Cancer in cardiovascular drug trials and vice versa: a personal perspective

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Introduction

Acknowledging uncertainties and balancing the opportunity for benefit with the offsetting potential to harm are integral concepts for clinical decision-making. Caregivers consciously risk profile (stratify) their patient to try to fit best currently available observational and clinical trial data to formulate a particular recommendation for each unique patient. Advice to adopt prudent lifestyle approaches, such as avoidance of smoking, maintaining adequate activity levels, and adhering to a nutritious diet, have such a favourable benefit/risk ratio that they have become fundamental tenets of cardiovascular preventive care. On the other hand, recommendations for the use of pharmacologic therapies in an effort to improve prognosis requires careful consideration of possible adverse consequences in relation to potential benefits. The fundamental principle of ‘Primum non nocere’, above all first, do no harm, rightfully dominates most clinicians’ therapeutic decision making. To initiate and maintain a pharmaceutical agent or recommend a procedure, the physician, patient, and even the payers must be adequately persuaded that in the long term, the risk/benefit considerations favour the intervention.

In cardiovascular medicine, strong and consistent information from both pioneering epidemiologic and clinical trial data have coalesced to generate convincing, indeed, compelling rationale for the use of pharmacologic agents in individuals with hypertension to lower arterial blood pressure in order to reduce their risk for subsequent major cardiovascular events.1–3 Similarly, there is consistent convincing data demonstrating the effectiveness of HMG-CoA reductase inhibitors (statins) in lowering cardiovascular event rates in both secondary and in a large segment of the primary prevention populations.4 Pharmacologic agents in these categories have achieved privileged regulatory and clinical usage status to be administered to asymptomatic individuals for the purpose of reducing cardiovascular event rates. At this elite level, in addition to sufficient safety experience, a particular agent must also have excellent tolerability and often even once daily dosing convenience to gain marketplace acceptance in this highly competitive field.

Any concerns about a drug-associated increased incidence for a serious irreversible non-cardiovascular illness would greatly curtail its use as a long-term preventive therapy.

Even though we do not expect our cardiovascular targeted interventions to reduce unrelated non-cardiovascular deaths and new cancers, these outcomes are routinely ascertained in trials to probe for unintended potential safety issues. Based on the demographics of patients enrolled in cardiovascular trials, a non-trivial number of unrelated incident cancers and deaths can be anticipated. Admittedly, because of the sample size and duration of exposure needed to test for cardiovascular efficacy, the proportion of patients that develop or die from cancer in even a large trial would generally lack sufficient statistical power to confidently exclude a cancer risk. However, the powerful negative connotation of the word cancer looms so large that even a marginal increase in reports of cancer can more than offset a more statistically robust cardiovascular benefit. It is in this context that a recent meta-analysis of cardiovascular trials of angiotensin receptor blockers (ARBs) purporting that these agents could be increasing the development of cancers was quite disconcerting to both physicians and patients.5 In this invited Current Opinion, the author reflects on some prior interfaces between cardiovascular endpoints and serious cancer events in clinical trials with the intent of providing a broader framework for interpreting current and future cancer reports in cardiovascular trials.

Angiotensin-converting enzyme inhibitors (ACEIs)

The evidence for the now established use of angiotensin-converting enzyme inhibitors (ACEIs) for the treatment of heart failure and asymptomatic left ventricular dysfunction was emerging approximately 25 years ago. The life-prolonging, major morbidity reducing property of ACEIs was first demonstrated in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), which enrolled patients with rather severe heart

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Evidence that these favourable actions could be extended to a broader population of patients with reduced left ventricular ejection fraction soon followed from the data generated by the Studies Of Left Ventricular Dysfunction (SOLVD) program. However, even this most welcomed positive cardiovascular news of a robust reduction in deaths from all causes as well as hospitalizations for heart failure in this 2569-patient, placebo controlled trial had to overcome the cloud of a small non-significant imbalance in cancer reports. With statistical and clinical significance based on over 1300 patients experiencing cardiovascular events, it is of interest that the investigators appropriately called attention to a non-statistically significant imbalance of reports of cancers of the gastrointestinal tract, liver, gallbladder, and pancreas in which there were 18 in the enalapril and 9 in the placebo groups, respectively; P not significant.

The SOLVD investigators were simultaneously conducting an even larger trial of 4228 patients with asymptomatic left ventricular dysfunction where they demonstrated that the ACEI-assigned group was less likely to develop heart failure or die (818 placebo vs. 660 enalapril assigned patients, 29% risk reduction, \( P < 0.001 \)). They again noted numerically a few more patients identified as having gastrointestinal tract cancers in the enalapril group (19 enalapril and 13 reports in placebo patients). It is of interest that despite reducing hundreds of cardiovascular events, there was concern about this imbalance of a handful of cancer reports. Although there was no difference in this overall incidence in cancer, as well as deaths attributed to cancer, in the two SOLVD trials, they reported 38 patients developing a cancer of any aetiology in the gastrointestinal tract in the enalapril and 22 in the placebo groups. The SOLVD investigators cautioned that although the \( P \)-value in isolation was nominally significant, it should be viewed in the context of multiple unadjusted exploratory comparisons. The reliability of the finding was further considered questionable since it was not due to any one particular histological type or location and, importantly, there was no temporal relationship between drug exposure and the frequency of cancer reporting. The investigators concluded that the findings were probably not causally related to the study treatment but rather a chance finding. However, they appropriately indicated that a link to cancer could not be excluded and that it would be prudent to examine this relationship in subsequent ACEI trials.

At that time, we were completing the Survival And Ventricular Enlargement (SAVE) trial, which randomized 2231 patients with left ventricular dysfunction following a myocardial infarction to either the ACEI captopril or placebo. SAVE extended the cardiovascular mortality and morbidity reducing benefits of ACEI to include high-risk myocardial infarction patients. The small number of reports of serious malignancies: 29 captopril and 25 in placebo assigned patients with 6 and 9 in gastrointestinal locations (captopril and placebo, respectively) provided additional reassuring data within the time frame of randomized clinical trials (RCTs) that the newly emerging cardiovascular benefits of ACEI were not offset by an important increase in new cancers (cited in FDA Report). It is also noteworthy that in cardiovascular RCTs, there are generally careful pre-specified definitions of the cardiovascular events and often independent adjudication committees. Occurrences of cancers do not receive the same level of scrutiny and verifications. Moreover, most protocols permit patients with cancers to be enrolled and designations of histologic type and stage are often not ascertained. Operationally, reports of neoplasms in cardiovascular trials are generally neither complete nor comprehensive.

Observational studies, although lacking the all-important randomization for less biased comparisons, do offer less selected populations with opportunities for longer durations of exposure. Lever et al. probed cancer incidence with the clinical use of antihypertensive agents and reported fewer first cancers in the patients prescribed ACEIs relative to other classes of drugs. In a larger also non-randomized observational experience, Friis et al. found no differences in cancer rates between those clinically chosen for ACEI therapy and those prescribed other antihypertensive agents. Although minimal risk cannot be fully excluded, the recent extensive data from over 30 000 subjects in ALLHAT compiling over 2500 cancer occurrences and 1000 deaths attributed to cancer deaths without a hint of difference between those randomized to the ACEI and other antihypertensive agents add reasonable certainty against a measurable cancer risk with the clinical use of this class of agents as a therapy to reduce cardiovascular events in adults.

With over 100 000 patients across a broad spectrum of cardiovascular and renal diseases having participated in randomized, placebo-controlled trials with ACEIs, this class has earned its highly respected place in our pharmacologic armamentarium as a therapy to prolong survival and reduce the incidence of major non-fatal cardiovascular adverse outcomes. Although physicians and patients must remain diligent to individually and continually weigh these benefits against the potential risks of angioedema, hypotension, hyperkalaemia, skin reactions, and during pregnancy, embryotoxicity, a worrisome signal for cancer risk with ACEI does not have to be in the risk/benefit equation.

### Angiotensin receptor blockers (ARBs)

The development of ARBs offered a new pharmacologic mechanism to inhibit the renin–angiotensin system. The early studies confirmed their blood pressure lowering properties and indicated that this class of agents was less likely to provoke angioedema or the nuisance and at times intolerable cough associated with ACEIs. This promise of a better-tolerated inhibitor of the renin–angiotensin system spurred an extensive international program of major cardiovascular outcome trials which defined the clinical efficacy of ARBs in various populations with or without concomitant ACEI therapy. In patients with hypertension, the demonstration in the Losartan Intervention for End Point Reduction in Hypertension (LIFE) trial of lower rates of cardiovascular morbidity and mortality with the ARB losartan compared with a commonly used beta-blocker established the importance of ARBs. In relatively rapid succession, clinical outcome benefits were verified by major trials in other populations.

Angiotensin receptor blockers were shown to reduce risk for adverse renal events in patients with type 2 diabetes with nephropathy. In populations where ACEIs were already proven to be effective in improving
prognosis, such as systolic heart failure, comparable clinical benefits were achieved with ARBs in those not treated with an ACEI. In head-to-head comparisons to an ACEI, ARBs were found to preserve the clinical benefits achieved with ACEI. However, the clinical benefits of using an ARB in combination with an ACEI was not consistently demonstrated. As with ACEIs, hypotension, renal deterioration, hyperkalaemia and the teratogenic risk during pregnancy are known, offsetting adverse actions for ARBs.

A concern about cancer with an ARB was first raised in the CHARM program, which tested the clinical efficacy of candesartan across the entire spectrum of left ventricular dysfunction in patients with symptomatic heart failure in three concurrently conducted populations according to left ventricular ejection fraction and use of an ACEI. In the pre-designated protocol, mortality and safety were to be assessed in the overall population of 7599 patients. During the first public presentation of the results at the European Society of Cardiology in 2003, we reported that randomization to candesartan was associated with a reduction in cardiovascular deaths with no significant increase in mortality from non-cardiovascular causes. During the brief time allotted for the initial presentation and in the concurrent online publication, we reported that there were, however, more deaths attributed to cancer in the combined candesartan groups than in placebo-assigned patients 86 (2.3%) vs. 59 (1.6%), P = 0.015. We also presented that the investigator reports of non-fatal neoplasms were, however, similar in the two treatment groups 185 (5.1%) vs. 194 (4.6%), P = 0.49. Although it seemed improbable for a drug to increase cancer deaths within the duration of a clinical trial without altering reports of cancer occurrences, we requested and presented a more extensive evaluation of the cancers in the entire candesartan development program. With information from over 20 000 patient years of exposure to candesartan and over 1000 reports of neoplasms, there were no differences in either fatal or non-fatal rates of cancer between the candesartan exposed or placebo groups. We thought that the larger experience was more reliable and attributed the imbalance in cancer deaths observed in the CHARM program to ‘the play of chance’.

However, 7 years later, with the cancer deaths in CHARM as its stated rationale, Sipahi et al. reported a meta-analysis focusing on cancer in ARB RCTs. With a collective total of 1598 cancer deaths from 93 515 patients in the trials of ARBs they included, no significant difference between the ARB and comparator groups was identified. This concern for cancer deaths (the motivation for performing this meta-analysis) was therefore not supported. However, they reported an 8% increase in the risk of developing a cancer among the ARB users (Figure 2A). Further dissecting the data to site-specific cancers, they found a particularly worrisome increase in the risk of lung cancer with the use of ARBs (0.9 vs. 0.7%, risk ratio 1.25, 95% CI 1.05–1.49; P = 0.01) (Figure 3A). Given the large numbers of patients being exposed to ARBs for cardiovascular risk reduction, this report received prominent visibility in both the medical as well as lay press. Network news headlines such as ‘Popular blood pressure drugs link to cancer’ prompted physicians and patients to re-evaluate their use of ARBs. It also stimulated investigators and regulatory authorities to re-examine their data and conduct more extensive meta-analyses of this reopened question of ARBs and cancer risk.

If this allegation was correct, it should be a major consideration in clinical decision-making. However, on just a cursory examination of the Sipahi paper, it appeared that several of the large international trials of ARBs were not included. There was some urgency in addressing this question since just the controversy of
concern could have immediate unintended negative consequences of having patients discontinue their therapies prescribed for proven indications to reduce cardiovascular and renal events. The trialists that were involved in studies with ARBs promptly cooperated to examine their more collective data. Within months of the question being raised, the investigators in trials with valsartan who aware that some of the trials they conducted were not included in the alerting meta-analysis reported their collective findings. In this single agent analysis, no increase in cancer deaths was observed (Figure 1B), and there were significantly fewer reports of new cancers among the patients randomized to the ARB (1454/24455, 6.0% valsartan and 1493/19570, 7.6% valsartan).

Figure 2 Risk of new cancer with the use of angiotensin receptor blockers (ARB) as obtained by three different analyses. (A) Sipahi et al.; (B) Califf for the valsartan investigators. American Diabetes Association Conference 2010; (C) Teo for the ARB Trialists Collaboration.

Figure 3 Risk of lung cancer with the use of angiotensin receptor blockers (ARB) as obtained by three different analyses. (A) Sipahi et al.; (B) Califf for the valsartan investigators. American Diabetes Association Conference 2010; (C) Teo for the ARB Trialists Collaboration.

Concern could have immediate unintended negative consequences of having patients discontinue their therapies prescribed for proven indications to reduce cardiovascular and renal events. The trialists that were involved in studies with ARBs promptly cooperated to examine their more collective data. Within months of the question being raised, the investigators in trials with valsartan who aware that some of the trials they conducted were not included in the alerting meta-analysis reported their collective findings. In this single agent analysis, no increase in cancer deaths was observed (Figure 1B), and there were significantly fewer reports of new cancers among the patients randomized to the ARB (1454/24455, 6.0% valsartan and 1493/19570, 7.6% valsartan).
placebo, $P = 0.020$) (Figure 2B). Importantly, lung cancers were statistically less frequently reported in the ARB group (0.6 valsartan vs. 1.0 placebo, risk reduction 0.72, 95% CI 0.58 – 0.90, $P = 0.003$) (Figure 3B).\(^{40}\) Aware of the limitations of this type of non-prespecified, unadjusted exploratory analysis, no claims for cancer protection were made.\(^{30}\)

To minimize selection biases, a more comprehensive analysis of 138 769 subjects in trials of ARBs was conducted under the leadership of Dr Koon Teo for the ARB Trialists Collaboration.\(^{31}\) Based on this analysis, with 2369 deaths attributed to cancer (Figure 1C), 8405 reports of cancer (Figure 2C), and 1132 subjects developing lung cancer (Figure 3C) in these ARB randomized trials, no significant increase in overall or site-specific cancer risk was found. Another recent extensive meta-analysis by Bangalore et al.\(^{32}\) also refuted the 2010 assertion of cancer risk by ARBs.

In addition to a meta-analysis of clinical trials, observational cohorts have been examined for potential association between the use of ARBs and also ACEI and the overall risk of cancer. Yoon et al.\(^{13}\) reported no increased incidence in cancer associated with either of these inhibitors of the renin–angiotensin system. These epidemiologic studies can have the advantage of a longer observation period than obtained in clinical trials. Of interest, they report a decreased risk of cancer with ARBs in the analysis restricted to cohort and nested case–control studies or the longer-term observation (greater than 5 years).\(^{33}\) Others probed large national administrative databases to evaluate the potential cancer risk of ARBs. Individual-level data from the Danish registries linked filled drug prescriptions to the users’ medical record and the National Cancer Registry. With over 10 000 cases of incident cancer in approximately 100 000 ARB and 200 000 ACEI users, they found no association between initiation of an ARB and risk of cancer.\(^{34}\) Similarly, the National Health Insurance program in Taiwan was used to assess cancers in a cohort of over 100 000 subjects with newly diagnosed hypertension.\(^{35}\) With over 9000 new cancer cases, they report reduced risk for cancer in the 40 124 patients prescribed an ARB compared with the 68 878 not using an ARB. Despite their large numbers and highly significant adjusted hazard ratio with impressively narrow confidence intervals (0.66, 95% CI 0.63–0.68), this report of protection from cancer with ARBs should also be considered questionable because of both the extreme one-third reduction in risk and the biologically implausible separation in rates within months of the start of the drug.\(^{35}\)

### Health regulatory agency responses

When the concern of cancer with ARBs was rekindled, both the FDA and European Medicines Agency each undertook their own extensive independent analysis. On 15 July 2010, the FDA announced that it was conducting a review of ARBs and cancer.\(^{29}\) In an apparent attempt to reduce anxieties, they indicated at that time that the agency has not concluded that ARBs increase the risk of cancer and offered a statement that ‘FDA believes that the benefits of these medications continue to outweigh their potential risks’.\(^{29}\) On 2 June 2011, with the completion of this analysis, the FDA issued a much more definitive safety communication with the headline ‘no increase in risk of cancer with certain blood pressure drugs—angiotensin receptor (ARBs)’.\(^{36}\) The data summary show that in their meta-analysis of approximately 156 000 patients, the agency found no association between ARBs and cancer-related death, or incident cancer events. The independent evaluation by the European Medicines Agency was issued as a press release on 20 October 2011 stating that their Committee for Medicinal Products for Human Use ‘has reviewed the possible link between use of angiotensin II receptor antagonists (ARBs) and the occurrence of new cancers and concluded that the evidence does not support any increased risk of cancer in patients using these medicines’.\(^{37}\) Although these definitive and authoritative statements should provide adequate reassurance to prescribers and more importantly patients, this period of uncertainty has likely had the unintended consequences of reducing confidence and patient compliance with these and possibly other effective medications to reduce cardiovascular events.

On the other hand, secondary probing of data is important and pharmacovigilance must be considered a continuous process. We must try to understand the exploratory nature of the safety analyses and avoid the worship of any $P$-value < 0.05. It is also important not to over interpret a finding in this era of sound bites and broad Internet dissemination of unfiltered information. The legal system recognizes multiple levels of evidence for criminal proceedings. Although probable cause is sufficient to issue a search warrant, the evidence must be beyond a reasonable doubt to establish guilt.\(^{38}\) For safety, there should be a low threshold to probe for probable cause for concern. However, the framework and the exploratory nature of these and the hypothesis formulating rather than testing comparisons must be placed in proper context.\(^{39}\)

### Cardiovascular events in cancer prevention randomized clinical trials

The negative connotation of the word cancer has such a powerful impact on the cardiovascular community that even a small hint of an association with minimal absolute risk could be enough to offset robust benefits demonstrated on pre-specified major cardiovascular outcomes, including death from all causes. Conversely, for those concentrating on cancer prevention and treatment, concerns for augmentation in cardiovascular events carry heightened negative connotations. Our group was involved in the cardiovascular safety assessment in two major RCTs testing whether celecoxib could reduce colorectal adenomas in those with a history of this neoplasm. Both demonstrated that celecoxib was highly effective in their primary objective of reducing advanced adenomas.\(^{40,41}\) With relatively few events, we reported a dose-dependent increase in cardiovascular event rates in those assigned to celecoxib compared with placebo.\(^{42}\) We indicated that the absolute cardiovascular event rates in this population selected for colonic polyps was low and there appeared to be a dose of celecoxib that did not differ from placebo for cardiovascular events.\(^{42}\) A meta-analysis of...
six celecoxib placebo-controlled RCT confirmed this dose-dependent cardiovascular risk with a non-significant hazard for the lowest dose (400 mg QD). Since celecoxib cardiovascular risk was dose dependent and the adenoma benefit less so, we speculated that a smaller dose may be warranted in a patient with low cardiovascular risks with legitimate concerns for colon cancer. The recent analysis indicating that the long-term use of aspirin was associated with a lower incidence of colorectal cancer supports the concept that medications can impact seemingly diverse disease processes. This serves as a reminder that our studies must strive to compile all serious events in participants.

Profiling
The concept of personalized medicine must go beyond the long awaited whole genome analysis. Many currently available demographic and clinical factors are used by astute physicians to individualize risk/benefit clinical decision-making with their patient. We need to accept levels of uncertainty and understand that life is associated with risks. Somehow we must try to maintain perspective of the individual’s estimate of absolute risks rather than the relative changes between groups. While questions of safety and exploratory analyses should be encouraged, we must be more mature in their interpretation and cognizant of the unintended consequences from hypothesis formulating findings of patients discontinuing their effective therapies. Absolute risk differences will permit derivation of the often ignored metric-number needed to harm and/or treat as well as the net absolute benefit. This last year of finger-pointing regarding ARBs and cancer should lead to more productive paths by serving as a reminder to go beyond P-values, consider data robustness, levels of evidence, contextual interpretation of potential risks as well as benefits. The art of medicine requires distilling dynamic information to make the most prudent individualized patient recommendations.

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