Society for Medical Oncology,[22] European Society of Cardiology,[23] National Cancer Center Network, and Canadian Cardiovascular Society.[24]

The role of preclinical studies in cardiac safety

In response to the growing awareness of potential cardiovascular liabilities of oncologic drugs, preclinical cardiac safety studies are increasingly being used for the early detection (and avoidance) of cardiotoxicity of evolving oncologic drugs. In addition, preclinical models may be useful to dissect mechanisms of toxicities for existing cancer drugs.[25] Phenotypic screens are used in early drug discovery efforts to identify and avoid potential safety hazards, as it is often difficult to determine the (multiple) mechanisms involved in various cardiotoxicities (which can include electrical, contractile, structural effects). Earliest screening efforts might involve in vitro studies (for higher throughput), with later screening efforts involving in vivo safety pharmacology (focusing on acute functional assessments) and toxicology studies focusing on longer-term effects with morphological readouts. In general, in vitro studies report on acute effects in cellular (myocyte) or ex vivo (isolated tissues or Langendorff hearts) models. In contrast, in vivo studies focus on longer-term effects in animal models. The later studies provide the advantage of evaluating cardiac liabilities in the setting of the entire CV system using end points translatable to clinic (eg, ventricular imaging and ejection fraction measures) but with the disadvantage of limited screening opportunities due to time, cost, and compound requirements. In addition, preclinical models may be useful to dissect mechanisms of toxicities for existing cancer drugs.[26]

In vitro and in vivo studies serve different roles in different phases of drug discovery (the former generally useful for hazard identification, the later more aligned with risk assessment), and both are essential to provide a more comprehensive assessment of potential cardiac safety liabilities. Preclinical models can also fulfill the secondary role of assessing mitigation of CV effects with combinational drugs or the safety of promising synergistic drug regimens. Identifying the most serious and prevalent clinical cardiac toxicities is critical to guide the development, validation, and use of preclinical studies as translational tools. This is particularly difficult for effects that are not easily detected clinically or may be irreversible situations where preclinical studies could be most valuable. There is clearly a need for collaborations between nonclinical and clinical experts to set relevant end points and identify appropriate biomarkers to guide preclinical studies.

Studies using human induced pluripotent stem-cell derived cardiomyocytes (hiPSC-CMs) are being used to assess cardiotoxicity in vitro, with the presumed advantage of using human-derived models as test systems. Commercially available cardiomyocytes have spurred growth in this area, with preparations varying in complexity (from single myocytes to 2D cultures, spheroids, organoids, and engineered heart tissues) and varying in functional and morphological characteristics[27,28] As different levels of myocyte "maturity" (ie, resemblance to adult native myocytes in form and function) tend to increase with the level of complexity, it is essential to demonstrate assay sensitivity for hiPSC-CM preparations under study. Functional end points typically evaluated include field potential waveforms (multielectrode array platforms) to assess electrophysiologic effects (delayed repolarization and conduction, altered spontaneous beating) and various measures of contractility (sarcomere length changes, edge tracking, various motion detection schemes), with measures of soluble (cardiac troponins) and morphological biomarkers possible.

Cost-effective and scalable procedures to produce hiPSCs with >90% purity are now achievable using a chemically defined process,[29] enabling tests with "personalized" cell lines. These cells have a promise in genomic prediction of chemotherapy-induced cardiotoxicity and have been shown to recapitulate individual patients' predilection to doxorubicin-induced cardiotoxicity (DIC). hiPSC-CMs from breast cancer patients who suffered clinical DIC have been found to be consistently more sensitive to doxorubicin toxicity compared to hiPSC-CMs from patients who did not experience DIC, with a 19-fold difference in sensitivity between cells from the 2 categories of patients. This indicates that iPSC-CMs may be a suitable platform for identifying and verifying the genetic basis and molecular mechanisms of DIC.[30]

Work is also under way to determine the genetic basis for this type of sensitivity, with a study of anthracycline-induced cardiotoxicity in 280 childhood cancer survivors finding that a particular variant (rs2229774, p.Ser427Leu) in *RARG* was highly associated with anthracycline-induced cardiotoxicity, showing a 4-fold increase in sensitivity.[31] Correction of the rs2229774 variant was found to reverse doxorubicin hypersensitivity in the patients' iPSCs, providing new insight into the pathophysiology of this severe adverse drug effect.

Oncologic drugs may affect cardiac function due largely to unintended overlapping on-target or off-target effects between cardiac and other tissues. The lack of selectivity of tyrosine kinase inhibitors, along with the distribution of multiple kinases across organs (including the heart), provides one example where it may be difficult to separate antitumor activity from cardiac toxicity. Minimizing and predicting potential tyrosine kinase–induced cardiotoxicity remain important challenges for drug developers and regulatory authorities and highlight the need for developing and implementing robust preclinical models that predict adverse clinical effects.

Early expectations of minimizing cardiac dysfunction with targeted therapeutics (including those against tumor-specific targets such as HER2) may be less successful due to less well-appreciated (or sometimes unknown) overlapping signaling pathways in cardiac and cancerous tissues revealed with drugs and drug combinations. Such pathways could be distinguished by identifying differences in the genomes/proteomes of normal and tumor tissues and obtaining cancer-specific gene-protein expression. The doses required for efficacy could be determined using animal models of disease or by developing 3-dimensional microfluidic organ systems, or tissue chips, which represent an integrated in vitro model of perfused tumor and cardiac tissues, with potential utility in screening. In the future, it may be possible to develop safer oncologic drugs by either identifying cancer-only targets or differentiating exposures required for efficacy from those that cause direct cardiac toxicity.

Overall, a multipronged preclinical approach—including in vitro, in vivo, and in silico approaches—is best suited to identify potential direct cardiotoxic effects of novel oncologic drugs, provide mechanistic insights, define who is at risk of toxicity, explore mechanisms, and inform on preventive and treatment strategies.[32]

Cardiac safety signals should not impede development of effective drugs

The unique features of early phase oncology studies provide a reason to validate emerging assays and biomarkers in patients to help characterize cardiac risk earlier and more precisely. The potential benefit-risk must always be evaluated; early identification of CV safety signals during drug development should be balanced with the potential benefit. For instance, if a drug being studied in phase 1 showed excellent responses in tumors but causes frequent serious or life-threatening CV toxicities, it should not be developed further. Precise characterization of cardiac safety signals may enable implementation of appropriate cardiac surveillance strategies or, if CV toxicity is dose related, use of lower/safer doses during early-phase clinical trials.

When possible, the CV safety profile of all anticancer drugs should be characterized, including, when appropriate, full characterization of electrophysiology (electrocardiogram/QT), left ventricular (LV) function (imaging/biomarker (BM)) and hemodynamic blood pressure (BP) effects. Depending on the population (metastatic vs curable) and the drug, some battery of cardiac tests may be recommended for each protocol and should depend on the prior knowledge about the drug/drug class. If possible, these assessments should be integrated into early-phase studies, without disrupting or impeding conduct, interpretation, or analysis of trial results. Potential CV safety of investigational anticancer drugs should be defined early in their development, ideally prior to exposing large populations in late phase clinical trials. Wherever possible, CV safety assessments should be integrated into routine early-phase oncology clinical trials with minimal disruption to study design, conduct, interpretation, and analysis.

A particular challenge is to put CV safety findings into context in early-stage oncology trials, which often involve small numbers of participants and may have a single-arm design, making it hard to determine whether the effect is due to the drug or not. Additional testing in later-phase oncology trials with a comparator arm can be informative. Additional challenges include the fact that early-phase studies, including first in human, are conducted in cancer patients, some of whom may be at higher than normal risk for CV disease. Moreover, patients may have already been exposed to therapies that are associated with CV complications. An additional challenge occurs due to requirement to perform dose escalation in early-stage trials often starting at subtherapeutic doses, making interpretation of both safety and efficacy in these patients problematic.

Clinically meaningful end points: Lessons from trastuzumab

It is clearly important to monitor safety signals that are clinically meaningful. For example, in early phase III clinical trials in patients with metastatic HER2-positive breast cancer, trastuzumab was associated with significant cardiac dysfunction and symptomatic heart failure in almost 25% of the patients.[33,34] As a result, in subsequent adjuvant studies, routine imaging was required for patients receiving trastuzumab at baseline and every 3 months during 1 year of treatment. In this setting, trastuzumab became rather safe, and incidence of symptomatic heart failure in adjuvant trials was consistently less than 3%. The most common abnormality detected during routine imaging is a significant decline in LVEF; however, the association between an asymptomatic LVEF decline and the risk of subsequent clinical heart failure has not been fully elucidated in this population. Given the inherent variability of LVEF measurement, there is also a risk that patients may be wrongly identified as having cardiotoxicity, which may compromise delivery of curative therapy. Overall, the current available evidence is insufficient to support a specific schedule of cardiac imaging during trastuzumab-based treatment, and further investigation is needed to determine whether routine cardiac monitoring results in improved CV outcomes.[35] A more promising approach might be to use existing tools to identify those at highest risk and only apply stringent cardiac monitoring strategies to these individuals. Until such data become available, it is reassuring to know that the rate of symptomatic HF is low based on clinical trial data when routine cardiac monitoring is performed. The goal should be to carry out the right testing and monitoring in the right patient at the

right time. In clinical practice, cardiovascular risk factors alone have not been able to predict which patients will develop trastuzumab cardiotoxicity, and the variability in cardiac adverse effects from trastuzumab suggests that genetics may play a role in a patient's individual risk for cardiotoxicity.

To advance understanding of the optimal management of patients with trastuzumab toxicity, the recently completed SAFE-HEaRt study evaluated cardiac safety of HER2 targeted therapy in patients with HER2-positive breast cancer and mildly reduced LVEF (≥40% no symptoms of heart failure).[36] This investigation tested the hypothesis that initiation or continuation of trastuzumab may be safe in patients with mildly reduced LVEF if they concomitantly receive optimal cardiac therapy including β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Future areas of study may incorporate newer techniques using hiPSC-CMs to predict the cardiotoxic response to trastuzumab.

The role of circulating biomarkers

Biomarkers–which are indicators of normal biological processes, pathogenic processes, or responses to an exposure or intervention–include molecular, histologic, radiographic, and physiologic characteristics. The cardiac biomarkers troponin, brain natriuretic peptide, and myeloperoxidase have potential in detecting subclinical cardiotoxicity during cancer treatment.[37] Biomarkers may not provide insight into the mechanism of drug toxicity, however.

Biomarkers can be used at baseline to define at-risk subgroups and help determine optimum cardiac treatment. Biomarkers are often part of comprehensive assessment of patients, in particular if the risk of cardiomyopathy and heart failure is high. The patients with preexisting CV comorbidities could be treated prior to initiation of cancer therapy, avoiding the inappropriate attribution of symptoms to drug toxicity.

Serial biomarkers have potential to define risk and track response to therapy, although the ultimate measure of effectiveness is the clinical outcome. Tracking cardiac biomarkers could identify patients at risk of oxidative stress, providing an early safety signal to facilitate early-stage trials.

To date, cardiac biomarkers have not been deployed optimally, with confusion remaining in areas including appropriate cutoffs and calculation of the reference change interval. Abnormal biomarkers may indicate a need for close surveillance but, based on current knowledge, are unlikely to provide sufficient data to mandate treatment.

In the future, the goal is to reduce morbidity in cancer patients by early risk factor modification, serial monitoring with imaging and/or biomarkers, cardioprotective medical therapy, and optimal medical therapy for cardiotoxicity when it occurs.[1]

Imaging end points for various outcomes

Cancer therapies can affect the CV system in multiple ways, with appropriate imaging end points reflecting the outcome of interest (Figures 1 and 2). These can be visualized using multiple CV imaging modalities, including echocardiography, positron emission tomography–computed tomography scanning, and cardiac magnetic resonance imaging.

Positron emission tomography or single-photon emission computed tomography radiotracers are tools to evaluate myocardial perfusion, cardiac function, and coronary vasculature. Outcome measures include perfusion defects, myocardial blood flow, coronary flow reserve, calcium score, and LVEF; additional measures are markers of inflammation, cell death, and metabolism.

Cardiac magnetic resonance imaging can characterize with high reproducibility cardiac size and function (LVEF, volumes, mass, strain). It is also possible to gain unique qualitative and quantitative insight into myocardial tissue through T1/T2 mapping, extracellular volume index, and delayed enhancement, enabling assessment of edema, inflammation, and fibrosis.

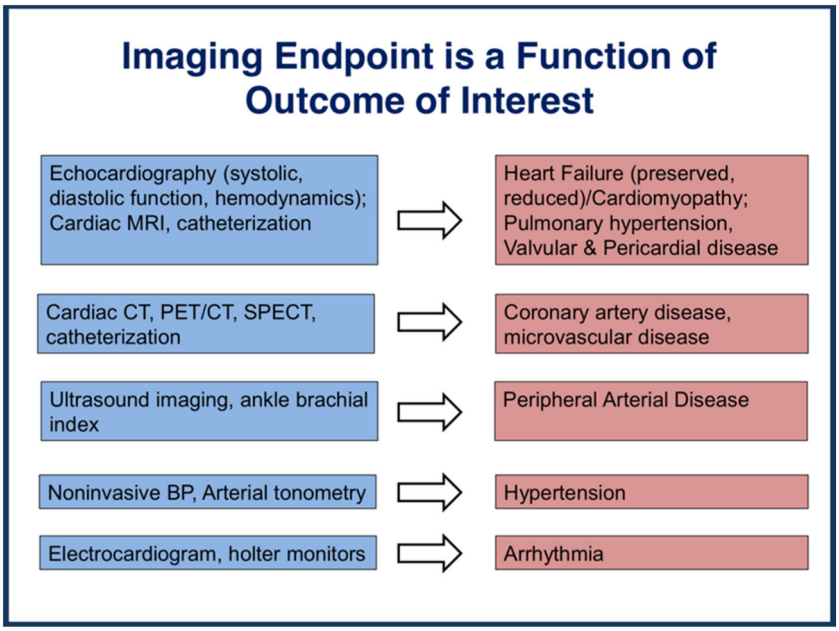
The core laboratory's role in optimizing data collection and collaboration

The CV imaging core laboratory's role is to ensure robust and consistent data collection. This includes involvement with protocol development; definition of CV imaging end points and choice of technique (echo, cardiac magnetic resonance); standardized image acquisition; protocol-based site instruction and training; independent, centralized, and standardized analysis and quality control; and data review and interpretation. The core laboratory provides dedicated personnel training, such as webcasts, instructional videos, and face-to-face meetings.[38,39] Core laboratory–established data quality and standards enable a rigorous image analysis plan to be developed, with a standard method for image transfer, a secure environment for data storage, and tailored case report forms.

Overall, there are sufficient data to suggest that biomarkers can be useful. However, consensus is needed on the types of testing—such as echo parameters and biomarkers—that should be used routinely so that results can be compared across institutions. The clinical significance of changes in biomarkers in the absence of symptoms needs to be better understood.

When possible, CV assessments should be integrated into early-phase studies, without disrupting or impeding conduct, interpretation, or analysis of trial results. Current limitations of CV safety assessment include multiple cardiotoxic exposures, small numbers, open-label nonrandomized design, selection bias, and variable end point definitions.

Figure 1



Imaging end point depends on the outcome of interest.

Figure 2

Echocardiographic Measure	Functional or Structural Alteration
2D/3D LV and RV size and mass	Ventricular structure
2D/3D LV and RV strain, strain rate, ejection fraction	Systolic function
E/a, e', a', E/e'	Diastolic function
Ea, $E_{es'}$, Ea/E_{es}	Ventricular/vascular stiffness
Twist, torsion	Systolic/diastolic deformation
Regurgitation, stenosis	Valvular disease
Stroke volume, cardiac output, pulmonary pressures, filling pressures	Hemodynamics

Quantitative echocardiography provides detailed phenotypic data.

Regulatory considerations: Trials should include patients with cardiac risk factors

A unique aspect of oncology drug development is the fact that because registration trials involve relatively small numbers of patients, they poorly predict the post-approval experience—either exaggerating or underestimating CV toxicity. Inclusion of patients with severe preexisting CV disease may translate to significant short-term risk of CV-related morbidity and mortality, potentially confounding the results of cancer trials. As a result, most trials aim to exclude patients with severe CV disease, including acute myocardial infarction, heart failure, stroke, or severe valvular heart disease (ie, severe symptomatic aortic stenosis or mitral regurgitation).

However, the frequency of concurrent cardiovascular disease (CVD) in adults with cancer is relatively high due in part to the increased incidence of both conditions with

advancing age and to the higher incidence of cancers in patients with known risk factors for CVD such as obesity or premalignant hematopoietic stem cell mutations. For this reason, a strong argument can be made that clinical trials in cancer should include patients with CVD. Evaluating both disease states concurrently would increase the ability to identify cardiac toxicities of anticancer drugs early in clinical development and help provide guidance to clinicians who treat patients in "real-world" rather than a clinical trial setting.

Several important issues have mitigated against inclusion of patients with known cardiac disease into clinical trials of oncologic agents:

- Attribution of causality of an adverse event (AE) to an experimental agent rather than to comorbid conditions is based on clinical judgment. Patients with preexisting CV comorbidities or risk factors make it more difficult for investigators to decide about the causality of the CV AEs.
- Most early-stage trials of new anticancer therapeutics enroll patients with late-stage cancer who have exhausted all approved regimens and who have relatively short survival expectations. Deaths on study are to be expected. However, even in patients with objective evidence of progressive disease, the proximate causes of death may be ascribed to failure of an organ system such as the CV system. This is more likely to occur in patients with intrinsic cardiac disease at the time of study enrollment. For example, a patient with preexisting LV dysfunction or coronary artery disease is more likely to develop congestive heart failure or serious arrhythmias during a serious infectious episode than is a patient with a more normal heart at baseline. These events are included in the safety profile of the new agent and may be interpreted to be associated with drug-induced CV toxicity.

  - Many registration trials follow patients for survival; therefore, trial durations are often not short. However, the main issue is that majority of cancer patients receive a therapy for a short duration and, subsequent to their disease progression, they receive multiple subsequent therapies. Therefore, understanding and detection of late CV toxicities in patients with metastatic cancer are challenging.

- Likewise, because exposure to the test agent is often relatively short, serious CV AEs that occur during these studies may delay or even prevent regulatory approval because of concerns of cardiotoxicity. In single-arm trials, as there is no comparator group to serve as a control for the rate of AEs, it is important from the sponsor's perspective to eliminate as many background events as possible through careful patient screening.
- Large trials are necessary to reliably determine the actual rate (compared to background) for CV toxicities. For instance, in CV trials investigating major adverse cardiac event (MACE) in the nondiabetic population, hundreds of patients would be needed to demonstrate noninferiority given the baseline incidence of MACE events in this population.[40]

Therefore, to advance potentially promising new anticancer therapeutics through drug development and testing, early-stage trials typically have included only patients with minimal preexisting cardiac disease. Early-stage trials should, however, incorporate sensitive screening techniques for cardiac toxicity to rapidly build an adequate safety data base that would allow for evaluation of inclusion of patients at higher CV risk who often are more representative of the therapeutic population. Stratification by CV risk is generally impractical due to the practical limitations of clinical relatively imprecise cardiac biomarkers. A potential solution to assess a compounds effect on a high-risk CV population would be to incorporate a separate substudy of patients with higher CV risk within the framework of a larger phase 3 trial. This approach would provide important insight into the safety and efficacy of a new drug among patients that would likely be more representative of a real-world cancer population.

Looking ahead, it would be ideal if clinical trial eligibility criteria only excluded patients with the highest level of CV risk. This would lead to greater generalizability of study results, making it easier to recruit patients, albeit at the risk of introducing confounding. The alternative is continued use of narrower eligibility criteria, with the pitfall of poor generalizability, longer accrual time, study duration and cost, and limited insight into the effects of CV risk on cancer outcomes. To expand eligibility, a 1-year cutoff could be used, after which mortality due to the CV disease typically plateaus.[41,42] Patients who have not had an acute event for 1 year are likely to have a reasonable level of risk for inclusion in clinical studies.

Need for early cardiologist involvement in trial design

There is a pressing need for early involvement of cardiology investigators to ensure appropriate trial design and definition of AE adjudication parameters as part of a broad effort to increase collaboration among clinicians, researchers, sponsors, and regulators to improve cardiac safety in oncology clinical trials. Cardiologists could have valuable input at the initial stages of clinical trial design and throughout the trial to ensure that any early signals of cardiotoxicity are detected and evaluated in close to real time. These could then be shared rapidly with clinicians