A frequent gene polymorphism affecting the heart-rate response to carvedilol

“...carvedilol may be not the best suited β-blocker for patients in whom rate control in chronic AF is a primary goal or it should be given at high doses.”

KEYWORDS: β-blockers • ADBR1 gene polymorphisms • atrial fibrillation • bisoprolol • carvedilol • heart failure

β-adrenoceptor antagonists, known as β-blockers, are a cornerstone in the treatment of the most prevalent cardiovascular syndromes, including heart failure, ischemic heart disease, atrial fibrillation and hypertension. Their beneficial effects are explained by competitive antagonism at β1-adrenoceptors, the dominant adrenergic receptors expressed in cardiac myocytes. By contrast, antagonism at β2-adrenoceptors accounts for side effects (e.g., vasospasm [‘cold extremities’], bronchospasm and hypoglycemia) and contraindications, such as asthma bronchiale. Accordingly, the majority of currently prescribed second-generation β-blockers (e.g., metoprolol, bisoprolol and atenolol) preferentially act at β1-adrenoceptors, that is, they possess higher affinity towards β1- than β2-adrenoceptors (‘β1-selective β-blockers’). Carvedilol is a third-generation β-blocker, which is generally classified as nonselective, but, in fact, has a 13-fold-higher affinity for human β2- than β1-adrenoceptors [1]. Carvedilol is also a potent α1-adrenoceptor antagonist [2], which balances the constrictive effect of β2-blockade, and has antioxidant effects of unknown relevance. Moreover, carvedilol directly blocks spontaneous diastolic Ca2+ release from cardiac ryanodine receptors, an activity thought to suppress ventricular arrhythmias, for example in heart failure, where the ryanodine receptor is thought to be ‘leaky’ [3,4]. Finally, carvedilol has unusually slow dissociation kinetics, that is, it ‘sticks to adrenoceptors’, which causes a longer time of action than predicted from its plasma half-life [5].

The β1-adrenoceptor gene (ADBR1) exhibits a frequent SNP that causes a change of Arg at position 389 to Gly [6]. Approximately 40 and 7% of Caucasians are heterozygous and homozygous for the rarer Gly389 variant, respectively. The polymorphism has gained much attention because, when overexpressed at very high levels in heterologous cell systems, the Gly389 variant stimulates cAMP synthesis fivefold less than the Arg389 variant, that is, it is a minus variant. Since chronic hyperactivity of β1-adrenoceptors is thought to adversely affect cardiovascular outcome and β-blockade improves it [7,8], it was initially assumed that the homozygous presence of the Arg389 variant would confer a higher risk in patients at high cardiac risk, on the one hand, and better response to β-blockade on the other hand. Indeed, in retrospective clinical analyses, some studies in transgenic mice and isolated human heart muscle preparations reported higher signaling activity of the Arg389 variant and greater responses to β-blockade (see overview in [9,10]). The only large prospective outcome study found no difference between homozygous Arg389 and Gly/X carriers in the placebo group, but benefit from the atypical β-blocker bucindolol only in the Arg389Arg group [11]. Several other studies failed to substantiate differences between the groups.

On this background, we performed a prespecified pharmacogenetics trial accompanying the CIBIS-ELD trial. CIBIS-ELD prospectively evaluated the tolerability of the two standard β-blockers carvedilol and bisoprolol in >800 elderly patients with heart failure, a group prone to side effects to β-blockers. The main findings of CIBIS-ELD were: using a 2-weekly uptitration scheme, only approximately 25% of the elderly patients with heart failure reached the respective guideline target dose; and bisoprolol caused greater heart-rate reductions and more bradycardia than carvedilol [12]. The hypothesis of the pharmacogenetic substudy of CIBIS-ELD was based on the above biochemical evidence that the Gly389 β1-adrenoceptor is a minus variant and stated that Arg389Arg carriers have a greater heart-rate response to β-blockers. The results in >500 patients available for the genetic
analysis were surprising and did not support our hypothesis (Figure 1) [9]. Predrug heart rate did not differ between the genotypes, neither in patients with sinus rhythm (SR) nor with atrial fibrillation (AF; ~20% of total cohort) [7]. In patients with SR, neither the genotype nor the type of β-blocker affected the heart-rate response to β-blockade (reduction from ~70 to 64 bpm) [3]. By contrast, patients with AF showed a smaller heart-rate response to carvedilol than to bisoprolol. The difference was entirely due to a markedly smaller effect of carvedilol in Arg389Arg carriers, whereas the effect of carvedilol and bisoprolol did not differ in Gly389 carriers [13]. Surprisingly, the differences between genotypes and β-blockers emerged only after 2 weeks of treatment. Acute responses were identical in all groups. Thus, the study identified a remarkable fading of bradycardic effects of carvedilol only in heart failure patients in AF that carry two alleles encoding the active β1-adrenoceptor variant Arg389.

**Is it a true pharmacogenetic effect?**

It could be argued that the results came along just by chance, adding to the noise in this scientific field. Arguments against this explanation are the relatively large number of patients studied in a randomized, prospective and double-blinded manner [9], the highly statistically significant effects (differences between genotypes and between carvedilol and bisoprolol p < 0.0001) [7], and the fact that the data are well in line with two other studies [3]. A register study in Japanese patients with heart failure reported the heart-rate-lowering effect of carvedilol to be smaller than that of bisoprolol, both in the entire cohort and the AF subgroup [14]. Also, a recent nonrandomized cohort study in patients with AF observed that the heart-rate-lowering effect of β-blockers in general was greater in Gly389 carriers [15]. In line with our data, the difference was most pronounced with carvedilol. Bisoprolol was not studied. Taken together, the difference in heart-rate response between Gly389 and Arg389Arg carriers is to date one of the best documented, independently reproduced and most pronounced pharmacogenetic effect in the cardiovascular field.

**Mechanisms?**

The mechanisms of the difference between genotypes, β-blockers, SR and AF, and acute and prolonged effects are currently unclear. Several self-evident explanations seem unlikely. The higher signaling activity of the Arg389 variant would have predicted a stronger response (to both β-blockers). The fact that basal heart rate and the response to β-blockers were essentially identical in patients with SR (and acutely in all groups) therefore suggests that compensatory mechanisms are in place that counteract the higher signal input through the Arg389 variant. The α1-adrenoceptor antagonist and vasodilating property of carvedilol predicts its blood pressure-lowering effect to be larger than that of bisoprolol. This could cause reflex sympathetic nervous activation via baroreceptors and therefore minimize the heart-rate-lowering effect of carvedilol. However, such an indirect effect would be seen acutely and in all patients, which was not the case. Instead, the data show slowly developing genotype-specific regulation of atrioventricular node (AVN) conduction, but not of pacemaking in the sinoatrial node. Catecholamines accelerate AVN conduction by stimulating the main depolarizing inward current, I_{Ca,L}, and shorten the effective refractory period by stimulating I_{Ks} (see review in [16]). β-blockers antagonize these effects and thereby slow AVN conduction velocity. In AF, they slow ventricular rate mainly by prolonging the effective refractory period and thereby increasing the filter function of the AVN. In dogs, both β1- and β2-adrenoceptors participate in the acceleration of conduction induced by sympathetic nerve stimulation, but the contribution of β2-adrenoceptors was smaller in the AVN than the sinoatrial node [17]. Since carvedilol is a preferential β2-blocker, one could hypothesize that it is simply not effective enough at low doses to block β1-adrenoceptors in the AVN. Why does the difference then develop only after 2 weeks and is seen only in Arg389Arg carriers? It is known that β-adrenoceptors are upregulated under chronic β-blockade and it is possible that upregulation of the higher activity Arg389 variant, but not the lower Gly389 variant, overcomes the effect of carvedilol. Alternatively, the observed long-term pharmacogenetic differences in the carvedilol response may be related to the fact that carvedilol is a ‘biased agonist’ at β-adrenoceptors. Carvedilol can activate arrestin-dependent, nonclassic, β1-dependent signal pathways, such as activation and internalization of EGFRs with subsequent phosphorylation of MAPKs [18]. This may somehow affect its effect on conduction. Obviously, more work is needed to answer this question.

**Practical consequences?**

The data show that Arg389Arg carriers with heart failure and AF (~50% of patients with AF and 10% of all patients with heart failure)
lack a sustained heart-rate-lowering response to medium doses of carvedilol. Whereas our own study was restricted to patients with heart failure, the recently published cohort study [15] included all patients with AF and came to similar conclusions, suggesting that the reduced heart-rate response to carvedilol pertains to all patients with AF. It is important to note that neither study

Figure 1. Heart-rate response to uptitration with the β-blockers bisoprolol (1.25–10 mg) or carvedilol (2 × 3.125–25 mg) in patients with chronic heart failure according to rhythm and β1-adrenoceptor genotype (Arg389Gly). (A & B) Resting heart rate at baseline (predrug), 14 (bisoprolol: 1.25 mg; carvedilol: 2 × 3.125 mg), 28 (bisoprolol: 2.5 mg; carvedilol: 2 × 6.25 mg), 42 (bisoprolol: 5 mg; carvedilol: 2 × 12.5 mg), 56 (bisoprolol: 10 mg; carvedilol: 2 × 25 mg) and 90 days (follow-up) after initiation of β-blocker therapy in patients with (A) sinus rhythm or (B) atrial fibrillation. Numbers in brackets indicate numbers of patients at the respective time points/dose level. (C & D) Resting heart rate at baseline (predrug), 1, 2 and 14 days after initiation of β-blocker treatment with the starting dose (bisoprolol: 1.25 mg; carvedilol: 3.125 mg) and after 28 days (bisoprolol: 2.5 mg; carvedilol: 2 × 6.25 mg) in patients with (C) sinus rhythm or (D) atrial fibrillation. Note that 25% of patients were pretreated with a β-blocker at <25% of target dose, likely explaining why carvedilol formally caused an increase in mean heart rate at 14 and 28 days after initiation of treatment in patients with atrial fibrillation (B and D, respectively).

***p < 0.0001 versus bisoprolol or Gly/X.

Adapted with permission from [12].
measured effects on outcome. In fact, beneficial effects of β-blockers on outcome in patients with heart failure and AF have never been prospectively studied. Retrospective analyses of large-outcome studies suggested significant benefits of treatment with carvedilol [13] and formally not with bisoprolol [19] or metoprolol [20]. On the other hand, a retrospective study in patients with heart failure observed an association of the Arg389Arg (plus Gln27/X for the β2-adrenoeceptor) genotype with a twofold higher mortality risk in patients treated with carvedilol, but not with metoprolol [21]. Despite small numbers and the retrospective design, these data point to a smaller effect of carvedilol in patients with specific β-adrenoeceptor genotypes. Clearly, more work is needed to substantiate this hypothesis. In any case, carvedilol may be not the best suited β-blocker for patients in whom rate control in chronic AF is a primary goal or it should be given at high doses.

Financial & competing interests disclosure
The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References
3 Eschenhagen T. Is ryanodine receptor phosphorylation key to the fight or flight response and heart failure? J. Clin. Invest. 120, 4197–4203 (2010).