CYP2D6: bisoprolol 2456/2457/2458

IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), NM = normal metaboliser (gene dose 1.25-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated CYP2D6 enzyme activity)

Brief summary and justification of choices:
Approximately 50% of bisoprolol is excreted in unchanged form in the urine. The other 50% is metabolised by CYP-3A4 and CYP2D6, with CYP2D6 potentially making only a relatively small contribution.
None of the four studies in patients and one study in healthy volunteers found an effect of the CYP2D6 phenotype on bisoprolol pharmacokinetics (Fontana 2022, Chan 2021, Nozawa 2005, Taguchi 2005, and Deroubaix 1996). In addition, Chan 2021 and Nozawa 2005 found no effect of the CYP2D6 phenotype on response to bisoprolol.
Based on this, the KNMP Pharmacogenetics Working Group decided that there is no evidence for a CYP2D6-bisoprolol interaction, and thus no reason to recommend a dose adjustment or an alternative (no/no-interactions).
You can find an overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below follows the KNMP definition for NM, PM, IM and UM, unless stated otherwise. The definition of NM, PM, IM and UM used in the table below may therefore differ from the definition 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
Fontana V et al. Chromosomal region 11p14.1 is associated with pharmacokinetics and pharmacodynamics of bisoprolol. Pharmgenomics Pers Med 2022;15:249-60.
PMID: 35356681.</td><td>3

PM: AA
IM: AA
UM: AA</td><td>591 patients were treated with bisoprolol 1.25-20 mg/day following a non-ST elevation-acute coronary syndrome. Bisoprolol clearance was determined 1 month after hospital discharge using a population pharmacokinetic model adjusting for age, body weight, sex, smoking, and concomitant use of a diuretic. Chronic kidney disease did not influence clearance and so, was not adjusted for. Patients were excluded if their bisoprolol plasma levels were below the lower limit of quantification, they had poor adherence to bisoprolol (defined as at least one pill missed in the week before blood sampling as assessed by the Brief Medication Questionnaire), or if they were categorised as an outlier in relation to bisoprolol plasma concentrations according to Tukey’s method.
Comedication with CYP2D6 inhibitors was not excluded.

Genotyping:
- 300x NM
- 246x IM
- 31x PM
- 14x UM

Results:
<table><tr><td colspan="2">Results for PM versus IM versus NM versus UM:</td></tr><tr><td rowspan="3">median bisoprolol clearance</td><td>NS</td></tr><tr><td>Results were also NS for each of the single genotypes.</td></tr><tr><td>In addition, no significant associations in the CYP2D6 region were observed in a genome-wide association analysis.</td></tr><tr><td colspan="2">For NM, the median bisoprolol clearance was 11.4 L/h.</td></tr></table>
Note: Genotyping was for *3, *4, *5, *9, *10, *41, and gene duplication. These are the most important variants in this population from the United Kingdom. Apart from *5 and gene duplication, pharmacogene-</td><td>Authors’ conclusion:
‘No associations were found with CYP2D6 or CYP-3A genotypes or metabolizer status despite the fact that these two P450 enzymes are involved in bisoprolol metabolism..’</td></tr>
</table>

<table>
<tr><td></td><td></td><td>tic variants were extracted from a genome-wide association study.</td><td></td></tr>
<tr><td>ref. 2
Chan SW et al. Influence of CYP2D6 and CYP3A5 polymorphisms on the pharmacokinetics and pharmacodynamics of bisoprolol in hypertensive Chinese patients. Front Med (Lausanne) 2021;8:683498. PMID: 34568359.</td><td>3

IM+PM: AA</td><td>99 patients with mild to moderate essential hypertension were treated with bisoprolol 2.5 mg/day for 6 weeks. Plasma concentrations 3 hours post-dose were only determined in 45 of these patients.
Clinic blood pressure was measured in sitting position.
Comedication with CYP2D6 inhibitors was not excluded. Impairment of hepatic or renal functions was excluded.
Multiple linear regression analysis was performed to test associations with plasma concentrations.

Genotyping:
- 56x NM
- 42x IM
- 1x PM

Results:
<table>
<tr><td colspan="3">Results for IM+PM compared to NM:</td></tr>
<tr><td colspan="2">change in clinic systolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in clinic diastolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in 24h ambulatory systolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in 24h ambulatory diastolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in daytime ambulatory systolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in daytime ambulatory diastolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in night-time ambulatory systolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in night-time ambulatory diastolic blood pressure</td><td>NS</td></tr>
<tr><td colspan="2">change in clinic heart rate</td><td></td></tr>
<tr><td colspan="2">change in 24h ambulatory heart rate</td><td>NS</td></tr>
<tr><td colspan="2">change in daytime ambulatory heart rate</td><td>NS</td></tr>
<tr><td colspan="2">change in night-time ambulatory heart rate</td><td>NS</td></tr>
<tr><td colspan="2">bisoprolol trough concentration on day 42</td><td>NS</td></tr>
<tr><td rowspan="2">bisoprolol concentration 3 hours post-dose</td><td>day 1</td><td>NS</td></tr>
<tr><td>day 42</td><td>NS</td></tr>
</table>

Note 1: Genotyping was for *2, *4, *5, *10, and *14. These are the most important variants in this Chinese population.

Note 2: The authors consider the *14 variant (formerly denoted as *14B) as inactive, whereas PharmVar indicates that *14 has reduced activity. However, PharmVar does not include the novel *14 allele found in mainland China yet.</td><td>Authors' conclusion:
'The common polymorphisms in CYP2D6 that were examined and the CYP3A5 *3 polymorphism appear to have no benefit in predicting the hemodynamic response to bisoprolol in these patients.'</td></tr>
<tr><td>ref. 3
Nozawa T et al. Influence of CYP2D6 genotype on metoprolol plasma concentration and beta-adrenergic inhibition during long-term treatment: a comparison with bisoprolol. J Cardiovasc Pharmacol 2005;46:713-20.</td><td>4

IM: AA</td><td>40 patients (ischaemic heart disease, hypertension and atrial fibrillation), 9x *10/*10, 16x *1/*10 or *2/*10, 14x no *10 (*1/*1, *1/*2 or *2/*2), 1x *2/*5, screened for *2, *4, *5, *10 and *14, bisoprolol dose guided by clinical effect, mean dose 3.7 mg/day, no CYP2D6 inhibitors as co-medication;

*10/*10 versus NM (1x*10 and no *10):
- no difference in peak and trough levels (both NS).
- no difference in daily dose and dose-corrected peak and trough levels (NS).
- no difference in change of heart rate, diastolic blood pressure and systolic blood pressure after administration of a β-agonist at the time of the trough level or the peak level (NS).</td><td>Authors' conclusion:
"Bisoprolol had a relatively constant β-adrenergic inhibition independent of CYP2D6 genotype."</td></tr>
<tr><td>ref. 4
Taguchi M et al. Pharmacokinetic variability of routinely administered biso-</td><td>3

IM: AA</td><td>40 patients, including 7 with mild heart failure, 9x *10/*10, 16x *1/*10 or *2/*10, 14x no *10 (*1/*1, *1/*2 or *2/*2), 1x *2/*5, screened for *2, *5, *10 and *14, bisoprolol dose guided by clinical effect, 2.5-5 mg/day, no CYP2D6 inhibitors as co-medication;

*10/*10 versus (1x *10 + no *10 + *2/*5):
- no difference in peak and trough levels (both NS).</td><td>Authors' conclusion:
"The relation between the creatinine clearance and the oral clearance of</td></tr>
</table>

prolol in middle-aged and elderly Japanese patients. Biol Pharm Bull 2005;28:876-81.		- development of a pharmacokinetic model confirmed that the CYP2D6*10 allele did not have a significant effect on non-renal clearance of bisoprolol.	bisoprolol was not altered by the CYP2D6 genotype."
ref. 5 Deroubaix X et al. Comparative bioavailability of a metoprolol controlled release formulation and a bisoprolol normal release tablet after single oral dose administration in healthy volunteers. Int J Clin Pharmacol Ther 1996;34:61-70.	3 PM: AA	12 healthy volunteers, 9x NM#, 3x PM, phenotyping, single dose of bisoprolol 10 mg, no co-medication other than contraceptives; PM versus NM#: - no significant difference in plasma concentrations after 12 and 24 hours (NS). NOTE: genotype unknown. Phenotyping can only distinguish between PM and the other phenotypes, so NM# is actually equal to IM, NM and UM.	Authors' conclusion: "Bisoprolol disposition was not associated with the CYP2D6 pattern."

Risk group	--

Comments:

- The article Fedorinov DS et al. Pharmacogenetic testing by polymorphic markers G1846A (CYP2D6*4) and C100T (CYP2D6*10) of the CYP2D6 gene in coronary heart disease patients taking β-blockers in the Republic of Sakha (YAKUTIA). Drug Metab Pers Ther 2018;33:195-200. PMID: 30325731 was not included in this risk analysis, because the data in this article are wrong. According to the article, the number of patients carrying both the 1846G>A and the 100C>T gene variant is higher than the number of patients carrying the 1846 G>A gene variant, which is not possible. In addition, in the total group of 201 patients using atenolol, metoprolol or bisoprolol, the article claims the presence of 10 1846G>T variants (*4) based on the number of patients with this gene variant and the presence of 42 1846G>T variants (*4) based on the gene variant frequency, all within the same table. This casts too much doubt about whether other data in this article can be trusted.

Date of literature search: 14 July 2022.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	3 AA	no	no	12 September 2022
	IM	4 AA	no	no	
	UM	--	no	no	

Mechanism:

Approximately 50% of bisoprolol is excreted in unchanged form in the urine. The other 50% is metabolised by CYP-3A4 and CYP2D6, with CYP2D6 potentially making only a relatively small contribution.