Thresholds for Using CV Outcome Studies to Evaluate Drug Safety During Development: Synopsis of the Feb. 19, 2014 CSRC/FDA/ACC Think Tank Meeting

A CSRC/FDA/ACC-sponsored Think Tank was convened at the American College of Cardiology headquarters in Washington, DC on Feb. 19, 2014 to discuss the use of CV Outcome (CVOT) studies to assess the cardiac safety of new medications during development. Efficacy CVOT studies have played a pivotal role in the development of many life-saving therapeutics in the cardiovascular arena (e.g., heart failure, treatment of acute coronary syndromes, stroke prophylaxis in atrial fibrillation). They have also been important in defining CV risks (e.g., the use of prophylactic antiarrhythmic therapy following acute myocardial infarction). Increasingly, CVOT safety studies are being utilized to assess the potential for CV risk in a variety of drug development arenas, including medications for diabetes mellitus, gastrointestinal, rheumatology, pulmonary, and obesity conditions. Requiring pre-approval randomized CVOT for safety has potential implications on drug development, including delays in bringing medications to patients who would benefit, the willingness of sponsors to make the needed investments, and in some cases, scientific challenges in performing the studies or evaluating the results in highly symptomatic disorders. On the other hand, public health is potentially impacted by medications with unrecognized CV adverse effects that are not appropriately considered in the benefit/risk analysis of a specific agent.

The purpose of this Think Tank was to explore and work towards developing consensus regarding the variables impacting the threshold for considering the need for randomized CV Safety Outcome Studies and understanding other potential alternative approaches to collect safety data. The Think Tank included presentations on the roles of safety CVOT studies, inherent issues, benefits, the value of information analysis and statistical approaches, and the use of case examples (aliskiren, varenicline, sibutramine, tegaserod, tiotropium, dronedarone, and rosiglitazone). Other methodologies for evaluating CV safety, including the FDA Sentinel effort, electronic databases, and prospective comparator-controlled observational studies were explored. Areas of consensus were arrived at through discussion.

General Points of Consensus

- It is impractical to require CVOT studies for every drug in every therapeutic area - so meaningful, rational thresholds are key
- Major biomarkers for CV risk should be adequately collected (e.g., BP). If a signal develops, it needs to be examined in future investigations. Standard definitions for events should be used. How real the signal is likely to be needs to be carefully considered.
- Small imbalances of events are fraught with difficulty in interpretation.
- Is there a potential mechanism of action to explain a signal? Might this be molecule-specific or a class effect?
- Hazard Ratios are one way to measure CV risk; the number needed to harm (with confidence intervals) is a key concept and appears to be more clinically relevant in low risk patient populations than the hazard ratio, where the absolute effects are most informative.

- Value of information analysis can be used to gain insight into the potential benefits of performing a specific study.
- Meta-analyses should be undertaken with a prospective protocol and are generally hypotheses-generating; similar issues exist for subgroup analysis and ideally they should be prospectively defined. Meta-analyses results need to be considered in the appropriate perspective. Whether the trial data that led to the concern should be included in the meta-analysis is controversial.
- Consider prospectively adjudicating CV events during development for a drug that might have a MOA of concern, be a member of a class that has a drug with known risk, or if the drug is used in "high" CV risk patients.
- Well-designed observational/registry studies may be of significant value and can also identify non-MACE risks.
- MACE need not be endpoint for all CVOT studies, as the MOA of a drug may point to another CV risk (e.g. CHF hospitalizations for a drug with negative inotropic effects).
- Having a diverse patient population studied when a CVOT is performed is important to understand the potential for risk in subgroups.

Specific Areas of Consensus
Regarding Thresholds for Performing CVOT Safety Studies

- The level of risk that needs to be excluded is highly dependent on the potential benefit. The optimal approach should consider the baseline CV risk of the patient population.
- When there a potential CV Risk observed with the drug:
    - If there a meaningful CV risk signal observed during development of the specific agent- favors CVOT study.
    - If there a well-known mechanistic molecular class effect- favors CVOT study.
    - If there is another drug in the class with a risk, but not a generalizable mechanistic effect and no signal in the current development program- favors alternative approaches.
    - How large an imbalance (i.e., risk signal), given the lack of confidence in small numerical differences, constitutes a meaningful signal must be considered and handled on an individualized basis.
- CV Risk of the target patient population
    - Low baseline CV risk of the patient population- favors alternative approaches.
    - Number needed to harm (absolute risk) to be considered for clinical relevance; hazard ratio is an indicator of harm.
    - Enrichment can be considered, but often not very practical in a low CV risk cohort.
- Highly symptomatic patient population
    - CVOT studies are very difficult from practical and scientific standpoints and thus favors alternative approaches.
        - Dropouts, inability to have an event driven design, potential ethical issues regarding the use of placebo.

- Biomarker findings
    - Validated, likely meaningful safety biomarker findings if the risk cannot already be well-estimated from previously available data (e.g., BP increase)- favors CVOT study.
    - No strong validated biomarker findings- alternative approach or no further evaluation needed without additional signals.