CARDIAC BIOMARKERS IN CARDIOVASCULAR CLINICAL TRIALS: CAVEATS AND CONSIDERATIONS

Cardiac biomarkers can not only serve important roles in the diagnosis, management and prognosis of cardiac diseases, but they can also be significant tools in evaluating treatments in cardiovascular (CV) clinical trials. They can be used in patient selection, stratification, risk mitigation and assessment of safety and efficacy endpoints. While cardiac biomarkers hold much promise, there are a number of challenges in developing robust markers that can accurately reflect changes in disease biology linked to the mechanism of action of a therapeutic intervention.

In a recent webinar, experts from Medpace spoke about the current state of cardiac biomarkers in clinical trials, including key considerations when selecting and optimizing a biomarker, the importance of sample preparation and what the future holds for both blood-based and imaging biomarkers.

Richard Lee, MD, senior medical director in the medical department at Medpace, and board certified in cardiothoracic surgery, explains how the focus of cardiac biomarkers has been primarily on their use as diagnostic tools. Moreover, the field has generally been limited to two biomarkers — cardiac troponin and natriuretic peptides.

In CV clinical trials, cardiac biomarkers are most commonly included in efficacy and safety endpoints. For safety endpoints, cardiac troponin — either high sensitivity or standard — are used as markers for safety and myocardial injury and toxicity. Natriuretic peptides like N-terminal (NT)-pro hormone B type natriuretic peptide (NT-proBNP), or BNP, are routinely used for acute and chronic heart failure.

Cardiac biomarkers are also being increasingly utilized to determine trial eligibility by establishing common quantitative baseline characteristics. For example, cardiac troponin is now being used to identify heart failure sub-phenotypes in heart failure trails, explains Dr. Lee.

While the aim in many cases is to use biomarkers to assess a patient's quantitative response to a study drug, it is important to ascertain a link between the drug's mechanism of action and an ensuing biological effect in order for it to be a reliable readout of a drug response. This is a part of the precision cardiology approach and could lead to their use as prognostic indicators.

THE DOUBLE-EDGED SWORD OF CARDIAC BIOMARKERS

While cardiac biomarkers hold promise as relatively non-invasive biological indicators of cardiac disease, drug response and prognosis, Dr. Lee says they can be a double-edged sword. If implemented properly, they can aid in predictive population enrichment and match the right population with the right trial. They can also aid in a priori risk-based stratification, which is particularly useful for large cohort studies. Moreover, as surrogates, they can serve as important efficacy endpoints for early proof-of-concept studies.

However, the current limitations in the number of cardiac biomarkers and high screen failure rates due to biomarkers represent pressing issues in conduct of clinical trials. Moreover, availability of biomarker assays at clinical trial sites can vary, as every site does not test every biomarker. Furthermore, different assays can be used at different sites, leading to intra- and inter-lab variability. Methodologies for validating biomarkers can also differ across central labs and local labs used by different sites.

There is also the issue of alternative biological sources of the biomarker. For example, Dr. Lee says that they've now learned that cardiac troponin does not always equate to MI or cell death. "A good example of this is the GALACTIC trial in which increases in cardiac troponin did not necessarily correlate to increased levels of myocardial ischemia," he explains.

THE UTILITY OF CARDIAC BIOMARKERS AND THEIR CAVEATS

James Januzzi, MD, staff cardiologist at Massachusetts General Hospital and Hutter Family professor of medicine at Harvard Medical School, specializes in biomarker testing in heart disease and treatment of heart failure. He furthered the discussion on the wide range of applications of cardiac biomarkers and delved into some of the associated caveats.

Dr. Januzzi says the challenges faced in CV trials are particularly augmented in smaller studies, like Phase II trials "where biomarkers play a larger role in many ways because we're looking at mechanistic associations rather than hard outcomes."

Nevertheless, he says, "Biomarkers are here to stay and they will continue to grow. And [they] may ultimately take an even larger role with respect to safety and understanding pharmacodynamics."

Moving from a sole focus on diagnostics, Dr. Januzzi emphasizes that the field should aim towards a more precision-based phenotypic approach to therapeutic development in which biomarkers are going to play a key role. This involves linking the appropriate phenotypic identification with the therapeutic because this is based on prognostic response.

Dr. Januzzi says, "Tying the diagnostic and prognostic nature of markers into a companion diagnostic, or theragnostic is the ultimate goal." And this is based on an understanding of the shared pathology between a biomarker and the therapeutic.

The major challenge in developing a robust, validated biomarker as a companion diagnostic for clinical endpoints is the delineation of clear and careful associations between the biomarker and therapeutic so that they're aligned along the same biological pathway.

The use of a biomarker as a prognostic tool in disease monitoring under a therapeutic intervention is another chief goal; essentially, this is using a predictive biomarker to see which patients will respond. The field of cardiac biomarkers is not there yet, but Dr. Januzzi says there's a path that has been clearly identified in recent years about how we might achieve this goal.

LINKING DISEASE BIOLOGY AND THERAPEUTIC BIOLOGY

A robust disease-monitoring biomarker is one where a treatment would reduce levels of the biomarker and that change would reflect a tangible change in biology.

An example of this is the well-validated link between changes in natriuretic peptides following treatment with neprilysin inhibitors and valsartan, where treatment with beta blockers or an ACE inhibitor reduces natriuretic peptides in heart failure and has a better prognosis, describes Dr. Januzzi. However, this in no way indicates that there is a direct biological link, he says.

This is one of the reasons why surrogate endpoints fail, as "inevitably it often speaks to an intermediate step that we're not considering. And so, the reduction of natriuretic peptides after ACE inhibitors, for example, is more likely related to the reverse remodeling effects of the drug, which reduces wall stress and thus reduces natriuretic peptides."

A clear biological change caused by the biology of the therapeutic intervention is thus key to the validity of a biomarker. Therefore, "the issue is that it's not so straightforward to simply grab a biomarker off the shelf," says Dr. Januzzi.

On the other hand, neprilysin inhibitors cause a pharmacologic increase in vasoactive substances, particularly atrial natriuretic peptide, which, in turn, directly suppresses release of the BNPs. This is, therefore, an example of how a therapy is in line with the biological release of a marker. And in turn, changes in natriuretic peptides are strongly associated with cardiac remodeling, improved outcome and improvements in symptoms.

"That is a shining example of lining up biology with therapy, but unfortunately, numerous challenges exist that have slowed down our process in terms of how we think about the use of biomarkers," he says.

To develop such robust biomarkers, strong knowledge of biomarker biology will be critical in order to link the impact of an intervention with the changes in biomarkers. The marker really should reflect the biological effects of the drug mechanistically, stresses Dr. Januzzi.

Dr. Januzzi says it's striking how often biomarkers that are used in clinical trials have "rather tenuous links to the things that are being monitored."

For example, the use of troponins as a toxicity marker may be dubious, as demonstrated in the GALACTIC study where a rise in troponin was found to be unrelated to cardiac remodeling and clinical outcomes.

These types of signals should be elucidated prior to the initiation of large Phase II and Phase III studies, says Dr. Januzzi. "We shouldn't go barreling ahead thinking that we understand everything."

Another frequent error that leads to inefficiencies, according to Dr. Januzzi, is that patients will be treated with a promising therapy and then "we'll measure things after the study is over to figure out how the drug works. That is the wrong way to do it."

This type of thinking needs to be reconfigured. Looking retrospectively like this leads to ambiguity if a signal is found because a link between the biomarker and pathology cannot be elucidated from a non-mechanistic study. This leads to frequently walking down the same path in clinical trials and falling into what's called the "usual suspects syndrome," says Dr. Januzzi. For example, the usual suspects in clinical trials in heart disease are troponin and NT-proBNP.

"The problem is you can't utilize the same two biomarkers for every single application in clinical trials, in part, because the biology may vary dramatically from therapy to therapy."

It is therefore critical to understand the biology of both the disease and the therapeutics being evaluated. Moreover, the focus should shift to outcome measures that help determine whether the drug is actually helping the patient.

Dr. Januzzi explained how "In a think tank with the FDA, NIH and others, we had a discussion around the place where biomarkers may play a role, and among the different factors to facilitate a better future state, this includes a substantial improvement in our foundational knowledge. This includes biological qualification of markers, perfection of reference range understanding and robust baseline data in diseased populations. We often identify how these markers look in non-disease, but understanding biological variation and other important analytical factors is necessary."

A FUNCTIONAL FUTURE STATE

Even if a robust biomarker is identified, it can run into regulatory hurdles, which is why close relationships between sponsors and regulators is critically important in order to reduce time to qualification, making it important to work hand in hand, Dr. Januzzi says.

This also means beginning to look at biomarkers critically earlier during the trial process. Dr. Januzzi describes a "biomarker Phase II," which involves applying an unbiased inductive approach using omics-based approaches, such as proteomics, metabolomics, genomics and transcriptomics, to identify plausible drug-marker pairs. This could lead to the identification of novel pathways that might ultimately be translated into therapeutic intervention.

The key, according to Dr. Januzzi, is to think earlier, more intuitively and inductively, and use unbiased targeted omics approaches.

This can also involve bringing together the old and the new. The idea is that a future state could encompass a broad-ranging combination of previously discovered biomarkers with omics approaches and clinical data to identify and build patterned integration models that could be translated into better prediction of response, reduced risk, as well as improved safety and response monitoring and prognosis.

SAMPLING PROTOCOLS

Another important aspect of working towards the successful application of cardiac biomarkers in CV trials is the establishment of robust protocols for the collection and measurement of biomarkers in samples.

The pre-analytical aspects in clinical trials are frequently under-recognized as being critically important, particularly for large trials, and if a biomarker is "finicky with respect to its behavior in vitro," Dr. Januzzi says.

Biomarkers can be affected by temperature, time of day of collection and fasting conditions, among others. For example, if a biomarker is temperature sensitive, a sample cannot be left sitting at room temperature for a prolonged period-of-time. These kinds of factors must be considered by clinical trialists who may sometimes overlook them if they do not have the background or training in clinical trial biomarkers.

Another challenge is that there is no uniform standard for the methods and timings of blood sampling during a clinical trial.

"When we think about how to approach the use of markers in clinical trials, we have made a call in a manuscript for sponsors, CROs, AROs and trialists to think very carefully about sampling strategies…the more uniformly we approach this issue, the more we can align studies up," Dr. Januzzi says.

Therefore, sampling strategies, including methods of blood draws, processing and storage, are all critically important.

Kelly Millhaem, MHA, director of clinical trial management at Medpace, says it is critical to ensure that site staff are fully trained and thoroughly understand the risks to including biomarker sampling in study protocols.

The challenge often is that while a scientific team develops a protocol that includes a biomarker, its implementation is up to the trial management or laboratory team. They're responsible for making sure that the sites are trained and understand the risk of collecting and sampling at the appropriate time, and storing and shipping them under the appropriate conditions in order for the correct data to be extracted from the assay. "Providing guidance to sites helps to make sure that we've got the most reliable results we can get," Millhaem says.

MITIGATING RISK AND THE PATIENT EXPERIENCE

Liz Moore, DNP, advanced clinical nurse practitioner at Medpace, says that until the future of biomarkers arrives, CV clinical trials will have to continue to include and learn from the current markers.

Study enrollment involving partnerships between the scientific and operational aspects of biomarker use is key to enrollment without compromising the targeted patient population.

For example, Moore presented a Phase II study that faced problems enrolling participants for almost eight months. The eligibility criteria included a minimum BNP at screening in order to define and enrich the study population, but which turned out to be a significant hindrance to enrollment.

"A critical review of recruitment data, including screen failure reasons and biomarker values, provided the medical and operational teams valuable insights into how best to proceed," Moore says. Recognizing the pitfall, an amendment was made to the trial which allowed for flexibility, namely lowering the BNP threshold requirements, leading to complete enrollment. The amendment led to expanded inclusion of both newly identified patients as well as previously screen failed patients that became eligible for inclusion.

These types of lessons learned will help inform the better use of biomarkers in future trials.

Millhaem says such demonstrated biomarker lessons can have a significant impact on enrollment and timeline, as well as re-framing the question of eligibility criteria.

Typically, sponsors will use comparisons to similar trials and take into account their guidelines. “But we also want to be thinking about how those that may have changed since the prior [trials], and how those guidelines may have been implemented,” Millhaem says. “We may need to allow ourselves more time than we initially planned.”

Central to the enrollment process is the patient experience. “It’s important to ensure a smooth experience for the patient. We’re not wanting to [expose] study subjects to unnecessary procedures or increased burden,” Millhaem says.

One way to mitigate risk is to tier screening procedures in order to reduce invasive procedures and minimize costs, explains Millhaem. For example, in screening activities, laboratory procedures could be completed first, when possible, to allow time to await the results before moving the patient through to any imaging or physical function testing. This is particularly important in at-risk populations, such as those in heart failure or advanced CV studies.

Another way to mitigate some of the challenges of encountering biomarkers at the screening visit is using pre-screened testing or historical values as a guide to help investigators decide whether a prospective participant should be brought in for an actual screening visit. This can be implemented through a pre-screen consent form to enable testing to be done locally. Moore says they have also allowed sites to use historical values to provide some flexibility without risking the patient population.

For sites that don’t perform biomarker testing as their standard-of-care practice, database mining can be conducted. For example, if a site does not assess NT-proBNP high sensitivity and may have a standard BNP instead, or other laboratory values, Millhaem says they can help them use this data to deduce whether patients would be eligible. This involves working with IT teams at clinical sites to help mine databases and narrow their searches.

ENGAGEMENT AND EDUCATION ACROSS THE STUDY PROCESS

Making sure trial sites are educated on biomarkers and their use in patient selection is also critical. This includes training principal investigators on how the biomarkers are expected to be used in the trial. This also becomes important as cardiac biomarkers are being used in other therapeutic areas.

For example, a nephrology study may include CV endpoints to demonstrate safety of a drug. In this scenario, Millhaem says the study team would develop educational materials for the investigators to explain what the biomarker does, how it acts, the biophysiological pathways it acts through, how patients will be affected and how it can be expected to change as a result of that study.

The key is to ensure that investigators are educated on the endpoints and on board with the plan. This will allow for proper selection of patients, and also ensure that the biomarker is not treated as just another lab test as part of blood sample collection.

Although biomarkers such as BNP and troponin may be utilized within the clinical environment as standard practice, their application within clinical research can be less clear with respect to safety activities, particularly when the effect of the investigational product on the biomarker and population is unknown.

Therefore, to complement biomarkers, inclusion of additional safety procedures such as imaging, vital signs, safety labs and ECGs will support safety and risk mitigation needs, Moore says.

Multiple confounding variables may also be present. For example, use of BNP should take into account potential differences within specific phenotypes and characteristics of patients, such as obesity and HFrEF, conditions where circulating levels of BNP may be decreased. Variables such as race, renal function, BMI and gender should also be acknowledged within protocols.

CONCLUSION

As the discovery and use of cardiac biomarkers continues to evolve, it is crucial to weigh the pros and cons of their application in CV trials. This involves assessing whether a biomarker adds value or contributes to risk with respect to patients and interpretation of results. Despite challenges in selection and interpretation, if used appropriately, biomarkers can aid in the safety and risk management of patients.

Importantly, a solid understanding of biomarker biology and relationships between the disease-identifying biomarker abnormality and therapeutic intervention is key to a successful CV study involving cardiac biomarkers.

Conscientious selection of markers, clear safety parameters, defined clinical endpoints and investigator and trialist education are key to promoting the safety and protection of vulnerable study populations in CV trials.

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