Comparison of ESC and ACC/AHA guidelines for myocardial revascularization: are the differences clinically relevant? The European perspective

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In this issue of the *Journal*, Stirrup et al.[1] present an accurate comparison of the American College of Cardiology and American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines for myocardial revascularization. In a user-friendly and well-illustrated format, the authors outline agreement, similarity, and discordance between the final documents drawn by the United States and European task forces. Points where specific equivalent recommendations are lacking are also indicated. The effort of Stirrup et al.[1] is more appreciable considering that, while only two comprehensive European guidelines were needed for the comparison,[2,3] nine ACC/AHA documents were examined and specific points extrapolated.[1]

Before any comments on specific differences potentially relevant, some preliminary considerations seem necessary. The choice of multiple documents of ACC/AHA conveys an impression of division or watertight compartment thinking where a common multidisciplinary approach is needed. The ACC and AHA have developed a rigorous methodology during their partnership lasting more than 30 years and their clinical practice guidelines are direct to a nation with an enough uniform system of care, also if best and worst states for health insurance costs exist. Differently, more than 30 national (also non-European) cardiac societies were actively involved in drafting the 2014 ESC/EACTS guidelines on myocardial revascularization and were encouraged to endorse, translate, and implement the guidelines. However, feasibility and affordability of the national implementation process may substantially vary among European countries in agreement with disparities in cultural, economic, social and political differences, with dissimilarity in university and post-university training, as well public health priority.[4] When health care measures are implemented, the national process can result in priorities different from those expected from the European guidelines alone.[5] Another relevant aspect is the durability of recommendations. As an example, the durability of cardiology guidelines recommendations for procedures and treatments promulgated by the ACC/AHA vary across individual guidelines and levels of evidence. Downgrades, reversals, and omissions are common among class I recommendations not supported by multiple randomized studies.[6] Another limitation of the rigorous methodology of clinical practice guidelines is a long improving development period. To avoid outdated guidelines, focused updates are published by more rapid turn-around time when needed. Noteworthy, some guidelines considered by Stirrup et al.[1] have been recently updated.[7,8] It should be considered that a number of performance measures and appropriateness criteria have been developed. Performance measures are derivative products of the guidelines that serve as tools for measuring quality and to secure health system improvement and accountability. In comparison with the guidelines, the development of appropriate use criteria is more recent. The first appropriateness document was published in 2005,[9] in response to growing utilization and cost of noninvasive cardiovascular imaging and recognition that randomized clinical trials marginally supported its use in guidelines recommendations.

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Recently, appropriate use criteria for coronary revascularization in patients with acute coronary syndromes have been published,[10] while those in patients with stable ischemic heart disease are forthcoming. Therefore, as outlined by the ESC, the guidelines never supersede the responsibility of health professionals. Guidelines can never provide the definitive answers for all possible clinical scenarios and should not be followed slavishly.

Entering the specific differences between the American and European guidelines, many class of recommendations are similar, with differences only in the level of evidence (LOE). However, some points deserve a thorough discussion. The indications for diagnostic imaging in patients with suspected coronary artery disease (CAD) are different for a few aspects. In particular, ESC/EACTS guidelines recommend diagnostic testing in stable CAD only in symptomatic patients and based on the probability of significant disease. In patients with intermediate probability (15%-85%) of CAD, functional testing using stress echocardiography, myocardial perfusion imaging (MPI), magnetic resonance imaging (MRI) or positron emission tomography (PET) is recommended (class I, LOE A for all four modalities), while computed tomography (CT) angiography is considered a class IIa (LOE A) indication. In case of high (>85%) probability of CAD, coronary angiography is recommended (class I, LOE A). The ACC/AHA guidelines look into the recommendation of diagnostic tests in greater detail.[11] Of note, while exercise electrocardiogram (ECG) is not mentioned in the ESC/EACTS guidelines, in the American guidelines it is recommended in patients with interpretable standard ECG (class I, LOE A). Exercise test with nuclear imaging or echocardiography is a class I indication (LOE B) only for patients with non-interpretable ECG. In patients unable to exercise, pharmacological stress MPI or echocardiography should be performed (class I, LOE B). CT angiography is reasonable (class IIa, LOE B) for patients with a low to intermediate pre-test probability of CAD and at least moderate physical functioning or no disabling comorbidity and in those who are incapable of at least moderate physical functioning or have disabling comorbidity. For patients with a low to intermediate pre-test probability of obstructive CAD, non-contrast cardiac CT to determine the coronary calcium content may be considered (class IIb, LOE C) according to ACC/AHA guidelines, while the role of calcium score is not mentioned in the European guidelines. Probably, this point will be addressed in future updates, according to the long-term warranty period of a zero calcium score.[12,13] An important difference in European and American guidelines is that the European guidelines recommend combined or hybrid imaging in symptomatic patients with intermediate probability of CAD, while no specific recommendation is included in the American guidelines. These latter only state that limited evidence were available on hybrid imaging at the time of writing. However, a more recent ACC/AHA update on these guidelines do not still reports a specific indication for hybrid imaging in the diagnostic work-up of patients with suspected CAD.[14]

In patients with low probability of CAD, the European guidelines do not recommend diagnostic imaging (class III, LOE A for stress echocardiography and MPI; LOE C for CT angiography, stress MRI, PET, and combined or hybrid imaging),[2] while in ACC/AHA guidelines diagnostic imaging (exercise and pharmacologic stress MPI, echocardiography or MRI) is a class III indication (LOE C) only in patients with an interpretable ECG capable of at least moderate physical exertion.[11]

A relevant problem for both European and American guidelines is that the indication for ischemia testing are stratified according to the presence or not of symptoms and graded according to selected cut-off of pre-test probability of disease. For the first point, this distinction does not take into consideration that many patients exhibit a myriad of atypical symptoms including dyspnea or heart palpitations, while other patients do not experience any symptoms at all but may have silent myocardial ischemia. For pre-test probability of CAD, many algorithm have been proposed.[11,15–18] Other guidelines recommended imaging patients at intermediate or high CAD risk based on the Framingham risk score.[19] The precise definition of intermediate probability of CAD is somewhat arbitrary. A definition of 10% and 90% was first introduced in 1980 and applied in several studies.[20] Other boundaries have also been proposed and used (i.e., between 15% and 85%, 20% and 80%, or 30% and 70%). In addition, other features should be considered in referring a patient to testing, such as the degree of uncertainty acceptable to the physician and patient; the likelihood of an alternative diagnosis; the accuracy of the diagnostic test selected, test accessibility, procedural cost, and risks of testing; and how tests results impact the therapeutic options and patient prognosis. Also noninvasive testing for ischemia in geriatric patients, young women with atypical angina and asymptomatic diabetic patients is a controversial issue.[1,21,22] With regard to asymptomatic diabetic patients, it has been demonstrated that post-stress left ventricular ejection fraction and stress-induced ischemia by gated MPI predict the temporal characteristic of the patient's cardiac risk at long-term follow-up, with patients with ischemia and ejection fraction ≤45% showing the major risk acceleration in time.[23] Conversely, a meta-analysis of studies including diabetic

patients with known or suspected CAD found a negative predictive value for cardiac death or nonfatal myocardial infarction of normal MPI of 95%, during a weighted mean follow-up of 36 months, resulting in estimated annualized event rate after a negative test of 1.60%, leading to define a ''relatively low-risk'' patients category.[24]

In diabetic patients, both guidelines consider coronary artery bypass grafting (CABG) to be a class I indication; however, according to the European guidelines, in diabetics with stable multivessel CAD and angiographic SYNTAX score $\leq$22, percutaneous coronary intervention (PCI) should be considered (class IIa, LOE B) as alternative to CABG. The rate of CABG is worldwide reducing and in Medicare enrollees the current ratio of PCI to CABG is 3:1. However, there is a great variation in this ratio across countries, with a PCI proportion of 84% in Germany.[25] Economic considerations, preference for less invasive procedures and differences in healthcare system organization may explain the heterogeneity. Given the current guidelines, CABG is probably underutilized in patients with multivessel disease, especially diabetics, still undergoing PCI, whereas CABG may be overused at least in some patients with left main CAD. Noteworthy, both the European and American guidelines recommend (class I, LOE C) for heart team involvement to facilitate and support efficient clinical workflows, particularly for complex CAD, to better evaluate patient comorbidities, surgical risk and long-term outcomes anticipation. Recently we demonstrated that the presence of stress-induced transient ischemic dilation (TID) provides independent and incremental prognostic information for the prediction of cardiac death or nonfatal myocardial infarction in patients with diabetes.[26] The addition of TID to a prediction model based on cardiovascular risk factors, left ventricular ejection fraction and ischemia significantly improves risk discrimination and reclassification for incident cardiac events. The effect of revascularization seems to be influenced by systolic function, stress-induced myocardial ischemia, and TID.

A further difference between European and American guidelines concerns the recommendations on new-generation drug-eluting stents (DES). The European guidelines state that new-generation DES should be considered by default in all clinical conditions and lesion subsets. In addition, the European guidelines state that new-generation DES are recommended over bare metal stents also in patients who may require earlier discontinuation of antiplatelet therapy. Conversely, the American guidelines pose several, strong contraindication to DES use, such as the inability to comply or tolerate a prolonged dual antiplatelet therapy (DAPT). In particular, according to American guidelines, balloon angioplasty or bare metal stents should be used in patients with high bleeding risk, inability to comply with 12 months of DAPT, or anticipated invasive or surgical procedures within the next 12 months, during which time DAPT may be interrupted (class I, LOE B). It should be considered that the American guidelines on PCI used for the comparison were published in 2011.[27] However, these differences were not leveled with updated editions and the 2016 ACC/AHA guidelines focused update on duration of DAPT in CAD patients again states that in current practice, BMS are generally reserved for patients who cannot receive DAPT for $>$1 month for active bleeding, non adherence to medical therapy or planned surgery.[28]

Also the assessment of patients after revascularization according to the presence of symptoms is addressed differently between the European and American guidelines. The European guidelines clearly differentiate between asymptomatic and symptomatic patients. In these latter stress testing is a class I indication for patients with new or worsening symptoms not consistent with unstable angina and stress imaging is preferred over the exercise ECG.[2,3] In asymptomatic patients, the European guidelines state that routine stress testing may be considered (class IIb, LOE C) $>$2 years after PCI and $>$5 years after CABG.[2] The American guidelines consider separately patients with new, recurrent, or worsening symptoms and those asymptomatic (or with stable symptoms). MPI, echocardiography or MRI, with either exercise or pharmacological stress or CT angiography are not recommended by the American guidelines for follow-up assessment of stable patients if performed more frequently than at 5-year intervals after CABG or 2-year intervals after PCI. The American guidelines state that MPI, echocardiography or MRI with either exercise or pharmacological stress can be useful for follow-up assessment at 2-year or longer intervals in stable CAD patients with prior evidence of silent ischemia or who are at high risk for a recurrent cardiac event and are unable to exercise to an adequate workload, or have an non interpretable ECG, or have a history of incomplete coronary revascularization (class IIa, LOE C).[11] Stress imaging is also reasonable in patients who have new or worsening symptoms not consistent with unstable angina and previously required imaging with exercise stress, or have known multivessel CAD, or have a high risk of multivessel CAD (class IIa, LOE B).[11] As clearly reported by Stirrup et al.[1] the other indications for the follow-up of asymptomatic as well symptomatic patients after revascularization are not directly comparable, due to the lack of specific equivalent recommendation.[1,2,11] Our group evaluated the long-term prognostic value of stress MPI performed between 12 and 18 months after

PCI. In a first study, patients were followed for a mean period of 37 ± 16 months.[29] At Cox analysis, the summed stress score ($P < .05$) and summed difference score ($P < .001$) were significant predictors of cardiac death, nonfatal myocardial infarction, and late revascularization procedures. Event-free survival curves showed a higher event rate in patients with than without ischemia ($P < .001$). Noteworthy, the occurrence of events was higher in the presence of ischemia in symptomatic and symptom-free patients (both $P < .001$). We also found that combining clinical variables and stress MPI is useful to characterize the risk of cardiac events and its temporal variation.[30] In particular, parametric survival models seem useful to estimate predicted time to risk and levels of risk at specific intervals after PCI. In another study we assessed predictors and temporal characteristics of cardiac risk in patients referred for stress MPI five years after CABG.[31] At multivariable Cox analysis, ischemia at MPI and diabetes was independent predictors of cardiac death and myocardial infarction. The parametric survival model revealed that the cardiac risk was greater for all time intervals and accelerated more over time in patients with ischemia than in those without ($P < .0001$). Thus, stress MPI performed five years after CABG is useful to characterize the risk of cardiac events and its temporal variation. Larger prospective studies are needed to assess whether stress MPI will have an impact on the outcome in asymptomatic patients after revascularization.[32]

There are probably reasonable grounds to maintain separate European and American guidelines for myocardial revascularization, due to differences in target audiences, health organizations, and resources. However, alignment on levels of evidence from the same sources seems desirable, and may even be facilitated by the decision of the ACCF/AHA toward engaging a separate evidence review committee comprised of methodologists, epidemiologists, and biostatisticians.[33] This process would be clearly enhanced by an appropriately constituted single group derived from both sides of the Atlantic that facilitate optimizing care.[34] The rise in health care costs may hamper the introduction of novel therapeutic approach in some countries. Consequently, it would be desirable to implement an economic framework on investment to address the potential cost-effectiveness of the recommendations. The process for initiating, revising, and updating clinical guidelines is continuously evolving. Major challenges are responding timely to the continually expanding evidence while maintaining rigorous processes and methodology, and bridging the gap between researchers and policy makers.

Disclosure

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