CYP2C19: prasugrel 2545/2546/2547

ADP = adenosine diphosphate, AUC = area under the concentration-time curve, EM = extensive metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), IM = intermediate metaboliser (*1/*2, *1/*3, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), LTA = light transmission aggregometry, NS = non-significant, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), S = significant, UM = ultrarapid metaboliser (*17/*17) (increased CYP2C19 enzyme activity), VASP = vasodilator-stimulated phosphoprotein assay, VerifyNow assay = an aggregation assay that measures the extent to which the platelet ADP receptor ($P2Y_{12}$) can be stimulated, wt = wild type

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:
Prasugrel is converted in two steps to the active metabolite, an unstable thiol compound that inhibits platelet aggregation through the formation of a disulphide bridge with a cysteine residue on the ADP receptor of platelets ($P2Y_{12}$). The steps are consecutively catalysed by carboxylesterases and by 4 different CYP450 enzymes, primarily CYP-3A4 and CYP2B6 and to a lesser extent CYP2C9 and CYP2C19.
There were no significant effects of CYP2C19 gene variations on the pharmacokinetics of prasugrel (Brandt 2007, Mega 2009 and Varenhorst 2009). CYP2C19 gene variations also have no significant effects on inhibition of platelet aggregation (Brandt 2007, Mega 2009, Varenhorst 2009 and Doll 2016) or the occurrence of cardiovascular side effects (Mega 2016, Doll 2016 and Lee 2018). Therefore, there is no evidence to support a gene-drug interaction and a need for adjustment of therapy (no/no-interactions).
One observational study also demonstrated that major adverse cardiovascular effects following percutaneous coronary intervention with stent placement is significantly less common in poor metabolisers (PM) who use prasugrel compared to PM who use clopidogrel (Deiman 2016). Another study showed a lower incidence of major adverse cardiovascular and cerebrovascular events following percutaneous coronary intervention in intermediate and poor metabolisers (IM+PM) treated with prasugrel compared to IM+PM treated with clopidogrel. Prasugrel can therefore be considered an alternative for patients with insufficient inhibition of platelet aggregation on clopidogrel as a result of a gene variation that leads to reduced CYP2C19 activity.
You can find an overview of the clinical and kinetic effects per phenotype in the background information text of the gene-drug interactions on 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 uses the KNMP definitions for EM, PM, IM and UM. As a result, the definitions of EM, PM, IM and UM in the table below can differ from the definitions used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Lee CR et al. Clinical outcomes and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. Circ Genom Precis Med 2018;11:e002069.	3	After a recommendation for use of prasugrel or ticagrelor instead of clopidogrel in CYP2C19 IM and PM, 751 genotyped high risk patients were treated with dual antiplatelet therapy after percutaneous coronary intervention. Patients were followed for 12 months. 90% of the patients not receiving clopidogrel were treated with prasugrel. Major adverse cardiovascular or cerebrovascular events were defined as death, myocardial infarction, stent thrombosis, admission for acute coronary syndrome/unstable angina, ischemic cerebrovascular accident, or transient ischemic attack. Clinically significant bleeding was defined as a bleeding event leading to an intervention, hospi-	Authors' conclusion: "The higher risk of major adverse cardiovascular or cerebrovascular events associated with clopidogrel use in CYP-2C19 loss of function allele carriers suggests that use of genotype-guided dual antiplatelet therapy in practice

<table>
<tr>
<td>PubMed PMID: 29615454.

ref. 1, continuation</td>
<td>IM+PM: AA

Prasugrel/ticagrelor versus clopidogrel: IM+PM: AA# EM+UM : AA</td>
<td>talisation, prolongation of hospitalisation, or death, and being classified as GUSTO (Global Use of Strategies to Open Occluded Arteries) moderate (requiring blood transfusion but not resulting in hemodynamic compromise) or severe/ life-threatening (intracerebral hemorrhage or resulting in hemodynamic compromise requiring treatment).
Results were corrected for covariates that differed across groups or were associated with the clinical outcome. Relevant co-medication was not excluded.

Genotyping:
Prasugrel/ticagrelor (90% prasugrel)
- 113x EM+UM
- 165x IM+PM
Clopidogrel
- 405x EM+UM
- 68x IM+PM

Results:
<table>
<tr><td colspan="4">IM+PM compared to EM+UM:</td></tr>
<tr><td></td><td></td><td>IM+PM</td><td>events per 100 patient-years for EM+UM</td></tr>
<tr><td rowspan="2">major adverse cardiovascular or cerebrovascular events</td><td>prasugrel/ ticagrelor</td><td>NS</td><td>15.0</td></tr>
<tr><td>clopidogrel</td><td>HR_{corr} = 2.71 (95% CI: 1.52-4.66) (S)</td><td>20.1</td></tr>
<tr><td rowspan="2">clinically significant bleeding</td><td>prasugrel/ ticagrelor</td><td>NS</td><td>4.2</td></tr>
<tr><td>clopidogrel</td><td>NS</td><td>7.3</td></tr>
<tr><td colspan="4">Results were similar when only patients with acute coronary syndrome as indication for percutaneous coronary intervention were analysed (NS for the difference in major adverse cardiovascular or cerebrovascular events on prasugrel/ ticagrelor for IM+PM compared to EM+UM; HR_{corr} = 3.68 (95% CI: 1.88-6.83) (S) for clopidogrel).</td></tr>
</table>
<table>
<tr><td colspan="3">Prasugrel/ticagrelor compared to clopidogrel:</td></tr>
<tr><td></td><td>IM+PM</td><td>EM+UM</td></tr>
<tr><td rowspan="2">major adverse cardiovascular or cerebrovascular events</td><td>HR_{corr} = 0.22 (95% CI: 0.10-0.45) (S)</td><td>NS</td></tr>
<tr><td colspan="2">The difference between IM+PM and EM+UM was significant (S).</td></tr>
<tr><td>clinically significant bleeding</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="3">Results were similar when only patients with acute coronary syndrome as indication for percutaneous coronary intervention were analysed (HR_{corr} = 0.10 (95% CI: 0.036-0.25) (S) for major adverse cardiovascular or cerebrovascular events for IM+PM for prasugrel/ticagrelor compared to clopidogrel; NS for EM+UM).</td></tr>
</table>
Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this patient group from the USA.</td>
<td>may improve clinical outcomes.”</td>
</tr>
<tr>
<td>ref. 2
Deiman BA et al. Reduced number of</td>
<td>3</td>
<td>73 PMs for CYP2C19 (CYP2C19 *2/*2) who underwent percutaneous coronary intervention with stent placement were treated with prasugrel 10 mg/day (n = 41) or</td>
<td>Authors’ conclusion: “This study provides evidence that for</td>
</tr>
</table>

<table>
<tr>
<td>cardiovascular events and increased cost-effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Neth Heart J 2016;24:589-99. PubMed PMID: 27573042.

ref. 2, continuation</td>
<td>Prasugrel versus clopidogrel: PM: AA#</td>
<td>clopidogrel 75 mg/day (n = 32) for at least one year. Patients received daily acetylsalicylic acid. Treatment with prasugrel started on day 1-5 after percutaneous coronary intervention. Until that time, they were given clopidogrel. Patients were monitored for at least 1.5 years after the stent placement.
Negative cardiovascular effects were defined as death due to cardiovascular cause, myocardial infarction, stent thrombosis, stroke or a second percutaneous coronary intervention in the same artery. Serious cardiovascular effects were defined as stent thrombosis, myocardial infarction and death.
None of the patients in the study had severe bleeding. More than 1.5 years after the percutaneous coronary intervention, chest pains only occurred as a result of in-stent stenosis.
Relevant co-medication was not excluded.

Results:
<table>
<tr><td colspan="3">% patients with negative effect for prasugrel versus clopidogrel:</td></tr>
<tr><td></td><td>prasugrel</td><td>value for clopidogrel</td></tr>
<tr><td>negative cardiovascular effects</td><td>x 0.12 (S)</td><td>41%</td></tr>
<tr><td>negative cardiovascular effects within 1.5 years</td><td>x 0.16 (S)</td><td>31%</td></tr>
<tr><td>serious cardiovascular effects within 1.5 years</td><td>x 0.10 (S)</td><td>25%</td></tr>
</table>
</td>
<td>CYP2C19-related poor metabolisers prasugrel may be more effective than clopidogrel to prevent major adverse cardiovascular events after PCI and this approach could be cost-effective.”</td>
</tr>
<tr>
<td>ref. 3
Ogawa H et al. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. J Cardiol 2016;68:29-36. PubMed PMID: 26521100.</td>
<td>3</td>
<td>773 patients with acute coronary syndrome who received percutaneous coronary intervention, were treated with low dose prasugrel (n = 390, loading dose 20 mg, maintenance dose 3.75 mg/day) or clopidogrel (n = 383, loading dose 300 mg, maintenance dose 75 mg/day). Treatment was in combination with acetylsalicylic acid and lasted 24-48 weeks. Patients were monitored for another 2 weeks after treatment. All bleeding that occurred up to 2 weeks after the end of the treatment was included. Only bleeding related to coronary artery bypass surgery was not included. The definition of serious and non-serious bleeding was based on the “Thrombolysis in Myocardial Infarction” definition (TRITON-TIMI-trial). The other clinical outcome measures were included over the first 24 weeks.
The remaining platelet activity was measured using the VerifyNow assay ($P2Y_{12}$ reaction sub-units).
Co-medication with other platelet aggregation inhibitors, anticoagulants, thrombolytics or chronic use of other NSAIDs was excluded, co-medication that affects CYP-2C19 was not excluded.

Genotyping prasugrel group:
- 153x EM
- 160x IM
- 77x PM

Results:
<table>
<tr><td colspan="3">Results for prasugrel versus clopidogrel:</td></tr>
<tr><td></td><td>prasugrel</td><td>value for clopidogrel</td></tr>
</table>
</td>
<td>Authors’ conclusion: “In conclusion, prasugrel at a LD/MD of 20/3.75 mg had stable antiplatelet effects, irrespective of the CYP2C19 genotype, after PCI in Japanese ACS patients. Although the incidence of MACE was 9.3% in the prasugrel group and 12.5% in the clopidogrel group in IM + PM patients, there were no significant differences in terms of the incidences of MACE and clinically relevant bleeding between the two treatments among patients of each CYP2C19 phenotype.”</td>
</tr>
</table>

ref. 3, continuation		death from cardiovascular cause, non-fatal myocardial infarction or non-fatal stroke for EM and IM+PM	NS	11.9% of the EM and 12.5% of the IM+PM	
		death from cardiovascular cause for EM and IM+PM	NS	0% of the EM and IM+PM	
		non-fatal myocardial infarction for EM and IM+PM	NS	11.1% of the EM and 12.1% of the IM+PM	
		non-fatal stroke for EM and IM+PM	NS	0.7% of the EM and 0.4% of the IM+PM	
		revascularisation for EM and IM+PM	NS	4.4% of the EM and 4.8% of the IM+PM	
		in-stent thrombosis for EM and IM+PM	NS	0% of the EM and 0.8% of the IM+PM	
		all bleeding for EM	NS	45.2% of the EM	
		all bleeding for IM+PM	HR = 1.80 (95% CI: 1.35 - 2.39) (S)	31.9% of the IM+PM	
	IM+PM: AA	The authors indicated that for prasugrel, the incidence of all bleeding was comparable between EM and IM+PM (NS). For clopidogrel, the incidence was significantly lower for IM+PM.			
		serious bleeding for EM and IM+PM	NS	1.5% of the EM and 1.2% of the IM+PM	
		non-serious bleeding for EM and IM+PM	NS	2.2% of the EM and 2.0% of the IM+PM	
		clinically relevant bleeding for EM and IM+PM	NS	6.7% of the EM and 6.5% of the IM+PM	
	Prasu-grel ver-sus clo-pidogrel: IM+PM: B	other bleeding for EM	NS	41.5% of the EM	
		other bleeding for IM+PM	HR = 1.92 (95% CI: 1.41-2.62) (S)	26.2% of the IM+PM	
		bleeding that resulted in discontinuing the treatment for EM and IM+PM	NS	1.5% of the EM and 1.6% of the IM+PM	
		remaining platelet activity for EM after 4, 12, 24, 26 and 48 weeks	NS		
		remaining platelet activity	lower (S)		

<table>
<tr>
<td>ref. 3, continuation</td>
<td></td>
<td>
<table>
<tr><td>for IM+PM after 4, 12, 24, 26 and 48 weeks</td><td></td><td></td></tr>
<tr><td>remaining platelet activity for EM and IM+PM, 2-4 hours and 5-12 hours after the loading dose</td><td>lower (S)</td><td></td></tr>
<tr><td colspan="3">The authors indicated that after 4 weeks the platelet inhibitor for IM+PM on prasugrel was comparable to the inhibition for EM on clopidogrel. For IM+PM on clopidogrel, the platelet inhibition was significantly lower.</td></tr>
</table>

Note: Genotyping was performed for *2 and *3. These are the most important gene variants in this Japanese patient group.
</td>
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<tr>
<td>ref. 4
Doll JA et al.
Impact of CYP2C19 metabolizer status on patients with ACS treated with prasugrel versus clopidogrel.
J Am Coll Cardiol 2016;67:936-47.
PubMed PMID: 26916483.</td>
<td>3

IM+PM: AA</td>
<td>2,630 patients with unstable angina pectoris or myocardial infarction without ST elevation were treated with prasugrel without revascularisation. Patients were followed for 30 months. The prasugrel dose was 10 mg/day for patients < 75 years and ≥ 60 kg and 5 mg/day for patients ≥ 75 years and/or < 60 kg. Patients also received acetylsalicylic acid (< 100 mg/day for approx. 80% of the patients). For 1,027 patients, the remaining platelet activity was determined after 1, 3, 6, 12, 18, 24 and 30 months ($P2Y_{12}$ reaction sub-units, VerifyNow assay).
IM with one *17 allele and one null allele were excluded from the study.
Relevant co-medication was not excluded. In addition, there were moderate differences between EM+UM and IM+PM. IM+PM had a lower body weight and were less likely to have a history of heart failure or coronary artery bypass graft surgery. In addition, they were less likely to suffer hyperlipidaemia and a family history of coronary artery disease and were more likely to be of Asian origin. The clinical outcome measures were corrected for all these factors, the measured remaining platelet activity was only corrected for age higher or lower than 75 years and for use of clopidogrel prior to prasugrel (started in the hospital (≤ 72 hours), use at home, no clopidogrel).

Genotyping:
- 825x (UM + *1/*17)
- 1,127x *1/*1
- 564x IM
- 114x PM

Results:
<table>
<tr><td colspan="2">(IM+PM) versus (EM+UM):</td></tr>
<tr><td>cardiovascular mortality, myocardial infarction or stroke</td><td>NS</td></tr>
<tr><td>cardiovascular mortality</td><td>NS</td></tr>
<tr><td>myocardial infarction</td><td>NS</td></tr>
<tr><td>stroke</td><td>NS</td></tr>
<tr><td>death (all causes)</td><td>NS</td></tr>
<tr><td>remaining platelet activity over time (1 - 30 months after start prasugrel)</td><td>NS</td></tr>
<tr><td>remaining platelet activity after 30 days</td><td>NS</td></tr>
</table>

Note 1: Clinical effects in patients who did not undergo
</td>
<td>Authors' conclusion: "CYP2C19 metabolizer status is not associated with the composite outcome of cardiovascular death, MI, or stroke in medically managed ACS patients treated with clopidogrel and prasugrel. … Reduced metabolizers had significantly higher mean P2Y12 reaction sub-units versus EM patients when treated with clopidogrel, but not with prasugrel."</td>
</tr>
</table>

ref. 4, continuation		revascularisation provide little information about a possible effect of CYP2C19 gene variants. For clopidogrel, there is a clear effect of CYP2C19 variants on the remaining platelet activity and on the clinical outcomes of patients who underwent a percutaneous coronary intervention, but not on clinical outcomes in patients who did not undergo percutaneous coronary intervention. Note 2: Genotyping was performed for *2-*8 and *17.	
ref. 5 Varenhorst C et al. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 2009;30:1744-52.	3 IM + PM: AA	50 patients with a coronary cardiac condition, who were using acetylsalicylic acid (35x EM+UM (*1/*1, *1/*17 or *17/*17), 15x IM+PM (*1/*2, *1/*8 or *2/*2)) received a loading dose of prasugrel 60 mg, followed by prasugrel 10 mg/day. Relevant co-medication was not excluded. Measures used to determine the remaining platelet aggregation were: - the platelet reactivity index (the reduction in the phosphorylation of vasodilator-stimulated phosphoprotein (VASP) by the activated platelet-ADP receptor $P2Y_{12}$ - the $P2Y_{12}$ reaction sub-units (determined according to the platelet aggregation in the presence of fibrinogen-coated beads (VerifyNow)). (IM+PM) versus (EM+UM): - no difference in the AUC of the active thiol metabolite of prasugrel (NS). - no difference in the remaining platelet aggregation, as measured using the two methods at 3 time points (24 hours after the loading dose, on Day 14 and on Day 29) (NS). Categorisation of patients who used CYP2C19 inhibitors into the IM+PM group had no effect on the results. Note: Genotyping was performed for *2 to *10, *12 to *14 and *17.	Authors' conclusion: "Variation in the gene encoding CYP2C19 in patients with stable CAD has no significant influence on the response to prasugrel."
ref. 6 Mega JL et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553-60.	4 IM + PM: AA	1,455 patients with acute coronary syndrome and a scheduled percutaneous coronary intervention (1,048x EM+UM (*1/*1, *1/*17 or *17/*17), 372x IM (*1/*2, *1/*3, *1/*4 or *1/*8), 35x PM (*2/*2, *2/*3, *2/*4, *2/*5 or *2/*8)) received a loading dose of prasugrel 60 mg, followed by prasugrel 10 mg/day for a maximum of 15 months. Co-medication was not excluded, but O'Donoghue et al. (Lancet 2009;374:989-97) ruled out a significant effect of proton pump inhibitors on the risk of the primary endpoint. The primary endpoint was cardiovascular death and/or myocardial infarction and/or stroke. Stent thrombosis was defined as being probable or confirmed by angiography. (IM+PM) versus (EM+UM): - no significant difference in the incidence of the primary endpoint (reduction from 9.8% to 8.5%) (NS). - no significant difference in the incidence of cardiovascular death (from 1.58% to 0.99%), the incidence of non-fatal myocardial infarction (from 8.1% to 6.6%) and the incidence of non-fatal stroke (from 0.82% to 1.0%) (NS). - no significant difference in the incidence of stent thrombosis (reduction from 1.0% to 0.5%) (NS). - no significant difference in the incidence of non-bypass-related bleeding (major and minor bleeding) (increase from 3.8% to 4.5%) (NS).	Authors' conclusion: "Common functional CYP genetic variants do not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovas-cular event rates in persons treated with prasugrel."

ref. 6, continuation	PM: AA IM: AA UM: AA	238 healthy volunteers (37x EM+UM (*1/*17 or *17/*17), 93x EM (*1/*1), 78x IM (*1/*2, *1/*3, *1/*4 or *1/*8), 18x PM (*2/*2, *2/*3, *2/*4, *2/*5 or *2/*8), 12x EM+IM (*1/*9, *1/*10, *2/*17 or *6/*17)) received a loading dose of prasugrel 10 mg or 60 mg (n = 41), or a loading dose of prasugrel 60 mg followed by prasugrel 10 mg/day (n = 167), or prasugrel 10 mg/day (n = 30). The EM+IM group was not included in the analysis. The absolute reduction in the maximum ADP-induced platelet aggregation was measured using LTA and 20 µM ADP. IM + PM versus EM + UM (*1/*1, *1/*17 or *17/*17)*:* - decrease in AUC of active metabolite by 6.1% (NS). - decrease in the absolute reduction of maximum platelet aggregation by 1.3 percentage points (NS; the average absolute reduction was 70.6 percentage points). PM versus IM versus EM versus EM+UM: - no difference in AUC of active metabolite following prasugrel 60 mg and following prasugrel 10 mg/day (NS). - no difference in the absolute reduction of the maximum platelet aggregation following prasugrel 60 mg and following prasugrel 10 mg/day (NS). Note: Genotyping was performed for *2 to *10, *12 to *14 and *17.	
ref. 7 Brandt JT et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429-36.	3 PM: AA IM: AA	71 healthy volunteers (54x EM, 16x IM (*1/*2), 1x PM (*2/*2)) received a single dose of 60 mg prasugrel. Co-medication was excluded. The platelet aggregation was measured after 4 hours using LTA and 20 µM ADP. PM versus IM versus EM: - the *2 allele was non-significantly associated with the $AUC_{0\text{-}24h}$ of the active metabolite (NS; 455 versus 504 versus 544 ng.h/mL). - the *2 allele was non-significantly associated with the inhibition of platelet aggregation (82.2 versus 81.7 versus 78.4%). Note: Genotyping was performed for *2 to *5.	Authors' conclusion: "For prasugrel, there was no relationship observed between CYP2C19 loss of function genotypes and exposure to the active metabolite of prasugrel or pharmacodynamic response."
ref. 8 SmPC Efient (prasugrel) 24-05-17.	0 PM: AA IM: AA UM: AA	<u>Pharmacokinetics</u>: In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Efient, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of prasugrel or its inhibition of platelet aggregation.	
ref. 9 SmPC Efient (prasugrel), USA, 09-03-18.	0 PM: AA IM: AA UM: AA	<u>Pharmacogenomics</u>: There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.	

Risk group	--

Comments:

- From 2009 onwards, only studies involving more than 750 patients or more than 40 PM on prasugrel were included. Furthermore, if several articles described the same patient group, only the most recent article was included.
- <u>Cost-effectiveness</u>:
  - Borse MS et al. CYP2C19-guided antiplatelet therapy: a cost-effectiveness analysis of 30-day and 1-year outcomes following percutaneous coronary intervention. Pharmacogenomics 2017;18:1155-66. PubMed PMID: 28745582.
    In USA patients with coronary artery disease undergoing percutaneous coronary intervention, the additio-

nal costs of CYP2C19-genotype-guided therapy per major cardiovascular or bleeding event avoided in the first 30 days after percutaneous coronary intervention were US$ 8525 and US$ 42,198 compared with universal clopidogrel and universal prasugrel, Calculated over a period of 1 year, genotype-guided therapy costed US$ 50,308 per event avoided compared to universal clopidogrel, and was both cheaper and better than universal prasugrel. At a willingness-to-pay threshold of US$ 50,000 per event avoided, variation of the input data showed that genotype-guided treatment was cost effective over 30 days and 1 year in 62% and 70% of cases, respectively.
In the CYP2C19 genotype-guided therapy, CYP2C19 EM received clopidogrel and CYP2C19 IM and PM received prasugrel.
Direct inpatient medical costs were calculated for the first 30 days and for the first year after percutaneous coronary intervention. Treatment with dual antiplatelet therapy was considered to last at least 1 year. Calculations were based on the perspective of the US healthcare payer. The calculations were based on clopidogrel costs of US$ 13 per 30 days, prasugrel costs of US$ 324 per 30 days, major adverse cardiovascular event costs of US$ 8883, stent thrombosis event costs of US$ 21,463, major bleeding event costs of US$ 8222, and a genetic test price of US$ 292. The event rate probabilities for major adverse cardiovascular events (defined as composite of cardiovascular death, myocardial infarction or ischemic stroke events), stent thrombosis (defined as definite or probable stent thrombosis events according to the Academic Research Consortium criteria) and major bleeding (defined as major bleeding events unrelated to coronary artery bypass graft surgery according to the Thrombolysis in Myocardial Infarction [TIMI] criteria) at 30 days and 1 year were obtained from the meta-analysis by Mega (Mega JL et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA 2010;304:1821-30), with enrichment from the TRITON TIMI-38 clinical trial that compared clinical outcomes following randomization to either clopidogrel or prasugrel in acute coronary syndrome patients undergoing percutaneous coronary intervention (Wiviott SD et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357:2001-15). The prevalence of IM+PM in the population was assumed to be 30%, in accordance with literature on the frequency of these phenotypes in US populations.

- Jiang M et al. CYP2C19 LOF and GOF-guided antiplatelet therapy in patients with acute coronary syndrome: a cost-effectiveness analysis. Cardiovasc Drugs Ther 2017;31:39-49. PubMed PMID: 27924429.
In 60-year-old patients with acute coronary syndrome undergoing percutaneous coronary intervention, CYP2C19-genotype-guided therapy was both cheaper and more effective than both treatment of all patients with clopidogrel 75 mg/day (US$ 456 reduced costs and 0.092 more Quality Adjusted Life-Years (QALYs)) and treatment of all patients with prasugrel 10 mg/day or ticagrelor 90 mg 2x per day (US$ 1846 reduced costs and 0.0433 more Quality Adjusted Life-Years (QALYs)). In the CYP2C19 genotype-guided therapy, patients with CYP2C19*1/*1 received clopidogrel and patients with CYP2C19 variants *2, *3, *4, *5, *6, *7, *8 or *17 received prasugrel or ticagrelor.
Prasugrel or ticagrelor in all patients was more effective but also more expensive than clopidogrel for all patients. The incremental costs were US$ 28,542/QALY and therefore did not exceed the limit of US$ 50,000/QALY. Prasugrel or ticagrelor for all patients was therefore also cost-effective.
Direct medical costs were first calculated for the 1 year of treatment with a $P2Y_{12}$ inhibitor in combination with acetylsalicylic acid 75-162 mg/day and then for the rest of life (up to 30 years). Calculations were based on the perspective of the health care insurance company in the USA. The calculated costs of genotype-guided therapy were US$ 76,450 and the calculated QALYs 7.5301. For clopidogrel for all patients this was US$ 76,906 and 7.4381 QALYs and for prasugrel or ticagrelor for all patients this was US$ 78,296 and 7.4868 QALYs. The calculation was based on clopidogrel costs of US$ 12 per month, prasugrel or ticagrelor costs of US$ 141 per month and a genetic test price of US$ 200. The risks of serious cardiovascular events (non-fatal stroke, non-fatal myocardial infarction or death due to cardiovascular cause) and in-stent thrombosis for clopidogrel were taken from the TRITON-TIMI 38 trial (Wiviott 2007) and the PLATO trial (Wallentin 2009) and those for the alternatives from a meta-analysis that compared clopidogrel to the alternatives (Tang 2014). The hazard ratios for serious cardiovascular incidents for patients with a CYP2C19 null allele compared to the entire population and compared to patients without the null allele were taken from the TRITON-TIMI 38 trial (Mega 2009). The frequency of severe bleeding not related to a coronary bypass graft in patients with genotype *1/*1 and the hazard ratio for *17 carriers (CYP2C19 *1/*17, *17/*17) compared to patients with genotype *1/*1 were taken from a Dutch prospective clinical study (Harmszea 2012). The frequencies used for carriers of variant alleles were also taken from this Dutch study (27.8% of carriers of a null allele and within the group without a null allele 40.6% with a *17 allele). Costs for the treatment of serious cardiovascular incidents, severe bleeding and percutaneous coronary intervention were obtained from the health care insurance company.
The prevalences used for carriers for variant alleles were taken from a Dutch study. This means that for the allele frequencies present in the Netherlands, genotype-guided therapy was cheaper and more effective than therapy with clopidogrel or with prasugrel or ticagrelor for all patients. Clopidogrel for all patients was the best strategy instead of genotype-guided therapy if the frequency on null allele carriers

was lower than 11.6%.
Treatment of all patients with prasugrel or ticagrelor resulted in the lowest incidence of non-fatal myocardial infarction (5.62%) and in-stent thrombosis (1.2%), but the highest incidence of serious bleeding (3.27%) and non-fatal stroke (0.91%). Genotype-guided treatment resulted in the lowest incidence of non-fatal stroke (0.72%), death by cardiovascular cause (2.42%) and serious bleeding (2.73%).
At a value for the hazard ratio for death by cardiovascular cause for carriers of a null allele compared to non-carriers of a null allele close to the lower limit of the confidence interval (HR < 1.94), clopidogrel could be more cost-effective for all patients than genotype-guided therapy.
Variation of input data (based on 95% confidence intervals or ± 20%) showed that genotype-guided therapy was the preferred strategy in 99.07% of cases at a maximum cost of US$ 50,000/QALY.

- Deiman BA et al. Reduced number of cardiovascular events and increased cost-effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Neth Heart J 2016;24:589-99. PubMed PMID: 27573042.
In Dutch patients who underwent percutaneous coronary intervention, genotype-guided treatment was cost-effective in comparison to clopidogrel for all patients. The costs per Quality Adjusted Life-Year (QALY) gained were lower than the limit of € 65,000/QALY, which is used as a measure of cost-effectiveness in the Netherlands. For genotype-guided therapy in which IM and PM received prasugrel and EM and UM received clopidogrel, the extra costs were € 9,111 per Quality Adjusted Life-Year (QALY) gained (€ 300.67 additional costs and 0.033 additional QALYs). For genotype-guided therapy in which PM received prasugrel and EM, IM and UM received clopidogrel, the extra costs were € 9,792/QALY gained (€ 101.97 additional costs and 0.0104 additional QALYs). For genotype-guided therapy in which IM and PM received ticagrelor and EM and UM received clopidogrel, the extra costs were € 5,972/QALY gained (€ 346.39 additional costs and 0.058 additional QALYs).
The treatment of all patients with ticagrelor or prasugrel instead of clopidogrel was also cost-effective, but resulted in a much larger increase in the costs per patient than genotype-guided therapy. For ticagrelor, the extra costs were € 8,010/QALY (€ 841.00 additional costs and 0.105 additional QALYs) and for prasugrel the extra costs were € 38,611/QALY (€ 695.00 additional costs and 0.018 additional QALYs).
The calculation of the costs and the QALYs gained was based on the cost-effectiveness analysis by Kazi 2014. The calculated pharmaceutical and genotyping costs per patient were € 25.00 for clopidogrel for all patients, € 325.67 for prasugrel for IM and PM, € 126.97 for prasugrel for PM, € 371.39 for ticagrelor for IM and PM, € 866.00 for ticagrelor for all patients and € 720.00 for prasugrel for all patients. The calculation was also based on clopidogrel 75 mg/day costs of € 25 per year, prasugrel 10 mg/day costs of € 720 per year and ticagrelor costs of € 866 per year and a genetic test price of € 83. The frequency of incidents was partially derived from 3,260 Dutch patients, of which 41 PM were treated with prasugrel and the rest with clopidogrel.
- Jiang M et al. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. Pharmacogenomics 2016;17:701-13. PubMed PMID: 27167099.
In 60-year-old patients with acute coronary syndrome undergoing percutaneous coronary intervention, CYP2C19-genotype-guided therapy was both cheaper and more effective than treatment of all patients with clopidogrel (US$ 1,302 reduced costs and 0.0666 more Quality Adjusted Life-Years (QALYs)), treatment based on platelet reactivity (US$ 881 reduced costs and 0.0408 more QALYs) and treatment of all patients with prasugrel or ticagrelor (US$ 2,678 reduced costs and 0.0351 more QALYs). CYP2C19-genotype-guided therapy involved IM and UM patients receiving prasugrel 10 mg/day or ticagrelor 90 mg 2x per day and the other patients receiving clopidogrel 75 mg/day. During therapy based on platelet reactivity, patients with more than 208 $P2Y_{12}$ reaction sub-units 6-12 hours after the loading dose of 600 mg clopidogrel were treated with prasugrel 10 mg/day or ticagrelor 90 mg 2x daily, whilst patients with ≤ 208 $P2Y_{12}$ reaction sub-units were treated with clopidogrel 75 mg/day. $P2Y_{12}$ reaction sub-units were measured using the VerifyNow assay.
Prasugrel or ticagrelor for all patients was not cost-effective in comparison to therapy based on platelet reactivity. The incremental costs were $ 315,263/QALY and therefore exceeded the limit of $ 50,000/QALY.
Calculation of the cost-effectiveness was performed as described for Jiang 2017. The calculated costs of clopidogrel for all patients were $ 76,510 and the calculated QALYs were 7.5583. The calculated costs for genotype-guided therapy were US$ 75,208 and 7.6249 QALYs. The costs for therapy based on platelet reactivity were US$ 76,089 and 7.5841 QALYs and for prasugrel or ticagrelor for all patients this was US$ 77,886 and 7.5898 QALYs. The cost of measuring platelet reactivity was US$ 23. The prevalence of carriers of null alleles (IM+PM) (28.4%) was taken from a meta-analysis of 9 studies (Mega 2010). The percentage of patients with low platelet inhibition following a loading dose of clopidogrel and the resulting odds ratio for serious cardiovascular incidents and bleeding were derived from a large study and a meta-analysis (Stone 2013 and Taglieri 2014).
The calculation was performed for a population with 28.4% carriers of a CYP2C19 null allele. This is comparable to the Dutch population (27.8% carriers; see the cost-effectiveness analysis by Jiang 2017).

Variation of the input data (based on the 95% confidence interval or ± 20%) showed that genotype-guided therapy was the preferred strategy in 98.76% of cases at a maximum cost of US$ 50,000/QALY. A reduction in the price of prasugrel and ticagrelor to the price of clopidogrel did not change this. In addition, genotype-guided therapy was the preferred therapy for all possible percentages of patients with low platelet inhibition on clopidogrel. Variation of the input data revealed that neither clopidogrel for all patients nor prasugrel or ticagrelor for all patients was ever the preferred strategy (in 0.00% of the cases).
An important reason for the fact that genotype-guided therapy is the preferred strategy, is that the TRITON-TIMI 38 trial found that the incidence of cardiovascular death (0.4 versus 2.1%), non-fatal stroke (0.24 versus 1.0%) and in-stent thrombosis (0.8 versus 1.1%) was lower for non-carriers of null alleles on clopidogrel than for patients on prasugrel.

- Jiang M et al. CYP2C19 genotype plus platelet reactivity-guided antiplatelet therapy in acute coronary syndrome patients: a decision analysis. Pharmacogenet Genomics 2015;25:609-17. PubMed PMID: 26398625.
  In 60-year-old patients with acute coronary syndrome undergoing percutaneous coronary intervention, CYP2C19-genotype-guided therapy was both cheaper and more effective than both treatment of all patients with clopidogrel 75 mg/day (US$ 91 reduced costs and 0.0257 more Quality Adjusted Life-Years (QALYs)) and treatment of all patients with prasugrel or ticagrelor (US$ 2,208 reduced costs and 0.0085 more Quality Adjusted Life-Years (QALYs)). CYP2C19-genotype-guided therapy involved EM and UM patients receiving clopidogrel 75 mg/day and PM patients receiving prasugrel or ticagrelor. IM patients received clopidogrel 225 mg/day and were tested for high platelet reactivity. IM patients with high platelet reactivity on clopidogrel were switched to prasugrel or ticagrelor.
  Prasugrel or ticagrelor in all patients was more effective but also more expensive than clopidogrel 75 mg/day for all patients. The incremental costs were US$ 139,588/QALY and therefore exceeded the limit of US$ 50,000/QALY. Prasugrel or ticagrelor for all patients was therefore not cost-effective.
  The calculation used a model that involved first calculating the medical costs for 1 year and then for the rest of life (up to 40 years). The calculated costs of genotype-guided therapy were US$ 71,887 and the calculated QALYs 7.886. The calculation was based on clopidogrel 75 mg/day costs of US$ 40 per month, prasugrel or ticagrelor costs of US$ 245 per month and a genetic test price of US$ 200. The risks of serious cardiovascular events and bleeding for clopidogrel were taken from the TRITON-TIMI 38 trial (reference Mega 2009) and those for the alternatives from a meta-analysis that compared clopidogrel to the alternatives (Tang 2014).
  Clopidogrel 75 mg/day for all patients was the best strategy instead of genotype-guided therapy if the CYP2C19 null allele frequency was lower than 2.6% or if there were more than 82.8% IM patients with high platelet activity on clopidogrel 225 mg/day. The null allele frequency is about 15% in Caucasians. One study found that 10.6% of the IM patients had high platelet reactivity on clopidogrel 225 mg/day.
  Variation of the input data (based on the 95% confidence interval or ± 20%) showed that genotype-guided therapy was the preferred
  strategy in 96.64% of cases at a maximum cost of US$ 50,000/QALY.
- Johnson SG et al. Financial Analysis of CYP2C19 Genotyping in Patients Receiving Dual Antiplatelet Therapy Following Acute Coronary Syndrome and Percutaneous Coronary Intervention. J Manag Care Spec Pharm 2015;21:552-7. PubMed PMID: 26108379.
  Treatment of patients with acute coronary syndrome undergoing stent placement with genotype-guided therapy instead of standard therapy costs US$ 444.85 less per patient in the year of treatment. Standard therapy was based on the market shares of the medicinal products (93% clopidogrel, 5% prasugrel and 2% ticagrelor). Genotype-guided therapy involved switching IM and PM patients on clopidogrel to prasugrel or ticagrelor (71.4% and 28.6% respectively in line with the market share ratio).
  Medical costs were calculated for patients who were treated for 1 year. 80% compliance with therapy was assumed. The calculation was based on clopidogrel costs of US$ 0.50 per day, prasugrel costs of US$ 8.00 per day, ticagrelor costs of US$ 8.71 per day and a genetic test price of US$ 315. The risks of serious cardiovascular events and bleeding were taken from the TRITON-TIMI 38 trial, which compared prasugrel to clopidogrel (Wiviott 2007 and reference Mega 2009) and from the PLATO trial, which compared ticagrelor to clopidogrel (Wallentin 2009).
  The costs of negative clinical consequences had the greatest effect on the results. Those of medication and genotyping were less significant.
  Patients with genotype *2/*17 were included in the EM/UM group.
- Jiang M et al. Review of pharmacoeconomic evaluation of genotype-guided antiplatelet therapy. Expert Opin Pharmacother 2015;16:771-9. PubMed PMID: 25660101.
  This is a review of 7 cost-effectiveness studies for CYP2C19 null allele-guided treatment of patients with acute coronary syndrome with novel platelet aggregation inhibitors (prasugrel or ticagrelor). The studies in the review (Crespin 2011, Guzauskas 2012, Panattoni 2012, Reese 2012, Lala 2013, Sorich 2013 and Kazi 2014) are all summarised separately below. In all cases, genotype-guided treatment involved treatment of EM/UM patients with clopidogrel and IM and PM patients with prasugrel or ticagrelor. The authors concluded that the cost-effectiveness of CYP2C19 null allele-guided therapy with prasugrel or ticagrelor has been demonstrated for high-risk patients.

Four studies found that CYP2C19 genotype-guided treatment with prasugrel was cost-effective compared to treatment of all patients with clopidogrel or prasugrel (Guzauskas 2012, Panattoni 2012, Reese 2012, Lala 2013).
Two studies found that treatment of all patients with ticagrelor was more cost-effective than genotype-guided treatment (Crespin 2011, Sorich 2013). A third study found that genotype-guided treatment with ticagrelor was cost-effective for patients undergoing percutaneous coronary intervention (Kazi 2014). This study found that either genotype-guided treatment or ticagrelor for all patients was the preferred treatment for all patients with acute coronary syndrome depending on the costs used in the model.
The results of the cost-effectiveness analyses were influenced by the costs of the platelet aggregation inhibitors and by the risks of IM and PM patients of negative clinical consequences of the use of clopidogrel compared to this risk when using novel platelet aggregation inhibitors.

- Kazi DS et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med 2014;160:221-32. PubMed PMID: 24727840.
The cost-effectiveness of 5 treatment strategies in 65-year-old patients undergoing drug-eluting stent placement after acute coronary syndrome was compared: treatment with clopidogrel, prasugrel or ticagrelor or CYP2C19 genotype-guided therapy with prasugrel or ticagrelor. Genotype-guided therapy involved EM and UM patients receiving clopidogrel and IM and PM patients receiving prasugrel or ticagrelor.
Using relative risks of IM+PM versus EM+UM from a meta-analysis including patients undergoing percutaneous coronary intervention for the calculation:
Genotyping with ticagrelor was the most effective therapy. The costs per gained Quality Adjusted Life Year (QALY) were US$ 24,700 compared to clopidogrel. Ticagrelor delivered more QALYs, but at much higher costs (US$ 104,800/QALY) and was therefore not cost-effective. Genotyping with ticagrelor was more cost-effective than genotyping with prasugrel (costs compared to clopidogrel US$ 25,600/QALY). Genotyping with prasugrel delivered more QALYs at lower costs than prasugrel. Genotyping with prasugrel is therefore the preferred strategy in patients intolerant to ticagrelor.
Using relative risks of IM+PM versus EM+UM from a meta-analysis including patients with all clopidogrel indications for the calculation:
Ticagrelor was the most effective therapy. The costs per QALY gained were US$ 52,600 compared to genotyping with ticagrelor. Genotyping with ticagrelor was more cost-effective than genotyping with prasugrel. The costs per QALY gained were US$ 30,200 and US$ 35,800 respectively.
Genotyping with prasugrel delivered more QALYs at lower costs than prasugrel. The costs of genotyping with prasugrel per QALY gained were US$ 35,800 compared to clopidogrel. Genotyping with prasugrel is the preferred strategy in patients intolerant to ticagrelor.
Prasugrel for all patients was more effective but also more expensive than clopidogrel for all patients. The incremental costs were US$ 124,400/QALY and therefore exceeded the limit of US$ 50,000/QALY. Prasugrel for all patients was therefore not cost-effective.
The calculation used a model in which patients were treated with clopidogrel, prasugrel or ticagrelor for 1 year after percutaneous coronary intervention or myocardial infarction. Medical costs were calculated. The calculation was based on clopidogrel costs of US$ 30 per month, prasugrel costs of US$ 220 per month, ticagrelor costs of US$ 261 per month and a genetic test price of US$ 235. The relative risk of serious cardiovascular events and bleeding for IM+PM and EM+UM on clopidogrel was taken from the meta-analyses by Mega 2010 (percutaneous coronary intervention) and Holmes 2011 (all clopidogrel indications). The risks of serious cardiovascular events and bleeding for prasugrel and ticagrelor and the ticagrelor-specific side effects of dyspnoea and bradyarrhythmia were taken from the TRITON-TIMI 38 trial which compared prasugrel to clopidogrel (Wiviott 2007 and Wiviott 2008) and from the PLATO trial which compared ticagrelor to clopidogrel (Wallentin 2009, Cannon 2010, Storey 2010 and Scirica 2011). Ticagrelor was less favourable compared to prasugrel when the decrease in QALYs due to ticagrelor-induced dyspnoea was assumed to be higher. The decrease in the model was assumed to be the same as that of a medical history of angina pectoris.
The outcome of genotyping with ticagrelor as the most cost-effective therapy when the calculation was made using data for percutaneous coronary intervention was not very sensitive to variation of input data. Variation of input data and costs of US$ 50,000/QALY showed that genotyping with ticagrelor was the preferred strategy in 63% of cases, ticagrelor in 19% and genotyping with prasugrel in 13%.

- Lala A et al. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis. J Thromb Haemost 2013;11:81-91. PubMed PMID: 23137413.
In 60-year-old patients with acute coronary syndrome undergoing percutaneous coronary intervention, the choice of clopidogrel and prasugrel based on the CYP2C19*2 allele delivered similar clinical outcomes with marginally fewer costs and more effectiveness than treatment with either clopidogrel or prasugrel. The total costs of treatment for 15 months were US$ 18 lower and the Quality Adjusted Life-Years (QALY) 0.004 higher compared to clopidogrel and they were US$ 899 lower and 0.0005 higher compared to prasugrel. The difference in costs and QALY increased on longer treatment.
The calculation was based on prasugrel costs of US$ 5.45 per day, clopidogrel costs of US$ 1.00 per day and a genetic test price of US$ 500. The risks of serious cardiovascular events and bleeding were taken

from FDA data and the TRITON-TIMI 38 trial, which compared prasugrel to clopidogrel (reference Mega et al, 2009). In this study, prasugrel was associated with fewer serious cardiovascular events, but with a higher risk of bleeding. Clopidogrel users with the *2 allele (27% of the population) had a 50% higher risk of serious cardiovascular events than those without this allele. Cost-effectiveness was defined as less than US$ 100,000 per QALY gained.
The strongest predictor was the relative risk of carriers compared to non-carriers of the *2 allele during treatment with clopidogrel. Genotype-guided treatment was dominant (more effective and cheaper) when the risk was increased by > 47%. Prasugrel was more cost-effective when the risk was increased by < 42%. Genotype-guided therapy was dominant over clopidogrel for all investigated relative risks (increase by 33-76%). This was no longer the case when clopidogrel costs were higher than $ 3.96 per day, at which point genotype-guided therapy was no longer dominant, but remained cost-effective. A reduction in the costs of genotyping from US$ 500 to US$ 60 did not have a substantial effect on the results. Genotype-guided therapy no longer represented a cost-saving compared to clopidogrel when the mutation prevalence was 10-25%, but it remained the most effective treatment.

- Panattoni L et al. The cost effectiveness of genetic testing for CYP2C19 variants to guide thienopyridine treatment in patients with acute coronary syndromes: a New Zealand evaluation. Pharmacoeconomics 2012;30:1067-84. PubMed PMID: 22974536.
Genotype-guided treatment of patients with acute coronary syndrome compared to clopidogrel or prasugrel only is possibly a cost-effective strategy in the total New-Zealand population, but especially in Maoris and patients from the Pacific Islands. Treatment was cost-effective compared to clopidogrel both when the incidences were taken from New Zealand hospitals and when taken from trials (NZ$ 8,702 per QALY (costs increased by NZ$ 474 and QALY by 0.019 year) versus NZ$ 24,617 per QALY (costs increased by NZ$ 565 and QALY by 0.065 years)). The treatment was especially cost-effective in Maoris (NZ$ 7,312 per QALY) and patients from the Pacific Islands (NZ$ 7,041 per QALY). Genotype-guided treatment was dominant (more effective and cheaper) than prasugrel when incidences from the trial were used and cost-effective when incidences from New Zealand hospitals were used (NZ$ 5,132 per QALY (costs increased by NZ$ 2,146 and QALY by 0.418 years)). The number of incidents was higher with prasugrel due to an increased incidence of stroke, bleeding and cardiovascular death.
The calculation was based on prasugrel costs of NZ$ 4.29 per day, clopidogrel costs of NZ$ 0.89 per day and a genetic test price of NZ$ 175. The risks of serious cardiovascular events and bleeding were taken from New Zealand hospitals and from the TRITON-TIMI 38 trial which compared prasugrel to clopidogrel (reference Mega et al, 2009). The incidences of myocardial infarction and cardiovascular death were much higher in New Zealand than in the TRITON-TIMI 38 trial. Standard therapy in New Zealand is 6 months clopidogrel therapy, while the trial treated patients for 15 months. Populations in New Zealand have different prevalences of *2 heterozygotes (15% in Europeans, 24% in Maoris, 29% in Asians and 45% in those from the Pacific Islands). Maoris and people from the Pacific Islands also have a relatively high frequency of the *3 allele, which was not included in this cost-effectiveness study. Data were analysed from patients between the ages of 45 and 80 years.
The authors stated that the ACCF/AHA Clopidogrel Clinical Alert emphasises the importance of determining the individual risk and to consider genetic or functional testing on this basis.
- Guzauskas GF et al. A risk-benefit assessment of prasugrel, clopidogrel, and genotype-guided therapy in patients undergoing percutaneous coronary intervention. Clin Pharmacol Ther 2012;91:829-37. PubMed PMID: 22453194.
In patients with acute coronary syndrome undergoing percutaneous coronary intervention, the choice of clopidogrel and prasugrel based on the CYP2C19*2 allele is associated with a 93% chance of an increase in QALY by 0.05 years compared to clopidogrel and a 66% chance of an increase in QALY by 0.03 years compared to prasugrel. Prasugrel was associated with fewer cardiovascular events, but more bleeding. An increase in QALY by 2 weeks based on the price of a genetic test alone (approximately US$ 200) is equivalent to US$ 5,000 per QALY gained, which is cost-effective.
The risks of serious cardiovascular events and bleeding were taken from the TRITON-TIMI 38 trial which compared prasugrel to clopidogrel (reference Mega et al, 2009). The relative risks for *2 carriers were taken from a meta-analysis of 9 studies (Mega, 2010).
Clopidogrel and prasugrel may deliver similar increases in QALY, but their risks and benefits differ. Sub-group analysis of the TRITON-TIMI 38 trial suggests that there are groups that have a higher risk of thrombosis and therefore a greater benefit of prasugrel (patients with existing in-stent thrombosis, myocardial infarction with ST elevation and diabetes mellitus) and groups with a higher risk of injury due to bleeding (patients with a history of stroke or TIA, patients > 75 years and patients with a body weight lower than 60 kg). The latter group showed a decrease in QALY compared to all patients on prasugrel.
The TRITON-TIMI 38 trial used a clopidogrel loading dose of 300 mg while a dose of 600 mg is more common nowadays. The authors calculated that an increased loading dose of 600 mg is unlikely to have a similar effect on the number of QALYs gained as genotyped-guided treatment.
- Reese ES et al. Cost-effectiveness of cytochrome P450 2C19 genotype screening for selection of antiplatelet therapy with clopidogrel or prasugrel. Pharmacotherapy 2012;32:323-32 and 581. PubMed PMID: 22461122.

Genotype-guided treatment was dominant over clopidogrel or prasugrel only (more effective and cheaper). The costs per clinical event prevented were US$ 6,760 lower compared to branded clopidogrel and US$ 11,710 lower compared to prasugrel. Generic clopidogrel resulted in genotype-guided treatment no longer delivering cost-savings compared to clopidogrel for all patients (costs per incident prevented US$ 2,300 higher). Genotype-guided treatment compared to clopidogrel led to 1 event prevented for every 23 genotyped patients, while compared to prasugrel this led to 1 event prevented for every 30 genotyped patients.
The calculation was based on prasugrel costs of US$ 6.55 per day, clopidogrel costs of US$ 6.22 per day (branded) or US$ 1.00 per day (generic) and a genetic test price of US$ 310. The risks of serious cardiovascular events and bleeding were taken from the TRITON-TIMI 38 trial (reference Mega et al, 2009), which compared prasugrel to clopidogrel in patients with acute coronary syndrome and elective percutaneous coronary intervention. The measure for effectiveness of the treatment used was the number of events prevented. The model included the following CYP2C19 polymorphisms: *1 to *8 and *17.
Secondary analysis of the data from the TRITON-TIMI 38 trial suggested that there was no difference in effectiveness between clopidogrel and prasugrel among EM patients.

Date of literature search: 8 October 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	PM	4 AA	No	No	19 November 2018
	IM	4 AA	No	No	
	UM	4 AA	No	No	

Mechanism
Prasugrel is converted in two steps to the active metabolite, an unstable thiol compound that inhibits platelet aggregation through the formation of a disulphide bridge with a cysteine residue on the ADP receptor of platelets ($P2Y_{12}$). The steps are consecutively catalysed by carboxylesterases and by 4 different CYP450 enzymes, primarily CYP-3A4 and CYP2B6 and to a lesser extent CYP2C9 and CYP2C19.