

# Genetic Variation, $\beta$ -blockers, and Perioperative Myocardial Infarction

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## ABSTRACT

Perioperative myocardial infarction is a common and potentially fatal complication after noncardiac surgery, particular among patients with cardiovascular risk factors.  $\beta$ -blockers have been considered a mainstay in prevention and treatment of perioperative myocardial infarction, yet recent evidence suggests that  $\beta$ -blockers may have an unfavorable risk profile in this setting, and the use has become controversial. What seems conspicuously absent from the current discussion is the appreciation of how much interindividual genetic variation influences the clinical response to  $\beta$ -blocker therapy. Genetic variation in the adrenergic signaling pathway is common, and has a major impact on adrenergic receptor function and  $\beta$ -blocker efficacy in other cardiovascular diseases, such as heart failure and hypertension. Genetic variation in the cytochrome P450 2D6, or CYP2D6, enzyme, which is responsible for the metabolism of most  $\beta$ -blockers, is also important and can lead to poor metabolizing of  $\beta$ -blockers (potential toxicity) or their ultra-rapid degradation (decreased efficacy). Here, we review the molecular, cellular, and physiologic consequences of polymorphisms in the adrenergic signaling pathway and CYP2D6 gene, and show that these are likely relevant factors influencing efficacy, safety,

and toxicity of  $\beta$ -blocker therapy in prevention and treatment of perioperative myocardial infarction.

THE use of  $\beta$ -blockers has been considered the standard of care to reduce myocardial ischemia and infarction both during and after noncardiac surgery, and has been recommended by international practice guidelines.<sup>1,2</sup> However, since the publication of the POISE study in 2008,<sup>3</sup> a large clinical trial with more than 8,000 patients that showed an increased risk of death and stroke among patients randomized to receive metoprolol in these settings, the use of  $\beta$ -blockers to reduce perioperative cardiac risk has become controversial. Although the debate is still ongoing and the controversy is far from being settled,<sup>4</sup> one crucial aspect regarding the efficacy and safety of  $\beta$ -blockers in the perioperative period has not been explored: the influence of genetic factors.

Ample evidence exists that the individual response to  $\beta$ -blockers in other clinical settings is substantially influenced by genetic variation in adrenergic signaling<sup>5–8</sup> and drug metabolism pathways, most notably in the cytochrome P450 2D6, or CYP2D6, enzyme,<sup>9–12</sup> which is responsible for the metabolism of most  $\beta$ -blockers.<sup>13</sup> Here we provide a concise overview of the genetic variability within these pathways relevant to  $\beta$ -blocker responses. Furthermore, we discuss potential links between genetic factors and the risk for the adverse outcomes during  $\beta$ -blocker treatment, such as hypotension and stroke, observed in recent clinical trials in the perioperative period.<sup>3,14–18</sup>

## Perioperative Myocardial Infarction—A Hidden Epidemic

Perioperative myocardial infarction, or MI, is a common and serious complication after surgery, often referred to as a “hidden epidemic.”<sup>19,20</sup> A recent study among 85,000 inpatient surgeries showed an overall incidence rate of 0.5% for peri-

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operative MI, which was associated with a 30–40% mortality rate.<sup>21</sup> The risk for perioperative MI is at least on an order of magnitude higher among patients with preexisting coronary artery disease undergoing major noncardiac surgery (reported risk: 5–6%).<sup>14,22–24,105</sup> Taking into account that an estimated 230 million surgeries are performed annually worldwide, more than 1 million patients are expected to suffer from perioperative MI or cardiac death each year.

### The Pathophysiology of Perioperative MI

Several important differences exist between perioperative MI and acute MI in a nonoperative setting.<sup>20</sup> Perioperative myocardial ischemia and infarction are often “silent,” with minimal classic clinical symptoms of an acute MI, such as chest pain or dyspnea.<sup>23,25–27</sup>

Two major causes of perioperative MI can be distinguished.<sup>28,29</sup> The first cause involves the destabilization of a vulnerable atherosclerotic plaque, followed by acute coronary artery thrombosis, and subsequent myocardial ischemia and infarction.<sup>30</sup> Causes for plaque destabilization in the perioperative period are manifold, but the most apparent are surgical stress resulting in hypertension, tachycardia, and increased catecholamine levels, and hypercoagulability caused by surgical trauma. This pathophysiological process is identical to an acute coronary syndrome.<sup>31</sup> Although potentially fatal, the minority of perioperative MIs, however, are caused by an acute coronary syndrome.

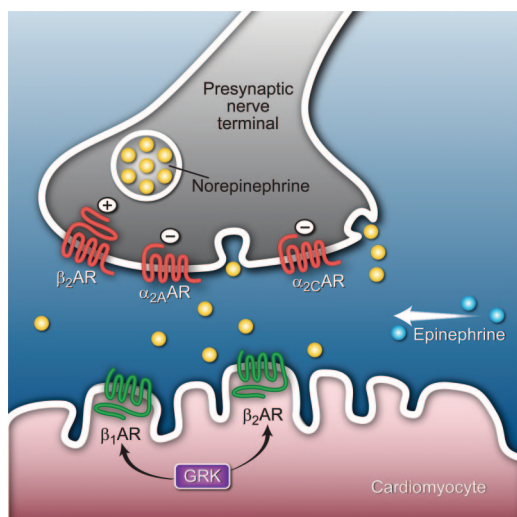
The second, more common, mechanism for perioperative MI is an imbalance between myocardial oxygen demand and supply. In the setting of stable coronary artery disease with fixed atherosclerotic lesions, events resulting in higher oxygen demands in the myocardium that cannot be met by the limited blood flow can lead to myocardial ischemia and infarction. Common reasons for high myocardial oxygen demand and/or reduced oxygen supply in the perioperative period include tachycardia, acute hemorrhage, hypotension, hypoxemia, hypertension (increased myocardial wall stress), fever, and sepsis syndrome. In addition, endothelial dysfunction also plays a crucial role.<sup>32,33</sup> Clinically, this type of perioperative MI resembles a non-ST segment elevation MI and is typically associated with a smaller increase in cardiac biomarkers than an acute coronary syndrome.<sup>23–25,34–41</sup>

Common to both mechanisms is the activation of the sympathetic nervous system, which increases heart rate and cardiac oxygen consumption by catecholamine-mediated activation of  $\beta$ -adrenergic receptors, or  $\beta$ AR, on the myocardium. A logical intervention to potentially prevent myocardial ischemia in the perioperative period is the administration of  $\beta$ AR antagonists, or  $\beta$ -blockers, to decrease myocardial energy expenditure.

### $\beta$ -blockers in the Prevention of Perioperative MI

Because of results showing a significant reduction in mortality among patients with acute coronary syndrome who were

treated with  $\beta$ -blockers,<sup>42,43</sup> clinicians concerned about perioperative myocardial infarction reasoned that  $\beta$ -blockers may provide the same benefits to surgical patients. Mangano *et al.* showed in the 1990s that prophylactic atenolol reduced perioperative myocardial ischemia by 50%, and the incidence of cardiac deaths after noncardiac surgery by 10% in patients with or at risk for coronary artery disease.<sup>44,45</sup> When bisoprolol was given to high-risk patients who had a positive dobutamine stress echocardiography 30 days before surgery in the unblinded DECREASE I trial, a similar observation was made: nonfatal MI and cardiac death rates were significantly lower in patients who received bisoprolol compared with placebo.<sup>46</sup> These consistent findings along with evidence from the efficacy of  $\beta$ -blockers in acute coronary syndrome led to a strong recommendation (class I and IIa) by the American College of Cardiology and the American Heart Association in their 2002 guideline for perioperative evaluation for noncardiac surgery.<sup>47</sup> However, a systematic review published in 2005, which included a meta-analysis of all randomized controlled trials that evaluated  $\beta$ -blockers in noncardiac surgery, raised new issues. This analysis showed that  $\beta$ -blockers were likely efficacious in lowering the rate of perioperative MI and cardiac death, but were also associated with a substantial risk for adverse cardiovascular side effects, such as hypotension and bradycardia requiring treatment, suggesting that there was risk of hypoperfusion of other organ systems.<sup>48</sup> Two large randomized controlled trials were published in 2006, in which patients undergoing major noncardiac surgery who received either metoprolol or placebo on the day of or 1 day before surgery had no difference in postoperative cardiovascular morbidity or overall mortality.<sup>15,17</sup> The authors from both trials concluded that  $\beta$ -blockers were not effective in reducing the rate of postoperative cardiac events. Two years later in 2008, the largest perioperative  $\beta$ -blocker study so far, the POISE trial, was published.<sup>3</sup> The POISE study randomized more than 8,300  $\beta$ -blocker-naïve patients to either extended-release metoprolol or placebo on the morning of and for 30 days after surgery, and used a composite of nonfatal MI, cardiovascular death, and nonfatal cardiac arrest as primary outcome. The results indicated that metoprolol usage was associated with reduced risk for MI and the composite endpoint (hazard ratio of 0.84 and 0.73, respectively), but also was associated with significantly higher risks for death and stroke (hazard ratio 1.33 and 2.17, respectively) compared with placebo. A subsequent meta-analysis including 33 trials with more than 12,300 patients, which was largely driven by the POISE data, found similar results and concluded that evidence did not support the use of  $\beta$ -blockers to prevent perioperative cardiovascular events in noncardiac surgery.<sup>49</sup> In the light of these data and the fact that patients who were chronically titrated to  $\beta$ -blockers had reportedly better outcomes (which is supported by two very recent studies<sup>50,51</sup>), the 2007 American College of Cardiology/American Heart Association guidelines<sup>2</sup> were again updated in 2009 to reflect the new evidence, and now recom-



**Fig. 1.** Cardiac adrenergic receptors and polymorphisms relevant to  $\beta$ -blocker responsiveness. Shown are the presynaptic  $\alpha_{2A}$ - and  $\alpha_{2C}$ ARs, which when activated by epinephrine or norepinephrine, decrease norepinephrine release from the presynaptic nerve terminal. Presynaptic  $\beta_2$ AR activation increases norepinephrine release: on the cardiomyocyte, catecholamine-activated  $\beta_1$ AR and  $\beta_2$ AR increase inotropy and chronotropy, and can under-signal dampening because of receptor phosphorylation by GRKs (G-protein coupled receptor kinase).

mend the use of  $\beta$ -blockers titrated to heart rate and blood pressure.<sup>1</sup>

$\beta$ -blockers are most often used in the treatment of hypertension, angina, and myocardial infarction, and, more recently, congestive heart failure. By antagonizing the action of norepinephrine and epinephrine on  $\beta_1$ - or  $\beta_2$ -adrenergic receptors expressed on cardiac myocytes, these agents can fully, or partially, block these actions of the sympathetic nervous system. The source of cardiac norepinephrine is, from its release from the prejunctional cleft of sympathetic neurons, innervating the heart (fig. 1). The release of norepinephrine is, in part, mediated by a negative feedback loop by  $\alpha_{2A}$ AR and  $\alpha_{2C}$ AR expressed on the prejunctional cleft: increased norepinephrine in the cleft binds these  $\alpha_2$ AR subtypes, which depress subsequent release.<sup>52</sup> This mechanism is one of several that are thought to regulate neurotransmitter release and potentially mitigate against “over-stimulation.” There is also evidence that prejunctional  $\beta_2$ AR can regulate release in a positive feedback loop,<sup>53</sup> although norepinephrine has a low affinity for the  $\beta_2$ AR subtype. The source for epinephrine is systemic in nature, arising from the adrenal gland. In the “basal-state,” sympathetic nervous activity at the heart is modest at best, as indicated by a small decrease in resting heart rate from a single dose of atenolol in normal subjects. However, when activated by the aforementioned perioperative conditions, such as pain and surgical stress, sympathetic nervous activity can be marked, with  $\beta$ -blocker administration causing a substantial reduction in heart rate, cardiac contractility, and myocardial oxygen consumption.

Recent evidence, however, suggests that there is substantial interindividual difference in how patients respond to  $\beta$ -blockers: Some patients experience strong side effects such as excessive hypotension and bradycardia, whereas others experience no measurable response. Several lines of evidence suggest that the individual genetic background is responsible for these observed response differences.

## Impact of Genetic Polymorphisms on $\beta$ -blocker Response

The most common form of genetic variation is the exchange of a single base pair in the DNA strand; this is referred to as single nucleotide polymorphism, or SNP (for a list of commonly used genetic terms, please refer to the appendix). The genome of a human contains approximately 3 billion ( $3 \times 10^9$ ) base pairs, and each individual harbors approximately 10–20 million SNPs. Most of these SNPs are silent as they fall outside of the coding region of genes, or exons. Of those in the coding region, some do not change the encoded amino acid because of redundancy of the genetic code. These are termed “synonymous” SNPs, and those that result in the encoding of a different amino acid are termed “nonsynonymous” SNPs. Noncoding SNPs, such as those in gene promoter regions, may also have significant effects leading to clinical phenotypes. Within the genes of interest that are discussed in this review, there is the 1 s coding for adrenergic receptors and cytochrome P450, as well as several important nonsynonymous SNPs known for their functional consequence on the receptor and enzyme function. Nonsynonymous SNPs commonly cause a reduced function or activity of the affected protein, but on rare occasions novel protein functions may result. In the next section, we will discuss the most important SNPs and gene variants within adrenergic receptors and the  $\beta$ -blocker-metabolizing cytochrome P450 2D6 enzyme.

## Genetic Variation of the Cardiac Adrenergic Axis

### $\alpha_2$ -adrenergic Receptors

As introduced above and summarized in figure 1, there are multiple receptor pathways that might influence  $\beta$ -blocker response, and if genetic variations in these pathways are present, they could represent the basis for interindividual variation in the response to perioperative  $\beta$ -blockers. The physiologic effect of  $\beta$ -blockers is dependent, in part, on the presence of a cardiac  $\beta$ AR agonist to antagonize. Thus polymorphisms (defined as a genetic variation with a prevalence of more than 5% in a population) of the  $\alpha_{2A}$  and the  $\alpha_{2C}$ AR, which partially control norepinephrine release, could alter  $\beta$ -blocker responsiveness.<sup>54,55</sup> Within the coding block of the intronless (consisting only of a single exon)  $\alpha_{2A}$ AR gene, there is one nonsynonymous polymorphism. At amino acid position 251, the most common allele results in Asparagine, but a relatively rare polymorphism results in an encoded



**Table 1.** Localization of Polymorphisms of Selected Adrenergic Receptors or Related Genes

Receptor/ Protein	Gene	Reference	"Variant"	Allele Frequency		Phenotype
				Caucasians	African-Americans	
$\alpha_{2A}$	ADRA2A	Asparagine-251	Lysine-251	0.0040	0.040	Increased Coupling
$\alpha_{2C}$	ADRA2C	—	Del322–325	0.04	0.43	Heart failure
$\beta_1$	ADRB1	Serine-49	Glycine-49	0.15	0.15	Downregulation
	—	Arginine-389	Glycine-389	0.73	0.58	Decreased coupling
$\beta_2$	ADRB2	Arginine-16	Glycine-16	0.61	0.50	Increased desensitization
	—	Glutamine-27	Glutamic acid-27	0.43	0.27	Reduced desensitization
	—	Threonine-164	Isoleucine-164 <sup>a</sup>	~0.02	~0.004	Loss-of-function
$\beta_3$	ADRB3	Tryptophan-64	Arginine-64	0.10	?	Loss-of-function
GRK5	GRK5	Glutamine-41	Leucine-41	0.01	0.23	Enhanced desensitization of $\beta_1$ AR

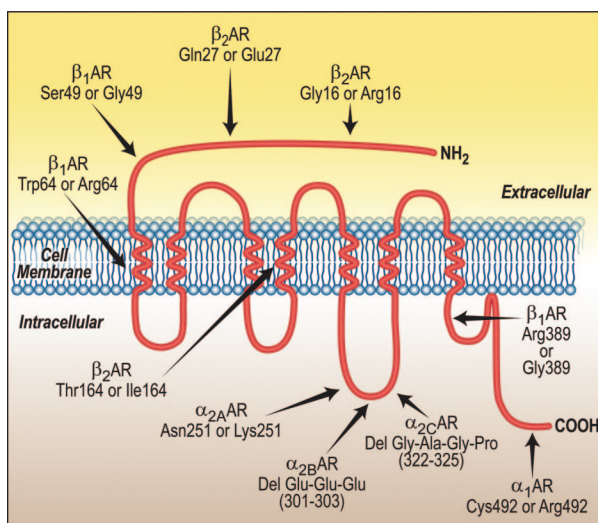
Lysine (table 1, fig. 2). In African-Americans the frequency of the  $\alpha_{2A}$ Lys251 allele is 4%; in Caucasians it is 0.4%. In functional studies using the wild-type and Lysine variant recombinantly expressed in Chinese hamster ovary cells, the  $\alpha_{2A}$ Lys251 receptor had an approximately 50% increase in function.<sup>56</sup> Thus, the minor variant represents a gain-of-function, and if present in an individual would be expected to be manifested as a decrease in norepinephrine release, compared with an individual expressing  $\alpha_{2A}$ Asn251, under the same stimulation. Given the rare prevalence of  $\alpha_{2A}$ Lys251, this variant has not been studied in clinical trials. In contrast, a coding polymorphism of the  $\alpha_{2C}$ AR, which consists of an in-frame deletion of 12 nucleotides and results in deletion of four amino acids, occurs in approximately 40% of African-Americans and approximately 3% in Caucasians. This deletion is in the third intracellular loop of the receptor, and results in a nearly complete loss of function because of

loss of receptor coupling to its cognate G-protein, or  $G_i$ .<sup>57</sup> This polymorphism, termed  $\alpha_{2C}$ Del322–325, has been associated with increased norepinephrine (or its transporter) in the cardiac presynaptic cleft,<sup>58</sup> increased risk for heart failure,<sup>59</sup> and a significantly reduced survival benefit in heart failure patients when taking the  $\beta$ -blocker bucindolol.<sup>54</sup> The other presynaptic adrenergic receptor that has been thought to have some control over norepinephrine release is the  $\beta_2$ AR, although the relevance is less certain as compared with the  $\alpha_{2A}$ - and  $\alpha_{2C}$ AR. The  $\beta_2$ AR is also polymorphic, and will be discussed below in the context of myocardial adrenergic receptor.

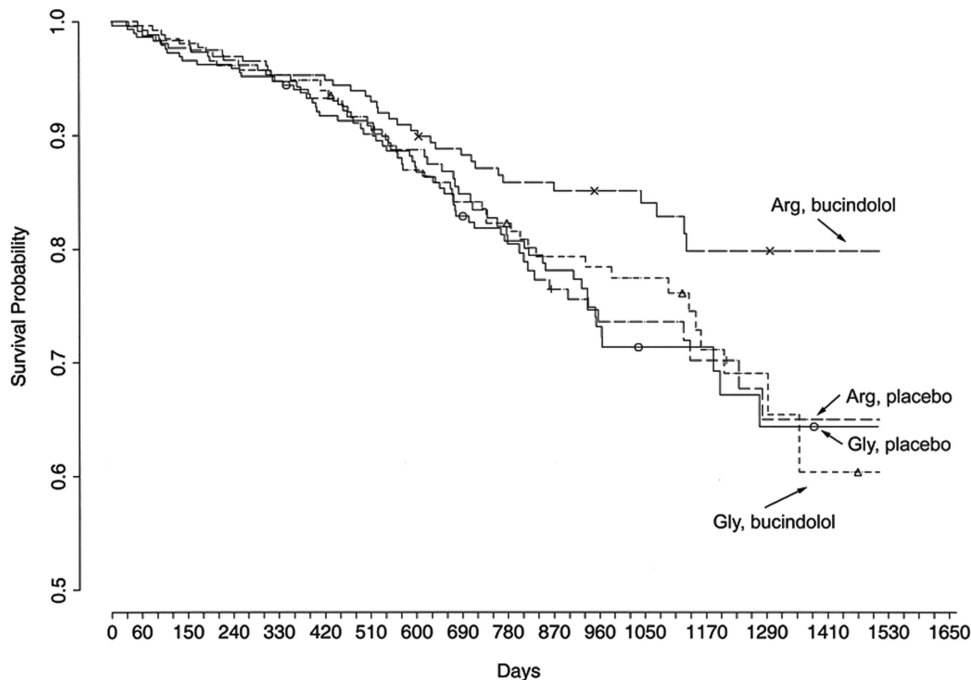
### $\beta_1$ -adrenergic Receptor Polymorphisms

$\beta_1$ AR are the predominant  $\beta$ AR in the heart and mediate an increase in heart rate and contractility.  $\beta_1$ AR are encoded by the ADRB1 gene, which consists only of a single coding block, or exon. Myocyte  $\beta_1$ AR are a major target for epinephrine and norepinephrine. Not only does this subtype increase cardiac inotropy and chronotropy, signaling of  $\beta_1$ AR has been shown to evoke specific proapoptosis signals.<sup>60</sup> A common polymorphism of the  $\beta_1$ AR is observed at amino acid position 389, where Arginine (Arg) or Glycine (Gly) can be found (table 1, fig. 2). The originally cloned  $\beta_1$ AR had a Glycine at this position, but it is now clear that in African-Americans, Glycine and Arginine allele frequencies are approximately the same, and in Caucasians the Arginine allele frequency is approximately 70%. In transfected cells, we found that  $\beta_1$ Arg389 exhibited a threefold-greater stimulation of adenylyl cyclase and cyclic adenosine monophosphate compared with  $\beta_1$ Gly389.<sup>61</sup> This was found to be because of an increase in the formation of the agonist-receptor- $G_s$  complex. The gain-of-function was also observed in [<sup>35</sup>S]GTP $\gamma$ S binding studies, confirming that the phenotype was because of enhanced coupling of the receptor to  $G_{\alpha s}$ .

Transgenic mice were then constructed<sup>62</sup> to express  $\beta_1$ Arg389 and -Gly389 receptor in cardiomyocytes in a targeted manner using the  $\alpha$ -myocin heavy chain promoter. In lines with equivalent expression, we found higher basal and



**Fig. 2.** Localization of the common polymorphisms of the adrenergic receptors. The schematic shows a prototypic 7-transmembrane spanning receptor. The amino acid positions within the respective receptor protein are given, whereas their physical positions within the prototypic receptor are approximated.



**Fig. 3.** Pharmacogenetics of the  $\beta$ -blocker bucindolol in chronic heart failure. Shown are Kaplan-Meier curves showing survival stratified by treatment group and the  $\beta_1$ Arg- or  $\beta_1$ Gly389 polymorphism. Those with the  $\beta_1$ Arg389 genotype receiving bucindolol had a 38% improvement in survival over placebo patients of the same genotype. Gly389 carriers on bucindolol showed no improvement. From Liggett SB *et al.*, *Proc Natl Acad Sci USA* 2006; 103:11288–93. Reprinted with permission from the National Academy of Sciences, USA.<sup>63</sup>

dobutamine-stimulated cardiac contractility in  $\beta_1$ Arg389 mice compared with -Gly389 mice at 3 months of age.<sup>62</sup> Interestingly, by 6 months of age Arg389 mice were unresponsive to agonist, whereas Gly389 mice retained responsiveness and showed only a minor decline in agonist-promoted contractility. At this juncture we considered the possibility of a “phenotypic switch,” which might imply that any pharmacogenomic effect would also have a time-dependent element. However, this possibility was subsequently shown not to be the case when we examined cardiac explants. In these transgenic mice, we also observed a decrease in heart rate to acutely or chronically administered  $\beta$ -blocker only in the Arg389 mice, which was the first evidence that this locus might have an effect on  $\beta$ -blocker outcomes in a clinical setting.<sup>62</sup> The basis for this appeared to be the greater potential for an enhanced inotropic state in hearts expressing  $\beta_1$ Arg389, and thus a higher potential to be antagonized by a  $\beta$ -blocker back toward baseline. Subsequent studies in explanted human hearts confirmed the enhanced function of  $\beta_1$ Arg389 in normal hearts, as well as hearts with end-stage failure.<sup>63</sup> The difference in maximal contraction between Arg389 and Gly389 failing human hearts was not as pronounced as was observed in normal hearts. So there was no switch in the phenotype, because Arg389 remained the hyperfunctioning receptor, but rather a dampening of the phenotypic difference between the variants as heart failure progresses. These results are consistent with studies of agonist-promoted desensitization (which occurs in heart failure

caused by the increased catecholamines) of these two receptors expressed in model cells, which showed that Arg389 undergoes greater desensitization than Gly389.<sup>64</sup> In clinical studies,  $\beta_1$ Arg389 has been associated with enhanced exercise capacity in heart failure<sup>65</sup> and an improved mortality outcome in response to  $\beta$ -blocker in heart failure.<sup>63</sup> It should be noted that in this latter study the  $\beta$ -blocker was bucindolol, which had failed to show a group mean improvement in survival. However, with patient stratification by  $\beta_1$ AR genotype, an improvement in survival was clearly evident for those with the  $\beta_1$ Arg389 genotype receiving bucindolol compared with those with the same genotype receiving placebo, or the Gly389 genotype receiving bucindolol or placebo (fig. 3). These results highlight the potential for pharmacogenomic markers to bring drugs, previously thought to be ineffective, into use for selected populations based on genotype. DNA from a placebo-controlled trial with other  $\beta$ -blockers (such as metoprolol and carvedilol) using similar outcomes is not available, so a direct comparison of these results with different drugs has not been carried out. However, other studies without placebo arms have suggested that the findings with bucindolol in heart failure may be unique to that  $\beta$ -blocker.<sup>66</sup> This may be because of the fact that bucindolol acts as an inverse agonist at  $\beta_1$ Arg389, but not Gly389, whereas metoprolol and carvedilol are neutral antagonists for both allelic forms of the receptor.<sup>63</sup> As introduced above, there appears to be a small but independent effect of the  $\alpha_2C$ Del322–325 genotype on heart failure out-

come in response to bucindolol as well.<sup>54</sup> The mechanisms behind this effect are not altogether clear, but appear to be because of a loss of counter-regulatory function during a marked decrease in norepinephrine that is found in a subset of heart failure patients treated with bucindolol. The  $\beta_1$ Arg389 polymorphism has also been associated with a greater decrease in blood pressure during atenolol treatment of hypertension<sup>67</sup> and improved treatment outcomes in hypertensive patients.<sup>68</sup>

A less common polymorphism of the  $\beta_1$ AR is found in the amino terminus, where Serine is substituted by Glycine. The  $\beta_1$ -Gly49 receptor appears to undergo enhanced agonist-promoted down-regulation in recombinantly expressed cell lines.<sup>69</sup> The low allele frequency of Gly49 has generally made investigations of this polymorphism not feasible because of statistical power considerations.

### $\beta_2$ -adrenergic Receptor Polymorphisms

$\beta_2$ AR, encoded by the ADRB2 gene, are widely expressed in virtually all cell types. Their presence on smooth muscle mediates relaxation and thus dilation of vasculature and the airways. Their somewhat more limited expression on cardiac myocytes mediates increased inotropy and chronotropy, as well as antiapoptotic effects. The  $\beta_2$ AR has three nonsynonymous, or amino acid-changing, polymorphisms at amino acid positions 16, 27, and 164. The most pronounced phenotype is the substitution of Isoleucine for Threonine at position 164, which is in the fourth transmembrane domain of the  $\beta_2$ AR. The  $\beta_2$ Ile164 receptor is markedly uncoupled from stimulation of adenylyl cyclase caused by impaired agonist-receptor interaction.<sup>70,71</sup> However, the variant is rare, with the heterozygous state being found in less than 5% of the population. A homozygous individual has never been reported. In heart failure patients,  $\beta_2$ Ile164 is associated with a marked decrease in exercise capacity in otherwise matched patients,<sup>72</sup> and also increased mortality.<sup>73</sup>  $\beta$ -blocker responsiveness has not been adequately assessed with this variant because of its low allele frequency. The other two polymorphisms at positions 16 and 27 are in the extracellular amino terminus of the  $\beta_2$ AR, and appear to have effects on agonist-promoted down-regulation of the receptor.<sup>74,75</sup> In terms of pharmacogenetics, these two polymorphisms have been primarily studied in the context of  $\beta$ -agonist treatment for asthma.<sup>76</sup> However, several studies have indicated that the polymorphism at 16 and/or 27 may have effects on heart failure survival during  $\beta$ -blocker therapy (including " $\beta_1$ -specific antagonists").<sup>77,78</sup> The molecular basis for these observations remains unclear.

### $\beta_3$ -adrenergic Receptor Polymorphisms

Of adrenergic receptors, the  $\beta_3$ AR is the least understood in terms of cardiovascular function.<sup>79</sup> Initial work showed that the  $\beta_3$ AR has an important role in regulating metabolism in adipocytes.<sup>80</sup> Recent data, however, suggest that  $\beta_3$ ARs mediate vasodilation when  $\beta_1$ AR and  $\beta_2$ AR are

not functional, perhaps preventing excessive overstimulation by catecholamines.<sup>81</sup> Other studies have demonstrated that activation of  $\beta_3$ AR increases formation of nitric oxide and evokes a decrease in inotropy.<sup>82,83</sup> One polymorphism has been identified in the coding region of this receptor (ADRB3 gene), at position 64 (Tryptophan/Arginine). One group has reported that the Arginine receptor has depressed agonist-promoted coupling to cyclic adenosine monophosphate production,<sup>84</sup> although another group has found no differences.<sup>85</sup> Several studies have suggested relationships between  $\beta_3$ AR alleles and cardiac or metabolic risk factors.<sup>86,87</sup> A recent paper showed that in diabetic patients  $\beta_3$ AR are often up-regulated, whereas  $\beta_1$ AR are simultaneously down-regulated,<sup>88</sup> which may result in an altered response to  $\beta$ -blocker therapy.

### GRK5 Polymorphisms

In addition to these variations in the relevant receptors, one polymorphism in the second messenger system within a G-protein-coupled receptor kinase (GRK5) has recently shown *in vitro* and *in vivo* evidence for relevance to  $\beta$ -blocker responsiveness.<sup>89</sup> The GRKs phosphorylate multiple G-protein coupled receptors during agonist activation, which acts to partially uncouple the receptor from  $G_s$ , and is a major mechanism of desensitization. A nonsynonymous polymorphism of GRK5, where the major allele Glutamine at amino acid position 41 is substituted by Leucine, has been found.<sup>89</sup> It is prevalent in African-Americans but not Caucasians, as seen in table 1. In transfected cells and transgenic mice, GRK5-L41 has been shown to exhibit enhanced desensitization of  $\beta_1$ AR.<sup>89</sup> In a mouse model of heart failure those mice expressing GRK5-L41 were partially protected from failure and had no additional benefit from  $\beta$ -blockers compared with mice expressing the Q41 allele. Similar findings were also observed in a prospective clinical trial in heart failure, where those not receiving  $\beta$ -blockers but with the L41 allele had survival similar to Q41 subjects on  $\beta$ -blocker and improved survival over Q41 subjects not receiving  $\beta$ -blocker. Thus GRK5-L41 acts as a "genetic  $\beta$ -blocker," and when present may obfuscate the need for these agents, or, may indicate that a lower dosage is necessary to achieve the desired outcome.

A recent study of the gene encoding the  $\alpha$  subunit of  $G_s$  (GNAS) showed that patients with a certain haplotype had a significantly different  $G_{\alpha s}$  expression, cyclic adenosine monophosphate production, and cardiac performance during cardiac surgery,<sup>90</sup> indicating that genetic variation within the adrenergic second messenger system may also play an important role for how patients respond to  $\beta$ -blockade.

### Genetic Variation of Drug Metabolism of $\beta$ -blockers—Cytochrome P450 2D6

Genetic variation not only influences the pharmacodynamics, but also the pharmacokinetics of  $\beta$ -blocker treatment.

**Table 2.** Common and Important CYP2D6 Polymorphisms

CYP2D6 Allele/Haplotype	Nucleotide Change	Metabolizer Class	Caucasians	African-Americans
1	Reference	EM(wild-type)	0.33–0.36	0.29–0.35
2	2850C>T, 4180G>C	EM	0.22–0.33	0.18–0.27
3	2549delA	PM	0.01–0.04	0
4	1846G>A	PM	0.12–0.21	0.06–0.08
5	CYP2D6 deleted	PM	0.02–0.07	0.06–0.07
6	1707delT	PM	0.01	0
9	2,615–2617delAAG	IM	0–0.02	0
10	100C>T	IM	0.01–0.02	0.03–0.08
17	1023C>T, 2850C>T	IM	0	0.15–0.23
29	1659G>A; 1661G>C; 2850C>T; 3183G>A; 4180G>C	IM	No data	No data
41	2988G>A	IM	No data	No data
UM	Multiple copies	UM	0.02	0.01–0.05

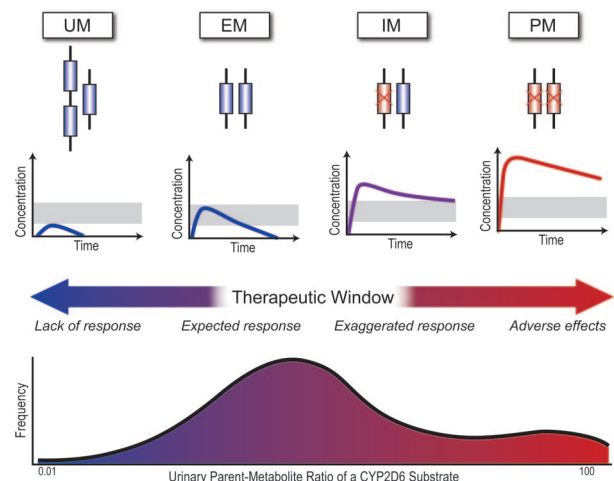
EM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer; UM = ultrarapid metabolizer.

Most  $\beta$ -blockers, such as metoprolol and propranolol, are extensively metabolized in the liver by cytochrome P450 2D6, or CYP2D6, a hepatic enzyme of the cytochrome P450 family.<sup>91</sup> CYP2D6 is responsible for the phase I metabolism of approximately 25% of all commonly used drugs and is thus one of the most important drug-metabolizing enzymes.<sup>92,93</sup> CYP2D6 is involved in the metabolism of antidepressants, antiemetics, anticancer drugs, antipsychotics, opioids (tramadol, morphine, codeine), and  $\beta$ -blockers.

The CYP2D6 gene is very polymorphic, with close to 100 known variants.<sup>93,94</sup> These CYP2D6 gene variants have a major impact on the CYP2D6 enzyme activity, with some variants resulting in a complete loss-of-function phenotype whereas others lead to a gain-of-function. With  $\beta$ -blockers, several studies have reported a clinically relevant, several-fold difference in metoprolol plasma concentrations among patients with different CYP2D6 variants.<sup>95–97</sup> The ability of the CYP2D6 enzyme to metabolize substrates has been stratified into four classes: ultra-rapid metabolizers (UM), extensive metabolizers (EM, considered the normal phenotype), intermediate metabolizers (intramuscular) and poor metabolizers (PM).<sup>93</sup> Table 2 lists the most important CYP2D6 alleles and haplotypes and their respective allele frequency. The genetic basis of these CYP2D6 phenotypes has also been ascribed to copy number variation within the CYP2D6 gene. Copy number variation is defined as a variable number of DNA segments compared with the reference genome and include deletion, but also duplication or multiplication of large segments (more than 1 kB) of DNA. For CYP2D6, the most functional allele determines the phenotype. If an individual has at least one fully functional CYP2D6 allele, the resultant phenotype is considered wild-type or extensive metabolizer. With one or two reduced-function alleles, an intermediate metabolizer phenotype results, and with two non-functional alleles, for example because of deletion, a PM phenotype results. On the contrary, if individuals possess more than two copies of a fully functional CYP2D6 allele (up to 13 have been described), likely after several ancestral du-

plication events, an UM phenotype ensues (fig. 4).<sup>94,98</sup> It is of note that substantial ethnic differences exist in the distribution of CYP2D6 alleles: PM are more common in people from European ancestry, whereas UM are more prevalent in people from North Africa and Oceania.<sup>98</sup>

The functional consequences of copy number variants or SNPs in CYP2D6 enzyme activity are nontrivial: Individuals with a PM phenotype are unable to adequately metabolize CYP2D6 substrates (e.g., drugs) and higher, potentially dan-



**Fig. 4.** Effects of CYP2D6 genotype on CYP2D6 substrate metabolism. Extensive metabolizers have one or two normal copies of the CYP2D6 gene and are considered wild-type. A normal  $\beta$ -blocker dose will likely result in a therapeutic drug concentration. Ultra-rapid metabolizers possess more than 2 functional copies (up to 13). A CYP2D6 substrate (e.g., metoprolol) will be rapidly metabolized and the drug effect minimal. Intermediate metabolizers have one or two hypofunctional CYP2D6 alleles, which result in a reduced CYP2D6 function. Substrate metabolism is reduced and higher drug concentrations result with the possibility of an exaggerated response. Poor metabolizers have two nonfunctional copies of CYP2D6, which result in a nonfunctional enzyme. This may lead to toxic drug concentrations.



gerous, plasma drug concentrations can result. Patients with an UM phenotype will rapidly metabolize the drug, and plasma drug concentrations from standard dosing can be too low to be efficacious. On the other hand, if a prodrug must be metabolized into an active form by CYP2D6, an opposite picture results: PM patients will not reach effective drug concentrations, whereas UM patients will develop increased plasma levels and are at higher risk for adverse drug effects. An example for the latter is the case of a fatal morphine poisoning in a neonate that was breastfed by a mother who received codeine.<sup>99</sup> Codeine is a prodrug that must be metabolized by CYP2D6 to morphine, and because the mother was a CYP2D6 UM and required high doses of codeine, toxic plasma concentrations of morphine resulted in the neonate.

It is of note that CYP2D6 is the only enzyme in the cytochrome P450 family that is not inducible, which results in a substantially higher contribution of genetic differences to enzyme activity level and clinical phenotype. However, CYP2D6 can be inhibited by many drugs and, as a consequence, a lower enzyme activity may result than may be expected simply based on the CYP2D6 genotype. This process is called phenocopying. Two of the clinically most important inhibitors of CYP2D6 are paroxetine,<sup>100</sup> a selective serotonin reuptake inhibitor, and statins.<sup>101</sup>

The evidence clearly supports a major role of CYP2D6 polymorphisms in the pharmacokinetics of  $\beta$ -blockers, but does this role also translate into relevant differences in clinical outcomes? Current evidence suggests so. Several studies independently found that patients with PM phenotype, who were treated with metoprolol, had a higher risk to develop bradycardia and lower blood pressure and had a higher incidence of adverse drug reactions.<sup>9–12</sup> UM subjects have been reported to not achieve a therapeutic effect of standard dosing of metoprolol<sup>10</sup> (fig. 5). It is of note, however, that rou-

tine genotyping for CYP2D6 variants is not commonly performed clinically.

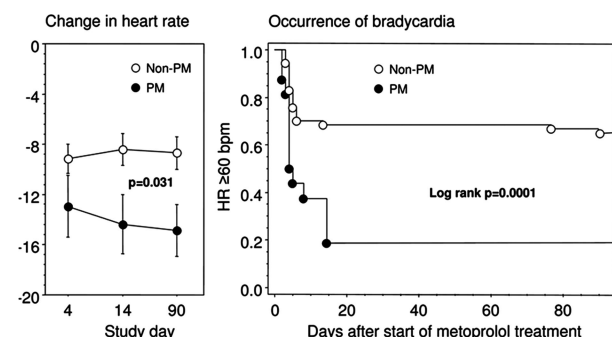
### Impact of Genetic Variation on the Use of $\beta$ -blockers in Perioperative MI

Data presented in the previous sections clearly show that gene variants have a significant impact on the individual response to  $\beta$ -blocker-therapy, but is there evidence to support the influence on perioperative myocardial infarction? A study published in 2005 with more than 700 patients with acute coronary syndrome who received standard  $\beta$ -blocker therapy in the emergency department shows a significant impact of ADRB2 genotype on survival.<sup>102</sup>

For perioperative  $\beta$ -blockade, three recent papers provide indirect evidence that genetic variation in CYP2D6-dependent metabolism as well as adrenergic signaling may influence outcomes.<sup>50,103,104</sup> Particularly the apparent decreased risk associated with atenolol, which is not metabolized by CYP2D6, compared with metoprolol, which undergoes extensive CYP2D6-dependent metabolism, is very interesting.

Whether, however, the conditions of perioperative MI are such that these polymorphisms have a significant impact on outcomes, remains a critical question that needs to be addressed. The idea that “one drug fits all” is being questioned in virtually all of clinical medicine. Given the apparent interindividual variation in efficacy and adverse effects of  $\beta$ -blockers for prevention of perioperative MI, the biologic plausibility, and the low costs of genotyping by modern methods, it seems to us that a rigorous pharmacogenomic investigation is indicated. Ultimately, this could lead to a “genetic scorecard” that would recommend when a  $\beta$ -blocker should be used and the dose, for prevention of perioperative MI. As these trials are being contemplated, we implore investigators in other current trials of perioperative MI prevention to collect blood for archival purposes so that a DNA bank can be established and subsequent pharmacogenomic hypotheses pursued.

In conclusion, we believe that there is strong evidence to suspect that polymorphisms in the adrenergic signaling pathway and CYP2D6-dependent  $\beta$ -blocker metabolism influence efficacy, safety and toxicity of  $\beta$ -blocker therapy in prevention and treatment of perioperative MI. It is to be expected that the emphasis on careful  $\beta$ -blocker dose titration, as recommended in the most recent American College of Cardiology/American Heart Association guidelines,<sup>1</sup> might lessen the disparate effects of genetic polymorphisms.



**Fig. 5.** Clinical relevance of CYP2D6 genotype on  $\beta$ -blocker treatment. Poor CYP2D6 metabolizers experience a greater reduction in heart rate (a) and a higher risk of bradycardia when treated with metoprolol. HR = heart rate; PM = poor metabolizer. Reprinted with permission from Macmillan Publishers Ltd.: [Clinical Pharmacology & Therapeutics] Rau T *et al.*, Impact of the CYP2D6 Genotype on the Clinical Effects of Metoprolol: A Prospective Longitudinal Study 2009; 85:269–72.

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## Appendix: Glossary

**Allele:** A version of a gene. Usually two or more versions exist.

**Codon:** Sequence of three nucleotides of DNA that encodes a single amino acid.

**Exon:** Nucleic acid sequence, usually within a gene, that is transcribed into messenger RNA and protein often after splicing which removes introns.

**Gene:** Commonly defined as a stretch of DNA that encodes for a protein or RNA; in humans, genes often consist of multiple exons and introns and may span tens of thousands of base pairs.

**Intron:** Nucleic acid sequence within a gene that is removed before the gene is transcribed into protein by splicing.

**Locus:** Specific position on a chromosome.

**Mutation:** Rare changes in the DNA sequence; in classic genetics mutations are often associated with specific traits.

**Nonsynonymous:** A DNA substitution that causes a change in the amino acid sequence of a protein.

**Polymorphism:** A variation in DNA sequence as compared with a "reference" sequence (usually the more common allele). Typically, polymorphisms are so noted when the frequency is greater than 1% in a given population. A single-nucleotide polymorphism changes only a single nucleotide and is the most common form of genetic variation.