CYP2D6: carvedilol 2344/2345/2346

bpm = beats per minute, Cl_{or} = oral clearance, C_{ss} = steady state plasma concentration, IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, NYHA class = degree of severity of heart failure according to the classification by the New York Heart Association, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose $\geq$ 2.75) (elevated CYP2D6 enzyme activity)

Brief summary and justification of choices:
Carvedilol is primarily converted by CYP2D6 to 4'-hydroxycarvedilol and 5'-hydroxycarvedilol. Data from pre-clinical studies suggest that these metabolites are active, with 4'-hydroxycarvedilol having 13-fold the potency of carvedilol and being the only metabolite contributing to β-blocker activity of carvedilol. Carvedilol is also converted, predominantly by CYP2C9, to the active metabolite desmethylcarvedilol. S-carvedilol has β-blocker and α-blocker activity. R-carvedilol, which is metabolised less quickly than S-carvedilol, has only α-blocker activity.
Some (6 out of 10) of the studies found an effect of the CYP2D6 predicted phenotype (i.e. genotype group) on the exposure to carvedilol (Sehrt 2011 (including 34 healthy IM and 13 healthy PM), Takekuma 2007 (including 10 IM patients), Honda 2006 (including 12 healthy IM), Honda 2005 (including 15 healthy NM (gene dose 1.25) + 2 healthy IM), Giessmann 2004 (including 6 healthy PM), and Zhou 1995 (including 7 healthy PM); no effect: Jung 2018 (including 8 healthy IM), Nikolic 2013 (including 17 IM patients), Saito 2010 (including 9 IM patients), and Horiuchi 2008 (including 4 IM patients)). In addition, a higher exposure in PM is mentioned in the Dutch and American SmPC (SmPC Carvedilol Sandoz 25-01-2021 and SmPC Coreg 14-09-2017 (USA). However, there is insufficient evidence to support a clinical effect and therefore the need for action (see below). Therefore, the KNMP Pharmacogenetics Working Group decided that there is a gene-drug interaction, but that no action is required (yes/no-interactions). Substantiation of this decision is provided below per phenotype.

PM: Only two out of the five studies found a clinical effect or possible clinical effect (Baudhuin 2010 (patients with heart failure, 5 PM) and Giessmann 2004 (healthy volunteers, 6 PM); no effect: Luzum 2017 (patients with heart failure, 1 PM), Shihmanter 2014 (patients with heart failure, 5 PM), and Sehrt 2011 (healthy volunteers, 13 PM)). However, the effect in Baudhuin 2010 only concerned the titrated maintenance dose (higher in PM). In addition, Giessmann 2004 involved healthy volunteers, whilst three studies involving patients with heart failure or angina pectoris revealed a clear difference in the pharmacokinetics of carvedilol between patients and volunteers (Horiuchi 2008 (24 patients with heart failure), Saito 2010 (40 patients with heart failure), and Takekuma 2006 (40 patients with congestive heart failure or angina pectoris)). The three studies investigating carvedilol exposure in patients with heart failure, even showed the pharmacokinetics of carvedilol to be non-significantly dependent on the CYP2D6 genotype (Nikolic 2013 (17 IM), Horiuchi 2008 (4 IM), Saito 2010 (9 IM)).

IM: Only one out of the six studies found a possible clinical effect (Saito 2010 (patients with heart failure, 9 IM); no effect: Sehrt 2011 (healthy volunteers, 34 IM), Jung 2018 (healthy volunteers, 8 IM), Luzum 2017 (patients with heart failure, 18 IM), Shihmanter 2014 (patients with heart failure, 11 IM), and Baudhuin 2010 (patients with heart failure, 18 IM)). In Saito 2010, 2 of the 9 IM had side effects that may have been caused by initial high exposure to carvedilol. However, clinical significance was not determined. On top of this, the study found no link between carvedilol exposure and side effects, arguing against an effect of the IM phenotype. In addition, the three studies investigating carvedilol exposure in patients with heart failure, found the pharmacokinetics of carvedilol to be non-significantly dependent on the CYP2D6 genotype (Nikolic 2013 (17 IM), Horiuchi 2008 (4 IM), Saito 2010 (9 IM)).

UM: There are two studies that provide data about UM or an UM enriched group (Shihmanter 2014 (patients with heart failure, 6 UM) and Baudhuin 2010 (patients with heart failure, 3 UM + 18 NM)). These found no differrence in dose, clinical effect and side effects. In addition, an UM was reported with a high rate of hospitalisations due to decompensated heart failure despite receiving guideline-concordant care and being adherent to medication regimen (Cabrera 2016). However, because no plasma concentration measurement was performed, any indication for a causal relationship between the UM phenotype and the poor outcome of carvedilol treatment was lacking,

An overview of the observed clinical and kinetic effects per phenotype is provided in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Jung E et al.
Influence of CYP-2D6 polymorphism on the pharmacokinetic/pharmacodynamic characteristics of carvedilol in healthy Korean volunteers.
J Korean Med Sci 2018;33:e182.
PMID: 29962926.</td><td>3</td><td>21 healthy men received carvedilol 12.5 mg once daily for 3 days, followed by 25 mg once daily for 5 days, and 12.5 mg once daily for 3 days.
Plasma concentrations were determined on day 1 and day 8. Heart rate, blood pressure and isoproterenol sensitivity were measured on day 0 (before carvedilol dosing), day 1 and day 8. Chronotropic dose 25 was defined as the dose of isoproterenol, which increases the heart rate by 25 beats per minutes. $AUC_{0\text{-}24hr}$ was determined, except for desmethylcarvedilol and 4'-hydroxycarvedilol after the first dose (day 1). Due to the concentration reaching the lower limit of quantification after approximately 12 hours, $AUC_{0\text{-}12hr}$ was determined in these cases. Adverse events were evaluated until 30 days after the last dose. All adverse events were mild and fully recovered without action.
Co-medication was excluded, but weight and body-mass index significantly increased with gene dose. In addition, there was a trend for a lower age for gene dose 0.5.

Genotyping:
- 6x gene dose 2
- 7x gene dose 1.25
- 8x gene dose 0.5

Results:
<table>
<tr><td colspan="5">Results compared to gene dose 2:</td></tr>
<tr><td></td><td></td><td>gene dose 0.5</td><td>gene dose 1.25</td><td>value for gene dose 2</td></tr>
<tr><td rowspan="2">change in heart rate measured 4 and 12 hr after dosing</td><td>day 1</td><td>NS</td><td>NS</td><td>-3.72 and -1.29 bpm</td></tr>
<tr><td>day 8</td><td>NS</td><td>NS</td><td>-7.50 and -3.00 bpm</td></tr>
<tr><td rowspan="2">change in systolic blood pressure measured 4 and 12 hr after dosing</td><td>day 1</td><td>NS</td><td>NS</td><td>-4.29 and 3.29 mmHg</td></tr>
<tr><td>day 8</td><td>NS</td><td>NS</td><td>-11.00 and -1.84 mmHg</td></tr>
<tr><td rowspan="2">change in diastolic blood pressure measured 4 and 12 hr after dosing</td><td>day 1</td><td>NS</td><td>NS</td><td>-5.29 and -0.58 mmHg</td></tr>
<tr><td>day 8</td><td>NS</td><td>NS</td><td>-10.17 and -5.17 mmHg</td></tr>
<tr><td>increase in chro-</td><td>day 1</td><td>NS</td><td>NS</td><td>7.67</td></tr>
</table></td><td>Authors' conclusion: "These findings showed that CYP2D6 genotype influenced the pharmacokinetic characteristics of carvedilol and no differences in pharmacodynamic response were observed in Korean healthy volunteers."</td></tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td>IM: A</td>
<td>
<table>
<tr><td>notropic dose 25 compared to day 0 (ratio)</td><td>day 8</td><td>NS</td><td>NS</td><td>19.94</td></tr>
<tr><td colspan="2">carvedilol-related adverse events</td><td>NS</td><td>NS</td><td>0%</td></tr>
<tr><td rowspan="2">geometric mean AUC_{0-24hr} carvedilol</td><td>day 1</td><td>x 1.64 (NS)</td><td>x 0.96 (NS)</td><td></td></tr>
<tr><td>day 8</td><td>x 1.49 (NS)</td><td>x 0.87 (NS)</td><td></td></tr>
<tr><td rowspan="2">geometric mean AUC_{0-12hr} or AUC_{0-24hr} 4’-hydroxycarvedilol</td><td>day 1</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>day 8</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td rowspan="2">geometric mean AUC_{0-24hr} 5’-hydroxycarvedilol</td><td>day 1</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>day 8</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td rowspan="2">geometric mean AUC_{0-12hr} or AUC_{0-24hr} desmethylcarvedilol</td><td>day 1</td><td>x 2.22 (S)</td><td>NS</td><td></td></tr>
<tr><td>day 8</td><td>NS</td><td>NS</td><td></td></tr>
</table>

Note: Genotyping was performed for *2 and *10. These are the most important gene variants in this Korean population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Luzum JA et al. CYP2D6 genetic variation and beta-blocker maintenance dose in patients with heart failure.
Pharm Res 2017;34:1615-25.
PMID: 28181117.</td>
<td>4

PM: AA
IM: AA</td>
<td>
65 patients with heart failure were treated with carvedilol.
The carvedilol maintenance dose was defined as the dose prescribed for the longest period within the available electronic medical record time window (mean 5.5 years). Patients were treated with this maintenance dose for a mean of 3.1 years. 70% of patients used the guideline-recommended target dose (50 mg/day immediate-release carvedilol or 80 mg/day controlled-release carvedilol).
Co-medication interacting was carvedilol was not excluded, but was adjusted for.
Results were adjusted for age, gender, body-mass index, self-reported race, and drug interactions.

Genotyping:
- 45x NM
- 19x IM
- 1x PM

Results:
<table>
<tr><td colspan="2">PM versus IM versus NM:</td></tr>
<tr><td>carvedilol maintenance dose</td><td>trend for an increase with decreasing enzyme activity (p = 0.093) (NS)</td></tr>
<tr><td></td><td>The same trend was observed when all 31 determined polymorphism were included in the phenotype definition (NS).</td></tr>
<tr><td>patients treated with the recommended target dose</td><td>In all phenotypes, the majority of patients reached the recommended target dose.</td></tr>
<tr><td>duration of treatment with carvedilol maintenance dose</td><td>NS</td></tr>
</table>
</td>
<td>Authors’ conclusion: “Consistent with the role of CYP2D6 in activation of carvedilol, tolerated maintenance dose of carvedilol was higher in CYP2D6*4 carriers compared to non-carriers.”</td>
</tr>
</table>

ref. 2, continuation		NOTE: Genotyping was for 31 polymorphisms (Affymetrix Plus Premier Pack), but analysis was predominantly based on *4. This is the most important gene variant in this population from the USA.	
ref. 3 Cabrera M et al. A use case to support precision medicine for frequently hospitalized older adults with polypharmacy. AMIA Jt Summits Transl Sci Proc 2016;2016:16-21. PMID: 27570642.	1 UM: D	A 78 year old Puerto Rican man was treated with carvedilol as primary drug for management of congestive heart failure. Despite receiving guideline-concordant care and being adherent to medication regimen, the patient had 23 hospitalisations over the past 5 years, most for decompensated heart failure (often concomitant with exacerbation of COPD), The patient smoked approximately 50 pack/year. He had several comorbidities including chronic kidney disease (estimated glomerular filtration rate of 23). He used 17 different medications. The patient was CYP2D6 UM (*1/*2(xN)), CYP2C9 NM, CYP2C19 NM, CYP3A4 NM, and CYP3A5 non-expressor (i.e. the phenotype of the large majority of patients). In addition, 10 potential drug-drug interactions were identified, 4 of which involving carvedilol. In three of these, carvedilol affects other drugs (the β-agonists albuterol and the fluticasone/vilanterol combination, and the α1-blocker tamsulosine). In the fourth, the CYP2C9 inhibitor losartan may increase carvedilol exposure. Authors indicated that the CYP2D6 UM phenotype might decrease carvedilol exposure, but carvedilol plasma concentrations were not measured. NB: CYP2D6 genotyping was performed for *2 through *10, *17, and gene duplication. These are the most important gene variants in the USA.	Authors' conclusion: "The testing identified patients' CYP2D6 rapid metabolizer status. This may have resulted in decreased exposure to carvedilol which was primary drug for congestive heart failure management in this patient."
ref. 4 Shihmanter R et al. Variation in the CYP2D6 genotype is not associated with carvedilol dose changes in patients with heart failure. J Clin Pharm Ther 2014;39:432-8. PubMed PMID: 24673480.	3 PM: AA IM: AA UM: AA	93 patients with heart failure were treated with carvedilol for an average of 4.2 years (initial dose 3.125-6.25 mg 2x daily, maximum dose 25 mg 2x daily). Co-medication with weak CYP2D6 inhibitors was not excluded. The following side effects were considered relevant: bradycardia, hypotension, fatigue, dizziness, diarrhoea, glucose intolerance, worsening of heart failure and hospital admission due to heart problems in the first year of treatment. Genotyping: - 71x NM or gene dose 1/0 (1 fully active and 1 inactive allele) (56x NM, 15x gene dose 1/0) - 11x gene dose 0.25-0.75 or gene dose 0.5/0.5 (2 alleles with reduced activity) - 5x PM - 6x UM Results: PM versus (gene dose 0.25-0.75 + gene dose 0.5/0.5) versus (NM + gene dose 1/0) versus UM: No difference at start, after 3 months, after 1 year or after 5 years in: - the dose (NS). There was also no difference for PM + gene dose 0.25-0.75 + gene dose 0.5/0.5 (NS). - the heart rate (NS) - the systolic blood pressure (NS) - the diastolic blood pressure (NS)	Authors' conclusion: "There were no significant differences of carvedilol dose and number of adverse drug reactions among genotype groups."

ref. 4, continuation		No difference in: - the percentage of patients with one or more side effects (NS). There was also no difference for PM + gene dose 0.25-0.75 + gene dose 0.5/0.5 (NS). Note: Regression analysis found that only body weight was a significant predictor of the dose. NOTE: Genotyping was performed for *2 to *11, *14A, *14B, *15, *17, *19, *20, *25, *26, *29 to *31, *35, *36, *40, *41 and gene duplication. The following alleles and duplications were found: *2 to *7, *9, *10, *17, *41, *2xN and *4xN.	
ref. 5 Nikolic VN et al. Population pharmacokinetics of carvedilol in patients with congestive heart failure. J Pharm Sci 2013;102:2851-8. PubMed PMID: 23728853.	3 IM: AA	52 patients with heart failure were treated with carvedilol (3.125-25 mg 2x daily). Strong CYP2D6 inhibitors were excluded, but other relevant co-medication was not. Genotyping: - 35x NM - 17x IM Result: Addition of the CYP2D6 genotype to a model for clearance did not improve this model (NS). This means that the CYP2D6 genotype has no effect on the clearance. Note: Regression analysis found that body weight, co-medication with digoxin and smoking were significant predictors of the clearance. NOTE: Genotyping was performed for *4.	Authors' conclusion: "Our findings showed that CYP2D6 genotypes did not influence the carvedilol clearance which is consistent with some recent studies already published in this field."
ref. 6 Sehrt D et al. Carvedilol pharmacokinetics and pharmacodynamics in relation to CYP2D6 and ADRB pharmacogenetics. Pharmacogenomics 2011;12:783-95. PubMed PMID: 21599570.	3 IM: A PM: A	110 healthy volunteers were given a single dose of 25 mg carvedilol. There was no co-medication. The clearance was determined using a population pharmacokinetic model. The allele-specific clearance was set to 0 for the null alleles. Genotyping: - 38x gene dose ≥ 2 (37x gene dose 2; 1x gene dose > 2) - 14x gene dose 1.25-1.5 - 34x IM (22x gene dose 0.5-1 (two reduced activity alleles); 12x gene dose 0.25-0.5 (one reduced activity and one inactive allele) - 13x PM Gene dose ≥ 2 versus gene dose 1.25-1.5 versus gene dose 0.5-1 versus gene dose 0.25-0.5 versus gene dose 0: - increase in the median AUC of R-carvedilol with decreasing gene dose (368 versus 430 versus 605 versus 558 versus 1356 nmol.h/L) (S) - increase in the median AUC of S-carvedilol with decreasing gene dose (143 versus 218 versus 212 versus 158 versus 279 nmol.h/L) (S) - increase in the median AUC of R-desmethyl-carvedilol and S-desmethylcarvedilol with decreasing gene dose (S) (The AUC of all metabolites was more than a factor of 10 lower than those of R-carvedilol and S-	Authors' conclusion: "There were significant CYP2D6 allele-specific differences in carvedilol pharmacokinetics, but the CYP2D6 genotype had no effect on heart rate, blood pressure or adverse effects."

ref. 6, continuation		carvedilol.) - decrease in the median AUC of R-4'-hydroxy-carvedilol with decreasing gene dose (S) - no difference in the median AUC of S-4'-hydroxy-carvedilol, R-5'-hydroxycarvedilol and S-5'-hydroxy-carvedilol with decreasing gene dose (NS) - linear regression analysis revealed that the CYP2D6 genotype explained 24.4% and 8.2% of the clearance of R-carvedilol and S-carvedilol respectively - in *1/*1, CYP2D6 was involved in 74% of the clearance of R-carvedilol and 50% of the clearance of S-carvedilol - the calculated allele-specific clearance was higher for *1 than for *2 and *35 (12.9, 8.3 and 5.9 L/h respectively for R-carvedilol). There was no significant difference between *9, *10, *17 and *41 (clearance of R-carvedilol 1.3-6.9 L/h). - the CYP2D6 genotype had no effect on the maximum or 24-hour reduction of the heart rate by carvedilol, either at rest or with exertion. - the CYP2D6 genotype had no effect on the maximum or 24-hour reduction of the blood pressure, either at rest or after exertion. There was also no effect on the blood pressure in an orthostatic stress test. - the CYP2D6 genotype had no effect on the occurrence of side effects (dizziness, fatigue or absence) NOTE: Genotyping was performed for *2 to *6, *9, *10, *17, *35, *41 and gene duplication.	
ref. 7 Saito M et al. Population pharmacokinetics of R- and S-carvedilol in Japanese patients with chronic heart failure. Biol Pharm Bull 2010;33:1378-84. PubMed PMID: 20686235.	3 IM: AA IM: B (1)	40 patients with heart failure were titrated to the highest possible dose of carvedilol (1.25-20 mg/day). Plasma concentrations were determined after achieving steady state. Relevant co-medication was not excluded. Genotyping: - 31x NM (12x *1/*1, 19x *1/*10) - 9x IM (5x *10/*10, 3x *5/*10, 1x *1/*5) IM versus NM: - decrease in mean weight-corrected Cl_{or} of R-carvedilol by 41% (from 0.62 to 0.37 L/h per kg) (NS) - decrease in mean weight-corrected Cl_{or} of S-carvedilol by 35% (from 1.10 to 0.71 L/h per kg) (NS) Side effects: - there was no link between carvedilol exposure and side effects - in some cases, side effects may have been caused by initial high exposure to carvedilol: A patient with hyperkalaemia had a plasma concentration of R-carvedilol 18.3 ng/mL and S-carvedilol 7.4 ng/mL 3 hours after administration of 5 mg carvedilol. The dose was reduced. A patient with bradycardia had a trough concentration of R-carvedilol 2.0 ng/mL and S-carvedilol 1.1 ng/mL following administration of 2.5 mg carvedilol 1x daily. It was not possible to increase the dose. Both patients were *5/*10. The authors indicated that the clearance of carvedilol in patients with heart failure was approximately half that of healthy individuals. This is probably a result of	Authors' conclusion: "Individual CL/F values for carvedilol were significantly lower in Japanese CHF patients with the CYP2D6 *1/*5, *5/*10 and *10/*10 genotypes."

ref. 7, continuation		reduced hepatic blood flow caused by reduced cardiac function. NOTE: Genotyping was performed for *5 and *10 (the most important alleles in Japanese individuals).	

ref. 8
Baudhuin LM et al. Relation of ADRB1, CYP2D6, and UGT1A1 polymorphisms with dose of, and response to, carvedilol or metoprolol therapy in patients with chronic heart failure.
Am J Cardiol 2010;106:402-8.
PubMed PMID: 20643254.
	3
	
	PM: A
	IM: AA
	
	UM: AA
		74 patients with heart failure were treated with carvedilol (20-200 mg/day; usually 50 mg/day (n=50); target value was 50 mg/day for ≤ 85 kg and 100 mg/day for > 85 kg). Relevant co-medication was not excluded.
		Response was defined as at least 3 of the following 5 criteria:
		- the duration of the dose titration to achieve the target or maximum tolerated dose is longer than the standard duration according to the protocol
		- achieving and tolerating the target value for the dose without worsening of symptoms of heart failure
		- increase in classification on the NYHA scale
		- increase in the left ventricular ejection fraction of ≥ 10%
		- ≥ 10% increase in the distance covered in the 6-minute walk test
		
		Genotyping:
		- 16x NM (12x *1/*1, 4x *2/*2A)
		- 21x “UM” (15x *1/*2A, 3x *2A/*2A, 2x *1/*1xN, 1x *1xN/*2)
		- 14x “strong IM” (5x *1/*2, 8x *2A/*4, 1x *2A/*10)
		- 18x IM (10x *1/*4, 5x *1/*5, 1x *1/*6, 1x *2/*4, 1x *2/*9)
		- 5x PM (4x *4/*4, 1x *4/*5)
		
		Results:
		- there was no significant difference in the allele frequencies between patients with a response (n = 42) and without a response (n = 32) (NS)
		- there was no significant difference in the response between the different genotype groups (NS)
		- difference in dose versus NM:
		  - PM: 19.69 mg/day (S)
		  - IM: -4.36 mg/day (NS)
		  - “strong IM”: -1.21 mg/day (NS)
		  - “UM”: 4.21 mg/day (NS)
		  - patients with the CYP2D6 PM haplotype required 21.31 mg/day more than patients without this haplotype (S)
		
		NOTE 1: Genotyping was performed for *2A, *2 to *6, *9, *10 and gene duplication.
		NOTE2: *2A was considered an allele with increased activity and *2 as an allele with reduced activity.
			Authors’ conclusion: “Polymorphisms in ADRB1, CYP2D6, and UGT1A1 were not associated with a response to metoprolol or carvedilol therapy in our cohort of patients with heart failure. The ADRB1 and CYP2D6 genotype, alone and in haplotype, were significantly associated with the dose of carvedilol.”

ref. 9 Horiuchi I et al. Pharmacokinetics of R- and S-carvedilol in routinely treated Japanese patients with heart failure. Biol Pharm Bull 2008;31:976-80.	4 IM: AA	24 patients with heart failure were treated with carvedilol 1.25-20 mg/day for > 1 week. None of the patients used strong CYP2D6 inhibitors as co-medication. Genotyping: - 8x gene dose 2 (6x *1/*1, 1x *1/*2, 1x *2/*2) - 9x gene dose 1-1.25 (9x *1/*10, 2x *2/*10, 1x *1/*5) - 4x gene dose 0.25-0.5 (3x *10/*10, 1x *5/*10) Gene dose 0.25-0.5 versus gene dose 1-1.25 versus gene dose 2: - no significant difference in mean Cl_{or} of S-carvedilol	Authors’ conclusion: “The present study showed that CYP2D6 *10 was not a major factor affecting the CL/F value of R- and S-carvedilol in HF patients, and that the CL/F values of R- and S-carvedilol were considerably lower in patients with HF than in healthy subjects.

ref. 9, continuation		or R-carvedilol. The mean Cl_{or} of R-carvedilol and S-carvedilol in patients with heart failure was much lower than in healthy volunteers (29.0% and 25.2% respectively of the clearance for healthy volunteers with gene dose 2 and significantly lower than the clearance in healthy volunteers with gene dose 0.25-0.5). The authors postulate that in patients with heart failure, the metabolic activity of CYP2D6 is reduced as a result of cardiac dysfunction and/or subsequent hypoxaemia, meaning that CYP2D6 polymorphisms in these patients do not have an effect on the carvedilol clearance. NOTE: Genotyping was performed for *2, *5, *10 and *14 (the most important alleles in Japanese individuals).	Our findings suggested that metabolic clearance of carvedilol via not only CYP2D6 but also other metabolizing enzymes is diminished in patients with HF."
ref. 10 Takekuma Y et al. Evaluation of effects of polymorphism for metabolic enzymes on pharmacokinetics of carvedilol by population pharmacokinetic analysis. Biol Pharm Bull 2007;30:537-42.	4 IM: A	A population pharmacokinetic model (1-compartment pharmacokinetic model with first order absorption (for oral dose)) was developed using the data from 40 patients in Takekuma, 2006 and 1 extra patient. The patients had congestive heart failure or angina pectoris and received carvedilol 1.25-40 mg/day. Co-medication with a strong effect on the C_{ss} of carvedilol was excluded. Genotyping: - 31x NM (13x *1/*1, 18x *1/*10) - 10x IM (5x *10/*10, 3x *1/*5, 1x *4/*10, 1x *5/*10) Inclusion of CYP2D6 polymorphisms in the population pharmacokinetic model significantly improved the objective function value. In the final model, the clearance for IM was reduced by 39%. NOTE: Genotyping was performed for *4, *5, *10 and *14 (the most important alleles in Japanese individuals).	Authors' conclusion: "Our results suggest that the factors responsible for inter-individual variation in carvedilol clearance in the Japanese population with heart disease are creatinine clearance and polymorphisms of UGT2B7 and CYP2D6. It was estimated that IM of CYP2D6 decreased the clearance by 39%."
ref. 11 Honda M et al. Multiple regression analysis of pharmacogenetic variability of carvedilol disposition in 54 healthy Japanese volunteers. Biol Pharm Bull 2006;29:772-8.	3 IM: A	54 healthy volunteers, of whom 23 also participated in Honda et al. (2005), received carvedilol 5 mg (n = 23) or 10 mg (n = 31) before breakfast. Blood samples were collected at 2 and 6 hours after administration. Clearance was calculated using a pharmacokinetic model. Genotyping: - 16x gene dose 2 (12x *1/*1, 2x *1/*2, 2x *2/*2) - 26x gene dose 1.25 (20x *1/*10, 6x *2/*10) - 12x gene dose 0.5 (12x *10/*10) Gene dose 0.5 (IM) versus gene dose 1.25 (NM) versus gene dose 2 (NM): - the plasma concentration of both enantiomers appeared higher for gene doses 0.5 and 1.25 than for gene dose 2 (significance not determined). - addition of CYP2D6*10 to the pharmacokinetic model improved the model significantly. Cl_{or} was significantly lower for gene doses 0.5 and 1.25 than for gene dose 2. - the mean weight-corrected Cl_{or} of R-carvedilol according to the model was 1.4 versus 2.2 versus 3.0 L/h per kg (decrease by 53% for IM versus gene dose 2 and by 44% for IM versus NM).	Authors' conclusion: "The oral clearance (CL/F) and also apparent volume of distribution (V/F) of both enantiomers were significantly lower in the subjects with the CYP2D6*10 allele than those with the CYP2D6 *1/*1, *1/*2, or *2/*2 genotype, confirming our previous finding that the bioavailability (F) and systemic clearance (CL) of R- and S-carvedilol in the liver is significantly altered in Japanese with the CYP2D6*10 allele."

ref. 11, continuation		- the mean weight-corrected Cl_{or} of S-carvedilol according to the model was 4.2 versus 4.6 versus 6.2 L/h per kg (decrease by 32% for IM versus gene dose 2 and by 19% for IM versus NM). - the mean weight-corrected apparent distribution volume (the distribution volume divided by the biological availability) for R-carvedilol according to the model was 4.2 versus 5.2 versus 7.2 L/kg, indicating a decrease in the biological availability with an increase in the gene dose. - the mean weight-corrected apparent distribution volume for S-carvedilol according to the model was 13.4 versus 14.6 versus 18.6 L/kg, indicating a decrease in the biological availability with an increase in the gene dose. NOTE: Genotyping was performed for *2, *5, *10 and *14 (the most important alleles in Japanese individuals).	
ref. 12 Takekuma Y et al. Contribution of polymorphisms in UDP-glucuronosyl-transferase and CYP2D6 to the individual variation in disposition of carvedilol. J Pharm Pharm Sci 2006;9:101-12.	4 *10 (IM + NM): A	40 patients with congestive heart failure or angina pectoris received carvedilol 1.25-20 mg/day in one or two doses per day. Following administration of a set dose over 6-10 days, blood samples were collected before and at 1, 2, 4, 6 and 10 hours after administration of carvedilol. Co-medication with a strong effect on the plasma concentration of carvedilol was excluded. Based on the calculated metabolic index for glucuronidation, the patients were divided into two groups: one with low glucuronidation activity (n = 23) and one with high glucuronidation activity (n = 17). Genotyping: - 30x NM (13x *1/*1, 17x *1/*10) - 10x IM (5x *10/*10, 3x *1/*5, 1x *4/*10, 1x *5/*10) Results: - the glucuronidation activity was lower in the group with a high AUC than in the group with a low AUC (S for dose 2x daily (n = 49)). - the frequency of *10 was higher in the group with low glucuronidation activity than in the group with high glucuronidation activity (S; increase by 61%; from 45.7% to 73.6%). - the authors explained the effect of *10 on the metabolic index for glucuronidation through an increase in the plasma concentration of carvedilol with virtually constant production of glucuronidated metabolites. - the frequency of *4 and *5 differed non-significantly between both glucuronidation groups. - the frequency of *1 was lower in the group with low glucuronidation activity than in the group with high glucuronidation activity (S; decrease by 57%; from 47.8% to 20.6%). The $t_{1/2}$ did not differ between the tested patients and healthy volunteers (Fujimaki M et al., 1990), but the AUC[a] was much higher in the patients than in healthy volunteers (Neugebauer et al., 1987) (2.69-85.1 versus 2.56-15.0 h/kL). NOTE: Genotyping was performed for *4, *5, *10 and *14 (the most important alleles in Japanese	Authors' conclusion: "Polymorphisms of UGT1A1, UGT2B7 and CYP2D6 strongly affect the pharmaco-kinetics and disposition of carvedilol in Japanese."

		individuals).	
ref. 13 Honda M et al. Effect of CYP2D6*10 on the pharmacokinetics of R- and S-carvedilol in healthy Japanese volunteers. Biol Pharm Bull 2005;28:1476-9.	3 *10 (IM + NM): A	23 healthy volunteers received carvedilol 5 mg (n = 9) or 10 mg (n = 14) before breakfast. Blood samples were collected at 2 and 6 hours after administration. Clearance was calculated using a pharmacokinetic model. Genotyping: - 6x gene dose 2 (5x *1/*1, 1x *1/*2) - 15x gene dose 1.25 (12x *1/*10, 3x *2/*10) - 2x gene dose 0.5 (2x *10/*10) Gene dose 0.5 + gene dose 1.25 versus gene dose 2: - decrease in the mean weight-corrected Cl_{or} of R-carvedilol by 38% (S; from 1.6 to 1.0 L/h per kg). - decrease in the mean weight-corrected Cl_{or} of S-carvedilol by 23% (S; from 2.6 to 2.0 L/h per kg). - decrease in the mean weight-corrected apparent distribution volume (the distribution volume divided by the biological availability) for R-carvedilol by 38% (S; from 3.9 to 2.4 L/kg). - decrease in the mean weight-corrected apparent distribution volume of S-carvedilol by 24% (S; from 9.2 to 7.0 L/kg). NOTE: Genotyping was performed for *2, *5, *10 and *14 (the most important alleles in Japanese individuals).	Authors' conclusion: "These results suggested that the systemic and/or pre-systemic metabolism of R- and S-carvedilol in the liver is significantly decreased in Japanese with the CYP2D6*10 allele."

ref. 14
Giessmann T et al.
CYP2D6 genotype and induction of intestinal drug transporters by rifampin predict presystemic clearance of carvedilol in healthy subjects.
Clin Pharmacol Ther 2004;75:213-22.
	4
	
	PM: B
		12 healthy volunteers received carvedilol 5 mg i.v. and after a washout period of 8 days they received carvedilol 12.5 mg/day oral for 2 days, followed by carvedilol 25 mg/day oral for 5 days. Co-medication and alcohol were excluded. A standard diet was used.
		
		Genotyping:
		- 6x NM or IM (*1/*1, *1/*3, *1/*4 or *1/*6)
		- 6x PM (*3/*4, *4/*4))
		
		PM versus IM + NM:
		- no significant differences in AUC, $t_{1/2}$ and clearance following i.v. administration.
		- day 7 of the oral administration:
		  - increase in $AUC_{0\text{-}24h}$ carvedilol by 97% (S; from 173 to 341 ng.h/mL).
		  - increase in $AUC_{0\text{-}24h}$ R-carvedilol by 145% (S; from 93.9 to 230 ng.h/mL).
		  - increase in $AUC_{0\text{-}24h}$ S-carvedilol by 92% (S; from 32.7 to 62.9 ng.h/mL).
		  - increase in the biological availability of carvedilol by 67% (S; from 21.5% to 36%).
		  - decrease in the systolic blood pressure during a cycle ergometry test by 10% (S; from 168 to 152 mmHg).
		  - no significant difference in heart rate and diastolic blood pressure during a cycle ergometry test.
		
		NOTE: Genotyping was performed for *3, *4, *5, *6 and gene duplications of *1 and *2 (the most important gene variations in whites).
			Authors' conclusion: "Variable plasma concentrations of carvedilol during long-term administration are predicted by CYP2D6 genotype and intestinal expression of P-glycoprotein and MRP2."

ref. 15 Zhou HH et al. Stereoselective disposition of	3	16 healthy volunteers received carvedilol 25 mg oral. Phenotyping: - 9x NM[#]	Authors' conclusion: "In poor metabolizers of debrisoquin the clearance of R-carve-

carvedilol is determined by CYP2D6. Clin Pharmacol Ther 1995;57:518-24.
 	
ref. 15, continuation
	PM: A	- 7x PM
		
		PM versus NM[#]:
		- R-carvedilol:
		  - increase in AUC by 157% (S, from 159.4 to 408.9 ng.h/mL).
		  - decrease in Cl_{or} by 67% (S; from 119.2 to 38.9 L/h).
		  - increase in $t_{1/2}$ by 76% (S, from 2.68 to 4.71 h).
		- S-carvedilol:
		  - the same trend, but differences were not significant.
		- increase in the ratio Cl_{or} S-carvedilol/R-carvedilol by 100% (S; from 2.03 to 4.06).
		- decrease in Cl_{or} carvedilol by 58% (S; from 156.6 to 66.0 L/h).
		- decrease in the clearance as a result of the formation of the metabolites 4'-hydroxycarvedilol and 5'-hydroxycarvedilol by 76% and 71% respectively (S; from 2.0 to 0.485 L/h and from 1.08 to 0.31 L/h).
		- no effect on the clearance as a result of the formation of the metabolite desmethylcarvedilol.
		
		NOTE: genotype unknown.
			dilol is further reduced, resulting in higher plasma concentrations and perhaps greater α-blockade."

ref. 16 SmPC Carvedilol Sandoz 25-01-21.	0 PM: A	Pharmacokinetics: *Genetic polymorphism* Results of pharmacokinetic studies in humans showed an important role of CYP2D6 in the metabolism of (R)- and (S)-carvedilol. As a result, the plasma concentrations of (R)- and (S)-carvedilol are elevated in poor metabolisers. Results on the clinical relevance are not clear-cut. *Biotransformation* Demethylation and hydroxylation of the phenol ring forms the three active metabolites with β-blocking effects. Compared to carvedilol, the vasodilative effect of these active metabolites is weak. The concentrations of the three active metabolites in humans are approximately 10-fold lower than those of the precursor. In poor metabolisers, the vasodilative active component can be increased..	
ref. 17 SmPC Coreg (carvedilol) 14-09-17, USA.	0 PM: B	CYP2D6 poor metabolizers: Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+)-enantiomer. Pharmacokinetics: Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+)-carvedilol compared with normal metabolizers. In contrast, plasma levels of S(-)-carvedilol are increased only by about 20% to 25% in poor metabolizers, indicating this enantiomer is metabolized to a lesser extent by cytochrome P450 2D6 than R(+)-carvedilol.	

[a] Corrected for the dose.
[#] Phenotyping usually does not distinguish between IM, NM and UM. Therefore, NM in these studies is usually equal to IM+NM+UM.

Risk group	-

Comments:
-

Date of literature search: 7 July 2022.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 B	Yes	No	12 September 2022
	IM	4 B	Yes	No	
	UM	3 D	Yes	No	

Mechanism:
Carvedilol is metabolised by hydroxylation and glucuronidation.
Carvedilol is primarily converted by CYP2D6 to 4'-hydroxycarvedilol and 5'-hydroxycarvedilol. Data from pre-clinical studies suggest that these metabolites are active, with 4'-hydroxycarvedilol having 13-fold the potency of carvedilol and being the only metabolite contributing to β-blocker activity of carvedilol.
Carvedilol is also converted, predominantly by CYP2C9, to the active metabolite desmethylcarvedilol.
S-carvedilol has β-blocker and α-blocker activity. R-carvedilol, which is metabolised less quickly than S-carvedilol, has only α-blocker activity.