EBM NOTEBOOK

Using evidence to resolve clinical controversies: Is aggressive antihypertensive therapy harmful?

Primus non nascor is one of the first maxims taught in any medical school curriculum. However, deciding that an intervention is harmful is a complicated issue because the clinician or policy maker is often faced with conflicting evidence. In this EBM Note, I will outline an approach to weighing the evidence, using as an example one of the most contentious issues in current hypertension management: the J-curve hypothesis. The belief that lowering diastolic blood pressure (DBP) too much may increase cardiovascular risk was first proposed in the late 1970s (1), and several studies purporting to establish or refute the J-curve theory have been published over the past 2 decades.

Step 1: Clarify the question and find the evidence
In the case of the J-curve debate, as with so many clinical controversies, posing the clinical question is crucial. Extremes in blood pressure (BP), like other physiological parameters, are incompatible with good health, and the question of interest to clinicians is not whether persons with lower BP have higher mortality risks but whether aggressive (compared with less aggressive) BP reduction results in poorer outcomes in patients with hypertension (2). In order to answer this question with the least likelihood of bias, one must systematically search for the relevant evidence. The most sensitive MEDLINE search strategies for studies of harm have been published and are available at the Centre for Evidence-Based Medicine Web site (http://ceb.mjt2.ox.ac.uk/docs/searching.html#aeti) (3).

Step 2: Critically appraise the identified studies
Criteria for evaluating the internal validity of studies on harm have already been published, and only one element will be reviewed here: Do the results address Hill’s diagnostic tests for causation (Table 1)? (4, 5) If the answer is “no,” then the study is of limited use in answering the question posed in step 1. Although pathophysiological rationale is often the only criterion addressed in studies of harm, our rapidly changing knowledge of pathophysiology, and the fertility of the human mind in finding explanations to support almost any observation, would imply that one should be cautious in relying on this criterion alone (6).

Step 3: Rank the evidence and decide if the results are important
This step requires careful consideration of the limitations of each study design, the strength of the reported association between exposure and outcome, and the consistency of the association across different study designs. Associations that are maintained, or strengthened, in higher-level studies are generally more convincing than those that weaken as the study design improves. The magnitude of association in studies of varying design relevant to the J-curve debate are described in Table 2.

Hypothesis-generating studies: Population surveys (in which the disease rate in one population is compared with that in another with a different level of the putative causative factor) are often the first studies invoked in discussions of BP control. Associations observed between variables at an aggregate level, however, are not necessarily reproduced at the individual patient level (ecological bias), and any findings must be confirmed in studies of individual patients. Case reports and case series (from which the J-curve hypothesis arose (1)) are prone to selection bias, and observations derived from them must be investigated in studies with greater methodological rigour (unless the outcome is rare and produced by dramatic, such as phocomelia in children exposed to thalidomide in utero).

Analytic studies (case-control studies, cohort studies, outcomes research): Although case-control and cohort studies are the only way to establish causation when the target outcome is rare, these studies often have substantial selection or measurement biases (7). For example, consider a case-control study that examined the relation between treated DBP and risk for cardiovascular disease (8). As a result, patients with advanced coronary artery disease or scleroderma were selectively excluded from the group with higher DBP (perhaps with higher BP tend to develop cardiac symptoms earlier than patients with lower DB but the same degree of atherosclerosis) (9).

A further problem with observational studies is that medications (e.g., antihypertensive drugs) are generally prescribed only to patients with indicated hypertension (which are associated with poor prognosis, e.g., myocardial infarction, stroke, or death). As a result, the medication is associated with the outcome, which could lead to the incorrect conclusion that the medication causes the outcome (confounding by indication). A recent cohort study showed that patients with DBP ≤ 90 mm Hg who were taking antihypertensive drugs had more cardiac morbidity than patients with similar BP who were not taking antihypertensive drugs, but no differences about the effects of aggressive antihypertensive therapy can be derived (10). In fact, to answer our question from step 1, we should look at the evidence.

Table 1. Diagnostic tests for causation (5)

| 1. Correct temporal association with exposure preceding outcome |
| 2. Gradient of risk with increasing duration or intensity of exposure |
| 3. Association consistent from study to study |
| 4. Positive result from a “dechallenge-rechallenge” study |
| 5. Pathophysiological rationale |
Comparison between treated patients with DBP > 90 mm Hg and treated patients with DBP ≤ 90 mm Hg (crude relative risk [RR] reported in Table 2).

Finally, the potential for unequal distribution of important prognostic factors (known and unknown) between exposed and unexposed patients limits the inference that can be drawn from observational studies. Thus, although an odds ratio (OR) or RR > 1 implies that exposure is associated with an increased risk for the outcome of interest, it is recommended that only an OR ≥ 4, or RR ≥ 3, should be accepted as evidence of increased risk in observational studies (although a lower OR or RR may be acceptable if the outcome is serious) (7).

In this light, the conclusion of a recent case-control study that showed that lowering DBP to <85 mm Hg increases the risk for cardiac arrest is suspect (the ORs for each strata of treated DBP were 1.2 for 80 mm Hg, 1.6 for 75 mm Hg, and 2.3 for 70 mm Hg) (8).

Randomised controlled trials (RCTs): RCTs provide the strongest evidence for causality, but they are rarely done to evaluate possible harm. Subgroup analyses of RCTs, however, often purport to find harm in ≥ 1 subgroup. Detailed criteria for deciding whether to believe reported differences in subgroup response have been published (6), but the key point is the consistency of the subgroup results across studies. In the absence of corroborating data from other studies, it seems safest to assume that the overall treatment effect shown in an RCT applies to each subgroup. For example, although post-hoc subgroup analysis of the Hypertension Detection and Follow-up Program suggested a J-curve with antihypertensive treatment in some subgroups, the overall trial results showed fewer coronary events in those patients randomised to the aggressive treatment arm (11, 12). Other RCTs have confirmed that antihypertensive therapy lowers the risk for cardiovascular events without evidence of a J-curve, and none of the RCTs that compared aggressive BP reduction with a less aggressive approach found a J-curve (13–18).

Step 4: Consider the implications for your patient

Step 4 involves the consideration of 4 issues. First, is your patient sufficiently similar to those in the identified studies that the study results are applicable? Second, your patient’s expectations, preferences, and values about the risks and benefits of therapy should be assessed and incorporated into the decision. Third, consideration of the magnitude of the risk, which can be estimated from the OR or RR, is perhaps most relevant to the individual patient when expressed as the number needed to harm (NNH) (see Glossary). Fourth, and most important, one should consider the consequences of acting upon the evidence. This point is particularly germane to the J-curve debate in light of the consistent message from cross-sectional surveys showing that most hypertensive patients are undertreated and poorly controlled (19). Based on these data and the current RCT evidence, it seems that efforts to improve BP control are likely to be rewarded with reductions in the incidence of stroke, myocardial infarction, and cardiovascular mortality.

References


Table 2. The strength of reported associations relative to study design

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Strength of association (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart (1)</td>
<td>Case series</td>
<td>RR 5.4 (1.6 to 18.7)</td>
</tr>
<tr>
<td>Siscovick et al. (8)</td>
<td>Case-control</td>
<td>OR 2.3 (1.4 to 3.8)</td>
</tr>
<tr>
<td>Merlo et al. (10)</td>
<td>Cohort</td>
<td>RR 1.7 (0.8 to 3.6)</td>
</tr>
<tr>
<td>Cooper et al. (11)</td>
<td>Subgroup of RCT</td>
<td>RR 1.5 (not provided)</td>
</tr>
<tr>
<td>Hansson et al. (17)</td>
<td>RCT</td>
<td>RR 1.1 (0.9 to 1.3)</td>
</tr>
</tbody>
</table>

*Comparison of event rates in patients with lowest treated diastolic blood pressure and referent categories. OR = odds ratio; RCT = randomised controlled trial; RR = relative risk.


