

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.

Methodological Appendix

1. Blinded analysis

A Manual of Operations, written prior to proceeding with adjudication of events, described the planned approach to adjudication and statistical analysis. In accordance with that plan, the independent review of cardiovascular safety proceeded as follows. An adjudication committee, composed of members not previously involved in the study (SDS, PF), created a special case report form and database to capture the data on each serious adverse event and death. The committee categorized each event as cardiovascular or not and, if cardiovascular, according to the type of event (see below). Pfizer Development Operations New York provided data on baseline demographics and exposure to study medication derived from “snapshots” of the project databases made on 03 November 2004 and updated on 06 Jan 2005. The study used a case report form to collect cardiovascular history systematically. The form included check boxes for angina, hypertension, congestive heart failure, atherosclerotic cardiovascular disease, myocardial infarction, peripheral edema, and cerebrovascular ischemia (TIA or CVA). Other relevant baseline data collected included age, sex, history of diabetes, history of smoking and alcohol use, use of low-dose aspirin, and use of cholesterol-lowering drugs. The study did not collect information on family history of cardiovascular disease.

The adjudication committee categorized each death and serious adverse event as cardiovascular or not. It classified the cause of each cardiovascular death as due to MI, sudden death, cardiovascular procedure, stroke, heart failure, presumed cardiovascular, or other. The committee categorized each non-fatal cardiovascular serious event as either MI, hospitalization for unstable angina, stroke (non-hemorrhagic, hemorrhagic, unknown), coronary revascularization (PCI, CABG, unknown, other, arrhythmia (by type), other cardiovascular (non-coronary revascularization, other cardiac surgery, thromboembolic event, cardiac arrest/resuscitated sudden death, other).

Statistics Collaborative (RF) summarized the blinded data to calculate how many of each type of event occurred. The Cardiovascular Safety Committee (JM, MP, JW, SS). reviewed the summarized blinded data to determine how best to aggregate events.

To capture the total number of events, both fatal and non-fatal, the Cardiovascular Safety Committee used the following categories: MI, stroke, pulmonary embolism, sudden death and resuscitated sudden death, hospitalization for unstable angina, arrhythmia, cardiovascular procedure; heart failure; presumed cardiovascular death, and other cardiovascular events.

The data on VIOXX pointed to an elevated risk of myocardial infarction or stroke, especially after about 18 months of treatment with VIOXX. Therefore, the primary safety endpoint for this analysis was the occurrence of stroke or MI. Formally, the log-rank test of the combined high/low dose data vs. placebo was specified with a one-sided p-value of 0.05 considered reason for further immediate exploration. All other p-values and statistical tests were to be considered exploratory.

In addition, the safety committee considered three categorization systems for statistical analysis:

Categorization 1: CV death, MIs, and strokes

- I. Cardiovascular death or non-fatal MI or non-fatal stroke
- II. Fatal MI or fatal stroke
- III. MI or stroke

If celecoxib led to increased cardiovascular risk, each of these endpoints would be expected to show elevated hazard for the celecoxib groups.

Categorization 2: Hierarchical system

- I. CV death
- II. CV death or MI
- III. CV death or MI or stroke
- IV. CV death or MI or stroke or CHF
- V. CV death or MI or stroke or CHF or angina
- VI. CV death or MI or stroke or CHF or angina or coronary revascularization

If celecoxib led to increased cardiovascular risk, each of these endpoints would be expected to show elevated hazard for the celecoxib groups. Further, the hazard ratio would be expected to decrease monotonically from Category I through Category VI and the hazard ratios would be expected to be higher in the 400 mg BID dose than in the 200 mg BID dose group.

Categorization 3: Tiered (mutually exclusive) system

- I. MI, stroke, hypertension, arterial thrombosis
- II. PE and DVT – both fatal and non-fatal
- III. All events not included in I and II

This third categorization was considered exploratory.

2. Unblinded analysis.

The randomization group in Pfizer Global Clinical Data Services, which is independent of the study team, provided the randomization codes directly to Statistics Collaborative which then unblinded the data, analyzing them according to the predefined plan below. The Cardiovascular Safety Committee reviewed the analyses, interpreted the findings, and presented both the data and the interpretation to the DSMB on December 10, 2004. At this point, the adjudication committee was still blind both to individual treatment assignments and to the overall results.

For each event or category of event, the graphical timelines showed the time of occurrence of each event by study and treatment group. Tables presented the number and percentage of events by treatment group and the rates per 1000 patient years. Kaplan-Meier curves showed the times to event for each treatment group along with a log-rank z-statistics for the pooled celecoxib arms to placebo. Hazard ratios along with their confidence intervals were constructed for the pooled arms and for each dose relative to placebo.

Cox models were constructed with terms for the baseline variable and the interaction of the baseline variable on the hazard ratio.

Because of the impossibility of removing the effects of selection on exposure, the analysis was based on the as-randomized population, i.e., intent-to-treat. Events that occurred more than 30 days after known cessation of study medication were identified, but included in the analysis. There were only three such events.

DEATH CLASSIFICATION AND NON-FATAL ENDPOINT DEFINITIONS

The classifications made by the Endpoints Committee will be based on widely accepted criteria, utilizing supporting source documentation and the clinical judgment and expertise of the Endpoints Committee. The criteria for some of the events classified by the CEC are listed below as a general guide for classification and adjudication.

I. DEATH CLASSIFICATION

The CEC will determine the most likely cause of death. The cause of death will be the underlying cause, not the immediate mode of death. Death will be classified in three categories, Cardiovascular, Non-Cardiovascular or Unknown.

Death will be classified in the following categories:

A. Cardiovascular Death

Cardiovascular death is defined as follows:

Fatal Myocardial Infarction:

Fatal myocardial infarction may be adjudicated in any one of the following three scenarios:

- Death occurring within 14 days after a documented myocardial infarction in which there is no conclusive evidence to another cause of death. Subjects who are being treated for myocardial infarction and die as a result of complications of this myocardial infarction (e.g., sudden death, pump failure or cardiogenic shock) will be classified as having a myocardial infarction related death.

- Autopsy evidence of a recent infarct with no other conclusive evidence of another cause of death.

- A Fatal Myocardial Infarction may be adjudicated for an abrupt death that has suggestive criteria for an infarct but does not meet the strict definition of a myocardial infarction. The suggestive criteria is as follows:
 - Presentation of chest pain
 - AND one of the following:
 - ECG changes indicative of an acute injury, or
 - Abnormal markers without evolutionary changes (e.g., subject died before a subsequent lab draw), or
 - Other evidence of wall motion abnormality

Pump Failure:

Death occurring within the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

If worsening heart failure is secondary to MI, then MI should be listed as the primary cause of death given that the subject suffered a MI within 14 days of death (as above).

Sudden Death:

Death that occurred suddenly and unexpectedly in an otherwise stable subject.

Presumed Sudden Death:

Death that occurred unexpectedly in an otherwise stable subject in which the subject was last seen ≥ 24 hours before death and circumstances are suggestive of sudden death.

Stroke:

Death occurring after a documented stroke.

Procedure-Related:

Death occurring during a cardiovascular procedure (CABG, PTCA, other) or as a result of later complications related to the procedure within 15 days. (Example: A subject who had a CABG up to fifteen days ago, who developed a subsequent myocardial infarction requiring inotropes, and who later died will still be classified as procedural related death.) The exact procedure will be recorded.

Other Cardiovascular:

Death must be due to a fully documented other cardiovascular cause not included above.

B. Non-Cardiovascular Death:

Deaths will be considered non-cardiovascular if there is no compelling cardiovascular cause of death. Examples of Non-CV sub classifications will include: Pulmonary, Malignancy, Infection, Hepatobilliary, GI, Renal, Procedural, Accidental, Suicide, and Other.

C. Unknown

All other cases of death, in the absence of a clearly defined non-cardiovascular cause, will be classified as Unknown if no other cause, as described above, can be found. These will be considered non-cardiovascular for the purposes of this analysis.

II. NON-FATAL ENDPOINT DEFINITIONS

A. Myocardial Infarction and Hospitalization for Unstable Angina

Myocardial infarction will be adjudicated when there is a clinical syndrome consistent with myocardial infarction (i.e., chest pain, pulmonary edema) and/or ECG changes consistent with an acute coronary syndrome in association with elevation of cardiac markers above the local upper limit of normal, or compelling angiographic evidence of acute myocardial infarction/ coronary occlusion.

Unstable angina will be adjudicated when there is a chest-pain syndrome consistent with coronary artery disease with ECG changes, cardiac marker elevation not sufficient for adjudication of myocardial infarction, or a clinical scenario that is consistent with cardiac chest pain in a patient with known coronary artery disease.

C. Stroke

Stroke is defined as a focal neurological deficit (resulting from a vascular cause involving the central nervous system) of sudden onset that is persistent (generally defined as not reversible within 24 hours) and which is not due to a readily identifiable cause (i.e., brain tumor, trauma). When an imaging study is available (or other clearly documented supporting source documentation), we will further differentiate stroke as hemorrhagic, non-hemorrhagic, or unknown, and use this information for adjudication.

Hemorrhagic: when there is documentation of a hemorrhage.

Non-hemorrhagic: when there is documentation a stroke occurred but a hemorrhage was not documented or seen on exam.

Unknown: when there is no clinical, radiological, or other substantial evidence to document either a hemorrhagic or non-hemorrhagic stroke but a stroke is believed to have occurred.

Transient ischemic attack (TIA) is defined as a focal neurologic deficit lasting less than 24 hours and without imaging evidence of a hemorrhagic stroke or infarct. TIA will be categorized separately from stroke.

D. Revascularization

Documented occurrence of a coronary revascularization procedure, including coronary artery bypass graft (CABG) surgery, or percutaneous coronary intervention (PCI), or a peripheral revascularization procedure (Carotid, Peripheral, Renal arteries, AAA) will meet the criteria for this event.

E. Resuscitated Sudden Death (RSD)

Resuscitated sudden death will be defined as sudden death or cardiac arrest, with or without premonitory heart failure or myocardial infarction, that is resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation, and after which the patient regains consciousness, even briefly. This definition excludes known transient losses of consciousness such as seizure or vasovagal episodes that do not reflect significant cardiac dysfunction.

F. Congestive Heart Failure

Admission to the hospital with clinical evidence of congestive heart failure, including signs or symptoms of heart failure in association with specific treatment for congestive heart failure (i.e., diuretic, inotropic support or vasodilator), **or** congestive heart failure complicating a hospital admission for another cause where congestive heart failure is a *major component* of the hospital admission.