J-curve Phenomenon Might Be Inherent: How to Know If It Is Treatment Induced?

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Excluding the subject with self-reported diagnosis hypertension, Kimm et al.,1) reported that J-curve phenomenon was observed in a large observational cohort for all-cause mortality, atherosclerotic cardiovascular mortality, and ischemic heart disease mortality. This study went a step farther than the study done by McEvoy et al.,2) which demonstrated J-curve phenomenon in a population cohort trying to exclude the effect of antihypertensive drug treatment. In this study, hypertensive subjects taking antihypertensive medication seems to be excluded at baseline in spite of some limitations.

J-curve phenomenon is a physiologic consequence as the diastolic blood pressure (DBP) is going down below the threshold where myocardial ischemia is induced.3) Myocardial injury related to low DBP was reported in the population.2) The principle is very simple and observed even in placebo group.4) And the study by Kimm et al.,1) is a population version of the J-curve phenomenon observed in placebo group in randomized clinical trial (RCT) which supports that J-curve phenomenon can be inherent to individual's characteristics.

It is very reasonable to compare the hazard of low DBP between treatment group and placebo group to draw true effect of antihypertensive treatment on J-curve phenomenon. If the hazard ratio (HR) is significantly higher than the placebo group, it makes sense to conclude that the J-curve phenomenon is treatment induced. In a recent analysis of RCT data including Systolic Blood Pressure Intervention Trial (SPRINT), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), J-curve phenomena were noted both in intensive treatment group and standard treatment group but HR was significantly higher not in intensive treatment group but in standard treatment group and the nadir in the intensive treatment group is lower compared with the standard treatment group.5)

In fact, such comparison between groups was tried for the placebo controlled RCTs. For example, individual patient data arranged for matched-pair analysis showed significant benefit of lowering DBP <70 mmHg in treatment group when compared to the placebo group with matched blood pressure level.6) Therefore, it may not be reasonable to down-titrate antihypertensive regimen when DBP <70 mmHg is encountered without considering the hazard reported in those DBP range in the placebo group or less tightly controlled group.
Study of Kimm et al.,\textsuperscript{11} suggests that J-curve phenomenon could be inherent. And it will provide a basis to decide whether J-curve phenomenon observed in a treated population is induced or not by testing whether the curve is significantly steeper or not or by testing whether the HR is significantly higher than untreated population or less tightly controlled group.

REFERENCES


