CYP2C19: ticagrelor 3515 to 3517

ADP = adenosine diphosphate, EM = extensive metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), HR = hazard ratio, HR_{corr} = corrected hazard ratio, IM = intermediate metaboliser (*1/*2, *1/*3, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), LTA = light transmission aggregometry, OR = odds ratio, PCI = percutaneous coronary intervention, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), UM = ultra-rapid metaboliser (*17/*17) (increased CYP2C19 enzyme activity), VASP = vasodilator-stimulated phosphoprotein assay, VerifyNow assay = an aggregation assay that measures the extent to which the platelet ADP receptor ($P2Y_{12}$) can be stimulated.

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:
Ticagrelor is primarily converted by CYP3A4 to an active metabolite.
None of three included studies found an effect of CYP2C19 gene variants on ticagrelor efficacy (Rath 2015, Tantry 2010, Wallentin 2010). The KNMP pharmacogenetics working group decided that there is no interaction between CYP2C19 and ticagrelor, and thus no therapy adjustment required in patients with a CYP2C19 gene variant (no/no-interactions).
You can find a overview of the investigated effects in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background text via your pharmacy or physician electronic decision support system.
Note: The other four studies included in the risk analysis suggest ticagrelor to be a suitable alternative for clopidogrel, at least for CYP2C19 PM (Zhong 2018, Shen 2016, Xiong 2015, Steg 2013).

The table below uses the KNMP nomenclature for EM, PM, IM and UM. As a result, the definitions of EM, PM, IM and UM in the table below can differ from the definitions used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Zhong Z et al. Effect of cytochrome P450 2C19 polymorphism on adverse cardiovascular events after drug-eluting stent implantation in a large Hakka population with acute coronary syndrome receiving clopidogrel in southern China. Eur J Clin Pharmacol 2018;74:423-31. PubMed PMID: 29243114.	3	934 patients with acute coronary syndrome receiving percutaneous coronary intervention and second generation drug eluting stent implantation were treated with CYP2C19 genotype-guided dual antiplatelet therapy for at least 1 year. All patients received a 300- or 600-mg loading dose of clopidogrel and a 300-mg dose of aspirin prior to percutaneous coronary intervention. Thereafter, EM were treated with clopidogrel 75 mg daily, IM with clopidogrel 150 mg daily and PM with ticagrelor 90 mg twice daily. All patients received acetylsalicylic acid 100 mg daily. Major adverse cardiovascular events were defined as cardiovascular death, non-fatal myocardial infarction, target vessel revascularization, or non-fatal stroke. Concomitant oral anticoagulant therapy was excluded, but other relevant co-medication was not. Before percutaneous coronary intervention, the percentage of patients with a single vascular lesion was significantly higher for PM than for EM and IM, and the percentage of patients using a statin was significantly	Authors' conclusion: "Based on the genotype-guided antiplatelet therapy, there was no significant association between the carrier status and the clinical outcome at 1, 6, and 12 months. In addition, no significant difference in the rates of bleeding was found among the three groups."

<table>
<tr>
<td>ref. 1, continuation</td>
<td>PM on ticagrelor versus EM on clopidogrel: AA</td>
<td>higher for EM than for IM and PM.

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

Results:
Percentage of patients with adverse events for PM on ticagrelor versus IM on clopidogrel 150 mg/day versus EM on clopidogrel 75 mg/day:
<table>
<tr><th></th><th></th><th>PM+tica versus IM+150 clopi versus EM+75 clopi</th><th>value for EM</th></tr>
<tr><td rowspan="3">major adverse cardiovascular events</td><td>1 month</td><td>NS</td><td>2.7%</td></tr>
<tr><td>6 months</td><td>NS</td><td>10.9%</td></tr>
<tr><td>12 months</td><td>NS</td><td>14.1%</td></tr>
<tr><td rowspan="3">death</td><td>1 month</td><td>NS</td><td>0.53%</td></tr>
<tr><td>6 months</td><td>NS</td><td>0.53%</td></tr>
<tr><td>12 months</td><td>NS</td><td>0.80%</td></tr>
<tr><td rowspan="3">non-fatal myocardial infarction</td><td>1 month</td><td>NS</td><td>0.27%</td></tr>
<tr><td>6 months</td><td>NS</td><td>1.3%</td></tr>
<tr><td>12 months</td><td>NS</td><td>1.6%</td></tr>
<tr><td rowspan="3">target vessel revascularisation</td><td>1 month</td><td>NS</td><td>1.9%</td></tr>
<tr><td>6 months</td><td>NS</td><td>9.0%</td></tr>
<tr><td>12 months</td><td>NS</td><td>11.1%</td></tr>
<tr><td rowspan="3">stroke</td><td>1 month</td><td>NS</td><td>0%</td></tr>
<tr><td>6 months</td><td>NS</td><td>0%</td></tr>
<tr><td>12 months</td><td>NS</td><td>0.53%</td></tr>
<tr><td rowspan="3">bleeding events</td><td>1 month</td><td>NS</td><td>3.5%</td></tr>
<tr><td>6 months</td><td>NS</td><td>7.2%</td></tr>
<tr><td>12 months</td><td>NS</td><td>9.6%</td></tr>
</table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese patient group.</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Shen DL et al.
Clinical value of CYP2C19 genetic testing for guiding the antiplatelet therapy in a Chinese population.
J Cardiovasc Pharmacol 2016;67:232-6.
PubMed PMID: 26727381.</td>
<td>3</td>
<td>After successful percutaneous coronary intervention, 628 coronary artery disease patients were treated with either genotype-guided therapy (n = 309) or with clopidogrel 75 mg/day once daily (n = 319). Genotype-guided therapy consisted of ticagrelor 90 mg twice daily for PM, clopidogrel 150 mg/day for IM and clopidogrel 75 mg/day for EM. All patients were treated with loading doses of acetylsalicylic acid 300 mg and clopidogrel 600 mg before percutaneous coronary intervention, unless they had already received these antiplatelet medications. In the perioperative period, patients were treated with heparin and low molecular weight heparin, according to 2012 Chinese PCI Guidelines. All patients received optimal pharmaceutical therapy for secondary prevention of coronary artery disease. Patients were followed for 12 months.
The outcome major adverse cardiovascular events was defined as the composite of death from any cause, myocardial infraction, or target vessel revascularisation. Multivariate logistic regression analysis was used to identify independent factors for this outcome.
Bleeding events were classified as in the GUSTO trial. All bleeding events were mild.</td>
<td>Authors' conclusion: 'Individual antiplatelet therapy guided by CYP-2C19 genetic testing significantly reduced the rate of major adverse cardiovascular events without an increase in the rate of bleeding in the near term in this Chinese population.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>Genotype-guided therapy versus clopidogrel 75 mg/day: AA#</td>
<td>Co-medication interacting with clopidogrel was excluded, but co-medication interacting with ticagrelor (CYP3A inhibitors or inducers) was not.

Genotyping of the genotype-guided group:
- 133x EM
- 139x IM
- 37x PM

Results:
<table>
<tr><td colspan="4">Results for genotype-guided therapy compared to clopidogrel 75 mg/day for all:</td></tr>
<tr><td></td><td></td><td>genotype-guided therapy</td><td>value for clopidogrel 75 mg/day for all (% of patients)</td></tr>
<tr><td rowspan="3">death, myocardial infarction or target vessel revascularisation</td><td>1 month</td><td>OR = 0.20 (95% CI: 0.06-0.68) (S)</td><td>5.6%</td></tr>
<tr><td>6 months</td><td>OR = 0.40 (95% CI: 0.17-0.96) (S)</td><td>7.8%</td></tr>
<tr><td>12 months</td><td>OR = 0.42 (95% CI: 0.20-0.91) (S)</td><td>9.4%</td></tr>
<tr><td rowspan="3">death</td><td>1 month</td><td>NS</td><td>0.9%</td></tr>
<tr><td>6 months</td><td>NS</td><td>1.6%</td></tr>
<tr><td>12 months</td><td>NS</td><td>2.5%</td></tr>
<tr><td rowspan="3">myocardial infarction</td><td>1 month</td><td>x 0.21 (S)</td><td>2.8%</td></tr>
<tr><td>6 months</td><td>trend for a decrease (p = 0.05) (NS)</td><td>3.8%</td></tr>
<tr><td>12 months</td><td>trend for a decrease (p = 0.065) (NS)</td><td>4.1%</td></tr>
<tr><td rowspan="3">target vessel revascularisation</td><td>1 month</td><td>NS</td><td>1.9%</td></tr>
<tr><td>6 months</td><td>NS</td><td>2.5%</td></tr>
<tr><td>12 months</td><td>NS</td><td>2.8%</td></tr>
<tr><td rowspan="3">bleeding events</td><td>1 month</td><td>NS</td><td>3.4%</td></tr>
<tr><td>6 months</td><td>NS</td><td>5.0%</td></tr>
<tr><td>12 months</td><td>NS</td><td>6.0%</td></tr>
<tr><td colspan="4">The percentage of patients with death, myocardial infarction or target vessel revascularisation and the percentage of patients with bleeding events did not differ between PM on ticagrelor 90 mg twice daily, IM on clopidogrel 150 mg/day and EM on clopidogrel 75 mg/day (NS).</td></tr>
</table>

NOTE: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Xiong R et al.
A randomized controlled trial to assess the efficacy and safety of doubling dose</td>
<td>3</td>
<td>224 PM with acute coronary syndrome were treated with either ticagrelor (n = 112; loading dose 180 mg, 90 mg twice daily thereafter) or with double dose clopidogrel (n = 112; loading dose 600 mg, 150 mg daily thereafter) for 30 days. All patients received acetylsalicylic acid 75 mg daily. Patients with percutaneous coronary intervention were excluded.</td>
<td>Authors' conclusion: 'In CYP2C19*2 carriers with acute coronary syndrome, ticagrelor is as effective as high clopidogrel in reducing platelet reactivity, parti-</td>
</tr>
</table>

<table>
<tr>
<td>clopidogrel versus ticagrelor for the treatment of acute coronary syndrome in patients with CYP2C19*2 homozygotes.
Int J Clin Exp Med 2015;8:13310-6.
PubMed PMID: 26550258.

ref. 3, continuation</td>
<td>Ticagrelor versus double dose clopidogrel:
PM: AA#</td>
<td>No patient had a major adverse cardiovascular event or a major bleeding event.
Platelet reactivity (P2Y12 reaction units (PRU) and percent inhibition) were measured with the VerifyNow $P2Y_{12}$ assay.
Relevant co-medication was not excluded.

Results:
<table>
<tr><td colspan="4">Results for ticagrelor compared to double dose clopidogrel:</td></tr>
<tr><td></td><td></td><td>ticagrelor</td><td>value for double dose clopidogrel</td></tr>
<tr><td rowspan="3">platelet reactivity (P2Y12 reaction units)</td><td>before treatment</td><td>NS</td><td>283.2</td></tr>
<tr><td>15 days</td><td>x 0.45 (S)</td><td>76.6</td></tr>
<tr><td>30 days</td><td>x 0.70 (S)</td><td>39.8</td></tr>
<tr><td colspan="2">% of patients with mild bleeding</td><td>HR = 0.35 (95% CI: 0.16-0.75) (S)</td><td>20.5%</td></tr>
</table>
</td>
<td>cularly in first days.
This study suggests that ticagrelor may be much better than doubling dose clopidogrel in patients with CYP-2C19*2 in according to platelet reactivity monitoring.’</td>
</tr>
<tr>
<td>ref. 4
Rath PC et al.
A study on the impact of CYP2C19 genotype and platelet reactivity assay on patients undergoing PCI.
Indian Heart J 2015;67:114-21.
PubMed PMID: 26071289.</td>
<td>3

PM: AA
IM: AA
*17: AA</td>
<td>100 patients with acute coronary syndrome undergoing percutaneous coronary intervention were treated with ticagrelor. In addition, 50 patients were treated with clopidogrel.
The platelet reactivity index (PRI) was used as a measure of platelet reactivity. The PRI is based on the VASP phosphorylation in the activated and inactivated states of the $P2Y_{12}$ receptor. The authors indicate that PRI > 50% implies significant platelet reactivity and PRI < 16% implies significant bleeding risk.
Relevant co-medication was not excluded.

Genotyping:
ticagrelor:
- 20x *1/*17+UM
- 17x *1/*1
- 43x IM
- 20x PM

clopidogrel:
- 5x *1/*17+UM
- 10x *1/*1
- 30x IM
- 5x PM

Results:
<table>
<tr><td>Platelet reactivity index on ticagrelor for PM versus IM versus *1/*1 versus *1/*17+*17/*17:</td></tr>
<tr><td>NS</td></tr>
<tr><td>For clopidogrel, an effect of the CYP2C19 genotype on the platelet reactivity index was observed.</td></tr>
</table>
<table>
<tr><td colspan="3">Results for ticagrelor compared to clopidogrel:</td></tr>
<tr><td></td><td>ticagrelor</td><td>value for clopidogrel</td></tr>
<tr><td>platelet reactivity index (PRI)</td><td>x 0.70</td><td>22.2% for EM+UM</td></tr>
<tr><td>% of patients with PRI indicating bleeding risk (PRI < 16%)</td><td>x 3.35</td><td>20%</td></tr>
<tr><td>% of patients with optimal PRI (16-50%)</td><td>x 0.70</td><td>44%</td></tr>
<tr><td>% of patients with high</td><td>x 0.06</td><td>36%</td></tr>
</table>
</td>
<td>Authors’ conclusion:
‘By having the platelet reactivity assay, one can be safely maintained on clopidogrel in non-carriers, or with increased dose of clopidogrel in intermediate metabolizers or with newer drugs such as ticagrelor or prasugrel in poor metabolizers. Patients on ticagrelor and prasugrel identified as non-carriers of gene mutations for clopidogrel metabolism could be offered clopidogrel resulting in economic benefits to the patients.’</td>
</tr>
</table>

ref. 4, continuation		on treatment platelet reactivity (PRI > 50%) | | | Significance of the differences was not determined. The authors indicated that about 40% of patients on ticagrelor were recommended a change to clopigogrel due to bleeding risk (i.e. non-PM with PRI < 16 on ticagrelor). In addition, another 34% of the patients could be changed to clopidogrel because of economic reasons (i.e. non-PM with PRI 16-50% on ticagrelor). The authors indicated that about 72% of patients on clopidogrel did not need to change the medication. NOTE: Genotyping was for *2, *3 and *17. These are the most important gene variants in this Indian population.	
ref. 5 Steg PG et al. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: an analysis from the prospective, randomized PLATO trial. Circulation 2013;128:1055-65. PubMed PMID: 23900047.	4 ticagrelor versus clopidogrel: AA[#]	Data from 5990 genotyped patients with at least 1 intracoronary stent (3018 on ticagrelor and 2972 on clopidogrel) from Wallentin 2010 were analysed. The total number of patients with at least 1 intracoronary stent on ticagrelor was 5640 and on clopidogrel was 5649. 88% of the patients underwent stenting during the trial, while 12% had a stent implanted before the trial. The median follow-up was 11.8 months. 1.6% of patients developed definite stent thrombosis. In the patients undergoing stenting during the trial, 59% of definite stent thromboses occurred in the subacute phase (from 24 hours to 30 days after PCI), 24% in the late phase (more than 30 days after PCI) and 17% in the acute phase (within 24 hours after PCI). Stent thrombosis increased the incidence of all-cause death with a factor of 95-170 and the incidence of major bleeding with a factor of 3-5, the latter probably related to treatment of stent thrombosis. Multivariate analysis was used to identify independent predictors of stent thrombosis. Relevant co-medication was not excluded, but multivariate analysis corrected for drug-eluting versus bare metal stents, acetylsalicylic acid dose at randomisation, clopidogrel dose pre-randomisation, total clopidogrel before randomisation and on day 1, and the use of glycoprotein IIb/IIIa at randomisation. Results: Percentage of with definite stent thrombosis for ticagrelor compared to clopidogrel (1.93% of patients): HR_{corr} = 0.65 (95% CI: 0.48-0.88) (S) The reduction in definite stent thrombosis for ticagrelor compared to clopidogrel was consistent, with no statistical interaction with the CYP2C19 genetic status (IM+PM compared to EM+UM). Neither for IM+PM nor for EM+UM, the hazard ratio of the incidence of stent thrombosis for ticagrelor compared to clopidogrel reached statistical significance (NS). NOTE: The authors did not investigate the significance of the incidence of definite stent thrombosis in IM+PM compared to EM+UM in ticagrelor. However, the numerical increase in definite stent thrombosis in IM+PM compared to EM+UM was similar for ticagrelor and clopidogrel in this study (increase by a factor of 1.50 for ticagrelor and a factor of 1.56 for clopidogrel).	Authors' conclusion: 'Ticagrelor reduced stent thrombosis compared with clopidogrel across all definitions: definite, definite or probable, and definite, probable, and possible. The reduction in definite stent thrombosis was consistent regardless of acute coronary syndrome type, presence of diabetes mellitus, stent type (drug-eluting or bare metal stent), CYP2C19 genetic status, loading dose of aspirin, dose of clopidogrel before randomization, and use of glycoprotein IIb/IIIa inhibitors at randomization.'

ref. 5, continuation		NOTE: Despite mentioning data on major bleeding before stent thrombosis, the authors did not investigate the significance of the higher incidence for ticagrelor (8.44 major bleeding events per 100 patient-years) compared to clopidogrel (6.77 major bleeding events per 100 patient-years). NOTE: Genotyping was for *2-*8 and *17. These are the most important gene variants in this patient group from Europe or Israel.	
ref. 6 Tantry US et al. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. Circ Cardiovasc Genet 2010;3:556-66.	3 PM: AA IM: AA *17: AA	92 patients with coronary artery disease (50x EM (28x *1/*1, 22x *1/*17), 35x IM (20x *1/*2, 1x *1/*3, 13x *2/*17, 1x *8/*17), 2x PM (both *2/*2), 5x UM) were treated with ticagrelor (loading dose 180 mg, followed by 90 mg 2x daily for 6 weeks or 12-16 days) in combination with acetylsalicylic acid 75-100 mg/day. Relevant co-medication was not excluded. Inhibition of platelet aggregation was measured after the loading dose and at the end of the maintenance period. The remaining platelet aggregation was measured using LTA and 5 and 20 µM ADP, the platelet reactivity index was measured using the VASP assay and the $P2Y_{12}$ reaction sub-units were measured using the VerifyNow assay. Three genotype groups were compared to each other: - *1/*1 versus IM versus PM versus (UM + *1/*17) - (EM+UM) versus (IM+PM) - *1/*1 versus (IM+PM) versus (UM + *1/*17) No significant effect of the genotype on the inhibition of platelet aggregation was found within any of the three genotype groups following the loading dose or maintenance dose, as measured using the four methods described above. NOTE: The study design and size were marginally suitable for demonstrating an effect of the CYP2C19 genotype. For 82 patients treated with clopidogrel (loading dose 600 mg, followed by 75 mg/day) in combination with acetylsalicylic acid 75-100 mg/day, the same study only found significant effects on the genotype for all measurements using the VerifyNow assay, for 3 measurements using the VASP assay ((EM+UM) versus (IM+PM) following both the loading dose and the maintenance dose and *1/*1 versus (IM+PM) versus (UM + *1/*17) following the maintenance dose) and for 1 measurement using LTA and 20 µM ADP ((EM+UM) versus (IM+PM) following the maintenance dose). NOTE: Alleles *2 to *8 and *17 were genotyped.	Authors' conclusion: "Whereas CYP2C19 genotype influenced the anti-platelet effect of clopidogrel, there was no effect of CYP2C19 genotype during ticagrelor therapy."
ref. 7 Wallentin L et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute corona-	4	4,938 patients with acute coronary syndromes, of whom 64% underwent a percutaneous coronary stent placement during the study (3,286x EM (1,849x *1/*1, 1,437x *1/*17), 1,263x IM (894x *1/*2-*8, 369x *2-*8/*17), 121x PM, 268x UM) were treated with ticagrelor (loading dose 180 mg, followed by 90 mg 2x daily for a median 277 days). Relevant co-medication was not excluded, but comparisons were corrected for the use of proton pump inhibitors and acetylsalicylic acid dose.	Authors' conclusion: "We did not record any evidence of interaction of the CYP2C19 genotype group in patients on ticagrelor, with almost identical ischaemic event rates between patients with and

ry syndromes: a genetic substudy of the PLATO trial. Lancet 2010;376:1320-8. **ref. 7, continuation**	IM+PM: AA	(IM + PM) versus (EM + UM): - no difference in the percentage of patients with the primary measure of outcome "cardiovascular death, myocardial infarction or stroke" (both 8.3%) NOTE: The study design and size were marginally suitable for demonstrating an effect of the CYP2C19 genotype. For 4,904 patients treated with clopidogrel (loading dose 300-600 mg, followed by 75 mg/day), the percentage of patients with cardiovascular death, myocardial infarction or stroke was a factor 1.14 higher for IM + PM than for EM + UM (10.7 versus 9.4%), but this difference was not significant. However, during the first 30 days of treatment, a significantly higher incidence of ischaemic events was found for IM + PM than for EM + UM. In addition to this, a significantly higher risk of bleeding was found for UM + *1/*17 for clopidogrel. NOTE: Alleles *2 to *8 and *17 were genotyped.	without any loss-of-function allele."
ref. 8 SPC Brilique (ticagrelor) 30-05-17.	0 ticagrelor versus clopidogrel: IM: AA# PM: AA# IM: E PM: E	Pharmacodynamics: PLATO genetic substudy CYP2C19 and ABCB1 genotyping of 10,285 patients in PLATO provided associations of genotype groups with PLATO outcomes. The superiority of ticagrelor over clopidogrel in reducing major CV events was not significantly affected by patient CYP2C19 or ABCB1 genotype. Similar to the overall PLATO study, total PLATO Major bleeding did not differ between ticagrelor and clopidogrel, regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO Major bleeding was increased with ticagrelor compared clopidogrel in patients with one or more CYP2C19 loss of function alleles, but similar to clopidogrel in patients with no loss of function allele.	
ref. 9 SPC Brilinta (ticagrelor), USA, 09-03-18.	0 IM: AA PM: AA	Pharmacogenetics: In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the Brilinta arm did not depend on CYP2C19 loss of function status.	

Risk group	--

Comments:

- For the period after 2010, only studies with at least 20 PM on ticagrelor were included. Smaller studies did not add enough to the evidence.
- Cost-effectiveness:
  - Wang Y et al. Cost-effectiveness of cytochrome P450 2C19 *2 genotype-guided selection of clopidogrel or ticagrelor in Chinese patients with acute coronary syndrome. Pharmacogenomics J 2018;18:113-120. PubMed PMID: 28117433.
    In 60-year old Chinese patients with acute coronary syndrome and percutaneous coronary intervention, universal ticagrelor use was cost-effective compared with universal clopidogrel (i.e. costs were US dollar (USD) 7254 and thus less than USD 42,423 per quality-adjusted life year (QALY) gained), but genotype-guided treatment was both more effective and cheaper. Genotype-guided treatment consisted of clopidogrel for EM 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 null allele carrier frequency used in the calculations was 44.2%. This is much higher than the 25% carrier frequency in Dutch Caucasians.

Cost-effectiveness analysis was from the Hong Kong health-care provider's perspective. Direct medical costs were calculated for treatment with clopidogrel or ticagrelor for 1 year, followed by life-long costs (25 years) after this treatment. Patients received dual antiplatelet treatment (either ticagrelor or clopidogrel in combination with aspirin) during the first year, followed by aspirin monotherapy in subsequent years. Ticagrelor was given in a loading dose of 180 mg followed by a 90 mg dose twice a day. Clopidogrel was given in a loading dose of 300 mg followed by a 75 mg dose daily. All model inputs and key assumptions were derived from published clinical trials (Nakamura M et al. Clinical outcome after acute coronary syndrome in Japanese patients: an observational cohort study. J Cardiol 2010;55:69-76 and Chen Z et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. Stroke 2000;31:1240-9) and published decision-analytic models (Nikolic E et al. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. Eur Heart J 2012;34: 220-8 and Lala A et al. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis. J Thromb Haemost 2013;11:81-91). The 1-year decision tree included the following events: nonfatal myocardial infarction, nonfatal stroke, stent thrombosis, fatal bleeding, and death from vascular or nonvascular causes. For treatment of all patients with clopidogrel the costs per patient were USD 5229 and the number of QALYs was 5.65, for genotype-guided treatment the costs were USD 5647 and the number of QALYs 5.81, and for treatment of all patients with ticagrelor the costs were 6056 and the number of QALYs 5.77. The calculation was based on clopidogrel costs of USD 43 per month, ticagrelor costs of USD 1029 per month, a genetic test price of USD 200, costs of no-event of USD 307, costs of myocardial infarction of USD 9323, post-myocardial costs of USD 590, costs of stroke of USD 3135, post-stroke costs of USD 627, costs of an episode of major bleeding of USD 4381, costs of stent thrombosis of USD 17,682 and costs of death of USD 794. The risks of serious cardiovascular events and bleeding were taken from studies in Chinese and from the PLATO trial (Chen M et al. Association between cytochrome P450 2C19 polymorphism and clinical outcomes in Chinese patients with coronary artery disease. Atherosclerosis 2012;220:168-71; Luo Y et al. Relationship between cytochrome P450 2C19* 2 polymorphism and stent thrombosis following percutaneous coronary intervention in Chinese patients receiving clopidogrel. J Int Med Res 2011;39:2012-9; Tang XF et al. Effect of the CYP2C19 2 and 3 genotypes, ABCB1 C3435T and PON1 Q192R alleles on the pharmacodynamics and adverse clinical events of clopidogrel in Chinese people after percutaneous coronary intervention. Eur J Clin Pharmacol 2013;69:1103-12; Shen D-L et al. Clinical value of CYP2C19 genetic testing for guiding the anti-platelet therapy in a Chinese population. J Cardiovasc Pharmacol 2015;67:232-6; and Kang H-J et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: a retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Am Heart J 2015;169:899–905). The CYP2C19 *2 allele carrier frequency was 51.8% in this population. Variation of input data showed a 98.5% probability of the genotype-guided strategy to be cost-effective compared with universal clopidogrel and ticagrelor at a willingness-to-pay threshold of USD 42,423 per QALY gained.

- 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 (ticagrelor or prasugrel). The studies in the review (Crespin 2011, Guzauskas 2012, Panattoni 2012, Reese 2012, Lala 2013, Sorich 2013 and Kazi 2014) are all summarised separately below. In all cases, genotype-guided treatment involved treatment of EM/UM patients with clopidogrel and IM and PM patients with ticagrelor or prasugrel. The authors concluded that the cost-effectiveness of CYP2C19 null allele-guided therapy with ticagrelor or prasugrel has been demonstrated for high-risk patients.
  Two studies found that treatment of all patients with ticagrelor was more cost-effective than genotype-guided treatment (Crespin 2011, Sorich 2013). A third study found that genotype-guided treatment with ticagrelor was cost-effective for patients undergoing percutaneous coronary intervention (Kazi 2014). This study found that either genotype-guided treatment or ticagrelor for all patients was the preferred treatment for all patients with acute coronary syndrome depending on the costs used in the model.
  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).
  The results of the cost-effectiveness analyses were influenced by the costs of the platelet aggregation inhibitors and by the risks of IM and PM patients of negative clinical consequences of the use of clopidogrel compared to this risk when using novel platelet aggregation inhibitors.
- Kazi DS et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med 2014;160:221-32. PubMed PMID: 24727840.
  The cost-effectiveness of 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

EM and UM patients receiving clopidogrel and IM and PM patients receiving prasugrel or ticagrelor.
Using relative risks of IM+PM versus EM+UM from a meta-analysis including patients undergoing percutaneous coronary intervention for the calculation:
Genotyping with ticagrelor was the most effective therapy. The costs per gained Quality Adjusted Life Year (QALY) were $ 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 EM+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 EM+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 EM 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 EM/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 EM/UM patients.

Date of literature search: 27 October 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmaco-genetics Working Group decision	PM	3 AA	no	no	19 November 2018
	IM	3 AA	no	no	
	UM	--	no	no	

Mechanism:
Ticagrelor is primarily converted by CYP3A4 to an active metabolite.