The J-Shaped Curve in Secondary Prevention
Shall Clinical Practice Change?

Peter M. Nilsson

Hypertension is an important risk factor not only in relation to primary prevention but also for secondary prevention. This was shown in the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) for secondary prevention of stroke and transient ischemic attack, when a more intense blood pressure control was associated with less recurrent events than less intense control.1 The evidence for more intense blood pressure control was associated with less prevention of stroke and transient ischemic attack, when a Against REcurrent Stroke Study (PROGRESS) for secondary prevention. This was shown in the Perindopril pROtection Cardiovascular Risk in Diabetes Trial in patients with type 2 diabetes mellitus,3 and even in normotensive patients prescribed angiotensin-converting enzyme inhibitors after a CHD event.4 On the other hand, a number of post hoc observational findings tell a different story with J-shaped curves visible in studies such as the Treating to New Targets Trial5 for patients with coronary artery disease (CAD), and in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial for high-risk patients.6 This has been illustrated by use of different graphs and spline curves. However, the same set of data can be presented in different ways by use of categorical or continuous variables. Even if the statistical power increases by use of continuous variables,7 the use of some spline curves has been criticized because they might present somewhat exaggerated graphs based on weak data at both ends of the curve attributed to fewer events. One such example was shown recently from the National Diabetes Register in Sweden for the association between in-study mean systolic blood pressure and prospective CHD risk in 12 500 patients with type 2 diabetes mellitus treated for 5 years with antihypertensive drugs.8

One weakness of observational studies addressing associations between blood pressure and cardiovascular risk in secondary prevention is the influence of reverse causation, in the sense that a low attained blood pressure might be a consequence, not a cause, of target organ damage, for example, after extensive myocardial damage or loss of hemodynamic control after a stroke. This problem can be dealt with in different ways, most often by excluding some groups of patients with a recent event or adjusting for a number of possible confounders. Another more sophisticated approach has been used by a Dutch group based on observational findings from the Secondary Manifestations of Arterial Disease (SMART) Study, published by Dorresteijn et al9 in this issue of Hypertension. The authors used data from 5788 patients with symptomatic vascular disease but made subanalyses in patients with or without recent CAD events, below or above the age of 65 years and having or not having >60 mm Hg pulse pressure. By this procedure they were able to show that their main finding of their study showing a J-shaped curve for cardiovascular risk with a nadir of 143/82 mm Hg was not substantially affected by reverse causation. In fact, patients with a recent CAD event had a better prognosis if blood pressure was elevated. This corresponds to similar findings in the Swedish national cardiology registers (Registry of Information and Knowledge About Swedish Heart Intensive Care Admissions [RIKS-HIA]), showing that an increased blood pressure level in patients coming to the emergency department with an acute coronary syndrome is associated with a better prognosis if the blood pressure is acutely elevated as compared with patients with a low blood pressure, reflecting impaired hemodynamic control and more extensive myocardial damage.10

The SMART Study is based on register information reflecting clinical practice in the Netherlands. Unfortunately, no information is available on ejection fraction in these patients, because this is not a standard procedure. If available, such information could be useful to disentangle the influence of blood pressure reduction, per se (caused not only by antihypertensive drugs but also by other drugs, with an indication for secondary prevention), from that of myocardial dysfunction and clinical, as well as subclinical, heart failure.

Finally, the authors of the SMART Study state that their findings do not invalidate current guidelines recommending a blood pressure target of <130/80 mm Hg but call for new randomized trials for intervention on blood pressure levels in secondary prevention. This ambition is worth supporting, and, in fact, such a trial is underway in secondary prevention of stroke and transient ischemic attack, because the European Society of Hypertension is now finalizing the planning of such a randomized study called Systolic Hypertension Optimal Study (A. Zanchetti, written and oral personal communication, 2011). The aim of this international trial would be to randomize patients with a previous stroke/transient ischemic attack to a systolic blood pressure goal <140, <130, or

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<20 mm Hg for evaluation of the risk of new events. A similar design would be of great importance also for patients with a previous CHD event.

There is no doubt that the control of hypertension is of great importance both in primary and secondary preventions. The major problem is that so many high-risk patients are not even at an acceptable blood pressure goal, <140/90 mm Hg, and the minor problem in perspective is perhaps that some patients might be too vigorously treated. On the other hand, physicians have to keep in mind that elderly patients with extensive target organ damage and more comorbidities might be more susceptible to intensive blood pressure lowering than other patients. If these susceptible patients could be well defined, authors of guidelines could give more tailored advice for individualized risk factor control, not only for control of hypertension but also of hyperglycemia in patients with diabetes mellitus. This would be one example of personalized medicine, waiting for more precise data based on the application of new biomarkers, technical investigations (tissue biomarkers), and genetic markers predicting prognosis. In the meantime, the art of medicine as visible during a skillful consultation should encourage physicians to use their best clinical judgment in order not to overtreat susceptible and fragile patients for blood pressure control.

Additional clinical information could be obtained if other ways of recording blood pressure could be used more often. Out-of-office methods include home blood pressure recordings, as well as 24-hour ambulatory blood pressure monitoring (ABPM) recordings. These methods should ideally be applied more often to get a better picture of the blood pressure burden in the individual patient. In a recent statement from the National Institute for Health and Clinical Excellence organization in the United Kingdom, the wider use of 24-hour ABPM has been advocated. We also know that some risk patients might have masked hypertension during nighttime, as well as hypertensive reactions during certain conditions. Therefore, the clinician could be better guided for the intensity and timing of blood pressure lowering by a wider use of 24-hour ABPM also in patients with secondary prevention. In fact, there are not many studies applying this methodology in secondary prevention and, therefore, a scarcity of data. Patients with type 2 diabetes mellitus of long duration often constitute a special risk group because of their high cardiovascular risk, especially after a CAD event. One other clinical problem could be the occurrence of autonomic neuropathy and hypertensive reactions. This calls for a closer look at such patients and the application of home blood pressure monitoring or 24-ABPM to obtain more reliable information on blood pressure control. In the SMART Study, <20% of the patients had a diagnosis of diabetes mellitus at baseline. Therefore, there is a need to gather more data from patients with a combination of diabetes mellitus and a previous cardiovascular event, especially after application of 24-hour ABPM for the evaluation of blood pressure burden.

In a recent meta-analysis of blood pressure goals for patients with type 2 diabetes mellitus that some researchers think is more or less an equivalent to CHD, it was pointed out that the totality of evidence in 2011 suggests a systolic blood pressure goal of between 130 and 135 mm Hg.\footnote{11} We still lack similar data to define a systolic blood pressure goal in secondary prevention, in patients with or without diabetes mellitus.

In conclusion, observational studies suggest that a J-shaped curve exists also in secondary prevention of hypertension. Reverse causation might create problems in statistical analyses that could at least partially be overcome by applying subgroup analyses, as carried out in the SMART Study. However, in the end there is no substitute for new randomized, controlled trials. Funding agents should realize that, when so much money is spent on the acute care of patients with CAD, CHD, and stroke, there is a good argument to also spend money on defining blood pressure goals for long-term secondary prevention.

Disclosures

P.M.N. is currently the secretary of the European Society of Hypertension.

References


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