Cardiovascular drugs and cancer: of competing risk, smallpox, Bernoulli, and d’Alembert

Franz H. Messerli1*, Sripal Bangalore2, Christian Torp-Pedersen3, Jan A. Staessen4,5, and John B. Kostis6

1Division of Cardiology, St. Luke’s Roosevelt Hospital, Columbia University College of Physicians and Surgeons, New York, NY, USA; 2Cardiac Catheterization Laboratory, The Leon H. Charney Division of Cardiology, New York University School of Medicine, New York, NY, USA; 3Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark; 4Department of Cardiovascular Diseases, Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, University of Leuven, Leuven, Belgium; 5Department of Epidemiology, Maastricht University, Maastricht, Netherlands; and 6Cardiovascular Institute, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Received 13 February 2012; revised 6 May 2012; accepted 8 May 2012; online publish-ahead-of-print 19 July 2012

Introduction

At a first glance cardiovascular disease and cancer have little in common. However, even a cursory review of the literature reveals a myriad of articles documenting an association between the two. This would indicate that either cardiovascular disease and/or its treatment affect cancer, or that cancer and/or its treatment affect cardiovascular disease, or still that both cancer and cardiovascular disease are affected by a common underlying mechanism. Among the various possible interactions, the most concerning one is that cardiovascular drug therapy when given over decades could possibly increase the risk of incident cancer, i.e. that cardiovascular drugs could prove to be carcinogenic.

Carcinogenicity of cardiovascular drugs

The article by Sipahi et al.1 reporting a small but significant risk of cancer associated with angiotensin receptor inhibitors was widely covered by news media and created anxiety among patients and uncertainty among physicians. Reassuringly, thorough and comprehensive re-analyses of the data2,3 and a cohort study4 found this issue to be ‘much ado about nothing’.5 Also, a Food and Drug Administration review6 launched in the wake of the controversial Sipahi study recently came to the conclusion that angiotensin receptor blockers do not pose a cancer risk to patients.

One problem with the analyses of cardiovascular drugs and cancer, which in general is overlooked, is that life per se is a game of multiple competing risks. Throughout life, every person continues to be exposed to multiple risks of death, such as cardiovascular diseases, cancers, accidents, and infections. Because death is not (at least not usually) a repetitive event and most often can be blamed on a single cause, these death risks compete with one another for the life of a person. If one regularly takes an antihypertensive drug or a statin and therefore does not die of a myocardial infarction, stroke, or heart failure, it becomes increasingly more likely that death will result from cancer, pneumonia, or an accident. Hence, the more one’s life is prolonged by cardiovascular drugs, the greater becomes the risk of dying from an extracardiovascular cause. Thus, any cause-specific analysis of mortality must be cognizant of the concept of competing risks.

Smallpox and variolation

The issues of competing risks were first recognized by Daniel Bernoulli and presented in the spring of 1760 to the Académie Royale des Sciences in Paris.7 By the 18th century, smallpox had become endemic and was ravaging Western Europe. Since most adults had been infected as children they were immune to smallpox as infection resulted either in death or immunity. Lifelong immunity could also be achieved, as was initially shown in China and India, by transferring the infectious material from a smallpox pustule to a healthy person, a practice called ‘variolation’. To this effect, scabs of dried smallpox pustules were ground into powder and subsequently a person wishing to acquire immunity was either inoculated with or inhaled this substance. Not surprisingly, variolation was occasionally fatal and Bernoulli concluded that the best way to evaluate the risk/benefit ratio of variolation was by mathematical reasoning. By using Edmond Halley’s life table from the city of Breslau8 he convincingly documented the benefits of eliminating smallpox as a cause of death. In his model, Bernoulli calculated that systematic variolation would lengthen the life expectancy at birth from 26 years and 7 months to 29 years and 9 months.9 Jean le Rond d’Alembert, a venerable member of the Académie Royale des Sciences, was not pleased with the Bernoulli’s results.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

* Corresponding author. Email: messerli.f@gmail.com.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2012. For permissions please email: journals.permissions@oup.com
He severely criticized the calculations asserting that Bernoulli had overstated the long-term benefits and played down the immediate risks of variolation. The pointed exchange between Bernoulli and d’Alembert is vividly described in Daston’s treatise on ‘Classical Probability in the Enlightenment’. It was from this dispute between Bernoulli and d’Alembert that the notion of competing risk was born 250 years ago.

**Reduction of mortality with cardiovascular drugs**

The reduction of cardiovascular mortality elicited by drugs not only depends on demographic factors such as age, race, sex, but also on severity of disease, co-morbidities, duration of exposure, and of course on the specific drug or drugs used. At one end of the spectrum are patients with cardiovascular risk factors but without established cardiovascular disease such as in the meta-analysis of Brugts et al. At the opposite end are high-risk patients such as in the TRACE study who had suffered a myocardial infarction, and had an average ejection fraction <35%. In the hypertensive sub-group of TRACE, life expectancy was 71 months in thetrandopril group compared with one of 32 months in the placebo group. Kostis et al. recently reported the results of the 22-year follow-up of the Systolic Hypertension in the Elderly Program (SHEP). Chlorthalidone-based stepped care therapy during the 4.5 years of the randomized phase increased life expectancy by 0.59 days in spite of the loss of 0.15 days due to death from competing non-cardiovascular causes.

**Kinetic model**

The competing risk model can be illustrated by a kinetic model as proposed by Diamond and Kaul (Figure 1). In the kinetic model, the normative state can transition to a cancer state resulting in death from cancer or a cardiovascular disease state resulting in death from cardiovascular causes. However, the cardiovascular disease state and cancer state will compete with each other for the outcome of death. It is likely that therapies that reduce the cardiovascular disease state may therefore increase the cancer state and hence death from cancer. Conversely, treatments reducing cancer mortality are prone to increase the risk of dying from cardiovascular disease. Details of the kinetic model are beyond the scope of this manuscript and the readers are encouraged to read the article by Diamond and Kaul.

**Assessment of true risk estimates**

The findings from SHEP bring up the question, to what extent the risk estimates of interest (cardiovascular morbidity and mortality) are changed when the risk of non-interest (extracardiovascular morbidity and mortality i.e. cancer) is accounted for. Clearly, such a consideration is only of interest with long-term cardiovascular therapy. As SHEP illustrates, 1 month of treatment with chlorthalidone prolongs life by about 1 day and it would take three decades of treatment to prolong life by 1 year. Although these numbers may become more significant with more efficacious treatment, the overall impact of the risk of non-interest on the risk of interest is likely to be small.

**Life expectancy and cancer risk**

Mean life expectancy at age 65 is presently 18.6 years (17.2 for men, 19.9 for women) in the USA. According to the National Cancer Institute, in subjects older than 65 years the risk of incident cancer is between 1.7 and 2.8% per year and increases with age. Based on these data and the projection that life expectancy can be more than doubled with cardiovascular therapy, the cancer incidence in a subpopulation treated for cardiovascular disease would be expected to increase from ~5% to ~12%. As illustrated in Figure 2, preventive and therapeutic strategies have substantially reduced the risk of cardiovascular and cerebrovascular death over the past 25 years. No such trend was observed in cancer death. Recent data from the Myocardial Infarction Data Acquisition System (n = 285,397) have shown that in the last 30 years...
mortality of patients with acute myocardial after discharge from the hospital is increasing because of higher mortality from non-cardiovascular causes such as cancer, diabetes, renal and respiratory diseases.\textsuperscript{18}

The ratio between cardiovascular death and cancer death has fallen by 45\%, i.e. from 2.9 to 1.6\textsuperscript{17} over a quarter of a century, indicating that now more and more people die of cancer who previously died of cardiovascular disease. Should this pattern continue at the same pace, the notion of the American Heart Association that in the past 100 years, only during the 1918 flu pandemic cardiovascular disease was not the number-one cause of death\textsuperscript{19} will become futile. By the year 2020, cancer is prone to strip heart disease of its status as the number-one killer of Americans. This transition has already happened in Canada where in 2008 for the first time, cancer was the leading cause of death in every province and territory.\textsuperscript{20}

Of note, the more efficacious cardiovascular drugs are, i.e. the better they protect against cardiovascular death, the more they will increase life expectancy and thus the risk of cancer. One can therefore make the simple point, unless a cardiovascular drug ‘causes’ cancer it cannot be considered an efficacious cardiovascular drug. Why then are we not seeing a significant risk of cancer in those treated with such drugs? This is exceedingly unlikely that in a follow-up period of a mere 3.9 years, a small increase in life expectancy of a few months will allow us to observe an increased cancer risk. However, cardiovascular drugs are usually prescribed for many years, even decades and the increase in life expectancy and thereby the risk of cancer becomes progressively more significant with time. In the 12-year follow-up of the TRACE study, the overall risk of hospital admission for cancer was elevated by 17\% in thetrandolapril group, albeit it did not quite reach statistical significance (\(P = 0.10\)).\textsuperscript{21}

### Antineoplastic therapy and cardiovascular risk

\textit{Mutatis mutandis}, the concept of competing risk also holds true for antineoplastic treatment and cardiovascular disease. The increase in 5-year survival after diagnosis of cancer from 49 to 67\%, which we have observed over the past 25 years,\textsuperscript{22} is prone to increase the likelihood of cancer patients dying from cardiovascular disease. Thus we can make the same argument that, unless antineoplastic therapy ‘causes’ cardiovascular disease it cannot be considered efficacious. However, the issue is made considerably more complex by the fact that some antineoplastic agents significantly increase cardiovascular risk factors\textsuperscript{23} and are also known to exert direct cardiotoxic effects.\textsuperscript{24} Also, some cancers with an aggressive course may be fatal before cardiovascular disease can develop.

### Smoking cessation

Paradoxically, even smoking cessation, although doubtless beneficial, may increase the relative risk of cancer. Smoking-attributable mortality in the USA is of similar magnitude for heart disease and malignant neoplasms (130 000 and 160 000 deaths per year, respectively\textsuperscript{25}). Smoking cessation reduces mortality and non-fatal myocardial infarction in patients with coronary artery disease and left ventricular dysfunction within 6 months by more than one-third.\textsuperscript{26,27} Yet the risk of lung cancer\textsuperscript{28} and other cancer\textsuperscript{29,30} was found to remain elevated for up to 10 years. The rapid protective effect of smoking cessation on cardiac disease will reduce the risk of dying from heart disease thereby comparatively increasing the risk of cancer for several years. As a consequence the ratio between heart disease and cancer will be lower in ex-smokers than in smokers.

And just to illustrate the concept of the competing risk with an example from Bernoulli’s time—when small pox was rampant—a long-term placebo-controlled trial of variolation would most likely have documented that such variolation, since it increased life expectancy, also increased the risk of cardiovascular death compared with placebo.

### True carcinogenicity vs. pseudocarcinogenicity

What then are the signals allowing us (and regulatory agencies) to distinguish between a cardiovascular drug that is truly carcinogenic and the one that merely appears to be carcinogenic because of competing risk (pseudocarcinogenicity)? In Table 1 we have listed some features that may prove helpful in making this distinction. Adding to the complexity of the situation is that increased survival per se may predispose to certain specific risk of disease and death. If for instance a patient has developed metabolic abnormalities secondary to long-term thiazide or beta-blocker therapy, morbidity and mortality associated with these abnormalities may increasingly

**Table 1** Findings allowing to distinguish between pseudocarcinogenicity and true carcinogenicity with cardiovascular drugs

<table>
<thead>
<tr>
<th></th>
<th>Pseudo carcinogenicity</th>
<th>True carcinogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality reduction</td>
<td>Required to be significant</td>
<td>None needed</td>
</tr>
<tr>
<td>Organ system affected by cancer</td>
<td>Can be any, corresponding to most prevalent cancer in the respective age group</td>
<td>Often one specific organ system regardless of age</td>
</tr>
<tr>
<td>Cancer risk affected by</td>
<td>Duration of exposure and relative efficacy of drug at reducing CV outcomes</td>
<td>Cumulative duration and dose, independent of efficacy</td>
</tr>
<tr>
<td>Molecular mechanism</td>
<td>None to be identified</td>
<td>Often identifiable</td>
</tr>
<tr>
<td>Experimental/animal models</td>
<td>No carcinogenicity documented</td>
<td>Often replication of carcinogenicity</td>
</tr>
</tbody>
</table>

CV, cardiovascular.
become manifest. Clearly, there are no ironclad findings differentiating pseudocarcinogenicity from true carcinogenicity.

**Conclusion**

Any analysis dealing with possible carcinogenicity of cardiovascular drugs (or cardiotoxicity of antineoplastic drugs) has to be mindful of the issue of competing risk. In short-term trials, the competing risk may have little clinical significance but is prone to become increasingly important with long-term therapy. As Bernoulli said ‘Je souhaite simplement que, dans une affaire qui concerne de si près au bien-être de la race humaine, aucune décision ne sera faite sans toutes les connaissances dont une petite analyse et de calcul peuvent fournir.’ (I simply wish that, in a matter which so closely concerns the wellbeing of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide.) We fully agree.

**References**