

## 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<sub>corr</sub> = 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<sub>12</sub>), 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<sub>12</sub>). Genotypes associated with decreased CYP2C19 activity (IM and PM) reduce the activation of clopidogrel. The genotype associated with increased CYP-2C19 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 cardio-vascular 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<sup>2</sup> (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<sup>2</sup> (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 tica-grelor. 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  $\geq$  3 (3 points for three or more publications with level of evidence score  $\geq$  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  $\geq$  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 costeffectiveness 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.

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

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.

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ref. 1, continua- tion		According to the r	•	•	• •	
tion		and mortality (20%				
		therapy, it was as				
		amputation) were				
		PM, respectively.		•		
		sample size for a	power of 0.8 to	find a HR of 1.5	was 239.	
		Construction				
		Genotyping:				
		- 153x NM				
		- 79x IM - 46x PM				
		- 40% FIVI				
		Results:				
		Results compare	d to NM:			
		Results compare	PM	IM	value	
					for NM	
		all-cause	x 1.87 (S)	x 1.40 (S)	16.3%	
	PM: F	mortality		similar if only pat		
	IM: F	montanty		ow-up were incl		
			value for NM:			
			and IM: x 1.71			
				Cox analysis sho	wed	
				umber to be an i		
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				group ( $HR_{corr} = 1$	,	
				and in the subgr		
				leting follow-up (		
			1.51; 95% CI:			
		number of	x 2.38 (S)	x 1.66 (S)	18.3%	
		amputation	Results were s	similar if only pat	tients	
		events	completing foll	ow-up were incl	uded:	
				27.1%, PM: x 2.0	63 (S),	
			and IM: x 2.05		-	
				Cox analysis sho		
			•	umber to be an i		
				of amputation ev		
				group (HR <sub>corr</sub> = 2 9) and in the sul		
				npleting follow-u	•	
			= 2.35; 95% C			
		remaining	x 1.41 (S)	x 1.24 (S)	174.6	
		platelet activity		× 1.27 (0)	17 - 1.0	
		(P2Y <sub>12</sub> reac-				
		tion units)				
		,,				
		Note: Genotyping	was for *2 and	*3. These are th	e most	
		important gene va				
ref. 2	3	155 patients with				Authors' conclusion:
Lan H et al.		(National Institute				"After routine clopi-
Anti-platelet thera-		5) completed 1-ye				dogrel treatment,
py in mild cerebral		type-guided antip				the efficacy in NM
infarction patients		75 mg/day (n = 78				patients was signifi-
on the basis of		clopidogrel 75 mg				cantly better than in
CYP2C19 metabo-		mg/day for IM and				PM and IM patients.
lizer status.		let therapy (a 300				After adjustment of
Cell Transplant		by clopidogrel 75				therapeutic protocol,
2019;28:1039-44.		day) during the fir				the therapeutic
PubMed PMID:		Clinical efficacy w	•			efficacy in PM and
31134829.		Scale, a clinician-				IM patients was
				markedly improved,		
		is widely applied f	or evaluating st	roke patient outo	comes.	
		is widely applied f Relevant co-medi			comes.	which was accom- panied by significant

ref. 2, continua- tion	Genoty- pe-gui- ded ver- sus not- genotype -guided therapy: PM: AA <sup>#</sup> IM: AA <sup>#</sup> NM: AA	Genotyping (based on the originally included group of - 78x NM - 52x IM - 25x PM Results: Results on genotype-gui guided therapy: global disability after treatment (Modified Rankin Scale score) cerebral infarction cerebral haemorrhage myocardial infarction events of other organs adverse drug reactions	reduction in recur- rence rate of cere- bral infarction."				
		cerebral infarction score before treatment (NIHSS score)	PM IM NM	witho and o	(abdominal but occult blo diarrhoea) re symptomatic	od, solved	
		Results for IM and PM o on clopidogrel:	n clopi PM	dogrel	Compared to	value for NM	
	PM: D IM: D	global disability after treatment (Modified Rankin Scale score) cerebral infarction score before treatment (NIHSS score)	treatment (Modified Rankin Scale score)cerebral infarctionNS score before treatment		x 1.41 (S) NS	1.51 4.31	
		Results for IM and PM o to NM on clopidogrel:		ylsalicy			
			PM		IM	value for NM	
		global disability after treatment (Modified Rankin Scale score)	x 1.3	5 (S)	x 1.10 (S)	1.49	
		cerebral infarction score before treatment (NIHSS score)	NS		NS	4.47	
		Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese patient group.					
ref. 3 Kheiri B et al. CYP2C19 pharma- cogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with	4	Meta-analysis of 6 randor genotype-guided therapy in patients undergoing pe Standard, i.e. not-genotyp consisted mainly of clopid of 2371 patients. The trial major adverse cardiovaso that used the Thrombolys	with st rcutand be-guid logrel. Is used culare e	andaro eous c led, an The 6 l differe events	d antiplatelet coronary inter ntiplatelet the trials include ent definition . Except for	therapy vention. rapy ed a total s of I trial	Authors' conclusion: "In patients under- going stent implan- tation, major adver- se cardiovascular events (MACE) with genotype-guided therapy was not sig-

disease: a meta- analysis of rando- mized clinical trials. Catheter Cardio- vasc Interv 2019;93:1246-52. PubMed PMID: 30403317. <b>ref. 3, continua-</b> 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 perfor- med 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		Г							
analysis of rando- mized clinical trials. Catheter Cardio- vasc Interv. 2019;33:1245-52. PubMed PMD: 90403317. ref. 3, continua- tion ref. 3, continua- tion for 3, continua- tion diameter cardio- source control to bleeding 5 studies with a total of 1867 patients reported data on major adverse cardiovascular events and on bleeding 5 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1867 patients reported data on stroke. 4 studies model. The authors postulate that for a primary endpoint of net clinical benefit, an appropilately powered trial would contain approximately 5000 patients. Results: Genoty- pegui- diovascular events with a case on f(tudies and the other long standard care: Value for patients with cardiovascular motrality % of patients wit	coronary artery					nificantly reduced;			
mized clinical trials.       months (range 1-24 months). Two of the trials were perfor- vase. Interv.       in the largest trial genotype-guided therapy was guided by both ABCB1 and CYP2C19 genotype.       in the largest trial genotype-guided therapy was guided by both ABCB1 and CYP2C19 genotype.       in the largest trial genotype-guided therapy was guided by both ABCB1 and CYP2C19 genotype.       in the largest trial genotype-guided therapy was guided by both ABCB1 and CYP2C19 genotype.       in the largest trial genotype-guided therapy was guided by patients reported data on moyocardial infaction. Hough this will require fun- cardiovascular mortality. 4 studies with a total of 1880 patients reported data on stoke. 4 studies with a total of 1875 patients reported data on stoke. 4 studies with a total of 1875 patients reported data on stoke. 4 studies with a total of 1875 patients reported data on stoke. 4 studies with a real-analysis, it 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:       Results: Results for genotype-guided therapy compared to standard care:       Value for standard care:         % of patients with major adverse car.       NS       12.2% 2018), abolished tete- rogenely and resulted in significance (S).         genoty- pe-guided therapy ded ver- sus not- genoty- ded ver- tion       % of patients with myccardial infacr- code with cardioxascular mortality       NS       1.2% 2018 and the other two studies not only inves- tion         % of patients with cardioxascular mortality <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>									
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2019:33:1246-52. PubMed PMD: 30403317.       both ABCB1 and CYP2/19 genotype. All studies reported data on major adverse cardiovascular events and on bleeding. 5 studies with a total of 18807 patients reported data on snet thrombosis. Of the 6 studies in the meta-analysis, 1 was also included separately in this risk analysis (Xie 2013).       reference rate of mycoardial infarction though the confirmation in activity actual mortality. A studies with a total of 1880 patients reported data on stent knombosis. 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 appropilately powered trial would contain approximately 5000 patients.         Resultis:       Resultis for genotype-guided therapy compared to standard care:         Value for diovascular events       NS       12.2% Exclusion of the only which was also the only one with honger than 12 months follow- up and the one with the lowest quality (Ja- dad scale 1) (Tuteja 2018), aboilshed tete- rogeneity and resulted in significance: RR = 0.5 (95% CI: 0.41-0.74) (S)         Resultis no only inves- tigating patients with acute coronary synfor- me also resulted in mycoardial infarc- tion       15.2% 2018) aboilshed tete- rogeneity and resulted in significance (S). % of patients with cardiovascular         % of patients with romotality       RR = 0.46 (95% CI: 0.28-0.70) (S) % of patients with cardiovascular       1.2% % of patients with cardiovascular			-			-			
PubMed PMID: 30403317.       All studies reported data on major adverse cardiovascular events and on bleeding. 5 studies with a total of 1867 patients reported data on stroke. 4 studies with a total of 1667 patients reported data on stroke. 4 studies with a total of 1680 patients reported data on stroke. 4 studies with a total of 1680 Of the 6 studies in the meta-analysis. I 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 appropitalely powered trial would contain approximately 5000 patients.         Results:       Results for genotype-guided therapy compared to standard care:         % of patients with major adverse car- diovascular events       NS       12.8% not-published study, 13.5% Not-published study, 13.5%         % of patients with major adverse car- diovascular events       NS       12.2% Not-published study, 14.074) (S)         % of patients with major adverse car- diovascular events       NS       12.2% Not-published study, 13.5%         % of patients with major adverse car- diovascular events       NS       12.2% Not-published study, 2018, abolished hete- rogeneity and resulted in significance: R R = 0.56 (95% CI: 0.41-0.74) (S)         % of patients with move actude infarcion significance (S).       8.1% NS       1.2% Significance (S).         % of patients with move actude and stroke therapy; AA <sup>N</sup> NS       1.2% Significance (S).         % of patients with move actude infarcion significance (S).       8.1% A 4.3% of patients with stroke       NS       1.2% Sig	2019;93:1246-52.				guided by				
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Genoty- pe-gui- ded variable       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 beneft, an appropriately powered trial would contain approximately 5000 patients.         Results:       Results for genotype-guided therapy compared to standard care:         Value       Value         % of patients with major adverse car- diovascular events       NS       12.8% to 2018         With was also the only one with longer than 12 months follow- up and the one with the lowest quality (Ja- dad scale 1) (Tuteja 2018), abolished hete- rogeneity and resulted in significance: R = 0.55 (6% C1: 0.41-0.74) (S)       15.2% 2018         Genoty- pe-gui- ded var- genotype       % of patients with acute coronary syndro- me also resulted in significance (S), myocardial infarc- 0.28-0.70 (S)       15.2% 2018         % of patients with scrue coronary syndro- me also resulted in significance (S), myocardial infarc- 0.28-0.70 (S)       6.1% 0.28-0.70 (S)         % of patients with scrue genotype       NS       1.2% 4.3%         % of patients with scrue wyocardial infarc- cardiovascular       NS       1.2% 50%         % of patients with stroke       NS       1.2% 50%         % of patients with stroke       NS       1.2% 50%						trials."			
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stroke% of patients with stent thrombosistrend for a decrease (p = 0.06, NS)% of patients withtrend for a decrease (p 4.0%				NS	1.2%				
stent thrombosis= 0.06, NS)% of patients withtrend for a decrease (p			stroke						
% of patients with trend for a decrease (p 4.0%					1.7%				
					4.00/				
					4.0%				
			bieeding	– U.UY, NO)	ļ				

rof 3 continue	Τ	Thorowso similar	t botore	h, hohuo #		
ref. 3, continua- tion		There was significant studies for major adv				
		almost all heterogen				
		Tuteja 2018.	ony alcapped			
		There was no signifi	cant heteroge	neity betweer	the	
		studies for cardiovas				
		There was no hetero				
		myocardial infarction	n, stroke, sten	t thrombosis a	and	
		bleeding.				
		There were no indicated adverse cardiovascu	•	lication blas to	or major	
ref. 4	3			aion of the op	bort in	Authors' conclusion:
Williams AK et al.	3	The cohort in this stud Lee 2018 with follow-				"CYP2C19 loss-of-
CYP2C19 genoty-		recommendation for u	• •	•		function (LOF) allele
pe-guided antiplate-		of clopidogrel in CYP2				carriers receiving
let therapy and 30-		patients were treated		-	• •	clopidogrel exhibited
day outcomes after		percutaneous coronal			y anor	a significantly
percutaneous coro-		Major adverse cardiov			events	higher net risk of
nary intervention.		were defined as death				major adverse
Circ Genom Precis		bosis, hospitalisation				cardiovascular or
Med		or transient ischemic	attack. Clinica	ally significant	bleeding	cerebrovascular
2019;12:e002441. PubMed PMID:		was defined as a Glol				events (MACCE) or bleeding over 30
30779635.		ded Arteries (GUSTO	) moderate or	severe/life-th	reatening	days compared with
00110000.		bleeding event.				the use of alterna-
		Results were correcte				tive therapy In
		groups or were assoc			me.	contrast, no signifi-
		Relevant co-medication	on was not ex	cluded.		cant difference in
				risk of MACCE or		
		Genotyping:	Due			bleeding was obser-
				sugrel/ticagrel	or	ved in clopidogrel-
		- 530x NM+UM - 120x IM+PM		4x NM+UM 9x IM+PM		treated patients without a LOF allele
			- 20			versus those treated
	Clanida	Results:				with alternative
	Clopido- grel ver-	Clopidogrel compare	ad to LIM+NM	+IM+PM on n	rasuarel/	therapy."
	sus UM+	ticagrelor:			asugrei	
	NM+IM+		IM+PM	NM+UM	value	
	PM on				for pra-	
	prasugrel				sugrel/ti	
	/ticagre-				cagrelor	
	lor:	% of patients with	HR <sub>corr</sub> =	NS	3.6%	
	IM+PM:	major adverse	4.81 (95%			
	E NM+UM:	cardiovascular or	CI: 2.12-			
	AA	cerebrovascular	10.8) (S)			
		events or clinically significant				
		bleeding				
		% of patients with	HR <sub>corr</sub> =	NS	2.2%	1
		major adverse	8.00 (95%		,	
		cardiovascular or	CI: 3.22-		1	
		cerebrovascular	20.8) (S)			
		events				4
		% of patients with	NS	NS	1.7%	
		clinically significant				
		bleeding			1	4
		Note: Orangton in the	for *0 *0	a *47 The second		
		Note: Genotyping was				
		most important gene v USA.	variants in this	s patient group	o nom me	
ref. 5	3	After a recommendati	on for use of	nrasuarel or ti	carrelor	Authors' conclusion:
Lee CR et al.		instead of clopidogrel				"The higher risk of
Clinical outcomes		ped high risk patients				major adverse
	1	I Pod myn nok paliento	more ireated	mar auar anti		

and sustainability of		therapy after pe						cardiovascular or			
using CYP2C19		were followed for						cerebrovascular			
genotype-guided		included in Cava					not recei-	events associated			
antiplatelet therapy		ving clopidogrel						with clopidogrel use			
after percutaneous		Major adverse c						in CYP2C19 loss of function allele			
coronary interven-		were defined as									
tion. Circ Genom Precis		bosis, admissior						carriers suggests that use of geno-			
Med			ngina, ischemic cerebrovascular accident, or transient								
2018;11:e002069.		ischemic attack.						type-guided dual antiplatelet therapy			
PubMed PMID:		as a bleeding ev						in practice may			
29615454.		tion, prolongatio						improve clinical			
		classified as GU						outcomes."			
ref. 5, continua-		Occluded Arterie									
tion		but not resulting									
		life-threatening									
		hemodynamic c Results were co									
		groups or were a									
		Relevant co-me					line.				
		Genotyping:									
			Clopidogrel Prasugrel/ticagrelor								
			- 405x NM+UM - 113x NM+UM								
		- 68x IM+PM			- 165x IM-	+PM					
		Populto:	Results:								
		IM+PM compa									
					IM+PM		events				
							per 100				
							patient-				
							years				
							for NM+				
							UM				
		major adver-	clop	idogrel	$HR_{corr} = 2$		20.1				
	IM+PM:	se cardiovas-			(95% CI:	1.52-					
	E	cular or cere-			4.66) (S)		45.0				
		brovascular events		ugrel/ grelor	NS		15.0				
		clinically		idogrel	NS		7.3				
		significant		ugrel/	NS		4.2				
		bleeding		grelor							
		Results were s			ly patients	with ac	cute coro-				
		nary syndrome									
		intervention we									
		6.83) (S) for m	-								
		vascular event				M com	pared to				
		NM+UM; NS fo	or pra	sugrel/ tio	cagrelor).						
	Olasia	Clopidogrel co	mnare	d to pres	suarel/ticec	irelor:	]				
	Clopido-										
	grel ver-	IM+PMNM+UMmajor adverseHRcorr = 4.65NS									
	sus pra- sugrel/ti-	cardiovascular		(95% C							
	cagrelor:	cerebrovascula		10.0) (5							
	IM+PM:	events The difference between IM+PM									
	E	and NM+UM was significant (S).									
	NM+UM:	clinically significant NS NS									
	AA	bleeding		L		L					
		Results were s									
		nary syndrome intervention we									
		3.97-27.7) (S)									

		brovascular ev to prasugrel/tic		M for clopidogrel co or NM+UM).	ompared	
		Note: Genotypir	ng was for *2, *	*3 and *17. These a	are the	
		most important		in this patient group		
rof C	2	USA.				Authors' conclusion:
<b>ref. 6</b> Zhong Z et al. Effect of cytochro- me P450 2C19 polymorphism on adverse cardiovas- cular events after drug-eluting stent implantation in a large Hakka popu- lation with acute coronary syndrome receiving clopido- grel in southern China. Eur J Clin Pharma- col 2018;74:423-31. PubMed PMID: 29243114.	3	934 patients wit percutaneous of drug eluting stel genotype-guide year. All patient of clopidogrel al taneous corona ted with clopido mg daily and PM patients receive Major adverse of diovascular dea vessel revascula Concomitant ora other relevant of Before percutan of patients with higher for PM th patients using a for IM and PM. Genotyping: - 377x NM - 426x IM - 131x PM Results:	Authors' conclusion: "Based on the geno- type-guided antipla- telet therapy, there was no significant association between the carrier status and the clinical outcome at 1, 6, and 12 months. In addi- tion, no significant difference in the rates of bleeding was found among the three groups."			
		Percentage of		adverse events for I dogrel 150 mg/day		
		NM on clopido			value for NM	
		major adver-	1 month	NS	2.7%	
		se cardiovas-	6 months	NS	10.9%	
	Cono	cular events	12 months	NS	14.1%	
	Geno- type-	death	1 month	NS	0.53%	
	guided		6 months	NS	0.53%	
	therapy:		12 months	NS	0.80%	
	PM: AA	non-fatal	1 month	NS	0.27%	
	IM: AA	myocardial	6 months	NS	1.3%	
		infarction	12 months	NS	1.6%	
		target vessel	1 month	NS	1.9%	
		revasculari-	6 months	NS	9.0%	
		sation	12 months	NS	11.1%	
		stroke	1 month	NS NS	0% 0%	
			6 months 12 months	NS NS	0%	
		bleeding				
		events				
		<b> └</b>				
				and *3. These are the Chinese patient or		
		important gene	variants in this	Chinese patient gr	oup.	

ref. 7	3		•	patients with minor		Authors' conclusion:				
Wu Y et al.				ated with clopidogre		"Among patients				
Impact of CYP2C19				bed in estimated glo		with minor stroke or TIA taking clopido-				
polymorphism in prognosis of minor			filtration rate (eGFR) quintiles (292-299 patients per quin- tile). Patients with severe renal dysfunction, defined as							
stroke or TIA pa-				grel-aspirin treat- ment, CYP2C19						
tients with declined			serum creatinine over 1.5 times of upper limit of normal value, were excluded. Patients were followed for 90 days.							
eGFR on dual anti-						LOF carrier state was associated with				
platelet therapy:				as ischemic or hem	•	higher risk of new				
CHANCE substudy.				ents was defined as		stroke in those with				
Pharmacogenomics				ocardial infarction,		eGFR < 75 ml/min/				
J				e classified accordi		$1.73 \text{ m}^2$ . There was				
2018;18:713-20.				Streptokinase and T		no significant diffe-				
PubMed PMID:				luded Coronary Art		rence in the indivi-				
29520080.			-	d as bleeding not re	•	dual outcomes of				
				namic compromise		bleeding in carriers				
				leeding that require		compared with non-				
				hemodynamic com		carriers in any renal				
			•	as fatal or intracrani		function group."				
				hemodynamic com						
		or surgical interv		acement, inotropic	support,					
		•			ot ovolu					
		ded.		on CYP2C19 was n						
		ded.								
		Constuning								
		Genotyping: - 619x NM+UM								
		- 857x IM+PM								
		Results:								
		Results for IM-	PM compared	to NIM+LIM:						
			eGFR (in	IM+PM	value					
			ml/min/1.73		for					
			m <sup>2</sup> )		NM+					
			,		UM					
		% of patients	all	HR <sub>corr</sub> = 1.51	6.6%					
	IM+PM: E	with stroke		(95% CI: 1.03-						
	E	= % of		2.21) (S)						
		patients with	≥ 102.5	NS	5.4%					
		combined	94.9-102.4	NS	7.8%					
		vascular	87.4-94.8	NS	8.9%					
		events	75.0-87.4	NS	8.8%					
			< 75.0	HR <sub>corr</sub> = 7.39	2.4%					
				(95% CI: 1.44-						
				37.95) (S)						
				ge of patients with						
				events was the sar						
		0/ of		ge of patients with s						
		% of patients	all	$HR_{corr} = 1.54$	6.3%					
		with ischemic stroke		(95% CI: 1.04- 2.27) (S)						
		SUUKE	> 100 5		E 40/					
			≥ 102.5	NS	5.4%					
			94.9-102.4	NS	7.8%					
			87.4-94.8 75.0-87.4	NS NS	8.0% 8.8%					
			< 75.0-87.4	$HR_{corr} = 7.39$	8.8% 1.6%					
			\$ 7 3.0	(95% CI: 1.44-	1.0 /0					
				(95% Cl. 1.44- 37.95) (S)						
		any bleeding	all	NS	2.4%					
		≥ 102.5	NS	1.6%						
			94.9-102.5	NS	3.9%					
			87.4-94.8	trend for an in-	0.9%					
			0.101.0		0.070	1				

rof 7 continue	<u> </u>				1	1
ref. 7, continua-				crease (p =		
tion			75 0 07 4	0.06; NS)	2 00/	
			75.0-87.4	NS	3.2%	
		minor blee-	< 75.0 all	NS NS	2.4% 1.5%	
		ding	≥ 102.5	NS	0.8%	
			94.9-102.4	NS	2.3%	
			87.4-94.8	NS	0.9%	
			75.0-87.4	NS	1.6%	
			< 75.0	trend for a de-	1.6%	
				crease (p =		
		madamata	all	0.09; NS) NS	0.2%	
		moderate				
		bleeding	≥ 102.5	NS	0%	
			94.9-102.4	-	0%	
			87.4-94.8	NS	0%	
			75.0-87.4	-	0%	
			< 75.0	-	0%	
			Because almost no moderate bleeding occurred, significance could not be			
				or most subgroups.		
		severe	all	NS	0%	
		bleeding	≥ 102.5	-	0%	
			94.9-102.4	-	0%	
			87.4-94.8	-	0%	
			75.0-87.4	NS	0%	
			< 75.0	-	0%	
				ost no severe blee		
				nificance could not		
		The median of		or most subgroups		
		ml/min/1.73m <sup>2</sup>		ml/min/1.73m <sup>2</sup> in th	ie < 75.0	
		The median e	the >			
		102.5 ml/min/1				
		102.0 111/1111/1				
		Note: A previou	s substudy of t	he study described	l in Wang	
		•	•	plus acetylsalicylic	-	
				acid alone in patien		
				chronic kidney dis		
				ion in stroke recurre		
		-		it this benefit was n		
				y disease patients.		
				n/1.73m <sup>2</sup> (median 6		
				erate kidney failure		
					•	
		Note: Genotypir	nd was for *2. *	3 and *17. These a	are the	
				n this Chinese pati		
ref. 8	3			e of prasugrel or ti		Authors' conclusion:
Cavallari LH et al.	-			C19 IM and PM, 18		"These data from
Multisite investiga-				th antiplatelet thera		real-world observa-
tion of outcomes				ention (PCI). Patien		tions demonstrate a
with implementation				6.7% of patients (n		higher risk for car-
of CYP2C19 geno-				S) was the indication		diovascular events
type-guided antipla-				ention. 83.6% of pa		in patients with a
telet therapy after				nd 98.2% of patient		CYP2C19 loss-of-
percutaneous coro-				clopidogrel, prasu		function allele if
nary intervention.				in IM+PM was pras		clopidogrel versus
JACC Cardiovasc				pidogrel 150 mg/da		alternative therapy
				1.7% of patients. A		is prescribed."
2018;11:181-91.				grel in 64.8% and t		
PubMed PMID:		in 35.2% of pati		-	-	
	L	00.270 01 pau				

00400574		Naster 1						
29102571.		Major adverse cardio						
ref. 8, continua-		myocardial infarction,				-		
tion		adverse cardiovascular events occurred in 108 patients in this study.						
		Results were correcte	ed for the	e probabilit	y of rece	eiving clopi-		
		dogrel versus alternat		•	•	J -F-		
		Relevant co-medication						
		A total sample size of	<sup>-</sup> 1,815 p	atients, wi	th at lea	st 30%		
		being IM or PM and 6			-			
		therapy, provided >90						
		to detect a hazard rat				-		
		adverse cardiovascul		between t	ne IM+F	'M-clopido-		
		grel and -alternative g	jioups.					
		Genotyping:						
		Clopidogrel 75 mg/d	av	Alternativ	e thera	VC		
		- 1050x NM+UM	чу	- 193x N		<i>.</i> ,		
	Clopido-	- 226x IM+PM (219x	(IM.	- 346x IN		99x IM.		
	grel 75	7x PM)	,	47x PM	•			
	mg/day	<u> </u>			/	]		
	versus	Results:						
	alternati-	Clopidogrel 75 mg/d	ay comp	pared to all	ternative			
	ve thera-		IM+PM		IM	NM+UM		
	py: IM: E	major adverse	HRcorr		x 3.6	NS		
	IM: E	cardiovascular		CI: 1.18-	(S)			
	E	events death	4.32) ( HR <sub>corr</sub>			NS		
	NM+UM:			- 3.70 CI: 1.37-				
	AA		10.35)					
		myocardial infarc-	NS	· /		NS		
		tion						
		ischemic stroke	NS			NS		
		major adverse	HRcorr			NS		
		cardiovascular		CI: 1.07-				
		events including stent thrombosis	3.12) (	3)				
		and unstable						
		angina						
		stent thrombosis	NS		ł			
		unstable angina	NS					
		Results were similar for IM+PM when only patients with						
		acute coronary syndrome as indication for percutaneous						
		coronary intervention were analysed (HR <sub>corr</sub> = 2.87 (95% CI: 1.35-6.09) (S) for major adverse events; HR <sub>corr</sub> =						
		2.10 (95% CI: 1.12-3.90) (S) for major adverse events						
		including stent thrombosis and unstable angina; HR <sub>corr</sub> = 2.93 (95% CI: 1.12-7.72) (S) for myocardial infarction;						
		NS for death and for ischemic stroke).						
		Moderate and sever			g bleedi	ng events,		
		defined according to	the GU	STO (Glob	al Utiliza	ation of t-		
		PA and Streptokinas						
		criteria, were observ						
		study population and	d were s	imilar acro	ss group	DS.		
			. 4					
		IM+PM on alternativ			ed to NN	I+UM on		
		clopidogrel, prasugr		-	11.4	evente		
				M+PM	IM	events per 100		
	IM+PM	11	1		1			
						patient-		
	on alter-					patient- vears		
						patient- years for NM+		

ref. 8, continua-	NM+UM		NC	NC	107	
tion	on main-	major adverse cardio- vascular events	NS	NS	13.7	
	ly clopi-	death	NS		6.6	
	dogrel 75	myocardial infarction	NS	<u> </u>	7.0	
	mg/day:	ischemic stroke	NS		2.4	
	AĂ	major adverse cardio-	NS		19.6	
		vascular events				
		including stent thrombo-				
		sis and unstable angina				
		stent thrombosis	NS		2.4	
		unstable angina	NS		5.7	
		Results were similar wher nary syndrome as indicati intervention were analyse NS).	on for percut d (all compa	aneous risons fo	coronary or IM+PM	
		Moderate and severe or li defined according to the C PA and Streptokinase for criteria, were observed in				
		study population and were	e similar acro	ss grou	DS.	
		Note: In this study, the obs 31.5% and the observed per ping a major adverse cardio clopidogrel 75 mg/day and Based on these data, the a number of patients needed cardiovascular event was 9				
ref. 9	3	Note: Genotyping was for * most important gene variar USA. For part of the patien *4, *4B, *6, *8, *10, *12 and Substudy of Wang 2016. 29	Authors' conclusion:			
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.		mic stroke or high-risk TIA and acetylsalicylic acid (n = acid alone (n = 1470). Patie Recurrent stroke was defin stroke. Combined vascular stroke, hemorrhagic stroke lar death. Bleeding was def according to GUSTO (Glob and Tissue Plasminogen A Arteries). Glycated albumin ned as high, indicating poo mic control, whereas those be low, indicating good sho patients (n = 1844) had gly Of the patients with good si cated albumin $\leq$ 15.5%), IN lesterolemia more often tha hazard ratios were corrected hyperlipidemia. Co-medication with influence ded.	"In patients with minor stroke or high- risk transient ische- mic attack, clopido- grel-aspirin when compared with aspi- rin alone reduced stroke recurrence only in noncarriers of CYP2C19 loss-of- function allele and normal glycated albumin levels."			
		Genotyping: Clopidogrel/acetylsalicylic acid - 609x NM+UM - 854x IM+PM	Acetylsa - 598x N - 872x IN	M+UM	id	

ref. 9, continua-						
tion		Results:				
		Results for acetylsalicy		/acetylsalicylic ac	id compared to	
			glycated albumin	IM+PM	NM+UM	
		stroke	> 15.5%	NS	NS	
				There was no d tween IM+PM a (NS).		
			≤ 15.5%	NS	HR <sub>corr</sub> = 0.18 (95% CI: 0.07- 0.42) (S)	
	IM+PM: E				petween IM+PM as significant (S).	
		combined vascular	> 15.5%	NS There was no d	NS ifference be-	
		event		tween IM+PM a (NS).	ind NM+UM	
			≤ 15.5%	NS	HR <sub>corr</sub> = 0.18 (95% CI: 0.08-	
				The difference b	0.42) (S) between IM+PM	
		ischemic	> 15.5%	and NM+UM wa	as significant (S). NS	
		stroke	- 10.070	There was no d tween IM+PM a	ifference be-	
				(NS).		
			≤ 15.5%	NS	$HR_{corr} = 0.11$ (95% CI: 0.04-	
					0.32) (S) between IM+PM	
		bleeding	> 15.5%	NS	as significant (S). NS	
				There was no d tween IM+PM a (NS).		
			≤ 15.5%	NS There was no d	NS ifference be-	
				tween IM+PM a (NS).		
				or *2, *3 and *17. riants in this Chin	These are the ese patient group.	
ref. 10	4	Meta-analys	s of 15 stu	dies including a to	otal of 4762	Authors' conclusion:
Pan Y et al. Genetic polymor-				ransient ischemic 2 patients, 2185 w	attack (TIA) using vere NM or UM.	"Carriers of CYP- 2C19 loss-of-func-
phisms and clopi-		2033 were IN	/I, and 544	were PM. 367 pa	tients were of	tion alleles are at
dogrel efficacy for acute ischemic				IM+PM and 275 N 1+PM and 1637 N	NM+UM), 4045 of IM+UM) 97 of	greater risk of stroke and composite vas-
stroke or transient ischemic attack: a		African ance	cular events than noncarriers among			
systematic review	natic review were post hoc analysis of randomised controlled trials and					
and meta-analysis. Circulation		13 were coh stroke and T	mic stroke or TIA treated with clopido-			
2017;135:21-33. PubMed PMID:		ischemic stro	•		grel."	
27806998.			•	oke. 10 studies M, 1716 IM, and		
		455 PM) rep	orted data o	on composite vas	cular events. 7	
		1899 IM or F	M) reported	2 patients (1623 ) d data on bleeding schemic stroke or	g events.	
		STOKE Was C		SCHEITIIC STUKE OF	nemormayic	

			•					
ref. 10, continua-		stroke. Composite vascular outcome was defined as stroke, myocardial infarction or vascular death.						
tion			•					
				•	was also included			
				analysis (Wang 20 ated with a fixed a	ffects model in the			
					tudies. Otherwise,			
			-effects mode					
		Results:						
		r	for IM. PM or	IM+PM compared	to NM+UM:			
			ancestry	IM	PM			
	IM: E	stroke	all	RR = 1.79	RR = 2.52			
	PM: E			(95% CI: 1.45-	(95% CI: 1.93-			
	1 IVI. L			2.22)	3.30)			
				RR = 1.92 (95%	<i>,</i>			
			European	RR = 2.46 (95%	,			
			Asian	RR = 1.93 (95%				
			African other	N N				
				s for the outcome				
				al, suggesting pos				
				quantification of the				
				dy bias and addition				
				sing studies, the R				
				% CI: 1.47-2.21).				
				of Wang 2016 acco				
				nts in the meta-and				
				showed that the ov consistent with th				
				tudies except War				
				ne 95% Cl became				
				of Wang 2016 (1.				
			1.57-2.35).					
				ion of studies with				
				ality score, high ri				
				17 alleles, the effe of new stroke in cl				
				remained similar.	opidogi ei-li ea-			
				of European ances	stry, stroke			
				3.64% of NM and				
			IM+PM.					
		com-	all	RR = 1.45	RR = 1.96			
		posite		(95% CI: 1.06-	(95% CI: 1.49-			
		vascu-		1.98)	2.58)			
		lar out-		RR = 1.51 (95%	o CI: 1.10-2.06)			
		blee-	all	N	S			
		ding	European	N				
			Asian	N				
			African		S			
			other	N				
				heterogeneity bet				
		11	•	vascular outcome	e, but not for			
			nd bleeding.	(A) (BAA (A) (A) (A)				
ref. 11	3			(CYP2C19 *2/*2) \		Authors' conclusion:		
Deiman BA et al. Reduced number of			ercutaneous	"This study provides evidence that for				
cardiovascular								
events and		32) or prasugrel 10 mg/day (n = 41) for at least one year. CYP2C19-related Patients received daily acetylsalicylic acid. Treatment with poor metabolisers						
increased cost-						prasugrel may be		
	1	prasugrel started on day 1-5 after percutaneous coronary prasugrel may be intervention. Until that time, clopidogrel was given. Patients more effective than						
effectiveness by genotype-guided		interventi	on. Until that	time, clopidoarel v	vas given. Patients			

antiplatelet therapy in patients undergoing percutaneous coro- nary interventions in the Netherlands. Neth Heart J 2016;24:589-99. PubMed PMID: 27573042. <b>ref. 11, continua-</b> <b>tion</b>		were monitored for at least 1.5 ye ment. Adverse cardiovascular events we to cardiovascular cause, myocard thrombosis, stroke, or a second p intervention in the same artery. M cular events were defined as sten infarction and death. None of the patients in the study H than 1.5 years after the percutane tion, chest pains only occurred as sis. Relevant co-medication was not e Results: % patients with adverse events f	ere defined a ial infarction ercutaneous ajor adverse t thrombosis nad major ble ous coronar a result of ir excluded.	as death due , stent coronary cardiovas- , myocardial eeding. More y interven- n-stent steno-	clopidogrel to pre- vent major adverse cardiovascular events after PCI and this approach could be cost-effective."
	Clopido-	prasugrel:	clopido-	value for	
	grel ver-		grel	prasugrel	
	sus pra-	adverse cardiovascular events	x 8.3 (S)	4.9%	
	sugrel: PM: E	adverse cardiovascular events	x 6.4 (S)	4.9%	
		within 1.5 years major adverse cardiovascular events within 1.5 years	x 10 (S)	2.4%	
ref. 12 Wang Y et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopido- grel for risk reduc- tion among patients with minor stroke or transient ischemic attack. JAMA 2016;316:70-8. PubMed PMID: 27348249.	3	2933 patients with minor ischemic aged 40 years or older, were treat acetylsalicylic acid (n = 1463) or v alone (n = 1470). Treatment starte symptom onset. All patients receiv 300 mg acetylsalicylic acid. Patier grel and acetylsalicylic acid receiv dose of 300 mg followed by clopic months and acetylsalicylic acid 75 weeks. Patients treated with acety received 75 mg/day for 3 months. for 90 days. Acute minor stroke w 3 or less at the time of randomizat tutes of Health Stroke Scale (NIH) to 42, with higher scores indicatin was defined as focal brain ischem symptoms within 24 hours after or high risk of stroke recurrence (def the time of randomisation on the A the risk of stroke on the basis of a cal features, duration of TIA, and diabetes; scores range from 0 to 7 cating greater short-term risk). New stroke was defined as ischer stroke. Combined vascular events stroke, hemorrhagic stroke, myoc- lar death. Bleeding was defined at according to GUSTO (Global Utiliz and Tissue Plasminogen Activato Arteries) criteria. Patients with a clear indication for (presumed cardiac source of emb requirement for long-term nonstur- nonsteroidal antiinflammatory druc- tion, or with heparin therapy or ora within 10 days before randomisati- patients included in the study wer-	ted with clop with acetylsal ed within 24 ved a loading ints treated w ved a clopido logrel 75 mg 5 mg/day for /lsalicylic aci Patients we as defined b tion on the N SS; scores ra g greater defined a with resol inset plus a m ined as a sca ABCD <sup>2</sup> , whic ige, blood pri- presence or 7, with higher inc or hemore avas defined ardial infarcti s any bleedin zation of Street r for Occlude anticoagula olus), with an dy antiplatele gs affecting p al anticoagul on were exc	idogrel and licylic acid hours of g dose of 75- ith clopido- ogrel loading /day for 3 the first 3 d alone re followed y a score of lational Insti- ange from 0 ficits). TIA ution of noderate-to- ore of $\geq$ 4 at h assesses essure, clini- absence of r scores indi- rhagic d as ischemic ion, or vascu- ng event eptokinase ed Coronary tion therapy n anticipated et drugs or for platelet func- ation therapy luded. No	Authors' conclusion: "Among patients with minor ischemic stroke or transient ischemic attack, the use of clopidogrel plus aspirin com- pared 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."

rof 12 continue			o time f	randomiastica	Other	a dication	T
ref. 12, continua- tion		was not excl		randomisation.	Uner con	legication	
		Genotyping:					
		Clopidogrel	/acetylsal	icylic Acetyls	alicylic ac	id	
			1 16.4	E00x4			
		- 609x NM+ - 854x IM+I			NM+UM IM+PM (6	84 v IM	
		181x PM)		188x	•	04A IIVI,	
					,		
		Results:					
			npared to	NM+UM for clop	oidogrel/a	cetylsali-	
		cylic acid:		IM+PM		value for	
						NM+UM	
	IM+PM:	% of patien	ts with	HR = 1.46 (95	% CI:	6.7%	
	E	stroke =		1.05-2.13) (S)			
		% of patien					
		events	asculai				
		any bleedin	Ig	NS		2.5%	
				en IM+PM and	-	vere found	
		In the acety	visaticylic :	acid alone group	).		
		Results for	clopidoar	el/acetylsalicylic	acid com	pared to	
		acetylsalicy		onacotyleancyne			
			PM	IM	NM+UM		
		stroke	NS	NS		51 (95%	
			The diff	erence between		-0.75) (S) nd NM+	
				significant (S).			
			The diff	erence between			
				also significant			
				proton pump inhi			
				oump inhibitor us			
		combined	NS	NS		50 (95%	
		vascular	The diff	aronoo hotwoon		-0.74) (S)	_
		event		erence between significant (S).	IIVI+FIVI a		
				erence between	IM+PM a	nd NM+	1
				also significant			
				proton pump inhi			
				as no difference users (NS).	ior the pro	oton pump	
		ischemic		NS	HR = 0.	51 (95%	1
		stroke		• •		-0.75) (S)	
				erence between significant (S).	IM+PM a	nd NM+	
		progres-		NS	HR = 0	38 (95%	
		sive				-0.84) (S)	
		ischemic		erence between			
		stroke	UM was	significant (S).		53 (050/	
		recurrent ischemic		NS		53 (95% -0.83) (S)	
		stroke	There w	as no difference			
			and NM	+UM (NS).	<u> </u>	<b>.</b>	
		large-		NS		62 (95%	
		artery athero-	There w	as no difference		-0.97) (S) IM+PM	
		sclerosis		+UM (NS).			
		small-		or a lower rate	HR = 0.	28 (95%	
L							.1

rof 12 continue		anter:				1
ref. 12, continua- tion		artery	(p = 0.05) (		CI: 0.12-0.65) (S)	-
		occlusion	and NM+UM (N	IS).	etween IM+PM	
		cardioge-			bsence of mode-	
		nic embo- lism	rate bleeding in	one or mo	ore groups	
		myocar-	not estimable d	ue to the a	bsence of	
		dial			e or more groups	
		infarction	-			
		any	NS		NS	
		bleeding	and NM+UM (N	IS).	etween IM+PM	
					exclusion of the	
			20 proton pump not be estimate			
			bitor users.			
		mild	trend for a h	igher I	NS	
		bleeding	bleeding rate			
			0.08) (NS			
			and NM+UM (N	IS).	etween IM+PM	
		moderate bleeding	not estimable d rate bleeding in		bsence of mode-	
		severe			bsence of severe	
		bleeding	bleeding in one			]
				+o ···		
			/ping was for *2,			
ref. 13	3				nese patient group me who received	Authors' conclusion:
Ogawa H et al.			s coronary interv			"In conclusion, pra-
Effects of CYP-		clopidogrel (ı	n = 383, loading o	dose 300 m	ng, maintenance	sugrel at a LD/MD of
2C19 allelic vari-					(n = 390, loading)	20/3.75 mg had
ants on inhibition of platelet aggregation					y/day). Treatment	stable antiplatelet effects, irrespective
and major adverse			ination with acety atients were mon		cid and lasted 24-	of the CYP2C19
cardiovascular		after treatme				genotype, after PCI
events in Japanese			that occurred up			in Japanese ACS
patients with acute coronary syndrome:					ng related to coro-	patients. Although the incidence of
The PRASFIT-ACS					ided. The definition	major adverse car-
study.			d non-serious ble is in Myocardial I		definition (TRITON	diovascular events
J Cardiol 2016;68:29-36.			he other clinical c			(IVIACE) was 9.5%
PubMed PMID:		included ove	r the first 24 wee	ks.		in the prasugrel group and 12.5% in
26521100.			ng platelet activity			the clopidogrel
			ssay (P2Y <sub>12</sub> react		,	group in IM + PM
			on with other plate ts, thrombolytics			patients, there were
		•	excluded, co-me			no significant diffe- rences in terms of
		2C19 was no			• •	the incidences of
						MACE and clinically
			clopidogrel group	:		relevant bleeding
		- 135x NM - 171x IM				between the two treatments among
		- 17 1X IW - 77x PM				patients of each
						CYP2C19 pheno-
		Results:				type."
		Results for	clopidogrel versu			
				clopido-	value for	
		cardiovaca	ular death, non-	grel NS	prasugrel 11.8% of	
			rdial infarction		the NM and	
				1		

	<u>т</u>		1					
ref. 13, continua- tion		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 <sup>#</sup>	The authors indicated that for clopidogrel, the inci- dence 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				
	Clopido- grel ver-	clinically relevant bleeding for NM and IM+PM	NS	4.6% of the NM and 3.0% of the IM+PM				
	sus low- dose pra-	other bleeding for NM	NS	43.8% of the NM				
	sugrel: IM+PM: AA <sup>#</sup>	other bleeding for IM+PM	HR = 0.52 (95% BI: 0.38-0.71) (S)	44.7% of the IM+PM				
		bleeding leading to discon- tinuation 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)					

ref. 13, continua-		remaining platelet ac	tivity	higher (S)		
tion		for NM and IM+PM,		/		
		hours and 5-12 hour				
		the loading dose				
		The authors indicate	d that fo	r clopidoare	I the platelet	
		inhibition was signific				
		to NM.				
		Note: Genotyping was	perform	ned for *2 a	nd *3. These are	4
		the most important ge				
		group.	no rane			
ref. 14	4	309 patients were trea	ated with	CYP2C19	aenotype-quide	d Authors'
Shen DL et al.		therapy post percutan				conclusions:
Clinical value of		clopidogrel 75 mg/day				"Individual antiplate-
CYP2C19 genetic		ticagrelor 90 mg twice				
testing for guiding		to a group of 319 patie				by CYP2C19 gene-
the antiplatelet		(clopidogrel 75 mg/da				
therapy in a		was clopidogrel 600 n				cantly reduced the
Chinese population.		Heparin and low-mole				note of marian advisor
J Cardiovasc Phar-		anticoagulant therapy				s se cardiovascular
macol		were followed for on a				events without an
2016;67:232-6.		medication was exclu-				increase in the rate
PubMed PMID:		Serious cardiovascula		were defin	ed as death	of bleeding in the
26727381.		myocardial infarction				near term in this
		treated artery.	01 10 100	odianoadon		Chinese population."
		a outou untory.				
		Genotyping (only in th	e aenot	vpe-auided	aroup):	
		- 133x NM	5	/	3	
		- 139x IM				
		- 37x PM				
	Genoty-					
	pe-gui-	Results:				
	ded ver-	Genotype-guided ve	rsus nor	n-genotype-	guided therapy:	7
	sus non-				% patients in	7
	genotype				non-genotype-	
	-guided				guided group	
	therapy:	Serious	x 0.45		9.4%	
	AA <sup>#</sup>	cardiovascular	OR = (	.42 (95%		
		events		0-0.91)		
		Myocardial	x 0.39	•	4.1%	
		infarction		o = 0.065)		_
		Death	NS		2.5%	_
		Revascularisation	NS		2.8%	_
		Bleeding	NS		6.0%	
		The decrease in seri				
		also significant at 1 r				
		1.48-16.29) and at 6	months	(x 0.41; OF	R = 2.48; 95%	
		CI: 1.04-5.92) (S).		. <b>.</b>		
		The decrease in my	ocardiai	intarctions v	vas significant	
		at 1 and 6 months.	unaina a rak	lo o din a		
		All bleeding involved			in	
	1	At the start of treatm				
		concentrations were	n a tran-			1
		group, and there was				
		group, and there was concentrations (p = 0	).055). H	łowever, ha	emoglobin and	
		group, and there was concentrations (p = 0 triglyceride concentra	).055). H ations w	lowever, ha ere not sign	emoglobin and ificant	
	Genoty-	group, and there was concentrations (p = 0	).055). H ations w	lowever, ha ere not sign	emoglobin and ificant	
	pe-gui-	group, and there was concentrations (p = 0 triglyceride concentr predictors of serious	0.055). ł ations w cardiov	lowever, ha ere not sign ascular eve	emoglobin and ificant nts.	
	pe-gui- ded the-	group, and there was concentrations (p = 0 triglyceride concentra	0.055). ł ations w cardiov	lowever, ha ere not sign ascular eve	emoglobin and ificant nts. I versus NM:	
	pe-gui-	group, and there was concentrations (p = 0 triglyceride concentr predictors of serious	0.055). ł ations w cardiov	lowever, ha ere not sign ascular eve	emoglobin and ificant nts.	

ref. 14, continua-	PM: AA	cardiovascular						
tion	IM: AA	events						
		Bleeding	NS	6.0%				
			There were no significant differences between the					
		genotype groups at 1						
			were genotyped. Thes					
ref. 15	3		in this Chinese patient		Authors'			
Xiong R et al.	3		e *2/*2 who had had ST e coronary syndrome w		conclusions:			
A randomized			s to either double clopi		"In CYP2C19*2			
controlled trial to			, followed by 150 mg/da		homozygotes with			
assess the efficacy			oading dose, followed b		ACS, ticagrelor is as			
and safety of			Relevant co-medication	n was not	effective as high-			
doubling dose clopidogrel versus		excluded.			dose clopidogrel in reducing platelet			
ticagrelor for the					reactivity, particular-			
treatment of acute		Results:			ly in the first days.			
coronary syndrome		Double clopidogrei d	ose versus ticagrelor:	Value	This study suggests			
in patients with				for tica-	that ticagrelor may			
CYP2C19*2 homo-				grelor	be much better than			
zygotes. Int J Clin Exp Med	Double	Serious	Did not occur in	0	doubling the dose of clopidogrel in homo-			
2015;8:13310-6.	clopido-	cardiovascular	either group (NS)		zygotes of CYP-			
PubMed PMID:	grel dose	events			2C19*2 according to			
26550258.	versus ti-	Major bleeding	Did not occur in		platelet reactivity			
	cagrelor:	Minor blooding	either group (NS) HR = 2.88 (95% CI:	7.1%	monitoring. Use of			
	PM: B	Minor bleeding	1.34-6.15) (S)	7.170	ticagrelor instead of			
		P <sub>2</sub> Y <sub>12</sub> reaction units	x 2.2 (S)	34.5	clopidogrel may			
		on day 15	// (C)	••	eliminate the need for genetic testing			
		P <sub>2</sub> Y <sub>12</sub> reaction units	x 1.4 (S)	27.9	and lead to less mild			
		on day 30			bleeding events."			
			nit value on day 0 was a	approxi-	, i i i i i i i i i i i i i i i i i i i			
		mately 280 in both g	roups.					
		NOTE: Allele *2 was o	enotyped. This is the m	nost common				
		allele in this Chinese						
ref. 16	4		udies including a total of	of 44.655	Authors'			
Niu X et al.		-	arterial disease using of		conclusions:			
CYP2C19 polymor-			ere performed in Wester		"It is suggested that			
phism and clinical			an populations. 97% of		CYP2C19 polymor-			
outcomes among patients of different		•	n 74% of the Western p		phism affects the			
races treated with			ous coronary interventio		efficacy of clopido- grel differently			
clopidogrel: a			total). Most patients rec	ceived loading	among Westerners			
systematic review			ng clopidogrel. Serious were reported in 22 stu	Idios	and Asians."			
and meta-analysis.			cular death in 11 studie					
J Huazhong Univ			nfarction in 13 studies (					
Sci Technolog Med		-	s (n=13,075), stent thro	,				
2015;35:147-56.			th in 5 studies (n=4881)					
PubMed PMID:			and major bleeding in	5 studies				
25877345.		(n=11,079).						
			using a fixed effects mo					
			heterogeneity for the re andom effects model w					
		those cases.	andom enects model w	103 USEU III				
			meta-analysis included	16 studies				
			prich 2014 meta-analys					
			sis, 13 in the Jang 2012					
		-	mes 2011 meta-analys					
		the Liu 2011 meta-ana	alysis.					

rof 16 continue		Souch of th	o articlos in the mote and	voie word					
ref. 16, continua- tion			e articles in the meta-anal parately in this risk analys	•					
		included separately in this risk analysis (Malek 2008, Collet 2009, Giusti 2009, Mega 2009, Shuldiner 2009, Sibbing							
			imon 2009).		0				
		Construirs							
		Genotyping Western pa		atients <sup>.</sup>					
		72.1% NM	47.5%						
		25.5% IM	42.5% I						
		2.4% PM	10% PN	Л					
		Populto							
		Results:	ersus (NM+UM):						
				RR	95% CI				
		Serious	Total	1.35	1.14-1.60				
		cardiova	Western	1.20	1.01-1.41				
		scular	Asian	1.96	1.61-2.38				
		events	< 50% PCI (Western)	NS					
			≥ 50% PCI, total	1.42	1.18-1.71				
			≥ 50% PCI, Western ≥ 50% PCI, Asian =	1.24	1.03-1.51 1.61-2.39				
			100% PCI, Asian	1.90	1.01-2.39				
			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 Western, n ≥ 2000	NS NS					
			NOTE.: The size of the		studies				
			was not independent of						
			percentage. Most smalle						
			higher PCI percentages						
			studies included more p PCIs. The base size of t						
			including < 50% PCI wa						
			0-30 days, total	NS					
			30 days - 1 year, total	NS,	0.98-1.31				
			The Asian and Mestern	trend					
			The Asian and Western not significant at 0-30 da						
			of Paré 2010, a large st						
			PCI, the heterogeneity b	between t	he				
			Western studies resolve						
			were significant (RR = 1 1.59).	.38, 95%	CI: 1.19-				
			The Western studies we	ere not sid	gnificant for				
			> 30 days, but the Asiar	studies	were (RR				
			= 1.83; 95% CI: 1.16-2.8						
			any studies (including e 2010) did not have an e						
		Cardiova	Total	2.07	1.40-3.05				
		scular							
		death	Western	3.59	1.81-7.12				
	IM+PM:		Asian	1.62	1.0-2.62				
	F	Myocardi	Total	1.66	1.35-2.04				
		al	Western	Trend	0.94-2.17				
		infarction	Asian	2.00	1.60-2.51				
		Stroke	Total	2.11	1.45-3.06				
			Western	2.26	1.22-4.19				

	1	<u>п</u>	<b>.</b>			Г <b>г</b>	
ref. 16, continua-			Asian		2.03	1.27-3.25	
tion		Stent	Total		1.72	1.44-2.05	
		thrombos	Western		1.62	1.17-2.24	
		is	Asian		3.29	2.05-5.28	
		Death	Total		NS		
			Western		NS		
			Asian		Trend	0.99-4.02	
		Bleeding		eeding, total	NS		
			Major, V		NS		
			Major, A	sian	NS		
			All, total		0.83	0.74-0.94	
			All, Wes		0.87	0.76-0.99	
	IM+PM:		All, Asia		0.76	0.60-0.96	
	AA <sup>#</sup>			ly heterogeneity			
				ular events (tota			
				00; total and We			
				and Western for			
			· ·	Asian) and stud	•	900, 900-	
		2000 and heteroge		atients) were so	urces of		
		U U		on in the Wester	n nonula	tion	
				of publication b			
				ar events in the			
				n of four missin			
		RR no long			golaaloo		
				ing < 50% PCI	were		
				is correction ma		uivalent to	
		addition of			,		
		NOTE: The	e PM perc	entage in the IM	1+PM gro	oup was	
				e Asian populat			
				(19% versus 8.6			
				n both populatio			
				pected among t	he Asian		
		population					
			/ I A . I I A .				
		IM versus	(NM+UM)			050/ 01	
					RR	95% CI	
		Serious		<u> </u>	1.26	1.01-1.56	
		cardiovasc		The RRs in the			
		events (14	studies,	Asian subgrou			
		n=3078)		size but neithe After exclusion			
				large study inc			
				the Western st			
				trend and the r			
				significant (RR			
				1.03-1.78). He			
				resolved after			
				Simon 2009 ar	nd Collet	2009, two	
				studies with re			
				percentages (6			
				and the results			
				significant (RR	= 1.32; 9	95% CI:	
				1.13-1.54).			
		Bleeding		Major	NS		
				All	NS	L	
				ly heterogeneity		atoms)	
				ular events (tota	and We	stern)	
		- all bleedi		of publication b	ion for th	o opdpoint	
				of publication b			
	IM: AA			ar events. Corre ed to the RR no			
			y studies i		ionger be	Jing	
L	1	1					1

rof 16 continue		aignificant				
ref. 16, continua- tion		significant.				
		PM versus (NM+UM				
			1	RR	95% CI	
	PM: E	Serious	Total	1.92	1.49-2.47	
		cardiovascular	Western	NS,	0.96-1.83	
		events (12 studies, n=9813)	Asian	trend 3.64	2.36-5.60	
		11-9013)	After exclusion			
			large study inc			
			the results in t			
			subgroup were			
		Bleeding	1.57; 95% CI: Major	1.11-2.1 NS	1).	
	PM: AA <sup>#</sup>	Dieeding	All	0.56	0.38-0.83	
	PIVI: AA"	There was no evide				
		the studies or evide	nce of publicatio	n bias fo	r any of the	
		outcome measures.				
<b>ref. 17</b> Sorich MJ et al.	4	Meta-analysis of 24 s				Authors' conclusions:
CYP2C19 genotype		total of 36,076 patien performed in Caucas	• • •			"The reported asso-
has a greater effect		Asian populations (nt				ciation between
on adverse cardio-		incorporated studies				CYP2C19 loss-of-
vascular outcomes		analysis for stent thro				function allele carri-
following percuta- neous coronary		additional five and tw				age and major cardiovascular
intervention and in		control studies includ				outcomes differs
Asian populations		also included for ster patients including 23,				based on the ethnic
treated with clopi-		was reported in 12 st			Dieeding	population of the
dogrel: a meta-ana- lysis.		RRs were calculated			andom	study and, to a lesser extent, the
Circ Cardiovasc		effects models. The s			ides RRs	clopidogrel indica-
Genet		calculated using the			_	tion."
2014;7:895-902.		Serious cardiovascul cardiovascular death				
PubMed PMID: 25258374.		infarction or non-fata				
23230374.		were not reported in				
		including the most ou		•		
		infarction and stroke	without inclusior	of other	outcomes	
		was used. Of the 23 studies in t	ho most signifies	nt moto	analysis 15	
		studies were also inc				
		9 in the Jang 2012 m				
		meta-analysis and 10	) in the Liu 2011	meta-an	alysis.	
		Five of the articles in				
		separately in this risk			iusti 2009,	
		Mega 2009, Sibbing	2009 and Simon	2009).		
		Genotyping:				
		Caucasian patients:	Asian p	atients:		
		72.1% NM	47.5%			
		26.0% IM	42.7% I			
		2.4% PM	11.2% F	- IVI		
		Results:				
		(IM+PM) versus (NM	M+UM):			
			,	RR	95% CI	
		Serious Total		1.32	1.17-1.49	
			sian, no PCI	NS	4.07.4.40	
			sian, PCI	1.23	1.07-1.40 1.61-2.26	
	IM+PM:	Asian, The di	fferences betwe	1.91 en the th		

						,
ref. 17, continua-	E		subgroups was signific			
tion			The calculated RR for			
			without PCI did not dev			
			relative risk was also n			
			patients with acute cor			
			not undergoing PCI (2		,	
			A meta-analysis of stud 200 (10 additional stud			
			patients) delivered sim			
			Moreover, there were			
			RR between Asian stu			
			genotyped for the *2 al			
			and that genotyped for			
			alleles (59% IM+PM).			
		Stent	Total	2.07	1.67-2.57	
		thrombosis	Caucasian	1.74	1.48-2.06	
			Asian	4.60	2.87-7.37	
		Bleeding	Total	NS		
		ll ũ	Caucasian, PCI	NS		
			Asian, PCI	NS		
			Caucasian, no PCI	NS		
		There was	moderate to large hetero	geneity b	etween	
		the studies	for:			
			rdiovascular events (IM+			
			n undergoing PCI; PM: to	otal; Cau	casian not	
		undergoin				
			erogeneity was lower for			
			here was no study hetero			
			<ul> <li>PCI studies, but there w Caucasian + PCI studies.</li> </ul>	as sludy	neteroge-	
			ately 74% of the study he	terogen	aity for	
			as explained by the popu			
			. Meta-regression analys			
			ation and the PCI percent			
			dy heterogeneity (S).			
			total; Caucasian not unde	ergoing F	PCI; Asian	
		undergoin	ig PCI)			
			no evidence of publicatio			
			erious cardiovascular eve		e Asian	
			sian subgroups undergoi			
			PM percentage in the IM			
			among the Asian populat			
			population (21% versus &			
			r effects in both population prefore expected among t			
		population.		ne Asiali		
		IM versus (	NM+UM):			
				RR	95% CI	
		Serious	Total	1.22	1.07-1.39	
		cardiova	Caucasian, no PCI	NS		
		scular	Caucasian, PCI	1.22	1.01-1.46	
		events	Asian, PCI	1.49	1.17-1.90	
		(18	The calculated RR for C			
	IM: E	studies,	not undergoing PCI did			
		22,079)	1.0.			
			In the Caucasian PCI gr	oup, 19%	6 of the	
			patients were derived fro	om a stud	dy	
			including ≤ 70% PCI, wh	nile this w	/as 11% in	
			the Asian PCI group.			
			moderate to large hetero	geneity b	etween	
		the studies				

ref. 17, continua-		- serious ca	ardiovascula	r events, PCI	in Cauc	asians	
tion							
		PM versus	(NM+UM):				
					RR	95% CI	
		Serious	Total		2.07	1.59-2.69	
		cardiova scular	Caucasian,		NS	4 95 9 94	
		events	Caucasian,	PCI	1.67	1.25-2.24 2.30-4.01	
	PM: E	(18	Asian, PCI	asian PCI gro	3.04		
		studies,		re derived fro			
		15,951)		70% PCI, whi			
			the Asian P				
				large heterog	geneity b	between	
		the studies					
	4			r events, no F		analyzan of	Authors'
<b>ref. 18</b> Mao L et al.	4			ort studies or rials including			conclusions:
Cytochrome				terial disease			"CYP2C19 polymor-
CYP2C19				years. 7670 p			phism is significantly
polymorphism and				formed in Eur			associated with risk
risk of adverse				determined d			of adverse clinical
clinical events in		studies.					events in clopido-
clopidogrel-treated patients: a meta-				ed negative cl			grel-treated pa- tients."
analysis based on				ath, diagnose			
23,035 subjects.			need for rev	ascularisation	i, ischae	mic stroke or	
Arch Cardiovasc		bleeding.	nical effects y	were reported	l in 20 et	ludies (n =	
Dis				rction in 11 st			
2013;106:517-27.				udies (n = 14			
PubMed PMID: 24080325.				idies (n = 436			
24000020.				leath in 13 stu		= 11,023)	
				s (n = 11,278)			
				, large and/or	•		
				e calculated us nt of low and/			
				were calcula		•	
		effects mode		Word Galeala		guintou	
				neta-analysis	, 14 stud	dies were	
				, 2012 meta-a			
			1 meta-analy	/sis and 13 in	the Liu	2011 meta-	
		analysis.					
				e meta-analys			
				is risk analysi i 2009, Mega			
				Simon 2009).		naianei	
		,	5				
		Results:					
		(IM+PM) ve	ersus (NM+L	JM):	- 1		
				<b>.</b>	OR	95% CI	
		Negative cl effects	Inical	Total	1.50	1.21-1.87	
	IM+PM:	enecis		Caucasian	1.27	1.02-1.58	
	E	Myocardial	infarction	Asian	2.75	1.88-4.01 1.35-1.95	
		Stent throm			2.08	1.67-2.60	
		Revascular			1.35	1.10-1.66	
		Ischaemic s			2.14	1.36-3.38	
		Death			NS		
		Bleeding			NS		
				The calculat			
		<u>  </u>		did not devia	ate from	1.0.	

ref. 18, continua- tion       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	
<ul> <li>negative clinical effects (total; Caucasian)</li> <li>Study heterogeneity was low, but significant (p &lt; 0.1) for:         <ul> <li>repeated need for revascularisation</li> <li>death</li> </ul> </li> <li>There was no evidence of unacceptable publication bias.         <ul> <li>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</li> </ul> </li> </ul>	
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	
<ul> <li>- repeated need for revascularisation</li> <li>- death</li> <li>There was no evidence of unacceptable publication bias.</li> <li>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</li> </ul>	
- 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	
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	
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	
greater than in Caucasians. As the increase in IM is linear and PM is quadratic with null allele frequency, the	
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.	
	rs' conclu-
	onalized anti-
galada initiapy (in conventional initiapy (in zoo))	et therapy
	ding to CYP-
	genotype after
	an significantly
	ase the inci-
tion a randomized	of major
control trial literapy involved conventional clopidogref therapy in this	se cardiovas-
Int J Cardiol 150 mg/day) in IM patients and double dose of clopidogred	events and the
2013;108:3730-40. In combination with cilostazol (200 mg loading dose IISK OF	180-day stent
Publiced PMID.	bosis in a
23850318. The outcome measure serious cardiovascular events	se population."
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.	
There vant co-medication was not excluded.	
Genotyping (only in the genotype-guided group):	
- 143x NM	
- 128x IM	
- 30x PM	
Genoty-	
pe-gui- Results:	
ded ver- Genotype-guided versus non-genotype-guided therapy:	
sus non- % patients in	
genotype non-genotype-	
-guided guided group	
therapy: Serious x 0.29 (S) 9.03%	
Cardiovascular events	
Death, myocardial x 0.17 (S) 6.02%	
infarction or stroke	
Death         x 0.11 (S)         3.01%           Museurial inferencian         x 0.14 (S)         3.24%	
Myocardial infarction x 0.14 (S) 2.34%	
Stent thrombosisx 0.22 (S)3.01%Revascularisationx 0.55 (NS,3.01%	
Revascularisation x 0.55 (NS, 3.01% trend, p =	
0.089)	
Stroke NS 0.66%	
Bleeding x 0.36 (NS, 3.68%	
trend, p =	
0.073)	

rof 10 continue	T	NOTE 1. Allelee *2 and *2 were repetimed. These are the	
ref. 19, continua- tion		NOTE 1: Alleles *2 and *3 were genotyped. These are the	
uon		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	
	4	Netherlands.	A soften and a
ref. 20	4	Meta-analysis of sixteen studies including a total of 20,785	Authors' conclusions:
Jang JS et al. Meta-analysis of		patients with coronary arterial disease using clopidogrel,	"In conclusion,
cytochrome P450		including 4814 Asian patients and 7035 null allele carriers.	carrier status for
2C19 polymor-		In seven studies including a total of 7948 patients, the	loss-of-function
phism and risk of		outcomes for PM and IM patients were determined	CYP2C19 is asso-
adverse clinical		separately. Mortality rates were reported in eight studies	ciated with an
outcomes among		(n=7451), non-fatal myocardial infarction in six studies	increased risk of
coronary artery		(n=6574), stent thrombosis in ten studies $(n=11,585)$ and major blooding in two studies $(n=7424)$ . The definitions of	adverse clinical
disease patients of		major bleeding in two studies (n=7434). The definitions of myocardial infarction and serious cardiovascular events	events in patients
different ethnic		differed between studies. Serious cardiovascular events	with coronary artery
groups treated with		were generally defined as death, myocardial infarction,	disease on clopido-
clopidogrel.		stent thrombosis or stroke.	grel therapy despite
Am J Cardiol		(IM+PM) versus (NM+UM):	differences in clini-
2012;110:502-8.		- increased risk of serious cardiovascular events (OR =	cal significance
PubMed PMID:		1.42; 95% CI: 1.13-1.78) (S).	according to ethnici-
22591668.		Similar results were obtained after resolving the	ty."
		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	
	IM+PM:	population and the frequency of null alleles while there is	
	F	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)	
		<ul> <li>no effect on the incidence of major bleeding (NS)</li> </ul>	
	IM: AA	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):	
	PM: E	- increased risk of serious cardiovascular events (OR =	
		1.75; 95% CI: 1.23-2.51) (S, no significant heterogeneity).	
ref. 21	4	Meta-analysis of eight studies including a total of 17,302	Authors'
LiYetal.		patients using clopidogrel. The patients in the studies were	conclusions:
The gain-of-		mainly Caucasian and mainly had stable coronary arterial	"Carriers of the
function variant allele CYP2C19*17:		disease or acute coronary syndrome. Bleeding was	CYP2C19*17 vari-
a double-edged		reported in six studies (n=12,228, including 9240 with	ant have greater therapeutic respon-
sword between		coronary arterial disease). Stent thrombosis was reported	siveness to clopido-
thrombosis and		in four studies (n=4690) and death in three studies	grel than non-
bleeding in		(n=2752). The definition of serious cardiovascular events	carriers, but they
clopidogrel-treated		differed between studies. Serious cardiovascular events	have an increased
patients.		were generally defined as myocardial infarction, stroke,	risk of developing
J Thromb Haemost		need for percutaneous coronary intervention or death.	bleeding as well."
		*17 versus (no *17):	I č

	T		[
2012;10:199-206.		- 12% decrease in the percentage of patients with serious	
PubMed PMID:		cardiovascular events (from 11.1% to 9.8%; OR = 0.86;	
22123356.		95% CI: 0.76-0.97) (S, no heterogeneity).	
	*17: AA#	The decrease was 16% among patients with only	
ref. 21, continua-		coronary arterial disease (from 11.9% to 10.0%; OR =	
tion		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).	
	*17: E	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% Cl: 0.45-0.79)	
ref. 22	4	Meta-analysis of 32 studies including a total of 42,016	Authors'
Holmes MV et al.		patients and 3545 cardiovascular events, of which 579	conclusions:
CYP2C19 geno-		concerned stent thrombosis and 1413 bleeding events.	"Although there was
type, clopidogrel		Six of the studies were randomised trials. The other 26	an association be-
metabolism,		only investigated clopidogrel therapy. Patients with acute	tween the CYP2C19
platelet function,		coronary syndrome were the subject of 21 studies, 8	genotype and clopi-
and cardiovascular		studies involved patients with stable coronary arterial	dogrel responsive-
events: a syste-		disease, mainly at the time of stent placement, and the	ness, overall there
matic review and		remaining 3 studies did not specify the nature of the	was no significant
meta-analysis.		coronary arterial disease. Meta-analysis of the risk of	association of geno-
JAMA		serious cardiovascular events was based on 26 studies	type with cardiovas-
2011;306:2704-14.		including a total of 26,251 patients and 1465	cular events."
PubMed PMID:		cardiovascular events. Eleven studies including a total of	
22203539.		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.	
		serious cardiovascular events. (IM+PM) versus (NM+UM):	

<b>6 66</b> (1			
ref. 22, continua-	IM+PM:	- increased risk of serious cardiovascular events (fixed	
tion	E	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 $\ge$ 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 = $1.20$ ; 0.5% CI: 1.06 1.5% for studies reporting > 100	
		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. continua-	1	The BR for serious cardiovascular events on clonidograd	·
ref. 22, continua- tion	IM: D	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)).	
	PM: E	<ul> <li>standardised mean platelet reactivity after a 600 mg loading dose was increased by approximately 0.35.</li> <li>PM versus (NM+UM):</li> <li>increased risk of serious cardiovascular events (fixed effects model; studies reporting &lt; 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).</li> <li>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.</li> </ul>	
		- standardised mean platelet reactivity after a 600 mg	
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	<ul> <li>loading dose was increased by approximately 1.0.</li> <li>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.</li> <li>(IM+PM) versus (NM+UM):</li> <li>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)</li> <li>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)</li> <li>increased risk of myocardial infarction (OR = 1.38; 95% CI: 1.08-1.77) (S)</li> <li>no significant increase was found in the risks of death,</li> </ul>	Authors' conclusions: "Compared with previous meta-ana- lyses, 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, continua-	1	need for percutaneous coronary intervention, stroke and	
tion		the composite measure of death and/or myocardial	
		infarction (NS)	
		- no effect on the incidence of bleeding (NS)	
		IM versus (NM+UM):	
	IM: E	- 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):	
	PM: E	- 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):	
	*17: AA#	- 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: AA	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	4	Genotype-driven increased clopidogrel doses in 333	Authors'
Mega JL et al.		patients with cardiovascular disease using clopidogrel 75	conclusions:
Dosing clopidogrel		mg/day and acetylsalicylic acid 81-325 mg. NM patients	"Among patients
based on CYP2C19 genotype and the		received 75 mg/day and 150 mg/day, each for two 14-day	with stable cardio- vascular disease,
effect on platelet		periods. IM and PM patients received 75, 150, 225 and 300 mg/day, each for 14 days. Co-medication with	tripling the mainte-
reactivity in patients		anticoagulants or proton pump inhibitors and smoking were	nance dose of clopi-
with stable cardio-		excluded. Platelet reactivity index was measured using the	dogrel to 225 mg
vascular disease. JAMA		VASP assay, P2Y <sub>12</sub> reaction units using the VerifyNow	daily in CYP2C19*2
2011;306:2221-8.		assay. Non-response was defined as $\geq 230 \text{ P2Y}_{12}$ reaction	heterozygotes achieved levels of
PubMed PMID:		units. Similar results were obtained at a limit of 208 P2Y <sub>12</sub>	platelet reactivity
22088980.		reaction units. Genotyping:	similar to that seen
		- 247x NM	with the standard
		- 80x IM	75-mg dose in non- carriers; in contrast,
		- 6x PM	for CYP2C19*2
		IM:	homozygotes, doses
		- at 225 mg/day, platelet reactivity index and P2Y <sub>12</sub> reaction units were not significantly different from those in	as high as 300 mg
		NM+UM patients at 75 mg/day.	daily did not result in comparable degrees
		At 150 mg/day, the platelet reactivity index was not	of platelet inhibition."
		significantly different, but P2Y <sub>12</sub> 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 <sub>12</sub> reaction units (S).	
	IM: D	- 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).	

ref. 24, continua-	<u> </u>	P2Y <sub>12</sub> reaction units also decreased significantly with	
tion		dose (S for the trend).	
		<ul> <li>- 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)</li> <li>- decreased percentage of non-responders at higher doses (52%, ~25%, 10% and 10% at 75, 150, 225 and 300 mg/day respectively) (S)</li> </ul>	
	PM: D	<ul> <li>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.</li> <li>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<sub>12</sub> reaction units (S).</li> <li>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<sub>12</sub> 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.</li> <li>3.5 fold increase in the percentage of non-responders at 75 mg/day versus NM+UM (from 23% to 80%) (NS) Side effects:</li> <li>the incidence of bleeding was higher among NM+UM patients at 75 mg/day (5 yersus 0) (NS)</li> </ul>	
		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.	
<b>ref. 25</b> 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	NOTE.: Allele *2 was genotyped. 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 maintenan- ce 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, continua- tion	IM: D	<ul> <li>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)</li> <li>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))</li> </ul>	AUC of the active metabolite H4 after loading and maintenance doses versus *1/*1: IM: 72% PM: 28%
	PM: D	<ul> <li>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))</li> <li>PM versus *1/*1 (both 300 mg/75 mg):</li> <li>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)</li> <li>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)</li> </ul>	Effect of a 2-fold dose increase on the AUC of the active metabolite H4 (% increase): IM: 66% PM: 110%
		<ul> <li>- 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))</li> <li>(*1/*17 + UM) versus *1/*1 (both 300 mg/75 mg):</li> <li>- 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)</li> </ul>	
	*17: A	<ul> <li>and 5% (NS) respectively in all seven studies combined</li> <li>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))</li> <li>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)</li> </ul>	
		<ul> <li>no difference in the percentage of volunteers with side effects (both 10%). There were no serious side effects.</li> <li>Effect of a 2-fold dose increase (from 300 mg/75 mg to 600 mg/150 mg) in the single study:</li> <li>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</li> </ul>	
		<ul> <li>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</li> <li>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</li> <li>NM: increase in the AUC of the active metabolite H4 by 77% after the loading dose and by 66% after the loading</li> </ul>	
	UM: AA#	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.	
<b>ref. 26</b> 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-

rondomized and a		included Observice as the direction with NOAD and	dogral with a start
randomized cross-		included. Chronic co-medication with NSAIDs or	dogrel with a gene-
over CLOVIS-2		anticoagulants was excluded, but the use of CYP2C19	dose effect. Clopido- grel resistance can
(Clopidogrel and		inhibitors was not. Residual platelet aggregation was	0
Response Variabi-		measured using the LTA and 20 $\mu M$ ADP, P2Y_{12} reaction	be overcome by
lity Investigation		units using the VerifyNow assay. Non-response was	increasing the dose
Study 2).		defined as residual platelet aggregation $\geq 64.5\%$ and $\geq 236$	in heterozygous
JACC Cardiovasc		P2Y <sub>12</sub> reaction units. There was no significant interaction	carriers but not in
Interv		between treatment before the study and CYP2C19 that	homozygous
2011;4:392-402.		changed the pharmacodynamic parameters.	carriers."
PubMed PMID:		Genotyping:	
21511218.		- 58x (NM + UM)	
		- 41x IM	
ref. 26, continua-		- 7x PM	
tion		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 <sub>12</sub> reaction units)	
		(NS)	
		- increased AUC <sub>0-6hours</sub> of the active metabolite H4 (from $10.67 \pm 22.68$ ng bour/mL) (NS)	
		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 <sub>12</sub> reaction units (S for the trend	
	IM: D	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 <sub>12</sub> reaction units.	
		- AUC <sub>0-6hours</sub> 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 <sub>12</sub> reaction units) (NS)	
		- the AUC <sub>0-6hours</sub> 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 <sub>12</sub> reaction units (S for the trend	
		NM+UM, IM, PM).	
		- smaller percentage decrease in residual platelet	
	PM: D	aggregation after 300 mg and 900 mg loading doses	
	י ועו. U	(~15% versus ~70% and ~25% versus ~80%	
		respectively) (S).	
		Similar results were found for P2Y <sub>12</sub> reaction units.	
		- AUC <sub>0-6hours</sub> 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.	
ref. 27	3	The effect of up to three additional loading doses was	Authors'
Bonello-Palot N et	5		conclusions:
DUILEIIU-FAIULIN EL	1	studied in 43 patients (26x NM, 13x IM (*1/*2), 4x PM	
al.		(*2/*2)), who were scheduled to undergo elective	"High BMI, acute

Shuldiner AR et al.reAssociation ofchcytochrome P450(n2C19 genotype withmthe antiplateletBieffect and clinicalacefficacy ofmclopidogrel therapy.acJAMAsr2009;302:849-57.yeinrecamPIcaPIcaPIcaCamPIcaCamPIcaCam <t< th=""><th>00E potiopto (1E0v NIM C7v IM DNA (in altration of the DNA))</th><th></th></t<>	00E potiopto (1E0v NIM C7v IM DNA (in altration of the DNA))	
IM: D PM: D IM + PM: E 44 4 4 4	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 $\mu$ M 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).	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."

			Andlering
ref. 29	3	The 598 patients from Frere et al., 2008 (non-ST-elevation	Authors'
Frére C et al.		acute coronary syndrome; clopidogrel 600 mg and	conclusions:
The CYP2C19*17		acetylsalicylic acid 250 mg at least 12 hours before	"The CYP2C19*17
allele is associated		coronary angiography; blood samples taken before	allele is associated
with better platelet response to		coronary angiography; glycoprotein Ilb/IIIa antagonists	with better platelet response to clopi-
•		prior to the study excluded, but other co-medication was	dogrel."
clopidogrel in		not excluded) were genotyped for *17: 382x no *17, 189x	uogrei.
patients admitted for non-ST acute		one *17, 25x *17/*17. Platelet reactivity index was	
coronary syndrome.		measured using the VASP assay, residual platelet	
J Thromb Haemost		aggregation using the LTA and 10 μM ADP.	
2009;7:1409-11.		*17/*17 versus (one *17) versus (no *17):	
2009,7.1409-11.		- significant association between the number of *17 alleles	
		with one outcome measure for ADP-induced platelet	
	UM: A	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%).	
ref. 30	3	153 patients (111x *1/*1, 42x (*1/*2 or *2/*2)) received	Authors'
Aleil B et al.		clopidogrel 75 mg/day (n=95) or 150 mg/day (n=58)	conclusions:
CYP2C19*2		maintenance doses. Relevant co-medication was not	"Increasing the dose
polymorphism is		excluded. Poor responder definition: platelet activity index	of clopidogrel from
not the sole		> 69%. Platelet reactivity index was measured using the	75 to 150 mg/day in
determinant of the		VASP assay.	poor responders
response to		*1/*2 + *2/*2:	resulted in a signi-
clopidogrel:		- higher prevalence in the poor responders than in the	ficant decrease in
implications for its	IM + PM:	responders (S; 91% increase from 22% to 42%).	PRI. This effect was
monitoring.	D	- higher prevalence in the poor responders receiving 150	not significantly
J Thromb Haemost		mg/day than in the poor responders receiving 75 mg/day	different between
2009;7:1747-9.		(NS; 53% increase from 39% to 60%).	carriers of CYP2C19
		(*1/*2 + *2/*2) versus *1/*1:	*2 and non carriers,
		- higher risk of high platelet reactivity index (OR = 3.393 (S;	indicating that a
		95% CI 1.062-10.841)).	weak response was
		- significantly higher platelet reactivity index at 75 mg/day	easily overcome."
		(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 construed	
ref. 31	2	NOTE: Allele *2 was genotyped.	Authors'
	2	7 patients (1x *1/*1, 5x *1/*2, 1x *2/*2) with stent	
Pena A et al.		thrombosis and clopidogrel resistance on clopidogrel 75	conclusions:
Can we override	IM: D	mg/day. Definition of clopidogrel resistance: residual	"Our report shows
clopidogrel	PM: D	platelet aggregation $\geq$ 50% or P2Y <sub>12</sub> reaction unit $\geq$ 235 (or linkibition percentage $\leq$ 15%). Posidual platelet aggregation	that a strategy of an
resistance?		inhibition percentage $\leq$ 15%). Residual platelet aggregation	incremental increa-
Circulation		was measured using the LTA and 20 µM ADP, P2Y <sub>12</sub>	se in the clopidogrel maintenance dose
2009;119:2854-7.		reaction units using the VerifyNow assay.	
		100% of the patients remained resistant after treatment	in patients accumu-
		with a 900 mg clopidogrel loading dose and a 150 mg/day	lating clinical resis-
		clopidogrel maintenance dose for 3 weeks.	tance (stent throm-
1		Increase to 225 mg/day in six patients: 67% remained resistant.	bosis), biological resistance (high
			I CONSIGNICE (INGI)
			nlatelet aggrega
		Increase to 300 mg/day in four patients: 50% remained	platelet aggrega-
		Increase to 300 mg/day in four patients: 50% remained resistant, the other 50% discontinued treatment due to side	tion), and a genetic
		Increase to 300 mg/day in four patients: 50% remained resistant, the other 50% discontinued treatment due to side effects (gastric and joint symptoms).	tion), and a genetic profile of resistance
		Increase to 300 mg/day in four patients: 50% remained resistant, the other 50% discontinued treatment due to side	tion), and a genetic

ref. 31, continua-		3 months. Two patients were excluded from prasugrel	patients) is time
tion		treatment due to low body weight and age > 75 years	consuming and
		respectively.	minimally effective."
		NOTE: Allele *2 was genotyped.	
ref. 32	3	2485 patients (1805x *1/*1, 633x *1/*2, 47x *2/*2) received	Authors'
Sibbing D et al. Cytochrome P450		600 mg clopidogrel loading doses prior to placement of a coronary stent. Patients with bare metal stents (the	conclusions: "CYP2C19*2 carrier
2C19 loss-of-func-		majority) received clopidogrel maintenance doses for $\geq 30$	status is significantly
tion polymorphism		days. Patients who used oral anticoagulants within 1 week	associated with an
and stent thrombo- sis following percu-		or glycoprotein IIb/IIIa inhibitors within 2 weeks were excluded. Follow-up was performed for 30 days.	increased risk of ST following coronary
taneous coronary		(IM+PM) versus NM:	stent placement."
intervention.		- the cumulative incidence of stent thrombosis after stent	
Eur Heart J 2009;30:916-22.		placement increased from 0.4% to 1.5% (HR = 3.81 (S; 95% CI 1.45-10.02)). The *2 allele was an independent	
2000,00.010 22.		variable for the risk of stent thrombosis in a multi-variable	
		model (HR = 3.86 (S; 95% Cl 1.47-10.14)).	
		<ul> <li>the cumulative incidence of ST-elevation myocardial infarction increased from 0.5% to 1.5% (HR = 2.96 (S;</li> </ul>	
		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).	
	IM: E	*1/*1 versus *1/*2 versus *2/*2: - the risk of stent thrombosis increased with the number of	
	PM: E	*2 alleles (S; cumulative incidence: 0.4% versus 1.4%	
		versus 2.1%).	
		NOTE: Allele *2 was genotyped.	
ref. 33	3	92 patients with 1-4 revascularisations and at least 1 stent	Authors'
Brackbill ML et al. Frequency of		who had recurrent acute coronary syndrome while on clopidogrel therapy. The median duration of clopidogrel	conclusions: "The present data
CYP3A4, CYP3A5,		use until acute coronary syndrome was 6 months. Control	indicate that patients
CYP2C9, and CYP2C19 variant		group including 94 patients in a pharmacogenetic database not using clopidogrel. Only CYP3A inhibitors were	currently receiving clopidogrel therapy
alleles in patients		excluded.	who present with
receiving		Group with acute coronary syndrome on clopidogrel versus	repeat ACS do not
clopidogrel that experience repeat		the control group: - non-significant 39% increase in *2 allele frequency (NS;	have higher frequency of the
acute coronary	IM + PM:	from 11.4% to 15.8%).	examined variant
syndrome. Heart	AA	- no difference in the *3 allele frequency (NS; both 0%).	alleles compared to
Vessels 2009;24:73-8.		NOTE: Alleles *2 and *3 were genotyped.	a control group."
ref. 34	3	772 patients (525x *1/*1, 221x *1/*2, 26x *2/*2) received	Authors'
Giusti B et al.		clopidogrel 600 mg and acetylsalicylic acid 325 mg prior to	conclusions:
Relation of cyto- chrome P450 2C19		placement of a drug eluting stent, unfractionated heparin	"The CYP2C19*2 allele was associa-
loss-of-function		70 IU/kg and, if needed, glycoprotein IIb/IIIa inhibitors during the procedure, followed by clopidogrel 75 mg/day	ted with the occur-
polymorphism to		and acetylsalicylic acid 325 mg/day. Co-medication was	rence of ST or ST
occurrence of drug- eluting coronary		not excluded. Blood samples were taken 12-18 hours after	and cardiac mortali- ty in high-risk vascu-
stent thrombosis.		stent placement (or after 6 days if glycoprotein Ilb/Illa inhibitors had been administered). Follow-up was	lar patients on dual-
Am J Cardiol		performed for 6 months. Stent thrombosis was defined as	antiplatelet treat-
2009;103:806-11.		angiographically confirmed or probable stent thrombosis.	ment."
		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%).	

ref. 34, continua-	IM + PM:	- the incidence of cardiovascular death increased by 167%	
tion	IM: E PM: E	<ul> <li>(S; from 1.5% to 4.0%).</li> <li>the incidence of stent thrombosis and/or cardiovascular death increased by 123% (S; from 2.7% to 6.1%).</li> <li>the prevalence of the phenotype in patients with stent thrombosis was 73% higher (S; from 31.3% to 54.1%).</li> <li>the prevalence of the phenotype in patients with stent thrombosis and/or cardiovascular death was 66% higher (S; from 31.2% to 51.7%).</li> <li>median residual platelet aggregation increased by 13% (S; from 45% to 51%).</li> <li>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)).</li> <li>*1/*2 versus *1/*1:</li> <li>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%).</li> <li>*2/*2 versus *1/*1:</li> <li>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%).</li> <li>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%).</li> </ul>	
		*1/*2 and *2/*2; from 2.7% to 7.7%).	
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	<ul> <li>NOTE: Allele *2 was genotyped.</li> <li>259 patients &lt; 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</li> <li>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.</li> <li>*2 versus (no *2):</li> <li>incidence of the primary endpoint per 100 patient years increased from 2.89% to 10.90% (HR<sub>corr</sub> = 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)).</li> <li>incidence of myocardial infarction per 100 patient years increased from 1.58 to 7.27 (HR<sub>corr</sub> = 5.57 (S; 95% CI 1.94-16.01)).</li> <li>incidence of stent thrombosis per 100 patient years increased from 1.44 to 6.79 (HR<sub>corr</sub> = 6.04 (S; 95% CI 1.75-20.80)). All cases of stent thrombosis led to ST-elevation myocardial infarction.</li> <li>incidence of ischaemic events other than stent thrombosis per 100 patient years increased from 1.99 to 5.09 (HR<sub>corr</sub> = 3.31 (S; 95% CI 1.05-10.47)).</li> <li>non-significant increase in the incidence of cardiovascular death and the incidence of urgent revascularisation per </li> </ul>	Authors' conclusions: "The <i>CYP2C19*2</i> genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after myocardial infarc- tion."

rof 25 continue		100 notions voors (from 0.00 to 1.45 and from 1.05 to	
ref. 35, continua-		100 patient years (from 0.26 to 1.45 and from 1.05 to	
tion		<ul> <li>2.18 respectively) (NS).</li> <li>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)).</li> </ul>	
		(one *2) versus (no *2):	
		- the incidence of the primary endpoint increased by 243% (NS; from 5.9% to 20.3%).	
		<ul> <li>*2/*2 versus (no *2):</li> <li>the incidence of the primary endpoint increased by 276% (NS; from 5.9% to 22.2%).</li> </ul>	
		*3 and *4: - the results did not change on inclusion of *3 and *4 in the	
		analysis.	
	4	NOTE: Alleles *2-*6 were genotyped.	A utla a ma ?
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	<ul> <li>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.</li> <li>(IM+PM) versus (NM+UM):</li> <li>incidence of the primary endpoint increased from 8.0% to 12.1% (HR = 1.53 (S; 95% CI 1.07-2.19)).</li> <li>incidence of stent thrombosis increased from 0.4% to 2.0% (HR = 3.09 (S; 95% CI 1.40-16.37)).</li> <li>incidence of non-fatal myocardial infarction increased from 7.5% to 10.1% (NS).</li> <li>incidence of non-fatal stroke increased from 0.24% to 0.88% (NS).</li> <li>no difference in the incidence of bleeding (minor and major bleeding): from 3.0% to 2.9% (NS).</li> </ul>	Authors' conclusions: "Among persons treated with clopido- grel, carriers of a reduced-function CYP2C19 allele had a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncar- riers."
	*17: AA	<ul> <li>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:</li> <li>the AUC of the active metabolite decreased with decreasing gene dose for both loading doses and for the maintenance dose (NS).</li> <li>platelet aggregation decreased with decreasing gene dose for both loading doses and for the maintenance dose (NS).</li> <li>Loading dose of 300 mg versus 600 mg:</li> <li>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.</li> </ul>	
		genotyped.	

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

2008;6:1439-41.		from 58.3 to 41.5 ng.h/mL).	
		- platelet reactivity index increased by 23% (S, from 50.0 to	
ref. 39, continua- tion	IM: D	61.5%).	
		There was a significant correlation between platelet reactivity index and the AUC of the active metabolite.	
		NOTE: *17 was not determined.	
<b>ref. 40</b> Chen BL et al.	4	18 healthy men (6x NM, 6x IM (5x *1/*2, 1x *1/*3), 6x PM	Authors' conclusion: "CYP2C19*2 and
Inhibition of ADP-		(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	CYP2C19*3 genetic
induced platelet		alcohol were excluded. Platelet aggregation was measured	polymorphisms
aggregation by		using the LTA and 5 $\mu$ M ADP.	reduced clopidogrel inhibition of ADP-
clopidogrel is related to		PM versus NM:	induced platelet
CYP2C19 genetic	PM: D	- ADP-induced platelet aggregation 4, 24 and 72 hours after the first dose of clopidogrel decreased by 39%, 49%	aggregation, with
polymorphisms.	1 101. 0	and 42% respectively (S; from 49.0 to 29.7%; from 48.7	the degree of inhibi-
Clin Exp Pharmacol Physiol		to 25.0% and from 45.4 to 26.5% respectively).	tion dependent on the genetic polymor-
2008;35:904-8.		IM versus NM:	phism present."
		- no significant decrease in ADP-induced platelet aggregation 4, 24 and 72 hours after the first dose of	
		clopidogrel.	
	IM: AA	- 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.	
ref. 41	4	NOTE: *17 was not determined. 24 healthy volunteers (8x NM, 8x IM (6x *1/*2, 2x *1/*3), 8x	Authors' conclusion:
Kim KA et al.	4	PM (6x *2/*2, 2x *2/*3)) received clopidogrel 300 mg on	"From these findings
The effect of CYP-		day 1 and 75 mg/day on days 2-7. Co-medication, smoking	it is clear that the
2C19 polymor- phism on the phar-		and relevant foods were excluded. Platelet aggregation	CYP2C19 genotype affects the plasma
macokinetics and		was measured using the LTA and 5 μM ADP. PM versus NM:	levels of clopidogrel
pharmacodynamics		- AUC <sub>0-24h</sub> increased by 194% (S, from 10.20 to 29.98	and modulates the
of clopidogrel: a possible mecha-		ng.h/mL).	antiplatelet effect of
nism for clopidogrel		- maximum percentage inhibition of ADP-induced platelet	clopidogrel."
resistance.		aggregation decreased by 40% in the first 24 hours (S; from 64.1% to 38.3%) and by 37% during the 7 days (S;	
Clin Pharmacol Ther 2008;84:236-		from 64.7% to 40.8%).	
42.		- AUEC (area under the effect-time curve) decreased by	
	PM: D	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 <sub>0-24h</sub> increased by 67% (NS, from 10.20 to 17.02	
		ng.h/mL).	
		<b>o</b> ,	
		- maximum percentage inhibition of ADP-induced platelet	
		- 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;	
		- 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%).	
	IM: AA	<ul> <li>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%).</li> <li>AUEC (area under the effect-time curve) decreased by</li> </ul>	
	IM: AA	- 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%).	
	IM: AA	<ul> <li>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%).</li> <li>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).</li> </ul>	
	IM: AA	<ul> <li>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%).</li> <li>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).</li> <li>There was a significant negative correlation between</li> </ul>	
	IM: AA	<ul> <li>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%).</li> <li>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).</li> <li>There was a significant negative correlation between clopidogrel pharmacokinetics and inhibition of platelet</li> </ul>	
	IM: AA	<ul> <li>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%).</li> <li>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).</li> <li>There was a significant negative correlation between</li> </ul>	

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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	Authors' conclusion: "Coexisting, rather than single, poly- morphisms of diffe- rent genes may be related to persistent platelet activation while on clopidogrel, which raises con- cern about harm in patients with ACS."
<b>ref. 43</b> 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 percuta- neous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol 2008;51:1925-34.	4 IM + PM: D	determined, but it is very uncommon. 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 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, continua-	<u> </u>	maintonance doce (S: from 11.00/ to 22.00/ and from	
tion		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	3	603 patients with non-ST-elevation acute coronary	Authors' conclusion:
Frére C et al.		syndrome (435x NM, 143x IM (*1/*2) + 23x PM (*2/*2))	"The present data
Effect of cytochrome p450		received clopidogrel 600 mg and acetylsalicylic acid 250	suggest that the CYPC19*2 allele
polymorphisms on		mg at least 12 hours before coronary angiography. Blood	influences post-
platelet reactivity		samples were taken prior to coronary angiography.	treatment platelet
after treatment with		Glycoprotein IIb/IIIa antagonists before the study were excluded, but other co-medication was not. Residual	reactivity and clopi-
clopidogrel in acute		platelet aggregation was measured using the LTA and 10	dogrel response in
coronary syndrome.		$\mu$ M ADP, platelet reactivity index using the VASP assay.	patients with non-
Am J Cardiol		PM versus IM versus NM:	ST elevation acute
2008;101:1088-93.		- significant association between the number of *2 alleles	coronary syndro-
		with three outcome measures of ADP-induced platelet	mes."
	IM: D	activity:	
	PM: D	- 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	
	PM: D	(S, 133% increase)	
		IM:	
		- 25% of the responders versus 19% of the non-	
	IM: AA <sup>#</sup>	responders (S, 24% decrease)	
		NOTE: *17 was not determined. *3 was also not	
		determined, but it is very uncommon.	
ref. 45	3	81 patients (54x NM, 25x IM (*1/*2), 2x PM (*2/*2))	Authors' conclusion:
Fontana P et al.		received clopidogrel 600 mg prior to balloon angioplasty,	"The 2C19*2 allele
Biological effect of increased		followed by clopidogrel 75 mg/day for 15 days. 42 patients	did not influence clopidogrel respon-
maintenance dose		(25x  NM, 15x  IM (*1/*2), 2x  PM (*2/*2)) were poor	siveness in our
of clopidogrel in		responders (platelet reactivity index $\ge$ 50%) and received clopidogrel 150 mg on days 16-30. Co-medication was not	population of cardio-
cardiovascular		excluded. All patients except one used acetylsalicylic acid	vascular outpa-
outpatients and		100 mg/day at the start of the study. Platelet reactivity	tients."
influence of the		index was measured using the VASP assay.	
cytochrome P450		PM versus IM versus NM:	
2C19*2 allele on		- no significant difference in platelet reactivity index after	
clopidogrel		the first 15 days (NS; 50.9% versus 50.6% versus 66.1%)	
responsiveness. Thromb Res		- no significant difference in decrease in platelet reactivity	
2008;121:463-8.	IM: AA	index in the poor responders after 15 days of clopidogrel	
2000, 121.400-0.	PM: AA	150 mg/day (NS; 23.4% versus 18.0% versus 18.9%).	
		NOTE: *17 was not determined. *3 was also not	
		·	

		determined, but it is very uncommon.	
ref. 46 Giusti B et al. Cytochrome P450 2C19 loss-of-func- tion 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	Authors' conclusion: "This study demon- strates, 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."
<b>ref. 47</b> Brandt JT et al. Common poly- morphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmaco- dynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429-36.	3 PM: D IM: D IM + PM: D	<ul> <li>determined, but it is very uncommon.</li> <li>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.</li> <li>PM versus IM versus NM: <ul> <li>there was a significant association between the *2 allele and AUC<sub>0-24h</sub> of the active metabolite (26.9 versus 41.5 versus 76.2 ng.h/mL).</li> <li>there was a significant association between the *2 allele and inhibition of platelet aggregation (3.8 versus 20.3 versus 39.1%).</li> </ul> </li> <li>IM + PM versus NM: <ul> <li>the percentage of poor responders (inhibition of platelet aggregation &lt; 20%) increased by 76% (S; from 41.4% to 72.2%).</li> </ul> </li> </ul>	Authors' conclusion: "The common loss of function polymor- phisms of CYP2C19 and CYP2C9 are associated with decreased exposure to the active meta- bolite of clopidogrel but not prasugrel. Decreased exposu- re to its active meta- bolite is associated with a diminished pharmacodynamic response to clopi- dogrel."
<b>ref. 48</b> 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	<ul> <li>NOTE: *17 was not determined.</li> <li>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.</li> <li>IM versus NM: <ul> <li>residual platelet aggregation on day 8 was increased by 32% (S; from 36.8% to 48.5%).</li> <li>*2 allele: <ul> <li>highest percentage of IM in the quartile of the highest platelet aggregation and lowest percentage in the quartile</li> </ul> </li> </ul></li></ul>	Authors' conclusion: "This study points out the CYP2C19 (*1/*2) polymor- phism as a candi- date in the explana- tion of clopidogrel poor responsive- ness as we replicate our previous fin- dings in a larger,

rof 49 continue		of the lowest platelet - non-notion (0, 47,00)	indonordant -t
ref. 48, continua- tion		<ul> <li>of the lowest platelet aggregation (S; 47.8% versus 30.4% versus 25% versus 8.3% for quartiles 1 to 4).</li> <li>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.</li> <li>NOTE: *17 was not determined. *3 was also not</li> </ul>	independent study population. The CYP2C19 (*1/*2) explained 10% of the observed varia- bility in clopidogrel responsiveness."
		determined, but it is very uncommon.	
ref. 49 Hulot JS et al. Cytochrome P450 2C19 loss-of-func- tion polymorphism is a major determi- nant of clopidogrel responsiveness in healthy subjects. Blood 2006;108:2244-7.	4 IM: D	<ul> <li>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.</li> <li>IM versus NM: <ul> <li>residual platelet aggregation on day 7 was increased by 47% (S; from 48.9% to 71.8%).</li> <li>platelet reactivity index on day 7 was increased by 36% (S; from 42.9% to 58.2%).</li> </ul> </li> <li>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.</li> <li>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).</li> </ul> <li>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.</li>	Authors' conclusion: "The CYP2C19*2 loss-of-function allele is associated with a marked decrease in platelet responsiveness to clopidogrel in young healthy male volun- teers and may therefore be an important genetic contributor to clopi- dogrel resistance in the clinical setting."
<b>ref. 50</b> FDA Drug Safety Communication: Reduced effective- ness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. 03-12-10.	0 PM: A	<ul> <li>NOTE: *17 was not determined.</li> <li>Warning 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: <ul> <li>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.</li> <li>inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function. <ul> <li>advise healthcare professionals to consider use of other platelet aggregation inhibitors or alternative Plavix doses in patients identified as poor metabolisers.</li> </ul> Additional information for healthcare professionals 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.</li></ul></li></ul>	
ref. 51	0	<u>Warning</u> : In patients who are poor CYP2C19 metabolisers,	
SmPC Plavix (clopi-	-	clopidogrel at recommended doses forms less of the active	
dogrel) 26-04-18.	PM: D	metabolite of clopidogrel and has a smaller effect on plate- let function. Tests are available to identify a patient's CYP- 2C19 genotype.	

ref. 51, continua-	Pharmacokinetic properties:	
tion	CYP2C19 is involved in the formation of both the active	
	metabolite and the 2-oxo-clopidogrel intermediate metabo-	
	lite. Clopidogrel active metabolite pharmacokinetics and	
	antiplatelet effects, as measured by ex vivo platelet aggre-	
	gation 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 metabo-	
	lisers, 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 $\mu$ M	
	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 recei-	
	ved the 600 mg/150 mg regimen, active metabolite expo-	
	sure 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 regi-	
	men. An appropriate dose regimen for this patient popula-	
	tion has not been established in clinical outcome trials.	
	Consistent with the above results, in a meta-analysis inclu-	
	ding 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 $\mu$ M ADP) was decreased with differences in IPA of 5.9%	
	and 21.4%, respectively, when compared to normal meta-	
	bolisers. 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), CHA-	
	RISMA (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 metabo-	
	lisers.	
	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	

		difference	s in outcome ir	n poor me	etabolise	rs			
ref. 52	0	Boxed wa		- poor me					
SmPC Plavix (clopi-	0	-	WARNING: DIMINISHED ANTIPLATELET EFFECT IN						
dogrel), USA, 10-			S WITH TWO L						
11-18.			CYP2C19 GEN						
		- 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, princi-							
		pally CY			430 (011	) syster	n, princi-		
			recommended	dococ f	orme loca	of the a	otivo		
			ite and so has a						
			its who are hon						
	PM: D		YP2C19 gene,						
	1 WI. D	zers").	TT 2019 gene,	(termed	011 20	19 0001	netaboli-		
			e available to ic	lentify na	atients wi	no are C	VP2C19		
			tabolisers.	ionary pe			11 2010		
			r use of anothe	r nlatelet	P2Y12 i	nhihitor i	n		
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		Warning:		11 2010	poor me		0.		
			d antiplatelet a	ctivitv in	patients	with imp	aired		
		CYP2C19							
			el is a prodrug.	Inhibitio	n of plate	elet addre	egation		
			ogrel is achieve						
			bolism of clopid	•					
			ed by genetic v				ito ouri		
		Pharmaco				••••			
			el active metab	olite pha	rmacokir	netics an	d anti-		
			fects, as measi	-					
			/s, differ accord	•	•	-			
			vho are homozy						
			C19 gene are t	-					
		zers." Ap	proximately 2%	of White	and 4%	of Black	patients		
		are poor i	netabolizers; th	e prevale	ence of p	oor meta	abolism		
		is higher i	n Asian patient	s (e.g., 1	4% of Cl	ninese). <sup>-</sup>	Tests		
		are availa	ble to identify p	atients w	/ho are C	YP2C19	) poor		
		metaboliz	ers.						
		A crossov	er study in 40 ł	nealthy s	ubjects, '	10 each i	in the		
			2C19 metaboliz						
			d antiplatelet re	•	•	•			
			per day and 60						
			a total of 5 days						
			and diminished						
			erved in the poo	or metabo	olizers as	s compar	ed to		
		the other			A	+ D -			
			abolite Pharmacok Metabolizer Status		Antiplatele	et Respons	es by		
		011 2010	dose	UM <sup>†</sup>	NM	IM*	PM		
				(n=10)	(n=10)	(n=10)	(n=10)		
		C <sub>max</sub> (ng/mL)	300 mg (24 hr)	24 (10)	32 (21)	23 (11)	11 (4)		
		(19/11L)	600 mg (24 hr)	36 (13)	44 (27)	39 (23)	17 (6)		
			75 mg (day 5)	12 (6)	13 (7)	12 (5)	4 (1)		
			150 mg (day 5)	16 (9)	19 (5)	18 (7)	7 (2)		
		IPA (%) <sup>‡</sup>	300 mg (24 hr)	40 (21)	39 (28)	37 (21)	24 (26)		
			600 mg (24 hr)	51 (28)	49 (23)	56 (22)	32 (25)		
			75 mg (day 5)	56 (13)	58 (19)	60 (18)	37 (23)		
			150 mg (day 5)	68 (18)	73 (9)	74 (14)	61 (14)		
		VASP-	300 mg (24 hr)	73 (12)	68 (16)	78 (12)	91 (12)		
		PRI (%)§	600 mg (24 hr)	51 (20)	48 (20)	56 (26)	85 (14)		
			75 mg (day 5)	40 (9)	39 (14)	50 (16)	83 (13)		
			150 mg (day 5)	20 (10)	24 (10)	29 (11)	61 (18)		
								L	

ref. 52, continua- tion
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AA<sup>#</sup>: 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</u> intervention (ticagrelor or prasugrel):

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  $\geq$  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<sub>12</sub> 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  $\leq$  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  $\geq$  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 clopido-grel 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 1year 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 genotypeguided 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. Reducedfunction 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<sub>12</sub> 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  $\pm$  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. Pharmaco-genomics 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  $\in$  2547 versus  $\in$  2799 in the IM+PM patients. In addition, calculations were based on costs of genetic testing of  $\in$  63.0, costs of hospitalisation of  $\notin$  200.0/day, costs of single repeat percutaneous coronary intervention of  $\notin$  1000.0, costs of vascular operation of  $\notin$  4400.0 and costs of rehabilitation of  $\notin$  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  $\in$  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  $\in$  9,111 per Quality Adjusted Life-Year (QALY) gained ( $\in$  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  $\in$  9,792/QALY gained ( $\in$  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  $\in$  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<sub>12</sub> 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<sub>12</sub> reaction sub-units were treated with clopidogrel 75 mg/day. P2Y<sub>12</sub> 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  $\pm$  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  $\pm$  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 genotypeguided 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-tohigh 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  $\geq$  45% or at clopidogrel costs of  $\geq$  \$ 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 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-	PM	4 F	yes	yes	23 December 2019
genetics Working	IM	4 F	yes	yes	]
Group decision	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<sub>12</sub>).

#### 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.	6-10 +
Essential		0-10 +
	Genotyping must be performed before drug therapy has been initiated to	
	guide drug and dose selection	

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

Clin	Clinical Implication Score Criteria		Given
		Score	Score
Clin	ical 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)	++	++
Lev	el of evidence supporting the associated clinical effect grade ≥ 3		
•	One study with level of evidence score $\geq 3$	+	
•	Two studies with level of evidence score $\geq 3$	++	
•	Three or more studies with level of evidence score $\geq 3$	+++	+++
Nur	nber needed to genotype (NNG) in the Dutch population to prevent one clinical effect		
gra	de ≥ 3		
•	100 < NNG ≤ 1000	+	
•	10 < NNG ≤ 100	++	++
•	NNG ≤ 10	+++	
PG	c 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+		10+	8+
Cor	responding Clinical Implication Score:	1	Essential