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Promises to Keep: *Informing Healthcare Decisions through Cardiovascular Outcome Studies*

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FEBRUARY IS NATIONAL HEART MONTH

Despite the global burden of cardiovascular disease, investment in cardiovascular drug development has stagnated over the past two decades, with relative underinvestment compared to other therapeutic areas. There are multiple reasons for this trend, but of primary concern is the high cost of conducting cardiovascular outcomes trials (CVOT) in the current regulatory and commercial environment that demands assessment of risks and benefits, using clinically evident cardiovascular endpoints against a background of established therapies. Frequently, the absolute treatment difference over existing therapies in these large, logistically complex trials, has unclear implications regarding the value that should be ascribed to innovative therapy. Because of their scale and international footprint, standard of care variations across the entire sample make results interpretation contingent on examination of subgroups, sequence of treatment prior to randomization, or regional standards of care which can modify treatment effects.

Risk Stratification Analyses
To permit identification of patients most likely to benefit from therapy

Nested Studies
To capture all healthcare utilization during an episode of care

Administrative Claims Analysis
Based upon the population randomized

Concurrent Longitudinal Cohort Study
From patients who screened failed

Pharmaceutical companies are therefore pursuing innovative strategies in cardiovascular R&D to reduce the risk and cost of cardiovascular drug programs and assure market receptivity once product authorization has been achieved.

Implications from Landmark Heart Failure Trials

Two drugs have been approved recently for use in heart failure — ivabradine and sacubitril-valsartan — the first drugs to be approved for the treatment of heart failure since eplerenone. Both drugs' CVOT are methodologically rigorous and highlight challenges informing transitions in treatment. For example, the *Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial* (SHIFT) is the first study to specifically test the effect of heart-rate reduction on outcomes in a population with heart failure. In patients treated with ivabradine, relative risk of the primary endpoint (cardiovascular death or hospital admission for worsening heart failure) fell by 18% compared with placebo treatment.

However, the authors of the SHIFT article commenting on the limitation of the study recognize weaknesses that may represent hurdles in the translation of the study results into clinical practice guidelines and healthcare decisions. First, study patient selection (patients in sinus rhythm with high baseline heart rate (≥70 bpm)) of necessity restricted study implication to a subset of overall population with chronic heart failure. In addition, results from the study were achieved alongside background treatment including a β blocker; thus, no inferences are possible about the relative effects of ivabradine in absence of β blockers background therapy. And, despite repeated encouragement to the investigators to comply with conventional guidelines regarding treatment of heart failure, recommended target doses of background treatments were often not reached during the study. Eventually, results from this *classic* CVOT must be interpreted within the context of the population of patients with heart failure, contingent on specific subgroups of patients and patient management characteristics.

Enabling Value in Heart Failure Studies

Approximately 77% of medical costs following diagnosis of heart failure (HF) accrue during hospitalizations, and these expenditures are accentuated by the presence of concurrent morbidities. In the United States data requirements for formulary placement and reimbursement strategies are likely to vary based upon insurance coverage.

Therefore a companion initiative is recommended as a component of late phase HF investigations which could enable each of the following to support formulary placement and reimbursement mechanisms: *"risk stratification"* analyses using demographic and disease-related information within protocols prognostically important to the outcome; *"nested studies"* within practice microenvironments to capture all resources associated with patient care in an "episode of care;" facilitation of a retrospective data extraction process for an *"administrative claims analysis"* in study subjects by obtaining permission for that analysis as part of the eligibility criteria for the original protocol; inclusion of non-randomized patients (screen failure subjects) into a *"concurrent longitudinal cohort study"* providing an independent verification of healthcare utilization by those patients that approximate the clinical characteristics and care as included in the randomized trial.

Promises to Keep

All history of CVOT in heart failure considered, CVOT designs can be exploited to accommodate diverse objectives, including commercialization efforts predicated on demonstrating value during the course of clinical development. These activities can either modify the design or method of executing these studies without jeopardizing the primary hypotheses or append companion retrospective and prospective observational studies to examine complementary hypotheses that can inform healthcare decisions.

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