Clinical pharmacogenomics of carvedilol: the stereo-selective metabolism angle

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“the three major enzymes/proteins carrying out carvedilol’s stereo-selective metabolism are the highly polymorphic CYP2D6, UGT1 and P-glycoprotein.”

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Carvedilol is an adrenergic receptor (AR) antagonist blocking several different AR types. Specifically, it acts as an inverse agonist at the β_1 - and β_2 -ARs, as well as blocks α_1 ARs in the vasculature, thereby causing vasodilatation [1]. In the heart, it is relatively β_1 AR-specific, since this AR type is by far the most predominant one in the adult human myocardium (both failing and nonfailing) [2]. Since it blocks almost all ARs in the body (with the exception of α_2 ARs), it can counter the deleterious effects of the sympathetic hyperstimulation that accompanies and aggravates chronic heart failure (CHF) [1,2]. Thus, it is used clinically with great success to treat CHF, hypertension, coronary artery disease and cardiac arrhythmias [1]. Recent studies indicate that its cardio-protective effects might be useful also in cancer chemotherapy, which oftentimes is cardiotoxic [3]. Carvedilol is very lipophilic undergoing mainly biliary elimination by the liver [1]. Importantly, the clinically used drug is a racemic mixture, with the *S*(-) enantiomer having much higher affinity for the cardiac β_1 ARs and β_2 ARs (in addition to its affinity for the α_1 ARs) than the *R*(C) enantiomer, which is essentially a pure α_1 AR-blocker [2]. This is crucial not only for the pharmacodynamic effects of this third generation β -blocker but also for its pharmacokinetics. Orally administered carvedilol undergoes extensive stereo-selective hepatic first-pass metabolism, resulting in almost double maximal plasma concentration (and bioavailability) of *R*-carvedilol compared with that of *S*-carvedilol [1]. Carvedilol is metabolized via aromatic ring and side-chain hydroxyl group oxidative Phase I reactions, mediated mainly by CYP2D6 (but also, to a lesser extent, CYP2C9). These are followed by Phase II conjugating reactions (glucuronidation, hydrophilic for renal; sulfation, lipophilic for hepatic/biliary tract elimination) [1]. Although carvedilol’s metabolism by CYP1A2, CYP2C9, CYP2D6 and CYP3A4 is clearly documented, whether other CYP enzymes participate is currently unclear [1]. Carvedilol is a substrate for uridine diphosphate glucuronosyltransferase 1A1, -2B4 and -2B7 and is metabolized in hepatic microsomes, as well [4]. Finally, P-glycoprotein, encoded by the *MDR1* gene binds carvedilol with high affinity and affects bioavailability [1]. Given that almost all these metabolizing enzymes display significant genetic variation in humans and some CYP enzymes display carvedilol enantiomer-selectivity, for example, CYP2D6 metabolizes *S*-carvedilol much more than *R*-carvedilol [1], it becomes clear that carvedilol’s pharmacokinetics is a very complex issue factoring into the drug’s clinical use.

In human liver microsomes, CYP2D6 appears mainly responsible for metabolizing *R*-carvedilol, followed by CYP3A4, CYP1A2 and CYP2C9 [5]. The *S*-enantiomer is primarily metabolized by CYP1A2 followed by CYP2D6 and CYP3A4 [5]. Thus, not only CYP2D6 but also CYP1A2 and CYP3A4 carry out the stereo-selective metabolism of carvedilol in humans. Nonetheless, plasma concentrations of carvedilol upon chronic treatment can be predicted by CYP2D6 genotyping in healthy subjects, as well as by intestinal P-glycoprotein and its close relative, multidrug resistance protein MRP-2 levels [1]. The human *CYP2D6* gene is highly polymorphic with over 70 alleles and 130 sequence variations [1]. This gives rise to four phenotypic groups: poor metabolizers (PMs) with no functional alleles

at all (5–10% frequency in Caucasians, rare in Asians and Africans [1]); intermediate metabolizers (IMs), with one null or two deficient alleles, most commonly *CYP2D6**9, *10, *17 and *41 (up to 50% of Asians carrying most commonly *CYP2D6**10 and up to 30% of Africans carrying usually *CYP2D6**17 [1]); extensive metabolizers, the normal *CYP2D6* phenotype, with two wild-type *CYP2D6* alleles and normal enzymatic activity (60–85% frequency in Caucasians [1]) and ultra-rapid metabolizers with more than two *CYP2D6* copies due to gene duplication (1–10% of Caucasians [1]). As far as carvedilol is concerned, a study in healthy Japanese subjects reported that oral clearance of both carvedilol enantiomers was significantly lower in *CYP2D6**10 allele carriers than in *CYP2D6**1/*1, *1/*2 or *2/*2 genotype carriers [6]. On the other hand, *CYP2C9**3, *CYP2C19**2, *CYP2C19**3, *CYP3A5**3, *UGT2B7**2 and *MDR1* C3435T did not significantly affect the pharmacokinetics of carvedilol in Japanese subjects [6]. The increased bioavailability of carvedilol observed in Japanese IM *CYP2D6**10 carriers was attributed to both reduced hepatic first-pass metabolism and decreased systemic clearance [6]. Therefore, carvedilol is often undermetabolized in Japanese patients due to the high frequency of the IM phenotype-imparting *CYP2D6**10 polymorphism, which overshadows the extreme rareness of the *CYP2D6* PM phenotype in this population [6]. Accordingly, retrospective analysis of carvedilol's side effects in clinical trials showed that *CYP2D6* PMs had a higher rate of dizziness during dose titration, presumably resulting from enhanced vasodilating effects of carvedilol [7], whose enantiomers are both α_1 AR-blockers [1,2].

S-carvedilol also undergoes higher, compared with *R*-carvedilol, glucuronidation in human liver and intestinal microsomes, similar to the levels of *CYP2D6*-dependent oxidation of the two enantiomers [8]. As already mentioned, this stereo-selective metabolism of carvedilol is carried out mainly by *CYP2D6* but also by *CYP1A2* in the liver and by *CYP3A4* in the gut [8]. Thus, not only the oxidation but also the subsequent *UGT1A*-dependent glucuronidation of carvedilol in intestinal epithelial cells is stereo-selective in humans [8], with both metabolic processes (oxidation and glucuronidation) proceeding at a higher rate for the *S*- than for the *R*-enantiomer, resulting in more *S*-carvedilol's presystemic clearance. This may translate into more pronounced carvedilol-induced vasodilatation (manifested clinically as orthostatic hypotension) than cardio-suppression. Intriguingly, the two enantiomers have been shown to even inhibit each other's glucuronidation through *UGT1A1*, *UGT2B4* and *UGT2B7* in human liver microsomes [9]. *UGT2B7* shows a preference for *S*-carvedilol's metabolism, whereas *R*-carvedilol is metabolized equally by these three *UGT* isoforms [9]. Additionally, PM-associated polymorphisms in human *UGT* genes (*UGT1A1**6 and *UGT2B7**3) are linked with poor glucuronidation of both enantiomers in Japanese subjects [1]. The mutual metabolic inhibition of the two enantiomers at the level of glucuronidation presents another obstacle in the effort to predict carvedilol's clinical bioavailability.

Finally, carvedilol is a known P-glycoprotein ligand [1]. P-glycoprotein negatively affects the drug's intestinal absorption. More importantly however, carvedilol, like two other clinically useful β -blockers, propranolol and bisoprolol, is a potent inhibitor of this plasma membrane transporter [10]. This leads to several, potentially significant drug–drug interactions of carvedilol, such as with cyclosporine and digoxin, two major P-glycoprotein substrates [10,11]. The interaction with digoxin might be more pronounced in men than in women, given the higher expression/activity of P-glycoprotein in males [11]. P-glycoprotein inhibition by carvedilol may also increase doxorubicin's cytotoxicity, although this is probably insignificant clinically, since P-glycoprotein inhibition can boost chemotherapeutic drug levels offsetting this and carvedilol exerts significant protective effects against chemotherapy-induced cardiotoxicity in its own right [3,12]. Indeed, carvedilol-induced P-glycoprotein blockade does not affect the *in vivo* intestinal absorption of clopidogrel to a significant extent and carvedilol does not seem to have a clinically relevant interaction with this common antiplatelet drug, which is also a P-glycoprotein substrate [13]. Of note, metoprolol, one of the three β -blockers currently US FDA-approved for human CHF treatment (the other two being carvedilol and bisoprolol), lacks inhibitory effects on P-glycoprotein [10]. This distinguishes metoprolol from both carvedilol and bisoprolol and suggests that metoprolol may be the β -blocker of choice in CHF when P-glycoprotein-dependent drug interactions are a clinical concern, for example, upon concomitant digoxin or cyclosporine treatment.

Unfortunately, there is a paucity of studies assessing the utility of carvedilol's stereo-selective pharmacokinetics for integration into clinical practice, whether pertaining to clinical efficacy or to need for dose adjustments due to drug–drug interactions. The very limited data available to date suggest that no dose adjustment is necessary in diabetic patients, despite the potential inhibition of carvedilol's *CYP2C9*-dependent metabolism by oral hypoglycemic agents like glibenclamide [14]. This is probably due to the higher *CYP2D6*-mediated metabolism of carvedilol compensating for the blocked *CYP2C9*-dependent elimination [14]. Additionally, in portal hypertension, one of the major therapeutic indications of carvedilol, the drug's efficacy against liver fibrosis is unaltered, despite delayed

clearance due to reduced hepatic blood flow and CYP2D6 expression levels [15]. This was attributed to the overall improvement of hepatic function and blood flow by the hepatic pharmacodynamic effects of carvedilol, which ultimately restored/enhanced the drug's own pharmacokinetics, as well [15]. A study in Japanese CHF patients found that the commonly used antiarrhythmic drug amiodarone can selectively inhibit *S*-carvedilol's metabolism, resulting both in a higher concentration-to-dose ratio for *S*-carvedilol and in a higher *S*-to-*R* enantiomer ratio in patients co-administered with the two drugs [16]. Given that the *R* enantiomer, whose metabolism is unaffected by amiodarone, essentially blocks α_1 ARs only while the *S* enantiomer is the cardiac β AR blocker (see above), the interaction of carvedilol with amiodarone may predispose to severe bradycardia and cardiac depression, especially in CHF patients, whose cardiac β_1 AR levels are significantly downregulated [2]. Studies in Japanese CHF populations have clearly indicated that both enantiomers undergo lower metabolism in CHF compared with healthy subjects, with *R*-carvedilol being metabolized significantly less than *S*-carvedilol [17]. In addition, their metabolism in CHF is dependent on CYP2D6 genotype, $\alpha(1)$ -acid glycoprotein (an α globulin of plasma with a very similar to P-glycoprotein drug-binding profile) and bodyweight [17]. It is also dependent on the type of formulation of oral carvedilol administered, in other words, immediate-(IR) versus controlled-release (CR) [18]. The enantiomers of CR-carvedilol have a longer half-life and slower overall metabolism than those of IR-carvedilol. On the other hand, a study in Israeli CHF patients found no significant differences in carvedilol dosages or rates of adverse drug reactions (ADRs) among CYP2D6 phenotypic groups, despite a similar CYP2D6 phenotypic distribution to the one in the European general population [19]. This study concluded that CYP2D6 genotype and number of ADRs were not predictive of carvedilol dose changes in CHF patients [19]. Similarly, a study by Sehr *et al.* in 2011 in European (German) subjects found no effect of the CYP2D6 genotype on heart rate, blood pressure or ADRs upon carvedilol administration (reviewed in [1]). Instead, it uncovered associations of β AR gene polymorphisms (β_1 AR Gly49 and β_2 AR Gln27) with greater reductions in exercise heart rates and resting blood pressure by carvedilol, in other words, it found genetic associations with the pharmacodynamics, rather than with the pharmacokinetics of the drug. In addition to the different ethnicities involved, another reason for the discrepancy between this and the Japanese studies discussed above may very well be the fact that the German study was done in healthy volunteers and not in CHF patients, in whom carvedilol's pharmacokinetics are significantly altered [1,17]. Nevertheless, this European study showcases the significant effect AR pharmacogenetics (for example, β_1 AR Gly49Ser and Arg389Gly; β_2 AR Arg16Gly and Gln27Glu) can have on carvedilol's pharmacodynamic responses in humans [20]. However, this is beyond the scope of the present article and will not be discussed any further here.

In summary, multiple variables complicate interpretation of the available studies regarding effects of the stereo-selective metabolism of carvedilol on the drug's patient response. Apart from being very few and commonly ridden with limited statistical power, the available studies differ in ethnicity, age, sex, bodyweight and co-morbidities of patient populations, in the formulation and/or delivery form of carvedilol used (immediate vs controlled release; oral vs parenteral) and some are conducted in healthy volunteers as opposed with other studies done in CHF patients. Another layer of complexity is added by the complicated pharmacodynamics of the drug, in other words, the multitude of its target receptors, which are also enantiomer-selective and can offset some of the effects of carvedilol's stereo-selective metabolism. Nevertheless, some conclusions regarding the contribution of carvedilol's stereo-selective metabolism to the drug's overall clinical pharmacogenomics can still be drawn. Thus, it appears that the three major enzymes/proteins carrying out carvedilol's stereo-selective metabolism are the highly polymorphic CYP2D6, UGT1 and P-glycoprotein. However, P-glycoprotein genotype seems to affect interactions of carvedilol with co-administered drugs only (for example, digoxin and cyclosporine). Therefore, when another strong P-glycoprotein substrate is administered concomitantly with carvedilol, care must be taken to properly adjust the second drug's dose or to substitute carvedilol with the equally effective metoprolol that lacks P-glycoprotein-dependent drug–drug interactions. Additionally, carvedilol's inhibitory effects on P-glycoprotein may be of value in enhancing cancer chemotherapy's efficacy in clinical oncology, especially since carvedilol *per se* is also cardio-protective [3]. Unlike P-glycoprotein, CYP2D6 and UGT1 genotypes do affect carvedilol's stereo-selective metabolism. Both of these enzymes metabolize carvedilol with a stereo-selective preference for the *S*-enantiomer. Given that this is essentially the β -blocker component of carvedilol, CYP2D6 and UGT1 pharmacogenetics may have significant impact on patient response. Indeed, at least in Japanese CHF patients, an ethnic group with high prevalence of the CYP2D6 IM phenotype, levels of the vasodilatory *R*-carvedilol may prevail over those of the β AR-blocking *S*-enantiomer, which can predispose to arrhythmias and to carvedilol's therapeutic failure, as cardiac sympathetic hyperstimulation may get incompletely buffered by the orally administered carvedilol. Even in that case however, prediction of the ultimate effect on patient's response is very risky, since the complex pharmacodynamics of

carvedilol may offset this effect of its stereo-selective metabolism. More specifically, whatever vasodilation-induced, baroreflex-mediated cardiac stimulation the higher *R*-carvedilol (than *S*-carvedilol) levels may impart could get counterbalanced by the low cardiac β_1 AR density of the CHF patient; this receptor is selectively downregulated in human failing hearts and carvedilol, paradoxically, does not upregulate it like the other β -blockers do [2]. On the other hand, the low prevalence of CYP2D6 PM and IM phenotypes in non-Asian populations probably accounts, in large part, for the discrepancies between European/Israeli and Japanese studies on the contributions of CYP2D6 phenotypes to carvedilol's clinical pharmacogenomics.

In conclusion, carvedilol's large therapeutic index preempts any significant impact of its stereo-selective metabolism by the polymorphic CYP2D6 and UGT enzymes on its safety or ADR propensity. In all likelihood, the only parameter that carvedilol's stereo-selective metabolism can possibly affect is the risk for therapeutic failure in CHF or hypertensive patients. However, it is virtually impossible to gauge this therapeutic failure risk due to the plethora of carvedilol's formulations/delivery forms and its complex pharmacodynamics. This notwithstanding, it can be concluded from the above reviewed studies that whenever a dose adjustment decision for carvedilol is needed, the drug's enantiomer-selective metabolism has to be taken into account, especially if the patient is of Asian ethnicity and has CHF. More studies with sufficient statistical power in Caucasian, Hispanic and black CHF patient populations are definitely warranted to assign a predictive value of pharmacodynamic response (or lack thereof) to carvedilol's stereo-selective and genetically polymorphic metabolism.

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