CYP2C19: clopidogrel 2548/2549/2550

ACS = acute coronary syndrome, ADP = adenosine diphosphate, AUC = area under the concentration-time curve, AUEC = area under the effect-time curve, CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, HR_{corr} = corrected hazard ratio, IM = intermediate metaboliser (*1/*2, *1/*3, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), LTA = light transmission aggregometry, NM = normal metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), NS = non-significant, OR = odds ratio, PCI = percutaneous coronary intervention, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), RR = relative risk, S = significant, SmPC = Summary of Product Characteristics, TIA = transient ischemic attack, UM = ultrarapid metaboliser (*17/*17) (increased CYP2C19 enzyme activity), VASP = vasodilator-stimulated phosphoprotein assay, VerifyNow assay = an aggregation assay to assess a patient's platelet reactivity to antiplatelet medications ($P2Y_{12}$), 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 health care professional should consider the next best option.

Brief summary and justification of choices:
Clopidogrel is a prodrug. It is mainly converted by CYP2C19 and CYP3A4 to 2-oxoclopidogrel and then to the active metabolite H4. H4 is an unstable thiol compound that inhibits platelet aggregation by formation of a disulphide bridge with a cysteine residue on the platelet ADP receptor ($P2Y_{12}$). Genotypes associated with decreased CYP2C19 activity (IM and PM) reduce the activation of clopidogrel. The genotype associated with increased CYP2C19 activity (UM) increases activation of clopidogrel.

UM: One study found significant effects of the *17 allele on platelet aggregation, but two other studies did not. Positive effects of *17 on clinical endpoints have been reported, which suggests that action may not be desirable. A meta-analysis identified both a reduced incidence of serious cardiovascular events and an increased incidence of bleeding events for *17. As the increased risk of bleeding concerns mainly minor bleeding, no action is needed for this gene-drug interaction (yes/no-interaction).

PM and IM: A significant increase in the incidence of cardiovascular events in coronary artery disease patients has been found for both PM and IM (meta-analyses: Niu 2015, Sorich 2014, Mao 2013, Jang 2012, Holmes 2011, and Liu 2011; studies: Williams 2019, Lee 2018, Shuldiner 2009, Sibbing 2009, Giusti 2009, Collet 2009, Mega 2009, and Simon 2009). The Holmes 2011 meta-analysis attributed the clinical effect to small study bias. The Sorich 2014 and Niu 2015 meta-analyses only found a significant increase in the incidence of cardiovascular events in the studies involving patients undergoing percutaneous coronary intervention. The Niu 2015 meta-analysis also found that the size of the majority of Western studies was not independent of PCI percentage. Most smaller studies had higher PCI percentages, while larger studies included more patients not undergoing PCIs. This could explain the small study bias observed by Holmes 2011. In addition, Williams 2019, Lee 2018, and Cavallari 2018, which are expansions of each other, found the use of alternative therapy for clopidogrel in percutaneous coronary patients to decrease the incidence of major cardiovascular events in IM+PM, but not in NM+UM. Moreover, Shen 2016 and Xie 2013 found genotype-guided therapy with NM on clopidogrel 75 mg/day, IM on clopidogrel 150 mg/day and PM on either ticagrelor (Shen 2016) or 150 mg/day of clopidogrel in combination with cilostazol (Xie 2013) to decrease the incidence of major cardiovascular events in percutaneous coronary intervention patients compared to non-genotype-guided therapy (clopidogrel 75 mg/day for all patients). In addition, the meta-analysis of Kheiri 2019 found genotype-guided therapy to decrease the incidence of myocardial infarction in percutaneous coronary intervention patients compared to non-genotype-guided clopidogrel therapy.
A meta-analysis and a study including more than 1000 cerebrovascular patients found an increased incidence of recurrence of stroke for both PM and IM (Pan 2017 and Wang 2016). In addition, Lan 2019 comparing genotype-guided to non-genotype-guided therapy in 155 patients with mild

non-cardiogenic cerebral infarction, showed that genotype-guided therapy significantly decreased the global disability after treatment (measured with the Modified Rankin Scale) for PM and IM. This study also showed increased global disability after clopidogrel treatment for PM and IM compared to NM. One substudy of Wang 2016 suggested the increased stroke recurrence risk for IM and PM to be restricted to patients with estimated glomerular filtration rates (eGFR) < 75.0 ml/min/1.73m^2 (Wu 2018). However, this was based on a relatively small number of patients per eGFR-subgroup (< 300) and has not been confirmed in a second large study. In addition, a low incidence of recurrent stroke was found in NM+UM in the subgroup with eGFR < 75.0 ml/min/1.73m^2 (2.3-3.7 times lower than in the other eGFR-subgroups), suggesting the difference between IM+PM and NM+UM in this subgroup to be driven by the low value for NM+UM. So, sufficient evidence to subdivide stroke patients in sub-groups with and without increased risk is lacking at the moment. A second substudy of Wang 2016 suggested clopidogrel therapy to be ineffective in stroke patients with short term hyperglycaemia (glycated albumin > 15.5%) (Lin 2017). However, this was independent of CYP2C19 phenotype, being observed both for NM+UM and IM+PM.

Lee 2019 showed an increased all-cause mortality and number of amputation events in PM and IM with severe critical limb ischaemia undergoing endovascular therapy. However, evidence is limited for peripheral arterial disease. There is only one study with more than 250 patients and this is also the only study investigating clinical outcomes instead of subclinical outcomes (angiography or platelet aggregation). In addition, only clopidogrel is indicated for complicated peripheral arterial disease with (threatening) re-occlusion of a stent or bypass, so an alternative therapy is lacking. Vorapaxar can be added to clopidogrel, but is not available in the Netherlands.

Based on the data above, it was concluded that a gene-drug interaction exists for PM and IM in percutaneous coronary intervention and stroke patients and that action is needed (yes/yes-interactions). There is not enough evidence for a gene-drug interaction for PM and IM in peripheral arterial disease at the moment, and alternative therapy is lacking for this indication. For these reasons, peripheral arterial disease was not added to the yes/yes-interactions.

You can find a detailed overview of the clinical and kinetic effects per phenotype in the background information text of the gene-drug interactions on the Kennisbank. You may also have access to this background information text via your pharmacy or physician electronic decision support system.

Substantiation for the (dose) recommendations for IM and PM patients is provided below.

Justification of (dose) recommendation

PM and IM: There is more evidence to support the fact that there is not a higher incidence of cardiovascular events in coronary artery disease patients not undergoing percutaneous coronary intervention for IM patients than for PM patients. The Sorich 2014 meta-analysis is the only study that reviews this effect separately for IM and PM. This study uses a meta-analysis of three studies involving a total of 1332 IM patients and 122 PM patients. The RR for IM patients is not only non-significant, but the value calculated also does not deviate from 1.0. The RR is non-significant for PM patients, but the calculated value is greater than 1.0. Due to this difference in level of evidence, adjustment of therapy in coronary artery disease patients is only recommended for IM undergoing percutaneous coronary intervention, while platelet aggregation testing is recommended for PM without coronary intervention to determine whether adjustment of therapy is desirable.

The meta-analysis of Pan 2017 found the incidence of recurrence of stroke to be increased both for IM and for PM. For this reason, adjustment of therapy in stroke patients is recommended for both IM and PM.

Dose increase by 200% is inadequate for PM patients to make inhibition of platelet aggregation equally strong as in NM patients at the standard dose. Dose increase by 200% in IM patients led to inhibition of platelet aggregation similar to NM patients at the standard dose. Both Xie 2013 (128 IM, 143 NM) and Shen 2016 (139 IM, 133 NM) found a reduction in the incidence of serious cardiovascular events for genotype-guided therapy where the maintenance dose of clopidogrel for IM patients was doubled to 150 mg/day and an alternative was selected for PM patients. Zhong 2018 and Shen 2016 found no significant differences in the incidence of cardiovascular events between NM patients on clopidogrel 75 mg/day, IM on clopidogrel 150 mg/day and PM on ticagrelor. Cavallari 2018 found no significant differences in the incidence of cardiovascular events between NM patients on mainly clopidogrel 75 mg/day and IM+PM on alternative therapy (prasugrel, ticagrelor or high dose clopidogrel). Therefore, only an alternative is recommended for PM patients, while increasing the maintenance dose from 75 mg/day to 150 mg/day is included as an option for IM patients. If a loading dose of 300 mg is used, the loading dose should also be doubled.

Prasugrel, ticagrelor and acetylsalicyl acid/dipyridamol are not metabolised by CYP2C19 (or to a lesser extent).

Recommendation concerning pre-emptive genotyping, including justification of choices:
The Dutch Pharmacogenetics Working Group considers genotyping before starting clopidogrel in percutaneous coronary intervention or stroke patients to be essential for drug efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection.
The clinical implication of the gene-drug interaction scores 8 out of the maximum of 10 points (with pre-emptive genotyping considered to be essential for scores ranging from 6 to 10 points):
The risk of serious life-threatening cardiovascular or cerebrovascular events is increased in percutaneous coronary intervention or stroke patients with a genotype resulting in diminished CYP2C19 enzyme activity (IM and PM). The cardiovascular events can be fatal (code F corresponding to grade 5) (Niu 2015, Jang 2012, Giusti 2009 and Mega 2009). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for CTCAE grade 5).
The increased risk for serious life-threatening cardio- or cerebrovascular events (code E corresponding to grade 4) has been shown in 8 studies and 7 meta-analyses. This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).
The number of percutaneous coronary intervention patients needed to genotype was calculated to be 93 in the study of Cavallari 2018. This study was performed in an USA population having a CYP2C19 IM+PM frequency comparable to that in the Dutch population. For this reason, this number needed to genotype was considered a good approximation of the number needed to genotype in the Netherlands. For stroke patients of European ancestry, the meta-analysis of Pan 2017 found recurrence of stroke in 9.78% of IM+PM and 3.64% of NM. This indicates that recurrence of stroke could be prevented in 6.14% of IM+PM by providing IM+PM with an alternative that is equally effective as clopidogrel in NM. This indicates that 16 IM+PM should be identified in order to prevent one event of recurrent stroke. With a CYP2C19*2-allele frequency of 13-18%, the IM+PM frequency in the Netherlands should be between 24% and 33%. Using the lowest estimate of 24%, 16 IM+PM would amount to a total of 87 patients needed to be genotyped to prevent one event of recurrent stroke. Both the calculated numbers needed to genotype of 93 and 87 result in 2 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (2 points for 10 < NNG ≤ 100).
The Summary of Product Characteristics (SmPC) of clopidogrel indicates that PM are at increased risk of a smaller effect on platelet function. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/ phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).
In addition to the clinical implication score indicating pre-emptive genotyping to be essential, 14 of the 15 cost-effectiveness analyses for percutaneous coronary intervention patients suggested genotype-guided therapy to be cost-effective (Wang 2018, Borse 2017, Jiang 2017, Mitropolou 2016, Deiman 2016, Jiang 2016, Jiang 2015, Patel 2014, Kazi 2014, Sorich 2013, Lala 2013, Panattoni 2012, Guzauskas 2012 and Reese 2012). Except for Wang 2018, all these cost-effectiveness analyses also suggested cost-effectiveness at European IM+PM frequencies (25-32%) and not only at the much higher Asian IM+PM frequencies (40-60%).

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

The meta-analyses in the table below mostly concern meta-analyses of observational studies, and occasionally include post-hoc analyses of the clopidogrel arm of randomised prospective studies.

Source	Code	Effect	Comments
ref. 1 Lee J et al. CYP2C19 polymorphism is associated with amputation rates in patients taking clopidogrel after endovascular intervention for critical limb ischaemia. Eur J Vasc Endovasc Surg 2019;58:373-82. PubMed PMID: 31395432.	3	278 patients with severe critical limb ischaemia (Rutherford classification V and VI) were treated with clopidogrel before and after endovascular therapy. Mean follow-up after endovascular therapy was 245 days. All patients had a follow-up of at least 14 days. 65% of patients completed the 12 month follow-up examination. 42% of patients completing follow-up underwent amputation. Co-medication with influence on CYP2C19 was not excluded. Co-medication with other platelet aggregation inhibitors and with anticoagulants was excluded. Bonferroni's correction was used to adjust for multiple (pairwise) comparison among the study group when the overall test was statistically significant. The multivariable Cox proportional hazard models were adjusted for 15 pre-specified clinical characteristics.	Authors' conclusion: "CYP2C19 genetic profiles can significantly influence clinical outcomes (in both amputation free survival and all-cause mortality) in critical limb ischaemia patients who are taking only clopidogrel after endovascular therapy."

<table>
<tr>
<td>ref. 1, continuation</td>
<td>PM: F
IM: F</td>
<td>According to the reported incidence of amputation (20%) and mortality (20%) during the first year after endovascular therapy, it was assumed that overall event rates (death or amputation) were 20%, 30%, and 40% for NM, IM, and PM, respectively. Based on this assumption, the calculated sample size for a power of 0.8 to find a HR of 1.5 was 239.

Genotyping:
- 153x NM
- 79x IM
- 46x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="3">all-cause mortality</td><td>x 1.87 (S)</td><td>x 1.40 (S)</td><td>16.3%</td></tr>
<tr><td colspan="3">Results were similar if only patients completing follow-up were included: value for NM: 23.4%, PM: x 2.14 (S), and IM: x 1.71 (S).</td></tr>
<tr><td colspan="3">Multivariable Cox analysis showed gene variant number to be an independent predictor of all cause mortality in both the total group (HR_{corr} = 1.39; 95% CI: 1.07-1.74) and in the subgroup of patients completing follow-up (HR_{corr} = 1.51; 95% CI: 1.12-2.17).</td></tr>
<tr><td rowspan="3">number of amputation events</td><td>x 2.38 (S)</td><td>x 1.66 (S)</td><td>18.3%</td></tr>
<tr><td colspan="3">Results were similar if only patients completing follow-up were included: value for NM: 27.1%, PM: x 2.63 (S), and IM: x 2.05 (S).</td></tr>
<tr><td colspan="3">Multivariable Cox analysis showed gene variant number to be an independent predictor of amputation events in both the total group (HR_{corr} = 2.65; 95% CI: 2.1-2.9) and in the subgroup of patients completing follow-up (HR_{corr} = 2.35; 95% CI: 1.97-2.72).</td></tr>
<tr><td>remaining platelet activity ($P2Y_{12}$ reaction units)</td><td>x 1.41 (S)</td><td>x 1.24 (S)</td><td>174.6</td></tr>
</table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Taiwanese patient group.</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Lan H et al.
Anti-platelet therapy in mild cerebral infarction patients on the basis of CYP2C19 metabolizer status.
Cell Transplant 2019;28:1039-44.
PubMed PMID: 31134829.</td>
<td>3</td>
<td>155 patients with mild non-cardiogenic cerebral infarction (National Institutes of Health Stroke Scale (NIHSS) score ≤ 5) completed 1-year treatment with either CYP2C19 genotype-guided antiplatelet therapy (n = 77) or with clopidogrel 75 mg/day (n = 78). Genotype-guided therapy consisted of clopidogrel 75 mg/day for NM and acetylsalicylic acid 100 mg/day for IM and PM. All patients received dual antiplatelet therapy (a 300 mg loading dose of clopidogrel, followed by clopidogrel 75 mg/day, and acetylsalicylic acid 100 mg/day) during the first 21 days after cerebral infarction. Clinical efficacy was assessed with the Modified Rankin Scale, a clinician-reported measure of global disability, that is widely applied for evaluating stroke patient outcomes. Relevant co-medication was not excluded.</td>
<td>Authors' conclusion: "After routine clopidogrel treatment, the efficacy in NM patients was significantly better than in PM and IM patients. After adjustment of therapeutic protocol, the therapeutic efficacy in PM and IM patients was markedly improved, which was accompanied by significant</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>Genotype-guided versus not-genotype-guided therapy:
PM: AA#
IM: AA#
NM: AA

PM: D
IM: D</td>
<td>Genotyping (based on the percentages found in the originally included group of 180 patients):
- 78x NM
- 52x IM
- 25x PM

Results:
<table>
<tr><td colspan="3">Results on genotype-guided compared to not-genotype-guided therapy:</td></tr>
<tr><td rowspan="3">global disability after treatment (Modified Rankin Scale score)</td><td>PM</td><td>x 0.80 (S)</td></tr>
<tr><td>IM</td><td>x 0.77 (S)</td></tr>
<tr><td>NM</td><td>NS</td></tr>
<tr><td colspan="2">cerebral infarction</td><td>NS</td></tr>
<tr><td colspan="2">cerebral haemorrhage</td><td>NS</td></tr>
<tr><td colspan="2">myocardial infarction</td><td>NS</td></tr>
<tr><td colspan="2">events of other organs</td><td>NS</td></tr>
<tr><td colspan="2">adverse drug reactions</td><td>higher (S; 9% versus 0% of patients)

The adverse drug reactions (abdominal pain without occult blood, and diarrhoea) resolved after symptomatic treatment.</td></tr>
<tr><td rowspan="3">cerebral infarction score before treatment (NIHSS score)</td><td>PM</td><td>NS</td></tr>
<tr><td>IM</td><td>NS</td></tr>
<tr><td>NM</td><td>NS</td></tr>
</table>
<table>
<tr><td colspan="4">Results for IM and PM on clopidogrel compared to NM on clopidogrel:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>global disability after treatment (Modified Rankin Scale score)</td><td>x 1.67 (S)</td><td>x 1.41 (S)</td><td>1.51</td></tr>
<tr><td>cerebral infarction score before treatment (NIHSS score)</td><td>NS</td><td>NS</td><td>4.31</td></tr>
</table>
<table>
<tr><td colspan="4">Results for IM and PM on acetylsalicylic acid compared to NM on clopidogrel:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>global disability after treatment (Modified Rankin Scale score)</td><td>x 1.35 (S)</td><td>x 1.10 (S)</td><td>1.49</td></tr>
<tr><td>cerebral infarction score before treatment (NIHSS score)</td><td>NS</td><td>NS</td><td>4.47</td></tr>
</table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese patient group.</td>
<td>reduction in recurrence rate of cerebral infarction.”</td>
</tr>
<tr>
<td>ref. 3
Kheiri B et al. CYP2C19 pharmacogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with</td>
<td>4</td>
<td>Meta-analysis of 6 randomized controlled trials comparing genotype-guided therapy with standard antiplatelet therapy in patients undergoing percutaneous coronary intervention. Standard, i.e. not-genotype-guided, antiplatelet therapy consisted mainly of clopidogrel. The 6 trials included a total of 2371 patients. The trials used different definitions of major adverse cardiovasculare events. Except for 1 trial that used the Thrombolysis in Myocardial Infarction defini-</td>
<td>Authors’ conclusion: “In patients undergoing stent implantation, major adverse cardiovascular events (MACE) with genotype-guided therapy was not sig-</td>
</tr>
</table>

<table>
<tr>
<td>coronary artery disease: a meta-analysis of randomized clinical trials. Catheter Cardiovasc Interv 2019;93:1246-52. PubMed PMID: 30403317.

ref. 3, continuation</td>
<td>Genotype-guided versus not-genotype-guided therapy: AA#</td>
<td>tion and 1 trial not providing a definition, all trials used the Bleeding Academic Research Consortium definition for bleeding events. The median follow-up in the trials was 9 months (range 1-24 months). Two of the trials were performed in Europe, 2 in China, 1 in the USA and 1 in Canada. In the largest trial genotype-guided therapy was guided by both ABCB1 and CYP2C19 genotype.
All studies reported data on major adverse cardiovascular events and on bleeding. 5 studies with a total of 1867 patients reported data on myocardial infarction and on cardiovascular mortality. 4 studies with a total of 1680 patients reported data on stroke. 4 studies with a total of 1675 patients reported data on stent thrombosis.
Of the 6 studies in the meta-analysis, 1 was also included separately in this risk analysis (Xie 2013).
Risk ratios were calculated with a random-effects model.
The authors postulate that for a primary endpoint of net clinical benefit, an appropiately powered trial would contain approximately 5000 patients.

Results:
<table>
<tr><td colspan="3">Results for genotype-guided therapy compared to standard care:</td></tr>
<tr><td></td><td></td><td>Value for standard care</td></tr>
<tr><td rowspan="3">% of patients with major adverse cardiovascular events</td><td>NS</td><td>12.8%</td></tr>
<tr><td>Exclusion of the only not-published study, which was also the only one with longer than 12 months follow-up and the one with the lowest quality (Jadad scale 1) (Tuteja 2018), abolished heterogeneity and resulted in significance:
RR = 0.55 (95% CI: 0.41-0.74) (S)</td><td>13.5%</td></tr>
<tr><td>Exclusion of Tuteja 2018 and the other two studies not only investigating patients with acute coronary syndrome also resulted in significance (S).</td><td>15.2%</td></tr>
<tr><td>% of patients with myocardial infarction</td><td>RR = 0.44 (95% CI: 0.28-0.70) (S)</td><td>6.1%</td></tr>
<tr><td>% of patients with cardiovascular mortality</td><td>NS</td><td>4.3%</td></tr>
<tr><td>% of patients with stroke</td><td>NS</td><td>1.2%</td></tr>
<tr><td>% of patients with stent thrombosis</td><td>trend for a decrease (p = 0.06, NS)</td><td>1.7%</td></tr>
<tr><td>% of patients with bleeding</td><td>trend for a decrease (p = 0.09, NS)</td><td>4.0%</td></tr>
</table>
</td>
<td>nificantly reduced; however, there was a signal towards reduction of MACE in acute coronary syndrome patients, as well as a lower rate of myocardial infarction, though this will require further confirmation in adequately powered trials.”</td>
</tr>
</table>

<table>
<tr><td>ref. 3, continuation</td><td></td><td>There was significant heterogeneity between the studies for major adverse cardiovascular events, but almost all heterogeneity disappeared after exclusion of Tuteja 2018.
There was no significant heterogeneity between the studies for cardiovascular mortality.
There was no heterogeneity between the studies for myocardial infarction, stroke, stent thrombosis and bleeding.
There were no indications for publication bias for major adverse cardiovascular events.</td><td></td></tr>
<tr><td>ref. 4
Williams AK et al. CYP2C19 genotype-guided antiplatelet therapy and 30-day outcomes after percutaneous coronary intervention. Circ Genom Precis Med 2019;12:e002441. PubMed PMID: 30779635.</td><td>3

Clopidogrel versus UM+NM+IM+PM on prasugrel/ticagrelor:
IM+PM: E
NM+UM: AA</td><td>The cohort in this study is an expansion of the cohort in Lee 2018 with follow-up being reduced to 30 days. After a recommendation for use of prasugrel or ticagrelor instead of clopidogrel in CYP2C19 IM and PM, 1063 genotyped patients were treated with dual antiplatelet therapy after percutaneous coronary intervention.
Major adverse cardiovascular or cerebrovascular events were defined as death, myocardial infarction, stent thrombosis, hospitalisation for unstable angina, ischemic stroke, or transient ischemic attack. Clinically significant bleeding was defined as a Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate or severe/life-threatening bleeding event.
Results were corrected for covariates that differed across groups or were associated with the clinical outcome.
Relevant co-medication was not excluded.

Genotyping:
Clopidogrel: - 530x NM+UM; - 120x IM+PM
Prasugrel/ticagrelor: - 204x NM+UM; - 209x IM+PM

Results:
Clopidogrel compared to UM+NM+IM+PM on prasugrel/ticagrelor:
<table>
<tr><td></td><td>IM+PM</td><td>NM+UM</td><td>value for prasugrel/ticagrelor</td></tr>
<tr><td>% of patients with major adverse cardiovascular or cerebrovascular events or clinically significant bleeding</td><td>HR_{corr} = 4.81 (95% CI: 2.12-10.8) (S)</td><td>NS</td><td>3.6%</td></tr>
<tr><td>% of patients with major adverse cardiovascular or cerebrovascular events</td><td>HR_{corr} = 8.00 (95% CI: 3.22-20.8) (S)</td><td>NS</td><td>2.2%</td></tr>
<tr><td>% of patients with clinically significant bleeding</td><td>NS</td><td>NS</td><td>1.7%</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>Authors’ conclusion: “CYP2C19 loss-of-function (LOF) allele carriers receiving clopidogrel exhibited a significantly higher net risk of major adverse cardiovascular or cerebrovascular events (MACCE) or bleeding over 30 days compared with the use of alternative therapy. …. In contrast, no significant difference in risk of MACCE or bleeding was observed in clopidogrel-treated patients without a LOF allele versus those treated with alternative therapy.”</td></tr>
<tr><td>ref. 5
Lee CR et al. Clinical outcomes</td><td>3</td><td>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</td><td>Authors’ conclusion: “The higher risk of major adverse</td></tr>
</table>

<table>
<tr>
<td>and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention.
Circ Genom Precis Med 2018;11:e002069. PubMed PMID: 29615454.

ref. 5, continuation</td>
<td></td>
<td>therapy after percutaneous coronary intervention. Patients were followed for 12 months. 66% of the patients were also included in Cavallari 2018. 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, hospitalisation, 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:
Clopidogrel - 405x NM+UM - 68x IM+PM
Prasugrel/ticagrelor - 113x NM+UM - 165x IM+PM

Results:
<table>
<tr><td colspan="4">IM+PM compared to NM+UM:</td></tr>
<tr><td></td><td></td><td>IM+PM</td><td>events per 100 patient-years for NM+UM</td></tr>
<tr><td rowspan="2">major adverse cardiovascular or cerebrovascular events</td><td>clopidogrel</td><td>HR_{corr} = 2.71 (95% CI: 1.52-4.66) (S)</td><td>20.1</td></tr>
<tr><td>prasugrel/ ticagrelor</td><td>NS</td><td>15.0</td></tr>
<tr><td rowspan="2">clinically significant bleeding</td><td>clopidogrel</td><td>NS</td><td>7.3</td></tr>
<tr><td>prasugrel/ ticagrelor</td><td>NS</td><td>4.2</td></tr>
<tr><td colspan="4">Results were similar when only patients with acute coronary syndrome as indication for percutaneous coronary intervention were analysed (HR_{corr} = 3.68 (95% CI: 1.88-6.83) (S) for major adverse cardiovascular or cerebrovascular events on clopidogrel for IM+PM compared to NM+UM; NS for prasugrel/ ticagrelor).</td></tr>
</table>
IM+PM: E

Clopidogrel versus prasugrel/ticagrelor: IM+PM: E NM+UM: AA
<table>
<tr><td colspan="3">Clopidogrel compared to prasugrel/ticagrelor:</td></tr>
<tr><td></td><td>IM+PM</td><td>NM+UM</td></tr>
<tr><td rowspan="2">major adverse cardiovascular or cerebrovascular events</td><td>HR_{corr} = 4.65 (95% CI: 2.22-10.0) (S)</td><td>NS</td></tr>
<tr><td colspan="2">The difference between IM+PM and NM+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} = 10.00 (95% CI: 3.97-27.7) (S) for major adverse cardiovascular or cere-</td></tr>
</table>
</td>
<td>cardiovascular or cerebrovascular events associated with clopidogrel use in CYP2C19 loss of function allele carriers suggests that use of genotype-guided dual antiplatelet therapy in practice may improve clinical outcomes.”</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>brovascular events for IM+PM for clopidogrel compared to prasugrel/ticagrelor; NS for NM+UM).

Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this patient group from the USA.</td><td></td></tr>
<tr><td>ref. 6
Zhong Z et al.
Effect of cytochrome P450 2C19 polymorphism on adverse cardiovascular events after drug-eluting stent implantation in a large Hakka population with acute coronary syndrome receiving clopidogrel in southern China.
Eur J Clin Pharmacol
2018;74:423-31.
PubMed PMID: 29243114.</td><td>3

Genotype-guided therapy:
PM: AA
IM: AA</td><td>934 patients with acute coronary syndrome receiving percutaneous coronary intervention and second generation drug eluting stent implantation were treated with CYP2C19 genotype-guided dual antiplatelet therapy for at least 1 year. All patients received a 300- or 600-mg loading dose of clopidogrel and a 300-mg dose of aspirin prior to percutaneous coronary intervention. Thereafter, NM were treated with clopidogrel 75 mg daily, IM with clopidogrel 150 mg daily and PM with ticagrelor 90 mg twice daily. All patients received acetylsalicylic acid 100 mg daily.
Major adverse cardiovascular events were defined as cardiovascular death, non-fatal myocardial infarction, target vessel revascularization, or non-fatal stroke.
Concomitant oral anticoagulant therapy was excluded, but other relevant co-medication was not.
Before percutaneous coronary intervention, the percentage of patients with a single vascular lesion was significantly higher for PM than for NM and IM, and the percentage of patients using a statin was significantly higher for NM than for IM and PM.

Genotyping:
- 377x NM
- 426x IM
- 131x PM

Results:
<table>
<tr><td colspan="4">Percentage of patients with adverse events for PM on ticagrelor versus IM on clopidogrel 150 mg/day versus NM on clopidogrel 75 mg/day:</td></tr>
<tr><td></td><td></td><td>PM+tica versus IM+150 clopi versus NM+75 clopi</td><td>value for NM</td></tr>
<tr><td rowspan="3">major adverse cardiovascular events</td><td>1 month</td><td>NS</td><td>2.7%</td></tr>
<tr><td>6 months</td><td>NS</td><td>10.9%</td></tr>
<tr><td>12 months</td><td>NS</td><td>14.1%</td></tr>
<tr><td rowspan="3">death</td><td>1 month</td><td>NS</td><td>0.53%</td></tr>
<tr><td>6 months</td><td>NS</td><td>0.53%</td></tr>
<tr><td>12 months</td><td>NS</td><td>0.80%</td></tr>
<tr><td rowspan="3">non-fatal myocardial infarction</td><td>1 month</td><td>NS</td><td>0.27%</td></tr>
<tr><td>6 months</td><td>NS</td><td>1.3%</td></tr>
<tr><td>12 months</td><td>NS</td><td>1.6%</td></tr>
<tr><td rowspan="3">target vessel revascularisation</td><td>1 month</td><td>NS</td><td>1.9%</td></tr>
<tr><td>6 months</td><td>NS</td><td>9.0%</td></tr>
<tr><td>12 months</td><td>NS</td><td>11.1%</td></tr>
<tr><td rowspan="3">stroke</td><td>1 month</td><td>NS</td><td>0%</td></tr>
<tr><td>6 months</td><td>NS</td><td>0%</td></tr>
<tr><td>12 months</td><td>NS</td><td>0.53%</td></tr>
<tr><td rowspan="3">bleeding events</td><td>1 month</td><td>NS</td><td>3.5%</td></tr>
<tr><td>6 months</td><td>NS</td><td>7.2%</td></tr>
<tr><td>12 months</td><td>NS</td><td>9.6%</td></tr>
</table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese patient group.</td><td>Authors' conclusion: "Based on the genotype-guided antiplatelet therapy, there was no significant association between the carrier status and the clinical outcome at 1, 6, and 12 months. In addition, no significant difference in the rates of bleeding was found among the three groups."</td></tr>
</table>

<table>
<tr>
<td>ref. 7
Wu Y et al.
Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy.
Pharmacogenomics J
2018;18:713-20.
PubMed PMID: 29520080.</td>
<td>3

IM+PM: E</td>
<td>Substudy of Wang 2016. 1476 patients with minor ischemic stroke or high-risk TIA, treated with clopidogrel and acetylsalicylic acid, were grouped in estimated glomerular filtration rate (eGFR) quintiles (292-299 patients per quintile). Patients with severe renal dysfunction, defined as serum creatinine over 1.5 times of upper limit of normal value, were excluded. Patients were followed for 90 days. Recurrent stroke was defined as ischemic or hemorrhagic stroke. Combined vascular events was defined as ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death. Bleeding events were classified according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries). So, minor bleeding was defined as bleeding not requiring transfusion or causing hemodynamic compromise. Moderate bleeding was defined as bleeding that required blood transfusion, but did not lead to hemodynamic compromise. Severe bleeding was defined as fatal or intracranial bleeding or other bleeding causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention.
Co-medication with influence on CYP2C19 was not excluded.

Genotyping:
- 619x NM+UM
- 857x IM+PM

Results:
<table>
<tr><td colspan="4">Results for IM+PM compared to NM+UM:</td></tr>
<tr><td></td><td>eGFR (in ml/min/1.73 m^2)</td><td>IM+PM</td><td>value for NM+UM</td></tr>
<tr><td rowspan="7">% of patients with stroke = % of patients with combined vascular events</td><td>all</td><td>HR_{corr} = 1.51 (95% CI: 1.03-2.21) (S)</td><td>6.6%</td></tr>
<tr><td>≥ 102.5</td><td>NS</td><td>5.4%</td></tr>
<tr><td>94.9-102.4</td><td>NS</td><td>7.8%</td></tr>
<tr><td>87.4-94.8</td><td>NS</td><td>8.9%</td></tr>
<tr><td>75.0-87.4</td><td>NS</td><td>8.8%</td></tr>
<tr><td>< 75.0</td><td>HR_{corr} = 7.39 (95% CI: 1.44-37.95) (S)</td><td>2.4%</td></tr>
<tr><td colspan="3">The percentage of patients with combined vascular events was the same as the percentage of patients with stroke.</td></tr>
<tr><td rowspan="6">% of patients with ischemic stroke</td><td>all</td><td>HR_{corr} = 1.54 (95% CI: 1.04-2.27) (S)</td><td>6.3%</td></tr>
<tr><td>≥ 102.5</td><td>NS</td><td>5.4%</td></tr>
<tr><td>94.9-102.4</td><td>NS</td><td>7.8%</td></tr>
<tr><td>87.4-94.8</td><td>NS</td><td>8.0%</td></tr>
<tr><td>75.0-87.4</td><td>NS</td><td>8.8%</td></tr>
<tr><td>< 75.0</td><td>HR_{corr} = 7.39 (95% CI: 1.44-37.95) (S)</td><td>1.6%</td></tr>
<tr><td rowspan="4">any bleeding</td><td>all</td><td>NS</td><td>2.4%</td></tr>
<tr><td>≥ 102.5</td><td>NS</td><td>1.6%</td></tr>
<tr><td>94.9-102.4</td><td>NS</td><td>3.9%</td></tr>
<tr><td>87.4-94.8</td><td>trend for an in-</td><td>0.9%</td></tr>
</table>
</td>
<td>Authors' conclusion: "Among patients with minor stroke or TIA taking clopidogrel-aspirin treatment, CYP2C19 LOF carrier state was associated with higher risk of new stroke in those with eGFR < 75 ml/min/1.73 m^2. There was no significant difference in the individual outcomes of bleeding in carriers compared with non-carriers in any renal function group."</td>
</tr>
</table>

<table>
<tr>
<td>ref. 7, continuation</td>
<td></td>
<td>
<table>
<tr><td></td><td></td><td>crease (p = 0.06; NS)</td><td></td></tr>
<tr><td></td><td>75.0-87.4</td><td>NS</td><td>3.2%</td></tr>
<tr><td></td><td>< 75.0</td><td>NS</td><td>2.4%</td></tr>
<tr><td>minor bleeding</td><td>all</td><td>NS</td><td>1.5%</td></tr>
<tr><td></td><td>≥ 102.5</td><td>NS</td><td>0.8%</td></tr>
<tr><td></td><td>94.9-102.4</td><td>NS</td><td>2.3%</td></tr>
<tr><td></td><td>87.4-94.8</td><td>NS</td><td>0.9%</td></tr>
<tr><td></td><td>75.0-87.4</td><td>NS</td><td>1.6%</td></tr>
<tr><td></td><td>< 75.0</td><td>trend for a decrease (p = 0.09; NS)</td><td>1.6%</td></tr>
<tr><td>moderate bleeding</td><td>all</td><td>NS</td><td>0.2%</td></tr>
<tr><td></td><td>≥ 102.5</td><td>NS</td><td>0%</td></tr>
<tr><td></td><td>94.9-102.4</td><td>-</td><td>0%</td></tr>
<tr><td></td><td>87.4-94.8</td><td>NS</td><td>0%</td></tr>
<tr><td></td><td>75.0-87.4</td><td>-</td><td>0%</td></tr>
<tr><td></td><td>< 75.0</td><td>-</td><td>0%</td></tr>
<tr><td></td><td colspan="3">Because almost no moderate bleeding occurred, significance could not be determined for most subgroups.</td></tr>
<tr><td>severe bleeding</td><td>all</td><td>NS</td><td>0%</td></tr>
<tr><td></td><td>≥ 102.5</td><td>-</td><td>0%</td></tr>
<tr><td></td><td>94.9-102.4</td><td>-</td><td>0%</td></tr>
<tr><td></td><td>87.4-94.8</td><td>-</td><td>0%</td></tr>
<tr><td></td><td>75.0-87.4</td><td>NS</td><td>0%</td></tr>
<tr><td></td><td>< 75.0</td><td>-</td><td>0%</td></tr>
<tr><td></td><td colspan="3">Because almost no severe bleeding occurred, significance could not be determined for most subgroups.</td></tr>
<tr><td colspan="4">The median eGFR was 61.8 ml/min/1.73m^2 in the < 75.0 ml/min/1.73m^2 group.
The median eGFR was 116.1 ml/min/1.73m^2 in the ≥ 102.5 ml/min/1.73m^2 group.</td></tr>
</table>

Note: A previous substudy of the study described in Wang 2016 showed that clopidogrel plus acetylsalicylic acid compared with acetylsalicylic acid alone in patients with normal renal function and mild chronic kidney disease resulted in a significant reduction in stroke recurrence and vascular events at 90 days, but this benefit was not apparent in moderate chronic kidney disease patients. The group with eGFR < 75.0 ml/min/1.73m^2 (median 61.8 ml/min/1.73m^2) approached moderate kidney failure.

Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this Chinese patient group.
</td>
<td></td>
</tr>
<tr>
<td>ref. 8
Cavallari LH et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. JACC Cardiovasc Interv 2018;11:181-91. PubMed PMID:</td>
<td>3</td>
<td>After a recommendation for use of prasugrel or ticagrelor instead of clopidogrel in CYP2C19 IM and PM, 1815 genotyped patients were treated with antiplatelet therapy after percutaneous coronary intervention (PCI). Patients were followed for 12 months. For 66.7% of patients (n = 1210), acute coronary syndrome (ACS) was the indication for percutaneous coronary intervention. 83.6% of patients received drug-eluting stents and 98.2% of patients received acetylsalicylic acid next to clopidogrel, prasugrel or ticagrelor. Alternative therapy in IM+PM was prasugrel in 64.2%, ticagrelor in 33.5%, clopidogrel 150 mg/day in 0.6% and clopidogrel 225 mg/day in 1.7% of patients. Alternative therapy in NM+UM was prasugrel in 64.8% and ticagrelor in 35.2% of patients.</td>
<td>Authors' conclusion: "These data from real-world observations demonstrate a higher risk for cardiovascular events in patients with a CYP2C19 loss-of-function allele if clopidogrel versus alternative therapy is prescribed."</td>
</tr>
</table>

<table>
<tr>
<td>29102571.

ref. 8, continuation</td>
<td>Clopidogrel 75 mg/day versus alternative therapy:
IM: E
IM+PM: E
NM+UM: AA

IM+PM on alternative therapy versus</td>
<td>
Major adverse cardiovascular events were defined as myocardial infarction, ischemic stroke, or death. Major adverse cardiovascular events occurred in 108 patients in this study.
Results were corrected for the probability of receiving clopidogrel versus alternative platelet therapy.
Relevant co-medication was not excluded.
A total sample size of 1,815 patients, with at least 30% being IM or PM and 60% of IM+PM receiving alternative therapy, provided >90% power with an alpha level of 0.05 to detect a hazard ratio of 2.0 for the occurrence of a major adverse cardiovascular event between the IM+PM-clopidogrel and -alternative groups.

Genotyping:
<table>
<tr><td>Clopidogrel 75 mg/day</td><td>Alternative therapy</td></tr>
<tr><td>- 1050x NM+UM</td><td>- 193x NM+UM</td></tr>
<tr><td>- 226x IM+PM (219x IM, 7x PM)</td><td>- 346x IM+PM (299x IM, 47x PM)</td></tr>
</table>
Results:
<table>
<tr><td colspan="4">Clopidogrel 75 mg/day compared to alternative therapy:</td></tr>
<tr><td></td><td>IM+PM</td><td>IM</td><td>NM+UM</td></tr>
<tr><td>major adverse cardiovascular events</td><td>HR_{corr} = 2.26 (95% CI: 1.18-4.32) (S)</td><td>x 3.6 (S)</td><td>NS</td></tr>
<tr><td>death</td><td>HR_{corr} = 3.76 (95% CI: 1.37-10.35) (S)</td><td></td><td>NS</td></tr>
<tr><td>myocardial infarction</td><td>NS</td><td></td><td>NS</td></tr>
<tr><td>ischemic stroke</td><td>NS</td><td></td><td>NS</td></tr>
<tr><td>major adverse cardiovascular events including stent thrombosis and unstable angina</td><td>HR_{corr} = 1.82 (95% CI: 1.07-3.12) (S)</td><td></td><td>NS</td></tr>
<tr><td>stent thrombosis</td><td>NS</td><td></td><td></td></tr>
<tr><td>unstable angina</td><td>NS</td><td></td><td></td></tr>
<tr><td colspan="4">Results were similar for IM+PM when only patients with acute coronary syndrome as indication for percutaneous coronary intervention were analysed (HR_{corr} = 2.87 (95% CI: 1.35-6.09) (S) for major adverse events; HR_{corr} = 2.10 (95% CI: 1.12-3.90) (S) for major adverse events including stent thrombosis and unstable angina; HR_{corr} = 2.93 (95% CI: 1.12-7.72) (S) for myocardial infarction; NS for death and for ischemic stroke).</td></tr>
<tr><td colspan="4">Moderate and severe or life-threatening bleeding events, defined according to the GUSTO (Global Utilization of t-PA and Streptokinase for Occluded Coronary Arteries) criteria, were observed in 2.3% of patients in the overall study population and were similar across groups.</td></tr>
</table>
<table>
<tr><td colspan="4">IM+PM on alternative therapy compared to NM+UM on clopidogrel, prasugrel or ticagrelor:</td></tr>
<tr><td></td><td>IM+PM</td><td>IM</td><td>events per 100 patient-years for NM+UM</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>ref. 8, continuation</td>
<td>NM+UM on mainly clopidogrel 75 mg/day: AA</td>
<td>
<table>
<tr><td>major adverse cardiovascular events</td><td>NS</td><td>NS</td><td>13.7</td></tr>
<tr><td>death</td><td>NS</td><td></td><td>6.6</td></tr>
<tr><td>myocardial infarction</td><td>NS</td><td></td><td>7.0</td></tr>
<tr><td>ischemic stroke</td><td>NS</td><td></td><td>2.4</td></tr>
<tr><td>major adverse cardiovascular events including stent thrombosis and unstable angina</td><td>NS</td><td></td><td>19.6</td></tr>
<tr><td>stent thrombosis</td><td>NS</td><td></td><td>2.4</td></tr>
<tr><td>unstable angina</td><td>NS</td><td></td><td>5.7</td></tr>
<tr><td colspan="4">Results were similar when only patients with acute coronary syndrome as indication for percutaneous coronary intervention were analysed (all comparisons for IM+PM NS).</td></tr>
<tr><td colspan="4">Moderate and severe or life-threatening bleeding events, defined according to the GUSTO (Global Utilization of t-PA and Streptokinase for Occluded Coronary Arteries) criteria, were observed in 2.3% of patients in the overall study population and were similar across groups.</td></tr>
</table>

Note: In this study, the observed prevalence of IM+PM was 31.5% and the observed percentages of IM+PM developing a major adverse cardiovascular events were 8.0% on clopidogrel 75 mg/day and 4.6% on alternative therapy, Based on these data, the authors calculated that the number of patients needed to genotype to prevent 1 major cardiovascular event was 93.

Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this patient group from the USA. For part of the patients either *4-*6, *8-*10 and *13 or *4, *4B, *6, *8, *10, *12 and *14 were also determined,</td>
<td></td>
</tr>
<tr>
<td>ref. 9
Lin Y et al.
Impact of glycemic control on efficacy of clopidogrel in transient ischemic attack or minor stroke patients with CYP2C19 genetic variants.
Stroke 2017;48:998-1004.
PubMed PMID: 28289237.</td>
<td>3</td>
<td>Substudy of Wang 2016. 2933 patients with minor ischemic stroke or high-risk TIA were treated with clopidogrel and acetylsalicylic acid (n = 1463) or with acetylsalicylic acid alone (n = 1470). Patients were followed for 90 days. Recurrent stroke was defined as ischemic or hemorrhagic stroke. Combined vascular events was defined as ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death. Bleeding was defined as any bleeding event according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries). Glycated albumine levels of > 15.5% were defined as high, indicating poor short-term (2-4 weeks) glycemic control, whereas those of ≤ 15.5% were considered to be low, indicating good short-term glycemic control. 63% of patients (n = 1844) had glycated albumine levels > 15.5%. Of the patients with good short-term glycemic control (glycated albumin ≤ 15.5%), IM+PM tended to have hypercholesterolemia more often than NM+UM (p = 0.05). However, hazard ratios were corrected for confounders, including hyperlipidemia.
Co-medication with influence on CYP2C19 was not excluded.

Genotyping:
Clopidogrel/acetylsalicylic acid
- 609x NM+UM
- 854x IM+PM

Acetylsalicylic acid
- 598x NM+UM
- 872x IM+PM</td>
<td>Authors’ conclusion: “In patients with minor stroke or high-risk transient ischemic attack, clopidogrel-aspirin when compared with aspirin alone reduced stroke recurrence only in noncarriers of CYP2C19 loss-of-function allele and normal glycated albumin levels.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 9, continuation</td>
<td>IM+PM: E</td>
<td>Results:
<table>
<tr><td colspan="4">Results for clopidogrel/acetylsalicylic acid compared to acetylsalicylic acid:</td></tr>
<tr><td></td><td>glycated albumin</td><td>IM+PM</td><td>NM+UM</td></tr>
<tr><td rowspan="3">stroke</td><td rowspan="2">> 15.5%</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td>≤ 15.5%</td><td>NS</td><td>HR_{corr} = 0.18 (95% CI: 0.07-0.42) (S)</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was significant (S).</td></tr>
<tr><td rowspan="3">combined vascular event</td><td rowspan="2">> 15.5%</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td>≤ 15.5%</td><td>NS</td><td>HR_{corr} = 0.18 (95% CI: 0.08-0.42) (S)</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was significant (S).</td></tr>
<tr><td rowspan="3">ischemic stroke</td><td rowspan="2">> 15.5%</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td>≤ 15.5%</td><td>NS</td><td>HR_{corr} = 0.11 (95% CI: 0.04-0.32) (S)</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was significant (S).</td></tr>
<tr><td rowspan="3">bleeding</td><td rowspan="2">> 15.5%</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td>≤ 15.5%</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="3">There was no difference between IM+PM and NM+UM (NS).</td></tr>
</table>
Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this Chinese patient group.</td>
<td></td>
</tr>
<tr>
<td>ref. 10
Pan Y et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Circulation 2017;135:21-33. PubMed PMID: 27806998.</td>
<td>4</td>
<td>Meta-analysis of 15 studies including a total of 4762 patients with stroke or transient ischemic attack (TIA) using clopidogrel. Of the 4762 patients, 2185 were NM or UM, 2033 were IM, and 544 were PM. 367 patients were of European ancestry (92 IM+PM and 275 NM+UM), 4045 of Asian ancestry (2408 IM+PM and 1637 NM+UM), 97 of African ancestry (28 IM+PM and 69 NM+UM), and 253 of other ancestry (48 IM+PM and 205 NM+UM). 2 studies were post hoc analysis of randomised controlled trials and 13 were cohort studies. 5 studies enrolled both ischemic stroke and TIA patients and 10 enrolled patients with ischemic stroke only.
All studies reported data on recurrent stroke. 10 studies with in total 3778 patients (1607 NM or UM, 1716 IM, and 455 PM) reported data on composite vascular events. 7 studies with in total 3522 patients (1623 NM or UM and 1899 IM or PM) reported data on bleeding events.
Stroke was defined as ischemic stroke or hemorrhagic</td>
<td>Authors' conclusion: "Carriers of CYP-2C19 loss-of-function alleles are at greater risk of stroke and composite vascular events than noncarriers among patients with ischemic stroke or TIA treated with clopidogrel."</td>
</tr>
</table>

<table>
<tr>
<td>ref. 10, continuation</td>
<td>IM: E
PM: E</td>
<td>stroke. Composite vascular outcome was defined as stroke, myocardial infarction or vascular death.
Of the 15 studies in the meta-analysis, 1 was also included separately in this risk analysis (Wang 2016).
Risk ratios were calculated with a fixed-effects model in the absence of heterogeneity between the studies. Otherwise, a random-effects model was used.

Results:
<table>
<tr><td colspan="4">Results for IM, PM or IM+PM compared to NM+UM:</td></tr>
<tr><td></td><td>ancestry</td><td>IM</td><td>PM</td></tr>
<tr><td rowspan="8">stroke</td><td rowspan="2">all</td><td>RR = 1.79 (95% CI: 1.45-2.22)</td><td>RR = 2.52 (95% CI: 1.93-3.30)</td></tr>
<tr><td colspan="2">RR = 1.92 (95% CI: 1.57-2.35)</td></tr>
<tr><td>European</td><td colspan="2">RR = 2.46 (95% CI: 1.06-5.72)</td></tr>
<tr><td>Asian</td><td colspan="2">RR = 1.93 (95% CI: 1.55-2.39)</td></tr>
<tr><td>African</td><td colspan="2">NS</td></tr>
<tr><td>other</td><td colspan="2">NS</td></tr>
<tr><td colspan="3">Funnel plots for the outcome of stroke were asymmetrical, suggesting possible publication bias. After quantification of the potential effect of small-study bias and addition of the 3 hypothetical missing studies, the RR was reduced to 1.80 (95% CI: 1.47-2.21).</td></tr>
<tr><td colspan="3">The study of Wang 2016 accounted for 31% of the patients in the meta-analysis. Sensitivity analysis showed that the overall effect (RR = 1.92) was consistent with the overall estimate from all studies except Wang 2016 (RR = 2.22), but the 95% CI became narrower with the addition of Wang 2016 (1.73-2.84 versus 1.57-2.35).
After exclusion of studies with small sample size, low quality score, high risk patients, or CYP2C19 *17 alleles, the effect size of IM+PM on risk of new stroke in clopidogrel-treated patients remained similar.</td></tr>
<tr><td colspan="3">In patients of European ancestry, stroke recurred in 3.64% of NM and 9.78% of IM+PM.</td></tr>
<tr><td rowspan="2">composite vascular outcome</td><td rowspan="2">all</td><td>RR = 1.45 (95% CI: 1.06-1.98)</td><td>RR = 1.96 (95% CI: 1.49-2.58)</td></tr>
<tr><td colspan="2">RR = 1.51 (95% CI: 1.10-2.06)</td></tr>
<tr><td rowspan="5">bleeding</td><td>all</td><td colspan="2">NS</td></tr>
<tr><td>European</td><td colspan="2">NS</td></tr>
<tr><td>Asian</td><td colspan="2">NS</td></tr>
<tr><td>African</td><td colspan="2">NS</td></tr>
<tr><td>other</td><td colspan="2">NS</td></tr>
<tr><td colspan="4">There was significant heterogeneity between the studies for composite vascular outcome, but not for stroke and bleeding.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 11
Deiman BA et al. Reduced number of cardiovascular events and increased cost-effectiveness by genotype-guided</td>
<td>3</td>
<td>73 PMs for CYP2C19 (CYP2C19 *2/*2) who underwent elective percutaneous coronary intervention with stent placement were treated with clopidogrel 75 mg/day (n = 32) or prasugrel 10 mg/day (n = 41) 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, clopidogrel was given. Patients</td>
<td>Authors' conclusion: "This study provides evidence that for CYP2C19-related poor metabolisers prasugrel may be more effective than</td>
</tr>
</table>

<table>
<tr>
<td>antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Neth Heart J 2016;24:589-99. PubMed PMID: 27573042.

ref. 11, continuation</td>
<td>Clopidogrel versus prasugrel: PM: E</td>
<td>were monitored for at least 1.5 years after the stent placement.
Adverse cardiovascular events were defined as death due to cardiovascular cause, myocardial infarction, stent thrombosis, stroke, or a second percutaneous coronary intervention in the same artery. Major adverse cardiovascular events were defined as stent thrombosis, myocardial infarction and death.
None of the patients in the study had major 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 adverse events for clopidogrel versus prasugrel:</td></tr>
<tr><td></td><td>clopidogrel</td><td>value for prasugrel</td></tr>
<tr><td>adverse cardiovascular events</td><td>x 8.3 (S)</td><td>4.9%</td></tr>
<tr><td>adverse cardiovascular events within 1.5 years</td><td>x 6.4 (S)</td><td>4.9%</td></tr>
<tr><td>major adverse cardiovascular events within 1.5 years</td><td>x 10 (S)</td><td>2.4%</td></tr>
</table>
</td>
<td>clopidogrel to prevent major adverse cardiovascular events after PCI and this approach could be cost-effective.”</td>
</tr>
<tr>
<td>ref. 12
Wang Y et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. JAMA 2016;316:70-8. PubMed PMID: 27348249.</td>
<td>3</td>
<td>2933 patients with minor ischemic stroke or high-risk TIA, aged 40 years or older, were treated with clopidogrel and acetylsalicylic acid (n = 1463) or with acetylsalicylic acid alone (n = 1470). Treatment started within 24 hours of symptom onset. All patients received a loading dose of 75-300 mg acetylsalicylic acid. Patients treated with clopidogrel and acetylsalicylic acid received a clopidogrel loading dose of 300 mg followed by clopidogrel 75 mg/day for 3 months and acetylsalicylic acid 75 mg/day for the first 3 weeks. Patients treated with acetylsalicylic acid alone received 75 mg/day for 3 months. Patients were followed for 90 days. Acute minor stroke was defined by a score of 3 or less at the time of randomization on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater deficits). TIA was defined as focal brain ischemia with resolution of symptoms within 24 hours after onset plus a moderate-to-high risk of stroke recurrence (defined as a score of ≥ 4 at the time of randomisation on the ABCD^2, which assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes; scores range from 0 to 7, with higher scores indicating greater short-term risk).
New stroke was defined as ischemic or hemorrhagic stroke. Combined vascular events was defined as ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death. Bleeding was defined as any bleeding event according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria.
Patients with a clear indication for anticoagulation therapy (presumed cardiac source of embolus), with an anticipated requirement for long-term nonstudy antiplatelet drugs or for nonsteroidal antiinflammatory drugs affecting platelet function, or with heparin therapy or oral anticoagulation therapy within 10 days before randomisation were excluded. No patients included in the study were treated with thromboly-</td>
<td>Authors’ conclusion: “Among patients with minor ischemic stroke or transient ischemic attack, the use of clopidogrel plus aspirin compared with aspirin alone reduced the risk of a new stroke only in the subgroup of patients who were not carriers of the CYP2C19 loss-of-function alleles. These findings support a role of CYP2C19 genotype in the efficacy of this treatment.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 12, continuation</td>
<td>IM+PM: E</td>
<td>
sis around the time of randomisation. Other comedication was not excluded.

Genotyping:
Clopidogrel/acetylsalicylic acid
- 609x NM+UM
- 854x IM+PM (673x IM, 181x PM)

Acetylsalicylic acid
- 598x NM+UM
- 872x IM+PM (684x IM, 188x PM)

Results:
<table>
<tr><td colspan="3">IM+PM compared to NM+UM for clopidogrel/acetylsalicylic acid:</td></tr>
<tr><td></td><td>IM+PM</td><td>value for NM+UM</td></tr>
<tr><td>% of patients with stroke =
% of patients with combined vascular events</td><td>HR = 1.46 (95% CI: 1.05-2.13) (S)</td><td>6.7%</td></tr>
<tr><td>any bleeding</td><td>NS</td><td>2.5%</td></tr>
<tr><td colspan="3">No differences between IM+PM and NM+UM were found in the acetylsalicylic acid alone group.</td></tr>
</table>
<table>
<tr><td colspan="4">Results for clopidogrel/acetylsalicylic acid compared to acetylsalicylic acid:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>NM+UM</td></tr>
<tr><td rowspan="3">stroke</td><td>NS</td><td>NS</td><td>HR = 0.51 (95% CI: 0.35-0.75) (S)</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was significant (S).</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was also significant after exclusion of the 20 proton pump inhibitor users (S). The difference could not be estimated in the proton pump inhibitor users.</td></tr>
<tr><td rowspan="3">combined vascular event</td><td>NS</td><td>NS</td><td>HR = 0.50 (95% CI: 0.34-0.74) (S)</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was significant (S).</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was also significant after exclusion of the 20 proton pump inhibitor users (S), but there was no difference for the proton pump inhibitor users (NS).</td></tr>
<tr><td rowspan="2">ischemic stroke</td><td colspan="2">NS</td><td>HR = 0.51 (95% CI: 0.34-0.75) (S)</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was significant (S).</td></tr>
<tr><td rowspan="2">progressive ischemic stroke</td><td colspan="2">NS</td><td>HR = 0.38 (95% CI: 0.17-0.84) (S)</td></tr>
<tr><td colspan="3">The difference between IM+PM and NM+UM was significant (S).</td></tr>
<tr><td rowspan="2">recurrent ischemic stroke</td><td colspan="2">NS</td><td>HR = 0.53 (95% CI: 0.34-0.83) (S)</td></tr>
<tr><td colspan="3">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td rowspan="2">large-artery atherosclerosis</td><td colspan="2">NS</td><td>HR = 0.62 (95% CI: 0.39-0.97) (S)</td></tr>
<tr><td colspan="3">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td>small-</td><td colspan="2">trend for a lower rate</td><td>HR = 0.28 (95%</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>ref. 12, continuation</td>
<td></td>
<td>
<table>
<tr><td>artery occlusion</td><td>(p = 0.05) (NS)</td><td>CI: 0.12-0.65) (S)</td></tr>
<tr><td></td><td colspan="2">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td>cardiogenic embolism</td><td colspan="2">not estimable due to the absence of moderate bleeding in one or more groups</td></tr>
<tr><td>myocardial infarction</td><td colspan="2">not estimable due to the absence of myocardial infarction in one or more groups</td></tr>
<tr><td>any bleeding</td><td>NS</td><td>NS</td></tr>
<tr><td></td><td colspan="2">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td></td><td colspan="2">Results were similar after exclusion of the 20 proton pump inhibitor users and could not be estimated in the proton pump inhibitor users.</td></tr>
<tr><td>mild bleeding</td><td>trend for a higher bleeding rate (p = 0.08) (NS)</td><td>NS</td></tr>
<tr><td></td><td colspan="2">There was no difference between IM+PM and NM+UM (NS).</td></tr>
<tr><td>moderate bleeding</td><td colspan="2">not estimable due to the absence of moderate bleeding in one or more groups</td></tr>
<tr><td>severe bleeding</td><td colspan="2">not estimable due to the absence of severe bleeding in one or more groups</td></tr>
</table>

Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this Chinese patient group.
</td>
<td></td>
</tr>
<tr>
<td>ref. 13
Ogawa H et al. Effects of CYP-2C19 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 clopidogrel (n = 383, loading dose 300 mg, maintenance dose 75 mg/day) or low dose prasugrel (n = 390, loading dose 20 mg, maintenance dose 3.75 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 subunits).
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 clopidogrel group:
- 135x NM
- 171x IM
- 77x PM

Results:
<table>
<tr><td colspan="3">Results for clopidogrel versus low-dose prasugrel:</td></tr>
<tr><td></td><td>clopidogrel</td><td>value for prasugrel</td></tr>
<tr><td>cardiovascular death, non-fatal myocardial infarction</td><td>NS</td><td>11.8% of the NM and</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 major adverse cardiovascular events (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. 13, continuation		or nonfatal ischemic stroke for NM and IM+PM		9.3% of the IM+PM		
		cardiovascular death for NM and IM+PM	NS	0.7% of the NM and 0% of the IM+ PM		
		non-fatal myocardial infarction for NM and IM+PM	NS	10.5% of the NM and 9.3% of the IM+PM		
		non-fatal ischemic stroke for NM and IM+PM	NS	0.7% of the NM and 0% of the IM+ PM		
		revascularisation for NM and IM+PM	NS	5.2% of the NM and 5.9% of the IM+PM		
		stent thrombosis for NM and IM+PM	NS	1.3% of the NM and 0.4% of the IM+PM		
		all bleeding for NM	NS	47.7% of the NM		
		all bleeding for IM+PM	HR = 0.56 (95% CI: 0.42-0.74) (S)	50.2% of the IM+PM		
	IM+PM: AA[#]	The authors indicated that for clopidogrel, the incidence of all bleeding was significantly lower for IM+PM compared to NM (HR = 0.66; 95% CI: 0.47-0.92) (S).				
		major TIMI bleeding for NM and IM+PM	NS	2.6% of the NM and 0.4% of the IM+PM		
		minor TIMI bleeding for NM and IM+PM	NS	2.0% of the NM and 3.0% of the IM+PM		
		clinically relevant bleeding for NM and IM+PM	NS	4.6% of the NM and 3.0% of the IM+PM		
	Clopidogrel versus low-dose prasugrel: IM+PM: AA[#]	other bleeding for NM	NS	43.8% of the NM		
		other bleeding for IM+PM	HR = 0.52 (95% BI: 0.38-0.71) (S)	44.7% of the IM+PM		
		bleeding leading to discontinuation of the treatment for NM and IM+PM	NS	1.3% of the NM and 0.8% of the IM+PM		
		remaining platelet activity for NM after 4, 12, 24, 26 and 48 weeks	NS			
		remaining platelet activity for IM+PM after 4, 12, 24, 26 and 48 weeks	higher (S)			

<table>
<tr>
<td>ref. 13, continuation</td>
<td></td>
<td>
<table>
<tr><td>remaining platelet activity for NM and IM+PM, 2-4 hours and 5-12 hours after the loading dose</td><td>higher (S)</td><td></td></tr>
<tr><td colspan="3">The authors indicated that for clopidogrel the platelet inhibition was significantly lower for IM+PM compared to NM.</td></tr>
</table>

Note: Genotyping was performed for *2 and *3. These are the most important gene variants in this Japanese patient group.
</td>
<td></td>
</tr>
<tr>
<td>ref. 14
Shen DL et al. Clinical value of CYP2C19 genetic testing for guiding the antiplatelet therapy in a Chinese population. J Cardiovasc Pharmacol 2016;67:232-6. PubMed PMID: 26727381.</td>
<td>4

Genotype-guided versus non-genotype-guided therapy: AA#

Genotype-guided therapy:</td>
<td>309 patients were treated with CYP2C19 genotype-guided therapy post percutaneous coronary intervention (NM: clopidogrel 75 mg/day, IM: clopidogrel 150 mg/day, PM: ticagrelor 90 mg twice daily). The patients were compared to a group of 319 patients on conventional therapy (clopidogrel 75 mg/day). The loading dose in both groups was clopidogrel 600 mg plus acetylsalicylic acid 300 mg. Heparin and low-molecular-weight heparins were used as anticoagulant therapy in the peri-operative period. Patients were followed for on average 12 months. Relevant co-medication was excluded.
Serious cardiovascular events were defined as death, myocardial infarction or revascularisation of the previously treated artery.

Genotyping (only in the genotype-guided group):
- 133x NM
- 139x IM
- 37x PM

Results:
<table>
<tr><td colspan="3">Genotype-guided versus non-genotype-guided therapy:</td></tr>
<tr><td></td><td></td><td>% patients in non-genotype-guided group</td></tr>
<tr><td>Serious cardiovascular events</td><td>x 0.45 (S); OR = 0.42 (95% CI: 0.20-0.91)</td><td>9.4%</td></tr>
<tr><td>Myocardial infarction</td><td>x 0.39 (NS, trend, p = 0.065)</td><td>4.1%</td></tr>
<tr><td>Death</td><td>NS</td><td>2.5%</td></tr>
<tr><td>Revascularisation</td><td>NS</td><td>2.8%</td></tr>
<tr><td>Bleeding</td><td>NS</td><td>6.0%</td></tr>
<tr><td colspan="3">The decrease in serious cardiovascular events was also significant at 1 month (x 0.23; OR = 4.92; 95% CI: 1.48-16.29) and at 6 months (x 0.41; OR = 2.48; 95% CI: 1.04-5.92) (S).
The decrease in myocardial infarctions was significant at 1 and 6 months.
All bleeding involved minor bleeding.</td></tr>
<tr><td colspan="3">At the start of treatment, the haemoglobin concentrations were lower in the genotype-guided group, and there was a trend towards lower triglyceride concentrations (p = 0.055). However, haemoglobin and triglyceride concentrations were not significant predictors of serious cardiovascular events.</td></tr>
</table>
<table>
<tr><td colspan="3">Genotype-guided therapy, PM versus IM versus NM:</td></tr>
<tr><td></td><td></td><td>% for NM</td></tr>
<tr><td>Serious</td><td>NS</td><td>5.3%</td></tr>
</table>
</td>
<td>Authors' conclusions: "Individual antiplatelet therapy guided by CYP2C19 genetic testing significantly reduced the rate of major adverse cardiovascular events without an increase in the rate of bleeding in the near term in this Chinese population."</td>
</tr>
</table>

<table>
<tr>
<td>ref. 14, continuation</td>
<td>PM: AA
IM: AA</td>
<td>
<table>
<tr><td>cardiovascular events</td><td></td><td></td></tr>
<tr><td>Bleeding</td><td>NS</td><td>6.0%</td></tr>
<tr><td colspan="3">There were no significant differences between the genotype groups at 1 and 6 months.</td></tr>
</table>
N.B.: Alleles *2 and *3 were genotyped. These are the most common alleles in this Chinese patient group.
</td>
<td></td>
</tr>
<tr>
<td>ref. 15
Xiong R et al.
A randomized controlled trial to assess the efficacy and safety of doubling dose clopidogrel versus ticagrelor for the treatment of acute coronary syndrome in patients with CYP2C19*2 homozygotes.
Int J Clin Exp Med 2015;8:13310-6.
PubMed PMID: 26550258.</td>
<td>3

Double clopidogrel dose versus ticagrelor:
PM: B</td>
<td>
Patients with genotype *2/*2 who had had ST-elevation or non-ST-elevation acute coronary syndrome were randomised for 30 days to either double clopidogrel dose (600 mg loading dose, followed by 150 mg/day) (n = 112) or ticagrelor (180 mg loading dose, followed by 90 mg twice daily) (n = 112). Relevant co-medication was not excluded.

Results:
<table>
<tr><td colspan="3">Double clopidogrel dose versus ticagrelor:</td></tr>
<tr><td></td><td></td><td>Value for ticagrelor</td></tr>
<tr><td>Serious cardiovascular events</td><td>Did not occur in either group (NS)</td><td></td></tr>
<tr><td>Major bleeding</td><td>Did not occur in either group (NS)</td><td></td></tr>
<tr><td>Minor bleeding</td><td>HR = 2.88 (95% CI: 1.34-6.15) (S)</td><td>7.1%</td></tr>
<tr><td>P_2Y_{12} reaction units on day 15</td><td>x 2.2 (S)</td><td>34.5</td></tr>
<tr><td>P_2Y_{12} reaction units on day 30</td><td>x 1.4 (S)</td><td>27.9</td></tr>
<tr><td colspan="3">The P_2Y_{12} reaction unit value on day 0 was approximately 280 in both groups.</td></tr>
</table>
NOTE: Allele *2 was genotyped. This is the most common allele in this Chinese patient group.
</td>
<td>Authors' conclusions:
"In CYP2C19*2 homozygotes with ACS, ticagrelor is as effective as high-dose clopidogrel in reducing platelet reactivity, particularly in the first days. This study suggests that ticagrelor may be much better than doubling the dose of clopidogrel in homozygotes of CYP-2C19*2 according to platelet reactivity monitoring. Use of ticagrelor instead of clopidogrel may eliminate the need for genetic testing and lead to less mild bleeding events."</td>
</tr>
<tr>
<td>ref. 16
Niu X et al.
CYP2C19 polymorphism and clinical outcomes among patients of different races treated with clopidogrel: a systematic review and meta-analysis.
J Huazhong Univ Sci Technolog Med Sci 2015;35:147-56.
PubMed PMID: 25877345.</td>
<td>4</td>
<td>
Meta-analysis of 36 studies including a total of 44,655 patients with coronary arterial disease using clopidogrel 75 mg/day. 21 studies were performed in Western populations, 15 in Asian populations. 97% of the Asian patients and more than 74% of the Western patients underwent percutaneous coronary intervention (more than 65% of the patients in total). Most patients received loading doses of 300 or 600 mg clopidogrel. Serious cardiovascular events were reported in 22 studies (n=25,564), cardiovascular death in 11 studies (n=8868), non-fatal myocardial infarction in 13 studies (n=2271), non-fatal stroke in 8 studies (n=13,075), stent thrombosis in 11 studies (n=5074), death in 5 studies (n=4881), bleeding in 10 studies (n=10,039) and major bleeding in 5 studies (n=11,079).
RRs were calculated using a fixed effects model, unless there was large study heterogeneity for the relevant outcome measure. A random effects model was used in those cases.
The 36 studies in the meta-analysis included 16 studies also included in the Sorich 2014 meta-analysis, 17 in the Mao 2013 meta-analysis, 13 in the Jang 2012 meta-analysis, 21 in the Holmes 2011 meta-analysis and 15 in the Liu 2011 meta-analysis.
</td>
<td>Authors' conclusions:
"It is suggested that CYP2C19 polymorphism affects the efficacy of clopidogrel differently among Westerners and Asians."</td>
</tr>
</table>

ref. 16, continuation

IM+PM: F

Seven of the articles in the meta-analysis were also included separately in this risk analysis (Malek 2008, Collet 2009, Giusti 2009, Mega 2009, Shuldiner 2009, Sibbing 2009 and Simon 2009).

Genotyping:

Western patients:	Asian patients:
72.1% NM	47.5% NM
25.5% IM	42.5% IM
2.4% PM	10% PM

Results:

(IM+PM) versus (NM+UM):

		RR	95% CI
Serious cardiovascular events	Total	1.35	1.14-1.60
	Western	1.20	1.01-1.41
	Asian	1.96	1.61-2.38
	< 50% PCI (Western)	NS	
	≥ 50% PCI, total	1.42	1.18-1.71
	≥ 50% PCI, Western	1.24	1.03-1.51
	≥ 50% PCI, Asian = 100% PCI, Asian	1.96	1.61-2.39
	100% PCI, Western	1.16	1.01-1.34
	Asian, n < 900	2.15	1.33-3.47
	Asian, n = 900-2000	1.92	1.55-2.39
	Western, n < 900	2.19	1.54-3.13
	Western, n = 900-2000	NS	
	Western, n ≥ 2000	NS	
	NOTE.: The size of the Western studies was not independent of the PCI percentage. Most smaller studies had higher PCI percentages, while larger studies included more patients without PCIs. The base size of both studies including < 50% PCI was n ≥ 2000.		
	0-30 days, total	NS	
	30 days - 1 year, total	NS, trend	0.98-1.31
	The Asian and Western subgroups were not significant at 0-30 days. After exclusion of Paré 2010, a large study including 18.7% PCI, the heterogeneity between the Western studies resolved and the results were significant (RR = 1.38; 95% CI: 1.19-1.59). The Western studies were not significant for > 30 days, but the Asian studies were (RR = 1.83; 95% CI: 1.16-2.88). Exclusion of any studies (including exclusion of Paré 2010) did not have an effect here.		
Cardiovascular death	Total	2.07	1.40-3.05
	Western	3.59	1.81-7.12
	Asian	1.62	1.0-2.62
Myocardial infarction	Total	1.66	1.35-2.04
	Western	Trend	0.94-2.17
	Asian	2.00	1.60-2.51
Stroke	Total	2.11	1.45-3.06
	Western	2.26	1.22-4.19

ref. 16, continuation	IM+PM: AA[#]		Asian	2.03	1.27-3.25
		Stent thrombosis	Total	1.72	1.44-2.05
			Western	1.62	1.17-2.24
			Asian	3.29	2.05-5.28
		Death	Total	NS	
			Western	NS	
			Asian	Trend	0.99-4.02
		Bleeding	Major bleeding, total	NS	
			Major, Western	NS	
			Major, Asian	NS	
			All, total	0.83	0.74-0.94
			All, Western	0.87	0.76-0.99
			All, Asian	0.76	0.60-0.96
		There was large study heterogeneity for: - serious cardiovascular events (total; Western; Western and n ≥ 900; total and Western for all PCI percentages; total and Western for < 30 days). Ethnicity (Western, Asian) and study size (< 900, 900-2000 and ≥ 2000 patients) were sources of heterogeneity. - myocardial infarction in the Western population			
		There was evidence of publication bias for the endpoint serious cardiovascular events in the Western studies. Correction by addition of four missing studies led to the RR no longer being significant. PS As studies including < 50% PCI were underrepresented, this correction may be equivalent to addition of these studies.			
		NOTE: The PM percentage in the IM+PM group was 2.2x larger among the Asian population than among the Western population (19% versus 8.6%). If IM and PM have similar effects in both populations, a larger IM+PM effect is therefore expected among the Asian population.			
	IM: AA	IM versus (NM+UM):			
				RR	95% CI
		Serious cardiovascular events (14 studies, n=3078)		1.26	1.01-1.56
			The RRs in the Western and Asian subgroups were similar in size but neither were significant. After exclusion of Paré 2010, a large study including 18.7% PCI, the Western studies showed a trend and the results were significant (RR = 1.36; 95% CI: 1.03-1.78). Heterogeneity resolved after further exclusion of Simon 2009 and Collet 2009, two studies with relatively low PCI percentages (69.5% and 73%) and the results remained significant (RR = 1.32; 95% CI: 1.13-1.54).		
		Bleeding	Major	NS	
			All	NS	
		There was large study heterogeneity for: - serious cardiovascular events (total and Western) - all bleeding			
		There was evidence of publication bias for the endpoint serious cardiovascular events. Correction by addition of six missing studies led to the RR no longer being			

<table>
<tr><td>ref. 16, continuation</td><td>PM: E

PM: AA#</td><td>significant.

<table>
<tr><td colspan="4">PM versus (NM+UM):</td></tr>
<tr><td></td><td></td><td>RR</td><td>95% CI</td></tr>
<tr><td rowspan="4">Serious cardiovascular events (12 studies, n=9813)</td><td>Total</td><td>1.92</td><td>1.49-2.47</td></tr>
<tr><td>Western</td><td>NS, trend</td><td>0.96-1.83</td></tr>
<tr><td>Asian</td><td>3.64</td><td>2.36-5.60</td></tr>
<tr><td colspan="3">After exclusion of Paré 2010, a large study including 18.7% PCI, the results in the Western subgroup were significant (RR = 1.57; 95% CI: 1.11-2.11).</td></tr>
<tr><td rowspan="2">Bleeding</td><td>Major</td><td>NS</td><td></td></tr>
<tr><td>All</td><td>0.56</td><td>0.38-0.83</td></tr>
<tr><td colspan="4">There was no evidence of large heterogeneity between the studies or evidence of publication bias for any of the outcome measures.</td></tr>
</table></td><td></td></tr>
<tr><td>ref. 17
Sorich MJ et al. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis.
Circ Cardiovasc Genet 2014;7:895-902.
PubMed PMID: 25258374.</td><td>4

IM+PM:</td><td>Meta-analysis of 24 studies (23 publications) including a total of 36,076 patients using clopidogrel. 16 studies were performed in Caucasian populations (n_{total} = 26,059), 8 in Asian populations (n_{total} = 10,017). The meta-analysis only incorporated studies including n ≥ 500 patients. The meta-analysis for stent thrombosis and bleeding included an additional five and two publications respectively. Case-control studies including ≥ 20 cases of thrombosis were also included for stent thrombosis (19 studies and 32,144 patients including 23,311 Caucasians in total). Bleeding was reported in 12 studies (n = 18,508).
RRs were calculated using fixed effects and random effects models. The summary below only includes RRs calculated using the random effects model.
Serious cardiovascular events were defined as cardiovascular death (or death), non-fatal myocardial infarction or non-fatal stroke. If these outcome measures were not reported in a study, the outcome measure including the most outcomes concerning death, myocardial infarction and stroke without inclusion of other outcomes was used.
Of the 23 studies in the most significant meta-analysis, 15 studies were also included in the Mao 2014 meta-analysis, 9 in the Jang 2012 meta-analysis, 13 in the Holmes 2011 meta-analysis and 10 in the Liu 2011 meta-analysis.
Five of the articles in the meta-analysis were also included separately in this risk analysis (Trenk 2008, Giusti 2009, Mega 2009, Sibbing 2009 and Simon 2009).

Genotyping:
Caucasian patients: Asian patients:
72.1% NM 47.5% NM
26.0% IM 42.7% IM
2.4% PM 11.2% PM

Results:
<table>
<tr><td colspan="4">(IM+PM) versus (NM+UM):</td></tr>
<tr><td></td><td></td><td>RR</td><td>95% CI</td></tr>
<tr><td rowspan="4">Serious cardiovascular events</td><td>Total</td><td>1.32</td><td>1.17-1.49</td></tr>
<tr><td>Caucasian, no PCI</td><td>NS</td><td></td></tr>
<tr><td>Caucasian, PCI</td><td>1.23</td><td>1.07-1.40</td></tr>
<tr><td>Asian, PCI</td><td>1.91</td><td>1.61-2.26</td></tr>
<tr><td colspan="4">The differences between the three</td></tr>
</table></td><td>Authors' conclusions:
"The reported association between CYP2C19 loss-of-function allele carriage and major cardiovascular outcomes differs based on the ethnic population of the study and, to a lesser extent, the clopidogrel indication."</td></tr>
</table>

ref. 17, continuation	E		subgroups was significant (S). The calculated RR for Caucasian patients without PCI did not deviate from 1. The relative risk was also not increased in patients with acute coronary syndrome not undergoing PCI (2 studies, n = 4217). A meta-analysis of studies including n ≥ 200 (10 additional studies, 3057 additional patients) delivered similar results. Moreover, there were no differences in RR between Asian studies that only genotyped for the *2 allele (48% IM+PM) and that genotyped for the *2 and *3 alleles (59% IM+PM).		
		Stent thrombosis	Total	2.07	1.67-2.57
			Caucasian	1.74	1.48-2.06
			Asian	4.60	2.87-7.37
		Bleeding	Total	NS	
			Caucasian, PCI	NS	
			Asian, PCI	NS	
			Caucasian, no PCI	NS	
		There was moderate to large heterogeneity between the studies for: - serious cardiovascular events (IM+PM and IM: total; Caucasian undergoing PCI; PM: total; Caucasian not undergoing PCI). Study heterogeneity was lower for IM and PM than for IM+PM. There was no study heterogeneity for Caucasian PM + PCI studies, but there was study heterogeneity for Caucasian + PCI studies. Approximately 74% of the study heterogeneity for IM+PM was explained by the population and the indication. Meta-regression analysis showed that both the population and the PCI percentage explained part of the study heterogeneity (S). - bleeding (total; Caucasian not undergoing PCI; Asian undergoing PCI)		
		There was no evidence of publication bias for the endpoint serious cardiovascular events for the Asian and Caucasian subgroups undergoing PCI .			
		NOTE: The PM percentage in the IM+PM group was 2.5x larger among the Asian population than among the Caucasian population (21% versus 8.5%). If IM and PM have similar effects in both populations, a larger IM+PM effect is therefore expected among the Asian population.			
	IM: E	IM versus (NM+UM):			
				RR	95% CI
		Serious cardiovascular events (18 studies, 22,079)	Total	1.22	1.07-1.39
			Caucasian, no PCI	NS	
			Caucasian, PCI	1.22	1.01-1.46
			Asian, PCI	1.49	1.17-1.90
			The calculated RR for Caucasian patients not undergoing PCI did not deviate from 1.0. In the Caucasian PCI group, 19% of the patients were derived from a study including ≤ 70% PCI, while this was 11% in the Asian PCI group.		
		There was moderate to large heterogeneity between the studies for:			

<table>
<tr>
<td>ref. 17, continuation</td>
<td>PM: E</td>
<td>
- serious cardiovascular events, PCI in Caucasians

PM versus (NM+UM):
<table>
<tr><td></td><td></td><td>RR</td><td>95% CI</td></tr>
<tr><td rowspan="4">Serious cardiovascular events (18 studies, 15,951)</td><td>Total</td><td>2.07</td><td>1.59-2.69</td></tr>
<tr><td>Caucasian, no PCI</td><td>NS</td><td></td></tr>
<tr><td>Caucasian, PCI</td><td>1.67</td><td>1.25-2.24</td></tr>
<tr><td>Asian, PCI</td><td>3.04</td><td>2.30-4.01</td></tr>
<tr><td colspan="4">In the Caucasian PCI group, 19% of the patients were derived from a study including ≤ 70% PCI, while this was 11% in the Asian PCI group.</td></tr>
<tr><td colspan="4">There was moderate to large heterogeneity between the studies for:
- serious cardiovascular events, no PCI</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 18
Mao L et al. Cytochrome CYP2C19 polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects. Arch Cardiovasc Dis 2013;106:517-27. PubMed PMID: 24080325.</td>
<td>4

IM+PM: E</td>
<td>
Meta-analysis of 21 cohort studies or post-hoc analyses of randomised, controlled trials including a total of 23,035 patients with coronary arterial disease using clopidogrel 75 mg/day for 1 month to 4 years. 7670 patients were IM or PM. 13 studies were performed in Europe or the US, 8 in Asia. The clinical effects determined differed between studies.
The meta-analysis defined negative clinical effects as myocardial infarction, death, diagnosed or suspected stent thrombosis, need for revascularisation, ischaemic stroke or bleeding.
Negative clinical effects were reported in 20 studies (n = 21,297), myocardial infarction in 11 studies (n = 9745), stent thrombosis in 13 studies (n = 14,261), need for revascularisation in 7 studies (n = 4366), ischaemic stroke in 5 studies (n = 6708), death in 13 studies (n = 11,023) and bleeding in 6 studies (n = 11,278).
In the event of moderate, large and/or significant study heterogeneity, ORs were calculated using a random effects model, in the event of low and/or non-significant study heterogeneity they were calculated using a fixed effects model.
Of the 21 studies in the meta-analysis, 14 studies were also included in the Jang 2012 meta-analysis, 15 in the Holmes 2011 meta-analysis and 13 in the Liu 2011 meta-analysis.
Eight of the articles in the meta-analysis were also included separately in this risk analysis (Malek 2008, Trenk 2008, Collet 2009, Giusti 2009, Mega 2009, Shuldiner 2009, Sibbing 2009 and Simon 2009).

Results:
<table>
<tr><td colspan="4">(IM+PM) versus (NM+UM):</td></tr>
<tr><td></td><td></td><td>OR</td><td>95% CI</td></tr>
<tr><td rowspan="3">Negative clinical effects</td><td>Total</td><td>1.50</td><td>1.21-1.87</td></tr>
<tr><td>Caucasian</td><td>1.27</td><td>1.02-1.58</td></tr>
<tr><td>Asian</td><td>2.75</td><td>1.88-4.01</td></tr>
<tr><td>Myocardial infarction</td><td></td><td>1.62</td><td>1.35-1.95</td></tr>
<tr><td>Stent thrombosis</td><td></td><td>2.08</td><td>1.67-2.60</td></tr>
<tr><td>Revascularisation</td><td></td><td>1.35</td><td>1.10-1.66</td></tr>
<tr><td>Ischaemic stroke</td><td></td><td>2.14</td><td>1.36-3.38</td></tr>
<tr><td>Death</td><td></td><td>NS</td><td></td></tr>
<tr><td rowspan="2">Bleeding</td><td></td><td>NS</td><td></td></tr>
<tr><td colspan="3">The calculated OR for bleeding did not deviate from 1.0.</td></tr>
</table>
</td>
<td>Authors' conclusions: "CYP2C19 polymorphism is significantly associated with risk of adverse clinical events in clopidogrel-treated patients."</td>
</tr>
</table>

<table>
<tr>
<td>ref. 18, continuation</td>
<td></td>
<td>There was moderate to large heterogeneity between the studies for:
- negative clinical effects (total; Caucasian)
Study heterogeneity was low, but significant (p < 0.1) for:
- repeated need for revascularisation
- death

There was no evidence of unacceptable publication bias.

NOTE: The frequency of null alleles in Asians was greater than in Caucasians. As the increase in IM is linear and PM is quadratic with null allele frequency, the PM percentage in the IM+PM group is greater among the Asian population than among the Caucasian population. If IM and PM have similar effects in both populations, a larger IM+PM effect is therefore expected among the Asian population.</td>
<td></td>
</tr>
<tr>
<td>ref. 19
Xie X et al. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: a randomized control trial. Int J Cardiol 2013;168:3736-40. PubMed PMID: 23850318.</td>
<td>3

Genotype-guided versus non-genotype-guided therapy: AA#</td>
<td>Patients with coronary arterial disease who underwent stent placement were randomised to CYP2C19 genotype-guided therapy (n = 301) or conventional therapy (n = 299) and followed for 6 months. All patients received 300 mg loading doses of acetylsalicylic acid and 100 IU/kg intravenous heparin before stent placement. Conventional therapy comprised a 300 mg clopidogrel loading dose followed by 75 mg/day. CYP2C19 genotype-guided therapy involved conventional clopidogrel therapy in NM patients, double dose (600 mg loading dose, followed by 150 mg/day) in IM patients and double dose of clopidogrel in combination with cilostazol (200 mg loading dose, followed by 100 mg twice daily) for PM patients.
The outcome measure serious cardiovascular events included death, myocardial infarction, stroke and need for revascularisation due to restenosis in the treated artery. Stent thrombosis included both confirmed, suspected and possible stent thrombosis.
Relevant co-medication was not excluded.

Genotyping (only in the genotype-guided group):
- 143x NM
- 128x IM
- 30x PM

Results:
<table>
<tr><td colspan="3">Genotype-guided versus non-genotype-guided therapy:</td></tr>
<tr><td></td><td></td><td>% patients in non-genotype-guided group</td></tr>
<tr><td>Serious cardiovascular events</td><td>x 0.29 (S)</td><td>9.03%</td></tr>
<tr><td>Death, myocardial infarction or stroke</td><td>x 0.17 (S)</td><td>6.02%</td></tr>
<tr><td>Death</td><td>x 0.11 (S)</td><td>3.01%</td></tr>
<tr><td>Myocardial infarction</td><td>x 0.14 (S)</td><td>2.34%</td></tr>
<tr><td>Stent thrombosis</td><td>x 0.22 (S)</td><td>3.01%</td></tr>
<tr><td>Revascularisation</td><td>x 0.55 (NS, trend, p = 0.089)</td><td>3.01%</td></tr>
<tr><td>Stroke</td><td>NS</td><td>0.66%</td></tr>
<tr><td>Bleeding</td><td>x 0.36 (NS, trend, p = 0.073)</td><td>3.68%</td></tr>
</table>
</td>
<td>Authors' conclusions:
"Personalized antiplatelet therapy according to CYP-2C19 genotype after PCI can significantly decrease the incidence of major adverse cardiovascular events and the risk of 180-day stent thrombosis in a Chinese population."</td>
</tr>
</table>

ref. 19, continuation		NOTE 1: Alleles *2 and *3 were genotyped. These are the most common alleles in this Chinese patient group. NOTE 2: The authors reported that the CURRENT-OASIS 7 trial during which the clopidogrel dose was doubled for all patients led to a decrease in the primary outcome measure and stent thrombosis, while major bleeding increased. NOTE 3: Cilostazol is currently not available in the Netherlands.	
ref. 20 Jang JS et al. Meta-analysis of cytochrome P450 2C19 polymorphism and risk of adverse clinical outcomes among coronary artery disease patients of different ethnic groups treated with clopidogrel. Am J Cardiol 2012;110:502-8. PubMed PMID: 22591668.	4 IM+PM: F IM: AA PM: E	Meta-analysis of sixteen studies including a total of 20,785 patients with coronary arterial disease using clopidogrel, including 4814 Asian patients and 7035 null allele carriers. In seven studies including a total of 7948 patients, the outcomes for PM and IM patients were determined separately. Mortality rates were reported in eight studies (n=7451), non-fatal myocardial infarction in six studies (n=6574), stent thrombosis in ten studies (n=11,585) and major bleeding in two studies (n=7434). The definitions of myocardial infarction and serious cardiovascular events differed between studies. Serious cardiovascular events were generally defined as death, myocardial infarction, stent thrombosis or stroke. (IM+PM) versus (NM+UM): - increased risk of serious cardiovascular events (OR = 1.42; 95% CI: 1.13-1.78) (S). Similar results were obtained after resolving the significant study heterogeneity by excluding 5 studies (OR = 1.60; 95% C: 1.33-1.93) (S). - the OR was 1.89 (95% CI: 1.32-2.72) for the 5 Asian studies and 1.28 for the 11 Western studies (95% CI: 1.00-1.64). Note: IM+PM included relatively more PM in Asian than in Western countries, because there is a quadratic relationship between the percentage of PM in the population and the frequency of null alleles while there is a linear relationship with the percentage of IM patients. - increase in the mortality rate from 0.73% to 1.47% (OR = 2.18; 95% CI: 1.37-3.47) (S, no heterogeneity) - increase in the risk of non-fatal myocardial infarction (OR = 1.42; 95% CI: 1.12-1.81) (S, no heterogeneity) - increase in the percentage of patients who developed stent thrombosis from 1.02% to 2.21% (OR = 2.41; 95% CI: 1.76-3.30) (S, no heterogeneity) - no effect on the incidence of major bleeding (NS) IM versus (NM+UM): - increased risk of serious cardiovascular events (OR = 1.43; 95% CI: 0.93-2.19) (NS, static heterogeneity). PM versus (NM+UM): - increased risk of serious cardiovascular events (OR = 1.75; 95% CI: 1.23-2.51) (S, no significant heterogeneity).	Authors' conclusions: "In conclusion, carrier status for loss-of-function CYP2C19 is associated with an increased risk of adverse clinical events in patients with coronary artery disease on clopidogrel therapy despite differences in clinical significance according to ethnicity."
ref. 21 Li Y et al. The gain-of-function variant allele CYP2C19*17: a double-edged sword between thrombosis and bleeding in clopidogrel-treated patients. J Thromb Haemost	4	Meta-analysis of eight studies including a total of 17,302 patients using clopidogrel. The patients in the studies were mainly Caucasian and mainly had stable coronary arterial disease or acute coronary syndrome. Bleeding was reported in six studies (n=12,228, including 9240 with coronary arterial disease). Stent thrombosis was reported in four studies (n=4690) and death in three studies (n=2752). The definition of serious cardiovascular events differed between studies. Serious cardiovascular events were generally defined as myocardial infarction, stroke, need for percutaneous coronary intervention or death. *17 versus (no *17):	Authors' conclusions: "Carriers of the CYP2C19*17 variant have greater therapeutic responsiveness to clopidogrel than non-carriers, but they have an increased risk of developing bleeding as well."

2012;10:199-206. PubMed PMID: 22123356. **ref. 21, continuation**	*17: AA[#] *17: E	- 12% decrease in the percentage of patients with serious cardiovascular events (from 11.1% to 9.8%; OR = 0.86; 95% CI: 0.76-0.97) (S, no heterogeneity). The decrease was 16% among patients with only coronary arterial disease (from 11.9% to 10.0%; OR = 0.82; 95% CI: 0.72-0.94) (S). - 23% increase in the percentage of patients with coronary arterial disease who experienced a bleeding event (from 6.5% to 8.0%; OR = 1.25; 95% CI: 1.07-1.47) (S, significant heterogeneity). Exclusion of a small study (n=300) that did not include patients with bleeding events in the first 30 days led to resolution of heterogeneity and a similar OR (1.21). Exclusion of a study that only defined bleeding as major bleeding instead of the generally accepted definitions of major and minor bleeding had a stronger effect (OR = 1.30; 95% CI: 1.09-1.55) (S). - decreased percentage of patients with stable arterial disease or atrial fibrillation who experienced bleeding events (NS) - no significant differences in the risk of death and the risk of stent thrombosis (NS). The authors stated that the low incidence of death and stent thrombosis and the differences between the studies in terms of follow-up duration and patient characteristics could possibly explain the lack of significant differences. - analysis of the data from three studies (n=951) investigating platelet response: decreased risk of high platelet reactivity during clopidogrel therapy (OR = 0.60; 95% CI: 0.45-0.79)	
ref. 22 Holmes MV et al. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. JAMA 2011;306:2704-14. PubMed PMID: 22203539.	4	Meta-analysis of 32 studies including a total of 42,016 patients and 3545 cardiovascular events, of which 579 concerned stent thrombosis and 1413 bleeding events. Six of the studies were randomised trials. The other 26 only investigated clopidogrel therapy. Patients with acute coronary syndrome were the subject of 21 studies, 8 studies involved patients with stable coronary arterial disease, mainly at the time of stent placement, and the remaining 3 studies did not specify the nature of the coronary arterial disease. Meta-analysis of the risk of serious cardiovascular events was based on 26 studies including a total of 26,251 patients and 1465 cardiovascular events. Eleven studies including a total of 10,291 patients separately reported data for IM patients (> 238 cardiovascular events) and PM patients (> 37 events). The definition of serious cardiovascular events differed between studies. The meta-analysis defined serious cardiovascular event as death and/or cardiovascular disease and/or stroke and/or stent thrombosis and/or percutaneous coronary intervention and/or hospitalisation due to acute coronary syndrome. Metabolite concentrations were determined in one study and platelet reactivity in four studies. There was no evidence that the nature of the coronary arterial disease (stable versus acute), co-medication with proton pump inhibitors or acetylsalicylic acid, the sponsor of the study or whether or not the genotype was blinded had any effect on the association of the genotype with serious cardiovascular events. (IM+PM) versus (NM+UM):	Authors' conclusions: "Although there was an association between the CYP2C19 genotype and clopidogrel responsiveness, overall there was no significant association of genotype with cardiovascular events."

ref. 22, continuation	IM+PM: E	- increased risk of serious cardiovascular events (fixed effects model: RR = 1.18; 95% CI: 1.09-1.28; random effects model: RR = 1.34; 95% CI: 1.15-1.56) (S). The effect size was similar to the effect size of high versus low doses of clopidogrel in randomised trials. The effect size decreased with the size of the studies, suggesting small study bias. In a fixed effects model, the RR was 1.83 (95% CI: 1.50-2.23) for studies reporting 1-99 serious cardiovascular events; 1.26 (95% CI: 1.09-1.45) for studies reporting 100-199 events, and 0.97 (95% CI: 0.86-1.09) for the four studies reporting ≥ 200 events. After correction for small study bias by adding eight hypothetically missing studies, the risk of serious cardiovascular events was less strongly increased (fixed effects model: RR = 1.10; 95% CI: 1.02-1.19 (S); random effects model: RR = 1.13; 95% CI: 0.96-1.33) (NS)). An RR of 1.10 is equivalent to an increased incidence of events in patients with acute coronary syndrome by 12 events per 1000 patients (95% CI: 2-22 events) from 114 to 126 events per 1000 patients (S). In patients with stable cardiovascular disease, this is equivalent to an increase by 8 events per 1000 patients (95% CI: 2-14 events) from 73 to 81 events per 1000 patients (S). - increased risk of stent thrombosis (fixed effects model: RR = 1.75; 95% CI: 1.50-2.03; random effects model: RR = 1.88; 95% CI: 1.46-2.41) (S). Assuming an incidence of 18 per 1000 patients, this is equivalent to an increase by 14 cases of stent thrombosis per 1000 patients. The increase is smaller in large studies (RR = 2.01; 95% CI: 1.60-2.53 for studies reporting < 100 events and RR = 1.54; 95% CI: 1.26-1.88 for studies reporting ≥ 100 events). - increased risk of myocardial infarction (fixed effects model: RR = 1.37; 95% CI: 1.13-1.65; random effects model: RR = 1.39; 95% CI: 1.10-1.74) (S). The increase is smaller in large studies (RR = 1.92; 95% CI: 1.15-3.21 for studies reporting < 100 events and RR = 1.29; 95% CI: 1.06-1.58 for studies reporting ≥ 100 events). - increased risk of non-fatal myocardial infarction (fixed effects model: RR = 1.48; 95% CI: 1.05-2.07; random effects model: RR = 1.45; 95% CI: 1.03-2.03) (S). There was no significance when small and large studies were analysed separately. - no significant increase in the risk of death and stroke (NS) - decreased risk of bleeding (fixed effects model after correction for small study bias and random effects model: RR = 0.84; 95% CI: 0.75-0.94) (S). An RR of 0.84 is equivalent to a decreased incidence of events in patients with acute coronary syndrome by 8 events per 1000 patients (95% CI: 3-12 events) from 50 to 42 events per 1000 patients (S). In patients with stable cardiovascular disease, this is equivalent to a decrease by 5 events per 1000 patients (95% CI: 2-8 events) from 31 to 26 events per 1000 patients (S). - no significant difference in the risk of major bleeding (NS) - there were no significant gene-drug interactions in the four placebo-controlled randomised trials in terms of the outcome measure serious cardiovascular events (NS).	

ref. 22, continuation	IM: D PM: E	The RR for serious cardiovascular events on clopidogrel treatment versus placebo was 0.78 (95% CI: 0.69-0.89) for NM+UM and 0.87 (95% CI: 0.70-1.09) for IM+PM. The 3031 IM+PM in the four studies together were insufficient to demonstrate a significant effect of clopidogrel in this group. - there were no significant gene-drug interactions in the four placebo-controlled randomised trials in terms of the outcome measure major bleeding (NS). The RR for major bleeding on clopidogrel treatment versus placebo was 1.28 (95% CI: 1.02-1.61) for NM+UM and 1.99 (95% CI: 1.31-3.02) for IM+PM. The 3031 IM+PM in the four studies together were therefore sufficient to demonstrate a significant effect of clopidogrel on major bleeding in this group. The higher risk of bleeding for IM+PM, however, does not correspond to the lower metabolite concentration and inhibition of platelet aggregation in this group. - the AUC of the active metabolite decreased by 0.14 µM.hour. The mean AUC of the active metabolite in the total population was 0.35 µM.hour. IM versus (NM+UM): - increased risk of serious cardiovascular events, but not significant in the large studies (fixed effects model; studies reporting < 100 events: RR = 1.77; 95% CI: 1.27-2.47) (S); studies reporting ≥ 100 events: RR = 0.94; 95% CI: 0.80-1.10 (NS)). - standardised mean platelet reactivity after a 600 mg loading dose was increased by approximately 0.35. PM versus (NM+UM): - increased risk of serious cardiovascular events (fixed effects model; studies reporting < 100 events: RR = 3.75; 95% CI: 2.40-5.86); studies reporting ≥ 100 events: RR = 1.52; 95% CI: 1.04-2.21 (S). An RR of 1.52 is equivalent to an increased incidence of cardiovascular events by 38 and 59 events per 1000 patients for patients with stable cardiovascular disease and patients with acute coronary syndrome respectively. - standardised mean platelet reactivity after a 600 mg loading dose was increased by approximately 1.0.	
ref. 23 Liu YP et al. Association of genetic variants in CYP2C19 and adverse clinical outcomes after treatment with clopidogrel: an updated meta-analysis. Thromb Res 2011;128:593-4. PubMed PMID: 21794898.	4	Meta-analysis of 20 studies including a total of 24,120 patients with coronary arterial disease using clopidogrel. Serious cardiovascular events were reported in IM+PM patients in 18 studies (n=21,441) and stent thrombosis in nine studies (n=9868). Serious cardiovascular events were reported in *17 patients in six studies (n=7623), stent thrombosis in two studies (n=2452) and bleeding in four studies. The definition of serious cardiovascular events differed between studies. Serious cardiovascular events were generally defined as death, myocardial infarction or stroke. (IM+PM) versus (NM+UM): - 11% increase in the percentage of patients with serious cardiovascular events (from 9.6% to 10.7%; OR = 1.26; 95% CI: 1.06-1.50) (S) - 158% increase in the percentage of patients who developed stent thrombosis (from 2.4% to 6.2%; OR = 2.58; 95% CI: 1.77-3.77) (S) - increased risk of myocardial infarction (OR = 1.38; 95% CI: 1.08-1.77) (S) - no significant increase was found in the risks of death,	Authors' conclusions: "Compared with previous meta-analyses, our analysis included more studies and more widely supported the conclusion that CYP2C19 loss-of-function alleles increase the rate of MACE and stent thrombosis among patients receiving clopidogrel and that the gain-of-function CYP2C19*17 allele confers protection against MACE."

ref. 23, continuation	IM: E PM: E *17: AA[#] UM: AA	need for percutaneous coronary intervention, stroke and the composite measure of death and/or myocardial infarction (NS) - no effect on the incidence of bleeding (NS) IM versus (NM+UM): - increased risk of serious cardiovascular events (OR = 1.32; 95% CI: 1.05-1.65) (S) - increased risk of stent thrombosis (OR = 1.97; 95% CI: 1.45-2.68) (S) - no effect on the incidence of bleeding (NS) PM versus (NM+UM): - increased risk of serious cardiovascular events (OR = 1.59; 95% CI: 1.13-2.25) (S) - increased risk of stent thrombosis (OR = 3.78; 95% CI: 1.67-8.53) (S) - decreased risk of bleeding (OR = 0.36; 95% CI: 0.19-0.66) (S) *17 versus (no *17): - 18% decrease in the percentage of patients with serious cardiovascular events by (from 11.9% to 9.7%; OR = 0.82; 95% CI: 0.69-0.98) (S) - no difference in the risk of stent thrombosis (NS) - no significant increase in the risk of bleeding (NS) (*1/*17 + null allele/*17) versus (no *17): - no significant decrease in the percentage of patients with serious cardiovascular events (NS) - no significant increase in the risk of bleeding (NS) UM versus (no *17): - no significant decrease in the percentage of patients with serious cardiovascular events (NS) - no significant increase in the risk of bleeding (NS)	
ref. 24 Mega JL et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. JAMA 2011;306:2221-8. PubMed PMID: 22088980.	4 IM: D	Genotype-driven increased clopidogrel doses in 333 patients with cardiovascular disease using clopidogrel 75 mg/day and acetylsalicylic acid 81-325 mg. NM patients received 75 mg/day and 150 mg/day, each for two 14-day periods. IM and PM patients received 75, 150, 225 and 300 mg/day, each for 14 days. Co-medication with anticoagulants or proton pump inhibitors and smoking were excluded. Platelet reactivity index was measured using the VASP assay, $P2Y_{12}$ reaction units using the VerifyNow assay. Non-response was defined as ≥ 230 $P2Y_{12}$ reaction units. Similar results were obtained at a limit of 208 $P2Y_{12}$ reaction units. Genotyping: - 247x NM - 80x IM - 6x PM IM: - at 225 mg/day, platelet reactivity index and $P2Y_{12}$ reaction units were not significantly different from those in NM+UM patients at 75 mg/day. At 150 mg/day, the platelet reactivity index was not significantly different, but $P2Y_{12}$ reaction units were significantly higher than in NM+UM patients at 75 mg/day. - 1.2-fold increase in platelet reactivity index at 75 mg/day versus NM+UM (from 57.5% to 70.0%) (S). 1.4-fold increase in $P2Y_{12}$ reaction units (S). - decreased platelet reactivity index at higher doses (70.0%, 61.4%, 52.7% and 48.9% at 75, 150, 225 and 300 mg/day respectively) (S for the trend).	Authors' conclusions: "Among patients with stable cardiovascular disease, tripling the maintenance dose of clopidogrel to 225 mg daily in CYP2C19*2 heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in non-carriers; in contrast, for CYP2C19*2 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition."

ref. 24, continuation	PM: D	$P2Y_{12}$ reaction units also decreased significantly with dose (S for the trend). - increase in the percentage of non-responders at 75 mg/day and 150 mg/day versus NM+UM by a factor of 2.3 and by a factor of approximately 2.1 respectively (from 23% to 52% and from 12% to ~25%) (NS) - decreased percentage of non-responders at higher doses (52%, ~25%, 10% and 10% at 75, 150, 225 and 300 mg/day respectively) (S) PM: - decreased percentage of non-responders at higher doses (80% and 60% at 75 and 300 mg/day respectively) (NS) However, the percentage of non-responders remained high. - 1.5-fold increase in platelet reactivity index at 75 mg/day versus NM+UM (from 57.5% to 86.6%) (S). 2.0-fold increase in $P2Y_{12}$ reaction units (S). - decreased platelet reactivity index at higher doses (86.6%, 77.8%, 73.0% and 68.3% at 75, 150, 225 and 300 mg/day respectively) (S for the trend). $P2Y_{12}$ reaction units decreased non-significantly with dose (NS for the trend). In both cases, the level at 300 mg/day was higher than the level in NM+UM patients at 75 mg/day. - 3.5 fold increase in the percentage of non-responders at 75 mg/day versus NM+UM (from 23% to 80%) (NS) Side effects: - the incidence of bleeding was higher among NM+UM patients at 150 than at 75 mg/day (5 versus 0) (NS) There was one bleeding event for IM+PM at 75, 225 and 300 mg/day. NOTE.: Allele *2 was genotyped.	
ref. 25 Simon T et al. Genetic polymorphisms and the impact of a higher clopidogrel dose regimen on active metabolite exposure and antiplatelet response in healthy subjects. Clin Pharmacol Ther 2011;90:287-95. PubMed PMID: 21716274.	4	40 healthy volunteers (10x *1/*1, 10x IM (*1/*2 and *1/*3), 10x PM (*2/*2 and *2/*3) and 10x UM/NM (UM and *1/*17)) in a cross-over study received a 300 mg loading dose of clopidogrel followed by 75 mg/day for four days or 600 mg loading dose followed by 150 mg/day for four days. The data were also analysed in combination with data from 327 healthy volunteers (163x *1/*1, 72x IM (*1/*2 and *1/*3), 3x PM (*2/*2 and *2/*3) and 89x UM/NM (~10x UM and 79x *1/*17)) who had received 300 mg loading doses of clopidogrel and/or 75 mg/day for four days in six other studies. Relevant co-medication was excluded. The percentage differences in the AUC of the active metabolite H4 were corrected for confounders. Residual platelet aggregation was measured using the LTA and 5 µM ADP, platelet reactivity index using the VASP assay. PM on 600 mg/150 mg versus NM on 300 mg/75 mg: - the AUC of the active metabolite H4 in PM patients was approximately 59% of that in NM patients in the single study and 45% of that in NM patients in all seven studies. - the difference in residual platelet aggregation was low (-4.2% in the single study and 0.1% in all seven studies) - platelet reactivity index was 1.6-fold higher in PM patients than in NM patients in both the single and in all seven studies and was > 50% in PM patients (61.3% in both cases) - the percentage of volunteers with side effects in the single study was 20% in PM patients and 10% in NM patients (for both the high and low doses). There were no serious side effects. IM versus *1/*1 (both 300 mg/75 mg):	Authors' conclusions: "PMs who were on the clopidogrel regimen of 600 mg loading dose/150 mg/day maintenance dose showed active metabolite (H4) exposure and maximal platelet aggregation levels similar to those in NMs who were on the regimen of 300 mg/75 mg/day. In contrast to the findings with respect to maximal platelet aggregation, PMs receiving high-dose clopidogrel did not have a day 5 VASP-PRI similar to that of NMs on standard-dose clopidogrel (61.3% in PMs, and 38.6% in NMs)."

ref. 25, continuation	IM: D PM: D *17: A UM: AA[#]	- decrease in the AUC of the active metabolite H4 by 9% after the loading dose and by 11% after the maintenance dose in the single study (NS) and by 23% and 28% respectively in all seven studies combined (S) - no difference in residual platelet aggregation after the loading and maintenance doses (absolute difference -3.6% in the single study (NS) and 4.8% in all seven studies combined (S)) - increase in platelet reactivity index after the loading and maintenance doses (difference 9.9% in the single study (NS) and 9.8% in all seven studies combined (S)) PM versus *1/*1 (both 300 mg/75 mg): - decrease in the AUC of the active metabolite H4 by 58% after the loading dose and by 71% after the maintenance dose in the single study (S) and by 64% and 72% respectively in all seven studies combined (S) - increase in residual platelet aggregation after the loading and maintenance doses (absolute difference 10.5% in the single study (NS) and 18.0% in all seven studies combined (S)) - increase in platelet reactivity index after the loading and maintenance doses (difference 43.8% in the single study and in all seven studies combined (S)) (*1/*17 + UM) versus *1/*1 (both 300 mg/75 mg): - decrease in the AUC of the active metabolite H4 by 5% after the loading dose and by 1% after the maintenance dose in the single study (NS) and increase by 11% (S) and 5% (NS) respectively in all seven studies combined - increase in residual platelet aggregation after the loading and maintenance doses (absolute difference 1.7% in the single study and 1.9% in all studies combined (NS)) - no significant difference in platelet reactivity index after the loading and maintenance doses (absolute difference 6.2% in the single study and -1.6% in all studies combined) (NS) - no difference in the percentage of volunteers with side effects (both 10%). There were no serious side effects. Effect of a 2-fold dose increase (from 300 mg/75 mg to 600 mg/150 mg) in the single study: - IM: increase in the AUC of the active metabolite H4 by 68% after the loading dose and by 66% after the loading and maintenance doses - PM: increase in the AUC of the active metabolite H4 by 53% after the loading dose and by 110% after the loading and maintenance doses - UM: increase in the AUC of the active metabolite H4 by 67% after the loading dose and by 64% after the loading and maintenance doses - NM: increase in the AUC of the active metabolite H4 by 77% after the loading dose and by 66% after the loading and maintenance doses The authors stated that the *17 allele is associated with cardiovascular protection in some but not all four studies investigating the clinical effect of this allele. NOTE: Alleles *2 to *6, *8 and *17 were genotyped. People with rare null alleles *4 to *6 or *8 were excluded from the cross-over study.	AUC of the active metabolite H4 after loading and maintenance doses versus *1/*1: IM: 72% PM: 28% Effect of a 2-fold dose increase on the AUC of the active metabolite H4 (% increase): IM: 66% PM: 110%
ref. 26 Collet JP et al. High doses of clopidogrel to overcome genetic resistance: the	3	Cross-over study including 106 patients with a history of myocardial infarction before the age of 45 years using clopidogrel 75 mg/day and/or acetylsalicylic acid 75 mg/day. The patients received loading doses of 300 or 900 mg clopidogrel. A limited number of NM patients were	Authors' conclusions: "Carriers of CYP-2C19 *2 display significantly lower responses to clopi-

randomized cross-over CLOVIS-2 (Clopidogrel and Response Variability Investigation Study 2). JACC Cardiovasc Interv 2011;4:392-402. PubMed PMID: 21511218. **ref. 26, continuation**	IM: D PM: D	included. Chronic co-medication with NSAIDs or anticoagulants was excluded, but the use of CYP2C19 inhibitors was not. Residual platelet aggregation was measured using the LTA and 20 µM ADP, $P2Y_{12}$ reaction units using the VerifyNow assay. Non-response was defined as residual platelet aggregation ≥ 64.5% and ≥ 236 $P2Y_{12}$ reaction units. There was no significant interaction between treatment before the study and CYP2C19 that changed the pharmacodynamic parameters. Genotyping: - 58x (NM + UM) - 41x IM - 7x PM IM with a loading dose of 900 mg versus NM+UM with a loading dose of 300 mg: - similar percentage of non-responders (4.88% versus 5.17% according to residual platelet aggregation and 2.44% versus 3.45% according to $P2Y_{12}$ reaction units) (NS) - increased $AUC_{0\text{-}6hours}$ of the active metabolite H4 (from 19.67 to 32.68 ng.hour/mL) (NS) IM versus NM+UM: - 1.4-fold increase in residual platelet aggregation at 75 mg/day (from 28.1% to 39.5%) (S). 1.3-fold increase in $P2Y_{12}$ reaction units (S for the trend NM+UM, IM, PM). - smaller percentage decrease in residual platelet aggregation after a 300 mg loading dose (~50% versus ~70%) (S), but not after a 900 mg loading dose (~70% versus ~80%) (NS). Similar results were found for $P2Y_{12}$ reaction units. - $AUC_{0\text{-}6hours}$ of the active metabolite H4 decreased by 24% after the 300 mg loading dose (S, from 19.67 to 14.97 ng.hour/mL) and by 20% after the 900 mg loading dose (NS), from 40.98 to 32.68 ng.hour/mL) PM with a 900 mg loading dose versus NM+UM with a 300 mg loading dose: - the percentage of non-responders remained higher (51.14% versus 5.17% according to residual platelet aggregation and 14.29% versus 3.45% according to $P2Y_{12}$ reaction units) (NS) - the $AUC_{0\text{-}6hours}$ of the active metabolite H4 remained lower (15.85 versus 19.67 ng.hour/mL) (NS) PM versus NM+UM: - 2.1-fold increase in residual platelet aggregation at 75 mg/day (from 28.1% to 59.3%) (S). 1.8-fold increase in $P2Y_{12}$ reaction units (S for the trend NM+UM, IM, PM). - smaller percentage decrease in residual platelet aggregation after 300 mg and 900 mg loading doses (~15% versus ~70% and ~25% versus ~80% respectively) (S). Similar results were found for $P2Y_{12}$ reaction units. - $AUC_{0\text{-}6hours}$ of the active metabolite H4 decreased by 49% after the 300 mg loading dose (S, from 19.67 to 9.94 ng.hour/mL) and by 61% after the 900 mg loading dose (S), from 40.98 to 15.85 ng.hour/mL) NOTE: Alleles *2 to *6 were genotyped, but only patients with *1 and/or *2 were included in the study.	dogrel with a gene-dose effect. Clopidogrel resistance can be overcome by increasing the dose in heterozygous carriers but not in homozygous carriers.”
ref. 27 Bonello-Palot N et al.	3	The effect of up to three additional loading doses was studied in 43 patients (26x NM, 13x IM (*1/*2), 4x PM (*2/*2)), who were scheduled to undergo elective	Authors’ conclusions: “High BMI, acute

Relation of body mass index to high on-treatment platelet reactivity and of failed clopidogrel dose adjustment according to platelet reactivity monitoring in patients undergoing percutaneous coronary intervention. Am J Cardiol 2009;104:1511-5. PubMed PMID: 19932784. **ref. 27, continuation**	IM + PM: D	percutaneous coronary intervention, and who had high platelet reactivity (VASP platelet reactivity index≥ 50) after a 600 mg clopidogrel loading dose. Relevant co-medication was not excluded. IM + PM: - higher percentage (IM + PM) in the group with high platelet reactivity after a single loading dose than in the group with good response (39.5% versus 16.7%) (S) (IM + PM) versus NM: - no difference in the percentage of patients not achieving a platelet reactivity index < 50 even after up to four loading doses (13.6 versus 13.7%) (NS) - 1.5-fold increase in the percentage of patients with high platelet reactivity after a single loading dose (from 51% to 77%) (S) - 1.3-fold increase in platelet reactivity index after a single loading dose (from 44% to 59%) (S) PM: - all PM patients achieved platelet reactivity index < 50 after additional loading doses: 25% after one additional loading dose and 75% after two additional loading doses The authors stated that a VASP platelet reactivity index < 50 has a high negative predictive value for the occurrence of thrombosis after percutaneous coronary intervention. NOTE: Allele *2 was genotyped.	coronary syndrome, diabetes mellitus, and CYP2C19*2 are associated with high on-treatment platelet reactivity (HTPR) after a 600-mg loading dose of clopidogrel. Dose adjustment over-comes HTPR in carriers of the CYP2C19*2 allele.“
ref. 28 Shuldiner AR et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849-57.	3 IM: D PM: D IM + PM: E 4 UM: AA	225 patients (158x NM, 67x IM+PM (including ~4x PM)) received acetylsalicylic acid 81-325 mg/day and clopidogrel loading doses of 600 mg (n=112), 300 mg (n=25) or 0 mg (90 patients already on clopidogrel 75 mg/day) prior to percutaneous coronary intervention. Bivalirudin or heparin and/or eptifibatide and acetylsalicylic acid 325 mg were given on the day of the treatment. The maintenance dose of clopidogrel was 75 mg/day and of acetylsalicylic acid 325 mg/day. Co-medication and smoking were not excluded. Follow-up was performed for 1 year. Cardiovascular events were defined as myocardial infarction, ischaemic stroke, stent thrombosis, unplanned revascularisation, hospitalisation for coronary ischaemia or cardiovascular death. Residual platelet aggregation was measured using the LTA and 20 µM ADP. PM versus IM versus NM: - residual platelet aggregation increased with the number of *2 alleles (S). (IM+PM) versus NM: - increased incidence of cardiovascular events from 10.0% to 20.9% (HR = 2.42 (S; 95% CI 1.18-4.99)). This increase was only observed in the subgroup who used clopidogrel at the time of the event or after 1 year (n=95; HR = 3.40 (S; 95% CI 1.36-8.46)), not in the group that no longer used clopidogrel at those times (HR = 1.39 (NS; 95% CI 0.39-4.88)). 429 healthy volunteers (148x no *17, 104x one *17, 16x *17/*17) received a 300 mg clopidogrel loading dose, followed by clopidogrel 75 mg/day for 6 days. *17/*17 versus (one *17) versus (no *17): - no difference in residual platelet aggregation (NS). NOTE. Patients were only genotyped for *2, volunteers for *2, *3, *5 and *17.	Authors' conclusions: “CYP2C19*2 geno-type was associated with diminished platelet response to clopidogrel treat-ment and poorer cardiovascular outcomes.” “Those with the CYP2C19*2 geno-type may benefit more from an anti-platelet regimen that does not inclu-de clopidogrel, such as the third-genera-tion thienopyridine prasugrel.” “Whether CYP2C19 *2 carriers may benefit from increa-sed dosing of clopi-dogrel is not yet known.”

ref. 29 Frére C et al. The CYP2C19*17 allele is associated with better platelet response to clopidogrel in patients admitted for non-ST acute coronary syndrome. J Thromb Haemost 2009;7:1409-11.	3 UM: A	The 598 patients from Frere et al., 2008 (non-ST-elevation acute coronary syndrome; clopidogrel 600 mg and acetylsalicylic acid 250 mg at least 12 hours before coronary angiography; blood samples taken before coronary angiography; glycoprotein IIb/IIIa antagonists prior to the study excluded, but other co-medication was not excluded) were genotyped for *17: 382x no *17, 189x one *17, 25x *17/*17. Platelet reactivity index was measured using the VASP assay, residual platelet aggregation using the LTA and 10 µM ADP. *17/*17 versus (one *17) versus (no *17): - significant association between the number of *17 alleles with one outcome measure for ADP-induced platelet activity (platelet reactivity index (45.79% versus 50.11% versus 55.9%; UM versus NM: 15% decrease)), but not with another (residual platelet aggregation (50.8% versus 55.5% versus 57.03%; UM versus NM: 10% decrease)). (*17/*17 or one *17) versus (no *17): - percentage of non-responders (platelet reactivity index > 50%) decreased by 21% (S; from 63% to 50%).	Authors' conclusions: "The CYP2C19*17 allele is associated with better platelet response to clopidogrel."
ref. 30 Aleil B et al. CYP2C19*2 polymorphism is not the sole determinant of the response to clopidogrel: implications for its monitoring. J Thromb Haemost 2009;7:1747-9.	3 IM + PM: D	153 patients (111x *1/*1, 42x (*1/*2 or *2/*2)) received clopidogrel 75 mg/day (n=95) or 150 mg/day (n=58) maintenance doses. Relevant co-medication was not excluded. Poor responder definition: platelet activity index > 69%. Platelet reactivity index was measured using the VASP assay. *1/*2 + *2/*2: - higher prevalence in the poor responders than in the responders (S; 91% increase from 22% to 42%). - higher prevalence in the poor responders receiving 150 mg/day than in the poor responders receiving 75 mg/day (NS; 53% increase from 39% to 60%). (*1/*2 + *2/*2) versus *1/*1: - higher risk of high platelet reactivity index (OR = 3.393 (S; 95% CI 1.062-10.841)). - significantly higher platelet reactivity index at 75 mg/day (S; 14% increase from 56.4% to 64.4%), but not at 150 mg/day (NS; 17% increase from 42.3% to 49.5%). - the platelet reactivity index of (*1/*2 + *2/*2) was lower at 150 mg/day than that of *1/*1 at 75 mg/day (NS; 49.5% and 56.4% respectively). - in poor responders: no difference in platelet reactivity index after dose increase from 75 mg/day to 150 mg/day (NS; 15.3% decrease to 13.6% decrease). NOTE: Allele *2 was genotyped.	Authors' conclusions: "Increasing the dose of clopidogrel from 75 to 150 mg/day in poor responders resulted in a significant decrease in PRI. This effect was not significantly different between carriers of CYP2C19 *2 and non carriers, indicating that a weak response was easily overcome."
ref. 31 Pena A et al. Can we override clopidogrel resistance? Circulation 2009;119:2854-7.	2 IM: D PM: D	7 patients (1x *1/*1, 5x *1/*2, 1x *2/*2) with stent thrombosis and clopidogrel resistance on clopidogrel 75 mg/day. Definition of clopidogrel resistance: residual platelet aggregation ≥ 50% or $P2Y_{12}$ reaction unit ≥ 235 (or inhibition percentage ≤ 15%). Residual platelet aggregation was measured using the LTA and 20 µM ADP, $P2Y_{12}$ reaction units using the VerifyNow assay. 100% of the patients remained resistant after treatment with a 900 mg clopidogrel loading dose and a 150 mg/day clopidogrel maintenance dose for 3 weeks. Increase to 225 mg/day in six patients: 67% remained resistant. Increase to 300 mg/day in four patients: 50% remained resistant, the other 50% discontinued treatment due to side effects (gastric and joint symptoms). Prasugrel 10 mg/day in four patients: 100% had optimal response. Bleeding or serious side effects did not occur for	Authors' conclusions: "Our report shows that a strategy of an incremental increase in the clopidogrel maintenance dose in patients accumulating clinical resistance (stent thrombosis), biological resistance (high platelet aggregation), and a genetic profile of resistance (2C19*2 genetic variant in 6 of the 7

ref. 31, continuation		3 months. Two patients were excluded from prasugrel treatment due to low body weight and age > 75 years respectively. NOTE: Allele *2 was genotyped.	patients) is time consuming and minimally effective."
ref. 32 Sibbing D et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J 2009;30:916-22.	3 IM: E PM: E	2485 patients (1805x *1/*1, 633x *1/*2, 47x *2/*2) received 600 mg clopidogrel loading doses prior to placement of a coronary stent. Patients with bare metal stents (the majority) received clopidogrel maintenance doses for ≥ 30 days. Patients who used oral anticoagulants within 1 week or glycoprotein IIb/IIIa inhibitors within 2 weeks were excluded. Follow-up was performed for 30 days. (IM+PM) versus NM: - the cumulative incidence of stent thrombosis after stent placement increased from 0.4% to 1.5% (HR = 3.81 (S; 95% CI 1.45-10.02)). The *2 allele was an independent variable for the risk of stent thrombosis in a multi-variable model (HR = 3.86 (S; 95% CI 1.47-10.14)). - the cumulative incidence of ST-elevation myocardial infarction increased from 0.5% to 1.5% (HR = 2.96 (S; 95% CI 1.20-7.28)). - the cumulative incidence of ischaemic stroke after stent placement increased from 0% to 0.6% (S). - no difference in the incidence of death, non-ST-elevation myocardial infarction, total myocardial infarction and a composite of myocardial infarction and death (NS). *1/*1 versus *1/*2 versus *2/*2: - the risk of stent thrombosis increased with the number of *2 alleles (S; cumulative incidence: 0.4% versus 1.4% versus 2.1%). NOTE: Allele *2 was genotyped.	Authors' conclusions: "CYP2C19*2 carrier status is significantly associated with an increased risk of ST following coronary stent placement."
ref. 33 Brackbill ML et al. Frequency of CYP3A4, CYP3A5, CYP2C9, and CYP2C19 variant alleles in patients receiving clopidogrel that experience repeat acute coronary syndrome. Heart Vessels 2009;24:73-8.	3 IM + PM: AA	92 patients with 1-4 revascularisations and at least 1 stent who had recurrent acute coronary syndrome while on clopidogrel therapy. The median duration of clopidogrel use until acute coronary syndrome was 6 months. Control group including 94 patients in a pharmacogenetic database not using clopidogrel. Only CYP3A inhibitors were excluded. Group with acute coronary syndrome on clopidogrel versus the control group: - non-significant 39% increase in *2 allele frequency (NS; from 11.4% to 15.8%). - no difference in the *3 allele frequency (NS; both 0%). NOTE: Alleles *2 and *3 were genotyped.	Authors' conclusions: "The present data indicate that patients currently receiving clopidogrel therapy who present with repeat ACS do not have higher frequency of the examined variant alleles compared to a control group."
ref. 34 Giusti B et al. Relation of cytochrome P450 2C19 loss-of-function polymorphism to occurrence of drug-eluting coronary stent thrombosis. Am J Cardiol 2009;103:806-11.	3	772 patients (525x *1/*1, 221x *1/*2, 26x *2/*2) received clopidogrel 600 mg and acetylsalicylic acid 325 mg prior to placement of a drug eluting stent, unfractionated heparin 70 IU/kg and, if needed, glycoprotein IIb/IIIa inhibitors during the procedure, followed by clopidogrel 75 mg/day and acetylsalicylic acid 325 mg/day. Co-medication was not excluded. Blood samples were taken 12-18 hours after stent placement (or after 6 days if glycoprotein IIb/IIIa inhibitors had been administered). Follow-up was performed for 6 months. Stent thrombosis was defined as angiographically confirmed or probable stent thrombosis. Residual platelet aggregation was measured using the LTA and 10 µM ADP. (IM+PM) versus NM: - the incidence of stent thrombosis increased by 152% (S; from 2.1% to 5.3%).	Authors' conclusions: "The CYP2C19*2 allele was associated with the occurrence of ST or ST and cardiac mortality in high-risk vascular patients on dual-antiplatelet treatment."

ref. 34, continuation	IM + PM: F IM: E PM: E	- the incidence of cardiovascular death increased by 167% (S; from 1.5% to 4.0%). - the incidence of stent thrombosis and/or cardiovascular death increased by 123% (S; from 2.7% to 6.1%). - the prevalence of the phenotype in patients with stent thrombosis was 73% higher (S; from 31.3% to 54.1%). - the prevalence of the phenotype in patients with stent thrombosis and/or cardiovascular death was 66% higher (S; from 31.2% to 51.7%). - median residual platelet aggregation increased by 13% (S; from 45% to 51%). - multivariable regression analysis showed that the *2 allele was an independent variable for the risk of stent thrombosis (OR = 3.43 (S; 95% CI 1.01-12.78)) and the risk of stent thrombosis and/or cardiovascular death (OR = 2.70 (S; 95% CI 1.00-8.42)). *1/*2 versus *1/*1: - the incidence of stent thrombosis increased by 138% (S for the trend *1/*1, *1/*2 and *2/*2; from 2.1% to 5.0%). - the incidence of stent thrombosis and/or cardiovascular death increased by 121% (NS for the trend *1/*1, *1/*2 and *2/*2; from 2.7% to 5.9%). *2/*2 versus *1/*1: - the incidence of stent thrombosis increased by 267% (S for the trend *1/*1, *1/*2 and *2/*2; from 2.1% to 7.7%). - the incidence of stent thrombosis and/or cardiovascular death was increased by 188% (NS for the trend *1/*1, *1/*2 and *2/*2; from 2.7% to 7.7%). NOTE: Allele *2 was genotyped.	
ref. 35 Collet JP et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009;373:309-17.	4 IM + PM: E	259 patients < 45 years (186x *1/*1, 64x *1/*2, 3x (*1/*3 or *1/*4), 9x *2/*2, 2x (*2/*3 or *2/*4)) who used clopidogrel 75 mg/day for a median 1.07 years after a myocardial infarction. Co-medication was not excluded, but corrections were made for recent proton pump inhibitor usage. Follow-up started 3 months after the myocardial infarction and lasted for up to 8 years. The primary endpoint was cardiovascular death and/or myocardial infarction and/or urgent coronary revascularisation while using clopidogrel. *2 versus (no *2): - incidence of the primary endpoint per 100 patient years increased from 2.89% to 10.90% (HR_{corr} = 5.38 (S; 95% CI 2.32-12.47)). The increased incidence of the primary endpoint was also observed in the period from 6 months after initiation of clopidogrel (HR = 3.00 (S; 95% CI 1.27-7.10) versus HR = 3.69 (S; 95% CI 1.69-8.05) for the total follow-up). The increased incidence of the primary endpoint was observed both after initiation of clopidogrel immediately after the myocardial infarction and when clopidogrel was started later (HR = 3.05 (S; 95% CI 1.14-8.19) versus HR = 6.82 (S; 95% CI 1.41-32.99)). - incidence of myocardial infarction per 100 patient years increased from 1.58 to 7.27 (HR_{corr} = 5.57 (S; 95% CI 1.94-16.01)). - incidence of stent thrombosis per 100 patient years increased from 1.14 to 6.79 (HR_{corr} = 6.04 (S; 95% CI 1.75-20.80)). All cases of stent thrombosis led to ST-elevation myocardial infarction. - incidence of ischaemic events other than stent thrombosis per 100 patient years increased from 1.99 to 5.09 (HR_{corr} = 3.31 (S; 95% CI 1.05-10.47)). - non-significant increase in the incidence of cardiovascular death and the incidence of urgent revascularisation per	Authors' conclusions: "The *CYP2C19*2* genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after myocardial infarction."

ref. 35, continuation		100 patient years (from 0.26 to 1.45 and from 1.05 to 2.18 respectively) (NS). - multivariable analysis showed that the *2 allele was the only independent variable for the risk of cardiovascular events (HR = 4.04 (S; 95% CI 1.81-9.02)). (one *2) versus (no *2): - the incidence of the primary endpoint increased by 243% (NS; from 5.9% to 20.3%). *2/*2 versus (no *2): - the incidence of the primary endpoint increased by 276% (NS; from 5.9% to 22.2%). *3 and *4: - the results did not change on inclusion of *3 and *4 in the analysis. NOTE: Alleles *2-*6 were genotyped.	
ref. 36 Mega JL et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-62.	4 IM + PM: F *17: AA	1459 patients with acute coronary syndrome and elective percutaneous coronary intervention (1064x NM+UM (*1/*1, *1/*17 or *17/*17), 357x IM (*1/*2, *1/*3, *1/*4 or *1/*8), 38x PM (*2/*2, *2/*3, *2/*4, *2/*5 or *2/*8)) received a 300 mg clopidogrel loading dose, followed by clopidogrel 75 mg/day for up to 15 months. Co-medication was not excluded, but O'Donoghue et al. (Lancet 2009;374:989-97) excluded 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 angiographically confirmed or probable stent thrombosis. (IM+PM) versus (NM+UM): - incidence of the primary endpoint increased from 8.0% to 12.1% (HR = 1.53 (S; 95% CI 1.07-2.19)). - incidence of cardiovascular death increased from 0.4% to 2.0% (HR = 4.79 (S; 95% CI 1.40-16.37)). - incidence of stent thrombosis increased from 0.8% to 2.6% (HR = 3.09 (S; 95% CI 1.19-8.00)). - incidence of non-fatal myocardial infarction increased from 7.5% to 10.1% (NS). - incidence of non-fatal stroke increased from 0.24% to 0.88% (NS). - no difference in the incidence of bleeding (minor and major bleeding): from 3.0% to 2.9% (NS). 148 healthy volunteers (44x NM+UM (*1/*17 or *17/*17), 53x NM (*1/*1), 43x IM (*1/*2, *1/*3, *1/*4 or *1/*8), 8x PM (*2/*2, *2/*3, *2/*4, *2/*5 or *2/*8)) received clopidogrel 300 or 600 mg loading doses either as single doses or followed by clopidogrel 75 mg/day. Platelet aggregation was measured using the LTA and 20 µM ADP. (NM+UM) versus NM versus IM versus PM: - the AUC of the active metabolite decreased with decreasing gene dose for both loading doses and for the maintenance dose (NS). - platelet aggregation decreased with decreasing gene dose for both loading doses and for the maintenance dose (NS). Loading dose of 300 mg versus 600 mg: - AUC of the active metabolite and reduction in platelet aggregation in IM patients at 600 mg was comparable to that of NM patients at 300 mg. The 600 mg loading dose was not tested in PM patients. NOTE: Alleles *2 to *10, *12 to *14 and *17 were genotyped.	Authors' conclusions: "Among persons treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers."

ref. 37 Simon T et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363-75.	4 PM: E IM: AA UM: AA	2208 patients with acute myocardial infarction, including 1535 undergoing percutaneous coronary intervention (1573x NM+UM (no null allele), 577x IM (one null allele), 58x PM (two null alleles)) received on average 300 mg clopidogrel loading doses, followed by clopidogrel maintenance doses of on average 75 mg/day. Co-medication was not excluded. The primary endpoint was death and/or myocardial infarction and/or stroke. Follow-up was performed for 1 year. 2164 patients were genotyped for *17: 1390x no *17, 674x one *17, 100x *17/*17. PM versus (NM+UM): - incidence of the primary endpoint increased from 13.3% to 21.5% (HR_{corr} = 1.98 (S; 95% CI 1.10-3.58)) for all patients. - incidence of the primary endpoint (HR_{corr} = 3.58 (S; 95% CI 1.71-7.51)) increased for patients undergoing percutaneous coronary intervention. - correction for the presence of the *17 allele or the use of proton pump inhibitors or calcium channel blockers did not have a significant effect on these risks. IM versus (NM+UM): - incidence of the primary endpoint decreased from 13.3% to 11.1% (HR_{corr} = 0.69 (S; 95% CI 0.51-0.93)) for all patients. - incidence of the primary endpoint decreased for patients undergoing percutaneous coronary intervention (NS). (no *17) versus (one *17) versus *17/*17: - incidence of the primary endpoint decreased with the number of *17 alleles (NS; 14.3% versus 11.4% versus 11.0%). NOTE: Alleles *2 to *5 and *17 were genotyped.	Authors' conclusions: "Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention."
ref. 38 Geisler T et al. CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. Pharmacogenomics 2008;9:1251-9.	4 IM + PM: D IM: D PM: D UM: AA	237 patients (175x NM (154x (*1/*1 or *1/*17), 21x *17/*17)), 52x IM (*1/*2 or *17/*2), 10x PM (*2/*2)); received a 600 mg clopidogrel loading dose before undergoing balloon angioplasty. ADP-induced platelet aggregation was measured ex vivo using the LTA and 10 µM ADP ~20 hours after administration. IM + PM versus NM: - increased residual platelet aggregation (OR = 4.6 (S; 95% CI 2.5-8.7)); median aggregation was 46% for IM, 54% for PM and 30% for NM). - increased risk of poor response (residual aggregation > 47%) (S; 4.4x increased for IM + PM (95% CI 2.5-8.7); OR = 3.7 for IM (95% CI 1.87-7.35) and 10.7 for PM (95% CI 2.56-44.88)). *17/*17 versus (*1/*17 + *2/*17) versus (*1/*1 + *1/*2 + *2/*2): - no difference in residual platelet aggregation (median aggregation was 37% versus 30% versus 36%).	Authors' conclusion: "Prediction of responsiveness after clopidogrel loading dose may substantially be improved by adding CYP2C19*2 genotype to nongenetic risk factors."
ref. 39 Umemura K et al. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. J Thromb Haemost	3 PM: D	47 healthy volunteers (18x NM, 20x IM, 9x PM) received a single dose of 300 mg clopidogrel. Platelet reactivity index (decrease in activated platelet ADP receptor P2Y12 stimulated phosphorylation of vasodilator-stimulated phosphoprotein (VASP)) was determined 4 hours after clopidogrel administration. PM versus NM: - AUC_{0-8h} of the active metabolite decreased by 43% (S; from 58.3 to 33.0 ng.h/mL). - platelet reactivity index increased by 40% (S, from 50.0 to 70.2%). IM versus NM: - AUC_{0-8h} of the active metabolite decreased by 29% (S;	Authors' conclusion: "The CYP2C19 pharmacogenomic status is a determinant for the formation of the active metabolite of clopidogrel and its antiplatelet effects to the active metabolite in healthy subjects."

2008;6:1439-41. **ref. 39, continuation**	IM: D	from 58.3 to 41.5 ng.h/mL). - platelet reactivity index increased by 23% (S, from 50.0 to 61.5%). There was a significant correlation between platelet reactivity index and the AUC of the active metabolite. NOTE: *17 was not determined.	
ref. 40 Chen BL et al. Inhibition of ADP-induced platelet aggregation by clopidogrel is related to CYP2C19 genetic polymorphisms. Clin Exp Pharmacol Physiol 2008;35:904-8.	4 PM: D IM: AA	18 healthy men (6x NM, 6x IM (5x *1/*2, 1x *1/*3), 6x PM (5x *2/*2, 1x *2/*3)) received clopidogrel 300 mg on day 1 and 75 mg on days 2 and 3. Co-medication, smoking and alcohol were excluded. Platelet aggregation was measured using the LTA and 5 µM ADP. PM versus NM: - ADP-induced platelet aggregation 4, 24 and 72 hours after the first dose of clopidogrel decreased by 39%, 49% and 42% respectively (S; from 49.0 to 29.7%; from 48.7 to 25.0% and from 45.4 to 26.5% respectively). IM versus NM: - no significant decrease in ADP-induced platelet aggregation 4, 24 and 72 hours after the first dose of clopidogrel. - there were significant differences in platelet aggregation after clopidogrel between the three genotypes NM, IM and PM. Clopidogrel significantly decreased ADP-induced platelet aggregation for all three genotypes. NOTE: *17 was not determined.	Authors' conclusion: "CYP2C19*2 and CYP2C19*3 genetic polymorphisms reduced clopidogrel inhibition of ADP-induced platelet aggregation, with the degree of inhibition dependent on the genetic polymorphism present."
ref. 41 Kim KA et al. The effect of CYP-2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. Clin Pharmacol Ther 2008;84:236-42.	4 PM: D IM: AA	24 healthy volunteers (8x NM, 8x IM (6x *1/*2, 2x *1/*3), 8x PM (6x *2/*2, 2x *2/*3)) received clopidogrel 300 mg on day 1 and 75 mg/day on days 2-7. Co-medication, smoking and relevant foods were excluded. Platelet aggregation was measured using the LTA and 5 µM ADP. PM versus NM: - AUC_{0-24h} increased by 194% (S, from 10.20 to 29.98 ng.h/mL). - maximum percentage inhibition of ADP-induced platelet aggregation decreased by 40% in the first 24 hours (S; from 64.1% to 38.3%) and by 37% during the 7 days (S; from 64.7% to 40.8%). - AUEC (area under the effect-time curve) decreased by 51% in the first 24 hours (S; from 1319.4 to 652.0%.h) and by 61% during the 7 days (S; from 9134.1 to 3593.8%.h). IM versus NM: - AUC_{0-24h} increased by 67% (NS, from 10.20 to 17.02 ng.h/mL). - maximum percentage inhibition of ADP-induced platelet aggregation decreased by 13% in the first 24 hours (NS; from 64.1% to 55.9%) and by 10% during the 7 days (NS; from 64.7% to 58.4%). - AUEC (area under the effect-time curve) decreased by 18% in the first 24 hours (NS; from 1319.4 to 1079.0%.h) and by 21% during the 7 days (NS; from 9134.1 to 7221.9%.h). There was a significant negative correlation between clopidogrel pharmacokinetics and inhibition of platelet aggregation. NOTE: *17 was not determined.	Authors' conclusion: "From these findings it is clear that the CYP2C19 genotype affects the plasma levels of clopidogrel and modulates the antiplatelet effect of clopidogrel."

ref. 42 Malek LA et al. Coexisting polymorphisms of P2Y12 and CYP2C19 genes as a risk factor for persistent platelet activation with clopidogrel. Circ J 2008;72:1165-9.	4 IM + PM: AA IM: D	105 patients undergoing balloon angioplasty due to acute coronary syndrome (81 homozygous for the wild type P2Y12 allele (67x CYP2C19 NM, 13x IM, 1x PM) and 24 carriers of a mutant P2Y12 allele (17x CYP-2C19 NM, 7x IM)) received a 300 mg acetylsalicylic acid loading dose followed by acetylsalicylic acid 75 mg/day, and a 300 or 600 mg clopidogrel loading dose, followed by clopidogrel 75 mg/day. Co-medication was not excluded. Platelet function was analysed by measuring the CADP-CT: the time taken by blood aspirated through a capillary towards a collagen coated membrane containing ADP (CADP) to occlude the aperture by plug formation (CT = closure time). The test stops automatically after 300 seconds (maximum CADP-CT) and is relatively insusceptible to acetylsalicylic acid. Follow-up was performed for 12 months. IM + PM versus NM in patients with wt P2Y12: - median CADP-CT decreased by 27% (NS; from 289 to 210 s). PM patients had a low CADP-CT of 81 s. IM versus NM in patients with mutant P2Y12: - median CADP-CT decreased by 67% (NS; from 286 to 95 s). During the follow-up period, 6 patients (5.7%) had recurrent cardiovascular events (4x non-fatal myocardial infarction, including 1 due to subacute stent thrombosis and 2x cardiovascular death (end-stage heart failure and sudden cardiac death)). The subacute stent thrombosis occurred in a patient with wt P2Y12 and mutant CYP2C19, the other 5 events in patients homozygous for the wt allele of both genes. The patients with cardiovascular events had a 63% lower median CADP-CT than the patients without negative consequences (S; 100 versus 271 s). NOTE: *17 was not determined. *3 was also not determined, but it is very uncommon.	Authors' conclusion: "Coexisting, rather than single, polymorphisms of different genes may be related to persistent platelet activation while on clopidogrel, which raises concern about harm in patients with ACS."
ref. 43 Trenk D et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol 2008;51:1925-34.	4 IM + PM: D	797 patients without myocardial infarction (552x NM, 228x IM (*1/*2) + 17x PM (*2/*2)) received a 600 mg clopidogrel loading dose before balloon angioplasty. All patients received a 100-140 U/kg intra-arterial dose of heparin. After balloon angioplasty, patients received clopidogrel 75 mg/day (for 30 days after placement of a bare metal stent and for 6 months after placement of a drug eluting stent) and acetylsalicylic acid ≥ 100 mg/day for life. Blood samples were taken before administration of the clopidogrel loading dose, during the surgery prior to heparin administration and 2-4 hours after the first clopidogrel maintenance dose. Chronic oral anticoagulants and clopidogrel shorter than 2 weeks before the study were excluded, but other co-medication was not. Follow-up was performed for 12 months. Platelet aggregation was measured using the LTA and 5 or 20 μM ADP. IM + PM versus NM: - the percentage of patients with residual platelet aggregation > 14% increased by 44% after the clopidogrel loading dose and by 84% after the first maintenance dose (S; from 43.3% to 62.4% and from 22.5% to 41.3% respectively) - median residual platelet aggregation increased by 109% after the loading dose and by 57% after the first	Authors' conclusion: "Patients carrying at least one CYP2C19 *2 allele are more prone to high-on clopidogrel platelet reactivity, which is associated with poor clinical outcome after coronary stent placement."

ref. 43, continuation		maintenance dose (S; from 11.0% to 23.0% and from 7.0% to 11.0% respectively) - surface expression of activation-dependent platelet proteins (P-selectin, activated GP IIa/IIIb, CD63, CD40L and GP IIb) after ADP stimulation increased by 3-69% after the loading dose and by 5-75% after the first maintenance dose (S). - no significant difference in the 1-year incidence of death and myocardial infarction. NOTE: *17 was not determined. *3 was also not determined, but it is very uncommon.	
ref. 44 Frére C et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol 2008;101:1088-93.	3 IM: D PM: D PM: D IM: AA[#]	603 patients with non-ST-elevation acute coronary syndrome (435x NM, 143x IM (*1/*2) + 23x PM (*2/*2)) received clopidogrel 600 mg and acetylsalicylic acid 250 mg at least 12 hours before coronary angiography. Blood samples were taken prior to coronary angiography. Glycoprotein IIb/IIIa antagonists before the study were excluded, but other co-medication was not. Residual platelet aggregation was measured using the LTA and 10 µM ADP, platelet reactivity index using the VASP assay. PM versus IM versus NM: - significant association between the number of *2 alleles with three outcome measures of ADP-induced platelet activity: - residual platelet aggregation (66.1% versus 56.1% versus 55.7%; PM versus NM: 19% increase). - platelet reactivity index (69.1% versus 59.1% versus 50.9%; PM versus NM: 36% increase). - increased surface expression of P-selectin (0.43 versus 0.39 versus 0.35 arbitrary units; PM versus NM: 23% increase). - significant association between the number of *2 alleles and non-response (residual platelet aggregation > 70%) (% non-responders: 43% versus 20% versus 25%). PM: - 3% of the responders versus 7% of the non-responders (S, 133% increase) IM: - 25% of the responders versus 19% of the non-responders (S, 24% decrease) NOTE: *17 was not determined. *3 was also not determined, but it is very uncommon.	Authors' conclusion: "The present data suggest that the CYPC19*2 allele influences post-treatment platelet reactivity and clopidogrel response in patients with non–ST elevation acute coronary syndromes."
ref. 45 Fontana P et al. Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of the cytochrome P450 2C19*2 allele on clopidogrel responsiveness. Thromb Res 2008;121:463-8.	3 IM: AA PM: AA	81 patients (54x NM, 25x IM (*1/*2), 2x PM (*2/*2)) received clopidogrel 600 mg prior to balloon angioplasty, followed by clopidogrel 75 mg/day for 15 days. 42 patients (25x NM, 15x IM (*1/*2), 2x PM (*2/*2)) were poor responders (platelet reactivity index ≥ 50%) and received clopidogrel 150 mg on days 16-30. Co-medication was not excluded. All patients except one used acetylsalicylic acid 100 mg/day at the start of the study. Platelet reactivity index was measured using the VASP assay. PM versus IM versus NM: - no significant difference in platelet reactivity index after the first 15 days (NS; 50.9% versus 50.6% versus 66.1%) - no significant difference in decrease in platelet reactivity index in the poor responders after 15 days of clopidogrel 150 mg/day (NS; 23.4% versus 18.0% versus 18.9%). NOTE: *17 was not determined. *3 was also not	Authors' conclusion: "The 2C19*2 allele did not influence clopidogrel responsiveness in our population of cardiovascular outpatients."

		determined, but it is very uncommon.	
ref. 46 Giusti B et al. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. Pharmacogenet Genomics 2007;17:1057-64.	3 PM: D IM: D	1419 patients with an acute coronary syndrome (974x NM, 405x IM (*1/*2), 40x PM (*2/*2)) received clopidogrel 600 mg oral and acetylsalicylic acid 500 mg IV prior to balloon angioplasty, 70 IU/kg unfractionated heparin and, if needed, glycoprotein IIb/IIIa inhibitors, during the procedure, and clopidogrel 75 mg/day and acetylsalicylic acid 100 mg/day after the procedure. Co-medication was not excluded. Blood samples were taken 24 hours after balloon angioplasty (or after 6 days if glycoprotein IIb/IIIa inhibitors had been administered). Residual platelet aggregation was measured using the LTA. PM versus NM: - residual platelet aggregation (induced by 10 µmol/L ADP) increased by 27% (S; from 49% to 62%). IM versus NM: - residual platelet aggregation (induced by 10 µmol/L ADP) increased by 10% (S; from 49% to 54%). PM versus IM versus NM: - significant difference in genotype distribution between poor responders (residual platelet aggregation ≥ 70%) and good responders. Percentage poor responders per genotype: 35% versus 27% versus 22%. - there was a significant association between the *2 allele and residual platelet aggregation after induction by 10 µmol/L ADP, 2 µmol/L ADP or 0.5 mg/mL arachidonic acid. Multivariate linear regression (corrected for six risk factors for poor anticoagulation) showed that the *2 allele was a significant and independent risk factor for poor response. NOTE. *17 was not determined. *3 was also not determined, but it is very uncommon.	Authors' conclusion: "This study demonstrates, for the first time, that the *2 CYP2C19 allele is associated with higher platelet aggregability and residual platelet reactivity in high-risk vascular patients on dual antiplatelet treatment."
ref. 47 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: D IM: D IM + PM: D	74 healthy volunteers (56x NM, 17x IM (*1/*2), 1x PM (*2/*2)) received clopidogrel 300 mg. Co-medication was excluded. Platelet aggregation was measured after 4 hours using the LTA and 20 µM ADP. PM versus IM versus NM: - there was a significant association between the *2 allele and $AUC_{0\text{-}24h}$ of the active metabolite (26.9 versus 41.5 versus 76.2 ng.h/mL). - there was a significant association between the *2 allele and inhibition of platelet aggregation (3.8 versus 20.3 versus 39.1%). IM + PM versus NM: - the percentage of poor responders (inhibition of platelet aggregation < 20%) increased by 76% (S; from 41.4% to 72.2%). NOTE: *17 was not determined.	Authors' conclusion: "The common loss of function polymorphisms of CYP2C19 and CYP2C9 are associated with decreased exposure to the active metabolite of clopidogrel but not prasugrel. Decreased exposure to its active metabolite is associated with a diminished pharmacodynamic response to clopidogrel."
ref. 48 Fontana P et al. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. J Thromb Haemost 2007;5:2153-5.	4 IM: D	94 healthy volunteers (68x NM, 26x IM (*1/*2)) received clopidogrel 300 mg on day 1 followed by clopidogrel 75 mg/day on days 2 to 7. Platelet aggregation was measured using the LTA and 20 µM ADP. IM versus NM: - residual platelet aggregation on day 8 was increased by 32% (S; from 36.8% to 48.5%). *2 allele: - highest percentage of IM in the quartile of the highest platelet aggregation and lowest percentage in the quartile	Authors' conclusion: "This study points out the CYP2C19 (*1/*2) polymorphism as a candidate in the explanation of clopidogrel poor responsiveness as we replicate our previous findings in a larger,

ref. 48, continuation		of the lowest platelet aggregation (S; 47.8% versus 30.4% versus 25% versus 8.3% for quartiles 1 to 4). - the *2 allele accounts for 10% of the variability in clopidogrel response. The association remained significant after correction for age, platelet count, haematocrit, collagen lag time and fibrinogen and Von Willebrand concentrations. NOTE: *17 was not determined. *3 was also not determined, but it is very uncommon.	independent study population. The CYP2C19 (*1/*2) explained 10% of the observed variability in clopidogrel responsiveness."
ref. 49 Hulot JS et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood 2006;108:2244-7.	4 IM: D	28 healthy men (20x NM, 8x IM (*1/*2)) received clopidogrel 75 mg/day for 7 days. Co-medication was excluded. Platelet aggregation was measured using the LTA and 10 µM ADP, platelet reactivity index using the VASP assay. IM versus NM: - residual platelet aggregation on day 7 was increased by 47% (S; from 48.9% to 71.8%). - platelet reactivity index on day 7 was increased by 36% (S; from 42.9% to 58.2%). - the decrease in platelet aggregation was not significant during the study for IM patients, but was significant for NM patients. Platelet reactivity index decreased significantly for both. - highest percentage of IM in the quartile of the highest platelet aggregation and lowest percentage in the quartile of the lowest platelet aggregation (NS; 71% versus 29% versus 14% versus 0% for quartiles 1 to 4). After genotyping for *3, *4, *5 and *6, one NM patient was actually found to be an IM patient (*1/*4). Correct classification of this person did not change the results. NOTE: *17 was not determined.	Authors' conclusion: "The CYP2C19*2 loss-of-function allele is associated with a marked decrease in platelet responsiveness to clopidogrel in young healthy male volunteers and may therefore be an important genetic contributor to clopidogrel resistance in the clinical setting."
ref. 50 FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. 03-12-10.	0 PM: A	<u>Warning</u> The U.S. Food and Drug Administration (FDA) has added a boxed warning to the label for Plavix. The boxed warning is about patients who do not effectively metabolise the drug (i.e. "poor metabolisers") and therefore may not receive the full benefits of the drug. The boxed warning in the drug label will include information to: • warn about reduced effectiveness in patients who are poor metabolisers of Plavix. Poor metabolisers do not effectively convert Plavix to its active form in the body due to reduced CYP2C19 activity. • inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function. • advise healthcare professionals to consider use of other platelet aggregation inhibitors or alternative Plavix doses in patients identified as poor metabolisers. <u>Additional information for healthcare professionals</u> The FDA recommends that healthcare professionals should be aware that although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolisers increases antiplatelet response, an appropriate dose regimen for poor metabolisers has not been established in a clinical outcome trial.	
ref. 51 SmPC Plavix (clopidogrel) 26-04-18.	0 PM: D	<u>Warning</u>: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP-2C19 genotype.	

ref. 51, continuation		Pharmacokinetic properties: CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, normal, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, normal and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to normal metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 µM ADP) of 24% (24 hours) and 37% (day 5) as compared to IPA of 39% (24 hours) and 58% (day 5) in the normal metabolisers and 37% (24 hours) and 60% (day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (day 5), which were greater than in the poor metabolisers receiving the 300 mg/75 mg regimen, and were similar to the other CYP-2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials. Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 µM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to normal metabolisers. The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), TRITON-TIMI 38 (n=1477), and ACTIVE-A (n=601), as well as a number of published cohort studies. In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to normal metabolisers. In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to normal metabolisers. In CURE, CLARITY, ACTIVE-A and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status. None of these analyses were adequately sized to detect	

<table>
<tr><td></td><td></td><td>differences in outcome in poor metabolisers.</td><td></td></tr>
<tr><td>ref. 52
SmPC Plavix (clopidogrel), USA, 10-11-18.</td><td>0

PM: D</td><td>Boxed warning:
WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE
- The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed “CYP2C19 poor metabolizers”).
- Tests are available to identify patients who are CYP2C19 poor metabolisers.
- Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.
Warning:
Diminished antiplatelet activity in patients with impaired CYP2C19 function.
Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19.
Pharmacokinetics:
Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. Patients who are homozygous for nonfunctional alleles of the CYP2C19 gene are termed “CYP2C19 poor metabolizers.” Approximately 2% of White and 4% of Black patients are poor metabolizers; the prevalence of poor metabolism is higher in Asian patients (e.g., 14% of Chinese). Tests are available to identify patients who are CYP2C19 poor metabolizers.
A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups.
<table>
<tr><td colspan="6">Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status</td></tr>
<tr><td></td><td>dose</td><td>UM† (n=10)</td><td>NM (n=10)</td><td>IM* (n=10)</td><td>PM (n=10)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>300 mg (24 hr)</td><td>24 (10)</td><td>32 (21)</td><td>23 (11)</td><td>11 (4)</td></tr>
<tr><td></td><td>600 mg (24 hr)</td><td>36 (13)</td><td>44 (27)</td><td>39 (23)</td><td>17 (6)</td></tr>
<tr><td></td><td>75 mg (day 5)</td><td>12 (6)</td><td>13 (7)</td><td>12 (5)</td><td>4 (1)</td></tr>
<tr><td></td><td>150 mg (day 5)</td><td>16 (9)</td><td>19 (5)</td><td>18 (7)</td><td>7 (2)</td></tr>
<tr><td>IPA (%)‡</td><td>300 mg (24 hr)</td><td>40 (21)</td><td>39 (28)</td><td>37 (21)</td><td>24 (26)</td></tr>
<tr><td></td><td>600 mg (24 hr)</td><td>51 (28)</td><td>49 (23)</td><td>56 (22)</td><td>32 (25)</td></tr>
<tr><td></td><td>75 mg (day 5)</td><td>56 (13)</td><td>58 (19)</td><td>60 (18)</td><td>37 (23)</td></tr>
<tr><td></td><td>150 mg (day 5)</td><td>68 (18)</td><td>73 (9)</td><td>74 (14)</td><td>61 (14)</td></tr>
<tr><td>VASP-PRI (%)§</td><td>300 mg (24 hr)</td><td>73 (12)</td><td>68 (16)</td><td>78 (12)</td><td>91 (12)</td></tr>
<tr><td></td><td>600 mg (24 hr)</td><td>51 (20)</td><td>48 (20)</td><td>56 (26)</td><td>85 (14)</td></tr>
<tr><td></td><td>75 mg (day 5)</td><td>40 (9)</td><td>39 (14)</td><td>50 (16)</td><td>83 (13)</td></tr>
<tr><td></td><td>150 mg (day 5)</td><td>20 (10)</td><td>24 (10)</td><td>29 (11)</td><td>61 (18)</td></tr>
</table>
</td><td></td></tr>
</table>

ref. 52, continuation		† Ultrarapid metabolizers have at least one gain-of-function allele. * Intermediate metabolizers have one but not two nonfunctional alleles. ‡ Inhibition of platelet aggregation with 5 μM ADP; larger value indicates greater platelet inhibition § Vasodilator-stimulated phosphoprotein–platelet reactivity index; smaller value indicates greater platelet inhibition Values are means (SD).	

AA[#]: the allele has a significant effect, but this effect is favourable instead of unfavourable.

Risk group	IM and PM with use of CYP3A4 inhibitors.

Comments:

- Due to the large number of studies investigating IM and PM patients, studies evaluating these phenotypes have only been included from 2009 if the clinical effectiveness was evaluated directly (i.e. not only platelet aggregation). For the same reason were only meta-analyses with more than 20,000 cardiac patients, studies or meta-analyses with more than 1000 cerebrovascular patients, and studies with more than 250 patients with peripheral endovascular intervention included from 2010. The only exceptions were studies that evaluated the effect of higher doses or alternatives. Studies from 2010 that only determined the effect of higher doses on patient groups preselected on high residual platelet activity at the standard dose were not included. Genotypeguided studies were not included if the choice for an alternative or dose adjustment was mainly guided by genotypes from a gene other than CYP2C19. Studies from 2012 investigating the effect of higher doses or alternatives were only included if clinical effects (i.e. not only platelet aggregation) were evaluated and from April 2016 only if more than 750 patients or more than 50 PM for percutaneous coronary intervention, and more than 300 patients or at least 25 PM for stroke or TIA were included.
  For *17, only a meta-analysis with more than 15,000 cardiac patients was included from 2010.
  Substudies of Wang 2016 published after 2018 were not included in the risk analysis because they did not add enough to the available information.
- <u>CYP2C19 genotype-guided clopidogrel therapy is better than standard therapy for percutaneous coronary intervention (ticagrelor or prasugrel)</u>:
  In the Netherlands, standard therapy of percutaneous coronary intervention (PCI) is ticagrelor or prasugrel, corresponding to the European Society of Cardiology Guidelines. However, Claassens 2019 showed CYP2C19 genotype-guided clopidogrel therapy to be non-inferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to net adverse clinical events and to result in a lower incidence of bleeding in patients with ST-segment elevation myocardial infarction undergoing primary PCI with stent implantation (Claassens DMF et al. A genotype-guided strategy for oral P2Y(12) inhibitors in primary PCI. N Engl J Med 2019;381:1621-31. PubMed PMID: 31479209).
  In this randomised, open-label, assessor-blinded trial, 1242 patients were treated with genotype-guided therapy (clopidogrel for NM+UM and ticagrelor or prasugrel for IM+PM) and 1246 patients were treated with standard therapy (ticagrelor or prasugrel). In both arms, ticagelor was preferred over prasugrel and used 38-39 times as often. Net adverse clinical events were defined as death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding defined according to Platelet Inhibition and Patient Outcomes (PLATO) criteria (including major bleeding related to coronary-artery bypass grafting (CABG) as well as non-CABG-related major bleeding), at 12 months. Bleeding was defined as PLATO major bleeding (CABG-related and non-CABG-related) or minor bleeding at 12 months. Genotyping was for *2 and *3.
- <u>Guidelines</u>:
  - Scott SA et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther 2013;94:317-23. PubMed PMID: 23698643.
    The authors state that many studies have shown that clopidogrel use by *1/*2 and *2/*2 patients is associated with reduced formation of active clopidogrel metabolites and higher platelet aggregation (Hulot 2006, Brandt 2007, Giusti 2007, Mega 2009, Shuldiner 2009 and Hulot 2011). Moreover, there is substantial evidence supporting a relationship between the CYP2C19 genotype and the clinical outcomes for clopidogrel-treated patients with acute coronary syndrome, especially those undergoing percutaneous coronary intervention (Collet 2009, Giusti 2009, Mega 2009, Shuldiner 2009, Sibbing 2009, Simon 2009 and Ayla 2011). Studies including patients with acute coronary syndrome, most of whom underwent percutaneous coronary intervention, showed the strongest relationship between genotype and clinical outcome. This means that genotype-based recommendations do not apply to other indications of clopidogrel, including treatment of acute coronary syndrome without percutaneous coronary intervention, stroke and peripheral arterial disease.
    Large meta-analyses have shown that among patients with acute coronary syndrome who have undergone percutaneous coronary intervention, patients with *1/*2 and *2/*2 have an increased risk of serious cardiovascular events compared to patients with *1/*1 (HR = 1.55 (95% CI: 1.11-2.17) for *1/*2 and HR = 1.76 (95% CI: 1.24-2.50) for *2/*2)) and an increased risk of stent thrombosis (HR = 2.67 (95%

CI: 1.69-4.22) for *1/*2 and HR = 3.97 (95% CI: 1.75-9.02) for *2/*2)) (Mega 2010). Other meta-analyses have confirmed the association between CYP2C19 genotype and stent thrombosis, with an OR for *1/*2 and *2/*2 ranging from 1.75 to 3.82 (Hulot 2010, Bauer 2011, Holmes 2011, Jin 2011, Sofi 2011, Jang 2012, Yamaguchi 2012, Singh 2012 and Zabalza 2013).
No effect of CYP2C19 null alleles on cardiovascular events was found in clopidogrel-treated patients with a low risk (e.g. trials with few patients undergoing percutaneous coronary intervention and stent placement and in patients with atrial fibrillation or stroke) (Paré 2010). Meta-analyses that included studies with low numbers of percutaneous coronary interventions, patients without coronary arterial disease, the period after clopidogrel treatment or non-cardiovascular outcome measures also did not find that CYP2C19 played an important role in the variation in clopidogrel response (Holmes 2011).
CYP2C19 genotype-guided antiplatelet therapy should therefore be mainly limited to patients with acute coronary syndrome undergoing percutaneous coronary intervention. Although there are limited data on patients undergoing elective percutaneous coronary intervention, these recommendations can also be considered for those patients. The fact that possible alternatives (prasugrel and ticagrelor) are not registered for this indication should nevertheless be considered here.
Based on the above and on articles on clopidogrel (Mega 2009 and Pena 2009), prasugrel (Mega 2009) or clopidogrel versus prasugrel (Wiviott 2007, Wallentin 2008 and Montalescot 2010) the CPIC advises an alternative for PM patients if possible. The CPIC classifies this recommendation as strong.
The CPIC states that the mean platelet activity among IMs on clopidogrel is higher than NMs on clopidogrel (Hulot 2006, Brandt 2007, Giusti 2007, Mega 2009 and Shuldiner 2009). Moreover, IMs with acute coronary syndrome, who underwent percutaneous coronary intervention, had an increased risk of serious cardiovascular events including stent thrombosis (Mega 2010). For these reasons, the CPIC recommends that IMs are given an alternative if possible. However, the CPIC states that residual platelet activity on clopidogrel is subject to significant interpatient variability in IM patients. In order to administer the most effective individualised therapy, other factors associated with an increased risk of cardiovascular events (or bleeding) should also be considered. The CPIC therefore classifies the genotype-guided recommendation as moderate.
The guideline states that there is inadequate substantiation for dose increases in IM and/or PM patients. There were no studies at that time that investigated the clinical outcome of dose increase.
Adequate evidence for an independent effect of *17 on clinical outcomes is not available. Some studies found that this allele led to stronger inhibition of platelet aggregation (Frere 2009, Mega 2009, Sibbing 2010 and Tiroch 2010) and possibly increased the risk of bleeding (Sibbing 2010 and Li 2012). Other studies did not find an effect of *17 (Shuldiner 2009, Geisler 2008, Simon 2009, Sorich 2012 and Lewis 2013). For this reason, and based on Sorich 2010, which compares prasugrel to clopidogrel, the CPIC advises that treatment does not need to be adjusted for *1/*17 and *17/*17. The CPIC classifies this recommendation as strong.
The authors stated that prasugrel was more effective than clopidogrel at preventing cardiovascular events in patients with acute coronary syndrome and elective percutaneous coronary intervention. However, prasugrel may not be an alternative to clopidogrel in all patients. Firstly, the risk of major bleeding (including fatal bleeding) is increased for prasugrel. Secondly, prasugrel is contraindicated in some patients (e.g. those with a history of transient ischaemic attack (TIA), stroke or intracranial haemorrhage). Thirdly, prasugrel is more expensive than clopidogrel.
The authors stated that ticagrelor was more effective at preventing cardiovascular events in patients with acute coronary syndrome than clopidogrel.
Genotype-based recommendations for patients with acute coronary syndrome undergoing percutaneous coronary intervention are:
UM: Clopidogrel should be given at the standard dose and application.
IM and PM: Give an alternative such as prasugrel or ticagrelor, unless these alternatives are contraindicated).
The PharmGKB uses a different definition of UM and NM than the KNMP. *1/*17 is classified as UM. As the recommendation is the same for UM as for NM, this does not make a difference in this case.
The authors stated that there is linkage disequilibrium between *2 and *17. Both polymorphisms never occur in the same allele. The effect of *17 may indeed therefore be caused by a lack of the *2 polymorphism.
The guidelines do not give recommendations on whether or not to genotype patients.
The authors stated that guidelines on the internet site of CPIC and PharmGKB are periodically updated. The guideline above was still the most recent version on 16 October 2018.

- European Society of Cardiology, Guideline for the Management of Acute ST-Elevation Myocardial Infarction, 2012.
  Treatment with acetylsalicylic acid in combination with prasugrel or ticagrelor is recommended in patients undergoing percutaneous coronary intervention (instead of acetylsalicylic acid and clopidogrel) (level of evidence I A). Clopidogrel may be used, but preferably only when prasugrel and ticagrelor are not available or contraindicated (level of evidence I C). This would involve a 600 mg loading dose, followed by a 75 mg/day maintenance dose.

Prasugrel and ticagrelor have more rapid and stronger activity and were found to be superior to clopidogrel in large clinical outcome trials. Prasugrel is contraindicated in patients with a history of stroke/TIA. It is generally not recommended in patients ≥ 75 years or in patients with a body weight < 60 kg, because it does not deliver net clinical benefits in these patients. The European authorisation file states that similar loading doses but reduced maintenance doses of 5 mg/day should be considered in these patients. However, there are no known clinical outcomes for this dose and there are alternative inhibitors of the P2Y12-ADP receptor for these patients. Prasugrel and ticagrelor must not be used in patients with a history of stroke or in patients with moderate to severe hepatic disease.
Addition of clopidogrel to acetylsalicylic acid is indicated as part of thrombolytic therapy (level of evidence I A). A 300 mg loading dose, followed by a 75 mg/day maintenance dose should be used for patients ≤ 75 years. Two studies have shown a reduced incidence of cardiovascular events or death when clopidogrel was added to acetylsalicylic acid in patients ≥ 75 years on thrombolytic therapy. Prasugrel and ticagrelor have not been studied as additions to thrombolytic therapy and must not be used.
Acetylsalicylic acid is to be used as long-term prevention in all patients who have had an ST-elevation myocardial infarction. Patients intolerant to acetylsalicylic acid can use clopidogrel 75 mg/day instead (level of evidence I B).
The CYP2C19 genotype is not mentioned in this guideline.

- European Society of Cardiology, Guideline for the Management of Acute Non-ST-Elevation Acute Coronary Syndrome, 2015.
  Clopidogrel (300-600 mg loading dose, followed by 75 mg/day maintenance dose) is recommended for patients not eligible for ticagrelor or prasugrel or those needing oral anticoagulant therapy (level of evidence I B).
  The CYP2C19 genotype is not mentioned in this guideline.
- European Society of Cardiology, Guideline for Myocardial Revascularisation, 2014.
  The guideline includes general recommendations on inhibition of platelet aggregation:
  Routine testing of platelet function or routine genotyping (clopidogrel and acetylsalicylic acid) to adjust platelet aggregation inhibitor therapy before or after elective stent placement is not recommended (level of evidence III A).
  The CYP2C19 genotype is not further mentioned in the recommendations:
  Dual antiplatelet therapy of acetylsalicylic acid and clopidogrel for at least 1 month is recommended in patients undergoing stent placement in a carotid artery (level of evidence I B).
  Potent $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) are recommended alongside acetylsalicylic acid instead of clopidogrel in patients undergoing repeat revascularisation due to stent thrombosis (level of evidence I C).
  Percutaneous coronary intervention in patients with stable coronary arterial disease:
  - treatment with clopidogrel can be considered in patients with a high likelihood of significant coronary arterial disease (level of evidence IIb C).
  - in patients on clopidogrel maintenance doses of 75 mg/day, a new 600 mg or higher clopidogrel loading dose can be considered as soon as the indication for PCI has been confirmed (level of evidence IIb C)
  - clopidogrel (600 mg or higher loading dose, 75 mg/day maintenance dose) is recommended for elective stent placement (level of evidence I A)

  Clopidogrel (600 mg loading dose, followed by 75 mg/day) should only be given around percutaneous coronary intervention (PCI) in patients with non-ST-elevation acute coronary syndrome and around primary PCI in patients with ST-elevation myocardial infarction if prasugrel or ticagrelor are not available (level of evidence I B).
  Percutaneous coronary intervention in patients needing oral anticoagulant therapy:
  - in patients with stable coronary arterial disease and atrial fibrillation with CHA2DS2-VASc score 2 and a low risk of bleeding (HAS-BLED 2), initial therapy with (novel) oral anticoagulants and acetylsalicylic acid (75–100 mg/day) and clopidogrel 75 mg/day for at least 1 month should be considered after placement of a bare metal stent or new generation drug eluting stent, followed by therapy including a (novel) oral anticoagulant and either acetylsalicylic acid 75–100 mg/day or clopidogrel 75 mg/day for 12 months (level of evidence IIa C)
  - in patients with acute coronary syndrome and atrial fibrillation with a low risk of bleeding (HAS-BLED 2), initial therapy with (novel) oral anticoagulants and acetylsalicylic acid (75–100 mg/day) and clopidogrel 75 mg/day for 6 months should be considered after stent placement, followed by therapy including a (novel) oral anticoagulant and either acetylsalicylic acid 75–100 mg/day or clopidogrel 75 mg/day for 12 months (level of evidence IIa C)
  - in patients with a high risk of bleeding (HAS-BLED 3), therapy with (novel) oral anticoagulants and acetylsalicylic acid (75–100 mg/day) and clopidogrel 75 mg/day should be considered for 1 month after stent placement, followed by therapy including a (novel) oral anticoagulant and either acetylsalicylic acid 75–100 mg/day or clopidogrel 75 mg/day (level of evidence IIa C)
  - therapy with (novel) oral anticoagulants and clopidogrel 75 mg/day can be considered in selected patients as an alternative to initial triple therapy (level of evidence IIb B)

In selected patients with percutaneous coronary intervention for acute coronary syndrome and a low risk of bleeding on acetylsalicylic acid and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) can be considered as anticoagulant therapy (level of evidence IIb B).
General recommendations on inhibition of platelet aggregation: Clopidogrel 75 mg/day must be used as an alternative in patients with stable coronary heart disease intolerant to acetylsalicylic acid (level of evidence I B). The same recommendation applies for long-term therapy after revascularisation (level of evidence I B).

- American College of Cardiology Foundation/American Heart Association, Guideline for the Management of ST-Elevation Myocardial Infarction, 2013.
In the Unresolved Issues and Future Research Directions section, the guideline states: Individual genetic variability in clopidogrel metabolism and effectiveness has been highlighted in patients with acute coronary syndrome. The roles of platelet function testing and genetic screening for clopidogrel metabolism in the acute phase of ST-elevation myocardial infarction care are uncertain, especially with the availability of alternative platelet aggregation inhibitors. More information specific to patients with ST-elevation myocardial infarction is needed with regard to the use of prasugrel and ticagrelor.
The CYP2C19 genotype is not mentioned in the recommendations itself, but is in the recommendations on primary percutaneous coronary intervention:
Primary percutaneous intervention: A clopidogrel loading dose (600 mg) or prasugrel or ticagrelor must be administered as soon as possible or at the time of primary percutaneous intervention to patients with ST-elevation myocardial infarction (level of evidence I B). In patients who have undergone stent placement, this should be followed by a clopidogrel maintenance dose (75 mg/day) or prasugrel or ticagrelor for 1 year (level of evidence I B). There is a IIb C level of evidence for continuation of maintenance therapy beyond 1 year in patients with a drug eluting stent.
Platelet response to clopidogrel may differ depending on patient characteristics such as the CYP2C19*2 polymorphism. Four studies found significantly lower levels of the active metabolite, reduced inhibition of platelet aggregation and an increased incidences of serious cardiovascular events and stent thrombosis in carriers of the CYP2C19*2 allele. The US Food and Drug Administration emphasises the possible effect of the CYP2C19 genotype on pharmacokinetics and clinical response to clopidogrel in the authorisation file. However, other studies have not confirmed the association between CYP2C19 polymorphisms and unfavourable outcomes. Future studies are needed to elucidate the risk of these genetic polymorphisms and to develop effective therapeutic strategies for carriers of CYP2C19 null alleles.
Patients with ST-elevation myocardial infarction on thrombolytic therapy: Clopidogrel (300 mg loading dose for patients ≤ 75 years and 75 mg for patients > 75 years (level of evidence I A) should be given alongside acetylsalicylic acid, followed by a maintenance dose of 75 mg/day for at least 14 days (level of evidence I A) and up to 1 year (level of evidence C; the recommendation was extrapolated from data obtained in patients with non-ST-elevation acute coronary syndrome).
Percutaneous coronary intervention after thrombolytic therapy: A clopidogrel loading dose (300 mg within 24 hours of thrombolytic therapy or 600 mg if given more than 24 hours after thrombolytic therapy) should be given before or during percutaneous coronary intervention to patients who did not receive a loading dose before, followed by a 75 mg/day maintenance dose (level of evidence I C). In patients with known coronary anatomy undergoing percutaneous intervention more than 24 hours after administration of a fibrin-specific antithrombolytic agent or more than 48 hours after administration of a non-fibrin-specific antithrombolytic agent, prasugrel can be used instead of clopidogrel.
- American College of Cardiology Foundation/American Heart Association, Guideline for the Management of Unstable Angina Pectoris and Non-ST-Elevation Myocardial Infarction, 2012.
Approval by the FDA of prasugrel and ticagrelor for the management of non-ST-elevation acute coronary syndrome is based on two studies that compared each of these two medicinal products to clopidogrel. Prasugrel and ticagrelor were superior to clopidogrel at reducing the incidence of clinical events, but this was associated with an increased risk of bleeding.
Data from a number of studies that show an association between an increased risk of cardiovascular events and the presence of ≥ one CYP2C19 null allele are described in detail in the ACCF/AHA Clopidogrel Clinical Alert.
This alert contains a summary of the unresolved issues around clopidogrel, the use of genotyping and the potential use of routine platelet aggregation testing. There are commercial kits available to determine the CYP2C19 genotype, but these tests are expensive and generally not paid for by insurance companies. Moreover, there are no prospective studies that show that routine use of these tests followed by adjustment of antiplatelet therapy improves the clinical outcomes. A recent meta-analyse (Holmes, 2011) showed an association between the CYP2C19 genotype and clopidogrel response, but no significant association with cardiovascular events. Various ongoing studies are investigating whether determination of the genotype and adjustment of therapy for patients with null alleles can improve the clinical outcomes. Current evidence does not provide a basis on which routine genetic testing in patients with acute coronary syndrome should be strongly recommended. However, this may be considered in individual cases, especially in patients with recurrent cardiovascular events on clopidogrel therapy.

The guideline does not express a preference for clopidogrel, prasugrel or ticagrelor. The recommendations are therefore analogous to those for ST-elevation myocardial infarction. A 600 mg clopidogrel loading dose followed by 150 mg/day for 6 days and then 75 mg/day could be reasonable in patients undergoing percutaneous coronary intervention who do not have a high risk of bleeding (level of evidence B).

- American College of Cardiology Foundation/American Heart Association, Guideline for Percutaneous Coronary Intervention, 2011.
  Recommendations for genetic testing for clopidogrel: Genetic testing may be considered to determine whether patients with a high risk of poor clinical outcomes have an elevated risk of inadequate antiplatelet therapy with clopidogrel (level of evidence IIb C). An alternative (e.g. prasugrel or ticagrelor) can be considered in those cases (level of evidence IIb C). Routine genetic testing of patients undergoing percutaneous coronary intervention on clopidogrel therapy is not recommended (level of evidence III C), though this may be of value in patients undergoing high-risk elective percutaneous coronary intervention.
  The guideline does not express a preference for clopidogrel, prasugrel or ticagrelor. The recommendations are therefore analogous to those for ST-elevation myocardial infarction. Patients receiving stents for indications other than acute coronary syndrome and who do not have a high risk of bleeding should be given clopidogrel 75 mg/day for at least 12 months (drug eluting stent) or 1-12 months (bare metal stent) (level of evidence B).
- CBO Guideline on Diagnosis, Prevention and Treatment of Venous Thromboembolism and Secondary Prevention of Arterial Thrombosis, 2009.
  Various studies have shown that the thienopyridine ticlopidine in combination with acetylsalicylic acid is more effective at preventing thrombotic events (mainly myocardial infarction and/or stent occlusion) after percutaneous coronary intervention with stent placement than the combination of acetylsalicylic acid and oral anticoagulants. Clopidogrel is equally effective as ticlopidine but is associated with fewer side effects and is therefore preferred. The CYP2C19 genotype and possible alternatives such as prasugrel and ticagrelor are not mentioned in this guideline. The guideline states that CYP3A4 and CYP3A5 are responsible for conversion of clopidogrel to the active metabolite.

- <u>Cost-effectiveness</u>:
  - Wang Y et al. Cost-effectiveness of cytochrome P450 2C19 *2 genotype-guided selection of clopidogrel or ticagrelor in Chinese patients with acute coronary syndrome. Pharmacogenomics J 2018;18:113-120. PubMed PMID: 28117433.
    In 60-year old Chinese patients with acute coronary syndrome and percutaneous coronary intervention, universal ticagrelor use was cost-effective compared with universal clopidogrel (i.e. costs were US dollar (USD) 7254 and thus less than USD 42,423 per quality-adjusted life year (QALY) gained), but genotype-guided treatment was both more effective and cheaper. Genotype-guided treatment consisted of clopidogrel for NM and ticagrelor for IM and PM. Genotype-guided treatment was cost-effective compared with universal clopidogrel use (additional costs of USD 2560 per QALY gained). Sensitivity analysis demonstrated that with costs of genotype testing up to USD 400, CYP2C19*2 genotype-guided antiplatelet treatment remained a cost-effective strategy compared with either universal use of generic clopidogrel or ticagrelor. Note: the lowest CYP2C19 nullallele carrier frequency used in the calculations was 44.2%. This is much higher than the 25% carrier frequency in Dutch Caucasians.
    Cost-effectiveness analysis was from the Hong Kong health-care provider's perspective. Direct medical costs were calculated for treatment with clopidogrel or ticagrelor for 1 year, followed by life-long costs (25 years) after this treatment. Patients received dual antiplatelet treatment (either ticagrelor or clopidogrel in combination with aspirin) during the first year, followed by aspirin monotherapy in subsequent years. Ticagrelor was given in a loading dose of 180 mg followed by a 90 mg dose twice a day. Clopidogrel was given in a loading dose of 300 mg followed by a 75 mg dose daily. All model inputs and key assumptions were derived from published clinical trials (Nakamura M et al. Clinical outcome after acute coronary syndrome in Japanese patients: an observational cohort study. J Cardiol 2010;55:69-76 and Chen Z et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. Stroke 2000;31:1240-9) and published decision-analytic models (Nikolic E et al. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. Eur Heart J 2012;34: 220-8 and 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). The 1-year decision tree included the following events: nonfatal myocardial infarction, nonfatal stroke, stent thrombosis, fatal bleeding, and death from vascular or nonvascular causes. For treatment of all patients with clopidogrel the costs per patient were USD 5229 and the number of QALYs was 5.65, for genotype-guided treatment the costs were USD 5647 and the number of QALYs 5.81, and for treatment of all patients with ticagrelor the costs were 6056 and the number of QALYs 5.77. The calculation was based on clopidogrel costs of USD 43 per month, ticagrelor costs of USD 1029 per month, a genetic test price of USD 200, costs of no-event of USD 307, costs of myocardial infarction of USD 9323, post-myocardial costs of USD 590, costs of stroke of USD 3135, post-stroke costs of USD 627, costs of an episode of

major bleeding of USD 4381, costs of stent thrombosis of USD 17,682 and costs of death of USD 794. The risks of serious cardiovascular events and bleeding were taken from studies in Chinese and from the PLATO trial (Chen M et al. Association between cytochrome P450 2C19 polymorphism and clinical outcomes in Chinese patients with coronary artery disease. Atherosclerosis 2012;220:168-71; Luo Y et al. Relationship between cytochrome P450 2C19* 2 polymorphism and stent thrombosis following percutaneous coronary intervention in Chinese patients receiving clopidogrel. J Int Med Res 2011;39:2012-9; Tang XF et al. Effect of the CYP2C19 2 and 3 genotypes, ABCB1 C3435T and PON1 Q192R alleles on the pharmacodynamics and adverse clinical events of clopidogrel in Chinese people after percutaneous coronary intervention. Eur J Clin Pharmacol 2013;69:1103-12; Shen D-L et al. Clinical value of CYP2C19 genetic testing for guiding the anti-platelet therapy in a Chinese population. J Cardiovasc Pharmacol 2015;67:232-6; and Kang H-J et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: a retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Am Heart J 2015;169:899–905). The CYP2C19 *2 allele carrier frequency was 51.8% in this population. Variation of input data showed a 98.5% probability of the genotype-guided strategy to be cost-effective compared with universal clopidogrel and ticagrelor at a willingness-to-pay threshold of USD 42,423 per QALY gained.

- 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 additional 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 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 NM 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 (Harmsze 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.

- Mitropoulou C et al. Economic analysis of pharmacogenomic-guided clopidogrel treatment in Serbian patients with myocardial infarction undergoing primary percutaneous coronary intervention. Pharmacogenomics 2016;17:1775-84. PubMed PMID: 27767438.

  For the IM+PM frequency in the Serbian population (28.9%), performing the CYP2C19 genetic test prior to drug prescription for ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention represents a cost-saving option and would save € 13 per person on average. Genotype-guided treatment was cost-saving for IM+PM frequencies higher than 25%.

  In the genotype-guided therapy, NM received clopidogrel and IM+PM received prasugrel or ticagrelor. Direct healthcare costs that are reimbursed by the Serbian health insurance were calculated over a period of 1 year. Genotyping was for *2 and *3, but *3 was not detected in the population. Calculations were based on the following data observed in 66 cases with in-hospital bleeding and 55 controls (86 NM and 35 IM+PM) from a cohort of 1059 consecutive patients: 59.3% of the NM patients had a minor or major bleeding event versus 42.85% of the IM+PM, while a reinfarction event occurred in 2.3% of the NM patients, compared with 11.2% of the IM+PM patients. There were subtle differences between the two patient groups, as far as the duration of hospitalization and rehabilitation is concerned, in favour of the NM group. The mean cost for the NM patients was estimated at € 2547 versus € 2799 in the IM+PM patients. In addition, calculations were based on costs of genetic testing of € 63.0, costs of hospitalisation of € 200.0/day, costs of single repeat percutaneous coronary intervention of € 1000.0, costs of vascular operation of € 4400.0 and costs of rehabilitation of € 12.5/day.

  Major adverse cardiovascular and cerebrovascular events were defined as death from any cause, nonfatal myocardial infarction, or stroke.

- 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 NM 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 NM, 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 NM 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.

- Plumpton CO et al. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. Pharmacoeconomics 2016;34:771-93. PubMed PMID: 26984520.
The authors performed a systematic literature review of economic evaluations of pharmacogenetic tests of CYP2C19 prior to prescription of clopidogrel, with a third-generation thienopyridine as an alternative. The authors conclude that evidence exists to support the cost-effectiveness of genotyping prior to clopidogrel with the majority of high quality studies indicating that genotyping was either better and cheaper, cost-saving or cost-effective across a variety of populations. The implication for clinicians and policy makers is that testing of CYP2C19 prior to start of clopidogrel should be considered for adoption as routine practice.
Four economic evaluations were retrieved: two conducted in the USA (Lala 2012 and Reese 2012), one in Australia (Sorich 2013) and one in New Zealand (Panattoni 2012). Reese 2012 was a cost-effectiveness analysis reporting events averted, the others were cost-utility analyses. Costs were calculated from the perspective of the healthcare provider in two studies (Panattoni 2012 and Sorich 2013).The quality of reporting in the economic evaluations was high for all studies. High quality was defined as reporting of more than 85% of items on a 24-item checklist for economic health evaluations. Lala 2012 stated that the evidence supporting the effectiveness of pharmacogenetics was retrieved from the FDA. The other studies mentioned trials and randomised studies, but referred to genetic sub-studies of trials that were primarily designed for other purposes as source for the evidence.
Three studies compared three strategies: clopidogrel for all patients, prasugrel for all patients, genetic testing with clopidogrel for those who tested negative and prasugrel for those who tested positive (Lala 2012, Reese 2012 and Panattoni 2012). All found genotyping to be both better and cheaper than the other two strategies. The fourth study considered ticagrelor as a comparator (Sorich 2013). Genotyping was cost-effective versus universal clopidogrel, but universal ticagrelor may be more cost-effective than genotyping, depending on the cost-effectiveness threshold, with the additional costs per quality adjusted life year gained being reported as ‘generally within what is considered acceptable’. Genetic testing prior to clopidogrel is recommended by the FDA, with actionable pharmacogenetic information noted by the EMA, PMDA (Pharmaceuticals and Medical Devices Agency, Japan) and HCSC (Health Canada (Sante Canada)).
- 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$ 2208 reduced costs and 0.0085 more Quality Adjusted Life-Years (QALYs)). CYP2C19-genotype-guided therapy involved NM 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 $ 139,588/QALY and therefore exceeded the limit of $ 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 $ 71,887 and the calculated QALYs 7.886. The calculation was based on clopidogrel 75 mg/day costs of $ 40 per month, prasugrel or ticagrelor costs of $ 245 per month and a genetic test price of $ 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 input data (95% confidence interval or ± 20%) showed that genotype-guided therapy was the preferred strategy in 96.64% of cases at a maximum cost of $ 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 $ 0.50 per day, prasugrel costs of $ 8.00 per day, ticagrelor costs of $ 8.71 per day and a genetic test price of $ 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 NM/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 seven 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 NM/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.

- Patel V et al. Cost-utility analysis of genotype-guided antiplatelet therapy in patients with moderate-to-high risk acute coronary syndrome and planned percutaneous coronary intervention. Pharm Pract (Granada) 2014;12:438. PubMed PMID: 25243032.
CYP2C19 genotype-guided therapy is cost-effective in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Genotype-guided therapy delivered 0.02 more Quality Adjusted Life-Years (QALY) at incremental costs of US$ 4,200/QALY compared to clopidogrel for all patients. Compared to prasugrel for all patients, genotype-guided therapy delivered more QALYs at lower costs. Genotype-guided treatment involved treatment of NM/UM patients with clopidogrel and IM and PM patients with prasugrel.
Prasugrel for all patients compared to clopidogrel for all patients cost $ 227,800 per gained QALY and was therefore not cost-effective.
Costs were calculated for events that occurred in the first 15 months. The calculation was based on prasugrel costs of $ 4.50 per day, clopidogrel costs of $ 0.19 per day and a genetic test price of $ 300.
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). In this study, prasugrel was associated with fewer serious cardiovascular events, but with a higher risk of bleeding. The authors stated that they also considered *1A and *17 to be alleles with reduced function. As the null allele frequency differs between ethnic groups, a mean null allele frequency of 30.54% was assumed.
The results of the calculations were influenced by the relative risk of myocardial infarction and stroke of IM and PM patients compared to NM/UM. The costs of clopidogrel had a smaller effect. Genotype-guided therapy was no longer cost-effective at a clopidogrel price exceeding $ 9.88 per day (costs of more than $ 50,000/QALY). Prasugrel therapy was only cost-effective compared to clopidogrel therapy at a null allele frequency of ≥ 45% or at clopidogrel costs of ≥ $ 3.99 per day.
Variation of input data and costs of $ 50,000/QALY showed that genotype-guided therapy was the preferred strategy in ~70% of cases, clopidogrel in ~25% and prasugrel in ~5%.

- 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 five 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 NM and UM patients receiving clopidogrel and IM and PM patients receiving prasugrel or ticagrelor.
Using relative risks of IM+PM versus NM+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 $ 24,700 compared to clopidogrel. Ticagrelor delivered more QALYs, but at much higher costs ($ 104,800/QALY) and was therefore not cost-effective. Genotyping with ticagrelor was more cost-effective than genotyping with prasugrel (costs compared to clopidogrel $ 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 NM+UM from a meta-analysis including patients with all clopidogrel indications for the calculation:
Ticagrelor was the most effective therapy. The costs per Quality Adjusted Life Year (QALY) gained were $ 52,600 compared to genotyping with ticagrelor. Genotyping with ticagrelor was more cost-effective than genotyping with prasugrel. The costs per QALY gained were $ 30,200 and $ 35,800 respectively. Genotyping with prasugrel delivered more QALYs at lower costs than prasugrel. The costs of genotyping with prasugrel per QALY gained were $ 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 $ 124,400/QALY and therefore exceeded the limit of $ 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 $ 30 per month, prasugrel costs of $ 220 per month, ticagrelor costs of $ 261 per month and a genetic test price of $ 235. The relative risk of serious cardiovascular events and bleeding for IM+PM and NM+UM on clopidogrel was taken from the Mega 2010 (percutaneous coronary intervention) and Holmes 2011 (all clopidogrel indications) meta-analyses. 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 $ 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%.

- Sorich MJ et al. Cost-effectiveness of using CYP2C19 genotype to guide selection of clopidogrel or ticagrelor in Australia. Pharmacogenomics 2013;14:2013-21. PubMed PMID: 24279856.
CYP2C19 genotype-guided therapy was more effective and cost-effective compared to treatment with clopidogrel in 62-year-old patients with acute coronary syndrome and a high risk of stent placement (costs per gained Quality Adjusted Life Year (QALY) AUS$ 6346). CYP2C19 genotype-guided therapy involved NM and UM patients receiving clopidogrel and IM and PM patients receiving ticagrelor. However, treatment with ticagrelor was more effective and cost-effective compared to genotype-guided therapy (costs per QALY gained AUS$ 22,821).
Direct medical costs were calculated for treatment with clopidogrel or ticagrelor for 1 year, followed by life-long costs (40 years) after this treatment. The calculation was based on clopidogrel costs of AUS$ 50.15 per month, ticagrelor costs of AUS$ 149.10 per month and a genetic test price of AUS$ 46.55. The risks of serious cardiovascular events and bleeding were taken from the PLATO trial (Cannon 2010, Wallentin 2011 and Nikolic 2013).
The estimates of the relative treatment effect for the CYP2C19 groups had the greatest effect on the calculated cost-effectiveness. The PLATO study found a non-significant decrease in serious cardiovascular events in NM/UM using ticagrelor instead of clopidogrel (HR = 0.90; 95% CI: 0.73-1.10). Ticagrelor becomes less cost-effective than genotype-guided therapy at an HR higher than 0.95 (costs higher than AUS$ 50,000/QALY). Variation of input data (95% confidence interval) at a maximum cost of AUS$ 50,000/QALY (approximately € 75,000/QALY) showed that ticagrelor was the preferred strategy in ~72% of cases and genotype-guided therapy in ~28%. This was ~60% and ~38% at a maximum cost of AUS$ 30,000/QALY.
The calculated value of missing information (and therefore research) was high: AUS$ 13-16 million for 5 years. This mainly improved uncertainty about the relative effect of ticagrelor and clopidogrel in NM/UM patients.

- 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 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 $ 18 lower and the Quality Adjusted Life-Years (QALY) 0.004 higher compared to clopidogrel and they were $ 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 $ 5.45 per day, clopidogrel costs of $ 1.00 per day and a genetic test price of $ 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 € 100,000 per QALY gained.
The strongest predictor was the relative risk of carriers compared to non-carriers of the *2 allele of 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 only cost-effective. Price decrease of genotyping from $ 500 to $ 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 for New Zealand hospitals and when taken from trials (NZ$ 8702 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$ 7312 per QALY) and patients from the Pacific Islands (NZ$ 7041 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$ 5132 per QALY (costs increased by NZ$ 2146 and QALY by 0.418 years). The incidence of events was higher with prasugrel driven by increased incidences 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 function 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 60-year-old 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 $ 200) is equivalent to $ 5000 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 nine studies (Mega, 2010).
  Clopidogrel and prasugrel may deliver similar increases in QALY, but their risks and benefits differ. Subgroup 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 prior stent thrombosis, ST-elevation myocardial infarction 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 < 60 kg). The latter group showed a decrease in QALY compared to all patients on prasugrel.
  The TRITON-TIMI 38 trial used a 300 mg clopidogrel loading dose while a 600 mg dose is nowadays more usual. 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 en 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 $ 6760 lower compared to branded clopidogrel and $ 11,710 lower compared to prasugrel. Generic clopidogrel led to genotype-guided treatment no longer delivering cost-savings compared to clopidogrel for all patients (costs per incident prevented $ 2300 higher). Genotype-guided treatment compared to clopidogrel led to one event prevented for every 23 genotyped patients, while compared to prasugrel this led to one event prevented for every 30 genotyped patients.
  The calculation was based on prasugrel costs of $ 6.55 per day, clopidogrel costs of $ 6.22 per day (branded) or $ 1.00 per day (generic) and a genetic test price of $ 310. The risks of serious

cardiovascular events and bleeding were taken from the TRITON-TIMI 38 trial which compared prasugrel to clopidogrel in patients with acute coronary syndrome and elective percutaneous coronary intervention (reference Mega et al, 2009). 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 NM patients.

- Crespin DJ et al. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. Value Health 2011;14:483-91. PubMed PMID: 21669373.
  Ticagrelor for all patients > 65 years with acute coronary syndrome led to an increase in QALY compared to genotype-guided treatment. Ticagrelor was cost-effective with an increase in costs of $ 10,059 per QALY gained (costs increased by $ 1.04 and QALY increased by 0.10 years). The costs per QALY were driven the most by the price of ticagrelor and the hazard ratio for death while on ticagrelor therapy compared to clopidogrel therapy. The costs remained lower than $ 50,000 per QALY gained up to a price of $ 693 per month or a HR of 0.93. The chance of costs below $ 50,000 per QALY gained was 97.7%. The data referred to above were based on a five-year period during which ticagrelor/clopidogrel therapy is given as standard in the first year and only in the event of recurrent acute coronary syndrome in the following four years. The cost-effectiveness is four-fold lower when the first year of treatment is analysed on its own (costs increased by $ 42,546 per QALY gained; costs increased by $ 0.80, QALY increased by 0.019 years).
  The calculation was based on hypothetical ticagrelor costs of $ 5.47 per day, clopidogrel costs of $ 1.00 per day and a genetic test price of $ 200. Risks of serious cardiovascular events and bleeding in the five years after acute coronary syndrome were taken from Medicare insurance data. Differences in risks between ticagrelor and clopidogrel were taken from the one-year PLATO trial (Wallentin, 2009), which compared ticagrelor to clopidogrel in patients with acute coronary syndrome. As patients in the PLATO test had not been genotyped, the risk reduction by clopidogrel for *2 carriers was set at 0. On this basis the risk reduction for non-*2 carriers was calculated from that of the total group. Various ethnic groups with different *2 allele frequencies were included in the model. The percentage of each ethnic group was taken from the Medicare data. Cardiovascular events that differed significantly between ticagrelor and clopidogrel (including myocardial infarction, dyspnoea and death) and bleeding were included in the cost-effectiveness model.
  In the PLATO trial, ticagrelor mainly reduced the risk of death. The risk of major bleeding did not increase significantly apart from the risk of major bleeding not related to coronary bypass surgery and fatal intracranial haemorrhage. The risk of other fatal bleeding decreased. The PLATO trial excluded CYP3A4 inhibitors, but not CYP2C19 inhibitors.

Date of literature search: 25 November 2019.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmaco-genetics Working Group decision	PM	4 F	yes	yes	23 December 2019
	IM	4 F	yes	yes	
	UM	4 A	yes	no	

Mechanism
Clopidogrel is a pro-drug, of which 85% is converted by esterases to an inactive metabolite. The remaining 15% is primarily converted by CYP2C19 and CYP3A4 to 2-oxoclopidogrel and subsequently to the active metabolite H4, an unstable thiol compound that inhibits platelet aggregation by formation of a disulphide bridge with a cysteine residue on the platelet ADP receptor ($P2Y_{12}$).

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 genotype 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+	8+
Corresponding Clinical Implication Score:		Essential