hand, it would have been perhaps better to give a strong recommendation for myocardial revascularization in high risk patients not enrolled in trials comparing optimal medical treatment vs optimal medical treatment plus a percutaneous coronary intervention and including patients with: symptoms refractory to anti-anginal treatment; positive stress test at very low workload; left main stem disease, low ejection reaction.

Another limitation of the 2019 Guidelines is lack of recommendation on the diagnostic work up in patients who have persistence or recurrence of angina after PCI. This is not a rare event as this occurs in about one third of patients after apparently successful PCI and the mechanisms of recurrence are multiple including structural and functional causes [19].

References

[1] Task Force MembersG. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, A. Budaj, R. Bugiardini, F. Crea, T. Cuisset, C. Di Mario, J.R. Ferreira, B.J. Gersh, A.K. Gitt, J.S. Hulot, N. Marx, L.H. Opie, M. Pfisterer, E. Prescott, F. Ruschitzka, M. Sabaté, R. Senior, D.P. Taggart, E.E. van der Wall, C.J. Vrints, ESC Committee for Practice Guidelines, J.L. Zamorano, S. Achenbach, H. Baumgartner, J.J. Bax, H. Bueno, V. Dean, C. Deaton, C. Erol, R. Fagard, R. Ferrari, D. Hasdai, A.W. Hoes, P. Kirchhof, J. Knuuti, P. Kolh, P. Lancellotti, A. Linhart, P. Nihoyannopoulos, M.F. Piepoli, P. Ponikowski, P.A. Sirnes, J.L. Tamargo, M. Tendera, A. Torbicki, W. Wijns, S. Windecker, Eur. Heart J. 34 (2013) 2949–3003.

[2] J. Knuuti, W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, E. Prescott, R.F. Storey, C. Deaton, T. Cuisset, S. Agewall, K. Dickstein, T. Edvardsen, J. Escaned, B.J. Gersh, P. Svitil, M. Gilard, D. Hasdai, R. Hatala, F. Mahfoud, J. Masip, C. Muneretto, M. Valgimigli, S. Achenbach, J.J. Bax, ESC Scientific Document Group, 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, Eur. Heart J. (2019 Aug 31) https://doi.org/10.1093/eurheartj/ehz425pii: ehz425.

[3] P.G. Camici, F. Crea, Coronary microvascular dysfunction, N. Engl. J. Med. 356 (2007) 830–840.

[4] F. Crea, P.G. Camici, C.N. Bairey Merz, Coronary microvascular dysfunction: an update, Eur. Heart J. 35 (2014) 1101–1111.

[5] J.C. Kaski, F. Crea, B.J. Gersh, P.G. Camici, Reappraisal of ischemic heart disease, Circulation 138 (2018) 1463–1480.

[6] M. A Valgimigli, H. Bueno, A.R. Byrne, J.P. Collet, F. Costa, A. Jeppsson, P. Jüni, A. Kastrati, P. Kolh, L. Mauri, G. Montalescot, F.J. Neumann, M. Petricevic, M. Roffi, P.G. Steg, S. Windecker, J.L. Zamorano, G.N. Levine, ESC scientific document group, ESC committee for practice guidelines (CPG), ESC National cardiac Societies, 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of cardiology (ESC) and of the European association for cardio-thoracic Surgery (EACTS), Eur. Heart J. 39 (3) (14 January 2018) 213–260. https://doi.org/10.1093/eurheartj/ehx419.

[7] R. Ferrari, P.G. Camici, F. Crea, N. Danchin, K. Fox, A.P. Maggioni, A.J. Manolis, M. Marzilli, G.M.C. Rosano, J.L. Lopez-Sendon, The "diamond" approach for a personalized treatment OF angina, Nat. Rev. Cardiol. 15 (2) (2018 Feb) 120–132.

[8] R. Pavasini, P.G. Camici, F. Crea, N. Danchin, K. Fox, A.J. Manolis, M. Marzilli, G.M.C. Rosano, J. Lopez-Sendon, F. Pinto, C. Balla, R. Ferrari, Anti-anginal drugs: systematic review and clinical implications, Int. J. Cardiol. 283 (2019 May 15) 55–63.

[9] C. Balla, R. Pavasini, R. Ferrari, Treatment OF angina: where are we? Cardiology 140 (2018) 52–67.

[10] U. Thadani, Management of stable angina — current guidelines: a critical appraisal, Cardiovasc. Drugs Ther. 30 (2016) 419–426.

[11] A.J. Manolis, L.E. Poulimenos, G. Ambrosio, et al., Medicall treatment of stable angina: a tailored therapeutic approach, Int. J. Cardiol. 220 (2016) 445–453.

[12] R. Ferrari, R. Pavasini, P.G. Camici, F. Crea, N. Danchin, F. Pinto, A.J. Manolis, M. Marzilli, G.M.C. Rosano, J. Lopez-Sendon, K. Fox, Anti-anginal drugs–beliefs and evidence: systematic review covering 50 years OF medical treatment, Eur. Heart J. 40 (2) (2019 Jan 7) 190–194.

[13] K. Fox, et al., Ivabradine in stable coronary artery disease without clinical heart failure, N. Engl. J. Med. 371 (2014) 1091–1099.

[14] K. Fox, et al., Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial, Lancet 372 (2008) 807–816.

[15] K. Fox, et al., Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial, Eur. Heart J. 30 (2009) 2337–2345.

[16] F.J. Neumann, M. Sousa-Uva, A. Ahlsson, F. Alfonso, A.P. Banning, U. Benedetto, R.A. Byrne, J.P. Collet, V. Falk, S.J. Head, P. Juni, A. Kastrati, A. Koller, S.D. Kristensen, J. Niebauer, D.J. Richter, P.M. Seferovic, D. Sibbing, G.G. Stefanini, S. Windecker, R. Yadav, M.O. Zembala, 2018 ESC/EACTS Guidelines on myocardial revascularization, Eur. Heart J. 40 (2019) 87–165.

[17] K. Stergiopoulos, W.E. Boden, P. Hartigan, S. Möbius-Winkler, R. Hambrecht, W. Hueb, R.M. Hardison, J.D. Abbott, D.L. Brown, Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischaemia: a collaborative meta-analysis of contemporary randomized clinical trials, JAMA Intern. Med. 174 (2014) 232–240.

[18] ISCHEMIA Trial Research GroupD.J. Maron, J.S. Hochman, S.M. O'Brien, H.R. Reynolds, W.E. Boden, G.W. Stone, S. Bangalore, J.A. Spertus, D.B. Mark, K.P. Alexander, L. Shaw, J.S. Berger, T.B. Ferguson, D.O. Williams, R.A. Harrington, Y. Rosenberg, International Study of comparative health Effectiveness with medical and invasive approaches (ISCHAEMIA) trial: rationale and design, Am. Heart J. 201 (2018) 124–135.

[19] F. Crea, C.N. Bairey Merz, J.F. Beltrame, C. Berry, P.G. Camici, J.C. Kaski, P. Ong, C.J. Pepine, U. Sechtem, H. Shimokawa, Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization, Eur. Heart J. (2019 Jan 4) https://doi.org/10.1093/eurheartj/ehy857.

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