Effects of Atenolol and Propranolol on Platelet Aggregation in Moderate Essential Hypertension

To the Editor: We read the paper “Effects of atenolol and propranolol on platelet aggregation in moderate essential hypertension: randomized crossover trial” by Punda et al with great interest (1). However, we would like to point out some issues which we found conflicting. Firstly, the presence of hypertension in patients, used for comparing the effects of two distinct β-blockers on platelet functions, is an independent factor which could directly influence the results. The mechanisms of platelet activation in hypertension include high shear force, activation of renin-angiotensin system, endothelial changes, and presence of comorbid conditions. The treatment of high blood pressure brings about a reversal of the changes seen in the cell. This could in part be due to the direct effect of the drug on the megakaryocyte and/or the platelets themselves, or it might simply be due to the reduction in blood pressure (2). The possibility that the regulation of hypertension could solely correct the platelet functions makes the comparison of the effects of the two drugs questionable. Secondly, the authors imply that there is no clear evidence that atenolol has an effect on platelet aggregation. In 1997, Knight et al reported that atenolol treatment did not alter platelet aggregation in unstimulated samples, lead an increment in fibrinogen binding as a response to thrombin activation, and did not block the effect of epinephrine on platelet fibrinogen binding (3). According to the results of this study, atenolol did not alter platelet activation significantly. At this point, it does not seem logical to create a model comparing the effects of propranolol and atenolol when there are reports addressing the ineffectiveness of atenolol on hypertension. Additionally, a metaanalysis by Carlberg et al, cited by Punda et al, found that antihypertensive effect of atenolol was not superior to placebo and was inferior to other antihypertensives in cardiovascular morbidity and mortality (4). According to this metaanalysis (4), it does not seem appropriate to administer atenolol to one arm of the hypertensive patients, as Punda et al did. Thirdly, the authors noted that the effects of propranolol on platelet aggregation were reported to be different in previous studies. They argue that these differences could originate from different doses of propranolol and a difference in the methods for measuring platelet aggregation. They claim that they studied spontaneous aggregation, despite the fact that others studied induced aggregation. In this case, is the method the authors chose for measuring the effects of propranolol on platelet aggregation appropriate for the exact determination of the effects of propranolol on platelet aggregation? It is unclear why this method could not be performed in vivo by using flow cytometry (5). Moreover, the serotonergic effects of platelets should not be overlooked as it is influenced by propranolol (6).

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Authors’ Reply: We appreciate the comments of our colleagues from Ankara on our paper about different effects of two β-blockers on platelet aggregability in hypertensive patients.

Our examinees were selected on purpose: arterial hypertension was a condicio sine qua non for enrolment. The aim was to see the possible differences in this respect between a cardioselective and a nonselective β-blocker, using a less conventional, ex vivo technique of platelet aggregability measurement. As the arterial pressure was quite comparable in both study groups (cf. our table 1), the enrolment of hypertensive patients could not introduce bias.

That β-blockers lower elevated blood pressure with a substantial improvement in the outcome has been demonstrated beyond any reasonable doubt in many large studies. However, these drugs are possibly less useful in asymptomatic elderly patients (1). It is generally held that all agents from this class show comparable antihypertensive activity, although there are many reports indicating that atenolol may be superior to nonselective congener in this respect (4-8). Indeed, our results show a marginally better blood pressure reduction with atenolol (e.g. 17% vs 15% for systolic blood pressure; see our table 2). Currently, β-adrenergic blockers stay firmly among the first-line antihypertensive drugs, particularly if there are concomitant “compulsive” indications, such as manifest coronary heart disease or congestive heart failure, but also in patients with tachyarrhythmias, thyrotoxicosis, essential tremor, or in pregnant women.

Accordingly, we disagree with the claim of Beyan, Kaptan, and Ifran that our atenolol study arm was inappropriate. the LIFE study (2), which strongly influenced the meta-analysis of Calberg and Samuelsson (3), included elderly hypertensive patients, aged around 67 (our examinees were about 43 years old), with left ventricular hypertension but no manifest coronary heart disease or heart failure, disfavoring atenolol. Unexpectedly, the observed differences were major in stroke and even negative in the incidence of myocardial infarction (2).

We agree that the main limitation of our study, as noted by Beyan, Kaptan, and Ifran, was insufficient comparative, complementary platelet function assessment, using such means as whole-blood flow cytometry (9) or aggregometry (10). Unfortunately, the same is true for other studies, and is probably the leading cause of incongruent results. For example, using flow cytometry, Knight et al (9) have shown that atenolol stimulates fibrinogen binding to activated GP IIb/IIIa, with no effect on ADP-induced platelet activation, slightly enhancing the aggregation process. On the other hand, according to the aggregometry results of Srivastava (10), atenolol had no effect on arachidonic acid-induced platelet clustering, but inhibited collagen and ADP-stimulated aggregation, and lowered thromboxane (TxB2) formation from arachidonic acid, curtailing the same process.

Evidently, the issue is still open. It could well be that disparate effects of β-blockers at the cellular level, such as lipophilicity, interference with ionic currents (“membrane stabilizing activity”), or serotoninergic action are partly responsible for the observed differences. Divergent techniques and discrepancies between in vitro and in vivo measurements are presumably responsible for the rest. However, even the smallest blood clotting discrepancies may result in significant outcome differences, particularly in high risk people.

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