The New ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes: the Good and the Not So Good

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Abstract: During the annual meeting in Paris, the European Society of Cardiology released the new guidelines for the diagnosis and management of chronic coronary syndromes that will replace the 2013 guidelines on stable coronary artery disease. We intend to provide a brief commentary on what, in our opinion, is good and what is not as good. Our careful analysis shows that the 2019 guidelines contain a number of positive innovations, including a new definition, a central role of non-invasive testing for myocardial ischaemia, the most contemporary prevalence of the disease, the fact that medical therapy remains paramount despite the important advances in revascularisation and many other good issues as well as some limitations. The section on medical therapy of chronic coronary syndromes patients shows some inconsistency between text and the suggested scheme as well as contradictions with recommendations of regulatory agencies. It is not immediate to appreciate what is

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good and what is not so good in guidelines, which are often read in a hurry. We have provided a short commentary for the readers who usually concentrate more on the figures and flowcharts rather than on the text. (Curr Probl Cardiol 2021;46:100554.)

Introduction

The recently released European guidelines (2019) for the diagnosis and management of chronic coronary syndromes (CCS) contain several new and revised concepts.[1,2] The guidelines propose the new definition of CCS that replaces coronary artery disease (CAD), redefine the clinical likelihood of having a CCS, address the application of various innovative and more contemporary diagnostic tests, emphasize the crucial role of healthy lifestyle behaviours and other preventive actions and medications, recognise dyspnoea as an equivalent to angina, present a new algorithm for anti-ischaemic medical therapy, cover a more precise use of antiplatelets, antithrombotic and lipid-lowering drugs according to different clinical scenarios, discuss an advanced series of tests to diagnose microvascular angina and highlight the importance of myocardial revascularisation and of coronary sinus constriction in patients with refractory angina.

The aim is to briefly provide comments on the key differences and steps forward in the present 2019 guidelines compared with the previous one.[2]

The New Terminology

The new terminology emphasises the fact that the disease is chronic, often progressive, characterised by long stable and silent periods and it can become unstable at any time. A schematic illustration of the natural history of CCS is provided with an optimistic, unproven role of revascularisation for the stabilisation of the disease.

The term CCS represents a step forward as it describes more accurately than the term CAD, the different clinical manifestations of the disease with an attempt to link different diagnostic and treatment algorithms to each pathophysiological and clinical presentation. The guidelines, however, are mostly dealing with obstruction of epicardial coronary arteries rather than the other conditions (ie, *vasospastic and microvascular angina/ischaemia*), thus minimising the impact of the whole concept. This is a pity because one of the main recent breakthroughs is that different pathophysiological mechanisms contribute to myocardial ischaemia

and CCS. Several patients with signs of myocardial ischaemia and symptoms of angina have no evidence of obstructive coronary artery disease, which can be due to epicardial vasospasm or coronary microvascular dysfunction.[3,4] This corresponds to different clinical scenarios in terms of diagnosis and treatment, which requires separate approaches. The clinical scenarios depicted by the guidelines do not fully reflect clinical practice as comorbidities often influence the choice of the diagnostic test and the medical or surgical management. In the absence of links with the multifaceted aspects of the disease, the substitution of CAD with CCS might remain only a linguistic and semantic improvement, difficult to be adopted by the scientific community.

Diagnostic Steps, Basic Assessments and Risk Calculations

Six steps for the diagnosis of CCS have been proposed.

The first 2 are related to the assessment of the symptoms, general conditions, and quality of life. The third step relates to basic testing: biochemistry, chest X-ray, resting electrocardiogram (ECG) and echocardiogram, the last to provide information on cardiac function and anatomy.

The fourth step relates to the assessment of pre-test probability, which is enriched by the evaluation of the clinical likelihood of having CCS due to an obstruction of the epicardial coronary artery. All these assessments are influenced by the prevalence of obstructive diseases among patients with suspected CCS, which has significantly decreased.[5] This is well documented in the text and is enriched by a schematic representation (Table 5 of the 2019 guidelines), which should always be kept in mind before referring patients for further diagnostic testing. As an example, 50% of the patients previously classified as having an intermediate likelihood of obstructive CAD, today have a probability of <15%, linked to a good prognosis *(<1% annual risk of cardiovascular death or myocardial infarction*). Therefore, fewer patients should be referred for a diagnostic test, thus saving unnecessary procedures and costs. The emerging prevalence of the other forms of ischaemia, such as vasospasm and alteration of the coronary microcirculation are not considered in the equation, probably because of a lack of data.

The guidelines encourage considering the clinical likelihood not only in terms of sex, age and nature of symptoms, as it was done before but also, when available, according to information about risk factors, ECG changes, left ventricular function, calcium score, etc. Another novelty is

the inclusion in the pre-test probability model of patients with only dyspnoea (*without angina*) or dyspnoea as the primary symptom. These algorithms are calculated only for obstructive CAD and not for non-obstructive CAD, which represents a sizeable portion of patients with angina that, unfortunately, have similar long-term outcomes as those with obstructive disease. In addition, the attributable pre-test probability is not derived from population studies but from studies where patients were referred to non-invasive imaging tests like coronary CT angiography. This, per se, represents a bias as these patients already underwent a pre-screening for the likelihood of the disease.

The fifth step relates to the choice of diagnostic test, which is based on patient characteristics and preference, availability, local expertise, etc. Of course, accurate diagnostic testing is more useful when the likelihood is intermediate. There are many diagnostic tests that can be used. Some recommendations, labelled as class 1, are new, including: (1), non-invasive functional imaging (*to detect ischaemia*) or coronary computed coronary angiography (CTA) to detect abnormal coronary anatomy are now recommended as the initial test; (2) functional imaging for myocardial ischaemia should also be performed if the coronary CTA suspects the presence of CCS with uncertain significance or is not diagnostic; (3) invasive angiography is recommended to diagnose CCS in patients with a high likelihood of the disease, severe symptoms refractory to medical therapy with angina at a low level of exercise or when a full clinical evaluation indicates a high event risk and (4) invasive functional assessment by FFR should be performed before revascularisation to ischaemia. There is substantial reconsideration of the role of exercise ECG, which, in 2013, was the central tool for the diagnosis and for the evaluation of symptoms or ischaemia during follow-up.[2] In 2019, exercise ECG is indicated only for risk assessment and it may be considered to control the effective efficacy of the treatment.

Issues related to microvascular and vasospastic angina are considered, although briefly, in a separate part of the guidelines. Microvascular angina should be suspected in symptomatic patients with typical exercise-related angina, evidence of ischaemia in non-invasive tests, and no stenosis or mild-to-moderate stenosis at coronary angiography or CTA. Microvascular angina can be the result of impaired microcirculatory conductance or of arteriolar dysregulation. In the first case, diagnosis should consider, when available, a guidewire-based coronary flow reserve and/or microcirculatory resistance measurements. Alternatively, taking advantage of the new technologies not available in 2013 and not widely available even in industrialised Countries, today transthoracic Doppler

echocardiography of the left anterior descending coronary artery or magnetic resonance or positron emission tomography are all recommended. The diagnosis of vasospastic angina relates to the demonstration of transient ST-segment elevation by ambulatory ECG monitoring during angina, usually at rest. In the positive patients, CTA or coronary angiography is indicated to rule out concomitant coronary stenosis, and, for angiographic documentation of coronary spasm, administration of acetylcholine or ergonovine remains the gold standard.[2]

The sixth step relates to risk assessment. All non-invasive diagnostic modalities are also useful for determination of the risk assessment, which is considered high when the annual cardiovascular mortality is estimated to be >3%. Every patient should undergo cardiovascular event risk stratification, which is particularly useful to identify those patients at high event risk who will benefit from revascularisation beyond the amelioration of the symptoms.

Patient Management

The current guidelines are first considering lifestyle vs pharmacologic management. There is a distinction between anti-ischaemic and preventive drugs, the latter including antiplatelet and antithrombotic drugs.

Lifestyle Management

This section emphasises the usual recommendations: smoking cessation, healthy Mediterranean diet, zero alcohol intake, weight management, and physical activity. Less common recommendations are also properly considered, including the effects of environmental factors, such as avoiding heavy traffic congestion areas, using particulate air filters and encouraging policies to reduce air and noise pollution. The negative effects of psychological factors, such as stress, depression and anxiety, should also be minimised either by proper counselling or even pharmacologically. Equally, advice and counselling related to sexual activity as well as erectile dysfunction, which is often a worry for patients with CCS, should be offered by health care providers. Annual flu vaccination is highly recommended (*evidence level 1, B*), especially in the elderly. The guidelines propose the role of a multidisciplinary preventative team and the increasing role of patient-reported feelings and outcome measures to provide relevant personalised and psychosocial information and possible solutions. This is important, as today, the patient's voice is more and more considered by other patients, sometimes even more than that of doctors.

Preventive Drugs

The goal is to prevent the progression of atherosclerosis of the epicardial coronary arteries and consequently thrombus formation and to prevent coronary spasm in case of vasospastic angina.

To slow down progression or even to avoid new onset of atherosclerosis in CCS patients, it is important to maintain normal function and continuity of the endothelium of the coronary arteries. This can be achieved with drugs that reduce cholesterol levels and blood pressure and, at the same time, exert direct effects on the endothelium.[6] As for cholesterol levels, the goal is to reduce low-density lipoprotein cholesterol by, at least, 50%. Actually, the guidelines on the management of dyslipidaemia (*also presented in Paris*) have further reduced the level to 55 mg/dL.[7] When statins are not sufficient to reach the goal, ezetimibe is highly recommended (*level 1, B*). A proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor is highly indicated in patients at high risk who do not achieve lipid goals with statins and ezetimibe (*level 1, A*).

Inhibitors of the renin-angiotensin enzyme (*ACE inhibitors*) need to be prescribed together with lipid-lowering therapy in patients at high risk or in patients with diabetes, hypertension, left ventricular dysfunction or heart failure. Unfortunately, even the current guidelines continue to mention (*although in brackets*) the phrase '*ACE inhibitor or angiotensin receptor blockers*' *(ARBs), in case of 'intolerance'* without any definition of the word *'intolerance'*, which, in the real world, is synonymous with a cough (*often unrelated to ACE inhibition*). It follows that, often and for various reasons unrelated to a real intolerance to ACE inhibitors, ARBS, which do not prevent myocardial infarction and cardiovascular death, are prescribed instead of ACE inhibitors. The problem is not related to the use of the ARBs, but rather to the deprivation of the evidence-based cardioprotection of ACE inhibitors.[8-10] There is no role for hormone replacement therapy.

As for the prevention of thrombus formation, aspirin (75-100 mg) continues to be highly recommended (*level 1, A*), independently from a history of myocardial infarction. The guidelines consider different scenarios according to whether the patients are in sinus rhythm or in atrial fibrillation or whether they have experienced a myocardial infarction or not. For those in sinus rhythm without a previous myocardial infarction, there is more room for clopidogrel (75 mg daily) as an alternative to aspirin. Clopidogrel, together with aspirin, is recommended if there is a history of peripheral artery disease, ischaemic stroke, or transient ischaemic attack and/or in those patients with moderate-to-high risk, provided that the

bleeding risk is low. In case of previous myocardial infarction, dual antiaggregation with aspirin and clopidogrel is indicated after stenting for either 1, 3 or 6 months, depending on the bleeding risk. Prasugrel or ticagrelor are for specific high-risk situations (*complex stenosis of the left main coronary artery or multivessel stenting*). In patients with CCS and atrial fibrillation, non-vitamin K antagonist oral anticoagulants (NOACs) are highly recommended in preference to vitamin K antagonists (VKA) when the CHA_2-DS_2-VASc score is $\geq$2 in males and $\geq$3 in females (*level 1, A*). Eventual addition of aspirin or clopidogrel to long-term oral anticoagulants may be considered in patients in atrial fibrillation with a history of myocardial infarction or at high risk, provided that the risk of bleeding is low. For patients after a percutaneous coronary intervention (PCI) with atrial fibrillation, triple therapy with aspirin, clopidogrel (*but not ticagrelor or prasugrel*) and preferably a NOAC over a VKA should be considered for $\geq$1 month.[11] Finally, the concomitant use of a proton pump inhibitor is highly recommended in these patients.

Anti-ischaemic, Antianginal Drugs

This is the most controversial part of the new guidelines. In some instance, recommendations contradict the therapeutic information of the drugs provided by the regulatory agencies (*EMA and FDA*). In the text, it is recognised that no randomised clinical trial (RCT) has compared the efficacy of most used anti-anginal drugs, that is, β-adrenergic blockers (BB) and calcium channel blockers (CCB), with all the other available ones. Similarly, it is acknowledged that there is no evidence that a BB with a CCB, alone or in combination, is superior to monotherapy with any class of antianginal drugs.[1] This is in agreement with previously published articles, editorials and meta-analyses.[12-17]

It is, therefore, surprising that the 2019 guidelines, despite what is stated in the text, continue, in the absence of new evidence, to recommend a stepwise strategy with first-, second-, even third- and in some instances fourth-line drugs. The first step recommends the use of a BB with level of evidence 1, A, that requires data from multiple RCTs, which, by admission in the text, does not exist! Two articles are cited to support such a high labelling. One study concluded that BBs are not more effective than other antianginal agents.[18] The other is a study in patients with silent ischaemia, again showing no superiority over the other treatments.[19] As a second step, if angina symptoms are not controlled by BBs or dihydropyridine CCBs, it is recommended a combination of the 2, again, without evidence. Then, in the flowchart and in the text, but not in

the figure, it is recommended to consider long-lasting nitrates in case the above combination is inadequate to control angina or is poorly tolerated. This sort of upgrade for long-lasting nitrates in the absence of new supporting studies in the last 10 years is very surprising. It contradicts what is stated in the text: '*There is a paucity of data comparing nitrates with BB or CCB from which to draw firm conclusions about their relative efficacies'*. Only at this stage, the previous second- and now third-line drugs should be considered. This is also surprising as a concern was raised that the so-called second-line drugs were introduced more recently and approved according to the most stringent contemporary protocols with larger sample size, longer follow-up and safety data compared with the first-line drugs.[14,16,17] There are only a few changes for these drugs. Trimetazidine has been upgraded from the previous level of recommendation IIb to IIa in the present ones. This is in keeping with the Heart Failure guidelines recommendations and it is the result of a recent meta-analysis involving 1628 patients, showing that the addition of trimetazidine to other antianginal drugs is beneficial.[20] Ranolazine is not indicated after PCI because of the results of the RIVER PCI trial.[21] Despite 2 well-conducted RCTs on 2300 patients showing that ivabradine is not inferior to atenolol (100 mg) and amlodipine (20 mg) in reducing angina,[22-24] ivabradine remains to be considered as a third step. This is probably because, in 2 large RCTs in patients with CCS, ivabradine failed to improve prognosis, although it reduced the symptoms of angina and improved quality of life.[25,26] However, as stated by the guidelines, none of the antianginal drugs, including BBs, improve prognosis; therefore, it is difficult to understand the entire reasoning about ivabradine. As cited in the text of the guidelines, in 2014, the European Medicines Agency (EMA) reviewed ivabradine indications based on the negative outcome of a sub-study of the SIGNIFY trial in 12,000 patients with angina and stated that the risk-benefit ratio of ivabradine is maintained, contraindicating concomitant use of verapamil and diltiazem.[27,28] This is, actually, a point of concern because the 2019 guidelines, when taking in specific-consideration patients with angina whose heart rate is $\geq$80 bpm, first suggest the use of a BB or a non-dihydropyridine CCB (*verapamil or diltiazem*). Then, as a second step, the combination of the 2 classes of drugs, and, as a third step, the addition of ivabradine. This triple combination is clearly contraindicated by the EMA and is reflected in ivabradine's label. Also the combination of a BB with verapamil or diltiazem is contraindicated, while there is a recent trial on a sizeable amount of patients (*almost 900*) showing safety and efficacy of ivabradine when combined with 50 mg of atenolol in patients with angina.[24]

For patients with angina and left ventricular dysfunction or heart failure, BBs are correctly indicated as the first step, followed by long-lasting nitrates or ivabradine. Whilst there are 2 large RCTs supporting the indication for ivabradine,[25,29-31] there are no data to support long-lasting nitrates in heart failure or left ventricular dysfunction. Finally, for patients with angina and low blood pressure (*which is not defined*), the suggestion of a BB or a non-dihydropyridine CCB (*even if at a low dose*) followed by a low dose of long-lasting nitrates seems unusual since all of these drugs are vasodilators and, therefore, reduce blood pressure. Ranolazine, trimetazidine and ivabradine, which have no effects on blood pressure, are recommended only as a third-line step. It is worth mentioning that, in patients with angina, blood pressure should not be reduced below 120 mm Hg systolic/80 mm Hg diastolic, as there is a J curve.[32,33]

It is somehow disappointing that the authors of the guidelines decided to maintain the previous and highly criticised classification of first- and second-line antianginal drugs. In the absence of superiority of any antianginal agent over another and with equivalence demonstrated only between BBs, CCBs, and I_f channel inhibitors (*ivabradine*), how is it possible to recommend a stepwise algorithm?

In the text of the guidelines, it is mentioned that second-line drugs, under some circumstances, may be used as a first step, but this is in contrast with the figures and flowcharts that attract the attention and the memory of the readers more than the text. It is our opinion that it would have been better to consider all of the available medications as equal and to provide suggestions for the clinicians not through hierarchical algorithms, but according to underlying pathology and comorbidities and allow them to make the most appropriate decision, as has been done for the hypertension guidelines.[33]

The follow-up of patients with CCS under medical treatment with or without revascularisation is well detailed and summarised in an algorithm according to the most common typology of patients. For patients with refractory angina, despite the use of second- and third-line pharmacologic agents and of successful revascularisation, a series of possibilities, including gene therapy, stem cell therapy, neuromodulation and external counterpulsation are mentioned, including the suggestion for coronary sinus restriction based on a recent positive RCT.[34]

Revascularisation

The 2019 guidelines are a bit scant in terms of indications for myocardial revascularisation of CCS patients. The reader is referred to the 2018

ESC myocardial revascularisation guidelines[35] probably related to the absence of new data and to the uncertainty of the symptomatic and prognostic advantage of myocardial revascularisation over medical therapy. There is also a lack of recommendations for a diagnostic work up and appropriate drug treatment in post-PCI patients who have a persistent occurrence of angina. These patients are common and, often, their treatment is a concern, as post-PCI patients usually continue to take the same antianginal drugs prescribed before the procedure, independently from the success of reperfusion. The list of key messages, gaps in evidence (*unfortunately too many*) and of messages on what to do and what not to do is most appreciated, although difficult to remember at a glance.

Conclusions

Each guideline is a step forward compared with the previous version, depending on the availability of new data. In this respect, there is no doubt that the 2019 guidelines should be complemented for the advanced suggestions in terms of diagnosis, preventative measures, antiplatelet and antithrombotic treatment of CCS. Unfortunately, in view of the paucity of data, the antianginal/ischaemic therapy is poorly addressed. The algorithm for medical therapy has been modified without clear scientific basis and, in some instances, against the recommendations of the regulatory agencies. This is a pity as, in our opinion, even in the absence of new data, there was room for improvement and more effort should have been made to link, when possible, treatment to underlying pathologies and patient comorbidities or risk factors.

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REFERENCES

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2019. https://doi.org/10.1093/eurheartj/ehz425.
2. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949–3003. https://doi.org/10.1093/eurheartj/eht296.

3. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *Eur Heart J* 2014;35:1101–11. https://doi.org/10.1093/eurheartj/eht513.
4. Kaski JC, Crea F, Gersh BJ, et al. Reappraisal of ischemic heart disease. *Circulation* 2018;138:1463–80. https://doi.org/10.1161/CIRCULATIONAHA.118.031373.
5. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2019. https://doi.org/10.1093/ehjci/jez054.
6. Valgimigli M, Merli E, Malagutti P, et al. Endothelial dysfunction in acute and chronic coronary syndromes. Evidence for a pathogenetic role of oxidative stress. *Arch Biochem Biophys* 2003;420:255–61. https://doi.org/10.1016/j.abb.2003.07.006.
7. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J* 2019. https://doi.org/10.1093/eurheartj/ehz455.
8. Kim Fox, EURopean trial On reduction of cardiac events with Perindopril instable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782–8. https://doi.org/10.1016/s0140-6736(03)14286-9.
9. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145–53. https://doi.org/10.1056/NEJM200001203420301.
10. The Task Force on ACE-inhibitors of the European Society of Cardiology. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. *Eur Heart J* 2004;25:1454–70. https://doi.org/10.1016/j.ehj.2004.06.003.
11. Valgimigli M, Bueno H, Byrne AR, et al. 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* 2018;39:213–60. https://doi.org/10.1093/eurheartj/ehx419.
12. Thadani Udho. Management of stable angina—current guidelines: a critical appraisal. *Cardiovasc Drugs Ther* 2016;30:419–26. https://doi.org/10.1007/s10557-016-6681-2.
13. Manolis AJ, Poulimenos LE, Ambrosio G, et al. Medical treatment of stable angina: a tailored therapeutic approach. *Int J Cardiol* 2016;220:445–53. https://doi.org/10.1016/j.ijcard.2016.06.150.
14. Ferrari R, Pavasini R, Camici PG, et al. Anti-anginal drugs-beliefs and evidence: systematic review covering 50 years of medical treatment. *Eur Heart J* 2019;40:190–4. https://doi.org/10.1093/eurheartj/ehy504.
15. Balla C, Pavasini R, Ferrari R. Treatment of angina: where are we? *Cardiology* 2018;140:52–67. https://doi.org/10.1159/000487936.
16. Ferrari R, Camici PG, Crea F, et al. The "diamond" approach for a personalized treatment of angina. *Nat Rev Cardiol* 2018;15:120–32. https://doi.org/10.1038/nrcardio.2017.131.

17. Pavasini R, Camici PG, Crea F, et al. Anti-anginal drugs: systematic review and clinical implications. *Int J Cardiol* 2019;283:55–63. https://doi.org/10.1016/j.ijcard.2018.12.008.
18. Shu de F, Dong BR, Lin XF, et al. Long-term beta blockers for stable angina: systematic review and meta-analysis. *Eur J Prev Cardiol* 2012;19:330–41.
19. Davies RF, Habibi H, Klinke WP, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. *J Am Coll Cardiol* 1995;25:619–25. https://doi.org/10.1016/0735-1097(94)00436-t.
20. Peng S, Zhao M, Wan J, et al. The efficacy of trimetazidine on stable angina pectoris: a meta-analysis of randomized clinical trials. *Int J Cardiol* 2014;177:780–5. https://doi.org/10.1016/j.ijcard.2014.10.149.
21. Weisz G, Genereux P, Iniguez A, et al. Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2016;387:136–45. https://doi.org/10.1016/S0140-6736(15)00459-6.
22. Tardif JC, Ford I, Tendera M, et al. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J* 2005;26:2529–36. https://doi.org/10.1093/eurheartj/ehi586.
23. Ruzyllo W, Tendera M, Ford I, et al. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs* 2007;67:393–405. https://doi.org/10.2165/00003495-200767030-00005.
24. Tardif JC, Ponikowski P, Kahan T. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J* 2009;30:540–8. https://doi.org/10.1093/eurheartj/ehn571.
25. Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo controlled trial. *Lancet* 2008;372:807–16. https://doi.org/10.1016/S0140-6736(08)61170-8.
26. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;371:1091–9. https://doi.org/10.1056/NEJMoa1406430.
27. European Medicines Agency. European Medicines Agency recommends measures to reduce risk of heart problems with Corlentor/Procoralan (ivabradine). Available at: https://www.ema.europa.eu/en/news/european-medicines-agency-recommendsmeasures-reduce-risk-heart-problems-corlentorprocoralan. 2019. Accessed March 28, 2019.
28. Ferrari R, Fox K. Heart rate reduction in coronary artery disease and heart failure. *Nat Rev Cardiol* 2016;13:493–501. https://doi.org/10.1038/nrcardio.2016.84. (2016).
29. Fox K, Ford I, Steg PG, 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* 2009;30:2337–45. https://doi.org/10.1093/eurheartj/ehp358.
30. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875–85. https://doi.org/10.1016/S0140-6736(10)61198-1.
31. Fox K, Ford I, Steg PG, et al. Bradycardia and atrial fibrillation in patients with stable coronary artery disease treated with ivabradine: an analysis from the SIGNIFY study. *Eur Heart J* 2015;36:3291–6. https://doi.org/10.1093/eurheartj/ehv451.
32. Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016;388:2142–52. https://doi.org/10.1016/S0140-6736(16)31326-5.
33. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.
34. Verheye S, Jolicoeur EM, Behan MW, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. *N Engl J Med* 2015;372:519–27. https://doi.org/10.1056/NEJMoa1402556.
35. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J.* 2019;40:87–165. https://doi.org/10.1093/eurheartj/ehy394.