

VIEWPOINT

Cause of Death in Clinical Research

Time for a Reassessment?

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Because coronary heart disease is the leading cause of death in the industrialized world (1), many clinical investigations of purported cardiac risk factors and new treatments focus on death as a primary end point. It is intuitively appealing to attempt to better understand the association between an exposure of interest and mortality by determining cause of death, particularly differentiating between cardiac and non-cardiac causes. This is usually done by reviewing death certificates or, less often, medical records.

The use of "cardiac death" instead of all-cause death as an end point in clinical investigation is, we believe, hazardous for many reasons. In reality, data obtained from death certificates or from medical records are haphazard, biased and often grossly inaccurate. Notwithstanding these concerns, determination of cause of death is inherently difficult owing to the presence of concurrent comorbid illnesses, a low autopsy rate and an inadequate understanding of complex disease processes. Coronary heart disease may, in fact, be present and significant at the time of death, and yet not be the primary reason a patient may die. The ultimate result of using specific causes of death as an end point is that "softness" is introduced into a study that otherwise would be based on the strength of the "hardest" end point of all: all-cause mortality.

Data that are typically obtained as part of high-quality prospective clinical investigations or trials are carefully and systematically obtained, with great efforts made to maintain consistent prespecified definitions, to reduce risk for errors, to minimize missing data elements and to avoid potential biases of ascertainment (2). This cannot be said for data obtained from death certificates or medical records (3), even when incorporated into formalized "classification committees" (4). Clinically important data may be missing because of clerical errors and because they are recorded by busy, harried practitioners who are not vested in high-quality epidemiologic outcomes research. Physicians recording death notes or death certificates often are unfamiliar with patients' long-term medical issues and may be confused by changing medical terminology (5). From the clinical inves-

tigator's point of view, there is no way that data quality and data definitions can be adequately assessed and controlled.

Most physicians do not receive any kind of formal training in filling out death certificates properly; it is very common for physicians to confuse underlying cause of death with mechanisms of death (6). The underlying cause of death is "the disease or injury that initiated the train of morbid events resulting in death;" this can be thought of as, "In the absence of the underlying cause, the patient would be alive today" (6). Conversely, a mechanism of death is "a physiologic or biochemical disturbance produced by a cause of death" (6). A study of 384 death certificates at a university teaching hospital showed that 59% were incorrectly filled out (3). Indeed, a very common error included recording a mechanism of death (such as multiple organ system failure) without providing an underlying cause (such as metastatic lung cancer). Some death certificates simply stated that patients died of "cardiac arrest" without any other information added. Ultimately, everyone dies of cardiac arrest (3)!

Death certificate and death note data may suffer from serious biases of ascertainment. Physicians who record these data may well be aware of prior test results or treatment; this knowledge may color their interpretations of cause of death, particularly among patients with multiple complex illnesses. Simply knowing that a patient had a stress nuclear study or was enrolled in an unstable angina trial, for example, may bias a physician into categorizing a death as cardiac when it may not have been. A recent study, for example, demonstrated a strong relationship between persistent minor electrocardiographic (ECG) abnormalities and cardiac death as assessed by death certificates (7). It is quite possible that the physicians who filled out the death certificates knew that the patients had abnormal ECGs and this might have biased their assessments.

Assessment of the accuracy of death certificates is inherently problematic because there is no standard for cause of death, except perhaps for the autopsy, which is now infrequently performed. Nonetheless, a number of careful studies have raised serious questions about the validity of death certificates and clinical determinations of cause of death (8–10). A study of 257 autopsied cases in Atlanta, Georgia found improper recording on the original death certificate of the underlying cause of death in 42% of cases, with

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underreporting of malignancies and overreporting of vascular deaths (9). Another study (10) of 272 randomly chosen autopsies found a major disagreement between the death certificate and autopsy in 29% of cases, leading to a change of cause of death to an entirely different etiologic category. The proportion of patients designated by the death certificate as dying of "circulatory" causes who had this confirmed by autopsy was only 75%; conversely, among patients found by autopsy to have died of circulatory causes, only 82% of death certificates noted this.

A very recent report from the Framingham Heart Study (11,12) compared causes of death among 2,683 decedents as identified by death certificates and by a physician panel. Of 942 patients listed by the death certificate of dying from coronary heart disease, only 645 (67%) had this confirmed by the physician panel. The situation was even worse for stroke, where the corresponding positive predictive value of the death certificate was only 59%. Inaccurate reporting of coronary heart disease death was strongly related to increasing age: among patients with ages of 65 to 74, 75 to 84 and ≥ 85 , differential rates of reported versus confirmed coronary heart disease deaths were 18%, 31% and 109%, respectively. Another noteworthy finding was that the physician panel could not confidently state a cause of death in 9% of patients; among these the death certificate listed coronary heart disease as the cause of death in 51%. The investigators cite this finding as suggesting that physicians may use the diagnosis of coronary heart disease as a "default" (11).

Even when a cause of death seems obvious, careful study may reveal gross inaccuracies. For example, a study of 109 deaths among patients with implantable defibrillators found that 17 were identified on clinical grounds as being due to "sudden cardiac death" (13). On the basis of autopsy and interrogation of the defibrillators, sudden death could only be confirmed in seven patients (42%). Furthermore, six patients died of noncardiac causes, including pulmonary embolism, cerebral infarction and ruptured aortic aneurysm.

Even if cardiac death could be accurately distinguished from noncardiac deaths, failure to use all-cause death as the primary end point may lead to inappropriate interpretations of data (4). If a particular type of observation or treatment is in fact associated with a lower likelihood of cardiac death, but is also associated with higher rates of noncardiac death, neither patients nor investigators should be comforted. In contrast, if there is no difference in noncardiac deaths among different patient groups, the use of all-cause mortality would only bias results toward the null hypothesis, much like nondifferential misclassification bias. Thus, any observed differences in all-cause mortality reflect at least as great a difference in cardiac mortality. This is indeed what was observed in the recent study of minor ECG changes and death: minor ECG changes strongly predicted all-cause death, but to a somewhat less degree than "cardiac death"

(7). Indeed, focus on cause-specific, rather than all-cause mortality, as an end point can lead to serious confusion, as in, for example, the controversy regarding cholesterol lowering and violent death or suicide (14,15) before the publication of the 4S Study (16). Another example would be the question of whether amiodarone should be used as a prophylactic agent, because a large trial demonstrated no effects on all-cause mortality, although a reduction in "arrhythmic deaths" was noted (4,17).

As Miss Buttercup in Gilbert and Sullivan's *HMS Pinafore* said when revealing a case of mistaken identity, "Things are seldom what they seem; skim milk masquerades as cream." Careful clinical investigators require high-quality data for analyses; therefore, they should not accept inherently inaccurate, unsystematic and biased data derived from death certificates and medical records. Even when records are properly filled out, determination of cause of death can be very difficult, particularly among elderly patients with multiple diseases. Rather, clinical investigators should rely on all-cause death as an objective, unbiased end point that is of primary interest to everyone in the general public and, similarly, should be of primary interest to medical professionals as well.

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