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VIEWPOINT

Cardio-Oncology Guidelines and Strength of the Evidence

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The European Society of Cardiology (ESC) recently published its first guidelines on cardio-oncology in a 133-page document with 837 references.[1] It is a joint venture with the European Hematology Association, the European Society for Therapeutic Radiology and Oncology, and the International Cardio-Oncology Society. The immense undertaking in reviewing and evaluating the published data by the writing committee members should be highly commended.

However, though detailed guidance is given, the vast majority of the recommendations are derived from Level of Evidence (LOE) C (low or very low), derived from expert opinion, case studies, retrospective studies, or registries.[1] Of the total 156 Class 1 recommendations in the current guidelines, only 5 (3%) carry LOE A (data derived from multiple randomized trials or meta-analyses), 33 (21%) carry LOE B (data derived from a single randomized clinical trial or a large nonrandomized trial), and 118 (76%) carry LOE C. Among the 5 Class 1 recommendations with LOE A, 3 are for managing cancer-associated venous thromboembolism, 1 for corrected QT interval monitoring of ribociclib, and 1 for evaluating suspected amyloid light chain cardiac amyloidosis using cardiac magnetic resonance. In addition, all 5 Class 3 recommendations carry LOE C.

Although the LOE to support strong recommendations is often not very high in cardiology guidelines because many clinical questions have not been addressed by high-quality randomized controlled clinical trials, a guideline with a vast majority of strong recommendations on the basis of LOE C is not common in general cardiology. Among all 272 recommendations in the current 2022 ESC guidelines on cardio-oncology, 76% are supported by LOE C. In contrast, in a systematic review of all 51 current guideline documents published by the American College of Cardiology (ACC)/American Heart Association (AHA) and ESC between 2008 and 2018, which included 6,329 recommendations, 42% of recommendations in the ACC/AHA guidelines and 55% of recommendations in the ESC guidelines were classified as LOE C (**Table 1**).[2] The ACC/AHA and ESC publish their guidelines using a similar grading scheme for grading of recommendations and LOE.

The goal of guidelines is to set the de facto standard for medical practice and therefore influence clinical decisions about individual patients, practice performance measures, insurance reimbursement, and education programs.[3] Clinical guidelines have also been used in the determination of the standard of care in medical malpractice litigation.[4] In general, the strength of a recommendation indicates the extent to which the medical community can be confident that adherence to the recommendation will do more good than harm; the quality of evidence indicates the extent to which we can be confident that an estimate of effects is correct.[5] The level of implementation of guidelines and adherence to guidelines have been used to measure the performance of clinical practice. Class 1 and Class 3 recommendations in the guidelines are explicit, and they are for and against certain interventions, respectively. They are usually followed in clinical practice. Whereas guideline recommendations are "should" (Class 1) or "should not" (Class 3) directives, ACC/AHA performance measures represent "must do" or "must not do" directives. Performance measures are used as the basis for public reporting

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TABLE 1 Levels of Evidence and Strength of Recommendation in the Guidelines

	Overall			Class 1			Class 2			Class 3		
Level of Evidence	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
ESC guidelines (n = 3,399)	484 (14.2)	1,053 (31.0)	1,862 (54.8)	349 (10.3)	472 (13.9)	801 (23.6)	82 (2.4)	505 (14.9)	928 (27.3)	53 (1.6)	76 (2.2)	133 (3.9)
ACC/AHA guidelines (n = 2,930)	248 (8.5)	1,456 (50)	1,271 (41.5)	180 (6.1)	619 (21.1)	473 (16.1)	41 (1.4)	680 (23.2)	605 (20.5)	27 (0.9)	166 (5.7)	139 (4.7)
ESC cardio-oncology guidelines (n = 272)	7 (2.6)	57 (21.0)	208 (76.4)	5 (1.8)	33 (12.1)	118 (43.4)	2 (0.7)	24 (8.8)	85 (31.3)	0	0	5 (1.8)

Values are n (%). ESC guidelines between 2008 and 2018: 3,399 recommendations in total. AHA/ACC guidelines between 2008 and 2018: 2,930 recommendations in total. ESC cardio-oncology guidelines for 2022: 272 recommendations in total. The ESC and AHA/ACC guideline data between 2008 and 2018 are summarized in Fanaroff et al.[2]

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology.

and pay-for-performance programs. Failure to deliver this care to an eligible patient suggests a quality lapse.[6] Therefore guideline panels that issue Class 1 recommendations must be confident that the benefits of the recommended intervention substantially outweigh the risks.[7]

There are no strict governing policies or criteria for making guideline recommendations on the basis of LOE. However, strong recommendations usually require high-quality evidence. Low-quality evidence generally results in uncertainty regarding the balance between the benefits and risks of using one intervention over another. Therefore, a weak recommendation is usually warranted.[8] There are, however, situations in which the discordance between strength of recommendation and LOE is allowed.[7] In some scenarios, assigning LOE C to a Class 1 recommendation is reasonable, especially when the critical outcome is related,[8] for example, when the benefits clearly outweigh the harm by conventional wisdom or widely accepted practice that is biologically sound or when a randomized trial or an observational study is neither feasible nor ethical, but clinical guidance is needed. For instance, in the current guidelines, patients categorized as low risk for cardiovascular (CV) toxicity should proceed with anticancer therapy without delay. In our view, this is a reasonable Class I recommendation with LOE C and is justifiable. Conversely, in scenarios with uncertain benefits but certain risks for harm, Class 3 recommendations with LOE C can be used. For instance, in patients with cancer, thrombocytopenia, and acute coronary syndrome, aspirin is not recommended if platelet count is <10,000/μL. In similar scenarios related to common practice or common sense for improved patient care—such as electrocardiography for all patients starting cancer therapy, baseline echocardiography before anthracycline therapy, and cardiology referral for high-risk and very high risk patients before anticancer therapy, which are unlikely or unnecessary to be studied by clinical trials—Class 1 recommendations supported by LOE C are reasonable. Assigning LOE C does not imply that the recommendation is weak in these scenarios.

However, in far more situations, the balance between benefit and harm or burden is not supported by common practice and has not been addressed by high-quality investigations. Therefore, strong recommendations based on low LOE are likely to result in uncertainty in clinical practice. The following are examples of Class 1 recommendations with LOE C in the current guidelines.

EXAMPLE 1. In patients treated with nilotinib or ponatinib (mainly for chronic myeloid leukemia), full CV risk assessment is recommended for all patients at baseline, every 3 months during the first year, and every 6 to 12 months thereafter. CV risk assessment includes a physical examination, blood pressure measurement, electrocardiography, lipid panel, and hemoglobin A_{1c}. Although nilotinib and ponatinib are associated with vascular events (eg, peripheral artery disease, stroke, myocardial infarction), the mechanism is not fully understood. There is no evidence to support the frequent follow-up of lipid panel and hemoglobin A_{1c} in these patients, especially those at low risk. In practice, the major concern of nilotinib is the risk for QT interval prolongation or torsade de pointes, while ponatinib in particular is associated with hypertension. Therefore, it may be reasonable to routinely perform electrocardiography during nilotinib treatment and measure blood pressure during ponatinib treatment instead of undertaking a full CV risk assessment. Such discordance between the strength of recommendation and LOE in the guidelines raises concerns over whether the uncertain incremental benefits are worth the additional costs and burden.

EXAMPLE 2. Right heart catheterization and discontinuation of dasatinib are recommended in patients who develop symptomatic or asymptomatic increases in peak tricuspid regurgitation velocity >3.4 m/s. Unlike other types of pulmonary arterial hypertension (PAH), which are almost all progressive and irreversible, dasatinib-related PAH usually resolves rapidly after discontinuation of treatment.[9] It is a reasonable recommendation for symptomatic patients to discontinue dasatinib and undergo invasive measurement. However, an arbitrary referral of an asymptomatic patient for an invasive procedure may be premature, particularly if based on a single measurement of tricuspid regurgitation velocity by echocardiography.[9] A repeat measurement in close follow-up could also be recommended for confirmation before taking further action, especially if the patient remains asymptomatic. In a long-term follow-up of patients with chronic myeloid leukemia treated with dasatinib, only 1 of the 14 patients with echocardiographic diagnoses of PAH required right heart catheterization.[10]

EXAMPLE 3. In high-risk and very high risk patients (as defined by the guidelines) receiving anthracyclines, echocardiography (LOE C), troponin, and natriuretic peptide monitoring (LOE B) are recommended every 2 cycles and within 3 months after completing treatment. This is a significant change from the current practice. An explicit Class 1 recommendation clearly runs beyond LOE and may lead to a drastic change of current practice patterns. In our view, a Class 2 recommendation may be more appropriate for this scenario. This will leave the choice of timing of cardiac assessment (more or less frequent) to the physician's discretion on the basis of an individual patient's situation, such as the type of malignancy, concomitant use of other cancer therapies with potential cardiotoxicity, and cumulative dose of anthracycline.

In clinical practice, it is not practical for individual health care providers to evaluate the evidence and arguments for themselves or to vet biases and potential errors from the consensus of the relevant experts. Practitioners trust the recommendations because of their assumed credibility and authority. High quality of evidence is associated with low level of bias and vice vera. However, recommendations based on weak evidence could be biased. This could then result in confusion and controversy when recommendations are applied to clinical practice, performance measures, insurance reimbursement, or malpractice litigation.

In situations in which high-quality evidence is not available, expert opinion and careful synthesis of low-quality evidence will continue to guide clinical practice. As an alternative, a consensus statement is usually made when the evidence is of lesser quality or not appropriate for formal ratings for guideline development but clinical guidance is still needed. Such consensus represents the prevailing opinions of an expert panel and serves mainly as an information source and nonbinding recommendation to help clinical decision making. As the desired outcomes of such recommendations are not guaranteed, because of the lack of high-quality evidence, the recommendations are not binding.

There is no doubt that the current guideline document provides a great source of information, and many recommendations will ultimately guide patient care in cardio-oncology. However, clinical guidelines are only as robust as the evidence and expert opinions they are based on[5] and are works in progress that need to be continually edited and updated as additional evidence is generated. The current guideline document acknowledges that there are limited trials and lack of high-quality evidence on which to base decision making.[1] Although assigning low or very low levels of evidence to strong recommendations or vice versa is allowed, with 73% of Class 1 and Class 2A recommendations (167 of 229) based on LOE C, the substantial prevalence of expert opinion or low-quality evidence can potentially endanger the authority and validity of guidelines. Therefore, the guidelines should acknowledge the lack of strong evidence for many of the recommendations and reinforce that practitioners should follow their judgment when implementing the guidelines in clinical practice.

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JACC: CARDIOONCOLOGY, VOL. 5, NO. 1, 2023
FEBRUARY 2023:149–152

REFERENCES

1. Lyon AR, Lopez-Fernandez T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229–4361.

2. Fanaroff AC, Califf RM, Windecker S, Smith SC Jr, Lopes RD. Levels of evidence supporting American College of Cardiology/American Heart Association and European Society of Cardiology guidelines, 2008-2018. *JAMA*. 2019;321:1069–1080.

3. Ransohoff DF, Pignone M, Sox HC. How to decide whether a clinical practice guideline is trustworthy. *JAMA*. 2013;309:139–140.

4. Samanta A, Mello MM, Foster C, Tingle J, Samanta J. The role of clinical guidelines in medical negligence litigation: a shift from the Bolam standard? *Med Law Rev*. 2006;14:321–366.

5. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490.

6. Jacobs AK, Anderson JL, Halperin JL, et al. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2014;130:1208–1217.

7. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66:719–725.

8. Brignardello-Petersen R, Carrasco-Labra A, Guyatt GH. How to interpret and use a clinical practice guideline or recommendation: users' guides to the medical literature. *JAMA*. 2021;326:1516–1523.

9. Lee SE, Hyun Kong J, Kim SH, et al. Change of right ventricular systolic pressure can indicate dasatinib-induced pulmonary arterial hypertension in chronic myeloid leukemia. *Cancer Med*. 2021;10:1515–1524.

10. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients trial. *J Clin Oncol*. 2016;34:2333–2340.

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