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Cardiovascular Safety Outcome Trials: A meeting report from the Cardiac Safety Research Consortium

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This White Paper provides a summary of presentations and discussions at a Cardiovascular Safety Outcome Trials Think Tank cosponsored by the Cardiac Safety Research Consortium, the US Food and Drug Administration, and the American College of Cardiology, held at American College of Cardiology's Heart House, Washington, DC, on February 19, 2014. Studies to assess cardiovascular (CV) risk of a new drug are sometimes requested by regulators to resolve ambiguous safety signals seen during its development or among other members of its class. Think Tank participants thought that important considerations in undertaking such studies were as follows: (1) *plausibility*—how likely it is that a possible signal indicating risk is real, based on strength of evidence, and/or whether a plausible mechanism of action for potential CV harm has been identified; (2) *relevance*— what relative and absolute CV risk would need to be excluded to determine that the drug had an acceptable benefit-to-risk balance for its use in the intended patient population; and (3) how plausibility and relevance influence the timing and approach to further safety assessment. (Am Heart J 2015;169:486-95.)

The Cardiac Safety Research Consortium (CSRC)[1] was created on the basis of the principles of US Food and Drug Administration's (FDA's) Critical Path Initiative to facilitate collaborations among academicians, industry professionals, and regulators to develop consensus approaches addressing cardiac and vascular safety issues that can arise in the development of new medical products.[2] This article presents discussions of relevance to biopharmaceutical sponsors, scientists, clinicians, and regulatory authorities involved in the development of new molecular entities and specifically the cardiovascular (CV) safety of drugs. The views expressed herein do not represent new regulatory policy.

A Think Tank cosponsored by the CSRC, the FDA, and the American College of Cardiology was convened at the American College of Cardiology's Heart House on 19th February 2014 to discuss when CV safety outcome trials are needed to assess the CV safety of drugs during development and after approval and commercialization. Public health may be affected by therapeutic agents with unrecognized CV toxicities that lead to adverse events and that are either not identified or well characterized in the standard preapproval development program.[3] Where concerns about such events have arisen, CV safety outcome studies have been performed in a variety of therapeutic areas, including arthritis and pain, coronary artery disease, diabetes, obesity, and pulmonary diseases, and have been proposed for other therapeutic areas, such as gastrointestinal disorders. At the same time, there are adverse consequences to conducting CV safety studies when they are not needed— they drain resources from development programs, potentially delay approval, diminish public confidence in a new therapy, and potentially discourage drug development. Thus, there needs to be a consideration for the appropriate threshold for deciding to conduct CV outcome studies.

A major goal of the meeting was to enumerate factors to consider in determining whether a preapproval or postapproval CV outcome study should be called for. A secondary goal was to explore alternative approaches for

collecting CV safety data. There were 4 major topic areas: (1) general overview of CV outcome trials to assess drug safety; (2) clinical studies that have addressed individual therapeutic agents; (3) the rationale for a regulatory requirement of a CV outcome study and the generalizability of data from a CV outcome study to other agents in the same class; and (4) alternative approaches to randomized, prospective CV outcome studies to evaluate drug safety, including use of observational studies, registries, and electronic health records (EHRs).

Therapies used for a variety of indications may have a negative impact on the CV system.[4,5] Although effects on clinical biomarkers (eg, QT interval, blood pressure [BP], or lipoproteins) may be indicative of CV risk from a drug, many surrogates may not be adequate to exclude CV risk, or the incidence of potentially serious CV adverse events (SAEs) may be too low to detect in a traditional development program, particularly if the primary end point under consideration is noncardiac, such as weight loss, lowering of hemoglobin A1c, treatment of arthritis, or treatment of opioid-induced constipation. Some well-known examples of cases of CV safety issues in drugs for non-CV disorders include terfenadine, cisapride, and rofecoxib.[6] To varying extents, these development programs were affected by unknown or unexpected concerns at the time of preclinical assessment (eg, corrected QT interval prolongation for terfenadine and cisapride and hypertension, salt and water retention with rofecoxib), enrollment of low-risk participants in clinical trials with the consequence of a relatively weak signal of harm, and ineffective postmarketing surveillance for CV events.

Examples of CV outcome studies in drug development

Routine use of CV safety outcome studies in the absence of identified safety signals has to date been mandated for only one therapeutic area—diabetes mellitus. The FDA's December 2008 Diabetes Guidance[7] does so; in addition, the FDA's 2007 draft guidance addressing antiobesity drugs states that "it may be appropriate for some weight-management products to have specialized safety assessments," but does not necessarily recommend CV safety outcome studies for all new drugs.[8] Results from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial, completed in 2009, indicated drug-induced increases in BP and heart rate,[9] signals of possible concern. The trial also showed increases in myocardial infarction (MI) and stroke rates on sibutramine relative to placebo. More broadly, uncertainty with the CV safety of new modalities for the treatment of obesity has generally led to requirements similar to those for new drug therapies for type 2 diabetes.

Regulatory decisions have been influenced by data from CV safety outcome studies. As a consequence of the results from the SCOUT trial,[9] at the FDA's request, sibutramine's sponsor voluntarily stopped marketing the drug in the United States. Meta-analysis of rosiglitazone on CV safety[10] raised the possibility of increased MI and death, and these concerns, reflected in labeling together with prescribing restrictions in a Risk Evaluation and Mitigation Strategy required of rosiglitazone's sponsor in September 2010, reduced the use of the drug by >90%. Subsequently, however, in November 2013, results of further analyses of outcomes data from the RECORD trial,[11] which had not been considered convincingly negative, led the FDA to remove these restrictions. To date, 2 large diabetes CV safety outcome trials for agents in the dipeptidyl peptidase 4 inhibitor class have been performed,[12,13] and neither has shown an increase in major adverse CV events (MACEs) relative to placebo in diabetic patients at elevated CV risk.

Plausibility

The first critical decision is always whether the development program has a signal that warrants a study of CV outcomes, either because of a suggestion of an adverse reaction or because of a mechanism of action detected in early development. For signals within the database suggestive of harm, the following are considerations.

Statistical plausibility. Within a development program, there are many possible findings and it is critical to be conscious of the risk of multiplicity due to various end points (acute MI, nonfatal stroke, CV death, hospitalization for heart failure) and the various subgroups that populate multicenter trials (age, gender, ethnicity, comorbid CV history, and geographic region). Hence, safety evaluation within a phase 3 program provides opportunity for a trend to be manifested in one or more risk assessments by chance alone.

Within-study considerations. Subgroup analyses of clinical trial data can be clinically informative if performed and interpreted with appropriate caution. For example, it might be biologically plausible that certain well-defined subgroups would respond differently to a particular drug than other equally well-defined subgroups. For example, in the EXAMINE trial,[12] CV death, a prespecified and adjudicated end point, was reduced significantly in the female subgroup on alogliptin vs placebo but neutral in the male study patients. However, subgroup differences should not be overinterpreted, and the analyses should ideally be prespecified. Both Matthews[14] and Sun et al[15] have distinguished between 2 tactics to subgroup formation: having a limited number of subgroups identified a priori with an apparent biological/clinical reason for anticipating a difference of interest, and subgroups whose apparent significance is derived post hoc and arises only as a result of having done the primary analysis. If the purported difference in subgroup mean responses is identified in a prespecified manner, the observation would be taken much more seriously than if it becomes evident through retrospective analysis.[14]

Cross-study considerations. Signals arising from meta-analysis of multiple studies within a development program raise additional issues.

Meta-analysis is a statistical method of pooling data from multiple independent studies, weighted according to their sample sizes, to determine an overall effect.[16] Considered an important methodology in evidence-based medicine, meta-analysis is a potentially useful technique in identifying CV safety issues, particularly within a particular drug development program where the drug of interest will be tested at several doses and in a variety of populations, controlling for heterogeneity.

As in primary data collection research, meta-analytic methods need to be carefully determined and performed at the highest scientific standards to yield clinically meaningful and reproducible findings. The fundamental steps in conducting a meta-analysis include the following: identification of a testable hypothesis, ideally with biologic plausibility, and clinical importance; identification of all pertinent studies; establishing criteria for whether the data from an identified study report will be incorporated into the meta-analytic dataset; data extraction (preferably participant-level data, but oftentimes study-level data are used and reported in the literature); conducting a quantitative test of the homogeneity of treatment effects among studies; deciding whether to use a random-effects model (typically the more appropriate approach for reasons discussed shortly) or a fixed-effects model; conducting the meta-analysis; evaluation of the robustness of the results; and appropriately circumspect dissemination of the results and the authors' interpretations and conclusions. Only 1 of these 9 steps is the conduct of the meta-analysis itself, and it is important to note that meta-analysts determine which existing data are entered into the database they create and then analyze.[16] In the case of a particular drug development program, the FDA may encourage the sponsor to perform a meta-analysis for CV safety using all the randomized, controlled data (from phase 2 and phase 3 trials) available in the development program and using participant-level data.

A key issue is whether the meta-analysis should include a study that spawned concern and was the stimulus to perform the meta-analysis.[10] That is, does one seek independent confirmation of a suspected signal? At least one analysis should exclude the hypothesis-generating study.

Although meta-analyses are a plausible way to increase sample size, there have been a number of examples where risk identified by meta-analyses was not confirmed by clinical trials.[10,11,17-20] An informative example was a meta-analysis of 17 trials involving inhaled short- and long-acting muscarinic antagonists indicated for chronic obstructive pulmonary disorder (COPD),[17] in which a fixed-effects model was used. Singh et al reported a relative risk ratio for CV events of 1.6 (95% CI 1.22-2.10), concluding that inhaled anticholinergics were associated with a significantly increased risk of CV death, MI, or stroke among patients with COPD. However, at the time, the UPLIFT trial, a 4-year, randomized, double-blind, placebo-controlled trial of Tiotropium HandiHaler involv-

ing almost 6,000 COPD patients and using an independent mortality adjudication committee[18] was nearing completion. The results from UPLIFT, which generated nearly 18,000 participant-years of exposure, showed no increases in MI, CV death, or all-cause mortality on the Tiotropium Handihaler.[18] Because of the strength of the UPLIFT clinical trial data and the potential limitations of the Singh et al[17] meta-analysis, the FDA concluded that there was not an increased risk of stroke, MI, or death associated with Tiotropium HandiHaler.[21]

Another example demonstrates how 2 meta-analyses of the same drug and CV clinical outcomes can result in different conclusions. In 2011, a meta-analysis evaluated the CV safety of varenicline, a nicotine receptor agonist/antagonist that is indicated for assistance in smoking cessation.[22] The summary statistic presented was a Peto odds ratio, and the authors concluded that varenicline significantly increased the risk of CV SAEs by 72%, odds ratio 1.72 (95% CI 1.09-2.71), which led to a great deal of press coverage. Based on the upper bound of the CI, the risk could be as high as 2.7-fold. However, the absolute difference in CV events was less than a quarter of 1% (0.24%): 52 of 4,908 (1.06%) on varenicline vs 27 of 3,308 (0.82%) on placebo. Although varenicline treatment was for a 12-week period and the drug is cleared from the body within a week after discontinuation, the meta-analysis examined events occurring at any time during follow-up. The study participants averaged a decade of smoking and, hence, were at increased risk for CV events. The European Medicines Agency noted various limitations of the meta-analysis, including the low number of events seen, the composite of events counted, the greater dropout over time in people receiving placebo, the lack of information on the timing of events, and the exclusion of studies in which no one had an event.[23]

In 2012, in an effort to address these identified limitations, a meta-analysis conducted by Prochaska and Hilton[24] included treatment-emergent CV SAEs in all published randomized controlled trials (RCTs) of varenicline use for smoking cessation, with these SAEs being defined as occurring during the drug treatment window and within 30 days of discontinuation from treatment. Applying the same event criteria to ensure comparability with the prior meta-analysis, the rates of treatment-emergent CV SAEs were 0.63% (32/5,431) on varenicline and 0.47% (18/3,801) on placebo, yielding an absolute and nonsignificant (P = .22) difference of 0.16%.[24] For comparison, Prochaska and Hilton[24] reported 2 relative estimates of effect, and they too were all clinically and statistically nonsignificant.

Although well-conducted and appropriately reported meta-analyses can provide useful information in many circumstances, less rigorous meta-analyses can provide misinformation.[21] In November 2013, the FDA held a public meeting entitled "Meta-analysis of randomized controlled clinical trials for safety evaluation"[25] and

released an associated paper encapsulating current thinking on this topic aimed to spark discussion and suggestions from attendees; comments submitted from the public on this topic will be considered by the FDA during their preparation of an Industry Guidance on meta-analyses.[26]

Mechanistic plausibility. The presence of biologic plausibility can help in interpretation. When considering "class effects," the likelihood of concern is enhanced if the drug's primary (known) target is associated with a CV risk, as compared with an unknown off-target effect, which other drugs in the class may not manifest. In this regard, it is important to understand drug and class effects on major CV risk biomarkers, such as changes in BP, lipoproteins and other metabolic parameters, and the coagulation cascade; if such signals are identified, they should be fully explored.[27] When there is another drug in the class with a known risk, but not a generalizable mechanistic effect, and no signal in the current development program has been observed, the case for further workup is less compelling.

Class effects hint at a mechanism, whether it is understood or not, so an adverse effect seen in multiple members of a pharmacologic class (eg, nonsteroidal anti-inflammatory agents) support plausibility that the findings will pertain to the drug under study. Where meta-analysis is considered to build a case for a signal across a class, see the earlier discussion of methodological considerations.

Without having any insight into a mechanism for CV harm, it is difficult to define an end point for further study. The MACE composite end point (comprising CV death, MI, and stroke) has been uniformly used, but there could be other considerations for "hard" CV end points. If the finding is an increase in sudden death, does one include arrhythmias and ischemic events in further studies? If the finding is MI, does one include noncardiac thrombotic events, angina, and CV interventions? Including components that are not related to the finding of interest has the effect of diluting a signal in the safety study.

Relevance—assessment of risk

This discussion is primarily about CV SAEs occurring in a setting of a development program for a product whose claims may not support much risk, either because of a modest benefit or because of the availability of many alternative therapies. Where a drug offers significant clinical benefit—preservation of life and reduction in hospitalizations—the tolerance for risk is higher, both in terms of well-characterized events and in terms of those for which the nature and upper bound are ill-defined. These situations rarely lead to a requirement for CV outcome studies. Cardiovascular outcome studies are more common when a drug intended for long-term use has a modest, albeit potentially important benefit.

A potential doubling of (CV) risk might be acceptable in a population of very low absolute risk where the primary indication is clinically meaningful and for which there are limited effective alternatives, but unacceptable in a population otherwise at high risk. The duration of therapy also must be taken into consideration because modest increases in CV risk over a period of multiple years could be consequential. That is, although we often speak about *relative* risk—because that is the way in which risk is usually analyzed and because we model risk conceptually as if relative risk from an intervention was preserved as one looks across the spectrum of absolute baseline risk—it is *absolute* risk that is most relevant to decision making.

The decisions affected include whether one should approve a drug at all, and, if so, whether its use ought to be restricted to a population with a low baseline risk. If available data raise a concern but do not enable one to make an adequately informed decision regarding the conditions of approval, one has various options to collect more information, which we discuss in subsequent sections. However, if further data are needed, it is likely that those data will need to be obtained from a population enriched by virtue of a high baseline risk, because the trial may otherwise not be feasible. In such cases, there is the usual unspoken assumption that the relative risk seen in the high-risk setting is also informative about the low-risk setting.

There are intrinsic difficulties in benefit-risk assessment for non-CV drugs because benefits and CV risks are, in general, often qualitatively dissimilar (one exception might be an effective oncologic therapeutic agent in which reductions in cancer deaths offset potential increases in CV morbidity or mortality). It is challenging to reconcile even small increases in irreversible adverse events such as MI or stroke with symptomatic benefits such as relief of arthritis pain, improvement in refractory constipation, or improvement in pulmonary function, even if they are clinically important. Other benefits such as smoking cessation, weight loss, or lowering of glycated hemoglobin—that may have outcome implications—might lead to greater acceptance of adverse CV events, but only if clear superiority to alternatives is shown. As major CV events are not very commonly observed during early cycle or midcycle evaluation of a new chemical entity, evaluation of new drugs requires careful evaluation of pharmacologic effects that might lead to such outcomes. During early drug development, the pathophysiologic links between a new chemical entity and CV events may not be apparent, but if the various concerns are given ample consideration (see Table I), it should lead to greater scrutiny of CV effects during phase 3 development.

Evaluation of benefit and risk in phase 3 clinical efficacy and safety studies also requires different approaches. Evaluation of benefit is usually performed through relatively small RCTs in which every participant has the clinical condition of interest, and hence, every participant randomized to the treatment arm of interest contributes efficacy data, making evaluation

Table I. Mechanistic-clinical findings that could incur concerns if observed during clinical development

Finding	CV concern
Antinatriuretic properties	Hypertension, heart failure
Moderate increases in BP	Increased risk of stroke, heart failure, and MI
Alterations in coagulation, platelet function	Thrombosis (deep venous, arterial, pulmonary embolism), ischemic cardiac events
Metabolic aberrations—lipids, glucose	Enhanced atherosclerosis
ECG abnormalities	Arrhythmias, sudden death, embolic stroke (AF)

Abbreviations: *ECG*, Electrocardiogram; *AF*, atrial fibrillation.

relatively precise as evidenced by acceptably narrow CIs around the treatment effect point estimate. For example, changes in glycated hemoglobin can be assessed by relatively small and short-term (12-24 weeks) RCTs, and these preapproval trials are unlikely to approach the duration of chronic use. The standard phase 3 RCTs are powered and designed, including the choice of dose(s) used, to test the primary efficacy end point, with the consequence that they are almost always underpowered to detect a meaningful difference in the incidence rates of serious CV events. Furthermore, serious CV events are relatively infrequent, in part, because high-risk candidate participants are excluded from eligibility to remove confounding influence on the efficacy results.

Safety evaluation during clinical efficacy RCTs in these examples would be unlikely to discover CV risk. The situation can be exacerbated by failure to characterize the study population for intrinsic CV risk and by failure to detect and characterize CV events because of a lack of prespecified diagnostic criteria, ambiguous and overlapping Medical Dictionary for Regulatory Activities terms,[28] and lack of event source documentation. Efficacy trials for most non-CV therapies do not prospectively adjudicate potential CV events. Some of these failings are remediable by paying closer attention to and adjudication of the CV events. Although a focus on MI, stroke, and CV death assessment may not be very difficult, the low event rates do, however, remain a problem even if the controlled trial data are pooled.

During the 3 customary phases of the drug development process, an algorithm for CV safety assessment is shown in the Figure. Proactively collecting and adjudicating information during early- and mid-drug development avoids problems associated with imprecise or missing data and is key to success. Assuming that no preclinical signal of CV toxicity has been identified, more intensive collection of CV information might occur during phase 2 and early phase 3 studies if the population targeted for a particular therapy will be one with increased CV risk (eg, older adults, patients with coronary artery disease, heart failure, or diabetes mellitus) or if there is some known potential for the drug to increase CV risk (eg, increasing BP, prothrombotic tendencies, and creating metabolic disturbances). It is also important to initiate a prospective CV adjudication process for potential CV events in phase 3 if there is a CV safety concern that was raised during earlier phase development, as noted previously.

## Is further safety information needed?

Plausibility of a risk and its clinical relevance determine the need for further study. A key purpose of the Cardiovascular Safety Outcome Trials Think Tank was to explore issues and concerns that might influence the need for randomized CV safety outcome studies, as well as to understand potential alternative approaches to collect safety data (see Table II). It was recognized that it is not practical to require CV outcome trials for every drug in every therapeutic area; the expense of these studies is enormous, they may take many years to complete, the likely yield for drugs without potential safety signals during the standard 3 phases of development is almost certainly very small, and their indiscriminate use could hamper innovative drug development for patients with unmet medical needs. Thus, it is of critical importance to use a large-scale CV outcome trial only when clearly needed. A number of factors go into this determination, including the presence of a meaningful imbalance in identified CV events during earlier stages of development, a known target-based MOA of concern, and the presence or absence of potentially important effects on CV biomarkers (Table I and Figure).

The level of risk that needs to be excluded is highly dependent on the potential benefit. It is important to consider the baseline CV risk of the patient population because it has a significant effect on the optimal approach to assessing potential CV risk. The Think Tank explored several specific scenarios (see Table II).

Cardiovascular risk in the target patient population. A low baseline CV risk of the patient population (eg, < 5-7 MACE events per 1,000 patients per year) favors alternative approaches to a conventional CV outcome trial because it would take an extraordinarily large study to identify an incremental risk in a patient population with such low CV risk. Although enrichment of a study population with patients at higher CV risk is an approach that is considered in other scenarios, obtaining a sufficiently high-risk study population may be infeasible. Observational and other studies in low-risk populations should therefore be considered. These may well be able to detect a substantial increase in CV risk (eg, ≥2-fold).

Figure

Conceptual developmental framework for CV safety considerations during drug development
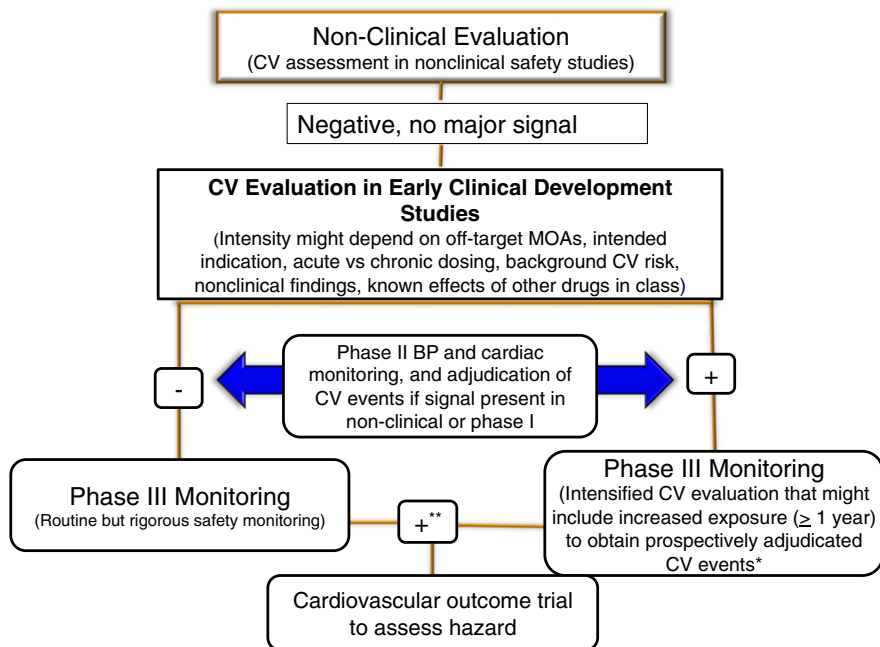
* Not powered to be a formal CV outcome study;

**CV signal has been identified that would lead to the requirement of a CV safety outcome study.

Conceptual developmental framework for CV safety considerations during phases of drug development that assist in the decision-making process to perform a CV outcome study.

Symptomatic patient populations. Cardiovascular outcome studies are difficult when patients are highly symptomatic (eg, arthritis syndromes and severe constipation) and the investigational agent is designed to reduce symptoms, particularly if the comparator is placebo, where high dropouts can be expected. In addition, the length of follow-up may be substantially different in the placebo and active arm cohorts, thereby impacting interpretation, which may be further confounded by an increased likelihood of missing data.

Study types and timing

Once it is concluded that additional data are needed, issues include what is needed preapproval and post-approval, the technical specification of requirements, and how most efficiently to satisfy these requirements.

What data and when are they obtained? One could conclude that the risk is plausibly so large that it would overwhelm treatment benefit, in which case information to rule out excessive harm would need to be obtained prior to approval. It is also possible that the net benefit is sufficiently established to support approval, but that it would still be useful to place some upper bound on a risk, in which case one would endeavor to obtain such information in the post-marketing setting. Another possibility is that some upper bound on risk is desirable preapproval, and some further resolution is desirable postapproval. This was the case for the FDA's 2008 guidance for evaluating drugs for the treatment of type 2 diabetes mellitus.[7] A rigorous but feasible upper limit of harm was defined for type 2 diabetes (ultimately, a postapproval upper bound of the 95% 2-sided CI of 1.3). For other clinical indications and drug classes, this upper bound may not be generalizable. It is unrealistic to consider the long-term use of a placebo treatment arm or a treatment involving an inferior control comparator treatment when studying drugs shown to have real clinical benefit.[29]

Specifying requirements. The CV safety concern is usually related to MI, so the choice of end points is typically the MACE composite end point, but other events including hospitalized heart failure and urgent CV revascularization for unstable angina may be used as well, depending on the mechanism of action of the therapeutic agent or the population targeted for treatment. The advantages of composite CV end points (faster

Table II. Considerations regarding need for CV safety outcome 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.
- Plausibility influences when to get additional information and how such data might be obtained.
  - ○ High plausibility favors the traditional outcomes study
    - ▪ Compelling evidence within a study
    - ▪ Evidence from other members of the pharmacologic class
    - ▪ Mechanism of action, especially from established biomarkers
  - ○ Low plausibility favors "alternative" approaches
  - ○ Meta-analyses and subgroup analyses
- Low absolute risk favors alternative approaches to augment safety information—or nothing.
- Highly symptomatic patient populations:
  CV outcome trials are difficult to design and conduct in highly symptomatic patients (inability to have an event-driven design, ethical issues regarding the use of placebo as well as differential, and often large, dropout rates); hence alternative approaches to CV outcome trials are preferred.
  Meta-analyses and subgroup analyses
  Should be undertaken with a prospective protocol using rigorous scientific methodologies and are generally hypotheses generating. Meta-analyses results need to be considered in the appropriate perspective and subgroup analyses should be predefined.
- CV event adjudication
  Consider prospectively adjudicating CV events during development for a drug with a potential safety signal 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 patients with high CV risk.
- MACE
  MACE need not be an end point for all CV outcome studies, as the MOA of a drug may point to another CV risk (eg, CHF hospitalizations for a drug with negative inotropic actions).

Abbreviations: *CHF*, congestive heart failure; *MOA*, mechanism of action.

accrual of a needed total number of events in event-driven trials, avoidance of statistical multiplicity issues) are well recognized. However, using a composite end point for a safety analysis that combines irreversible events (eg, MI and stroke) with reversible events such as hospitalization for unstable angina *not* requiring urgent revascularization may dilute the composite. Furthermore, forming a composite from a set of events that do not necessarily represent the same suspected drug activity (eg, atherogenic vs arrhythmogenic) can add noise and lead to loss of power to detect the original CV concern.

Typically, the primary efficacy analysis uses the intent-to-treat population to understand if the drug is efficacious in all participants randomized to treatment or control and to minimize the potential for informative censoring. However, this may not be the best approach to assess drug safety, where the participants actually exposed (the per-protocol population) is more relevant or where the effect of a drug seems unlikely to persist long after exposure is stopped. In particular, drug trials assessing symptomatic indications such as the treatment of obesity suffer from large drug discontinuation rates (often approaching 50%), which may dilute any safety signal.

Efficiency considerations. We have previously made reference to a "hybrid" approach of obtaining a certain level of information prior to approval and further resolution postapproval. This obviously avoids multiyear delays in approval of effective therapeutic agents. However, to whatever extent one is concerned about the final confidence limits, how and whether to review interim results requires substantial thought and preparation to preserve the integrity of the trial.[12]

Alternatives to dedicated CV outcome studies. When relatively small CV safety signals arise during the course of clinical efficacy trials or subsequent meta-analyses, it is controversial whether the time and resources to perform a major CV safety outcome study are appropriate when a new and beneficial therapy might be delayed in getting to patients with unmet medical needs. This is particularly true when event rates are so low that there are serious practical concerns surrounding completion of the CV safety outcome study or the impact of very low-risk events on the overall benefit-risk balance. Thus, it is of interest to determine whether there are alternate means to a CV safety outcome trial to ascertain the magnitude of a possible CV safety signal.

Identification by sponsors of substantial financial concerns for CV safety outcome studies may preclude further development of otherwise promising compounds, particularly when use of the drug might be limited in scope (eg, orphan drug and relatively uncommon indications). In addition, when the CV outcome studies are required preapproval, they may delay the introduction of novel therapies for unmet medical needs for a number of years. Hence, it is essential to determine more cost-effective solutions to provide regulators and clinical scientists with information to assess CV safety. Usually, CV safety outcome studies would be required to characterize credible CV signals that have been detected through reliable methodology and have both biologic plausibility and a potential public health impact. However, it may not be reasonable to require the same commitment for compounds without any such concern (eg, the meta-analysis–driven signals for some medications for type 2 diabetes).

Some of the data sources and methodologies discussed in this section may deserve regulatory consideration to

determine if they could be used as alternate sources of information in the event of a suspected low-frequency CV safety signal. The approaches described here are less resource-intensive than CV safety outcome studies and therefore have the potential to provide the public and regulators with information about CV safety rapidly without placing an undue burden on trial sponsors and delaying the development of medications to address important medical needs. Compared with CV safety outcome studies, they are less rigorously performed, as they are nearly always nonblinded and nonrandomized. In a recent report by Madigan et al,[30] heterogeneity among observational databases generated different results that led to 21% to 36% of drug outcomes yielding estimated relative risks that ranged from statistically significantly decreased risk to statistically significantly increased risk. The choice of data source could affect results. Hence, broad databases and clinical trial techniques such as end point adjudication by blinded observers may help to overcome these areas of potential bias.

Alternative strategies may include the following:

1. *A de novo prospective registry/observational study*. In this method of evaluation, all patients who are prescribed the medication of interest are enrolled in a prospective, unblinded, nonrandomized observational study. Often, limited data collection is involved, and data are collected via minimal patient contact. This methodology is a cost-effective mechanism to specifically gather information on the end point of interest. In addition, it has maximum flexibility in allowing for site selection and ease of data collection. The population that is prescribed the "study" medication is generally a broader one than that evaluated in clinical development programs, and these strategies should capture more of the real world experience with the drug. A major limitation of this type of study is the lack of a control group to estimate background CV risk and potential selection bias regarding to whom the treatment is administered. Thus, this trial design can be greatly strengthened by using a comparator group.

2. *A prospective registry/observational study built on an existing registry platform*. A prospective registry study adds additional but limited data collection requirements to an existing registry. For example, one might request a new data field for patient exposure to a study drug of interest to the National Cardiovascular Data Registry (NCDR), a registry active among more than 2,000 cardiologists and more than 2,200 hospitals and 700 practices.[31] This database is already in use by regulators for postmarketing assessment and, at times, as a platform for clinical trials. As an alternative to a CV safety outcome study, the addition of supplementary data collection activities is a highly cost-efficient strategy. However, like all registries, use of this strategy is limited by methodological concerns. As one example, because the NCDR is deployed only to cardiologists, any CV safety signals would be gathered only for those patients referred for CV care. Because access to NCDR is not deployed to other medical subspecialities, it would not provide an adequate solution if the registry were intended to capture the incidence of CV events or specific subgroup information for a widely prescribed non-CV agent. In addition, there may be practical constraints, including institutional review board concerns as well as the technical aspects surrounding data access and data integration.

3. *A prospective registry/observational study built on an EHR platform*. The emergence of EHR technologies may help to develop cost-effective strategies to evaluate postapproval drug safety. Electronic health record platforms potentially offer the advantage of standardized, ongoing, consecutive data capture that involves clinical practice settings and populations, much greater sample sizes, and a reduced data entry burden. Additional benefits are that patients can potentially be matched with control patients using different clinical factors such as comorbidities, other medical use, and demographics. However, although this technology is rapidly evolving, current challenges include the lack of acceptable EHR study methodologies for CV safety assessments as well as practical and technical issues such as intraoperability and research process models.[32,33]

4. *Retrospective analysis built from data warehouses*. The emergence of "Big Data" from accountable care organizations and large-scale medical centers holds hope for the ascertainment of true incident rates predicated on the power of statistical modelling from extremely large databases. One of the best examples of this structure is the Mini-Sentinel Initiative,[34] a distributed database model that currently includes health information on approximately 150 million persons. Data come from insurance claims and administrative databases, including outpatient dispensing codes, impatient and outpatient diagnoses, and procedural codes. Theoretically, Mini-Sentinel should be able to provide the number of exposed lives as well as outcome information that will allow for assessment of CV event incidence with high statistical fidelity in a cost-effective manner. Mini-Sentinel continues active project teams for statistical methods development, identification of health outcomes, and validation of health outcomes. The distributed nature of the approach limits the number of searches and the ability to assess potential safety issues in a more real-time manner. In the future, the EHR approach may be able to offer similar capabilities in a nondistributed manner.

Summary and recommendations

Cardiovascular safety surrogates as shown in Table I should be explored early in development to identify

agents with possible CV pathophysiologic concerns for intensive clinical outcome studies and to eliminate drugs that are likely to show low benefit-risk in further development. A development program should enable integration of safety data from different trials, including common, protocol-mandated definitions of events, and planned CV event acquisition procedures to obtain data serving these definitions. Prospectively collected data are more useful than retrospective collections, and the CSRC has developed CV safety adjudication forms that can be used for this purpose.[35] A prespecified statistical analysis plan to define the point estimate and upper bound of the associated CI to define absolute risk for the benefit-risk determination should be formulated for programs in which there is reasonable evidence of CV risk.

The need for CV outcome studies should be based on evidence of plausible risk, as indicated by data in the same pharmacologic class, statistical evidence from the development program itself (including adverse events and biomarkers with an established relationship to risk), mechanistic considerations, and clinical judgment regarding the disease being observed, and that judgment should be tempered by the potential for false-positive attributions of risk and the risk-benefit assessment. In marginal cases, the use of postmarketing risk monitoring rather than premarketing or postmarketing controlled trials could be considered.

Disclosures

References

1. Cardiac Safety Research Consortium web site. Available at, https://www.cardiac-safety.org/. [Accessed 1st September 2014].
2. Finkle J, Bloomfield D, Uhl K, et al. New precompetitive paradigms: focus on cardiac safety. Am Heart J 2009;157:825-6.
3. Hiatt WR, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs—insights from the rosiglitazone experience. N Engl J Med 2013;369:1285-7.
4. Stockbridge N, Morganroth J, Shah RR, et al. Dealing with global safety issues: was the response to QT-liability of non-cardiac drugs well coordinated? Drug Saf 2013;36:167-82.
5. Turner JR, Panicker GK, Karnad DR, et al. Cardiovascular safety monitoring during oncology drug development and therapy. Am J Ther 2014;21:512-22.
6. Turner JR, Durham TA. Integrated cardiac safety: assessment methodologies for noncardiac drugs in discovery, development, and postmarketing surveillance. Hoboken, NJ: John Wiley & Sons. 2009.
7. FDA. Guidance for Industry. Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Effective December 2008. Available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. [Accessed 1st September 2014].
8. FDA. Guidance for Industry. Developing products for weight management. Draft, February 2007. Available at, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071612.pdf. [Accessed 1st September 2014].
9. James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010;363:905-17.
10. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
11. Mahaffey KW, Hafley G, Dickerson S, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J 2013;166:240-249.e1.
12. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.
13. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.
14. Matthews JNS. Introduction to randomized controlled clinical trials. 2nd ed. Chapman & Hall/CRC. 2006.
15. Sun X, Ioannidis JP, Agoritsas T, et al. How to use a subgroup analysis: users' guide to the medical literature. JAMA 2014;311:405-11.
16. Turner JR, Durham TA. Meta-methodology: conducting and reporting meta-analyses. J Clin Hypertens (Greenwich) 2014;16:91-3.
17. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008;300:1439-50.
18. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.
19. Singh S, Loke YK, Enright PL, et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ 2011;342:d3215.
20. Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med 2013;369:1491-501.

EMA Press Release. European Medicines agency confirms positive benefit-risk balance for Champix. 21 July 2011. Available at, http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109177.pdf. [Accessed 8 August 2014].

21. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium—the FDA's conclusions. N Engl J Med 2010;363:1097-9.

22. Singh S, Loke YK, Spangler JG, et al. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ 2011;183:1359-66.

23. EMA Press Release. European Medicines agency confirms positive benefit-risk balance for Champix. 21 July 2011. Available at, http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109177.pdf. [Accessed 02 September 2014].

24. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. BMJ 2012;344:e2856.

25. FDA Public Meeting, November 25, 2013. Meta-Analysis of Randomized Controlled Clinical Trials for Safety Evaluation. Available at, http://www.fda.gov/downloads/drugs/newsevents/ucm375830.pdf. [Accessed 02 September 2014].

26. FDA White Paper released in conjunction with the meeting referenced immediately above. Available at, http://www.fda.gov/downloads/Drugs/NewsEvents/UCM372069.pdf. [Accessed 02 September 2014].

27. Sager P, Heilbraun J, Turner JR, et al. Assessment of drug-induced increases in blood pressure during drug development: report from the Cardiac Safety Research Consortium. Am Heart J 2013;165:477-88.

28. MedDRA. Available at, www.meddra.org. [Accessed 1st September 2014].

29. Becker MC, Wang TH, Wisniewski L, et al. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. Am Heart J 2009;157:606-12.

30. Madigan D, Ryan PB, Schuemie M, et al. Evaluating the impact of database heterogeneity on observational study results. Am J Epidemiol 2013;178:645-51.

31. National Cardiovascular Data Registry. Available at, https://www.ncdr.com/webncdr/. [Accessed 8 August 2014].

32. Holbrook A, Keshavjee K, Troyan S, et al. Applying methodology to electronic medical record selection. Int J Med Inform 2003;71:43-50.

33. Weiskopf NG, Weng C. Methods and dimensions of electronic health record data quality assessment: enabling reuse for clinical research. J Am Med Inform Assoc 2013;20:144-51.

34. Mini-Sentinel. Available at, http://www.mini-sentinel.org/methods/default.aspx. [Accessed 8 August 2014].

35. Cardiovascular case report forms for use in non cardiovascular clinical trials. Available at, https://www.cardiac-safety.org/cardiovascular-case-report-forms-for-use-in-non-cardiovascular-clinical-trials. [Accessed 02 September 2014].