

JACC REVIEW TOPIC OF THE WEEK

Gaining Efficiency in Clinical Trials With Cardiac Biomarkers



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ABSTRACT

The momentum of cardiovascular drug development has slowed dramatically. Use of validated cardiac biomarkers in clinical trials could accelerate development of much-needed therapies, but biomarkers have been used less for cardiovascular drug development than in therapeutic areas such as oncology. Moreover, there are inconsistencies in biomarker use in clinical trials, such as sample type, collection times, analytical methods, and storage for future research. With these needs in mind, participants in a Cardiac Safety Research Consortium Think Tank proposed the development of international guidance in this area, together with improved quality assurance and analytical methods, to determine what biomarkers can reliably show. Participants recommended the development of systematic methods for sample collection, and the archiving of samples in all cardiovascular clinical trials (including creation of a biobank or repository). The academic and regulatory communities also agreed to work together to ensure that published information is fully and clearly expressed. (J Am Coll Cardiol 2021;77:1922-33) © 2021 by the American College of Cardiology Foundation.

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HIGHLIGHTS

- Validated cardiovascular biomarkers are lacking, and their use in clinical trials is inconsistent.
- Evidence-based guidance is needed to optimally employ cardiovascular biomarkers in clinical trials.
- A standardized biomarker database would be useful.
- Performance of cardiovascular biomarkers should be evaluated in earlier phase trials before incorporation in Phase 3 trials.

Despite the extensive prevalence of cardiovascular diseases, drug and device development in this area has stagnated over the past 2 decades, with underinvestment compared with other therapeutic areas such as oncology (1). The high cost of cardiovascular clinical trials is one factor, with regulators and payers often demanding large trials with clinically evident “hard” endpoints. Additionally, to advance development of new therapies, there is a need to more fully characterize the pathophysiology of cardiovascular diseases, which frequently involve complex syndromes (2).

It has been noted that across therapeutic categories, clinical development programs that utilize patient selection biomarkers, when compared with those who do not, have higher success rates at each phase of development and an increased likelihood of approval by the U.S. Food and Drug Administration (FDA) (3). However, there remain inconsistencies in the use of cardiac biomarkers in clinical trials, such as the types of samples to be analyzed; how, when, and how often these are collected; the methods of analysis used; and how these should be stored for future research. These inconsistencies reveal a need for recommendations on how and when to use cardiac biomarkers in clinical trials.

To consider these challenges, the Cardiac Safety Research Consortium convened a Think Tank at the FDA’s White Oak campus on January 22, 2020, on the subject of “Driving Efficiencies in Clinical Trials through the use of Cardiac Biomarkers.” Attendees included representatives from academia, industry, regulatory authorities, and medical centers. The objectives of the meeting were to identify major issues and formulate potential solutions and to recommend best practices based on a number of factors: a summarizing of the current status of cardiac biomarker-

based clinical trial endpoints and trial designs that can be used for safety or efficacy assessment; identifying situations where cardiac biomarkers cannot be used; prioritizing barriers to biomarker use and proposing ways to overcome these in the near future; and suggesting immediate next steps.

CURRENT STATUS OF CARDIAC BIOMARKERS IN CLINICAL TRIALS

Generally, the use of biomarkers in cardiovascular disease focuses primarily on diagnosis and prognosis (Figure 1). Many potential cardiac biomarkers have been proposed; however, their use in clinical trials has been less widespread than in therapeutic areas such as oncology and rare diseases (4). In cardiovascular disease, molecular, histological, imaging, genotyping, and device-derived digital biomarkers are available for use in drug development (5). Table 1 details important definitions of what biomarkers represent; Figure 2 details potential roles of biomarkers in clinical trials.

There are many reasons to collect biomarker data in clinical trials (Table 2); however, validated cardiac biomarkers do not exist for all of these categories. To develop biomarkers forward for each of these applications, robust validation efforts involving a wide range of patients will be needed, with accurate biomarker results rapidly attainable, delivering good precision and defined biological variability. For efficacy, the biomarker must reflect a key component of pathophysiology for a disease state and provide independently useful information on diagnosis, prognosis, progression, or therapy; and should provide clinically useful information to guide treatment strategies on top of available data (6).

A systematic review of cardiovascular clinical trial publications (2) found that cardiac troponin was the most commonly assessed biomarker in clinical trials, being involved in 122 studies, natriuretic peptides were increasingly measured, present in 105 studies. At the time of writing, the authors also found that 388 unique clinical trials registered on ClinicalTrials.gov involved troponin or natriuretic peptides. Most of these were interventional trials, and some involved >1 biomarker. In follow-up, as of March 2, 2020, a search for “heart diseases” and various biomarker-related terms was carried out on ClinicalTrials.gov: with “N-terminal pro-B-type natriuretic peptide” there were 928 results; with “BNP” there were 927; with “troponin” there were 779; with “B-type natriuretic peptide” there were 587; and with “NT-proBNP” there were 581 results. The natriuretic

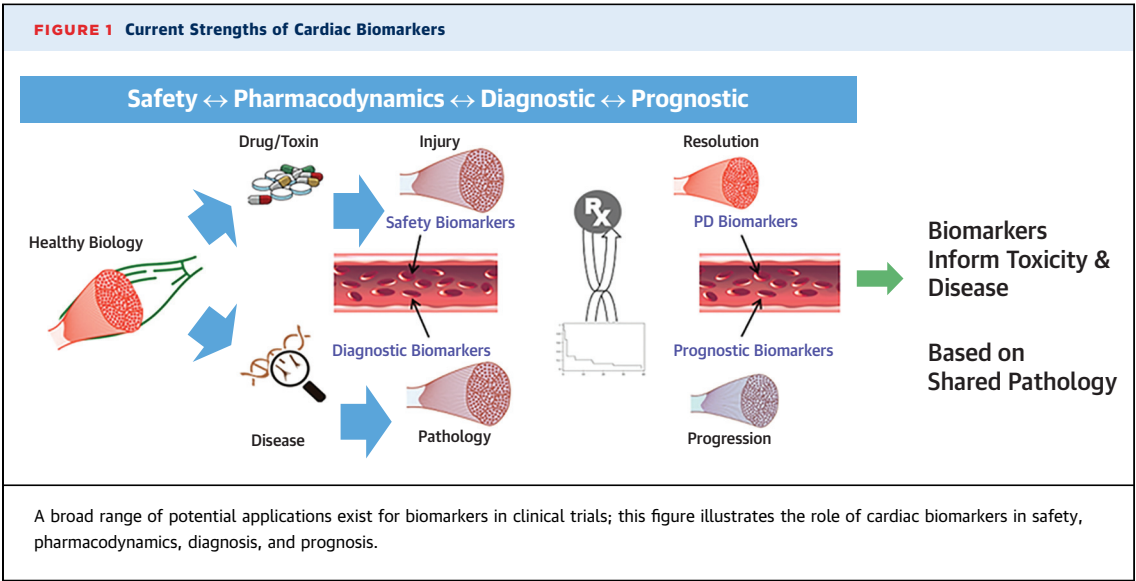
ABBREVIATIONS AND ACRONYMS

FDA = U.S. Food and Drug Administration

HF = heart failure

HFREF = heart failure with reduced ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide



peptides (B-type natriuretic peptide [BNP], N-terminal pro-B-type natriuretic peptide [NT-proBNP]) (7) are specifically important in studies of heart failure (7–9). These are used routinely as an inclusion/exclusion criterion, as a measure of toxicity, as an outcome or surrogate endpoint, to help explain efficacy, and as a target for therapy (2,10). The proportion of heart failure trials involving biomarkers for each of these applications is shown in Figure 3. The strength of evidence for individual biomarkers for diagnosis or prognosis of heart failure (HF) is shown in Table 3.

WHEN SHOULD BIOMARKERS BE ROUTINELY COLLECTED?

Given increasing importance of biomarkers in cardiovascular trials, there was general consensus where biomarkers should be routinely collected for various indications.

TABLE 1 Biomarker Definitions and Examples
NIH definition:
"A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or the response to a therapeutic intervention" (1).
Other definitions of a biomarker (1):
A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.
Molecular, histological, radiographic, or physiological characteristics are types of biomarkers.
A biomarker is not an assessment of how an individual feels, functions, or survives.
NIH = National Institutes of Health.

AS A BASELINE MEASURE. Besides serving as inclusion criteria for studies (an area where greater standardization is yet needed), it was agreed that universal collection and centralized storage of biomarkers from baseline across trials of cardiovascular therapy could enable important cross-trial comparisons, informing similarities and differences in mechanistic and predictive biomarkers between study populations.

SURROGATES FOR SAFETY. From a regulatory perspective, safety is an assessment using "all tests reasonably applicable," which can involve biomarkers. The characteristics of biomarkers used as surrogate endpoints and tools for toxicity monitoring in heart failure clinical trials are illustrated in Table 4. A positive step in the preclinical space is the establishment of a consortium, DataCelerate, to capture preclinical, clinical and safety data across the industry (11). Prominent inclusion of biomarker data in this consortium would be recommended.

SURROGATES FOR EFFICACY. Examples of HF clinical trials where biomarkers have successfully been used to predict efficacy are shown in Table 5. An example of biomarker "response" to therapy associated with reduced cardiac events, improved health status, and reverse cardiac remodeling, is the reduction of NT-proBNP following treatment with sacubitril/valsartan for HF with reduced ejection fraction (HFrEF) (12–14). In other studies, values of this biomarker <1,000 pg/ml, measured soon after intensification of HFrEF therapy, have been shown to associate with better prognosis and improved cardiac structure and function (15).

Although attractive, the use of a biomarker to judge “response to therapy” is a challenging topic, because for each drug-biomarker combination, there exists the need to understand: 1) whether a therapy affects a biomarker in a manner that indicates effect of the treatment; 2) whether change in the biomarker reflects the benefit of the therapy; 3) when and how frequently a biomarker should be resampled; and 4) what metric should be used to judge “response” (e.g., percent change vs. a hard target). For most biomarkers, the answer to each is unclear, and more work in this area is greatly needed as it might lead to their use as a surrogate endpoint for expedited regulatory approval of promising therapies.

Accelerated approval can be based on the “reasonably likely surrogate” of a study effect on the biomarker in phase 3, with confirmation of the effect on outcome in phase 4. The determination that a surrogate endpoint is “reasonably likely” to predict clinical benefit is inevitably a matter of regulatory judgment, and involves a pragmatic approach, as there should be: an excellent understanding of the pathophysiology of the disease; strong mechanistic plausibility between the surrogate and the clinical outcome(s) of interest; clinical data that support the concept that an effect on the biomarker is reasonably likely to predict the outcome of interest; and prediction of the clinical effect size based on the change in the biomarker—the latter needed to allow planning of the confirmatory study in phase 4.

Use of biomarkers in the development of cardiovascular therapies would be particularly useful under certain circumstances. Examples include slowly progressive cardiovascular disease (years), stable symptoms, stable patient function/cardiovascular status, and infrequent clinical events. Biomarkers may also be helpful as surrogate endpoints in cases where trials to demonstrate efficacy would have to be impractically long or large or would pose ethical concerns, and in supporting applications for accelerated approval. Last, accelerated approval based on biomarkers seems most likely to be acceptable in rare diseases, with potential examples including hypertrophic cardiomyopathy, amyloid cardiomyopathy, cardiomyopathies due to storage diseases, and infectious cardiomyopathies, such as that caused by Chagas disease. If studies showed clinical efficacy of the candidate therapy in patients with the disease, with the goal of preventing progression (or development) of the disease at an earlier point, regulators would likely consider use of a biomarker in asymptomatic or mildly symptomatic individuals as a basis for

FIGURE 2 Biomarker Categories in Clinical Trials



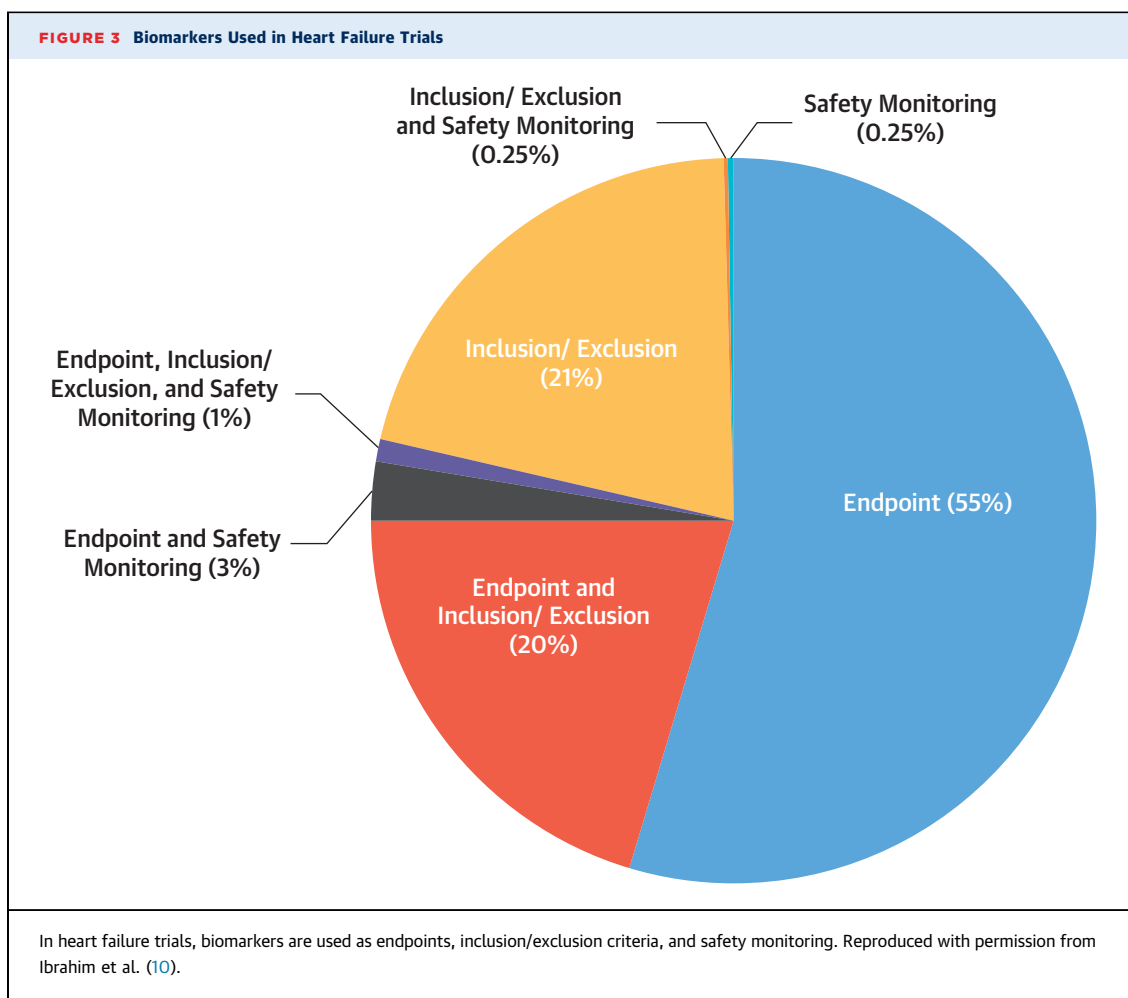
Cardiac biomarkers fall into multiple categories, including safety, diagnostic, susceptibility/risk, prognosis, prediction, response, and monitoring.

accelerated approval with demonstration of clinical benefit as a post-marketing requirement; ideally, the post-marketing study should be enrolled at the time of accelerated approval.

TABLE 2 Reasons to Collect Biomarker Data

Goal of Biomarker Use	Process or Response Measured
Target engagement/proximal PD	Biological response in proportion to drug exposure (PK/PD)
Monitoring disease severity and progression	Characterization of disease stage, provide frame of reference for effect of intervention
Prognostic marker	Likelihood of clinical event in patients with disease
Predictive marker: monitoring response to therapy	Critical for decision-making and dose selection
Diagnostic marker	Detection of condition of interest or identification of a specific disease subtype
Patient stratification	Identification of responder population, fast progressors, susceptibility/risk markers
Intermediate endpoints	Provide evidence of intended mechanism-based biological effect
Surrogate endpoints	Establishment of assessments robustly predictive of clinical benefit
Safety markers	Detection of toxicity as a result of drug exposure
Complementary or companion diagnostic	Precision tools to help guide therapy

PD = pharmacodynamic; PK = pharmacokinetic.



WHEN CARDIAC BIOMARKERS MIGHT NOT BE USED IN CLINICAL TRIALS

Biomarkers are not required when it is possible to assess how the patient feels (patient-reported outcomes), functions (physical performance), and survives (mortality) in the context of a practicable and ethical clinical trial. Cardiovascular issues—such as myocardial infarction, stroke, amputation, revascularization, and hospitalization—straddle all 3 of these factors.

Cardiac biomarkers should not be used in cases where they might be misleading—such as when they have not been fully validated, or not validated in the patient population or disease state being studied in a clinical trial.

For example, in patients with heart failure with preserved ejection fraction (HFpEF), biomarkers have been inconsistent at predicting outcome or functional improvement. This inconsistency emphasizes the need for early investigation of biomarker strategies to

assess target engagement/pharmacodynamics and thereby improve decision-making and probability of success. In a similar fashion, biomarkers have returned inconsistent prognostic information in those with acute HF, where short-term post-treatment improvement in BNP was associated with near-term benefit from inotropic therapy, but this association was lost in longer follow-up (16). In a similar fashion, a 48-h infusion of the renal natriuretic peptide ularitide for acute HF reduced NT-proBNP and high-sensitivity cardiac troponin by discharge, but these biomarker reductions did not translate into meaningful short- or longer-term outcomes (17).

These results provide reason to pause and consider why biomarkers could not predict benefits of the treatments studied in HF syndromes. Part of the disconnect in acute HF is the expectation that biomarker changes related to a short-term treatment would translate into long-term benefit. For all forms of HF, a deeper understanding of drug-biomarker interaction, gleaned from earlier phase studies is

needed. Newer biomarker approaches to potentially understanding molecular mechanisms in HF include (18-20):

- *Phenomapping*: cluster analysis of detailed phenotypic data reveals distinct subpopulations that may be amenable to precision medicine approaches.
- *Expression profiling*: transcriptomics and pathway analysis demonstrating associations of regulators of contraction, oxidative phosphorylation, remodeling, and matrix with HFpEF phenotype.
- *Exploration of novel risk markers besides NT-proBNP or troponin*: for example, insulin-like growth factor binding protein-7 has been linked to diastolic abnormalities and left atrial volume expansion, such that it may have particular utility in HFpEF (21), whereas CA125 and adrenomedullin have associations with intravascular congestion (22,23). The latter biomarkers might be expected to provide utility in studies of decongestive therapies in acute HF.
- *Exploratory biomarker assessments* in large-scale clinical trials, including development of a novel multimarker predictive algorithm.

CURRENT STATUS OF CARDIAC BIOMARKERS IN EARLY DRUG DISCOVERY

In addition to their role in clinical trials, cardiac safety biomarkers in early drug discovery can help bridge nonclinical and clinical studies. Just as patient selection is important in clinical trials, so is the model used in the preclinical space. Important considerations for “biomodels” and biomarkers are shown in Table 6. Cross-fertilization between clinical and nonclinical studies is essential in establishing mechanistic insights and defining utility.

In early drug discovery, assay sensitivity of safety biomarkers is a critical consideration, as assay sensitivity is intimately linked with biomarker thresholds and compound exposure (amount and time); whether an effect is functionally adverse, reversible, and easy to monitor, and translates to humans; and what is an appropriate risk-benefit profile (for example, for oncologic therapy vs. one for a less serious condition).

Overall, early nonclinical biomarkers may be best considered for hazard identification, for hypothesis generation, and to guide clinical trial monitoring. It may be helpful to consider grading the sensitivity of the assay with the stage of development, with the expectation that multiple safety assays applied across more complex models during drug discovery and

TABLE 3 Strength of Evidence for Individual Biomarkers for Diagnosis or Prognosis of HF

Biomarker	Diagnostic Capability	Prognostic Capability
BNP	+++ (for HF)	+++
NT-proBNP	+++ (for HF)	+++
NGAL	+ (for kidney injury)	+++
High-sensitivity troponins	+++ (for myocardial injury)	+++
Procalcitonin	++ (for bacterial infection)	+++
ST2	0	+++
Galectin-3	0	++
Growth- differentiation factor-15	0	++
Mid-regional atrial natriuretic peptide	+++ (for HF)	+++
Adrenomedullin	++ (for congestion)	+++
CA125	++ (for congestion)	+++

Modified from Iqbal N, Wentworth B, Choudhary R, et al. Cardiac biomarkers: new tools for heart failure management. Cardiovasc Diagn Ther 2012;2:147-64.

BNP = B-type natriuretic peptide; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NGAL = neutrophil gelatin-associated lipocalin; ST2 = suppression of tumorigenicity 2.

development will ultimately inform on the safety liabilities of a molecule. Examples of preclinical in vitro models include myocyte-based studies involving acutely isolated myocytes and human-derived pluripotent stem cell-derived cardiomyocyte preparations (2-dimensional cultures, 3-dimensional engineered heart tissues, organoids). Other preclinical functional biomarkers include electrophysiology (delayed/abnormal repolarization) and contractility (motion, force). Preclinical soluble/morphological biomarkers include structural markers of cardiotoxicity (necrosis, apoptosis, cell viability), cardiac troponins, heart fatty acid binding protein, lactate dehydrogenase, the CK-MB form of creatine kinase, and microRNAs. Combinations of biomarkers also

TABLE 4 Characteristics of Biomarkers Used Surrogate Endpoints and Tools for Toxicity Monitoring in Heart Failure Clinical Trials

Surrogate Endpoint in CT	Tool for Toxicity Monitoring
Correlation between the impact of an intervention on the biomarker and the impact of that intervention on endpoint across interventions	Strong knowledge of biomarker biology
Biomarker should reflect B/R related to drug	Knowledge of potential AEs linked to abnormal biomarker results
Establish sampling strategies for the measurement of the biomarker and relative to the outcome	Establish sampling strategies with defined cutoffs
The effect of the intervention should be reflected by the biomarker	Understanding of temporal relationship between biomarker abnormalities and AEs
	Biomarker as “mediator” of AE to understand the mechanism of the AE

Modified from Ibrahim NE, Januzzi JL. Established and emerging roles of biomarkers in heart failure. Circ Res 2018;123:614-29.

AE = adverse event; B/R = benefit/risk; CT = clinical trial.

TABLE 5 Heart Failure Clinical Trials Where Biomarkers Were Used to Predict Efficacy

Trial (Study First Author) (Ref. #)	Findings	Role of Biomarker
RALES (Zannad et al.) (37)	Collagen biomarkers identified a group of patients showing greater benefit from spironolactone	Identify potential MoA
Australia-New HF-CT (Richards et al.) (38)	Baseline NT-proBNP predicted greater benefit from carvedilol	Understand benefits of a drug downstream to its MoA
CORONA (Cleland et al.) (39)	Lowest tertile NT-proBNP predicted benefit from rosuvastatin therapy in HFrEF	Identify a cohort of patients that derive benefit from a studied therapy
CORONA (Gullestad et al.) (40)	Galectin-3 values <19.0 ng/ml may predict benefit from rosuvastatin treatment in HFrEF	Identify a cohort of patients that derive benefit from a studied therapy
ST2 in CHF (Gaggini et al.) (41)	ST2 predicted benefit from high-dose beta blockade	Identify a cohort of patients that derive benefit from a studied therapy
Novel Biomarkers (Cao et al.) (42)	Neurotrimin may predict patients who respond to HF therapy	Identify a cohort of patients that derive benefit from a studied therapy

HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MoA = mechanism of action; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

have potential to provide a more comprehensive safety assessment.

For cardiac safety biomarkers in early drug discovery, the highest future priority is to define the strengths and limitations of in vitro models (which includes detailed characterizations of such models), along with an assessment of the advantages of human-derived versus animal-based models with respect to study questions. Defining fit for purpose applications for acute versus chronic studies using either in vitro or in vivo approaches involves consideration of study duration (acute vs. chronic effects), availability of resources, utility of single versus multiparametric endpoints, and overall translational fidelity. Dialogue between those with expertise in nonclinical and clinical settings will be essential to the interpretation of nonclinical findings and how they may translate to clinical effects. Oncological drug safety is likely to be the initial pathway for these in vitro human-derived cardiac safety biomarkers.

Gaps to remedy in the preclinical space (Figure 4) relate to:

- **Assays:** there is a need for clinical alignment on assay platforms to drive nonclinical alignment on

these platforms; assay availability across regions to mitigate issues of exporting samples; and assay feasibility, including the potential for multiple biomarkers on a single platform to reduce blood volume requirements, cost, and operational challenges.

- **Translational use:** gaps to remedy are: efficient biomarker clinical qualification; determining biomarker relation to functional endpoints; establishing biostatistical approaches and analytical tools; robust nonclinical and clinical reference range data on preferred assay platform solutions (including addressing pre-analytical collection variables); more broad Health Authority acknowledgment to use in an exploratory manner to generate foundational knowledge “at scale” if not immediately informing patient safety; and stronger and earlier prospective translational strategy within companies.

Focusing on potential preclinical uses for mechanistic assays in drug discovery and development (Figure 5), priorities over the next 1 to 3 years will be to calibrate assays with respect to current public clinical data and implement this information into study design; and over the next 3 to 5 years, will be to expand the public clinical reference dataset and encourage agency- and consortium-led database collation and interrogation.

POSSIBLE FUTURE APPLICATIONS OF CLINICAL BIOMARKERS

A 2019 FDA guidance document (24) indicates that biomarkers have potential utility in HF studies for enriching the appropriate cohort for study, stratification based on risk prediction, early proof of concept, and dose selection. In the future, known biomarkers—coupled with clinical, imaging, genomic

TABLE 6 The “Biomodel” and the Biomarker: Considerations for Nonclinical Biomarkers

	Clinical Biomarker	Nonclinical Biomarker
“Biomodel”	Established (human)	May need to be validated
Biomarker	May be well accepted/defined, reproducible	More flexible, experimental, utility ultimately defined by clinical studies
Linkage	Use may be guided by nonclinical studies	Importance ultimately defined by clinical studies
Purpose + expectations	Patient safety/efficacy	Guide selection of drug candidates, assess safety of drug and drug combinations Personalized therapies
Alternative considerations	Surrogate markers	Surrogate models and markers

FIGURE 4 Gaps to Remedy for Optimal Use of Biomarkers in Cardiac Trials

Factors to Facilitate Future State

Foundational Knowledge

- More Advanced Biological Qualification
- Reference Ranges; Robust Baseline Data (including disease populations)
- Demonstration of Biomarker Translatability
- More internal company knowledge to facilitate integration

Industry/Regulatory Mindset

- HA Letter of Support
- Biomarker qualification and reduced time to qualification
- Clear Acceptance Criteria by HA
- "Safe Harbor" space from HA
- More Guidance on how to Successfully integrate in an exploratory or qualified setting
- Practical approaches to demonstrate biomarker value

Resources

- Collaboration/Data Sharing/Informatics
- Biomarker Assay Availability and Fit-for-Purpose Validation
- Reduced cost
- More established company infrastructure and budget allocation
- Innovation by large companies and implementation by small companies

Process-Based

- Specimen Access/Retention
- Informed Consent

Desired Future State

Broad Biomarker Implementation

- Improved ranking of compounds
- Improved understanding of target engagement, MoA and efficacy
- Improved development strategy & speed/quality to market
- Faster dose escalation
- More confidence in setting MTD & ability to monitor toxicity
- Increased safety to market
- Decreased drug attrition in late stage
- Reduced/refined animal use
- Flexible interactions with regulatory authorities

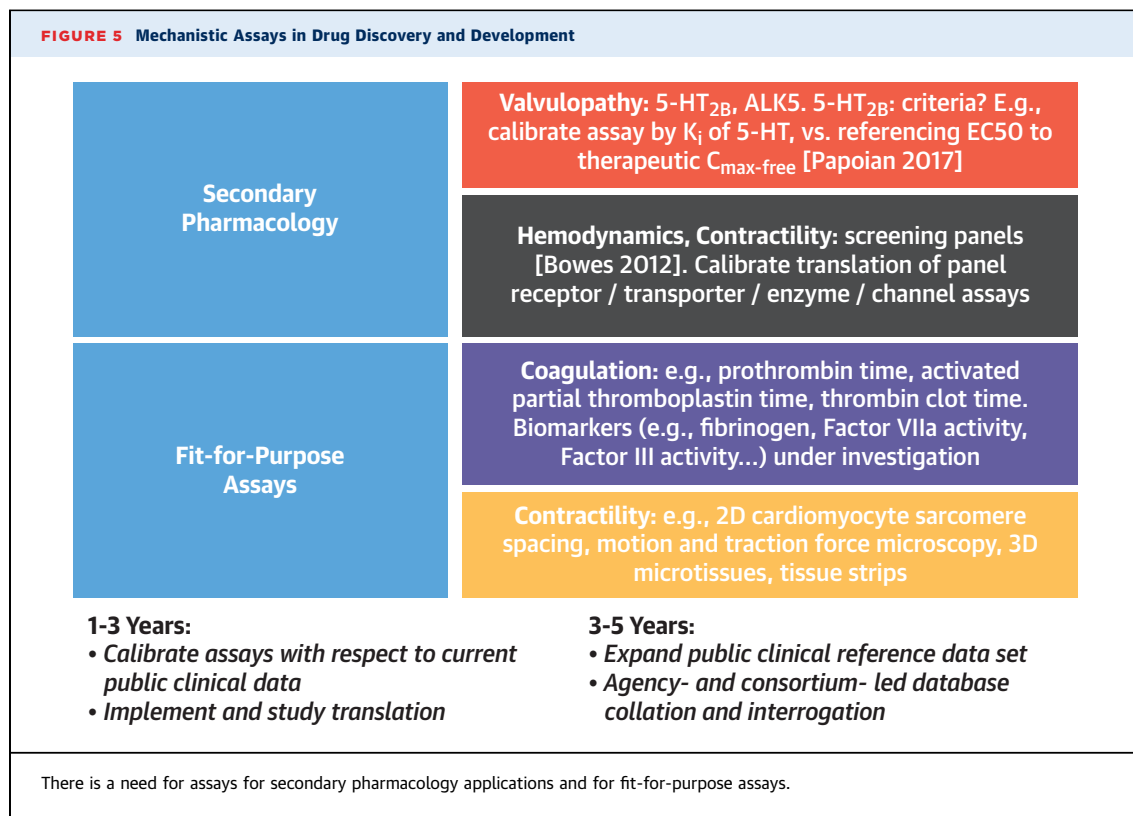
To achieve the desired future state for cardiac biomarkers, multiple gaps must be remedied in areas such as foundational knowledge, advancing their use in a regulatory setting, and development of additional resources and processes. HA = health authorities; MoA = mechanism of action; MTD = maximum tolerated dose.

and metabolomic data—may have a significant role in personalized medicine across the spectrum of heart disease (**Central Illustration**). The path to personalized medicine depends on focusing on the best ways to develop new therapies and optimize prescribing by steering patients to the right drug at the right dose at the right time (25). Future priorities for biomarkers in clinical trials include examining the possibility of adopting progressive approval frameworks such as those utilized for oncology/orphan drugs with intermediate endpoints that might be accepted for initial approval.

It was suggested that far too many studies have simply examined biomarkers that are already known, such as NT-proBNP or high-sensitivity cardiac troponin. In doing so, opportunities to identify novel biomarkers with far greater predictive value have been lost. Looking ahead, rather than using the "same old" biomarkers or even exploring single candidate biomarkers to help demonstrate safety and efficacy, a more fruitful approach would be an inductive strategy using multi-omics and machine learning to inform target proteins or pathways affected by therapies and/or predictive of their

benefit (26). Machine learning-driven multiprotein panels appear to be superior to single biomarkers and standard risk scores for numerous applications in cardiovascular disease and may help increase success rates in cardiovascular trials. They may also reveal previously unsuspected biological pathways in heart disease. For example, utilizing proximity extension assays, of 625 proteins assessed, Michelhaugh and Januzzi Jr. (26) found a core set of 5 proteins (NT-proBNP, endothelial cell-specific molecule-1, cathepsin L1, osteopontin, and macrophage colony-stimulating factor-1) common across stages C and D HFREF.

To allow for more accuracy for the application sought (e.g., diagnosis, prognosis), using machine learning, output from 'omics approaches may be empaneled with results for each biomarker weighted to allow for more accurate results than each biomarker individually. Examples of successful translation of 'omics findings into usable machine learning-based clinical panels include development of multimarker diagnostic panels for obstructive coronary artery disease (27–29), peripheral arterial disease (30), or aortic valve stenosis (31), as well as



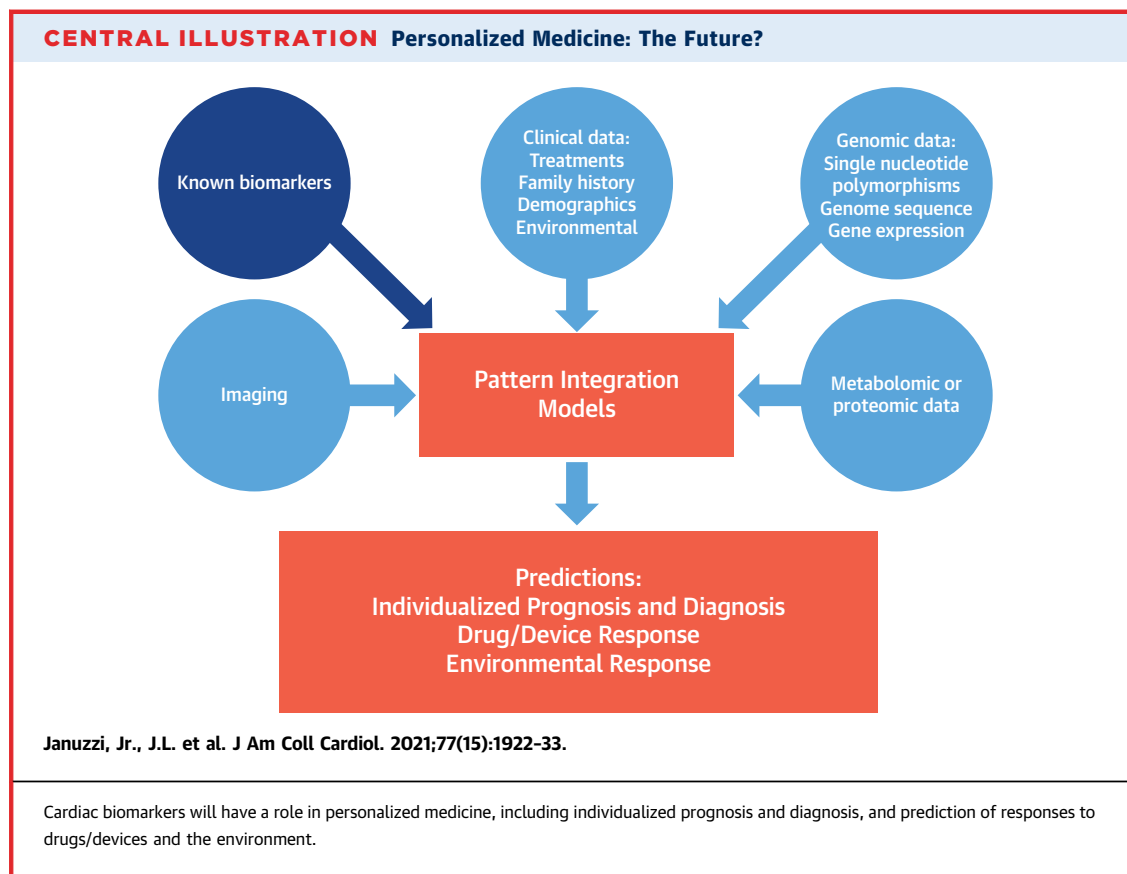
prognostic panels to predict new-onset HF (32) or acute kidney injury following diagnostic coronary angiography (33), and to prognosticate the “triple-MACE” endpoint of nonfatal myocardial infarction/nonfatal stroke/cardiovascular death commonly used in recent studies of therapies for type 2 diabetes (34).

Using approaches merging multi-omics with machine learning, drug developers might develop companion/complementary diagnostics for biomarker-driven/intermediate endpoints, create and/or revise guidance documents and scientific standards for cardiovascular outcome trials, and assess the successes and limitations of such an approach. In addition, these panels could be evaluated in regulatory setting, starting with biomarker qualification.

INTERMEDIATE-PHASE TRIALS. Biomarkers may play a role in trials at phase 2, 3, and 4 (Figure 3); however, their use differs substantially at each step. In phase 2 trials, biomarkers are frequently employed to support mechanistic hypotheses, whereas in phase 3 studies, they are utilized for inclusion/exclusion criteria, as well as efficacy and safety evaluation. In phase 4 analyses, biomarkers are most often utilized to provide further supportive data regarding an approved therapy. However, a universal problem

with this construct is the fact that studies at each step are typically designed without biomarkers in mind and ignore the need to consider developing biomarkers that specifically associate with the therapies being evaluated. It is necessary to emphasize the importance of integrating biomarkers much earlier into the clinical trial cycle of a therapeutic, to better understand how such markers might inform future results of larger studies. To improve understanding of the safety of HF therapeutics, more information should be expected regarding the biological link between the biomarker and therapeutic effects (positive or negative), and such analyses should be embedded as key secondary endpoints, rather than exploratory. Only through such an emphasis will a focus on how treatments affect biomarkers, and in turn how biomarkers inform response to and/or benefit from a therapy, be prioritized.

To move the field forward, a proposal was made for a “biomarker stage” in trial execution possibly between phases 1 or 2 of a new therapeutic. One consideration would be to start with a targeted or nontargeted proteomic approach, focusing on the most promising established and emerging biomarker options, and then taking an inductive approach to identify new candidates. Predictive algorithms using



bioinformatics tools involving several biomarkers may be informative, but would then require larger studies for validation, such as in ensuing phase 2 analyses. Through this approach, predictive markers could have a role in informing decision-making in early development.

BIOMARKER DATABASE. Another area for long-term improvement is the need to reach consensus on what cardiac biomarker information should be collected for safety and/or effectiveness purposes, and how this information (including names and techniques) and coding should be standardized to ensure consistency for future analyses, including meta-analyses.

RECOMMENDATIONS

Think Tank participants agreed that one reason this field is so complex is the lack of quality assurance carried out on currently used biomarkers (35,36). As a result, there is a lack of certainty about what biomarkers can reliably show. For example, novel biomarkers are valuable in HF diagnosis and prognosis; yet, additional guidance is needed on how best to include them in clinical trials—and during which

phase of clinical trials. International guidance on biomarkers in cardiac safety from a body such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use would be particularly helpful.

More data are needed to determine whether biomarkers might be used to inform long-term treatment decisions or to help decide when treatment should be changed or stopped. Greater standardization of the cut-offs currently used for various applications across trials would make it easier to carry out aggregated analyses.

The academic and regulatory communities should work together to ensure that all published information about biomarkers, including analytic information, is fully and clearly expressed, with more thorough testing of biomarkers in dedicated studies. Biomarkers with improved accuracy are needed to characterize and segment populations with cardiovascular disease into mechanistically distinct cohorts. Inclusion of exploratory biomarkers in large clinical trials would be helpful for validation.

There is a need for guidance on a systematic and standardized way to collect samples for future research (including the creation of a biobank or

repository), taking into account elements such as duration of sample retention. Infrastructure is needed for standardized reporting and cataloging of biomarker data, to help enhance biomarker discovery. First steps could include standardization of the collection and retention of samples for natriuretic peptides and troponins. These steps will help ensure more robust biomarker assessments and prepare for the possibility that sample archiving will be performed in the majority of patient trials. Ultimately, it is aspirational (although conceivable in the near-term) that biomarkers would eventually be incorporated into clinical practice guidelines to trigger specific therapies in patients most likely to benefit, allowing for a more personalized approach to treatment of heart disease.

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