A new combination therapy in stable angina pectoris

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This editorial refers to ‘Efficacy of the I<sub>1</sub> current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial’, by J.-C. Tardif et al. on page 540

Ischaemic heart disease is the leading cause of death in high, middle, and low income countries. The improvement in management and survival of heart disease in the last decades, together with an increasingly ageing population, continues to increase the absolute number of patients with heart disease. Optimal medical therapy includes satisfactory antianginal therapy and intensive risk factor modification as the first-line treatment in the majority of cases. This very large group of patients presents with a natural diversity with regard to symptoms, side effects of medications, expectations, and co-morbidity. Most patients need multiple medications and a multidisciplinary approach. Combination therapy is often necessary both to control angina symptoms and to modify risk factors such as hypertension. A primary approach consisting of medium doses of two medications rather than the highest doses of one medication is gaining popularity in hypertension due to fewer side effects than one high dose medication, with equal or better effect. The same approach may also be appropriate in angina pectoris. The European guidelines on management of angina pectoris suggests primarily a full dose of monotherapy with a beta-1 blocker and secondly a combination therapy with a dihydropyridine calcium channel blocker in cases where there is an insufficient effect. However, the effect of such a combination is rather small and works only in the first 6 h after taking the medication. On the other hand, much lower doses of beta-blockers are used in clinical practice, and the adherence to beta-blockers is relatively poor. These facts point to the need to investigate alternative strategies such as new combination therapies.

Tardif et al. have evaluated the effect of combination therapy with atenolol 50 mg o.d. and ivabradine 5 and 7.5 mg b.i.d. vs. atenolol alone in a randomized double-blind controlled study. In addition to 50 mg of atenolol o.d., ivabradine at both 5 and 7.5 mg b.i.d. is shown to improve total exercise duration (primary outcome) and all exercise test variables significantly. The combination therapy is very well tolerated, with few side effects. The major outcome is exercise duration at the trough of drug activity. It is one of the largest studies of combination therapy in angina pectoris. As the achieved effects are demonstrated at the trough of drug activity, this signifies that the combination works all the time. The study answers some very important clinical questions but raises others. Thus, in patients with angina pectoris who cannot tolerate full dose beta-blockers, the addition of ivabradine is one of the best evidence-based solutions. It is now well documented that heart rate reduction with ivabradine is effective and can be used safely both alone and in combination with beta-blockers to alleviate angina and improve exercise capacity. Another emerging question is whether heart rate reduction per se should be an appropriate and necessary target for risk factor modification in angina pectoris and perhaps also in high risk subjects.

For many centuries, physicians have used the pulse and pulse rate as a significant signal that reflects the health status of the body and mind. It is now well documented that a high heart rate is associated with total and cardiovascular mortality in a wide range of populations. Heart rate affects the cardiovascular system in a complex way: a higher heart rate is associated with many major risk factors for atherosclerosis such as smoking, diabetes, hypertension, hypercholesterolaemia, obesity, a sedentary lifestyle, C-reactive protein, and other inflammatory markers. On the other hand, a higher heart rate, by itself, increases the mechanical load imposed on the arterial wall, and it aggravates many other prognostic factors such as endothelial dysfunction, viscosity, and arterial stiffness, and increases the risk of developing diabetes and hypertension, thereby leading to atherosclerosis and plaque rupture. However, these factors may increase the heart rate, thus leading to a vicious circle aggravating the process of atherosclerosis. Breaking the vicious circle of a high heart rate can thus improve the prognosis. This has been supported by...
evidence from heart rate-reducing therapy such beta-blockers or calcium channel blockers after myocardial infarction, beta-blockers in heart failure, and some evidence from pure heart rate-reducing therapy in subjects with heart failure and pulse >70 in a subgroup analysis in the Beautiful study.17

Even though the theoretical background supporting the effects of pure heart rate reduction in atherosclerosis is convincing, there are few randomized clinical trials. The study by Tardif et al. widens the indications for selective heart rate reduction by use of ivabradine in angina pectoris: ivabradine can be added to medium doses of beta-blockers with a significant improvement in the clinical efficacy. There are still some important questions that remain to be addressed in future studies: does ivabradine have any additional effect on top of a maximum dose of beta-blockers? Do beta-blockers or calcium channel blockers have any additional effect when used on top of a maximum dose of ivabradine? Another emerging question is whether targeting heart rate as a modifiable risk factor in angina patients and other high risk subjects will reduce the mortality and morbidity from cardiovascular diseases.

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References