Trials of CCBs

In a communication dated July 7, 1997, Bayer Inc. informed Canadian pharmacists and physicians of the completion of Health Canada's review of calcium-channel blockers (CCBs).[1] Bayer's stated intention was to put to rest concerns about the safety and effectiveness of CCBs and to promote the results of 2 studies, both sponsored by Bayer: the Shanghai Trial of Nifedipine in the Elderly (STONE)[2] and the Systolic Hypertension in Europe study (Syst-Eur).[3] Both trials were characterized by Bayer as using "high quality methodology" and showing "beneficial effects," in contrast to the limited findings and methodologies of the studies that discredited the CCBs.

STONE involved 1797 elderly people with hypertension and used alternate allocations, so that half of the patients received nifedipine and half placebo. The subjects in both groups received captopril or a thiazide diruetic (or both) until the blood pressure goal was attained. STONE had marked methodological limitations, including failure to randomize the participants, to blind the investigators and to account for all enrolled patients.

Syst-Eur has now provided evidence that one agent in the class of at least 35 CCBs, a class of agents that has been on the market for more than 3 decades, conveys a health benefit to patients with isolated systolic hypertension. However, there are a number of issues related to this trial's alleged high-quality methodology that should be considered. Syst-Eur enrolled 4695 patients who were followed for 2 years on average. The proportion of patients given additional enalapril and hydrochlorothiazide makes it difficult to attribute the benefit solely to nitrendipine. A large number of enrolled patients (237) were lost to follow-up. This number is almost twice the total number of stroke events in the trial and is up to 100 times the typical number of participants lost to follow-up in major trials in the US and northern Europe. The reported reduction in stroke risk in Syst-Eur was similar to that of the Systolic Hypertension in the Elderly Program (SHEP).[4] However, the 29% reduction in the risk of congestive heart failure in Syst-Eur (which was not statistically significant) was approximately half that observed in the recent reanalysis of SHEP (49%).[5] This is particularly important from a public health perspective, given that heart failure is the most common clinical complication of isolated systolic hypertension.

Syst-Eur subjects who were randomly assigned to receive only placebo and who survived have now been offered active treatment.[6] We question under what conditions patients fully informed of the SHEP results would knowingly choose a probability of no treatment, with an increased risk of stroke, and then accept active treatment at the completion of the study. A proper design from the public health point of view would have been a direct comparison of nitrendipine with low-dose diuretics. Syst-Eur appears to have violated major international ethical standards of human research by withholding an effective treatment (i.e., diuretics) from the control group. The World Medical Assocation's 1975 Declaration of Helsinki states that "In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method."[7]

The debate on the long-term safety of the CCBs will continue, despite the assurances of Bayer, until long-term clinical trials, ones that use clinically relevant outcomes and that can identify important differences between antihypertensive agents, are completed.

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[Dr. Shannon, Bayer Inc., responds:]

In their letter, Ms. Sukkari and Dr. Sasich suggest that Bayer's intention in a recent communication[1] was

to promote the results of 2 studies to the physician and pharmacist communities.

Issues related to the use of CCBs have been prominent in the medical literature, as well as the lay press, for over 2 years. Most of the studies quoted have been retrospective, observational studies from which hypotheses can be generated but from which conclusions cannot be drawn.[2] Bayer felt it was important to inform physicians that 2 recent prospective, randomized controlled trials (STONE[3] and Syst-Eur[4]) were available and provided high-quality evidence for clinical decision-making.

Although STONE has been criticized for its lack of traditional randomization of patients to treatment groups, the consistency of its results with those of Syst-Eur and other major outcome trials (that of the UK Medical Research Council,[5] SHEP[6] and the Swedish Trial in Old Patients with Hypertension [STOP-Hypertension][7]) add to the credibility of the STONE conclusions.

Syst-Eur was conceived and implemented by the European Working Party on High Blood Pressure in the Elderly in 1989. Bayer sponsored the trial and supplied the study drug. As with all major outcome trials, an independent ethical committee comprising clinical hypertension experts adjudicated ethical concerns. Although Bayer was not represented on this committee, we strongly contest the assertion that the highest ethical standards were not applied to Syst-Eur. The ethical and scientific considerations relevant to studies such as Syst-Eur have been presented in the peer-reviewed medical literature.[8,9]

We do, however, agree that one of the questions now remaining in the treatment of hypertension is whether one class of agent is better than another in preventing morbid

or fatal events in hypertensive patients.

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H-1B or not to be?

The article "Deportation proceedings against Canadian MDs may hold lesson for others heading south" (*Can Med Assoc J* 1997;157[7]: 934-5), by Milan Korcok, outlined the problems 2 Canadian physicians encountered after seeking to practise in the US. However, it omitted an important legal fact.

Under the North American Free Trade Agreement, Canadian physicians are not permitted to practise in the US "on TN visas"; these documents only allow them to teach or perform research. The proper temporary category for physicians wishing to practise in the US is H-1B, and to declare that documents for this category "are rarely granted" is a gross overstatement. My firm has obtained approval of well over 100 H-1B petitions on behalf of Canadian physicians.

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HIV and blood, circa 1982

After reading Dr. John Hoey's editorial "Human rights, ethics and the Krever inquiry" (*Can Med Assoc J* 1997;157[9]:1231), I would like to share my efforts to prevent the spread of HIV through Red Cross blood products in New Brunswick in the early 1980s.

At that time, I was a minor member of the [Red Cross's] provincial board and had no independent authority. During one of our meetings the question of testing donated blood for HIV was raised, and we debated the issue for half an hour. I was the only physician present, and I strongly recommended that such testing be done. The nonmedical board members were not really opposed to testing, but they were worried about the questions it might raise. They were concerned that people who were "healthy" but positive for HIV would, as a result of donating blood, learn from the Red Cross that they had a potentially fatal disease.

I said that testing should be done but was even more adamant that HIV-positive donors must be informed and must not be allowed to make further donations. After an argument, the topic was suddenly dropped without a vote being taken. The minutes of the meeting, distributed later, contained no mention of the discussion or the debate about the problems involved, and the topic was not raised again.

I resigned from the board shortly after. Hoey is correct in stating that nonmedical members of the Red Cross at that time were eager not to give any hint that the Red Cross was hostile to gay people. Because the whole political world seemed to be of the same opinion, I did not write letters to the editor or others — I was sure they would never be published.

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Coping with acronyms

The article "A place in the shade: reducing the risks of UV exposure" (*Can Med Assoc J* 1997;157[2]: 175-6), by Drs. Konia J. Trouton and Christina J. Mills, contains a total of 7 different acronyms. The acronyms themselves are easily identified because they appear in capital letters. But their definitions are hard to find because they are in lowercase letters.

Perhaps *CMAJ* could save its hapless readers some time by providing a glossary of the acronyms for each article.

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Primary prevention of heart disease and stroke

Dr. James P. McCormack and colleagues, in their article "Primary prevention of heart disease and stroke: a simplified approach to estimating risk of events and making drug treatment decisions" (*Can Med*