CYP2D6: metoprolol 1554/1555/1556

AUC = area under the concentration-time curve, AUEC = area under the time-effect curve, bpm = beats per minute, 95% CI = 95% confidence interval, Cl_{or} = oral clearance, C_{ss} = steady state plasma concentration, CTCAE = Common Terminology Criteria for Adverse Events, DBP = diastolic blood pressure, ECG = electrocardiogram, HR = heart rate, HM = α-hydroxy-metoprolol, IM = intermediate metaboliser (gene dose 0.25-1) (reduced CYP2D6 enzyme activity), MR = metabolic ratio, NM = normal metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), NS = non-significant, NYHA = (categorisation of the severity of heart failure according to) the New York Heart Association, OR_{adj} = adjusted odds ratio, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), *R*-M = *R*-metoprolol, RR = relative risk, S = significant, SBP = systolic blood pressure, *S*-M = *S*-metoprolol, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 2.75) (elevated CYP2D6 enzyme activity)

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the healthcare professional should consider the next best option.

Brief summary and justification of choices:
CYP2D6 converts metoprolol to inactive metabolites. The metoprolol dose required to achieve a therapeutic plasma concentration is therefore lower for patients with reduced CYP2D6 activity (IM and PM) and higher for patients with elevated CYP2D6 activity (UM) (Meloche 2022, Batty 2014, Rau 2009, Goryachkina 2008, Jin 2008, Seeringer 2008, Ismail 2006, Terra 2005, Nozawa 2005, Fux 2005, Zineh 2004, Kirchheiner 2004, Taguchi 2003, Rau 2002, Huang 1999, Koytchev 1998, Laurent-Kenesi 1993, Lennard 1983, and American SmPC Toprol-XL). Little correlation with the plasma concentration was found for the anti-hypertensive effect of metoprolol (statistically significant effects were found in a meta-analysis (Meloche 2020) and in 5 of 12 studies: Batty 2014, Rau 2009, Bijl 2009, Yuan 2008, and Laurent-Kenesi 1993; not significant: Chen 2018, Hamadeh 2014, Nozawa 2005, Fux 2005, Zineh 2004, Kirchheiner 2004, and Koytchev 1998), but a clear correlation was found for the effect as β-adrenergic blocker (lowering of the heart rate) (significant in a meta-analysis (Meloche 2020) and in 12 of 13 studies: Chen 2022, Meloche 2022, Gao 2017, Hamadeh 2014, Batty 2014, Rau 2009, Bijl 2009, Goryachkina 2008, Nozawa 2005, Kirchheiner 2004, Koytchev 1998, and Laurent-Kenesi 1993; not-significant Lewis 1991).
Because studies have shown a distinct effect on metoprolol plasma concentrations in IM, PM and UM patients, the KNMP Pharmacogenetics Working Group concluded that there is a gene-drug interaction.

PM: Wuttke 2002 including 9 PM found a higher percentage of PM in the group of patients with side effects, but a meta-analysis of 3 studies with 32 PM and 6 patient studies with 4-17 PM did not find an increase in adverse events or discontinuation due to adverse events for PM, IM+PM or for PM versus IM versus NM (Meloche 2020, Hamadeh 2014, Batty 2014, Rau 2009, Fux 2005, Zineh 2004, and Clark 1984).
In most of the studies, PM had little or no effect on blood pressure. Rau 2009 found an increase in the percentage of patients reaching the blood pressure target value for 17 PM, but Yuan 2008 found no increase in the prevalence of effective blood pressure reductions for 60 IM+PM, and Zineh 2014 found no increase in responders (patients with ≥10% reduction in diastolic blood pressure) for 4 PM.
In most patient studies, the heart rate reduction was greater for PM. However, only one of these studies (with 11 PM) investigated symptomatic bradycardia and did not find a significant effect of CYP2D6 on symptomatic bradycardia (Hamadeh 2014). This indicates that this effect might also be beneficial (higher effectiveness of metoprolol). In addition, Batty 2014 including 12 PM found that the difference in heart rate reduction compared to NM disappeared with a longer treatment duration (from 3 months).
Therefore, the clinical consequences of PM appear to be limited. However, as the effect on the metoprolol plasma concentration is large, the KNMP: Pharmacogenetics Working Group decided to issue a warning (yes/yes-interaction). For certain patients, a more gradual increase of the initial dose and/or a lower target dose may be more favourable.

IM: Chen 2022 found a higher rate of discontinuation due to intolerance and a higher incidence of all adverse events and cardiovascular adverse events (including bradycardia < 55 bpm) for 381 IM with cardiovascular diseases aged ≥ 60 years. There was no increase in non-cardiovascular adverse events. However, a meta-analysis of 3 studies with 594 non-PM did not find an increase in adverse events for IM and 4 patient studies with 4-112 IM did not find an increase in adverse events or discontinuation due to adverse events for IM, IM+PM or for PM versus IM versus NM (Meloche 2020, Hamadeh 2014, Batty 2014, Fux 2005, and Zineh 2004).
In most of the studies, IM had little or no effect on blood pressure. In addition, Yuan 2008 found no increase in

the prevalence of effective blood pressure reductions for 60 IM+PM.
In most patient studies, the heart rate reduction was greater for IM. However, only one of these studies investigated symptomatic bradycardia and did not find it in the 15 IM (Hamadeh 2014). This indicates that this effect might be beneficial (higher effectiveness of metoprolol). In addition, Batty 2014 including 112 IM found that the difference in heart rate reduction compared to NM disappeared with a longer treatment duration (from 3 months).
Therefore, the clinical consequences of IM appear to be limited. However, as the effect on the metoprolol plasma concentration is considerable, the KNMP: Pharmacogenetics Working Group decided to issue a warning (yes/yes-interaction). For certain patients, a more gradual increase of the initial dose and/or a lower target dose may be more favourable.

UM: Three studies and a meta-analysis examined the clinical consequences of UM.
Goryachkina 2008 found for 7 UM with a recent acute myocardial infarction that the heart rate only decreased by 9 beats/minute to 69 beats per minute. Furthermore, the percentage UM in the group with a disruption of the ventricular rhythm was 11 times higher than in the group without disruption (22% versus 2%). However, the dose that was used was low: average 0.9 mg/kg per day, which is equivalent to 72 mg/day for a patient weighing 80 kg. The maximum dose of metoprolol for secondary prevention of a myocardial infarction is 200 mg/day. The authors also indicated that underdosage may have occurred, because a significant number of patients did not achieve an effective dose of metoprolol.
The meta-analysis of Meloche 2020 did not show a difference in resting heart rate (5 studies with 711 non-PM) and blood pressure reduction (5 studies with 764 non-PM) for UM.
Meloche 2022, including 68x UM+gene dose 2.5, found a decrease in heart rate reduction with increasing gene dose. However, the difference in heart rate with NM was small. The mean values for both groups were between 60 and 70 bpm.
Hamadeh 2014 found a decrease in the heart rate reduction by 2% for 7x UM + 1x gene dose 2.25. The reduction in systolic and diastolic blood pressure did not differ significantly between the genotypes. These were hypertension patients and the target value of the dose was 200 mg/day.
So, the detrimental effect of UM on the reduction of the heart rate appears to be limited at an adequate dose. Furthermore, the maximum dose of metoprolol for many indications is higher than or equal to the dose of 200 mg/day at which a good reduction in heart rate was observed. The maximum dose is 400 mg/day for angina pectoris, 200 mg/day for arrhythmia and secondary prevention of a myocardial infarction and 150 mg/day (immediate release) or 200 mg/day (controlled release) for heart failure. However, as the effect on the metoprolol plasma concentration is considerable, the KNMP: Pharmacogenetics Working Group decided to issue a warning (yes/yes-interaction). As a general rule, it would be favourable for UM to use the maximum dose for the relevant indication as a target dose.

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. A substantiation of the dose recommendation is provided below.

Justification of dose recommendation

Dose adjustments have been calculated on the basis of AUC, C_{ss} or Cl_{or} of metoprolol or - if known - S-metoprolol. Where the effect is only known versus NM + IM + UM (e.g. in Laurent-Kenesi 1993), the effect of NM + IM + UM is assumed to be similar to that of NM, due to the much lower prevalence of IM and UM.

PM: In order to achieve a plasma concentration comparable to that of NM, the dose for PM must be reduced to 25% of the normal dose. For a total of 62 PM from 11 studies, the weighted mean of the calculated dose adjustments was a reduction to 19% (range 3%-34%; median 18%) (Rau 2009, Goryachkina 2008, Seeringer 2008, Ismail 2006, Fux 2005, Terra 2005, Kirchheiner 2004, Zineh 2004, Rau 2002, Laurent-Kenesi 1993, and Lennard 1983). This was rounded off to 25% to be more achievable in clinical practice. This value corresponds well to the calculated value of 22% based on the median plasma concentration for 12 PM (Batty 2014).

IM: In order to achieve a plasma concentration comparable to that of NM, the dose for IM must be reduced to 50% of the normal dose. For a total of 234 IM from 12 studies, the weighted mean of the calculated dose adjustments was a reduction to 51% (range 15%-95%, median 44%) (Rau 2009, Goryachkina 2008, Jin 2008, Ismail 2006, Fux 2005, Nozawa 2005, Terra 2005, Zineh 2004, Taguchi 2003, Rau 2002, Huang 1999, and Koytchev 1998). This was rounded off to 50% to be more achievable in clinical practice. This value corresponds well to the calculated value of 48% based on the median plasma concentration for 112 IM (Batty 2014).

UM: In order to achieve a plasma concentration comparable to that of NM, the dose for UM must be increased to 250% of the normal dose. For a total of 35 UM from 5 studies, the weighted mean of the calculated dose adjustments was an increase to 247% (range 166%-468%, median 219%) (Goryachkina 2008, Seeringer 2008, Ismail 2006, Fux 2005, and Kirchheiner 2004,). This was rounded off to 250% to be more achievable in clinical practice. However, a dose increase that exceeds the maximum registered dose can cause problems if the metabolites can cause side effects. Furthermore, the maximum dose of metoprolol for many indications is higher than or equal to the dose of 200 mg/day at which a good reduction in heart rate was observed. Therefore, we recommend the use of the maximum dose for the relevant indication for UM.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting metoprolol to be potentially beneficial for the prevention of side effects and drug effectiveness. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 0 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):
Severe clinical effects were only observed in UM in the study of Goryachkina 2008. The percentage UM in the group with a disruption of the ventricular rhythm was 11 times higher than in the group without disruption (22% versus 2%). However, the metoprolol concentration did not differ significantly between the groups with and without disruption, arguing against a causative role of the UM phenotype. For this reason, this severity code D (CTCAE grade 3) was ignored for the clinical implication score. No other severe clinical effects were observed (maximum severity code C, corresponding to CTCAE grade 2). This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).
The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 (only points for at least one study showing an association with a clinical effect grade ≥ 3) and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG < 1000).
The Dutch Summaries of Product Characteristics (SmPCs) Selokeen 13-5-2021 (metoprolol for injection) and Metoprololtartraat Mylan 15-6-2021 (metoprolol tablets) do not mention any variant CYP2D6 genotype/phenotype. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points for at least one genotype/phenotype mentioned in the SmPC).

The table below uses the KNMP nomenclature for NM, PM, IM and UM. As a result, the definitions of NM, PM, IM and UM in the table below can 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
Chen J et al. Impact of the CYP2D6 genotype on metoprolol tolerance and adverse events in elderly Chinese patients with cardiovascular diseases. Front Pharmacol 2022;13:876392. PMID: 35462926.</td><td>3

IM: C</td><td>1036 patients with cardiovascular diseases aged ≥ 60 years (mean 74 years) were treated with metoprolol for 12 weeks.
The metoprolol maintenance dose was defined as the dose at 12 weeks if metoprolol was not discontinued.
Comedication with CYP2D6 inhibitors, other antihypertensives and other antiarrhythmic drugs was not excluded. Patients with moderate or severe liver and renal diseases were excluded.
ORs were determined by logistic regression and adjusted for gender, Age-Adjusted Charlson Comorbidity Index (ACCI), the number of concomitant drugs, and categories of metoprolol initial doses.

Genotyping:
- 651x NM
- 381x IM

Results:
<table>
<tr><td colspan="3">Results compared to NM:</td></tr>
<tr><td></td><td>IM</td><td>value for NM</td></tr>
<tr><td>% of patients discontinuing metoprolol due to intolerance</td><td>x 1.5 (S)</td><td>8.3%</td></tr>
<tr><td colspan="3">% of patients with adverse events</td></tr>
<tr><td>all adverse events</td><td>OR_{adj} = 1.37 (95% CI: 1.05-1.79) (S)</td><td>48.4%</td></tr>
<tr><td>cardiovascular adverse events</td><td>OR_{adj} = 1.60 (95% CI: 1.22-2.09) (S)</td><td>38.2%</td></tr>
<tr><td>postural hypotension</td><td>x 1.8 (S)</td><td>6.0%</td></tr>
<tr><td>bradycardia (< 55 bpm)</td><td>x 1.3 (S)</td><td>21.5%</td></tr>
<tr><td>asystole</td><td>x 3.9 (S)</td><td>0.8%</td></tr>
<tr><td>second- or third-degree atrioventricular block</td><td>Trend for an increase (p = 0.101) (NS).</td><td>11.4%</td></tr>
<tr><td>syncope</td><td>x 3.1 (S)</td><td>2.0%</td></tr>
</table></td><td>Authors' conclusion:
'We conclude that IMs have lower tolerance and higher incidence of metoprolol-related adverse events than NMs in elderly Chinese patients with cardiovascular diseases. CYP-2D6 genotyping is justifiable in elderly patients to minimize the risk of adverse events and ensure the benefits of metoprolol.'</td></tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td></td>
<td>
<table>
<tr><td>cold extremities</td><td>NS</td><td>9.2%</td></tr>
<tr><td>non-cardiovascular adverse events</td><td>NS</td><td>17.8%</td></tr>
<tr><td>dyspnoea</td><td>NS</td><td>8.8%</td></tr>
<tr><td>sleep disturbances + fatigue</td><td>NS</td><td>3.5%</td></tr>
<tr><td>headache or dizziness</td><td>Trend for a decrease (p = 0.092) (NS).</td><td>5.5%</td></tr>
<tr><td>depression</td><td>NS</td><td>2.6%</td></tr>
<tr><td colspan="3">Maintenance daily dose (median value without and mean value with correction for body weight) in patients with different initial metoprolol doses</td></tr>
</table>
<table>
<tr><td></td><td>initial dose</td><td></td><td></td></tr>
<tr><td rowspan="10">maintenance dose</td><td rowspan="2">all</td><td>x 0.50 (S)</td><td>50 mg</td></tr>
<tr><td>x 0.81 (S)</td><td>0.52 mg/kg</td></tr>
<tr><td rowspan="2">≤ 12.5 mg</td><td>NS</td><td>12.5 mg</td></tr>
<tr><td>NS</td><td>0.35 mg/kg</td></tr>
<tr><td rowspan="2">18.75-25 mg</td><td>x 1.00 (S)[a]</td><td>25 mg</td></tr>
<tr><td>x 0.70 (S)</td><td>0.44 mg/kg</td></tr>
<tr><td rowspan="2">31.25-50 mg</td><td>x 1.00 (S)[a]</td><td>50 mg</td></tr>
<tr><td>x 0.84 (S)</td><td>0.57 mg/kg</td></tr>
<tr><td rowspan="2">> 50mg</td><td>x 1.00 (S)[a]</td><td>50 mg</td></tr>
<tr><td>x 0.71 (S)</td><td>0.73 mg/kg</td></tr>
<tr><td></td><td></td><td colspan="2">[a] NMs and IMs have the same median values but different distribution shapes of maintenance doses. In Mann–Whitney U test, NMs have higher mean rank than IMs, leading to the statistical significance between two groups.</td></tr>
</table>

Note: Genotyping was performed for *2, *5, *10, and *14. These are the most important gene variants in this Chinese population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Meloche M et al. Leveraging large observational studies to discover genetic determinants of drug concentrations: a proof-of-concept study.
Clin Transl Sci 2022;15:1063-73.
PMID: 35122397.</td>
<td>4

PM: A
IM: A
UM: A</td>
<td>996 patients were treated with metoprolol (mean dose 84.3 mg/day (range 6.25-400 mg/day).
Plasma samples were collected at random timepoints relative to the previous metoprolol dose.
Relevant comedication was not excluded, but all models corrected for CYP2D6 inhibitors. 3.6% of patients used either one or more moderate and/or strong CYP2D6 inhibitors.
Multiple linear regression analysis was used to investigate associations.

Genotyping:
- 68x UM+gene dose 2.5
- 542x NM
- 342x IM
- 44x PM

Results:
<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>UM+ gene dose 2.5</td><td>value for NM</td></tr>
<tr><td rowspan="2">resting heart rate</td><td colspan="3">Increase with increasing CYP2D6 gene dose (S, both without adjustment and with adjustment for age, female sex, metoprolol dose, weight, atrial flutter or atrial fibrillation, heart rate-lowering drugs, and CYP2D6 inhibitors).</td><td rowspan="2">approx 64 bpm</td></tr>
<tr><td colspan="3">Mean resting heart rate was slightly below 60 ppm for PM and between 60 and 70 ppm</td></tr>
</table>
</td>
<td>Authors' conclusion:
'CYP2D6-inferred phenotype was significantly associated with both metoprolol and α-OH-metoprolol in unadjusted and adjusted models. Models for meto prolol daily dose showed consistent results.'</td>
</tr>
</table>

<table>
<tr><td>ref. 2, continuation</td><td></td><td>
<table>
<tr><td></td><td colspan="4">for the other phenotypes.</td><td></td></tr>
<tr><td rowspan="2">daily metoprolol dose</td><td>x 0.91</td><td>x 0.85</td><td>x 1.08</td><td rowspan="2">88.6 mg</td></tr>
<tr><td colspan="3">S for the comparison between the phenotypes, both without adjustment and with adjustment for age, female sex, weight, and CYP2D6 inhibitors.</td></tr>
<tr><td rowspan="3">metoprolol plasma concentration</td><td>x 2.67</td><td>x 1.50</td><td>x 0.82</td><td rowspan="3">101 ng/ml</td></tr>
<tr><td colspan="3">S for the comparison between the phenotypes, both without adjustment and with adjustment for age, female sex, metoprolol dose, weight, and CYP2D6 inhibitors.</td></tr>
<tr><td colspan="3">Adjustment for the metoprolol dose increased the association.</td></tr>
<tr><td rowspan="2">α-hydroxymetoprolol plasma concentration</td><td>x 0.05</td><td>x 0.31</td><td>x 1.24</td><td rowspan="2">52.2 ng/ml</td></tr>
<tr><td colspan="3">S for the comparison between the phenotypes, both without adjustment and with adjustment for age, female sex, metoprolol dose, weight, and CYP2D6 inhibitors.</td></tr>
</table>

Note: Genotyping was performed for *2 through *12, *14, *15, *17, *19, *20, *29, *41, *69, *109 and gene multiplication. These are the most important gene variants in this Canadian population.
</td><td></td></tr>
<tr><td>ref. 3
Meloche M et al. CYP2D6 polymorphism and its impact on the clinical response to metoprolol: a systematic review and meta-analysis.
Br J Clin Pharmacol 2020;86:1015-33.
PMID: 32090368.</td><td>3</td><td>Meta-analyses of 11 studies investigating the effect of CYP2D6 phenotype on clinical effects of metoprolol in patients (10 studies) or healthy volunteers (1 study).
If articles translated genotypes to phenotypes, the genotype-phenotype translation of the article was used. Otherwise, genotypes were translated to phenotypes according to the KNMP Pharmacogenetics Working Group.
The meta-analysis of heart rate reduction was based on 4 titrated dose studies in patients with a total of 686 non-PM and 35 PM and 1 fixed-dose study in healthy volunteers with 25 non-PM and 4 PM.
The meta-analyses of blood pressure reduction were based on 4 titrated dose studies in patients with a total of 686 non-PM and 35 PM (the same titrated dose studies as in the heart rate reduction meta-analysis) and 1 fixed-dose study in patients with 78 non-PM and 43 PM.
The meta-analysis of adverse events was based on 3 studies in patients with a total of 324 non-PM and 32 PM.
The meta-analysis of bradycardia (< 60 bpm) was based on 4 studies in patients with a total of 594 non-PM and 49 PM.
The meta-analysis of daily metoprolol dose was based on 8 studies in patients with a total of 728 non-PM and 81 PM.
Of the 11 studies in these meta-analyses, 9 were also included in this risk analysis separately (Batty 2014, Hamadeh 2014, Yuan 2008, Fux 2005, Terra 2005, Kirchheiner 2004, Zineh 2004, Rau 2002, Wuttke 2002). This concerns 4 of the 5 studies for heart rate reduction, 4 of the 5 studies for blood pressure reduction, 2 of the 3 studies for adverse events, 3 of the 4 studies for bradycardia (< 60 bpm), and 6 of the 8 studies for metoprolol daily dose.
Meta-analyses were performed with a random-effects model, but prospective registration of the protocol was not mentioned. The search and selection strategy was transparent and data extraction was standardised.
Quality of the included studies and risk of bias was judged using the following quality components: study design, randomisation, appropriateness of group comparisons, baseline characteristics,</td><td>Authors' conclusion:
'Patients without any CYP2D6 metabolic capacities appear to have increased reduction in diastolic blood pressure, heart rate and systolic blood pressure during metoprolol treatment and may be at a higher risk of bradycardia compared to patients with active CYP2D6 phenotypes. Further prospective data are required to determine whether CYP2D6 is associated with clinical events in patients treated with metoprolol, as well as to demonstrate the clinical utility of an individualized approach of prescribing metoprolol using</td></tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>PM: A

IM: A
UM: AA</td>
<td>
patients' diseases and medications, dosing regimens and concomitant medications, and genotype-phenotype translation. However, the results were not reported and studies were not excluded based on these results.
Publication bias was not analysed.

Results:
<table>
<tr><td colspan="2">Results for PM compared to non-PM:</td></tr>
<tr><td rowspan="3">resting heart rate reduction</td><td>mean difference (MD) = 3.16 (95% CI: 0.94-5.37) (S)</td></tr>
<tr><td>The result was also significant for the titrated-dose studies in patients only: MD = 3.1 (95% CI: 0.1-6.1) (S).</td></tr>
<tr><td>Pairwise comparison with NM showed a significant difference for PM (S), but not for IM and UM (NS).</td></tr>
<tr><td rowspan="4">systolic blood pressure reduction</td><td>mean difference (MD) = 2.88 (95% CI: 1.47-4.29) (S)</td></tr>
<tr><td>The result was also significant for the titrated-dose studies only: MD = 2.7 (95% CI: 0.5-4.9) (S).</td></tr>
<tr><td>Pairwise comparison with NM showed a significant difference for PM (MD = 4.15 (95% CI: 0.18-8.12) (S)), but not for IM and UM (NS).</td></tr>
<tr><td>Only a trend (p = 0.093) was found for PM compared to non-PM if the meta-analysis was performed with the DerSimonian-Laird method instead of the Hartung-Knapp method.</td></tr>
<tr><td rowspan="3">diastolic blood pressure reduction</td><td>mean difference (MD) = 2.93 (95% CI: 1.53-4.32) (S)</td></tr>
<tr><td>The result was also significant for the titrated-dose studies only: MD = 2.5 (95% CI: 0.7-4.3) (S).</td></tr>
<tr><td>Pairwise comparison with NM showed a significant difference for PM and IM (S), but not for UM (NS).</td></tr>
<tr><td rowspan="3">adverse events</td><td>NS for the OR</td></tr>
<tr><td>31% of the non-PM had an adverse event.</td></tr>
<tr><td>Pairwise comparison with NM also showed no significant difference for PM and IM (NS).</td></tr>
<tr><td rowspan="4">bradycardia (< 60 bpm)</td><td>OR = 3.70 (95% CI: 1.12-12.50) (S)</td></tr>
<tr><td>32% of the non-PM and 55% of the PM had bradycardia (< 60 bpm).</td></tr>
<tr><td>The effect was more important in the 2 smaller studies (with 24 and 88 patients, respectively), as opposed to the 2 larger studies (with 218 and 313 patients, respectively).</td></tr>
<tr><td>Pairwise comparison with NM showed a significant difference for IM (OR = 1.61 (95% CI: 1.04-2.51) (S)), but not for PM (NS).</td></tr>
<tr><td rowspan="2">metoprolol daily dose</td><td>NS for the mean difference (MD)</td></tr>
<tr><td>Pairwise comparison showed all phenotypes to have similar doses (NS).</td></tr>
<tr><td colspan="2">Heterogeneity between the studies was high and significant for the following endpoint:
- bradycardia (< 60 bpm)

Heterogeneity between the studies was low and not significant for the following endpoint:
- daily metoprolol dose

Heterogeneity between the studies was absent for the following endpoints:
- heart rate reduction
- blood pressure reduction</td></tr>
</table>
</td>
<td>CYP2D6-inferred phenotypes..’</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>- adverse events</td><td></td></tr>
<tr><td>ref. 4
Chen L et al.
The association of ADRB1 and CYP2D6 polymorphisms with antihypertensive effects and analysis of their contribution to hypertension risk.
Am J Med Sci 2018;355:235-9.
PMID: 29549925.</td><td>4

IM: AA</td><td>261 patients with essential hypertension were treated with metoprolol (25 mg direct release metoprolol twice a day or 40.5 mg sustained release metoprolol tartrate once a day) for 12 weeks. Comedication with effect on metoprolol treatment and comorbidity owing to liver or kidney disease was excluded.

Genotyping:
- 40x *1/*1
- 116x *1/*10
- 105x *10/*10

Results:<table><tr><td colspan="2">Results for *10/*10 versus *1/*10 versus *10/*10:</td></tr><tr><td>blood pressure changes</td><td>NS</td></tr></table>
Note: Genotyping was performed for *10. This is the most important gene variant in this Chinese population.</td><td>Authors’ conclusion:
‘The effects of CYP2D6 polymorphism on responses to metoprolol were not statistically significant in our study.’</td></tr>
<tr><td>ref. 5
Gao X et al.
Impact of CYP-2D6 and ADRB1 polymorphisms on heart rate of post-PCI patients treated with metoprolol.
Pharmacogenomics 2017 Nov 2 (online ahead of print).
PMID: 29095089.</td><td>3

IM: AA#</td><td>Percutaneous coronary intervention was performed in 319 patients treated with sustained release metoprolol tartrate once a day (9 patients on a dose of 11.88 mg, 230 patients on a dose of 23.75 mg and 80 patients on a dose of 47.5 mg) and resting heart rate was measured at least 24h after taking metoprolol. The target heart rate was defined as < 70 bpm.
Comedication with drugs affecting the cardiac conduction system such as antidepressants, calcium channel antagonists, amiodarone, digoxin, ivabradine or other beta-blockers was excluded, but CYP2D6 inhibitors were not. Neither was adjusted for CYP-2D6 inhibitors in multivariate logistic regression analysis.

Genotyping:
- 61x *1/*1
- 151x *1/*10
- 107x *10/*10

Results:<table><tr><td colspan="5">Results for *10/*10 versus *1/*10 versus *1/*1:</td></tr><tr><td colspan="2"></td><td>*10/*10</td><td>*1/*10</td><td>value for *1/*1</td></tr><tr><td colspan="2">% of patients with a resting heart rate < 70 bpm</td><td>x 2.9
S for *10/*10 versus *1/*10 versus *1/*1
OR = 7.2 (95% CI: 3.5-14.7) (S) compared to *1/*1 in multivariate logistic regression analysis.</td><td>x 1.5
NS compared to *1/*1 in multivariate logistic regression analysis.</td><td>24.6%</td></tr><tr><td colspan="5">Resting heart rate in patients using different daily metoprolol doses</td></tr><tr><td></td><td>dose</td><td></td><td></td><td></td></tr><tr><td rowspan="8">resting heart rate</td><td rowspan="2">11.88 mg</td><td>x 0.92
S compared to *1/*1</td><td>x 1.00
NS compared to *1/*1</td><td rowspan="2">75.0 bpm</td></tr><tr><td rowspan="2">23.75 mg</td><td>x 0.92
S compared to *1/*1</td><td>x 0.99
NS compared to *1/*1</td><td rowspan="2">72.0 bpm</td></tr><tr><td rowspan="2">47.5 mg</td><td>x 0.84
S compared to *1/*1</td><td>x 0.94
NS compared to *1/*1</td><td rowspan="2">77.8 bpm</td></tr><tr><td rowspan="2"></td><td>S for *10/*10 versus *1/*10 versus *1/*1</td><td></td></tr><tr><td>There was no significant interac-</td><td></td></tr></table></td><td>Authors’ conclusion:
‘CYP2D6*10 polymorphisms were associated with the heart rate of post-percutaneous coronary intervention patients treated with metoprolol succinate sustained-release tablets.’</td></tr>
</table>

<table>
<tr><td>ref. 5, continuation</td><td></td><td>
<table>
<tr><td></td><td></td><td>tion between CYP2D6 and metoprolol dose (NS), indicating that the CYP2D6 effect was dose independent.</td><td></td></tr>
</table>

Note: Genotyping was performed for *10. This is the most important gene variant in this Chinese population.</td><td></td></tr>
<tr><td>ref. 6
Hamadeh IS et al.
Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate.
Clin Pharmacol Ther 2014;96:175-81.
PubMed PMID: 24637943.</td><td>3

PM: A
IM: A
UM: A</td><td>218 patients with uncomplicated hypertension received metoprolol for 8 weeks (initial dose 50 mg 2x per day for 2 weeks, followed by titration to 100 mg 2x per day based on response). Chronic use of medication with possible effect on blood pressure was excluded, but use of CYP2D6 inhibitors was not. Patients with a heart rate <55 beats/minute without use of a β-blocker, were excluded.

Genotyping:
- 184x NM + gene dose 1 or 0.75 (121x NM, 63x gene dose 1 or 0.75)
- 15x IM (gene dose 0.5 or 0.25)
- 11x PM
- 8x UM + gene dose 2.25 (7x UM, 1x gene dose 2.25)

Results:
<table>
<tr><td colspan="3">Decrease in the heart rate versus NM + gene dose 0.75-1 (-11.4 beats/minute)</td></tr>
<tr><td>PM</td><td>IM</td><td>UM + gene dose 2.25</td></tr>
<tr><td>x 1.46</td><td>x 1.63</td><td>x 0.98</td></tr>
<tr><td colspan="3">S for the trend and for PM+IM versus NM+UM+gene dose 1. CYP2D6 genotype was one of the most important predictors of the variability in heart rate response (S).</td></tr>
</table>
<table>
<tr><td>Incidence of clinical bradycardia (resting heart rate <60 beats/minute) versus NM + gene dose 0.75-1 (25% of the patients)</td></tr>
<tr><td>NS for the trend</td></tr>
</table>
<table>
<tr><td colspan="3">Incidence of symptomatic bradycardia versus NM + gene dose 0.75-1 (1.6% of the patients, n = 3)</td></tr>
<tr><td>PM</td><td>IM</td><td>UM + gene dose 2.25</td></tr>
<tr><td>x 5.6 (n=1)</td><td>x 0 (n=0)</td><td>x 0 (n=0)</td></tr>
<tr><td colspan="3">NS (significance not determined)</td></tr>
</table>
<table>
<tr><td>PM versus IM versus (NM + gene dose 0.75-1) versus (UM + gene dose 2.25):</td></tr>
<tr><td>no difference in:
- reduction in systolic blood pressure (NS)
- reduction in diastolic blood pressure (NS)
- daily dose (NS)
- occurrence of side effects (NS)</td></tr>
</table>

N.B.: Genotyping was performed for *2 to *4, *6, *10, *17, *41 and gene duplication.</td><td>Authors' conclusion:
'Other than a significant difference in heart rate response, CYP2D6 polymorphisms were not a determinant of the variability in response or tolerability to metoprolol.
……
In this well-powered, carefully genotyped study, there is no evidence for the clinical utility of CYP2D6 genotyping to guide metoprolol therapy.'</td></tr>
<tr><td>ref. 7
Batty JA et al.
An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: a MERIT-HF substudy.
Clin Pharmacol Ther</td><td>4</td><td>313 patients with heart failure (NYHA II-IV), left ventricular ejection fraction ≤ 0.4 and treated with optimum standard treatment received metoprolol controlled release 1x daily for an average of 339 days (200-555 days). Depending on the severity of the heart failure, the patient was started on a dose of 12.5 or 25 mg/day, after which the dose was increased fortnightly to a target value of 200 mg/day. CYP2D6 inhibitors/substrates and other medicines with β-blocker activity were excluded.

Genotyping:
- 189x NM
- 112x IM
- 12x PM

Results:</td><td>Authors' conclusion:
'Plasma metoprolol concentrations were 2.1-/4.6-fold greater in the IM/PM groups as compared with the NM group. Metoprolol induced significantly lower heart rates and diastolic blood</td></tr>
</table>

2014;95:321-30. PubMed PMID: 24193112. **ref. 7, continuation**	IM: A PM: A	Decrease in the heart rate versus NM at various times after the start of metoprolol Time point / IM / PM / Decrease for NM (in beats/minute) 2 weeks: NS / NS / -5.0 4 weeks: x 1.33 (S) / x 1.52 (S) / -7.9 6 weeks: x 1.36 (S) / x 1.51 (S) / -9.7 8 weeks: x 1.14 (S) / x 1.25 (S) / -13.7 3 months: NS / NS / -15.9 6 months: NS / NS / -16.4 first measurement after achieving maximum dose: x 1.16 (S) / x 1.32 (S) / -21.4 (= -25.9%) 8 weeks, per mg metoprolol: x 1.31 / x 1.46 / S for the trend / -0.13 beats per minute per mg The authors indicated that the disappearance of any difference after eight weeks was probably caused by saturation of the β-blockade at higher doses. However, there is a difference in the first measurement after achieving the maximum dose. Furthermore, the heart rate reduction is greater at this time than with prolonged use of the maximum dose. Risk of bradycardia (≤ 60 beats/minute) versus NM (37.6% of the patients) IM: OR = 1.72 (95% CI: 1.07-2.76) (S) / PM: NS Decrease in the diastolic blood pressure versus NM at various times after the start of metoprolol Time point / IM / PM / Decrease for NM (in mm Hg) 2 weeks: NS / x 2.68 (S) / -2.8 4 weeks: x 1.56 (S) / x 2.22 (S) / -3.2 6 weeks: NS / NS / -3.8 8 weeks: NS / NS / -5.3 3 months: x 2.25 (S) / x 3.21 (S) / -2.8 6 months: NS / NS / -2.8 first measurement after achieving maximum dose: x 1.17 (S) / x 1.46 (S) / -11.4 (= -14.4%) PM versus NM and IM versus NM: no difference in: - reduction in systolic blood pressure (NS) - the risk of premature discontinuation of metoprolol (NS) - the risk of death and hospital admission (NS) - the risk of a side effect or disease symptom (NS) - the dose of metoprolol at any time point (NS) - the percentage of patients that achieved the target dose of 200 mg/day (NS) - the percentage IM and PM in the group that tolerated a dose of ≥ 100 mg/day and in the group that tolerated a dose <100 mg/day (NS; data from a previous study) Median plasma concentration[b] of S-metoprolol after 3 months versus NM IM: x 2.1 / PM: x 4.5 S for the trend. N.B.: Genotyping was performed for *4. Similar results were	pressures during early titration, indicating a CYP2D6 *4 allele dose-response effect. These effects were not observed at maximal dose, suggesting a saturable effect. Genotype did not adversely affect surrogate treatment efficacy.' Median C_{ss} S-metoprolol versus NM: PM: 450% IM: 210%

ref. 7, continuation		found if patients were categorised as NM, IM and PM based on the plasma concentration of *S*-metoprolol.	
ref. 8 Rau T et al. Impact of the CYP2D6 genotype on the clinical effects of metoprolol: a prospective longitudinal study. Clin Pharmacol Ther 2009;85:269-72.	4 PM: A PM: AA[#] IM: A	88 patients, 17x PM, 8x IM, 63x NM, of which 95% with arterial hypertension, dose of metoprolol retard based on clinical effect and double blind for genotype, over a period of 90 days. Screened for *3, *4, *5, *6, *10, *41 and duplication. Co-medication: no CYP2D6 inhibitors and no differences between PMs and NMs+IMs. PM versus NM+IM: - increase in the median C_{ss} from 14.2 to 69.6 ng/mL (S by 390%). - no difference in initial dose of metoprolol (median 47.5 mg/day). - less frequent dose increase during the study (6% versus 20% of the patients, S). - increase in the reduction of HR from 9.1 to 14.9 beats/min (S by 64%). - increase in the percentage of patients with bradycardia in all ECGs (4, 14 and 90 days after start of metoprolol) from 8% to 59% (RR = 7; 95% CI 2.9-16.4). - no difference in the QTc interval (NS). - no difference in the reduction of SBP (NS). - increase in the reduction of DBP from 3.6 to 10.3 mmHg (S by 186%). - increase in the reduction of the arterial blood pressure from 5.2 to 11.1 mmHg (S by 113%). - the percentage of patients that achieved the target value for blood pressure (135/85 mmHg) during the treatment increased from 28% to 58% (S by 107%). - no significant increase in the percentage of patients with one or more side effects (NS). PM versus IM versus NM: - mean C_{ss}: 85.5 versus 36.6 versus 15.3 ng/mL (S). - decrease in HR: 14.9 versus 10.7 versus 8.9 beats/min (S for the trend). - decrease in DBP: 10.23 versus 4.7 versus 3.5 mmHg (S for the trend).	Authors' conclusion: 'Metoprolol evoked significantly and persistently greater reductions in heart rate, diastolic blood pressure, and mean arterial pressure in PMs than in non-PMs.' C_{ss} versus NM: PM: 559% IM: 239%
ref. 9 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: A	Heart rate was determined in 740 users of metoprolol (451x *1/*1, 255x *1/*4 and 34x *4/*4) and DBP in 809 users (496x *1/*1, 276x *1/*4 and 37x *4/*4). Screening was performed for the most common variant allele: *4. Co-medication with CYP2D6 inhibitors was not excluded, but sporadic. PM versus NM: - HR is 8.5 beats/min lower (S; 95% CI 4.3-12.8). This was 7.1 beats/min after exclusion of 56 people with atrial fibrillation (S). - reduction in the dose by CYP2D6-metabolised β-blockers (of which 88% metoprolol) from 0.48 to 0.38 standard daily doses (S by 21%). - increased risk of bradycardia: OR = 3.86 (S; 95% CI 1.68-8.86). The OR was 2.94 after exclusion of 56 people with atrial fibrillation (S). - HR reduction in people who started metoprolol (n=12) is 7.3 beats/min greater (S; 95% CI 1.2-13.4). - no significant difference in change of blood pressure after discontinuation of metoprolol (n=7) (NS). - no difference in SBP (NS). - DBP is 4.8 mmHg lower (S; 95% CI 0.1-9.4). - DBP reduction in people who started metoprolol (n=14) is non-significantly greater (NS). IM versus NM: - HR is 2.5 beats/min lower (S; 95% CI 0.55-4.43). This was	Authors' conclusion: 'In CYP2D6*4/*4 PMs, the adjusted heart rate in metoprolol users was 8.5 beats/min lower compared with *1/*1 NMs, leading to an increased risk of bradycardia in PMs.'

ref. 9, continuation	IM: AA	2.3 beats/min after exclusion of 56 people with atrial fibrillation (S). - no increase in the risk of bradycardia (NS). - HR reduction in people who started metoprolol (n=72) is non-significantly greater (NS). - no significant difference in change of blood pressure after discontinuation of metoprolol (n=49) (NS). - no difference in SBP (NS). - no difference in DBP (NS). The authors concluded that dose adjustment based on antihypertensive effect is not performed correctly in practice, as PMs had a lower HR and higher risk of bradycardia after dose adjustment. Co-administration of CYP2D6 inhibitors did not influence the results.	
ref. 10 Goryachkina K et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. Eur J Clin Pharmacol 2008;64:1163-73.	4 IM: A PM: A UM: D	181 patients with recent acute myocardial infarction, 3x PM (*4/*4), 58x IM (50x *1/*4, 4x *4/*10, 2x *1/*3, 1x *10/*10, 1x *3/*10), 113x NM (110x *1/*1, 3x *1/*10), 7x UM, screened for *3, *4, *10 and gene duplication, of which 141 were using metoprolol (90% immediate release; 10% retard), dose of metoprolol based on clinical effect (mean 0.6 mg/kg in PM and 0.9 mg/kg in the other phenotypes (NS)), no CYP2D6 inhibitors as comedication. Pharmacokinetics were determined in 110 patients (2x PM, 32x IM, 71x NM, 5x UM). Patient 111 (genotypically IM (*1/*4), phenotypically PM) was not included in the analysis. PM versus IM versus NM versus UM: - HR upon discharge (15-20 days after admission): 53 versus 61 versus 62 versus 69 beats/min (S). - median AUC[b] metoprolol: 5185 versus 905 versus 559 versus 336 nM.h.kg/mg (S). - median MR AUC metoprolol/HM: 1031 versus 1.3 versus 0.5 versus 0.4 (S). - median trough concentration metoprolol[b]: 222 versus 33 versus 11 versus 18 nM/mg per kg (S). The trough concentration could only be measured in IM and PM and was estimated in NM and UM. - median resting HR: 58 versus 68 versus 70 versus 73 beats/min (S). - median AUEC (in relation to HR): no significant increase with the gene dose (NS). PM: - most pronounced bradycardia upon discharge from the hospital. UM: - almost no therapeutic effect achieved. HR decreased from average 78 to 69 beats/min after start metoprolol. - increased prevalence in group with disruptions to the ventricular rhythm (n=23) (from 2% to 22%; S by 1000%). This causes an increase in the median number of active CYP2D6 alleles in this group from 1.6 to 2.1 (S). The metoprolol concentration does not differ significantly between both groups. The authors indicate that a significant number of patients did not achieve effective concentrations of metoprolol (30-500 nM) and that underdosage appeared to have occurred in this study.	Authors' conclusion: 'Metoprolol disposition and effects are mainly controlled by CYP2D6 genotype. Patients with gene duplication are at high risk of not benefiting from treatment due to lower metoprolol concentrations. Higher CYP2D6 activity seems to be associated with VRDs complicating AMI, being a negative prognostic factor for patients' survival.' AUC[b] versus NM: PM: 928% IM: 162% UM: 60%
ref. 11 Yuan H et al. Effects of polymorphism of the beta(1) adrenoreceptor and CYP2D6 on the	3	276 patients with essential hypertension, screened for *2, *5 and *10, patients randomised to metoprolol dose 100 mg/day for all phenotypes (60x PM+IM (1x *5/*5, 3x *5/*10, 56x *10/*10), 43x IM+NM (10x *1/*5, 18x *1/*10, 15x *2/*10)), 40x NM (21x *1/*1, 17x *1/*2, 2x *2/*2)) or 25 mg/day for PM+IM, 50 mg/day for IM+NM and 100 mg/day for NM (68x PM+IM (2x *5/*5, 6x *5/*10, 60x *10/*10), 27x IM+NM (5x *1/*5, 14x *1/*10, 8x *2/*10), 38x	Authors' conclusion: 'The same dose of metoprolol achieved different therapeutic effects in

therapeutic effects of metoprolol. J Int Med Res 2008;36:1354-62. **ref. 11, continuation**	PM+IM: AA	NM (20x *1/*1, 16x *1/*2, 2x *2/*2)), for 8 weeks, CYP2D6 inhibitors were not excluded. PM+IM versus NM: *Genotype-independent dose:* - increase in the reduction of SBP from 5.1 to 11.4 mmHg (S by 124%). - increase in the reduction of DBP from 4.4 to 8.9 mmHg (S by 102%). - no significant increase in the prevalence of effective blood pressure reduction (NS). *Genotype-dependent dose:* - no significant differences in reduction in SBP, DBP and prevalence of effective blood pressure reduction (NS). IM+NM versus NM: *Genotype-independent dose:* - increase in the reduction of SBP from 5.1 to 12.9 mmHg (S by 153%). - no significant increase in the decrease in DBP (NS). - no significant increase in the prevalence of effective blood pressure reduction (NS). *Genotype-dependent dose:* - no significant differences in reduction in SBP, DBP and prevalence of effective blood pressure reduction (NS).	patients with different CYP-2D6 and β_1 adrenoreceptor polymorphisms.'
ref. 12 Jin SK et al. Influence of CYP2D6*10 on the pharmacokinetics of metoprolol in healthy Korean volunteers. J Clin Pharm Ther 2008;33:567-73.	3 IM: A	18 healthy study subjects, 6x *1/*1, 7x *1/*10, 5x *10/*10, screened for *5 and *10, single dose of 100 mg metoprolol, no co-medication; *10/*10 versus *1/*1: - AUC increased from 443.7 to 2545.3 ng.h/mL (S by 474%) - $t_{1/2}$ increased from 2.7 to 5.0 hours (S by 85%). - increased concentration ratio metoprolol/HM (S). *1/*10 versus *1/*1: - no significant increase in AUC and $t_{1/2}$ (NS). *10/*10 versus NM (*1/*1 + *1/*10): - AUC increased from 740.9 to 2545.3 ng.h/mL (S by 244%). N.B.: *10 and *5 are the most common alleles in the Asian population.	AUC versus NM: IM: 344%
ref. 13 Seeringer A et al. Enantiospecific pharmacokinetics of metoprolol in CYP2D6 ultrarapid metabolizers and correlation with exercise-induced heart rate. Eur J Clin Pharmacol 2008;64:883-8.	3 PM: AA[#] UM: A	Enantiomer-selective analysis of the blood samples by Kirchheiner, 2004. 29 healthy study subjects, 4x PM (gene dose 0), 13x NM (8x gene dose 2, 5x gene dose 1.5 or 1.25), 12x UM (8x gene dose 3, 4x gene dose 2.5 or 2.25), screened for *2, *3, *4, *5, *6, *9, *10, *35, *41 and gene duplication, single dose of 100 mg metoprolol, no co-medication; PM versus NM: - AUC S-metoprolol increased from 365.9 to 1803.7 ng.h/mL (S for the trend gene dose, by 393%). - AUC R-metoprolol increased from 261.1 to 1746 ng.h/mL (S for the trend gene dose, by 569%). - decrease in the AUC ratio *S*-M/*R*-M from 1.5 to 1.0 (S for the trend PM, NM, UM; by 33%). - increase in concentration required for half-maximum reduction of exertion HR: S-metoprolol from 17 to 21 ng/mL (NS by 23%); R-metoprolol from 11 to 20 ng/mL (NS by 82%). - concentrations in PM close to concentrations that yield maximum effect, concentrations in NM still in the steep section of the dose-effect curve. UM versus NM: - AUC S-metoprolol decreased from 365.9 to 189.8 ng.h/mL (S	Authors' conclusion: 'A slight enantiopreference towards metabolism of R-metoprolol by CYP-2D6 was observed in NMs and even more in the UM group, but the effect was far from being enantioselective. Since S-metoprolol is the main active beta-blocking enantiomer, rapid and ultrarapid CYP2D6 metabolizers might profit from the enantiopre-

ref. 13, continuation		by 48%). - AUC R-metoprolol decreased from 261.1 to 126.8 ng.h/mL (S by 51%). - increase in the AUC ratio *S*-M/*R*-M from 1.5 to 1.6 (S for the trend PM, NM, UM; by 6.7%). - decrease in concentration required for half-maximum reduction of exertion HR: S-metoprolol from 17 to 11 ng/mL (NS by 35%); R-metoprolol from 11 to 7 ng/mL (NS by 36%). Due to the very strong correlation between the concentrations of *S*-M and *R*-M, it was not possible to perform a separate analysis of the β-blocking properties of both enantiomers.	ference of CYP-2D6 to metabolize the less active R-metoprolol, and indeed have a better concentration-response relationship, which then diminishes the loss of effect caused by rapid and ultra-rapid metabolism of metoprolol.' AUC S-metoprolol versus NM: PM: 493% UM: 52%
ref. 14 Ismail R et al. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. J Clin Pharm Ther 2006;31:99-109.	4 PM: AA IM: AA UM: A	91 patients with cardiovascular disease, 58x NM (17x *1/*1, 41x *1/*10), 29x IM (14x *10/*10, 3x *9/*10, 3x *1/*4, 1x *1/*5, 3x *4/*10, 5x *5/*10), 1x PM (*4/*4), 3x UM (2x *1/*1xn, 1x *1/*10xn), screened for *3, *4, *5, *8, *9, *10, *17 and duplication, dose of metoprolol based on clinical effect (50-400 mg/day; average 1.9 mg/kg), no CYPD6 inhibitors as co-medication. *10/*10 versus *1/*1: - increase in plasma concentration after 4 hours from 0.93 to 1.23 ng/mL per mg (NS by 32%). - decrease in Cl_{or} from 58.7 to 46.5 L/h (NS by 21%). PM versus NM: - increase in plasma concentration after 4 hours from 1.18 to 3.57 ng/mL per mg (NS by 203%). - increase in logarithm (concentration ratio metoprolol/HM) from -0.13 to 1.58 (NS). IM versus NM: - increase in plasma concentration after 4 hours from 1.18 to 1.24 ng/mL per mg (NS by 5%). - increase in logarithm (concentration ratio metoprolol/HM) from -0.13 to 0.15 (NS). UM versus NM: - decrease in plasma concentration after 4 hours from 1.18 to 0.35 ng/mL per mg (NS by 70%). - decrease in logarithm (concentration ratio metoprolol/HM) from -0.13 to -0.39 (S).	plasma concentration after 4 hours versus NM: PM: 303% IM: 105% UM: 30%
ref. 15 Terra SG et al. Beta1-adrenergic receptor polymorphisms and left ventricular remodeling changes in response to beta-blocker therapy. Clin Pharmacol Ther 2005;77:127-137.	4 PM: A IM: A	61 patients with heart failure, of which 51 were CYP2D6-genotyped, 4x PM, 10x IM (no fully functional allele, at least 1 reduced functional allele), 37x NM (at least 1 fully functional allele), screened for *2, *3, *4, *6, *9, *10, *17, *29 and *41 alleles, metoprolol retard initial dose 12.5-25 mg/day titrated up to max. 200 mg/day or tolerable dose, no CYP2D6 inhibitors as co-medication; *kinetic endpoint* - PM: increase in C_{ss} *S*-metoprolol from 14.93 to 53.09 ng/mL versus NM (S by 256%). - IM: increase in C_{ss} *S*-metoprolol from 14.93 to 22.90 ng/mL versus NM (S by 48%). *clinical endpoints* HR, SBP, final daily dose and the need to increase other medica-	Authors' conclusion: 'Thus…we do not have any evidence that S-metoprolol concentration contributes importantly to the tolerability of metoprolol.' C_{ss} S-metoprolol versus NM: PM: 356% IM: 148%

		tion differed non-significantly between the three phenotypes.	
ref. 16 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.	4 IM: A	72 patients (ischaemic heart disease, hypertension and atrial fibrillation) of which 38 metoprolol, 8x *10/*10, 17x *1/*10 of *2/*10, 13x no *10 (*1/*1, *1/*2 or *2/*2), dose of metoprolol based on clinical effect, 39-96 mg/day, no CYP2D6 inhibitors as co-medication; *kinetic endpoint* - *10/*10: increase in peak and trough concentrations versus 1x*10 and versus no *10 (both S). Increase in trough concentrations versus NM (1x*10 + no *10) from 14.2 to 45.5 ng/mL (S by 221%). - 1x *10: increase in peak and trough concentrations versus no *10 (NS by 51% and 25% respectively). *clinical endpoints* - *10/*10: change in HR following administration of β-agonist at the moment of trough concentration is significantly reduced versus no *10 and 1x *10. HR at peak concentration, SBP, DBP and dose of metoprolol differed non-significantly. N.B.: not measured enantioselectively.	C_{ss} versus NM: IM: 321%
ref. 17 Fux R et al. Impact of CYP-2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. Clin Pharmacol Ther 2005;78:378-87.	4 PM: A IM: A UM: A	121 patients, of which 90% with hypertension, 4x PM (0-0), 21x IM (0.5-0.5 or 0.5-0), 91x NM+IM (1-0, 1-0.5, 1-1) and 5x UM (duplication 1), with allele activity 1 = *1 or *2, 0.5 = *9, *10 or *41 and 0 = *3, *4, *5, *6, *7 or *8, dose of metoprolol based on clinical effect, no CYP2D6 inhibitors as co-medication; *kinetic endpoint* - PM: C_{ss}[a] increased from 0.047 to 1.34 ng/mL/mg versus NM+IM (S by 2762%). - IM: C_{ss}[a] increased from 0.047 to 0.34 ng/mL/mg versus NM+IM (S by 587%). - UM: C_{ss}[a] decreased from 0.047 to 0.0088 ng/mL/mg versus NM+IM (S by 79%). *clinical endpoints* - PM+IM: trend (NS) towards cold extremities being more common than in UM+NM, other side effects such as headache, dizziness, sleeping problems and fatigue were non-significantly more common. Sexual dysfunction was significantly less common than for UM+NM. SBP and DBP differed non-significantly from UM+NM. N.B.: not measured enantioselectively.	Authors' conclusion: 'CYP2D6 genotype-derived phenotype was not significantly associated with a propensity for adverse effects to develop during treatment with metoprolol. However, the results concerning tolerability of metopolol in PMs were inconclusive because of the small number of PMs enrolled.' C_{ss}[a] versus NM+IM: PM: 2862% IM: 687% UM: 21%
ref. 18 Zineh I et al. Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. Clin Pharmacol Ther 2004;76:536-44.	4 PM: A IM: A	50 patients with hypertension, 42x NM (24x high activity ≥1.75, 8x middle-high activity =1.5, 10x low activity 1-1.25) 4x IM (activity 0.5-0.75) and 4x PM (activity 0) (activity score is the sum of activity per allele, activity for *1 and *2 is 1, for *9, *29, *41, *45 and *46 is 0.75, for *10 and *17 is 0.5 and for *3, *4, *5 and *6 is activity 0), dose of metoprolol based on effect and adverse events, max. 400 mg/day, co-medication included CYP2D6 inhibitors (with 6x NM); *kinetic endpoints* - PM: increase in $AUC^{a}_{S\text{-}M}$ from 5.1 to 16.2 ng/mL/mg compared to NM high activity (S by 218%), t½ is 7.1 hours. Increase in $AUC^{a}_{S\text{-}M}$ from 5.5 to 16.2 ng/mL/mg compared to NM (high and medium-high activity) (NS by 196%). - IM (activity 0.5-0.75): increase in $AUC^{a}_{S\text{-}M}$ from 5.1 to 7.9 ng/mL/mg versus NM high activity (S by 55%), t½ is 5.3 hours.	Authors' conclusion: 'These data, therefore, provide no evidence for an association between variable pharmacokinetic drug exposure, adverse effects, or efficacy of metoprolol.'

ref. 18, continuation		- IM (activity 0.5-1): increase in AUC^{a}_{S-M} from 5.5 to 7.0 ng/mL/mg compared to NM (high and medium-high activity) (NS by 29%). - NM: AUC^{a}_{S-M} differed significantly between high, medium-high and low activity. *clinical endpoints* - PM: A total of 75% experienced general side effects, 0% dose-limiting side effects (both differed non-significantly from NM). The number of responders (≥ 10% decrease in DBP, 50%) and the dose differed non-significantly from NM. The prevalence of PM in the responder group is 4% (differs non-significantly from the prevalence in the non-responder group). - IM (activity 0.5-0.75): A total of 50% experienced general side effects, 25% dose-limiting side effects (both differed non-significantly from NM). - NM: A total of 43% experienced general side effects, 14% dose-limiting side effects. N.B.: registration of side effects by means of open interviews	AUC^{a} S-metoprolol versus NM:. PM: 296% IM: 129%
ref. 19 Kirchheiner J et al. Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2004;76:302-12.	3 PM: A UM: A	29 healthy study subjects, 4x PM (gene dose 0), 13x NM (8x gene dose 2, 5x gene dose 1.5 or 1.25), 12x UM (8x gene dose 3, 4x gene dose 2.5 or 2.25), screened for *3, *4, *5, *6, *9 and *10, single dose of 100 mg metoprolol, no co-medication; *kinetic endpoints* - PM: increase in AUC from 595.6 to 3249.0 µg.h/L versus NM (S by 446%), t½ is 7.6 hours. - UM: decrease in AUC from 595.6 to 272.5 µg.h/L versus NM (S by 54%), t½ is 2.8 hours. *clinical endpoints* - PM: resting HR decreased by 21% more than for NM (S). Decrease in SBP and DBP and AUC for exertion HR differed non-significantly from NM. - UM: resting HR decreased by 14.3% less than for NM (S). Decrease in SBP and DBP and AUC for exertion HR differed non-significantly from NM. N.B.: not measured enantio-selectively.	Authors' conclusion: 'Pharmacodynamic differences between UMs and NMs were by far not as large as differences in pharmacokinetic parameters. Neither CYP 2D6 genotype nor metoprolol plasma concentrations significantly correlated with blood pressure in the healthy volunteers.' AUC versus NM: PM: 546% UM: 46%
ref. 20 Taguchi M et al. Effect of CYP-2D6*10 on pharmacokinetic variability of routinely administered metoprolol in middle-aged and elderly Japanese patients. Eur J Clin Pharmacol 2003;59:385-8.	4 IM: A	34 patients, 9x *1/*1, 5x *1/*2, 7x *1/*10, 6x *2/*10, 7x *10/*10, metoprolol 40-120 mg/day, no CYP2D6 inhibitors as co-medication; - for *10/*10 the Cl_{or} is reduced by 60.4% compared to *1/*1 + *1/*2 and by 52.0% compared to *1/*10 + *2/*10 (both S). Cl_{or} is reduced by 57.0% compared to NM (*1/*1 + *1/*2 + *1/*10 + *2/*10) (S). N.B.: indication for metoprolol is not mentioned	Cl_{or} versus NM: IM: 43.0%
ref. 21 Wuttke H et al. Increased frequency of cytochrome P450 2D6 poor metabolizers among	4	24 patients with specific (bradycardia, AV-block) and non-specific (nausea, dizziness, fatigue) severe, unexpected adverse events within 2 weeks after start of metoprolol, 9x PM (*3/*4, *4/*4, *4/*5, *4/*6 and *5/*5), 1x *41/*4, 2x *1/*4, 1x *1/*5, 1x *2/*3, 2x *2/*4, 4x *1/*41, 2x *1/*2 and 2x *1/*1, no CYP2D6 inhibitors as co-medication;	Authors' conclusion: 'An obvious clinical recommendation as a result of this and former studies is

patients with metoprolol-associated adverse effects. Clin Pharmacol Ther 2002;72:429-37. **ref. 21, continuation**	PM: C	The prevalence of the PM genotype was 38% within the group with side effects and is a factor 5 higher than in the general population.	the initiation of metoprolol at low doses to avoid overdosage in the 7% of poor metabolizers in the population or the use of a CYP-2D6-independent β-blocker.'
ref. 22 Rau T et al. Effect of the CYP2D6 genotype on metoprolol metabolism persists during long-term treatment. Pharmacogenetics 2002;12:465-72.	4 PM: A IM: A	91 patients (hypertension, ischaemic heart disease, heart failure), 8x PM (0-0), 9x 0.5-0, 1x 0.5-0.5, 21x 1-0, 21x 1-0.5, 31x 1-1 (0 = *3, *4, *6, 0.5 = *9, *10, *41, 1 = *1, *2), 7 patients excluded due to co-medication or therapy non-compliance, dose of metoprolol retard based on clinical effect, mean 47.5 mg/day, no CYP2D6 inhibitors as co-medication; - PM: increase in $C_{ss}{}^{b}$ from 13.3 to 82.0 ng/mL versus 1-1 (S by 517%). Increase in $C_{ss}{}^{b}$ from 14.2 to 82.0 ng/mL versus NM (1-1 + 1-0.5) (NS by 476%). - 0.5-0 + 0.5-0.5: increase in $C_{ss}{}^{b}$ from 13.3 to 51.8 ng/mL versus 1-1 (S by 290%). - 1-0 + 1-0.5: increase in $C_{ss}{}^{b}$ from 13.3 to 20.3 ng/mL versus 1-1 (NS by 53%). - IM (0.5-0 + 0.5-0.5 + 1-0): increase in $C_{ss}{}^{b}$ from 14.2 to 30.8 ng/mL versus NM (1-1 + 1-0.5) (NS by 116%). N.B.: not measured enantioselectively.	Authors' conclusion: 'This study demonstrated that the CYP2D6-genotype remains a major determinant of metoprolol plasma concentrations during long-term therapy.' 'Yet, at present, neither the relative risks of the CYP2D6 genotype subgroups nor the absolute frequency of adverse effects are known.' $C_{ss}{}^{b}$ versus NM: PM: 576%. IM: 216%
ref. 23 Huang JD et al. Pharmacokinetics of metoprolol enantiomers in Chinese subjects of major CYP2D6 genotypes. Clin Pharmacol Ther 1999;65:402-7.	3 IM: A	40 healthy study subjects, 6x *1/*1, 10x *1/*10, 12x *10/*10, single dose of 100 mg metoprolol, no co-medication; values for S-metoprolol - *10/*10: increase in AUC from 1411 to 3588 nM.h versus *1/*1+*1/*2 (S by 154%), t½ is 5.2 hours, AUC ratio S-M/R-M is 1.26. Increase in AUC from 1620 to 3588 nM.h versus NM (*1/*1+*1/*2+*1/*10) (NS by 121%). - *1/*10: increase in AUC from 1411 to 1899 nM.h versus *1/*1+*1/*2 (S by 35%), t½ is 4.1 hours, AUC ratio S-M/R-M is 1.46.	AUC S-metoprolol versus NM: IM: 221%
ref. 24 Koytchev R et al. Influence of the cytochrome P450 2D6*4 allele on the pharmacokinetics of controlled-release metoprolol. Eur J Clin Pharmacol 1998;54:469-74.	4 IM: A	22 healthy study subjects, 6x *1/*4, 16x *1/*1, metoprolol retard 200 mg/day, no co-medication; *kinetic endpoints* - *1/*4: increase in AUC compared to *1/*1 from 1820 to 4438 ng/mL.h (S by 144%), t½ is 7.2 hours. *clinical endpoints* - *1/*4: decrease in the HR is 185.4% greater than for NM (S). The decrease for *1/*4 is 11.7 beats/minute. Change in SBP and DBP is greater but NS. N.B.: not measured enantio-selectively.	AUC versus NM: IM: 244%
ref. 25 Laurent-Kenesi MA et al. Influence of CYP2D6-dependent metabolism	4	14 healthy subjects, 7x PM and 7x NM# (phenotyped using dextromethorphan), metoprolol 100 mg twice daily; *kinetic endpoints* - PM: increase in C_{ss} from 36 to 185 ng/mL (S by 414%) versus NM and ratio S-/R-M is 1.23 and reduced by 30% (S).	C_{ss} metoprolol versus NM+IM+UM:

on the steady-state pharmacokinetics and pharmacodynamics of metoprolol and nicardipine, alone and in combination. Br J Clin Pharmacol 1993;36:531-8.	PM: B	*clinical endpoints* - PM: Resting HR, SBP and DBP differed non-significantly from NM. Decrease in exertion tachycardia was 40.4% greater (S), decrease in SBP with exertion was 185.7% greater (S) N.B.: genotype not known. Phenotyping can only distinguish between PM and the other phenotypes, so NM# is equal to NM+IM+UM.	PM: 514%
ref. 26 Lewis RV et al. Influence of debrisoquine oxidation phenotype on exercise tolerance and subjective fatigue after metoprolol and at-nolol in healthy subjects. Br J Clin Pharmacol 1991 ;31:391-8.	3 PM: AA	12 healthy subjects, 3x PM and 9x NM# (phenotyped using debrisoquine), single dose of 50-100 mg metoprolol; - PM: change in HR, fatigue score and exertion time differed non-significantly from NM. Fatigue score is not correlated to a decrease in HR or an increase in the exertion time. N.B.: genotype not known. Phenotyping can only distinguish between PM and the other phenotypes, so NM# is equal to IM, NM and UM.	
ref. 27 Clark DWJ et al. Adverse effects from metoprolol are not generally associated with oxidation status. Br J Clin Pharmacol 1984;18:965-966.	3 PM: AA	74 patients, 37 discontinued metoprolol due to side effects (hypotension, dizziness, Raynaud's syndrome, lively dreams, etc.) and 37 controls who used metoprolol without reported side effects, phenotyped with sparteine, 4x PM and 33x NM# in each group, co-medication unknown; - Number of PMs in group that discontinued is equal to number of PMs in control group. Dose of metoprolol is lower for PMs in group that discontinued than for PMs in control group and also lower than for NMs in group that discontinued (NS). Dose in discontinued group differed non-significantly from controls, 138 vs 150 mg/day. N.B.: genotype not known. Phenotyping can only distinguish between PM and the other phenotypes, so NM# is equal to IM, NM and UM. N.B.: indication for metoprolol is not known	Authors' conclusion: 'This investigation does not support the concept that prior knowledge of oxidiser status will enable a physician to predict the possibility of adverse drug reactions to metoprolol. However, it does not exclude that poor oxidiser status may be important in relation to adverse drug reactions in an occasional subject.'
ref. 28 Lennard MS et al. Differential stereoselective metabolism of metoprolol in extensive and poor debrisoquin metabolizers. Clin Pharmacol Ther 1983;34:732-7.	3 PM: A	12 study subjects (8 with hypertension), 6x PM and 6x NM# (phenotyped using debrisoquine), single dose of 200 mg metoprolol, no co-medication: - PM: increase in $AUC_{S\text{-}M}$ from 679 to 3431 ng/mL.h (NS by 405%) versus NM, ratio *S*-M/*R*-M is 0.90 and reduced by 34.3% compared to NM (both S). The variability in the stereoselective metabolism is related to the phenotype. N.B.: genotype not known. Phenotyping can only distinguish between PM and the other phenotypes, so NM# is equal to IM, NM and UM.	AUC S-metoprolol versus NM+IM+UM: PM: 505%
ref. 29 American SmPC Toprol-XL (metoprolol succinate)	0	<u>Pharmacogenomics</u>: CYP2D6 is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by several drugs. Poor metabolizers of CYP2D6 will	

01-06-22. **ref. 29, continuation**	PM: A	have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity. Pharmacokinetics: Metoprolol is metabolized predominantly by CYP2D6. In healthy subjects with CYP2D6 normal metabolizer phenotype, coadministration of quinidine 100 mg, a potent CYP2D6 inhibitor, and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate-release metoprolol 50 mg t.i.d. resulted in steady state concentration of metoprolol 2- to 5-fold what is seen with metoprolol alone. Normal metabolizers who concomitantly use CYP2D6 inhibiting drugs will have increased (several-fold) metoprolol blood levels, decreasing metoprolol's cardioselectivity.	

[a] corrected for dose
[b] corrected for dose and body weight.
AA[#]: there was a significant effect, but this effect was positive instead of negative.

Risk group	IM with CYP2D6 inhibitor

Comments:

- Unless stated otherwise, the kinetic parameters relate to the racemic mixture of *S*-metoprolol and *R*-metoprolol.
- For the period after March 2009, clinical studies were only included if they involved more than 200 patients or if data for UM were also present. Kinetic studies were only included if AUC, C_{ss} or Cl_{or} was determined for metoprolol, if the study distinguished between NM and IM and if data were available for at least 3 UM, 6 PM or 25 IM. Other studies did not contribute sufficiently to the burden of proof. A meta-analysis of kinetic studies involving a total of 235 patients was not included (Blake CM et al. A meta-analysis of CYP2D6 metabolizer phenotype and metoprolol pharmacokinetics. Clin Pharmacol Ther. 2013;94:394-9. PMID: 23665868). For all 148 patients in the meta-analysis that were not included in this risk analysis, no distinction was made between NM and IM. The study of Thomas 2020 (Thomas CD et al. Examination of metoprolol pharmacokinetics and pharmacodynamics across CYP2D6 genotype-derived activity scores. CPT Pharmacometrics Syst Pharmacol 2020;9:678-85. PMID: 33067866) was not included in the risk analysis, because the pharmacokinetic study was small and the pharmacodynamic study analysed the same patients as Hamadeh 2014.
  The less relevant studies were not included from the literature from 2006 onwards. These are studies in which the effect of the genotype is not the main subject (for example, interaction studies in which genotyping was also performed) and studies in which the ratio α-hydroxymetoprolol/metoprolol was the only endpoint.
  Studies in which only phenotyping was performed and that did not provide any new findings/insights compared to studies in which genotyping was performed were not included in the risk analysis.
- KNMP Pharmacogenetics Working Group: The definition of bradycardia in the studies is far too vague, namely <60 beats/minute. A heart rate below 60 beats/minute is referred to as bradycardia, but this does not mean that any pathology or symptoms are present. In the case of treatment with a β-blocker, physicians aim to achieve bradycardia between 50 and 60 beats/minute (and at least substantially lower than the initial heart rate), because this gives them confirmation that the patient has pharmacologically active concentrations of the medicine and because a reduction in the heart rate forms an integral part of the intended effect (e.g. for angina pectoris or aortic dissection). In some cases (e.g. a patient with aortic dissection), physicians will even accept a heart rate below 50 beats/minute, provided that the patient is not experiencing any symptoms that could be related to this bradycardia (e.g. dizziness). Severe cardiac events were registered in only 1 study.
- Other guidelines:
  - Rüdesheim S et al. Physiologically based pharmacokinetic modeling of metoprolol enantiomers and α-hydroxymetoprolol to describe CYP2D6 drug-gene interactions. Pharmaceutics 2020;12:1200. PMID: 33322314.
    The authors developed a physiologically based pharmacokinetic (PBPK) model employing data of 48 different clinical studies with a dosing range of 5-200 mg and with a total of 461 participants, of whom 275 with a known CYP2D6 genotype or phenotype.
    Based on this model, the following dose adjustments were calculated:

phenotype	gene dose	adjusted dose
PM	0	12.5%
IM	0.5	25%
	1	50%
NM	1.25	60%
	1.5	75%
	2	100%
UM	3	175%

Date of literature search: 27 June 2022.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 C	yes	yes	12 September 2022
	IM	4 C	yes	yes	
	UM	4 C	yes	yes	

Mechanism:
Metoprolol is primarily metabolised by CYP2D6 to O-desmethylmetoprolol and α-hydroxymetoprolol. The activity of metoprolol metabolites is neglectable. The active S-enantiomer of metoprolol is metabolised by CYP2D6 to a lesser extent than the less active R-enantiomer of metoprolol. A CYP2D6 genetic polymorphism may cause a change in the plasma concentration of metoprolol and the ratio S-metoprolol/R-metoprolol.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	0+
Corresponding Clinical Implication Score:		Potentially beneficial