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Abstract

Guidelines for the diagnosis, management, and surveillance of cancer patients have evolved with the single goal of improving patient care based on available data when available, or in the absence of firm data, on the standard practices of those with broad experience in actual hands-on patient care. Two initiatives intended to disseminate information to cardio-oncologists, were discussed in this session: the first, from the American Society of Clinical Oncology was focused on available data and the confidence level of that data; the second, from The European Society of Cardiology was a position paper. Interestingly, notwithstanding the somewhat different focus, there is considerable agreement between these two initiatives. Nevertheless, guidelines my not be applicable to all afflicted patients, and may raise questions as to when deviations from published standards should be considered. Such deviations may result in allegations of failure to meet standards of care or legal liability.

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I am submitting the Report of Session VII for the special issue on Cardio Oncology

Giorgio Minotti

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REPORT OF SESSION OF THE SECOND INTERNATIONAL COLLOQUIUM ON CARDIO-ONCOLOGY KRAKOW, POLAND, May 3-4, 2018

HELPING THE CARDIO-ONCOLOGIST: FROM REAL LIFE TO GUIDELINES

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ABSTRACT

Guidelines for the diagnosis, management, and surveillance of cancer patients have evolved with the single goal of improving patient care based on available data when available, or in the absence of firm data, on the standard practices of those with broad experience in actual hands-on patient care. Two initiatives intended to disseminate information to cardio-oncologists, were discussed in this session: the first, from the *American Society of Clinical Oncology* was focused on available data and the confidence level of that data; the second, from *The European Society of Cardiology* was a position paper. Interestingly, notwithstanding the somewhat different focus, there is considerable agreement between these two initiatives. Nevertheless, guidelines my not

be applicable to all afflicted patients, and may raise questions as to when deviations from published standards should be considered. Such deviations may result in allegations of failure to meet standards of care or legal liability.

SESSION SUMMARY

The seventh and final session of the symposium focused primarily on the status of guidelines related to Cardio-Oncology. Several initiatives have made serious attempts to place general knowledge, practice patterns, and the available extensive commentary found in the literature in a useful perspective. Crucial issues addressed in these various documents relate to the management of cancer patients who are deemed to be at increased cardiac risk. These risks may be due to the malignancy itself, to the treatment administered, or to underlying and often unrelated cardiac conditions. Patients who have demonstrated adverse events during or after exposure to potentially toxic treatments are considered in these documents, as is the possibility of benefit that results from long-term surveillance following treatment. The goal of these guidelines or consensus statements is to recognize cardiac dysfunction sufficiently early so that meaningful intervention can be initiated, thereby improving both quality of life and the duration of cardiac stability during treatment and in the period of survivorship.

The opening speaker for this session was Professor Saro H. Armenian, who led the initiative of the American Society of Clinical Oncology (ASCO), published in the Journal of Clinical Oncology in 2017. Dr. Armenian noted that Cardiovascular diseases (CVD) such as heart failure, myocardial infarction, and stroke, are serious adverse

effects of certain cancer-directed therapies that can interfere with the efficacy of treatment, decrease quality of life, or impact the actual survival of the patient with cancer. It is important for oncologists and advanced care practitioners to initiate the discussion regarding the potential for CVD in individuals in whom the risk is sufficiently high before starting therapy. Established international guidelines/position statements (e.g. ASCO, European Society of Cardiology (ESC), and American Society of Echocardiography) may help guide these discussions and clinical practice.[1,2,3] Hearing about potential complications from therapy early in the cancer journey can be difficult for patients with cancer to process, because their primary focus is surviving their malignancy. However, clear provider-patient communication may facilitate appropriate monitoring and implementation of potential preventive strategies. A baseline CVD risk assessment by the oncology care provider(s) is important before therapy. For high-risk patients, a tailored and detailed plan for CVD monitoring throughout treatment and beyond should also be established. Patients also need to be advised that cardiovascular complications such as cardiac dysfunction can be a progressive disorder and may initially be asymptomatic. Early and late warning signs and symptoms should therefore be discussed and reported to the primary oncology team or to a cardiologist. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed with all patients with cancer before and after completion of their cancer therapy. An overall approach in the form of a road map depicting the evolution of clinical questions is depicted in Figure 1.

Dr. Armenian also discussed the fact that despite well-recognized importance of guideline-directed care, many CVD screening guidelines for cancer patients are

consensus-based, due in large part to the paucity of longitudinal studies. These differences are provided in Table 1.[4] Consideration should be given to implementation of value-framework of care which when implemented, can help optimize uptake and dissemination of guideline-based care within the medical community. This value framework is centered around key concepts: 1) screening is a cascade of events rather than a single screening test, and the decision to screen or not to screen should take into consideration the downstream effects (both positive and negative) of the screening results; 2) CVD in cancer patients are heterogeneous and a “one-size-fits-all” approach may not be appropriate in a given population, due to differences in cardiotoxic treatment exposures, patient characteristics, and baseline risk factors; and 3) determining the value of screening strategies is complex, but not impossible.[5] The last point is especially important, as researchers are often hesitant to perform key cost-effectiveness analyses to examine the health benefits as well as costs (health and economic) of different screening strategies. Studies in the pediatric oncology community are emerging to suggest that more intense screening may not always be beneficial for certain low-risk subgroups of patients.[6,7] These studies utilize simulation (Markov) modeling to examine the lifespan and the healthspan of cancer survivors treated with cardiotoxic therapies, obviating the need for large cohort studies that would be followed for years after completion of therapy. Similar studies are needed but are lacking for adult-oncology patients. In the meantime, clinicians should adhere to established screening guidelines, recognizing the importance of patient and provider education regarding the potential long-term CVD risks associated with established as well as emerging anti-cancer therapies.

Despite existing CVD screening recommendation, cancer survivors are often unaware of their long-term health risks, and are not receiving recommended risk-based surveillance.[8] This may be due to the fact that the vast majority of cancer survivors are no longer followed at a cancer center, but instead are followed by community-based health providers, many of whom are understandably unfamiliar with the health risks of survivors.[1, 8,9,10,11] Ironically, the period in time where the risk of health complications is the greatest also coincides with a time when the level of engagement in comprehensive survivorship care at a cancer center is the lowest.[8,9] However, receipt of risk-based medical care should not be contingent on whether survivors receive their medical care at a cancer center or by a primary care provider. There are important logistic and health system barriers that limit the ability of cancer centers to see cancer survivors for decades after completion of their primary treatment. These include but are not limited to lack of primary care expertise at cancer hospitals, distance to the cancer center, and health insurance coverage issues.[8,11] It is in this context that new paradigms in healthcare delivery and risk-based screening should be explored, taking into consideration advances in telemedicine and telehealth (mHealth) along with real-time assessment of the costs and benefits of these screenings. mHealth-based monitoring and medical management has emerged as a viable alternative to standard clinical care for many populations with chronic disease such as those with diabetes, hypertension, or chronic heart failure and should be explored in at-risk cancer survivors as well.[12,13,14,15] Ultimately, ongoing multi-disciplinary collaborations between the oncology, cardiology, primary care and other subspecialty communities are essential to reduce therapeutic

exposures and improve surveillance, prevention, and treatment of CVD in patients at highest risk for therapy-related CVD.

Dr. Armenian discussed briefly the different perspective offered by the ASCO and the ESC initiatives.[1,2] While the paper generated by ASCO looked at the evidence available at the time this paper was written, and attempted to rank that evidence as to the degree of certainty. In contrast, the EJC paper was intended as a position paper, as is reflected in its title. Interestingly, despite some variation in focus, major similarities in these initiatives exist, and both serve a valuable function.

A second presentation in this session, also with focus on guidelines, but from a different vantage point was provided by Professor Wojciech Jurczak of Krakow, Poland, and Professor Michael S. Ewer of Houston Texas. The presentation started with an historical perspective of practice guidelines, and how knowledge is conveyed both horizontally to one's peers and vertically to future generations of practitioners. Insight and progress must be integrated as we share our knowledge and ability in this context. These concepts go back at least as far as ancient Egypt.[16] Until quite recently, much of what we learned came directly from our teachers, our textbooks and our personal experiences. Our practice standards continually evolved were altered as we integrated new tools and knowledge into our profession. In times when how we treated patients changed slowly we could rely on traditional learning tools, but more recently our practice patterns have evolved much more rapidly. Additionally, there is a trend to narrow the variance of what may be considered acceptable practice. This, along with an ever-expanding cache of relevant, albeit sometimes irrelevant, data

immediately available to our patients fosters some uncertainty in the minds of both physicians and those they care for. It raises the question from physicians as to whether or not they are fully up-to-date and advocating the best available treatment, while patients ask why a specific recommendation is being made, on what authority it is being advocated, and about what may be approved or unapproved alternatives.

One strategy to answer these questions is the creation of practice guidelines. In the ideal setting they will be timely, comprehensive, based on data sufficiently robust to be authoritative, and enjoy the endorsement of a widely respected group of knowledgeable practitioners (Table 2). Yet guidelines are sometimes controversial. There may be more than one accepted standard of care regarding the management for a specific condition. Some may ask whether the available guidelines truly reflect the various legitimate schools of thought; do they sometimes usurp a clinician's discretion to elect among various treatment options?[17] Guidelines are created so that, when applied to the intended population, they will result in a predominance of the desired outcome. Yet, with the uncertainties of medical care and the diversity of the population to be treated, the desired outcome is not invariably achieved. At what point in this distribution of uncertainty should our confidence level be sufficiently high so as to include a practice guideline in our clinical armamentarium? (Figure 2)

A concern addressed in this session regarding guidelines was whether they are sufficiently objective and have sufficient transparency with regard to their creation to instill confidence, Guidelines produced by the National Comprehensive Cancer Network (NCCN), for example, are accompanied by a list of panel members—often twenty or more for a single set of guidelines. Any potential conflicts of interest by panel member are clearly delineated as is the version number and date of creation.[18] With regard to cardiotoxicity of anti-cancer treatment several sets of guidelines have been published. In some instances, support by industry with clear financial implications has raised the specter of taint, but several are now available that have been created with broad input from highly respected clinicians and researchers by internationally recognized professional bodies.[1,2] Nevertheless, a number of general questions regarding guidelines were raised in this session. As clinicians and teachers we must be aware that some of the bases for guideline recommendations are not prospective controlled studies; how much of what we do is based on solid science? Even when created with a serious intent, practice guidelines may be troubling.

From a legal perspective guidelines shift the burden of proof in the event of subsequent controversy. If a clinician follows guidelines, those implying that he or she did not meet the standard of care for a particular patient will usually be required to demonstrate why the guidelines should not have been followed in that instance.[19] Physicians generally have more

confidence and perceive protection from allegations of failure to have met the standard of care if they have follow the guidelines. The corollary is that if a physician does not follow the guidelines the burden shifts to him or her to justify the deviation. Furthermore, guidelines are increasingly incorporated into physician performance or institutional quality measurements. Understandably, physicians, often intuitively, don't want to have that highly unpleasant and sometimes unpredictable experience of having their standards of care questioned—something that may happen when guidelines are not followed. In that regard, guidelines may be thought by some to be more like firm and rigid rules than merely an attempt to provide, as their designation implies, guidance.

In many instances guidelines may rest on the best evidence we have, and panels formed by professional organizations are very well positioned to help put the available evidence into perspective. With regard to many of our clinical uncertainties, we will never have ideal prospective trials; we must use the data we have in an effort to best address the needs of our patients; that is what guidelines, imperfect as they may sometimes be, are intended to accomplish.

Table 1

Table 1 depicts the various levels of confidence in recommendations. Such information is important in helping patients understand what the uncertainty of what is being recommended. Recommendations are not static, and may move from one classification to another, or even be eliminated as new data becomes available.

Type of Recommendation

Recommendation	Definition
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
(In)Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Adapted from: AHRQ Methods Guide for Comparative Effectiveness Reviews 2011; ICSI; GRADE; and USPSTF

Table 2

Some criteria for evaluating practice guidelines

1. Have they been created objectively and by a sufficiently broad group that has neither financial nor academic biases nor conflicts of interest, and has there been adequate opportunity for non-panel members to comment;
2. Have alternate schools of thought been considered; if a strategy is preferred by the panel, have other approaches been acknowledged as reasonable alternatives that are acceptable to a substantial group of respected clinicians;
3. Has recent new data been incorporated and have the guidelines undergone timely reconsideration;
4. Have the guidelines balanced various conflicting perspectives sufficiently, as oncologists may have a different priority (tumor control, for example) from those of consulting cardiologists (preserving cardiac reserve);
5. Have the guidelines considered the variability of our patient populations, and allowed for wide fluctuations in how individual patients may react or respond.

Figure 1 Road map depicting clinical questions related to risk assessment of cardiac dysfunction in cancer patients

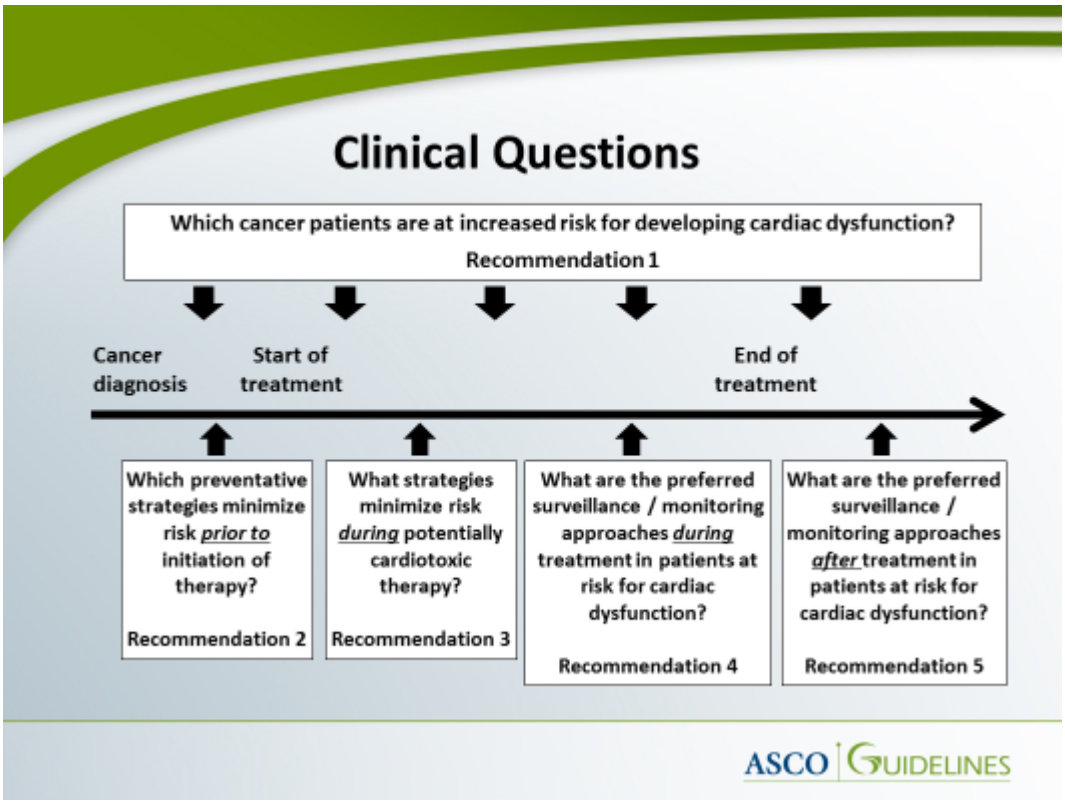

Figure 2 Normal distribution of risk and benefit sowing the dilemma of at what point in this continuum should be recommended or implemented.

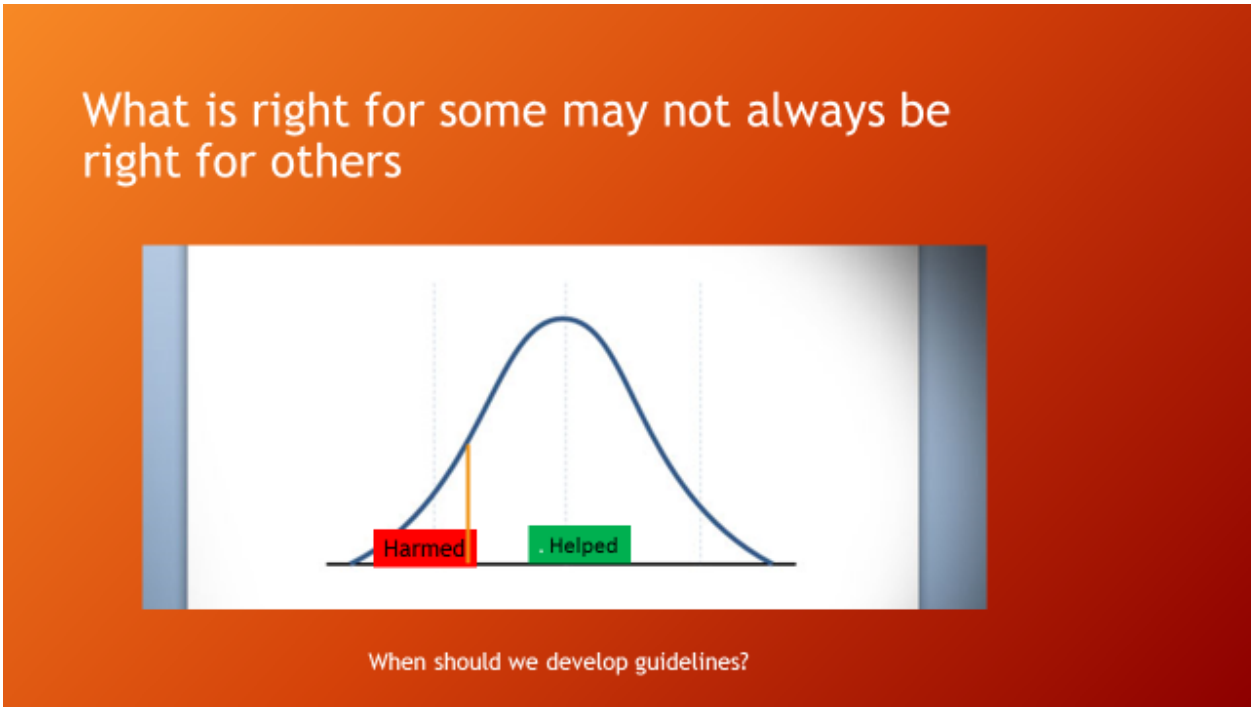

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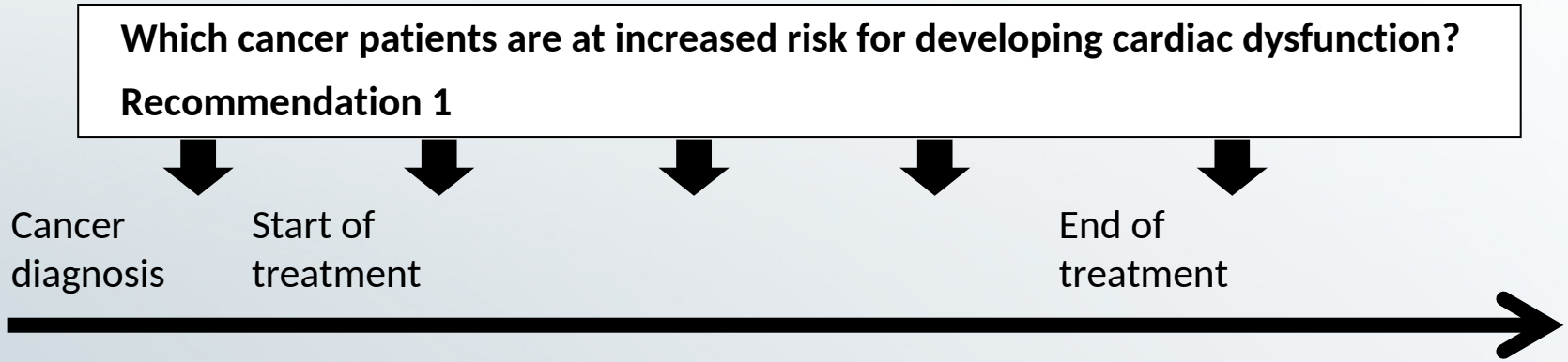
FIGURE 1

Clinical Questions

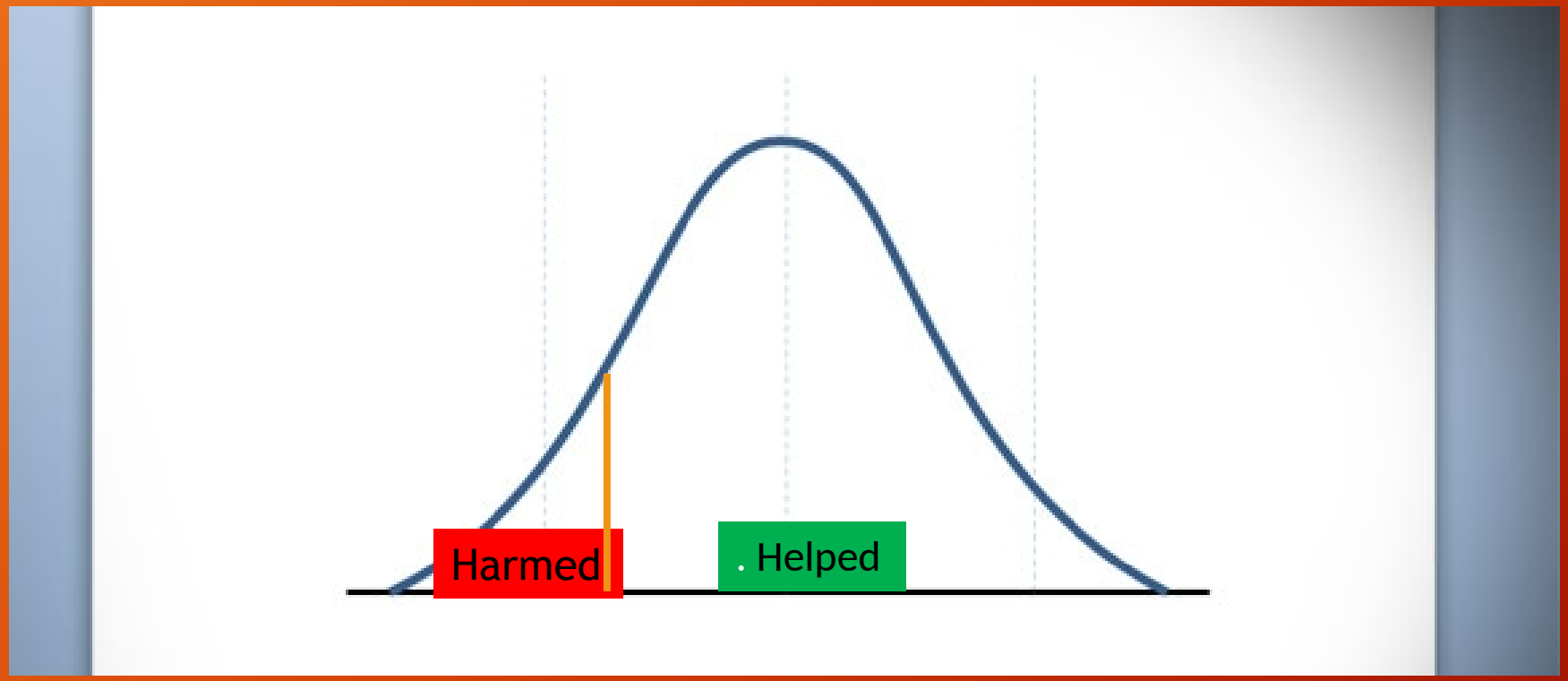


Study design and analysis:

- Large population-based cohort studies
- Long-term and complete follow-up
- Validated CV outcomes
- Treatment dose-specific information
- Comparison to no exposure
- Multivariable regression analysis (adjusting for confounders)

FIGURE 2

What is right for some may not always be right for others



When should we develop guidelines?

No conflict of interest to declare