CYP2D6: atenolol 2453/2454/2455

AUC = area under the concentration-time curve, 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), $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated CYP2D6 enzyme activity)

Brief summary and justification of choices:
Atenolol is primarily excreted via the urine in unchanged form.
None of the four studies, including a large study with more than 1000 patients and three studies in healthy volunteers, found an effect of the CYP2D6 phenotype on effectiveness of atenolol (Bijl 2009, Lewis 1985, Dayer 1985, Freestone 1982). In addition, none of the two studies investigating pharmacokinetics in healthy volunteers found an effect of the CYP2D6 phenotype on exposure to atenolol (Lewis 1985, Dayer 1985).
Based on this, the KNMP Pharmacogenetics Working Group decided that there is no evidence for a CYP2D6-atenolol 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.

Source	Code	Effect	Comments
ref. 1 Bijl MJ et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. Clin Pharmacol Ther 2009;85:45-50.	4 PM: AA IM: AA	Heart rate was determined for 1,003 users of atenolol (680x *1/*1, 270x *1/*4 and 53x *4/*4) and diastolic blood pressure (DBP) in 1,068 users (716x *1/*1, 295x *1/*4 and 57x *4/*4). Screening was performed for the most common variant allele: *4. Co-medication with CYP2D6 inhibitors was not excluded, but was sporadic and did not affect the results. PM versus NM: - no significant difference in heart rate (NS). - no significant difference in diastolic blood pressure (NS). IM versus NM: - no significant difference in heart rate (NS). - no significant difference in diastolic blood pressure (NS).	Authors' conclusion: "In users of atenolol no association between CYP2D6 genotype and heart rate or blood pressure was observed."
ref. 2 Lewis RV et al. Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol 1985;19:329-33.	3 PM: AA	10 healthy volunteers, 6x NM#, 4x PM, single dose of atenolol 100 mg, no CYP2D6 inhibitors as co-medication; PM versus NM#: - no difference in AUC and $t_{1/2}$ (both NS). - no difference in the reduction of exertion tachycardia at different time points after taking atenolol (2, 6, 12 and 24 hours) (all NS). NOTE Genotype unknown.	Authors' conclusion: "There was no relationship between the debrisoquine to 4-hydroxydebrisoquine ratio and the pharmacokinetics or pharmacodynamics of atenolol."
ref. 3 Dayer P et al. Interindividual variation	3	10 healthy volunteers, 6x NM#, 4x PM, single dose of atenolol 50 mg, no CYP2D6 inhibitors as co-medication;	Authors' conclusion: "Oxydative polymorphism did not

of beta-adrenoceptor blocking drugs, plasma concentration and effect: influence of genetic status on behaviour of atenolol, bopindolol and metoprolol. Eur J Clin Pharmacol 1985;28:149-53.	PM: AA	PM versus NM#: - no differences in the concentration-time curve (NS). - no difference in the reduction of exertion tachycardia at different time points after taking atenolol (3, 9 and 24 hours) (all NS). NOTE Genotype unknown.	significantly influence the pharmacological effect of atenolol.”
ref. 4 Freestone S et al. Comparison of two long-acting preparations of metoprolol with conventional metoprolol and atenolol in healthy men during chronic dosing. Br J Clin Pharmacol 1982;14:713-8.	4 PM: AA	Eight healthy volunteers, 6x NM#, 2x PM, atenolol 100 mg/day for 1 week, exertion tachycardia was measured before starting atenolol and on day 7, no CYP2D6 inhibitors as co-medication; PM versus NM#: - no difference in the reduction of exertion tachycardia at trough concentrations of atenolol (NS). NOTE Genotype unknown.	Authors’ conclusion: “Response to atenolol was not influenced by phenotype.”

NM#: Phenotyping can only distinguish between PM and the other phenotypes. NM# is therefore equal to NM + IM + UM.

Risk group	--

Comments:
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Date of literature search: 14 July 2022.

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

Mechanism:
Atenolol is primarily excreted via the urine in unchanged form.