Supplement to:

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update

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GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C19* and clopidogrel therapy is published in full on the CPIC website (1). Relevant information will be reviewed periodically and updated guidelines published online.

LITERATURE REVIEW

The PubMed® database (1966 to September 2020) was searched for the following keywords: (CYP2C19 OR cytochrome P450 2C19) AND (clopidogrel). The search was limited to studies conducted in humans and written in the English language, and review articles were excluded. Using these search terms, 770 publications were identified since the evidence review for the 2013 CPIC guideline for clopidogrel was completed. Study inclusion criteria included publications that incorporated analyses for the association between *CYP2C19* genotype and clopidogrel pharmacokinetic parameters or clopidogrel-related clinical outcomes in patients. Following the application of these criteria, 275 publications were reviewed and included in the evidence tables (**Tables S1-S4**). In addition to the references presented in these tables, the level of evidence was also informed by data curated for the 2013 CPIC guideline for clopidogrel (2).

Due to publication on Oct 28, 2021 of the CHANCE-2 clinical trial(3), a large randomized controlled clinical trial of *CYP2C19* genotype-guided antiplatelet therapy in over 6,000 patients with an ischemic stroke or transient ischemic attack, an updated literature search was completed to identify additional recent publications focused on neurovascular indications. The PubMed® database (September 2020 to October 2021) was searched for the following keywords: (CYP2C19 OR cytochrome P450 2C19) AND (clopidogrel) AND (neurovascular OR stroke OR ischemic attack). Following the application of these criteria, 14 additional publications

were reviewed and included in the evidence tables for pharmacodynamics and neurovascular indications (**Tables S1, S3**).

GENETIC TEST INTERPRETATION

Haplotypes, or star (*) alleles, are determined by a specific single nucleotide polymorphism (SNP) or a combination of SNPs that are interrogated in the genotyping analysis. Rare deletion and duplication events affecting the *CYP2C* gene locus have also been described (see Botton et al for a comprehensive summary (4), the PharmVar GeneFocus on *CYP2C19* (5), and the PharmVar Structural Variation document at https://www.pharmvar.org/gene/CYP2C19). Many of the gene deletion and duplication events involve more than one of the *CYP2C* genes and can even encompass a large number of genes within this chromosomal region. To date, PharmVar has defined deletion events encompassing the entire *CYP2C19* gene under the *CYP2C19*36* designation and those with partial *CYP2C19* gene deletion events (that include at least exon 1) as *CYP2C19*37* (4, 5). *CYP2C* copy number variants appear to be rare and are typically not part of clinical pharmacogenetic testing.

The genotypes that constitute the haplotypes, or star (*) alleles for *CYP2C19*, and the rsIDs for each of the specific genomic nucleotide alterations that define the alleles, are described in the ***CYP2C19* Allele Definition Table** online (1, 6). The genotype results are generally reported as a diplotype, which includes one maternal and one paternal allele (e.g., *CYP2C19*1/*2*). The functional assignment of *CYP2C19* alleles are summarized in the ***CYP2C19* Allele Functionality Table** online (1, 6).

AVAILABLE GENETIC TEST OPTIONS

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by providers and is available at http://www.ncbi.nlm.nih.gov/gtr. Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (7). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (***CYP2C19* Allele Definition Table**, ***CYP2C19* Allele Functionality Table**, and ***CYP2C19* Allele Frequency Table**) may be used to assemble lists of known functional and actionable genetic variants and their population frequencies, which may inform decisions as to whether pharmacogenetic tests are adequately comprehensive with the interrogated alleles (1, 6). Furthermore, the Association for Molecular Pathology has published a recommendation for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for *CYP2C19* (8).

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Tables S1-S3** is graded on a scale of high, moderate, and weak based upon the level of evidence:

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalizability to routine practice, or the indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type/reference or variant-containing CYP2C19, *in vitro* CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2C19* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for recommendations adopted from the rating scale for evidence-based guidelines on the use of antiretroviral agents (9):

- **Strong** recommendation for the statement: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Moderate** recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation**: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (10-12). See https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/ for resources to support the adoption of CPIC guidelines within an EHR (1, 11). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating *CYP2C19* genotype results in an EHR to guide clopidogrel therapy.

Effective incorporation of pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic test results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR. To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted drug metabolism phenotype (**Table 1, main manuscript; *CYP2C19* Diplotype to Phenotype Table** (1, 6)). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient's summary section; these phenotypes are best

stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Clopidogrel Pre- and Post-Test Alerts and Flow Chart** for example CDS alerts; https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/) (1).

Because pharmacogenetic test results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include complete diplotype to phenotype translation tables, diagram(s) that illustrate how *CYP2C19* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/) (1, 13).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (see https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/ (1)).

TABLE S1. EVIDENCE LINKING CYP2C19 TO CLOPIDOGREL PHENOTYPE – PHARMACOKINETICS AND PHARMACODYNAMICS

Type of Experimental Model	Major Findings	References	Level of Evidence[a,b]
Metabolism			
Clinical	CYP2C19 phenotype influences the pharmacokinetics of clopidogrel in a graded fashion, with CYP2C19 PMs having the lowest active metabolite levels and CYP2C19 UMs having the highest active metabolite levels in patients treated with clopidogrel.	Braun, *et al.* (2013) (14) Gurbel, *et al.* (2013) (15) Gurbel, *et al.* (2014) (16) Erlinge, *et al.* (2014) (17) Karazniewicz-Lada, *et al.* (2014) (18) Simon, *et al.* (2015) (19) Wang, *et al.* (2015) (20) Bin Sayeed, *et al.* (2015) (21) Liang, *et al.* (2015) (22) Danese, *et al*. (2016) (23) Li, *et al.* (2017) (24) Kitazono, *et al.* (2018) Karazniewicz-Lada, *et al.* (2020) (25)	High
Platelet Reactivity			
Clinical	CYP2C19 IMs and PMs are associated with higher on-treatment platelet reactivity in patients treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Amoah, *et al.* (2013) (26) Braun, *et al.* (2013) (14) Kreutz, *et al.* (2013) (27) Tsantes, et al. (2013) (28) Saucedo, *et al.* (2013) (29) Zhang, *et al.* (2013) (30) Nishio, *et al.* (2013) (31) Zou, *et al.* (2013) (32) Tousoulis, *et al.* (2013) (33) Al-Azzam, *et al.* (2013) (34) Correll, *et al.* (2013) (35) El-Halabi, *et al.* (2013) (36) Hong, *et al.* (2013) (37)	High

		Palmerini, *et al.* (2014) (38) Tresukosol, *et al.* (2014) (39) Tan, *et al.* (2014) (40) Mizobe, *et al.* (2014) (41) Park, *et al.* (2014) (42) Jeong, *et al.* (2014) (43) Peace, *et al.* (2014) (44) Siller-Matula, *et al*. (2014) (45) Gurbel, *et al.* (2014) (16) Hokimoto, *et al.* (2014) (46) Erlinge, *et al.* (2014) (17) Guo, *et al.* (2014) (47) Zhang, *et al.* (2014) (48) Simon, *et al.* (2015) (19) Larsen, *et al.* (2015) (49) Arya, *et al.* (2015) (50) Cui, *et al.* (2015) (51) Sun, *et al.* (2015) (52) Peng, *et al.* (2015) (53) Chen, *et al.* (2015) (54) Wang, *et al.* (2015) (20) Bin Sayeed, *et al.* (2015) (21) Arima, *et al*. (2015) (55) Konishi, *et al.* (2015) (56) Nakamura, *et al.* (2015) (57) Nooney, *et al.* (2015) (58) Collet, *et al.* (2015) (59) Kim, *et al.* (2015) (60) Yang, *et al.* (2015) (61) Golukhova, *et al.* (2015) (62) Arima, *et al.* (2015) (55) Qiu, *et al.* (2015) (63) Han, *et al.* (2015) (64) Wang, *et al.* (2016) (65) Ou, *et al*. (2016) (66) Carreras, *et al.* (2016) (67)	

		Kirac, *et al.* (2016) (68) Doll, *et al.* (2016) (69) Choi, *et al.* (2016) (70) Sun, *et al.* (2016) (71) Choi, *et al.* (2016) (72) Danese, *et al*. (2016) (23) Forni Ogna, *et al.* (2016) (73) Backovic, *et al.* (2016) (74) Backovic, *et al.* (2016) (75) Liu, *et al.* (2016) (76) Yi, *et al.* (2016) (77) Yi, *et al.* (2016) (78) Lin, *et al.* (2016) (79) Li, *et al.* (2017) (24) Garcia-Lagunar, *et al.* (2017) (80) Saydam, *et al.* (2017) (81) Marchini, *et al.* (2017) (82) Nie, *et al.* (2017) (83) Forni Ogna, *et al.* (2017) (84) Amin, *et al.* (2017) (85) Siasos, *et al.* (2017) (86) Oledzki, *et al.* (2017) (87) Tan, *et al.* (2017) (88) Marginean, *et al.* (2017) (89) Alhazzani, *et al.* (2017) (90) Li, *et al*. (2017) (91) Li, *et al.* (2017) (92) Yi, *et al.* (2017) (93) Zhang, *et al.* (2017) (94) Rao, *et al.* (2017) (95) Ge, *et al.* (2017) (96) Gross, *et al.* (2018) (97) Mirzaev, *et al.* (2018) (98) Wang, *et al.* (2018) (99) Li, *et al.* (2018) (100) Hou, *et al.* (2018) (101)	

		Hassani Idrissi, *et al.* (2018) (102) Ebisawa, *et al.* (2018) (103) Nie, *et al.* (2018) (104) Golukhova, *et al.* (2018) (105) Hernandez-Suarez, *et al.* (2018) (106) Hernandez-Suarez, *et al.* (2018) (107) Tomek, *et al.* (2018) (108) Lin, *et al.* (2018) (109) Yi, *et al*. (2018) (110) Su, *et al.* (2019) (111) Pandey, *et al.* (2019) (112) Cedillo-Salazar, *et al*. (2019) (113) Akram, *et al*. (2019) (114) Peng, *et al*. (2019) (115) Lee, *et al.* (2019) (116) Ma, *et al.* (2019) (117) Patel, *et al.* (2019) (118) Saiz-Rodriguez, *et al.* (2019) (119) Saiz-Rodriguez, *et al.* (2019) (120) Saiz-Rodriguez, *et al.* (2019) (121) Alakbarzade, *et al*. (2020) (122)* Jirungda, *et al.* (2020) (123) Lewis, *et al.* (2020) (124) Mohareb, *et al.* (2020) (125) Zhang, *et al.* (2020) (126) Gairolla, *et al*. (2020) (127) Fu, *et al*. (2020) (128) Sun, *et al.* (2020) (129) Rath, *et al.* (2020) (130) Lv, *et al.* (2021) (131) Shi, *et al.* (2021) (132) Shi, *et al.* (2021) (133)	
Clinical	CYP2C19 IMs are associated with higher on-treatment platelet reactivity in patients treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Tang, *et al.* (2013) (134) Nagashima, *et al.* (2013) (135) Liu, *et al.* (2013) (136) Nakata, *et al*. (2013) (137)	High

		Yang, *et al.* (2013) (138) Jia, *et al.* (2013) (139) Tatarunas, *et al.* (2014) (140) Tresukosol, *et al.* (2014) (39) Hokimoto, *et al*. (2014) (141) Xie, *et al.* (2014) (142) Park, *et al.* (2014) (42) Gurbel, *et al.* (2014) (16) Isshiki, *et al.* (2014) (143) Karazniewicz-Lada, *et al.* (2014) (18) Liu, *et al.* (2014) (144) Konishi, *et al.* (2015) (56) Li, *et al.* (2015) (145) Hokimoto, *et al.* (2015) (146) Liu, *et al.* (2015) (147) Tang, *et al.* (2015) (148) Zhang, *et al.* (2016) (149) Li, *et al.* (2016) (150) Liu, *et al.* (2016) (151) Dong, *et al.* (2016) (152) Yi, *et al.* (2016) (77) Yi, *et al.* (2016) (78) Li, *et al.* (2017) (24) Tatarunas, *et al.* (2017) (153) Tatarunas, *et al.* (2017) (154) Nie, *et al.* (2017) (83) Zhang, *et al.* (2017) (155) Amin, *et al.* (2017) (85) Yi, *et al.* (2017) (93) Tan, *et al.* (2018) (156) Hou, *et al.* (2018) (101) Chouchene, *et al.* (2018) (157) Wang, *et al.* (2018) (99) Li, *et al.* (2018) (100) Joo, *et al.* (2018) (158) Lin, *et al.* (2018) (109)	

		Yi, *et al.* (2018) (110) Tomek, *et al.* (2018) (108) Li, *et al.* (2019) (159) Akram, *et al.* (2019) (114) Feng, *et al.* (2019) (160) Lyerly, *et al.* (2019) (161) Tanaka, *et al.* (2019) (162) Tan, *et al.* (2020) (163) Shimamatsu, *et al.* (2020) (164) Zhang, *et al.* (2020) (126) Karazniewicz, *et al.* (2020) (25) Li, *et al.* (2020) (165)	
Clinical	CYP2C19 PMs are associated with higher on-treatment platelet reactivity in patients treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Nagashima, *et al.* (2013) (135) Tang, *et al.* (2013) (134) Yang, *et al.* (2013) (138) Jia, *et al.* (2013) (139) Hokimoto, *et al.* (2014) (141) Xie, *et al.* (2014) (142) Tresukosol, *et al.* (2014) (39) Park, *et al.* (2014) (42) Lai, *et al.* (2015) (166) Cui, *et al.* (2015) (51) Tang, *et al.* (2015) (148) Konishi, *et al.* (2015) (56) Li, *et al.* (2015) (145) Hokimoto, *et al.* (2015) (146) Liu, *et al.* (2015) (147) Zhang, *et al.* (2016) (149) Khalaf, *et al.* (2016) (167) Li, *et al.* (2016) (150) Liu, *et al.* (2016) (151) Dong, *et al.* (2016) (152) Li, *et al.* (2017) (24) Zhang, *et al.* (2017) (155)	High

		Wang, *et al.* (2018) (99) Li, *et al.* (2018) (100) Joo, *et al.* (2018) (158) Tahara, *et al.* (2018) (168) Zhang, *et al.* (2018) (169) Li, *et al.* (2019) (159) Feng, *et al.* (2019) (160) Tanaka, *et al.* (2019) (162) Tan, *et al.* (2020) (163) Shimamatsu, *et al.* (2020) (164) Zhang, *et al.* (2020) (126) Li, *et al.* (2020) (165)	
Clinical	CYP2C19 PMs are associated with higher on-treatment platelet reactivity in patients treated with clopidogrel compared to CYP2C19 IMs.	Nagashima, *et al.* (2013) (135) Nakata, *et al.* (2013) (137) Liu, *et al.* (2013) (136) Tousoulis, *et al.* (2013) (33) Hokimoto, *et al.* (2014) (141) Xie, *et al.* (2014) (142) Liu, *et al.* (2014) (144) Isshiki, *et al.* (2014) (143) Konishi, *et al.* (2015) (56) Li, *et al.* (2015) (145) Hokimoto, *et al.* (2015) (146) Liu, *et al.* (2015) (147) Tang, *et al.* (2015) (148) Dong, et al. (2016) (152) Li, *et al.* (2016) (150) Liu, *et al.* (2016) (151) Li, *et al.* (2017) (24) Amin, *et al.* (2017) (85) Siasos, *et al.* (2017) (86) Wang, *et al.* (2018) (99) Li, *et al.* (2018) (100)	High

		Tahara, *et al.* (2018) (168) Feng, *et al.* (2019) (160) Shimamatsu, *et al.* (2020) (164)	
Clinical	*CYP2C19*17* allele carriers are associated with lower on-treatment platelet reactivity in patients treated with clopidogrel compared to non-**17*-allele carriers.	Hong, *et al.* (2013) (37) Siller-Matula, *et al.* (2014) (45) Lin, *et al.* (2016) (79) Huang, *et al.* (2017) (170)* Oledzki, *et al.* (2017) (87) Lewis, *et al.* (2020) (124) Rath, *et al.* (2020) (130)	Moderate

[a]Rating scheme described in the **Supplemental Material**

[b]In addition to the references presented in this table, the level of evidence was also informed by data curated for the 2013 CPIC guideline for clopidogrel and/or meta-analysis data (2). Meta-analyses are indicated by an asterisk (*).

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S2. EVIDENCE LINKING CYP2C19 TO CLOPIDOGREL PHENOTYPE – CARDIOVASCULAR INDICATIONS

Efficacy			
Clinical	CYP2C19 IMs and PMs are associated with higher risk of adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS and/or PCI patients treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Carlquist, *et al.* (2013) (171) Kang, *et al.* (2013) (172) Tsantes, *et al.* (2013) (28) Amoah, *et al.* (2013) (26) Zou, *et al.* (2013) (32) Nishio, *et al.* (2013) (31) Cresci, *et al.* (2014) (173) Palmerini, *et al.* (2014) (38) Sorich, *et al.* (2014) (174)* Xie, *et al.* (2014) (142) Mizobe, *et al.* (2014) (41) Martinez-Quintana, *et al.* (2014) (175) Wei, *et al*. (2015) (176) Chen, *et al.* (2015) (54) Sun, *et al.* (2015) (52) Arima, *et al.* (2015) (55) Collet, *et al.* (2015) (59) Depta, *et al.* (2015) (177) Niu, *et al.* (2015) (178)* Wang, *et al.* (2016) (65) Kirac, *et al.* (2016) (68) Ou, *et al.* (2016) (66) Sun, *et al.* (2016) (71) Khalil, *et al*. (2016) (179) Tang, *et al.* (2016) (180) Choi, *et al.* (2016) (70) Doll, *et al.* (2016) (69) Rytkin, *et al.* (2017) (181) Marchini, *et al.* (2017) (82) Li, *et al.* (2017) (24)	High

		Tornio, *et al.* (2018) (182) Rodriguez-Gonzalez, *et al.* (2018) Hou, *et al*. (2018) (101) Bai, *et al.* (2018) (183) Fathy, *et al.* (2018) (184) Zhang, *et al*. (2019) (185) Li, *et al.* (2019) (159) Ayesh, *et al*. (2019) (186) Wang, *et al.* (2019) (187) Xi, *et al.* (2019) (188)* Zhou, *et al.* (2020) (189) Verma, *et al.* (2020) (190) Lewis, *et al.* (2020) (124) Tan, *et al.* (2020) (163) Zhang, *et al.* (2020) (126) Mohareb, *et al.* (2020) (125) Lee, *et al.* (2021) (191)	
Clinical	CYP2C19 IMs are associated with higher risk of adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS and/or PCI patients treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Peng, *et al.* (2013) (192) Xie, *et al.* (2013) (193) Kim, *et al.* (2013) (194) Tang, *et al.* (2013) (134) Hokimoto, *et al.* (2014) (141) Sorich, *et al.* (2014) (174)* Niu, *et al.* (2015) (178)* Yang, *et al.* (2015) (61) Kulmyrzaeva, *et al.* (2016) (195) Zhang, *et al.* (2016) (149) Mugosa, *et al.* (2016) (196) Dong, *et al.* (2016) (152) Li, *et al.* (2017) (24) Hou, *et al.* (2018) (101) Tan, *et al.* (2018) (156) Rodriguez-Gonzalez, *et al.* (2018) (197)	Moderate

		Mohammad, *et al.* (2018) (198) Joo, *et al.* (2018) (158) Xi, *et al.* (2019) (188)* Tan, *et al.* (2020) (163)	
Clinical	CYP2C19 PMs are associated with higher risk of adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS and/or PCI patients treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Peng, *et al.* (2013) (192) Paulu, *et al.* (2013) (199) Xie, *et al.* (2013) (193) Kim, *et al.* (2013) (194) Tang, *et al.* (2013) (134) Hokimoto, *et al.* (2014) (141) Sorich, *et al.* (2014) (174)* Lai, *et al.* (2015) (166) Yang, *et al.* (2015) (61) Liu, *et al.* (2015) (147) Kupstyte, *et al.* (2015) (200) Collet, *et al.* (2015) (59) Li, *et al.* (2015) (145) Konishi, *et al.* (2015) (56) Niu, *et al.* (2015) (178)* Chikata, *et al*. (2016) (201) Afzal, *et al.* (2016) (202) Komosa, *et al.* (2016) (203) Zhang, *et al.* (2016) (149) Dong, *et al.* (2016) (152) Ma, *et al.* (2016) (204) Park, *et al.* (2016) (205) Li, *et al.* (2017) (24) Tahara, *et al.* (2018) (168) Joo, *et al.* (2018) (158) Xi, *et al.* (2019) (188)* Yu, *et al.* (2020) (206) Tan, *et al*. (2020) (163) Morales-Rosado, *et al.* (2021) (207)	High

Clinical	CYP2C19 IMs and PMs are associated with higher risk of adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in stable CAD patients with or without PCI treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Wallentin, *et al.* (2010) (208) Tousoulis, *et al.* (2013) (33) Viviani Anselmi, *et al.* (2013) (209) Liu, *et al.* (2013) (136) Kim, *et al.* (2013) (194) Golukhova, *et al.* (2015) (62) Arima, *et al.* (2015) (55) Tabata, *et al.* (2016) (210) Siasos, *et al.* (2017) (86) Tan, *et al.* (2017) (88) Verma, *et al.* (2020) (190)	Moderate
Clinical	CYP2C19 IMs and PMs are associated with higher risk of adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke) in patients with vascular diseases (non-ACS and non-stable CAD patients) and atrial fibrillation treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Pare, *et al.* (2010) (211) Guo, *et al.* (2014) (47) Diaz-Villamarin, *et al.* (2016) (212) Lee, *et al.* (2019) (116) Ferrari, *et al.* (2019) (213) Ma, *et al.* (2019) (117) Patel, *et al* (2021) (214)	Moderate
Bleeding			
Clinical	CYP2C19 RMs and UMs are NOT associated with a significantly increased bleeding risk in ACS and/or PCI treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 IMs and PMs).	Carlquist, *et al.* (2013) (171) Park, *et al.* (2013) (215) Cresci, *et al.* (2014) (173) Kwon, *et al.* (2016) (216) Wang, *et al.* (2016) (65) Novkovic, *et al.* (2018) (217) Sychev, *et al.* (2020) (218) Lee, *et al.* (2021) (191)	Moderate
High-dose Clopidogrel			
Clinical	High-dose clopidogrel (150 mg/day and higher) can increase the degree of platelet inhibition in ACS/PCI and stable CAD patients who are CYP2C19 IMs or PMs compared to standard dose clopidogrel (75 mg/day).	Jeong, *et al.* (2013) (219) Latkovskis, *et al.* (2014) (220) Samardzic, *et al.* (2015) (221) Zhang, *et al.* (2015) (222)* Rossi, *et al.* (2014) (223)	High

		Carreras, *et al.* (2016) (67) Chen, *et al.* (2016) (224) Chen, *et al.* (2017) (225)	
Clinical	In CYP2C19 IMs, high-dose clopidogrel (150 mg/day and higher) can significantly increase the degree of platelet inhibition compared to standard dose clopidogrel (75 mg/day).	Collet, *et al.* (2011) (226) Mega, *et al.* (2011) (227) Jeong, *et al.* (2013) (219) Horenstein, *et al.* (2014) (228) Carreras, *et al*. (2016) (67) Chen, *et al.* (2016) (224)	Moderate
Clinical	In CYP2C19 PMs, high-dose clopidogrel (150 mg/day and higher) can significantly increase the degree of platelet inhibition compared to standard dose clopidogrel (75 mg/day).	Collet, *et al.* (2011) (226) Mega, *et al.* (2011) (227) Jeong, *et al.* (2013) (219) Rossi, *et al.* (2014) (223) Horenstein, *et al.* (2014) (228) Carreras, *et al.* (2016) (67) Chen, *et al.* (2016) (224)	Weak
Clinical	In CYP2C19 IMs, clopidogrel 225 mg/day can increase the degree of platelet inhibition to a level comparable to standard dose clopidogrel (75 mg/day) in CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Mega, *et al.* (2011) (227) Rossi, *et al.* (2014) (223) Horenstein, *et al.* (2014) (228) Carreras, *et al.* (2016) (67)	Moderate
Clinical	In CYP2C19 PMs, clopidogrel 300 mg/day can increase the degree of platelet inhibition to a level comparable to standard dose clopidogrel (75 mg/day) in CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Mega, *et al.* (2011) (227) Rossi, *et al.* (2014) (223) Horenstein, *et al.* (2014) (228) Carreras, *et al.* (2016) (67)	Weak
Clinical	CYP2C19 IMs and PMs are associated with higher on-treatment platelet reactivity compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs) in patients treated with high-dose clopidogrel.	Barker, *et al.* (2010) (229) Cuisset, *et al.* (2011) (230) Jeong, *et al.* (2013) (219) Latkovskis, *et al.* (2014) (220) Horenstein, *et al.* (2014) (228) Samardzic, *et al.* (2015) (221)	High
Clinical	In CYP2C19 IM or PM ACS/PCI and stable CAD patients, high-dose clopidogrel (150 mg/day and higher) can improve	Samardzic, *et al.* (2015) (221) Zhang, *et al.* (2015) (222)* Chen, *et al.* (2017) (225)	Weak

	clinical outcomes compared to standard dose clopidogrel (75 mg/day).	Tang, *et al.* (2018) (231)	
Antiplatelet Treatment Comparison			
Clinical	CYP2C19 IMs and PMs are associated with significantly higher on-treatment platelet reactivity with clopidogrel compared to prasugrel in ACS and/or PCI patients.	Grosdidier, *et al.* (2013) (232) Ogawa, *et al.* (2016) (233) So, *et al.* (2016) (234) Ueno, *et al.* (2017) (235) Ebisawa, *et al.* (2018) (103) Shimamatsu, *et al.* (2020) (164) Jin, *et al.* (2020) (236)	High
Clinical	CYP2C19 IMs and PMs are associated with significantly higher on-treatment platelet reactivity with clopidogrel compared to prasugrel in stable CAD patients with or without PCI.	Sardella, *et al.* (2012) (237) Gurbel, *et al.* (2014) (16) Sardella, *et al.* (2015) (238)	Moderate
Clinical	CYP2C19 IMs and PMs are associated with significantly higher on-treatment platelet reactivity with clopidogrel compared to ticagrelor in stable CAD patients with or without PCI.	Sardella, *et al.* (2015) (238) Xiong, *et al.* (2015) (239)	Moderate
Clinical	Among CYP2C19 IMs or PMs, treatment with clopidogrel is associated with higher cardiovascular event risk compared with treatment with prasugrel or ticagrelor.	Ogawa, *et al.* (2016) (233) Doll, *et al.* (2016) (69) Zhang, *et al*. (2016) (240) Dong, *et al.* (2016) (152) Dieman, *et al.* (2016) (241) Chen, *et al.* (2017) (225) Cavallari, *et al.* (2018) (242) Lee, *et al.* (2018) (243) Williams, *et al.* (2019) (244) Martin, *et al.* (2020) (245) Hulot, *et al.* (2020) (246) Sawayama, *et al*. (2020) (247) Xi, *et al.* (2020) (248) Mohareb, *et al.* (2020) (125) Yoon, *et al.* (2020) (249)*	High

		Biswas, *et al.* (2021) (250)* Lee, *et al.* (2021) (191)	
Clinical	A *CYP2C19*-guided therapy strategy (treatment with an alternative agent in CYP2C19 IMs or PMs and treatment with clopidogrel in NMs [may include RMs and UMs]) is associated with decreased risk of high on-treatment platelet reactivity when compared to a strategy of standard-dose clopidogrel therapy in all patients.	Roberts, *et al.* (2012) (251) Malhotra, *et al.* (2015) (252) Lee, *et al.* (2016) (253) Tam, *et al.* (2017) (254) Koltowsky, *et al.* (2017) (255)	High
Clinical	A *CYP2C19*-guided therapy strategy (treatment with an alternative agent in CYP2C19 IMs or PMs and treatment with clopidogrel in NMs [may include RMs and UMs]) is associated with decreased risk of low on-treatment platelet reactivity when compared to a strategy of ticagrelor therapy in all patients.	Malhotra, *et al.* (2015) (252)	Weak
Clinical	A *CYP2C19*-guided therapy strategy (treatment with ticagrelor or prasugrel in CYP2C19 IMs or PMs and treatment with standard-dose clopidogrel in NMs [may include RMs and UMs]) is associated with a decreased risk of major cardiovascular events when compared to a strategy of standard-dose clopidogrel in all patients.	Xie, *et al.* (2013) (256) Shen, *et al.* (2016) (257) Sanchez-Ramos, *et al.* (2016) (258) Li, *et al.* (2017) (256) Ozawa, *et al.* (2018) (259) Notarangelo, *et al.* (2018) (260) Cavallari, *et al.* (2018) (242) Janssen, *et al.* (2019) (261) Tan, *et al.* (2019) (262) Tuteja, *et al.* (2020) (263) Hulot, *et al.* (2020) (246) Pereira, *et al.* (2020) (264)	High
Clinical	A *CYP2C19*-guided therapy strategy (treatment with ticagrelor or prasugrel in CYP2C19 IMs or PMs and treatment with standard-dose clopidogrel in NMs [may include RMs and UMs) is NOT associated with a significantly higher bleeding risk when compared to a strategy of standard-dose clopidogrel in all patients.	Xie, *et al.* (2013) (256) Shen, *et al.* (2016) (257) Sanchez-Ramos, *et al.* (2016) (258) Notarangelo, *et al.* (2018) (260) Tan, *et al.* (2019) Janssen, *et al.* (2019) (261) Hulot, *et al.* (2020) (246)	Weak

		Pereira, *et al.* (2020) (264)	
Clinical	A *CYP2C19*-guided therapy strategy (treatment with ticagrelor or prasugrel in CYP2C19 IMs or PMs and treatment with standard-dose clopidogrel in NMs [may include RMs and UMs]) is NOT associated with a significantly increased risk of major cardiovascular events when compared to a strategy of ticagrelor or prasugrel therapy in all patients.	Claassens, *et al.* (2019) (265) Martin, *et al.* (2020) (245)	Moderate
Clinical	A *CYP2C19*-guided therapy strategy (treatment with ticagrelor or prasugrel in CYP2C19 IMs or PMs and treatment with standard-dose clopidogrel in NMs [may include RMs and UMs]) is associated with a decreased risk of bleeding when compared to a strategy of ticagrelor or prasugrel therapy in all patients.	Claassens, *et al.* (2019) (265)	Moderate

[a]Rating scheme described in the **Supplemental Material**

[b]In addition to the references presented in this table, the level of evidence was also informed by data curated for the 2013 CPIC guideline for clopidogrel and/or meta-analysis data (2). Meta-analyses are indicated by an asterisk (*).

ACS, acute coronary syndrome; CAD, coronary artery disease; IM, intermediate metabolizer; NM, normal metabolizer; PCI, percutaneous coronary intervention; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S3. EVIDENCE LINKING CYP2C19 TO CLOPIDOGREL PHENOTYPE – NEUROVASCULAR INDICATIONS

Type of Experimental Model	Major Findings	References	Level of Evidence[a,b]
Efficacy			
Clinical	CYP2C19 IMs and PMs are associated with a higher risk of a new cardiovascular or cerebrovascular event in stroke patients while treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Sen, *et al.* (2014) (266) Zhang, *et al.* (2014) (48) Spokoyny, *et al.* (2014) (267) McDonough, *et al.* (2015) (268) Sun, *et al.* (2015) (269) Qiu, *et al.* (2015) (63) Han, *et al.* (2015) (64) Yi, *et al.* (2016) (77) Yi, *et al.* (2016) (78) Zhao, *et al.* (2016) (270) Wang, *et al.* (2016) (271) Wang, *et al.* (2016) (272) Pan, *et al.* (2017) (273)* Yi, *et al*. (2017) (93) Li, *et al.* (2017) Zhang, *et al*. (2017) (94) Rao, *et al.* (2017) (95) Han, *et al.* (2017) (274) Tornio, *et al.* (2018) (182) Tomek, *et al.* (2018) (108) Yi, *et al.* (2018) (275) Yi, *et al*. (2018) (110) Lin, *et al.* (2018) (109) Tanaka, *et al.* (2019) (162) Fu, *et al.* (2020) (128) Lv, *et al.* (2021) (131) Al-Rubaish, *et al.* (2021) (276)	High

		Li, *et al.* (2021) (277)	
Clinical	CYP2C19 IMs are associated with a higher risk of a new cardiovascular or cerebrovascular event in stroke patients while treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Jeong, *et al.* (2015) (278) Yi, *et al.* (2016) (77) Yi, *et al.* (2016) (78) Pan, *et al.* (2017) (273)* Yi, *et al.* (2018) (110) Lyerly, *et al.* (2019) (161) Liu, *et al.* (2020) (279)	Moderate
Clinical	CYP2C19 PMs are associated with a higher risk of a new cardiovascular or cerebrovascular event in stroke patients while treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Jeong, *et al*. (2015) (278) Zhu, *et al.* (2016) (280) Pan, *et al.* (2017) (273)* Liu, *et al.* (2020) (279)	Moderate
Clinical	CYP2C19 IMs and PMs are associated decreased clopidogrel response (e.g., modified Rankin scale) in stroke patients compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Jia, *et al.* (2013) (139) Yi, *et al.* (2016) (77) Yi, *et al.* (2016) (78) Wang, *et al.* (2016) (272) Lan, *et al.* (2019) (281) Wang, *et al.* (2020) (282)	Weak
Clinical	CYP2C19 IMs are associated decreased clopidogrel response (e.g., modified Rankin scale) in stroke patients compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Yi, *et al.* (2016) (77) Yi, *et al.* (2016) (78) Lan, *et al.* (2019) (281)	Weak
Clinical	CYP2C19 PMs are associated decreased clopidogrel response (e.g., modified Rankin scale) in stroke patients compared to CYP2C19 IMs and NMs (might include CYP2C19 RMs and UMs).	Lan, *et al.* (2019) (281)	Weak
Clinical	CYP2C19 IMs and PMs are associated with a higher risk of a new ischemic event and decreased clopidogrel response (e.g., modified Rankin scale) in patients with intracranial aneurysms undergoing stent-assisted coiling while treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Ge, *et al.* (2017) (96)	Weak
Clinical	CYP2C19 IMs and PMs are associated with higher risk of a new ischemic event in patients undergoing a percutaneous	Lin, *et al.* (2014) (283) Zhu, *et al.* (2016) (280)	Weak

	neurointervention procedure treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Lin, *et al.* (2016) (79) Saiz-Rodriguez, *et al.* (2019) (119) Saiz-Rodriguez, *et al.* (2019) (120) Saiz-Rodriguez, *et al.* (2019) (121) Patel, *et al.* (2021) (214) Li, *et al.* (2021) (284)	
Clinical	CYP2C19 RMs and UMs are associated with lower risk of a new ischemic event in patients undergoing a percutaneous neurointervention procedure and treated with clopidogrel compared to CYP2C19 NMs.	Lin, *et al.* (2016) (79) Saiz-Rodriguez, *et al.* (2019) (119) Saiz-Rodriguez, *et al.* (2019) (120)	Weak
Clinical	CYP2C19 IMs and PMs are associated with a higher risk of an adverse cardiovascular or cerebrovascular event in intracranial atherosclerotic disease patients treated with clopidogrel compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs).	Patel, *et al.* (2021) (285) Hoh, *et al.* (2016) (286)	Weak
Bleeding			
Clinical	*CYP2C19* genotype is NOT associated with differences in bleeding risk in stroke patients treated with clopidogrel.	McDonough, *et al.* (2015) (268) Sun, *et al.* (2015) (269) Wang, *et al.* (2016) (271) Han, *et al.* (2017) (274) Pan, *et al.* (2017) (273)* Tomek, *et al.* (2018) (108) Lin, *et al.* (2018) (109) Wu, *et al.* (2018) (287)	Moderate
Clinical	CYP2C19 IMs and PMs are associated with lower bleeding risk in patients with intracranial aneurysms undergoing stent-assisted coiling treated with clopidogrel compared to CYP2C19 NMs.	Ge, *et al.* (2017) (96)	Weak
Clinical	CYP2C19 RMs and UMs, but not CYP2C19 IMs and PMs, are associated with differences in bleeding risk in patients undergoing a percutaneous neurointervention procedure treated with clopidogrel compared to CYP2C19 NMs.	Lin, *et al.* (2016) (79) Saiz-Rodriguez, *et al.* (2019) (119) Saiz-Rodriguez, *et al.* (2019) (120) Saiz-Rodriguez, *et al.* (2019) (121) Patel, *et al.* (2021) (214)	Weak

		Li, et al. (2021) (284)	
High-dose Clopidogrel			
Clinical	In CYP2C19 IM patients with minor ischemic stroke, high-dose clopidogrel (150 mg/day) can improve clinical outcomes compared to standard dose clopidogrel (75 mg/day).	Wu, et al. (2020) (288)	Weak
Antiplatelet Treatment Comparison			
Clinical	CYP2C19 IMs and PMs are associated with significantly higher on-treatment platelet reactivity with clopidogrel compared to prasugrel in stroke patients. In CYP2C19 NMs, no significant differences were found.	Kitazono, *et al.* (2018) (289)	Weak
Clinical	CYP2C19 IMs and PMs are associated with significantly higher on-treatment platelet reactivity with clopidogrel compared to ticagrelor in stroke patients. In CYP2C19 NMs, no significant differences were found.	Wang, *et al.* (2019) (290) Yang, *et al.* (2020) (291) Yang, *et al.* (2020) (292) Zhou, *et al.* (2020) (293)	Moderate
Clinical	CYP2C19 NMs, RMs, or UMs had a reduced rate of stroke and composite events with clopidogrel (+ aspirin) compared to aspirin only in stroke patients. In CYP2C19 IMs and PMs, the rate was not significantly different with clopidogrel vs. aspirin-only treatment.	Wang, *et al.* (2016) (271) Mo, *et al.* (2020) (294) Meschia, *et al.* (2020) (295)	Moderate
Clinical	CYP2C19 IMs and PMs are associated with significantly higher risk for ischemic stroke, transient ischemic attack, myocardial infarction, and death with clopidogrel in stroke patients compared to CYP2C19 NMs (might include CYP2C19 RMs and UMs). *CYP2C19* polymorphisms were not associated with the primary outcome in aspirin only treated patients.	Yi, *et al.* (2018) (275)	Weak
Clinical	CYP2C19 IMs and PMs are associated with significantly lower incidence of early neurological deterioration with clopidogrel (+aspirin) compared to aspirin only in stroke patients. There was no significant difference in incidence of early neurological deterioration in CYP2C19 NMs.	Yi, *et al.* (2018) (296)	Weak

Clinical	CYP2C19 IMs and PMs are associated with significantly higher Modified Rankin Scale scores with clopidogrel compared to aspirin in stroke patients. In CYP2C19 NMs, no significant differences were found.	Lan, *et al.* (2019) (281)	Weak
Clinical	CYP2C19 IMs and PMs are associated with significantly lower incidence of early neurological deterioration with clopidogrel (+aspirin) compared to clopidogrel only in stroke patients. There was no significant difference in incidence of early neurological deterioration in CYP2C19 NMs.	Lin, *et al.* (2018) (109)	Weak
Clinical	Among CYP2C19 IMs or PMs, treatment with ticagrelor (+aspirin) is associated with significantly lower risk of major cardiac or cerebrovascular events compared to treatment with standard-dose clopidogrel (+aspirin) in stroke patients.	Wang, *et al*. (2021) (3)	Moderate
Clinical	Among CYP2C19 IMs or PMs, treatment with ticagrelor (+aspirin) is associated with significantly higher risk of minor bleeding events compared to treatment with standard-dose clopidogrel (+aspirin) in stroke patients. No significant differences in major bleeding events were found.	Wang, *et al*. (2021) (3)	Moderate

[a]Rating scheme described in the **Supplemental Material**

[b]In addition to the references presented in this table, the level of evidence was also informed by data curated for the 2013 CPIC guideline for clopidogrel and/or meta-analysis data (2). Meta-analyses are indicated by an asterisk (*).

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S4. EVIDENCE LINKING CYP2C19 TO CLOPIDOGREL PHENOTYPE – META-ANALYSES SINCE 2013

Indication	# of Studies	# of Patients	Study Inclusion Date	*CYP2C19* Genotype Risk (or Mitigation of Risk)	References
ACS, PCI	9	16,132	April 2020	Prasugrel or ticagrelor versus clopidogrel in no function allele (**2, *3, *4, *5, *6, *8*) carriers: **MACE:** RR 0.58 (0.45-0.76) p < 0.0001 **CV death:** RR 0.44 (0.25-0.74) p = 0.002 **MI:** RR 0.60 (0.44-0.81) p = 0.0008 **Stent thrombosis**: RR 0.67 (0.38-1.18) p = 0.17 **Bleeding**: RR 1.06 (0.88-1.28) p = 0.55	Biswas, *et al.* 2021 (250)
ACS, PCI	8	6,708	April 2020	Genotype-guided antiplatelet therapy versus non-genotype-guided antiplatelet therapy: **MACE:** RR 0.71 (0.51-0.98) p = 0.04 **MI:** RR 0.56 (0.40-0.78) p < .01 **Stent thrombosis**: RR 0.56 (0.30-1.06) p = 0.07 **Bleeding**: RR 0.81 (0.56-1.16) p = 0.25	Lyu, *et al.* 2020 (297)
ACS, stable CAD	12	5,829	January 2020	Prasugrel or ticagrelor versus clopidogrel in no function allele carriers (star alleles not specified): **MACE:** RR 0.52 (0.38-0.73) p = 0.0001 **CV death:** RR 0.41 (0.18-0.95) p = 0.04 **All-cause death:** RR 0.44 (0.26-0.74) p = 0.002 **MI:** RR 0.59 (0.35-0.99) p = 0.05 **Stent thrombosis:** RR 0.55 (0.41-0.74) p < 0.0001	Yoon, *et al.* 2020 (249)
Ischemic stroke, TIA	21	4,312	March 2019	Clopidogrel treated **2* or **3* allele carriers versus clopidogrel treated non-carriers: **High on-clopidogrel platelet reactivity:** RR 1.69 (1.47-1.95) p < 0.001	Alakbarzade, *et al.* (2020) (122)
PCI	6	2,371	March 2018	Genotype-guided antiplatelet therapy versus non-genotype-guided antiplatelet therapy: **MACE:** RR 0.67 (0.35-1.27) p = 0.22	Kheiri, *et al.* (2019) (298)

				MI: RR 0.44 (0.28-0.70) p < 0.01 **CV death:** RR 0.68 (0.27-1.74) p = 0.42 **Stent thrombosis**: RR 0.37 (0.13-1.06) p = 0.06 **Bleeding**: RR 0.68 (0.43-1.06) p = 0.09	
PCI	13	6,845	March 2018	Genotype-guided antiplatelet therapy versus non-genotype-guided antiplatelet therapy: **MACE**: OR 0.64 (0.38-1.05) **Bleeding**: OR 0.73 (0.45-1.25)	Kheiri, *et al.* (2019) (299)
PCI	20	15,056	January 2017	Clopidogrel treated **2* or **3* allele carriers versus clopidogrel treated non-carriers: **MACE:** OR 1.99 (1.64-2.42) p < 0.001 **Stent thrombosis:** OR 4.77 (2.84-8.01) p < 0.001 **Bleeding:** OR 0.66 (0.46-0.96) p < 0.001	Xi, *et al.* (2019) (188)
Stroke, TIA	15	4,762	June 2016	Clopidogrel treated **2*, **3*, or **8* allele carriers versus clopidogrel treated non-carriers: **Stroke:** RR 1.92 (1.57-2.35) p < 0.001 **Vascular events:** RR 1.51 (1.10-2.06) p = 0.01 **Bleeding**: RR 0.89 (0.58-1.35) p = 0.59	Pan, *et al.* (2017) (273)
CAD (no PCI), CVD, PCI	13	14,239	February 2016	Clopidogrel treated **17* allele carriers versus clopidogrel treated non-carriers: **MACCE:** OR 0.76 (0.60-0.98) p = 0.03 **Stent thrombosis**: OR 1.07 (0.47-2.41) p = 0.88 **High platelet reactivity**: OR 0.61 (0.43-0.88) p = 0.008 **Bleeding:** OR 1.89 (1.09-3.25) p = 0.02	Huang, *et al.* (2017) (170)
PCI	19	10,960	June 2014	**2* allele carriers treated with high dose clopidogrel versus non-**2* allele carriers treated with standard dose clopidogrel: **MACE:** RR 1.68 (1.19-2.37) p = 0.003 **Stent thrombosis:** RR 1.75 (1.31-2.34) p = 0.0001 **High on-treatment platelet reactivity:** RR 1.21 (1.05-1.39) p = 0.008	Zhang, *et al.* (2015) (222)

PCI	8	2,331	February 2014	Clopidogrel treated **2* allele carriers versus clopidogrel treated non-carriers: **High on-clopidogrel platelet reactivity:** OR 2.22 (1.85-2.65)	Hou, *et al.* (2014) (300)
CAD (no PCI), PCI	24	36,076	November 2013	Clopidogrel treated no function allele (**2* and others not specified) carriers versus clopidogrel treated non-carriers: **MACE:** RR 1.32 (1.17-1.49) **Stent thrombosis:** RR 2.03 (1.74-2.36) **Bleeding**: RR 0.91 (0.73-1.13)	Sorich, *et al.* (2014) (174)
CAD (no PCI), PCI	22	25,564	August 2013	Clopidogrel treated no function allele (**2, *3, *4, *5, *6, *7, *8*) carriers versus clopidogrel treated non-carriers: **MACE:** RR 1.42 (1.18-1.71) $p < 0.001$ **CV death**: RR 2.07 (1.40-3.05) $p < 0.001$ **MI**: RR 1.66 (1.35-2.04) $p < 0.001$ **Stent thrombosis:** RR 1.72 (1.44-2.05) $p < 0.001$ **Bleeding:** RR 1.20 (1.06-1.35) $p = 0.003$	Niu, *et al.* (2015) (178)

ACS = acute coronary syndrome; CAD = coronary artery disease; CV = cardiovascular; CVD = cerebrovascular disease; MACCE = major adverse cardiovascular and cerebrovascular events; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack

TABLE S5. COMPARISON OF GUIDELINE AND LABEL RECOMMENDATIONS FOR CYP2C19-CLOPIDOGREL

Guideline or Label	Year	CYP2C19 UM	CYP2C19 RM	CYP2C19 NM	CYP2C19 IM	CYP2C19 PM	Recommendations for *CYP2C19* Testing
CPIC	2022	**ACS/PCI:** If considering clopidogrel, use at standard dose (75 mg/day) **Non-ACS/PCI CV:** No recommendation **NV:** No recommendation	**ACS/PCI:** If considering clopidogrel, use at standard dose (75 mg/day) **Non-ACS/PCI CV:** No recommendation **NV:** No recommendation	**ACS/PCI:** If considering clopidogrel, use at standard dose (75 mg/day) **Non-ACS/PCI CV:** If considering clopidogrel, use at standard dose (75 mg/day) **NV:** If considering clopidogrel, use at standard dose (75 mg/day)	**ACS/PCI:** Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication **Non-ACS/PCI CV:** No recommendation **NV:** Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically indicated and no contraindication	**ACS/PCI:** Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication **Non-ACS/PCI CV:** Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication **NV:** Avoid clopidogrel if possible. Consider an alternative $P2Y_{12}$ inhibitor at standard dose if clinically indicated and no contraindication.	n/a

DPWG	2018	NO action is required for this gene-drug interaction.	NO action is required for this gene-drug interaction.	Standard dosing	**PCI, STROKE, TIA**: Choose an alternative or double the dose to 150 mg/day (600 mg loading dose). Prasugrel, ticagrelor and acetylsalicylic acid/dipyridamole are not metabolized by CYP2C19 (or to a lesser extent). **OTHER INDICATIONS** No action required	**PCI, STROKE, TIA:** Avoid clopidogrel. Prasugrel, ticagrelor and acetylsalicylic acid/ dipyridamole are not metabolised by CYP2C19 (or to a lesser extent). **OTHER INDICATIONS** Determine the level of inhibition of platelet aggregation by clopidogrel. Consider an alternative in poor responders. Prasugrel and ticagrelor are not metabolised by CYP2C19 (or to a lesser extent)	n/a
RNPGx	2017	No recommendation	No recommendation	Standard dosing	Alternative antiplatelet therapy; based on current knowledge, it is not recommended to increase the	Alternative antiplatelet therapy; based on current knowledge, it is not recommended to increase the	Testing for the main *CYP2C19* deficiency alleles before instituting clopidogrel treatment is recommended (a test is essential for coronary angioplasty with stenting and based on the current state of

					clopidogrel dose in patients carrying the *CYP2C19*2* or **3* allele	clopidogrel dose in patients carrying the *CYP2C19*2* or **3* allele	knowledge this test is potentially useful in the other indications).
FDA	2016					**BOXED WARNING:** Consider use of another platelet $P2Y_{12}$ inhibitor in patients identified as CYP2C19 poor metabolizers	Tests are available to identify patients who are CYP2C19 poor metabolizers
EMA	Accessed 2021					In patients who are poor CYP2C19 metabolizers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function.	Tests are available to identify patients who are CYP2C19 poor metabolizers
PMDA	Accessed 2021					In clinical pharmacological studies, CYP2C19 poor metabolizers had diminished inhibition of platelet aggregation.	No comment
HCSC	Accessed 2021					In patients who are CYP2C19 poor metabolizers,	No comment

						clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.	
Swissmedic	Accessed 2021					The weak metabolism by CYP2C19 is	No comment

						associated with a reduced antiplatelet effect of clopidogrel. A higher dosage (initial dose 600 mg, followed by 150 mg/day) in slow metabolizers increases the antiplatelet effect. The use of higher doses of clopidogrel in slow metabolizers should be considered. An appropriate dose for this patient population has not yet been determined in clinical outcome studies.	
AHA	2016						There are specific drugs for which pharmacogenetic variant information can be reasonably used today, and this has become part of routine care at early adopter centers. A common philosophy in such centers is that genetic variant data can be viewed like physiological data or other biomarkers (eg, of renal or liver function) that have an impact on drug effects…The Clinical Pharmacogenetics Implementation Consortium

							publishes guidelines for implementation of pharmacogenetic test results into clinical practice and actionable prescribing decisions, with prioritization of tests offered in Clinical Laboratory Improvement Amendments–approved laboratories. Notably, the Clinical Pharmacogenetics Implementation Consortium guidelines center around how to apply a pharmacogenetic test result, not around whether and when to order the test. Warfarin and clopidogrel are two better known examples of drugs used commonly in heart disease patients that have FDA pharmacogenetic labeling to guide choice and dose of drug.
AHA/ACC	2016				**Refers to the 2011 ACCF/AHA/ SCAI PCI Guideline:** CLASS IIb When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate $P2Y_{12}$ inhibitor (e.g., prasugrel or ticagrelor) might	**Refers to the 2011 ACCF/AHA/ SCAI PCI Guideline:** CLASS IIb When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate $P2Y_{12}$ inhibitor (e.g., prasugrel or ticagrelor) might	The role of platelet function testing and genetic testing in patients treated with DAPT is addressed in the 2011 ACCF/ AHA/SCAI PCI guideline and the 2014 ACC/AHA NSTE-ACS guideline. To date, no RCT has demonstrated that routine platelet function testing or genetic testing to guide $P2Y_{12}$ inhibitor therapy improves outcome; thus, the routine use of platelet function and genetic testing is not recommended (Class III: No Benefit). **2011:** CLASS IIb

					be considered (Level of Evidence: C)	be considered (Level of Evidence: C)	Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. (Level of Evidence: C) CLASS III: NO BENEFIT The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended. (Level of Evidence: C) **2014:** Although higher platelet reactivity has been associated with a greater incidence of adverse events in patients undergoing stent implantation, a strategy of adjusting antiplatelet therapy based on routine platelet function testing has not been beneficial in reducing ischemic complications. Similarly, a strategy of routine genetic phenotype testing has also not been beneficial and thus is not recommended. A more detailed discussion of these issues and current recommendations about platelet function testing and genetic testing are in the 2011 PCI Guideline.
ESC	2020						Based on the results of the Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes

							(TROPICAL-ACS) and POPULAR Genetics trials, an approach of DAPT de-escalation guided by either platelet function testing (TROPICAL-ACS: NSTE-ACS and STEMI patients) or *CYP2C19*-directed genotyping (POPULAR Genetics: STEMI patients) may be considered in selected NSTE-ACS patients as an alternative to 12 months of potent platelet inhibition, especially for patients deemed unsuitable for maintained potent platelet inhibition. For further details, please refer to the updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in PCI. **2019 Updated Expert Consensus Statement** (Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding $P2Y_{12}$ Receptor Inhibitor Treatment in Percutaneous Coronary Intervention): Patients with stable CAD (elective PCI): *CYP2C19* genotyping in patients on clopidogrel treatment may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after elective PCI in stable CAD.

							CYP2C19 genotyping to escalate treatment in LoF allele carriers (especially **2* and **3*) during clopidogrel treatment is not recommended as a routine but may be considered in specific clinical scenarios (heterozygous and homozygous allele carriage should be taken into account). *CYP2C19* genotyping to screen for LoF alleles to determine the drug that would remain when DAPT de-escalation (e.g., triple treatment in which one antiplatelet agent is planned to be omitted) is being considered is not recommended. <u>Patients with acute coronary syndrome (NSTEMI/STEMI):</u> *CYP2C19* genotyping in patients on clopidogrel may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after PCI for ACS. Genotyping to escalate treatment in LoF allele carriers is not recommended, because of lack of data from dedicated studies. Genotyping to screen for LoF alleles when DAPT de-escalation is being considered in an individual patient is not recommended, because of lack of data from dedicated studies.

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; AHA, American Heart Association; CAD, coronary artery disease; CPIC, Clinical Pharmacogenetics Implementation Consortium; CV, cardiovascular indications; DAPT, dual antiplatelet therapy; DPWG, Dutch Pharmacogenetics

Working Group; EMA, European Medicines Agency; ESC, European Society of Cardiology; FDA, U.S. Food and Drug Administration; HCSC, Health Canada (Santé Canada); IM, intermediate metabolizer; LoF, loss of function; n/a, not applicable; NM, normal metabolizer; NSTE, non-ST elevation; NV, neurovascular indications; PCI, percutaneous coronary intervention; PM, poor metabolizer; PMDA, Pharmaceuticals and Medical Devices Agency, Japan; RCT, randomized controlled trial; RM, rapid metabolizer; RNPGx, French National Network of Pharmacogenetics; SCAI, Society for Cardiovascular Angiography and Interventions; UM, ultrarapid metabolizer

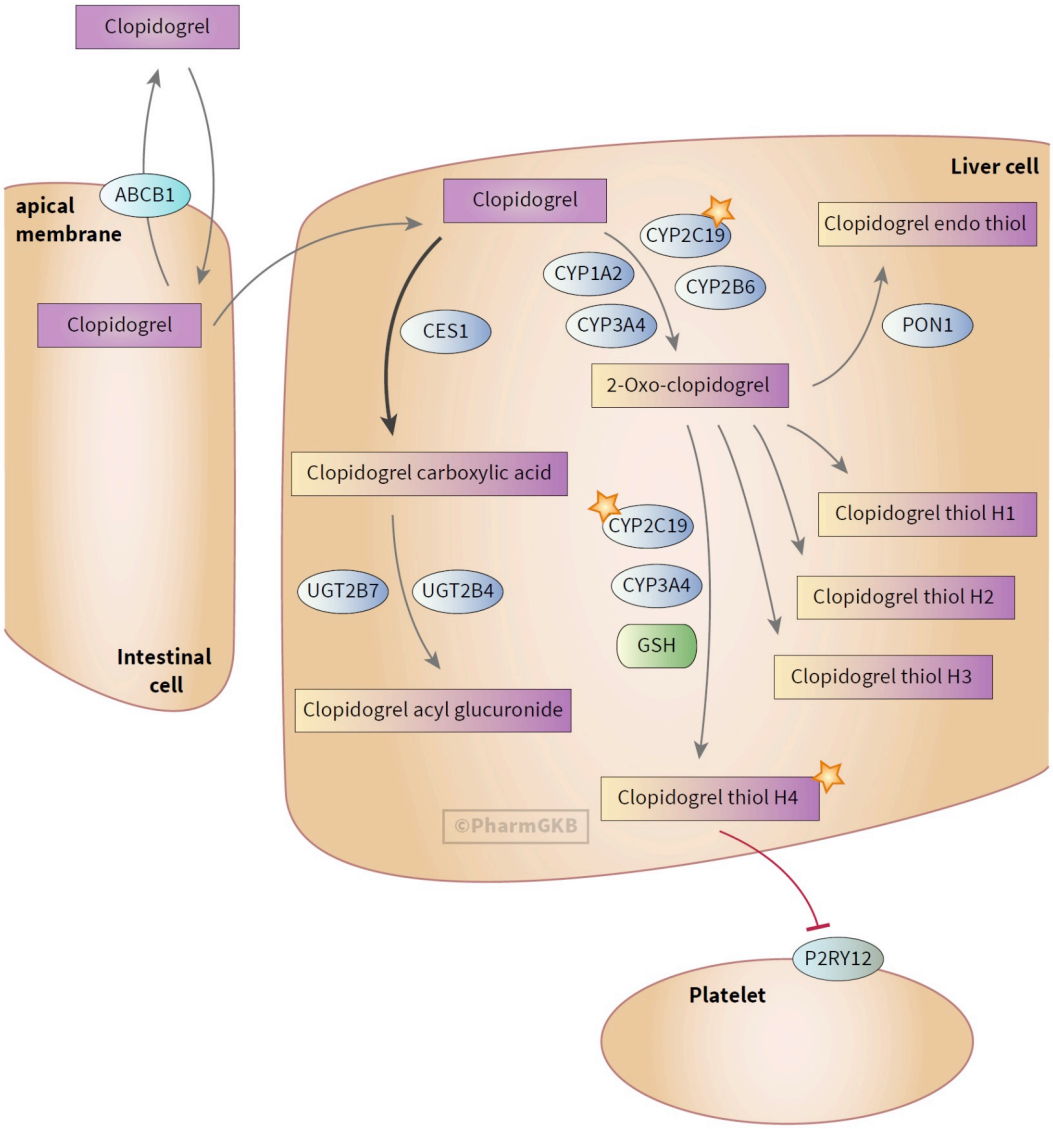

FIGURE S1. HEPATIC METABOLISM OF CLOPIDOGREL.
For a detailed and updated description, please see: https://www.pharmgkb.org/pathway/PA154424674. Image is available under a Creative Commons BY-SA 4.0 license (301).

REFERENCES

(1) CPIC. *CPIC® Guideline for Clopidogrel and CYP2C19*. <https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/> (2021). Accessed April 28 2021.

(2) Scott, S.A. *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clinical pharmacology and therapeutics* **94**, 317-23 (2013).

(3) Wang, Y. *et al.* Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA. *N Engl J Med*, (2021).

(4) Botton, M.R. *et al.* Structural variation at the CYP2C locus: Characterization of deletion and duplication alleles. *Hum Mutat* **40**, e37-e51 (2019).

(5) Botton, M.R. *et al.* PharmVar GeneFocus: CYP2C19. *Clinical pharmacology and therapeutics* **109**, 352-66 (2021).

(6) PharmGKB. *Gene-specific Information Tables for CYP2C19*. <https://www.pharmgkb.org/page/cyp2c19RefMaterials> (2021). Accessed April 28 2021.

(7) Kalman, L.V. *et al.* Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. *Clin Pharmacol Ther* **99**, 172-85 (2016).

(8) Pratt, V.M. *et al.* Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. *J Mol Diagn* **20**, 269-76 (2018).

(9) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf> (2018). Accessed April 28 2021.

(10) Hicks, J.K., Dunnenberger, H.M., Gumpper, K.F., Haidar, C.E. & Hoffman, J.M. Integrating pharmacogenomics into electronic health records with clinical decision support. *Am J Health Syst Pharm* **73**, 1967-76 (2016).

(11) Hoffman, J.M. *et al.* Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *J Am Med Inform Assoc* **23**, 796-801 (2016).

(12) Liu, M. *et al.* A Tutorial for Pharmacogenomics Implementation Through End-to-End Clinical Decision Support Based on Ten Years of Experience from PREDICT. *Clin Pharmacol Ther* **109**, 101-15 (2021).

(13) Caudle, K.E. *et al.* Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genet Med* **19**, 215-23 (2017).

(14) Braun, O.O. *et al.* Enhanced active metabolite generation and platelet inhibition with prasugrel compared to clopidogrel regardless of genotype in thienopyridine metabolic pathways. *Thromb Haemost* **110**, 1223-31 (2013).

(15) Gurbel, P.A. *et al.* The influence of smoking status on the pharmacokinetics and pharmacodynamics of clopidogrel and prasugrel: the PARADOX study. *J Am Coll Cardiol* **62**, 505-12 (2013).

(16) Gurbel, P.A. *et al.* The effect of CYP2C19 gene polymorphisms on the pharmacokinetics and pharmacodynamics of prasugrel 5-mg, prasugrel 10-mg and clopidogrel 75-mg in patients with coronary artery disease. *Thromb Haemost* **112**, 589-97 (2014).

(17) Erlinge, D. *et al.* Clopidogrel metaboliser status based on point-of-care CYP2C19 genetic testing in patients with coronary artery disease. *Thromb Haemost* **111**, 943-50 (2014).
(18) Karazniewicz-Lada, M., Danielak, D., Rubis, B., Burchardt, P., Oszkinis, G. & Glowka, F. The influence of genetic polymorphism of Cyp2c19 isoenzyme on the pharmacokinetics of clopidogrel and its metabolites in patients with cardiovascular diseases. *J Clin Pharmacol* **54**, 874-80 (2014).
(19) Simon, N., Finzi, J., Cayla, G., Montalescot, G., Collet, J.P. & Hulot, J.S. Omeprazole, pantoprazole, and CYP2C19 effects on clopidogrel pharmacokinetic-pharmacodynamic relationships in stable coronary artery disease patients. *Eur J Clin Pharmacol* **71**, 1059-66 (2015).
(20) Wang, X.Q., Shen, C.L., Wang, B.N., Huang, X.H., Hu, Z.L. & Li, J. Genetic polymorphisms of CYP2C19 2 and ABCB1 C3435T affect the pharmacokinetic and pharmacodynamic responses to clopidogrel in 401 patients with acute coronary syndrome. *Gene* **558**, 200-7 (2015).
(21) Bin Sayeed, M.S. *et al.* Prevalence of CYP2C19 alleles, pharmacokinetic and pharmacodynamic variation of clopidogrel and prasugrel in Bangladeshi population. *Clin Exp Pharmacol Physiol* **42**, 451-7 (2015).
(22) Liang, Y. *et al.* Active metabolite concentration of clopidogrel in patients taking different doses of aspirin: results of the interaction trial. *J Thromb Haemost* **13**, 347-52 (2015).
(23) Danese, E. *et al.* Relationship between pharmacokinetics and pharmacodynamics of clopidogrel in patients undergoing percutaneous coronary intervention: comparison between vasodilator-stimulated phosphoprotein phosphorylation assay and multiple electrode aggregometry. *J Thromb Haemost* **14**, 282-93 (2016).
(24) Li, C. *et al.* Gene variants in responsiveness to clopidogrel have no impact on clinical outcomes in Chinese patients undergoing percutaneous coronary intervention - A multicenter study. *Int J Cardiol* **240**, 360-6 (2017).
(25) Karazniewicz-Lada, M. *et al.* Impact of genetic variants of selected cytochrome P450 isoenzymes on pharmacokinetics and pharmacodynamics of clopidogrel in patients co-treated with atorvastatin or rosuvastatin. *Eur J Clin Pharmacol* **76**, 419-30 (2020).
(26) Amoah, V. *et al.* Near patient anti-platelet response testing over time and gene analysis in patients admitted with acute coronary syndromes. *Platelets* **24**, 643-8 (2013).
(27) Kreutz, R.P. *et al.* Cytochrome P450 3A4*22, PPAR-alpha, and ARNT polymorphisms and clopidogrel response. *Clin Pharmacol* **5**, 185-92 (2013).
(28) Tsantes, A.E. *et al.* Impact of the proton pump inhibitors and CYP2C19*2 polymorphism on platelet response to clopidogrel as assessed by four platelet function assays. *Thromb Res* **132**, e105-11 (2013).
(29) Saucedo, J.F. *et al.* Decrease in high on-treatment platelet reactivity (HPR) prevalence on switching from clopidogrel to prasugrel: insights from the switching anti-platelet (SWAP) study. *Thromb Haemost* **109**, 347-55 (2013).
(30) Zhang, L. *et al.* Genetic determinants of high on-treatment platelet reactivity in clopidogrel treated Chinese patients. *Thromb Res* **132**, 81-7 (2013).
(31) Nishio, R. *et al.* Paraoxonase-1 activity affects the clopidogrel response in CYP2C19 loss-of-function carriers. *Thromb Res* **132**, 558-64 (2013).
(32) Zou, J.J., Fan, H.W., Chen, S.L., Tan, J., He, B.S. & Xie, H.G. Efffect of the ABCC3 -211C/T polymorphism on clopidogrel responsiveness in patients with percutaneous coronary intervention. *Clin Exp Pharmacol Physiol* **40**, 504-9 (2013).

(33) Tousoulis, D. *et al.* The impact of CYP2C19 genotype on cardiovascular events and platelet reactivity in patients with coronary artery disease receiving clopidogrel. *Int J Cardiol* **168**, 1594-6 (2013).
(34) Al-Azzam, S.I. *et al.* Factors that contribute to clopidogrel resistance in cardiovascular disease patients: environmental and genetic approach. *Int J Clin Pharmacol Ther* **51**, 179-86 (2013).
(35) Correll, M. *et al.* Mutational analysis clopidogrel resistance and platelet function in patients scheduled for coronary artery bypass grafting. *Genomics* **101**, 313-7 (2013).
(36) El-Halabi, M.M. *et al.* CYP2C19 genetic polymorphism, rabeprazole and esomeprazole have no effect on the antiplatelet action of clopidogrel. *J Cardiovasc Pharmacol* **62**, 41-9 (2013).
(37) Hong, J.M., Shin, D.H., Lim, Y.A., Lee, J.S. & Joo, I.S. Ticlopidine with Ginkgo Biloba extract: a feasible combination for patients with acute cerebral ischemia. *Thromb Res* **131**, e147-53 (2013).
(38) Palmerini, T. *et al.* Impact of gene polymorphisms, platelet reactivity, and the SYNTAX score on 1-year clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention: the GEPRESS study. *JACC Cardiovasc Interv* **7**, 1117-27 (2014).
(39) Tresukosol, D. *et al.* Effects of cytochrome P450 2C19 and paraoxonase 1 polymorphisms on antiplatelet response to clopidogrel therapy in patients with coronary artery disease. *PLoS One* **9**, e110188 (2014).
(40) Tan, D.S., Yeo, A.H., Ho, H.K., Wee, H.L. & Ong, H.Y. Asian study of clopidogrel (ASCLOP) responsiveness: the contributions of genetic and non-genetic factors. *Int J Cardiol* **171**, e21-3 (2014).
(41) Mizobe, M. *et al.* Impact of CYP2C19 polymorphism on clinical outcome following coronary stenting is more important in non-diabetic than diabetic patients. *Thromb Res* **134**, 72-7 (2014).
(42) Park, Y. *et al.* Pharmacodynamic effects of cilostazol versus clopidogrel in stented patients under proton pump inhibitor co-administration: the ACCEL-PARAZOL study. *J Atheroscler Thromb* **21**, 1121-39 (2014).
(43) Jeong, Y.H., Bliden, K.P., Shuldiner, A.R., Tantry, U.S. & Gurbel, P.A. Thrombin-induced platelet-fibrin clot strength: relation to high on-clopidogrel platelet reactivity, genotype, and post-percutaneous coronary intervention outcomes. *Thromb Haemost* **111**, 713-24 (2014).
(44) Peace, A.J. *et al.* alpha2A-Adrenergic receptor polymorphism potentiates platelet reactivity in patients with stable coronary artery disease carrying the cytochrome P450 2C19*2 genetic variant. *Arterioscler Thromb Vasc Biol* **34**, 1314-9 (2014).
(45) Siller-Matula, J.M. *et al.* Interplay between genetic and clinical variables affecting platelet reactivity and cardiac adverse events in patients undergoing percutaneous coronary intervention. *PLoS One* **9**, e102701 (2014).
(46) Hokimoto, S. *et al.* Impact of CYP3A5 polymorphism on platelet reactivity at percutaneous coronary intervention and after 9 months of aspirin and clopidogrel therapy in Japanese patients with coronary artery disease. *Eur J Clin Pharmacol* **70**, 667-73 (2014).
(47) Guo, B., Tan, Q., Guo, D., Shi, Z., Zhang, C. & Guo, W. Patients carrying CYP2C19 loss of function alleles have a reduced response to clopidogrel therapy and a greater risk of in-

stent restenosis after endovascular treatment of lower extremity peripheral arterial disease. *J Vasc Surg* **60**, 993-1001 (2014).
(48) Zhang, S. *et al.* VASP phosphorylation and genetic polymorphism for clopidogrel resistance in Chinese patients with non-cardioembolic ischemic stroke. *Thromb Res* **134**, 1272-7 (2014).
(49) Larsen, P.D. *et al.* Prevalence and significance of CYP2C19*2 and CYP2C19*17 alleles in a New Zealand acute coronary syndrome population. *Intern Med J* **45**, 537-45 (2015).
(50) Arya, V., Mahajan, P., Saraf, A., Mohanty, A., Sawhney, J.P. & Bhargava, M. Association of CYP2C19, CYP3A5 and GPIIb/IIIa gene polymorphisms with Aspirin and Clopidogrel Resistance in a cohort of Indian patients with Coronary Artery Disease. *Int J Lab Hematol* **37**, 809-18 (2015).
(51) Cui, H. *et al.* Correlation Between SNPs in Candidate Genes and VerifyNow-Detected Platelet Responsiveness to Aspirin and Clopidogrel Treatment. *Cardiovasc Drugs Ther* **29**, 137-46 (2015).
(52) Sun, B. *et al.* Diversity of platelet function and genetic polymorphism in clopidogrel-treated Chinese patients. *Genet Mol Res* **14**, 1434-42 (2015).
(53) Peng, L. *et al.* Joint effects of CYP2C19*2 and smoking status on clopidogrel responsiveness in patients with acute coronary syndrome. *Int J Cardiol* **180**, 196-8 (2015).
(54) Chen, Y., Huang, X., Tang, Y., Xie, Y. & Zhang, Y. Both PON1 Q192R and CYP2C19*2 influence platelet response to clopidogrel and ischemic events in Chinese patients undergoing percutaneous coronary intervention. *Int J Clin Exp Med* **8**, 9266-74 (2015).
(55) Arima, Y. *et al.* Comparison of the effect of CYP2C19 polymorphism on clinical outcome between acute coronary syndrome and stable angina. *J Cardiol* **65**, 494-500 (2015).
(56) Konishi, A. *et al.* Impact of cytochrome P450 2C19 loss-of-function polymorphism on intra-stent thrombi and lesion outcome after everolimus-eluting stent implantation compared to that after first-generation drug-eluting stent implantation. *Int J Cardiol* **179**, 476-83 (2015).
(57) Nakamura, M. *et al.* Optimal cutoff value of P2Y12 reaction units to prevent major adverse cardiovascular events in the acute periprocedural period: post-hoc analysis of the randomized PRASFIT-ACS study. *Int J Cardiol* **182**, 541-8 (2015).
(58) Nooney, V.B., Hurst, N.L., Chirkov, Y.Y., De Caterina, R. & Horowitz, J.D. Post receptor determinants of acute platelet response to clopidogrel in patients with symptomatic myocardial ischemia. *Vascul Pharmacol* **65-66**, 17-22 (2015).
(59) Collet, J.P. *et al.* Genetic and platelet function testing of antiplatelet therapy for percutaneous coronary intervention: the ARCTIC-GENE study. *Eur J Clin Pharmacol* **71**, 1315-24 (2015).
(60) Kim, H. *et al.* Evaluation of the INNOVANCE PFA P2Y assay and its association with CYP2C19 genotypes. *Platelets* **26**, 148-53 (2015).
(61) Yang, J. *et al.* CYP2C19 LOF alleles confer no risk for HTPR but higher risk for recurrent ischemic events in clopidogrel treated elderly ACS patients. *Int J Cardiol* **189**, 225-7 (2015).
(62) Golukhova, E.Z., Ryabinina, M.N., Bulaeva, N.I., Grigorian, M.V., Kubova, M. & Serebruany, V.L. Clopidogrel response variability: impact of genetic polymorphism and

platelet biomarkers for predicting adverse outcomes poststenting. *Am J Ther* **22**, 222-30 (2015).
(63) Qiu, L.N. *et al.* Influence of CYP2C19 polymorphisms on platelet reactivity and clinical outcomes in ischemic stroke patients treated with clopidogrel. *Eur J Pharmacol* **747**, 29-35 (2015).
(64) Han, Y. *et al.* Influence of Genetic Polymorphisms on Clopidogrel Response and Clinical Outcomes in Patients with Acute Ischemic Stroke CYP2C19 Genotype on Clopidogrel Response. *CNS Neurosci Ther* **21**, 692-7 (2015).
(65) Wang, X. *et al.* Relationship between clopidogrel-related polymorphisms and variable platelet reactivity at 1 year: A cohort study from Han Chinese. *J Res Med Sci* **21**, 111 (2016).
(66) Ou, W., He, Y., Li, A., Liu, B. & Jin, L. Genotype Frequencies of CYP2C19, P2Y12 and GPIIIa Polymorphisms in Coronary Heart Disease Patients of Han Ethnicity, and Their Impact on Clopidogrel Responsiveness. *Int Heart J* **57**, 586-92 (2016).
(67) Carreras, E.T. *et al.* Diabetes mellitus, CYP2C19 genotype, and response to escalating doses of clopidogrel. Insights from the ELEVATE-TIMI 56 Trial. *Thromb Haemost* **116**, 69-77 (2016).
(68) Kirac, D. *et al.* Effects of genetic factors to stent thrombosis due to clopidogrel resistance after coronary stent placement. *Cell Mol Biol (Noisy-le-grand)* **62**, 51-5 (2016).
(69) Doll, J.A. *et al.* Impact of CYP2C19 Metabolizer Status on Patients With ACS Treated With Prasugrel Versus Clopidogrel. *J Am Coll Cardiol* **67**, 936-47 (2016).
(70) Choi, I.J. *et al.* CYP2C19 loss-of-function alleles are not associated with clinical outcome of clopidogrel therapy in patients treated with newer-generation drug-eluting stents. *Medicine (Baltimore)* **95**, e4049 (2016).
(71) Sun, H. *et al.* Impact of CYP2C19 Variants on Clinical Efficacy of Clopidogrel and 1-Year Clinical Outcomes in Coronary Heart Patients Undergoing Percutaneous Coronary Intervention. *Front Pharmacol* **7**, 453 (2016).
(72) Choi, J.L. *et al.* The Diagnostic Utility of the Point-of-Care CYP2C19 Genotyping Assay in Patients with Acute Coronary Syndrome Dosing Clopidogrel: Comparison with Platelet Function Test and SNP Genotyping. *Ann Clin Lab Sci* **46**, 489-94 (2016).
(73) Forni Ogna, V. *et al.* Effect of long-term adherence to clopidogrel on the VASP-PRI after elective coronary stent implantation: a randomized controlled study. *Br J Clin Pharmacol* **82**, 1486-97 (2016).
(74) Backovic, D. *et al.* Influence of Cyp2c19*2 Gene Variant on Therapeutic Response During Clopidogrel Treatment in Patients with Carotid Artery Stenosis. *J Med Biochem* **35**, 26-33 (2016).
(75) Backovic, D. *et al.* Clopidogrel High On-Treatment Platelet Reactivity in Patients with Carotid Artery Stenosis Undergoing Endarterectomy. A Pilot Study. *Curr Vasc Pharmacol* **14**, 563-9 (2016).
(76) Liu, R. *et al.* Associations of CYP3A4, NR1I2, CYP2C19 and P2RY12 polymorphisms with clopidogrel resistance in Chinese patients with ischemic stroke. *Acta Pharmacol Sin* **37**, 882-8 (2016).
(77) Yi, X. *et al.* Association of Cytochrome P450 Genetic Variants with Clopidogrel Resistance and Outcomes in Acute Ischemic Stroke. *J Atheroscler Thromb* **23**, 1188-200 (2016).

(78) Yi, X., Zhou, Q., Wang, C., Lin, J., Cheng, W. & Chi, L. Concomitant Use of Proton Pump Inhibitors and Clopidogrel Is Not Associated with Adverse Outcomes after Ischemic Stroke in Chinese Population. *J Stroke Cerebrovasc Dis* **25**, 2859-67 (2016).
(79) Lin, M. *et al.* Association between CYP2C19 Polymorphisms and Outcomes in Cerebral Endovascular Therapy. *AJNR Am J Neuroradiol* **37**, 108-13 (2016).
(80) Garcia-Lagunar, M.H. *et al.* Genotyping of six clopidogrel-metabolizing enzyme polymorphisms has a minor role in the assessment of platelet reactivity in patients with acute coronary syndrome. *Anatol J Cardiol* **17**, 303-12 (2017).
(81) Saydam, F. *et al.* The CYP2C19*2 and CYP2C19*17 Polymorphisms play a Vital Role in Clopidogrel Responsiveness after Percutaneous Coronary Intervention: A Pharmacogenomics Study. *Basic Clin Pharmacol Toxicol* **121**, 29-36 (2017).
(82) Marchini, J.F. *et al.* Decreased platelet responsiveness to clopidogrel correlates with CYP2C19 and PON1 polymorphisms in atherosclerotic patients. *Braz J Med Biol Res* **50**, e5660 (2017).
(83) Nie, X.Y. *et al.* Haplotype of platelet receptor P2RY12 gene is associated with residual clopidogrel on-treatment platelet reactivity. *J Zhejiang Univ Sci B* **18**, 37-47 (2017).
(84) Forni Ogna, V. *et al.* Comparative Long-Term Effect of Three Anti-P2Y12 Drugs after Percutaneous Angioplasty: An Observational Study Based on Electronic Drug Adherence Monitoring. *Front Pharmacol* **8**, 738 (2017).
(85) Amin, A.M. *et al.* The effect of CYP2C19 genetic polymorphism and non-genetic factors on clopidogrel platelets inhibition in East Asian coronary artery disease patients. *Thromb Res* **158**, 22-4 (2017).
(86) Siasos, G. *et al.* Genotyping, Platelet Activation, and Cardiovascular Outcome in Patients after Percutaneous Coronary Intervention: Two Pieces of the Puzzle of Clopidogrel Resistance. *Cardiology* **137**, 104-13 (2017).
(87) Oledzki, S. *et al.* Variability of platelet response to clopidogrel is not related to adverse cardiovascular events in patients with stable coronary artery disease undergoing percutaneous coronary intervention. *Eur J Clin Pharmacol* **73**, 1085-94 (2017).
(88) Tan, S.S.N. *et al.* Association of CYP2C19*2 polymorphism with clopidogrel response and 1-year major adverse cardiovascular events in a multiethnic population with drug-eluting stents. *Pharmacogenomics* **18**, 1225-39 (2017).
(89) Marginean, A. *et al.* The Impact of CYP2C19 Loss-of-Function Polymorphisms, Clinical, and Demographic Variables on Platelet Response to Clopidogrel Evaluated Using Impedance Aggregometry. *Clin Appl Thromb Hemost* **23**, 255-65 (2017).
(90) Alhazzani, A.A., Munisamy, M. & Karunakaran, G. Pharmacogenetics of CYP2C19 genetic polymorphism on clopidogrel response in patients with ischemic stroke from Saudi Arabia. *Neurosciences (Riyadh)* **22**, 31-7 (2017).
(91) Li, X.G. *et al.* Association of genetic variant and platelet function in patients undergoing neuroendovascular stenting. *Postgrad Med J* **93**, 555-9 (2017).
(92) Li, W. *et al.* Baseline platelet parameters for predicting early platelet response and clinical outcomes in patients with non-cardioembolic ischemic stroke treated with clopidogrel. *Oncotarget* **8**, 93771-84 (2017).
(93) Yi, X., Wang, Y., Lin, J., Cheng, W., Zhou, Q. & Wang, C. Interaction of CYP2C19, P2Y12, and GPIIIa Variants Associates With Efficacy of Clopidogrel and Adverse Events on Patients With Ischemic Stroke. *Clin Appl Thromb Hemost* **23**, 761-8 (2017).

(94) Zhang, J. *et al.* Association between platelet function and recurrent ischemic vascular events after TIA and minor stroke. *Int J Clin Pharmacol Ther* **55**, 789-97 (2017).
(95) Rao, Z. *et al.* The association between high on-treatment platelet reactivity and early recurrence of ischemic events after minor stroke or TIA. *Neurol Res* **39**, 719-26 (2017).
(96) Ge, H. *et al.* Influence of CYP2C19 genetic polymorphisms on clinical outcomes of intracranial aneurysms treated with stent-assisted coiling. *J Neurointerv Surg* **9**, 958-62 (2017).
(97) Gross, L. *et al.* Genotype-Phenotype Association and Impact on Outcomes following Guided De-Escalation of Anti-Platelet Treatment in Acute Coronary Syndrome Patients: The TROPICAL-ACS Genotyping Substudy. *Thromb Haemost* **118**, 1656-67 (2018).
(98) Mirzaev, K.B. *et al.* The ABCB1, CYP2C19, CYP3A5 and CYP4F2 genetic polymorphisms and platelet reactivity in the early phases of acute coronary syndromes. *Drug Metab Pers Ther* **33**, 109-18 (2018).
(99) Wang, J.Y. *et al.* CRISPLD1 rs12115090 polymorphisms alters antiplatelet potency of clopidogrel in coronary artery disease patients in Chinese Han. *Gene* **678**, 226-32 (2018).
(100) Li, H. *et al.* Association of N6AMT1 rs2254638 Polymorphism With Clopidogrel Response in Chinese Patients With Coronary Artery Disease. *Front Pharmacol* **9**, 1039 (2018).
(101) Hou, X., Han, W., Gan, Q., Liu, Y. & Fang, W. CYP2C19 and ABCB1 genetic polymorphisms correlate with the recurrence of ischemic cardiovascular adverse events after clopidogrel treatment. *J Clin Lab Anal* **32**, e22369 (2018).
(102) Hassani Idrissi, H., Hmimech, W., Khorb, N.E., Akoudad, H., Habbal, R. & Nadifi, S. A synergic effect between CYP2C19*2, CYP2C19*3 loss-of-function and CYP2C19*17 gain-of-function alleles is associated with Clopidogrel resistance among Moroccan Acute Coronary Syndromes patients. *BMC Res Notes* **11**, 46 (2018).
(103) Ebisawa, S. *et al.* Comparison of platelet aggregation response in switching regimen from prasugrel to clopidogrel between CYP2C19 extensive versus non-extensive metabolizers. *Cardiovasc Interv Ther* **33**, 277-84 (2018).
(104) Nie, X.Y. *et al.* Genetic mutations in PEAR1 associated with cardiovascular outcomes in Chinese patients with acute coronary syndrome. *Thromb Res* **163**, 77-82 (2018).
(105) Golukhova, E.Z., Grigoryan, M.V., Ryabinina, M.N., Bulaeva, N.I. & Serebruany, V.L. Body Mass Index and Plasma P-Selectin before Coronary Stenting Predict High Residual Platelet Reactivity at 6 Months on Dual Antiplatelet Therapy. *Cardiology* **139**, 132-6 (2018).
(106) Hernandez-Suarez, D.F. *et al.* Pharmacogenetic association study on clopidogrel response in Puerto Rican Hispanics with cardiovascular disease: a novel characterization of a Caribbean population. *Pharmgenomics Pers Med* **11**, 95-106 (2018).
(107) Hernandez-Suarez, D.F. *et al.* Effect of cilostazol on platelet reactivity among patients with peripheral artery disease on clopidogrel therapy. *Drug Metab Pers Ther* **33**, 49-55 (2018).
(108) Tomek, A. *et al.* Impact of CYP2C19 Polymorphisms on Clinical Outcomes and Antiplatelet Potency of Clopidogrel in Caucasian Poststroke Survivors. *Am J Ther* **25**, e202-e12 (2018).
(109) Lin, J. *et al.* Dual therapy with clopidogrel and aspirin prevents early neurological deterioration in ischemic stroke patients carrying CYP2C19*2 reduced-function alleles. *Eur J Clin Pharmacol* **74**, 1131-40 (2018).

(110) Yi, X., Han, Z., Zhou, Q., Cheng, W., Lin, J. & Wang, C. Concomitant Use of Proton-Pump Inhibitors and Clopidogrel Increases the Risk of Adverse Outcomes in Patients With Ischemic Stroke Carrying Reduced-Function CYP2C19*2. *Clin Appl Thromb Hemost* **24**, 55-62 (2018).
(111) Su, Q. *et al.* Association of CYP2C19 Polymorphism with Clopidogrel Resistance in Patients with Acute Coronary Syndrome in China. *Med Sci Monit* **25**, 7138-48 (2019).
(112) Pandey, C.P. *et al.* Aspirin & clopidogrel non-responsiveness & its association with genetic polymorphisms in patients with myocardial infarction. *Indian J Med Res* **150**, 50-61 (2019).
(113) Cedillo-Salazar, F.R. *et al.* Association of CYP2C19*2 polymorphism with clopidogrel resistance among patients with high cardiovascular risk in Northeastern Mexico. *Arch Cardiol Mex* **89**, 324-9 (2019).
(114) Akram, N. *et al.* Cytochrome 2C19 and paraoxonase-1 polymorphisms and clopidogrel resistance in ischemic heart disease patients. *Per Med*, (2019).
(115) Peng, W., Shi, X., Xu, X. & Lin, Y. Both CYP2C19 and PON1 Q192R Genotypes Influence Platelet Response to Clopidogrel by Thrombelastography in Patients with Acute Coronary Syndrome. *Cardiovasc Ther* **2019**, 3470145 (2019).
(116) Lee, J. *et al.* CYP2C19 Polymorphism is Associated With Amputation Rates in Patients Taking Clopidogrel After Endovascular Intervention for Critical Limb Ischaemia. *Eur J Vasc Endovasc Surg* **58**, 373-82 (2019).
(117) Ma, Q., Chen, G.Z., Zhang, Y.H., Zhang, L. & Huang, L.A. Clinical outcomes and predictive model of platelet reactivity to clopidogrel after acute ischemic vascular events. *Chin Med J (Engl)* **132**, 1053-62 (2019).
(118) Patel, S., Arya, V., Saraf, A., Bhargava, M. & Agrawal, C.S. Aspirin and Clopidogrel Resistance in Indian Patients with Ischemic Stroke and its Associations with Gene Polymorphisms: A Pilot Study. *Ann Indian Acad Neurol* **22**, 147-52 (2019).
(119) Saiz-Rodriguez, M. *et al.* Influence of CYP450 Enzymes, CES1, PON1, ABCB1, and P2RY12 Polymorphisms on Clopidogrel Response in Patients Subjected to a Percutaneous Neurointervention. *Clin Ther* **41**, 1199-212 e2 (2019).
(120) Saiz-Rodriguez, M., Belmonte, C. & Abad-Santos, F. CYP2C19 Ultrarapid Phenotype as a Risk Predictor of Subsequent Events During Clopidogrel Treatment in Patients Undergoing a Percutaneous Neurointervention. *Clin Pharmacol Ther* **105**, 1074-5 (2019).
(121) Saiz-Rodriguez, M. *et al.* Influence of CYP2C19 Phenotype on the Effect of Clopidogrel in Patients Undergoing a Percutaneous Neurointervention Procedure. *Clin Pharmacol Ther* **105**, 661-71 (2019).
(122) Alakbarzade, V., Huang, X., Ster, I.C., McEntagart, M. & Pereira, A.C. High on-clopidogrel platelet reactivity in ischaemic stroke or transient ischaemic attack: Systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* **29**, 104877 (2020).
(123) Jirungda, S., Pussadhamma, B., Komanasin, N., Senthong, V. & Leuangwatthananon, W. Interaction of CYP2C19 G681A polymorphism and omeprazole on clopidogrel responsiveness and impact in patients with acute coronary syndrome. *Coron Artery Dis* **31**, 266-72 (2020).
(124) Lewis, J.P. *et al.* Pharmacogenomic polygenic response score predicts ischaemic events and cardiovascular mortality in clopidogrel-treated patients. *Eur Heart J Cardiovasc Pharmacother* **6**, 203-10 (2020).

(125) Mohareb, M.W., AbdElghany, M., Zaki, H.F. & El-Abhar, H.S. Diabetes and CYP2C19 Polymorphism Synergistically Impair the Antiplatelet Activity of Clopidogrel Compared With Ticagrelor in Percutaneous Coronary Intervention-treated Acute Coronary Syndrome Patients. *J Cardiovasc Pharmacol* **76**, 478-88 (2020).
(126) Zhang, Z., Chen, M., Zhang, L. & Zhao, Q. The impact of cytochrome 450 and Paraoxonase polymorphisms on clopidogrel resistance and major adverse cardiac events in coronary heart disease patients after percutaneous coronary intervention. *BMC Pharmacol Toxicol* **21**, 1 (2020).
(127) Gairolla, J. *et al.* Clopidogrel response in ischemic stroke patients: Is polymorphism or gender more important? Results of the CRISP study. *J Clin Neurosci* **76**, 81-6 (2020).
(128) Fu, H., Hu, P., Ma, C., Peng, F. & He, Z. Association of clopidogrel high on-treatment reactivity with clinical outcomes and gene polymorphism in acute ischemic stroke patients: An observational study. *Medicine (Baltimore)* **99**, e19472 (2020).
(129) Sun, J. *et al.* Should CYP2C19 Genotyping Be Recommended as a Straight Forward Approach to Optimize Clopidogrel Utilization in Patients with Ischemic Stroke Complicated by Type 2 Diabetes Mellitus? *Pharmgenomics Pers Med* **13**, 645-53 (2020).
(130) Rath, C.L., Jorgensen, N.R. & Wienecke, T. Clopidogrel responder status is uninfluenced by CYP2C19*2 in Danish patients with stroke. *PLoS One* **15**, e0236260 (2020).
(131) Lv, H. *et al.* High On-Treatment Platelet Reactivity as Predictor of Long-term Clinical Outcomes in Stroke Patients with Antiplatelet Agents. *Transl Stroke Res*, (2021).
(132) Shi, G.X., Zhao, Z.H., Yang, X.Y., Lin, M. & Chen, Z.X. Correlation study of CYP2C19 gene polymorphism and clopidogrel resistance in Han Chinese patients with cerebral infarction in Guizhou region. *Medicine (Baltimore)* **100**, e24481 (2021).
(133) Shi, H.T. *et al.* The Dynamic Effect of Non-CYP3A4-Metabolized and CYP3A4-Metabolized Statins on Clopidogrel Resistance in Patients With Cerebral Infarction. *Front Pharmacol* **12**, 738562 (2021).
(134) Tang, X.F. *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* **69**, 1103-12 (2013).
(135) Nagashima, Z. *et al.* Platelet reactivity in the early and late phases of acute coronary syndromes according to cytochrome P450 2C19 phenotypes. *J Cardiol* **62**, 158-64 (2013).
(136) Liu, Y., Liu, N., Li, W., Shao, H., Zhi, H. & Li, J. Relationship of CYP2C19*2 and CYP2C19*3 gene polymorphism with clopidogrel response variability and recurrent cardiovascular events in Chinese patients undergoing percutaneous coronary intervention. *Pharmacology* **91**, 165-72 (2013).
(137) Nakata, T. *et al.* Relationship between CYP2C19 loss-of-function polymorphism and platelet reactivities with clopidogrel treatment in Japanese patients undergoing coronary stent implantation. *Circ J* **77**, 1436-44 (2013).
(138) Yang, J., Zhao, H.D., Tan, J., Ding, Y.L., Gu, Z.Q. & Zou, J.J. CYP2C19 polymorphism and antiplatelet effects of clopidogrel in Chinese stroke patients. *Pharmazie* **68**, 183-6 (2013).
(139) Jia, D.M. *et al.* CYP2C19 polymorphisms and antiplatelet effects of clopidogrel in acute ischemic stroke in China. *Stroke* **44**, 1717-9 (2013).

(140) Tatarunas, V. *et al.* The role of clinical parameters and of CYP2C19 G681 and CYP4F2 G1347A polymorphisms on platelet reactivity during dual antiplatelet therapy. *Blood Coagul Fibrinolysis* **25**, 369-74 (2014).
(141) Hokimoto, S. *et al.* Impact of CYP2C19 polymorphism and proton pump inhibitors on platelet reactivity to clopidogrel and clinical outcomes following stent implantation. *Thromb Res* **133**, 599-605 (2014).
(142) Xie, C. *et al.* The effects of CES1A2 A(-816)C and CYP2C19 loss-of-function polymorphisms on clopidogrel response variability among Chinese patients with coronary heart disease. *Pharmacogenet Genomics* **24**, 204-10 (2014).
(143) Isshiki, T. *et al.* Prasugrel, a third-generation P2Y12 receptor antagonist, in patients with coronary artery disease undergoing elective percutaneous coronary intervention. *Circ J* **78**, 2926-34 (2014).
(144) Liu, T. *et al.* CYP2C19 polymorphisms and coronary heart disease risk factors synergistically impact clopidogrel response variety after percutaneous coronary intervention. *Coron Artery Dis* **25**, 412-20 (2014).
(145) Li, S., Shi, Y., Wang, H., Zhang, W. & Liu, J. Impact of cytochrome P450 2C19*2 polymorphism on intra-stent thrombus assessed by follow-up optical coherence tomography in Chinese patients receiving clopidogrel. *J Thromb Thrombolysis* **40**, 88-96 (2015).
(146) Hokimoto, S. *et al.* Impact of esomeprazole on platelet reactivity and clinical outcome according to CYP2C19 genotype in coronary heart disease patients during dual antiplatelet therapy. *Thromb Res* **135**, 1081-6 (2015).
(147) Liu, J., Nie, X.Y., Zhang, Y., Lu, Y., Shi, L.W. & Wang, W.M. CYP2C19*2 and Other Allelic Variants Affecting Platelet Response to Clopidogrel Tested by Thrombelastography in Patients with Acute Coronary Syndrome. *Chin Med J (Engl)* **128**, 2183-8 (2015).
(148) Tang, N., Yin, S., Sun, Z., Xu, X. & Qin, J. The relationship between on-clopidogrel platelet reactivity, genotype, and post-percutaneous coronary intervention outcomes in Chinese patients. *Scand J Clin Lab Invest* **75**, 223-9 (2015).
(149) Zhang, M., Liu, X., Wang, L., Wang, Y., Ju, L. & Li, J. Cigarette smoking might weaken the prognostic significance of cytochrome P450 2C19*2 polymorphism in acute myocardial infarction patients. *J Cell Mol Med* **20**, 1247-54 (2016).
(150) Li, S. *et al.* Correlation between the CYP2C19 phenotype status and the results of three different platelet function tests in cardiovascular disease patients receiving antiplatelet therapy: an emphasis on newly introduced platelet function analyzer-200 P2Y test. *Ann Lab Med* **36**, 42-8 (2016).
(151) Liu, X. *et al.* Effect of genetic and coexisting polymorphisms on platelet response to clopidogrel in Chinese Han patients with acute coronary syndrome. *J Genet* **95**, 231-7 (2016).
(152) Dong, P., Yang, X. & Bian, S. Genetic Polymorphism of CYP2C19 and Inhibitory Effects of Ticagrelor and Clopidogrel Towards Post-Percutaneous Coronary Intervention (PCI) Platelet Aggregation in Patients with Acute Coronary Syndromes. *Med Sci Monit* **22**, 4929-36 (2016).
(153) Tatarunas, V., Kupstyte, N., Zaliunas, R., Giedraitiene, A. & Lesauskaite, V. The impact of clinical and genetic factors on ticagrelor and clopidogrel antiplatelet therapy. *Pharmacogenomics* **18**, 969-79 (2017).

(154) Tatarunas, V. *et al.* The impact of CYP2C19*2, CYP4F2*3, and clinical factors on platelet aggregation, CYP4F2 enzyme activity, and 20-hydroxyeicosatetraenoic acid concentration in patients treated with dual antiplatelet therapy. *Blood Coagul Fibrinolysis* **28**, 658-64 (2017).
(155) Zhang, H.Z., Kim, M.H., Guo, L.Z. & Serebruany, V. CYP2C19 but not CYP2B6, CYP3A4, CYP3A5, ABCB1, PON1 or P2Y12 genetic polymorphism impacts antiplatelet response after clopidogrel in Koreans. *Blood Coagul Fibrinolysis* **28**, 56-61 (2017).
(156) Tan, S.S.N., Koh, K.T., Tiong, L.L., Ong, T.K. & Fong, A.Y.Y. Late stent thrombosis in a patient with CYP2C19*3/*17 genotype and clopidogrel high on-treatment platelet reactivity. *Pharmacogenomics* **19**, 1151-7 (2018).
(157) Chouchene, S. *et al.* Clopidogrel utilization in patients with coronary artery disease and diabetes mellitus: should we determine CYP2C19*2 genotype? *Eur J Clin Pharmacol* **74**, 1567-74 (2018).
(158) Joo, H.J. *et al.* Effects of genetic variants on platelet reactivity and one-year clinical outcomes after percutaneous coronary intervention: A prospective multicentre registry study. *Sci Rep* **8**, 1229 (2018).
(159) Li, X., Wang, Z., Wang, Q., Xu, Q. & Lv, Q. Clopidogrel-associated genetic variants on inhibition of platelet activity and clinical outcome for acute coronary syndrome patients. *Basic Clin Pharmacol Toxicol* **124**, 84-93 (2019).
(160) Feng, Z.M., Lin, Y.Q., Deng, B.Q., Shu, X.R., Ke, X. & Nie, R.Q. Pharmacodynamic changes of platelet reactivity status in patients with chronic kidney disease after coronary artery stenting. *Biomed Pharmacother* **113**, 108773 (2019).
(161) Lyerly, M.J., Bartlett, K. & Albright, K.C. Role of CYP2C19 alleles in the management of recurrent ischemic stroke. *Neurol Clin Pract* **9**, 140-4 (2019).
(162) Tanaka, T. *et al.* Association of CYP2C19 Polymorphisms With Clopidogrel Reactivity and Clinical Outcomes in Chronic Ischemic Stroke. *Circ J* **83**, 1385-93 (2019).
(163) Tan, D.S. *et al.* CYP2C19 phenotype in South-East Asian Acute Coronary Syndrome patients and impact on major adverse cardiovascular events. *J Clin Pharm Ther* **45**, 52-8 (2020).
(164) Shimamatsu, J. *et al.* Prasugrel effectively reduces the platelet reactivity units in patients with genetically metabolic dysfunction of cytochrome P450 2C19 who are treated with long-term dual antiplatelet therapy after undergoing drug-eluting stent implantation. *Heart Vessels* **35**, 312-22 (2020).
(165) Li, Z. *et al.* Body weight, CYP2C19, and P2Y12 receptor polymorphisms relate to clopidogrel resistance in a cohort of Chinese ischemic stroke patients with aspirin intolerance. *Eur J Clin Pharmacol* **76**, 1517-27 (2020).
(166) Lai, Y.S., Yang, L.T., Kao Yang, Y.H. & Liu, P.Y. Pharmacologic strategy for one repeated stent thrombosis patient with hyporesponsiveness to standard dual antiplatelet therapy. *J Formos Med Assoc* **114**, 1022-4 (2015).
(167) Khalaf, H., Al Meman, A.A. & Rasool, S. Impact of Cytochrome P450 2C19*2 and *3 on Clopidogrel Loading Dose in Saudi Patients with Acute Coronary Syndrome. *Drug Metab Lett* **10**, 65-70 (2016).
(168) Tahara, N., Shinke, T., Otake, H., Nishio, R., Konishi, A. & Hirata, K.I. Impact of Cytochrome P450 2C19 Reduced-Function Polymorphism on Lesions and Clinical Outcome in Japanese Patients After Drug-eluting Stent Implantation. *Kobe J Med Sci* **64**, E56-E63 (2018).

(169) Zhang, Q. *et al.* Effects of different CYP2C19 genotypes on prognosis of patients complicated with atrial fibrillation taking clopidogrel after PCI. *Exp Ther Med* **16**, 3492-6 (2018).
(170) Huang, B., Cui, D.J., Ren, Y., Han, B., Yang, D.P. & Zhao, X. Effect of cytochrome P450 2C19*17 allelic variant on cardiovascular and cerebrovascular outcomes in clopidogrel-treated patients: A systematic review and meta-analysis. *J Res Med Sci* **22**, 109 (2017).
(171) Carlquist, J.F. *et al.* Cardiovascular risk among patients on clopidogrel anti-platelet therapy after placement of drug-eluting stents is modified by genetic variants in both the CYP2C19 and ABCB1 genes. *Thromb Haemost* **109**, 744-54 (2013).
(172) Kang, Y.H. *et al.* Association of PON1 genotype and haplotype with susceptibility to coronary artery disease and clinical outcomes in dual antiplatelet-treated Han Chinese patients. *Eur J Clin Pharmacol* **69**, 1511-9 (2013).
(173) Cresci, S. *et al.* Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. *Circ Cardiovasc Genet* **7**, 277-86 (2014).
(174) Sorich, M.J., Rowland, A., McKinnon, R.A. & Wiese, M.D. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta-analysis. *Circ Cardiovasc Genet* **7**, 895-902 (2014).
(175) Martinez-Quintana, E. *et al.* Positive clinical response to clopidogrel is independent of paraoxonase 1 Q192R and CYP2C19 genetic variants. *J Clin Pharmacol* **54**, 843-9 (2014).
(176) Wei, Y.Q., Wang, D.G., Yang, H. & Cao, H. Cytochrome P450 CYP 2C19*2 Associated with Adverse 1-Year Cardiovascular Events in Patients with Acute Coronary Syndrome. *PLoS One* **10**, e0132561 (2015).
(177) Depta, J.P. *et al.* Clinical outcomes associated with proton pump inhibitor use among clopidogrel-treated patients within CYP2C19 genotype groups following acute myocardial infarction. *Pharmacogenomics J* **15**, 20-5 (2015).
(178) Niu, X. *et al.* CYP2C19 polymorphism and clinical outcomes among patients of different races treated with clopidogrel: A systematic review and meta-analysis. *J Huazhong Univ Sci Technolog Med Sci* **35**, 147-56 (2015).
(179) Khalil, B.M. *et al.* Genetic and Nongenetic Factors Affecting Clopidogrel Response in the Egyptian Population. *Clin Transl Sci* **9**, 23-8 (2016).
(180) Tang, X.F. *et al.* CYP2C19 genotyping combined with on-clopidogrel platelet reactivity in predicting major adverse cardiovascular events in Chinese patients with percutaneous coronary intervention. *Thromb Res* **147**, 108-14 (2016).
(181) Rytkin, E. *et al.* Do CYP2C19 and ABCB1 gene polymorphisms and low CYP3A4 isoenzyme activity have an impact on stent implantation complications in acute coronary syndrome patients? *Pharmgenomics Pers Med* **10**, 243-5 (2017).
(182) Tornio, A. *et al.* Investigating Real-World Clopidogrel Pharmacogenetics in Stroke Using a Bioresource Linked to Electronic Medical Records. *Clin Pharmacol Ther* **103**, 281-6 (2018).
(183) Bai, X.F. *et al.* Combination of the CYP2C19 metabolizer and the GRACE risk score better predicts the long-term major adverse cardiac events in acute coronary syndrome undergoing percutaneous coronary intervention. *Thromb Res* **170**, 142-7 (2018).

(184) Fathy, S. *et al.* Pharmacogenetic and clinical predictors of response to clopidogrel plus aspirin after acute coronary syndrome in Egyptians. *Pharmacogenet Genomics* **28**, 207-13 (2018).
(185) Zhang, Y.Y. *et al.* Association between CYP2C19*2/*3 Polymorphisms and Coronary Heart Disease. *Curr Med Sci* **39**, 44-51 (2019).
(186) Ayesh, B.M., Al-Astal, I.R. & Yassin, M.M. The clinical effects of CYP2C19 *2 allele frequency on Palestinian patients receiving clopidogrel after percutaneous coronary intervention. *Int J Clin Pharm* **41**, 96-103 (2019).
(187) Wang, Z. *et al.* Two common mutations within CYP2C19 affected platelet aggregation in Chinese patients undergoing PCI: a one-year follow-up study. *Pharmacogenomics J* **19**, 157-63 (2019).
(188) Xi, Z., Fang, F., Wang, J., AlHelal, J., Zhou, Y. & Liu, W. CYP2C19 genotype and adverse cardiovascular outcomes after stent implantation in clopidogrel-treated Asian populations: A systematic review and meta-analysis. *Platelets* **30**, 229-40 (2019).
(189) Zhou, M.C., Cao, S.P., Zhong, H.L. & Zheng, P. Subacute stent thrombosis in a patient with type 2 diabetes and clopidogrel resistance: A case report. *Int J Clin Pharmacol Ther* **58**, 449-53 (2020).
(190) Verma, S.S. *et al.* Genomewide Association Study of Platelet Reactivity and Cardiovascular Response in Patients Treated With Clopidogrel: A Study by the International Clopidogrel Pharmacogenomics Consortium. *Clinical pharmacology and therapeutics* **108**, 1067-77 (2020).
(191) Lee, C.R. *et al.* Impact of the CYP2C19*17 Allele on Outcomes in Patients Receiving Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *Clinical pharmacology and therapeutics* **109**, 705-15 (2021).
(192) Peng, Y. *et al.* The CYP2C19 genotype does not impact the long-term prognosis of patients with coronary artery disease. *Atherosclerosis* **227**, 106-11 (2013).
(193) Xie, X. *et al.* CYP2C19 phenotype, stent thrombosis, myocardial infarction, and mortality in patients with coronary stent placement in a Chinese population. *PLoS One* **8**, e59344 (2013).
(194) Kim, H.S. *et al.* CYP2C19 poor metabolizer is associated with clinical outcome of clopidogrel therapy in acute myocardial infarction but not stable angina. *Circ Cardiovasc Genet* **6**, 514-21 (2013).
(195) Kulmyrzaeva, N. *et al.* Gene polymorphism of CYP2C19*2, *3 and CYP3A4*1B and early stent thrombosis: case reports and literature review. *Per Med* **13**, 423-8 (2016).
(196) Mugosa, S. *et al.* PREDICT score and CYP2C19 polymorphism independently predict lack of efficacy of clopidogrel in cardiology patients. *Clin Exp Pharmacol Physiol* **43**, 379-81 (2016).
(197) Rodriguez-Gonzalez, F. *et al.* CYP2C19 or CYP3A5 Genotyping Does Not Predict Clinical Response to Clopidogrel. *J Clin Pharmacol* **58**, 1274-83 (2018).
(198) Mohammad, A.M. & Al-Allawi, N.A.S. CYP2C19 Genotype is an Independent Predictor of Adverse Cardiovascular Outcome in Iraqi Patients on Clopidogrel After Percutaneous Coronary Intervention. *J Cardiovasc Pharmacol* **71**, 347-51 (2018).
(199) Paulu, P. *et al.* Lack of association between clopidogrel responsiveness tested using point-of-care assay and prognosis of patients with coronary artery disease. *J Thromb Thrombolysis* **36**, 1-6 (2013).

(200) Kupstyte, N. *et al.* Effect of clinical factors and gene polymorphism of CYP2C19*2, *17 and CYP4F2*3 on early stent thrombosis. *Pharmacogenomics* **16**, 181-9 (2015).
(201) Chikata, Y. *et al.* Simultaneous subacute coronary artery stent thrombosis in a carrier of two CYP2C19 loss-of function polymorphisms (*2/*3). *Int J Cardiol* **212**, 148-50 (2016).
(202) Afzal, A., Patel, B., Patel, N., Sattur, S. & Patel, V. Simultaneous Two-Vessel Subacute Stent Thrombosis Caused by Clopidogrel Resistance from CYP2C19 Polymorphism. *Case Rep Med* **2016**, 2312078 (2016).
(203) Komosa, A. *et al.* Association between high on-treatment platelet reactivity and occurrence of cerebral ischemic events in patients undergoing percutaneous coronary intervention. *Thromb Res* **138**, 49-54 (2016).
(204) Ma, W. *et al.* Relationship of paraoxonase-1 Q192R genotypes and in-stent restenosis and re-stenting in Chinese patients after coronary stenting. *Atherosclerosis* **251**, 305-10 (2016).
(205) Park, M.W. *et al.* Evaluation of the incremental prognostic value of the combination of CYP2C19 poor metabolizer status and ABCB1 3435 TT polymorphism over conventional risk factors for cardiovascular events after drug-eluting stent implantation in East Asians. *Genet Med* **18**, 833-41 (2016).
(206) Yu, D., Ma, L., Zhou, J., Li, L., Yan, W. & Yu, X. Influence of CYP2C19 genotype on antiplatelet treatment outcomes after percutaneous coronary intervention in patients with coronary heart disease. *Exp Ther Med* **19**, 3411-8 (2020).
(207) Morales-Rosado, J.A. *et al.* Next-Generation Sequencing of CYP2C19 in Stent Thrombosis: Implications for Clopidogrel Pharmacogenomics. *Cardiovasc Drugs Ther* **35**, 549-59 (2021).
(208) Wallentin, L. *et al.* Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* **376**, 1320-8 (2010).
(209) Viviani Anselmi, C. *et al.* Routine assessment of on-clopidogrel platelet reactivity and gene polymorphisms in predicting clinical outcome following drug-eluting stent implantation in patients with stable coronary artery disease. *JACC Cardiovasc Interv* **6**, 1166-75 (2013).
(210) Tabata, N. *et al.* Patients with both CYP2C19 loss-of-function allele and peripheral endothelial dysfunction are significantly correlated with adverse cardiovascular events following coronary stent implantation. *J Cardiol* **67**, 104-9 (2016).
(211) Pare, G. *et al.* Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med* **363**, 1704-14 (2010).
(212) Diaz-Villamarin, X. *et al.* Genetic polymorphisms influence on the response to clopidogrel in peripheral artery disease patients following percutaneous transluminal angioplasty. *Pharmacogenomics* **17**, 1327-38 (2016).
(213) Ferrari, M. *et al.* Clopidogrel pharmacogenetics: associations between genotype and stent thrombosis risk in patients with stent placement. *J Cardiovasc Med (Hagerstown)* **20**, 46-8 (2019).
(214) Patel, P.D. *et al.* CYP2C19 Loss-of-Function Associated with First-Time Ischemic Stroke in Non-surgical Asymptomatic Carotid Artery Stenosis During Clopidogrel Therapy. *Transl Stroke Res*, (2021).

(215) Park, M.W. *et al.* Impact of the CYP2C19*17 polymorphism on the clinical outcome of clopidogrel therapy in Asian patients undergoing percutaneous coronary intervention. *Pharmacogenet Genomics* **23**, 558-62 (2013).
(216) Kwon, T.J. *et al.* Influence of platelet reactivity on BARC classification in East Asian patients undergoing percutaneous coronary intervention. Results of the ACCEL-BLEED study. *Thromb Haemost* **115**, 979-92 (2016).
(217) Novkovic, M., Matic, D., Kusic-Tisma, J., Antonijevic, N., Radojkovic, D. & Rakicevic, L. Analysis of the CYP2C19 genotype associated with bleeding in Serbian STEMI patients who have undergone primary PCI and treatment with clopidogrel. *Eur J Clin Pharmacol* **74**, 443-51 (2018).
(218) Sychev, D.A. *et al.* CYP2C19*17 May Increase the Risk of Death Among Patients with an Acute Coronary Syndrome and Non-Valvular Atrial Fibrillation Who Receive Clopidogrel and Rivaroxaban. *Pharmgenomics Pers Med* **13**, 29-37 (2020).
(219) Jeong, Y.H. *et al.* Influence of CYP2C19*2 and *3 loss-of-function alleles on the pharmacodynamic effects of standard- and high-dose clopidogrel in East Asians undergoing percutaneous coronary intervention: the results of the ACCEL-DOUBLE-2N3 study. *J Thromb Haemost* **11**, 1194-7 (2013).
(220) Latkovskis, G. *et al.* Role of genetic factors on the effect of additional loading doses and two maintenance doses used to overcome clopidogrel hyporesponsiveness. *Medicina (Kaunas)* **50**, 19-27 (2014).
(221) Samardzic, J. *et al.* CYP2C19*2 genotype influence in acute coronary syndrome patients undergoing serial clopidogrel dose tailoring based on platelet function testing: Analysis from randomized controlled trial NCT02096419. *Int J Cardiol* **186**, 282-5 (2015).
(222) Zhang, L. *et al.* Effect of high-dose clopidogrel according to CYP2C19*2 genotype in patients undergoing percutaneous coronary intervention- a systematic review and meta-analysis. *Thromb Res* **135**, 449-58 (2015).
(223) Rossi, J.S. *et al.* Clopidogrel dose adjustment after outpatient screening for CYP2C19 variant alleles: a pilot study. *Pharmacogenomics* **15**, 915-23 (2014).
(224) Chen, K., Zhang, R., Liu, H., Guo, X., Li, P. & Liu, X. Impact of the CYP2C19 Gene Polymorphism on Clopidogrel Personalized Drug Regimen and the Clinical Outcomes. *Clin Lab* **62**, 1773-80 (2016).
(225) Chen, S. *et al.* Effects of Dual-Dose Clopidogrel, Clopidogrel Combined with Tongxinluo Capsule, and Ticagrelor on Patients with Coronary Heart Disease and CYP2C19*2 Gene Mutation After Percutaneous Coronary Interventions (PCI). *Med Sci Monit* **23**, 3824-30 (2017).
(226) Collet, J.P. *et al.* High doses of clopidogrel to overcome genetic resistance: the randomized crossover CLOVIS-2 (Clopidogrel and Response Variability Investigation Study 2). *JACC Cardiovasc Interv* **4**, 392-402 (2011).
(227) Mega, J.L. *et al.* Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA* **306**, 2221-8 (2011).
(228) Horenstein, R.B. *et al.* Effectiveness of clopidogrel dose escalation to normalize active metabolite exposure and antiplatelet effects in CYP2C19 poor metabolizers. *J Clin Pharmacol* **54**, 865-73 (2014).
(229) Barker, C.M., Murray, S.S., Teirstein, P.S., Kandzari, D.E., Topol, E.J. & Price, M.J. Pilot study of the antiplatelet effect of increased clopidogrel maintenance dosing and its

relationship to CYP2C19 genotype in patients with high on-treatment reactivity. *JACC Cardiovasc Interv* **3**, 1001-7 (2010).
(230) Cuisset, T. *et al.* Usefulness of high clopidogrel maintenance dose according to CYP2C19 genotypes in clopidogrel low responders undergoing coronary stenting for non ST elevation acute coronary syndrome. *Am J Cardiol* **108**, 760-5 (2011).
(231) Tang, Y.D. *et al.* Randomized Comparisons of Double-Dose Clopidogrel or Adjunctive Cilostazol Versus Standard Dual Antiplatelet in Patients With High Posttreatment Platelet Reactivity: Results of the CREATIVE Trial. *Circulation* **137**, 2231-45 (2018).
(232) Grosdidier, C. *et al.* Effect of CYP2C19*2 and *17 genetic variants on platelet response to clopidogrel and prasugrel maintenance dose and relation to bleeding complications. *Am J Cardiol* **111**, 985-90 (2013).
(233) Ogawa, H. *et al.* Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. *J Cardiol* **68**, 29-36 (2016).
(234) So, D.Y. *et al.* A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. *Pharmacogenomics J* **16**, 71-8 (2016).
(235) Ueno, T. *et al.* Changes in P2Y12 reaction units after switching treatments from prasugrel to clopidogrel in Japanese patients with acute coronary syndrome followed by elective coronary stenting. *Cardiovasc Interv Ther* **32**, 341-50 (2017).
(236) Jin, C. *et al.* Pharmacodynamic study of prasugrel or clopidogrel in non-ST-elevation acute coronary syndrome with CYP2C19 genetic variants undergoing percutaneous coronary intervention (PRAISE-GENE trial). *Int J Cardiol* **305**, 11-7 (2020).
(237) Sardella, G. *et al.* Pharmacodynamic effect of switching therapy in patients with high on-treatment platelet reactivity and genotype variation with high clopidogrel Dose versus prasugrel: the RESET GENE trial. *Circ Cardiovasc Interv* **5**, 698-704 (2012).
(238) Sardella, G. *et al.* Comparison of therapy with Ticagrelor, Prasugrel or high Clopidogrel dose in PCI patients with high on treatment platelet reactivity and genotype variation. TRIPLETE RESET trial. *Int J Cardiol* **194**, 60-2 (2015).
(239) Xiong, R., Liu, W., Chen, L., Kang, T., Ning, S. & Li, J. A randomized controlled trial to assess the efficacy and safety of doubling dose clopidogrel versus ticagrelor for the treatment of acute coronary syndrome in patients with CYP2C19*2 homozygotes. *Int J Clin Exp Med* **8**, 13310-6 (2015).
(240) Zhang, Y. *et al.* High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19 intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. *Acta Cardiol* **71**, 309-16 (2016).
(241) Deiman, B.A. *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* **24**, 589-99 (2016).
(242) Cavallari, L.H. *et al.* Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv* **11**, 181-91 (2018).
(243) Lee, C.R. *et al.* Clinical Outcomes and Sustainability of Using CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. *Circ Genom Precis Med* **11**, e002069 (2018).

(244) Williams, A.K. *et al.* CYP2C19 Genotype-Guided Antiplatelet Therapy and 30-Day Outcomes After Percutaneous Coronary Intervention. *Circ Genom Precis Med* **12**, e002441 (2019).
(245) Martin, J. *et al.* Frequency and clinical outcomes of CYP2C19 genotype-guided escalation and de-escalation of antiplatelet therapy in a real-world clinical setting. *Genet Med* **22**, 160-9 (2020).
(246) Hulot, J.S. *et al.* Routine CYP2C19 Genotyping to Adjust Thienopyridine Treatment After Primary PCI for STEMI: Results of the GIANT Study. *JACC Cardiovasc Interv* **13**, 621-30 (2020).
(247) Sawayama, Y. *et al.* Comparison Between Clopidogrel and Prasugrel Associated With CYP2C19 Genotypes in Patients Receiving Percutaneous Coronary Intervention in a Japanese Population. *Circ J* **84**, 1575-81 (2020).
(248) Xi, Z. *et al.* Ticagrelor Versus Clopidogrel in Patients with Two CYP2C19 Loss-of-Function Alleles Undergoing Percutaneous Coronary Intervention. *Cardiovasc Drugs Ther* **34**, 179-88 (2020).
(249) Yoon, H.Y., Lee, N., Seong, J.M. & Gwak, H.S. Efficacy and safety of clopidogrel versus prasugrel and ticagrelor for coronary artery disease treatment in patients with CYP2C19 LoF alleles: a systemic review and meta-analysis. *Br J Clin Pharmacol* **86**, 1489-98 (2020).
(250) Biswas, M., Kali, M.S.K., Biswas, T.K. & Ibrahim, B. Risk of major adverse cardiovascular events of CYP2C19 loss-of-function genotype guided prasugrel/ticagrelor vs clopidogrel therapy for acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis. *Platelets* **32**, 591-600 (2021).
(251) Roberts, J.D. *et al.* Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet* **379**, 1705-11 (2012).
(252) Malhotra, N. *et al.* A pharmacodynamic comparison of a personalized strategy for anti-platelet therapy versus ticagrelor in achieving a therapeutic window. *Int J Cardiol* **197**, 318-25 (2015).
(253) Lee, J.H. *et al.* Switching from prasugrel to clopidogrel based on Cytochrome P450 2C19 genotyping in East Asian patients stabilized after acute myocardial infarction. *Platelets* **27**, 301-7 (2016).
(254) Tam, C.C. *et al.* Genotyping-guided approach versus the conventional approach in selection of oral P2Y12 receptor blockers in Chinese patients suffering from acute coronary syndrome. *J Int Med Res* **45**, 134-46 (2017).
(255) Koltowski, L. *et al.* Optimal aNtiplatelet pharmacotherapy guided by bedSIDE genetic or functional TESTing in elective PCI patients: A pilot study: ONSIDE TEST pilot. *Cardiol J* **24**, 284-92 (2017).
(256) Xie, X. *et al.* Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: a randomized control trial. *Int J Cardiol* **168**, 3736-40 (2013).
(257) Shen, D.L. *et al.* Clinical Value of CYP2C19 Genetic Testing for Guiding the Antiplatelet Therapy in a Chinese Population. *J Cardiovasc Pharmacol* **67**, 232-6 (2016).

(258) Sanchez-Ramos, J. *et al.* Results of genotype-guided antiplatelet therapy in patients who undergone percutaneous coronary intervention with stent. *Int J Cardiol* **225**, 289-95 (2016).
(259) Ozawa, T. *et al.* Dual Antiplatelet Therapy Guided by CYP2C19 Polymorphisms after Implantation of Second-Generation Drug-Eluting Stents for Management of Acute Coronary Syndrome. *Int Heart J* **59**, 21-6 (2018).
(260) Notarangelo, F.M. *et al.* Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Patients With Acute Coronary Syndromes: The PHARMCLO Trial. *J Am Coll Cardiol* **71**, 1869-77 (2018).
(261) Janssen, P.W.A. *et al.* Tailored P2Y12 inhibitor treatment in patients undergoing non-urgent PCI-the POPular Risk Score study. *Eur J Clin Pharmacol* **75**, 1201-10 (2019).
(262) Tan, K. *et al.* The effect of CYP2C19 genotype-guided antiplatelet therapy on outcomes of selective percutaneous coronary intervention patients: an observational study. *Per Med* **16**, 301-12 (2019).
(263) Tuteja, S. *et al.* Prospective CYP2C19 Genotyping to Guide Antiplatelet Therapy Following Percutaneous Coronary Intervention: A Pragmatic Randomized Clinical Trial. *Circ Genom Precis Med* **13**, e002640 (2020).
(264) Pereira, N.L. *et al.* Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. *JAMA* **324**, 761-71 (2020).
(265) Claassens, D.M.F. *et al.* A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. *N Engl J Med* **381**, 1621-31 (2019).
(266) Sen, H.M., Silan, F., Silan, C., Degirmenci, Y. & Ozisik Kamaran, H.I. Effects of CYP2C19 and P2Y12 Gene Polymorphisms on Clinical Results of Patients Using Clopidogrel after Acute Ischemic Cerebrovascular Disease. *Balkan J Med Genet* **17**, 37-41 (2014).
(267) Spokoyny, I. *et al.* Reduced clopidogrel metabolism in a multiethnic population: prevalence and rates of recurrent cerebrovascular events. *J Stroke Cerebrovasc Dis* **23**, 694-8 (2014).
(268) McDonough, C.W. *et al.* CYP2C19 metabolizer status and clopidogrel efficacy in the Secondary Prevention of Small Subcortical Strokes (SPS3) study. *J Am Heart Assoc* **4**, e001652 (2015).
(269) Sun, W. *et al.* Variant recurrent risk among stroke patients with different CYP2C19 phenotypes and treated with clopidogrel. *Platelets* **26**, 558-62 (2015).
(270) Zhao, Z. *et al.* Impact of genetic polymorphisms related to clopidogrel or acetylsalicylic acid pharmacology on clinical outcome in Chinese patients with symptomatic extracranial or intracranial stenosis. *Eur J Clin Pharmacol* **72**, 1195-204 (2016).
(271) Wang, Y. *et al.* Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. *JAMA* **316**, 70-8 (2016).
(272) Wang, Y., Cai, H., Zhou, G., Zhang, Z. & Liu, X. Effect of CYP2C19*2 and *3 on clinical outcome in ischemic stroke patients treated with clopidogrel. *J Neurol Sci* **369**, 216-9 (2016).
(273) Pan, Y. *et al.* Genetic Polymorphisms and Clopidogrel Efficacy for Acute Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis. *Circulation* **135**, 21-33 (2017).

(274) Han, S.W. *et al.* Effects of Triflusal and Clopidogrel on the Secondary Prevention of Stroke Based on Cytochrome P450 2C19 Genotyping. *J Stroke* **19**, 356-64 (2017).
(275) Yi, X., Lin, J., Zhou, J., Wang, Y., Huang, R. & Wang, C. The secondary prevention of stroke according to cytochrome P450 2C19 genotype in patients with acute large-artery atherosclerosis stroke. *Oncotarget* **9**, 17725-34 (2018).
(276) Al-Rubaish, A.M. *et al.* Prevalence of CYP2C19*2 carriers in Saudi ischemic stroke patients and the suitability of using genotyping to guide antiplatelet therapy in a university hospital setup. *Drug Metab Pers Ther*, (2021).
(277) Li, C., Jia, W., Li, J., Li, F., Ma, J. & Zhou, L. Association with CYP2C19 polymorphisms and Clopidogrel in treatment of elderly stroke patients. *BMC Neurol* **21**, 104 (2021).
(278) Jeong, T.D. *et al.* CYP2C19 genotype and early ischemic lesion recurrence in stroke patients treated with clopidogrel. *J Stroke Cerebrovasc Dis* **24**, 440-6 (2015).
(279) Liu, G., Yang, S. & Chen, S. The correlation between recurrent risk and CYP2C19 gene polymorphisms in patients with ischemic stroke treated with clopidogrel for prevention. *Medicine (Baltimore)* **99**, e19143 (2020).
(280) Zhu, W.Y. *et al.* Association of CYP2C19 Polymorphisms with the Clinical Efficacy of Clopidogrel Therapy in Patients Undergoing Carotid Artery Stenting in Asia. *Sci Rep* **6**, 25478 (2016).
(281) Lan, H., Ying, T., Xi-Hua, S. & Yi, L. Anti-Platelet Therapy in Mild Cerebral Infarction Patients on the Basis of CYP2C19 Metabolizer Status. *Cell Transplant* **28**, 1039-44 (2019).
(282) Wang, D. *et al.* Age-dependent association of CYP2C19 polymorphisms with clinical outcome of clopidogrel therapy in minor stroke patients with large-artery atherosclerosis. *Eur J Clin Pharmacol* **76**, 1263-71 (2020).
(283) Lin, Y.J. *et al.* The association between CYP2C19 genotype and of in-stent restenosis among patients with vertebral artery stent treatment. *CNS Neurosci Ther* **20**, 125-30 (2014).
(284) Li, Y.J., Chen, X., Tao, L.N., Hu, X.Y., Wang, X.L. & Song, Y.Q. Association between CYP2C19 polymorphisms and clinical outcomes in patients undergoing stent procedure for cerebral artery stenosis. *Sci Rep* **11**, 5974 (2021).
(285) Patel, P.D. *et al.* CYP2C19 Loss-of-Function is Associated with Increased Risk of Ischemic Stroke after Transient Ischemic Attack in Intracranial Atherosclerotic Disease. *J Stroke Cerebrovasc Dis* **30**, 105464 (2021).
(286) Hoh, B.L. *et al.* CYP2C19 and CES1 polymorphisms and efficacy of clopidogrel and aspirin dual antiplatelet therapy in patients with symptomatic intracranial atherosclerotic disease. *J Neurosurg* **124**, 1746-51 (2016).
(287) Wu, Y. *et al.* Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. *Pharmacogenomics J* **18**, 713-20 (2018).
(288) Wu, H. *et al.* Effectiveness and safety of high dose clopidogrel plus aspirin in ischemic stroke patients with the single CYP2C19 loss-of-function allele: a randomized trial. *BMC Neurol* **20**, 395 (2020).
(289) Kitazono, T., Ikeda, Y., Nishikawa, M., Yoshiba, S., Abe, K. & Ogawa, A. Influence of cytochrome P450 polymorphisms on the antiplatelet effects of prasugrel in patients with

non-cardioembolic stroke previously treated with clopidogrel. *J Thromb Thrombolysis* **46**, 488-95 (2018).
(290) Wang, Y. *et al.* Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial. *BMJ* **365**, l2211 (2019).
(291) Yang, Y. *et al.* Ticagrelor Is Superior to Clopidogrel in Inhibiting Platelet Reactivity in Patients With Minor Stroke or TIA. *Front Neurol* **11**, 534 (2020).
(292) Yang, Y. *et al.* Effect of ticagrelor versus clopidogrel on platelet reactivity measured by thrombelastography in patients with minor stroke or TIA. *Aging (Albany NY)* **12**, 20085-94 (2020).
(293) Zhou, M. *et al.* Antiplatelet effect of ticagrelor with aspirin in acute minor stroke and transient ischemic attack stratified by CYP2C19 metabolizer status: subgroup analysis of the PRINCE trial. *Aging (Albany NY)* **13**, 3994-4006 (2020).
(294) Mo, J. *et al.* Efficacy of Clopidogrel-Aspirin Therapy for Stroke Does Not Exist in CYP2C19 Loss-of-Function Allele Noncarriers With Overweight/Obesity. *Stroke* **51**, 224-31 (2020).
(295) Meschia, J.F. *et al.* Efficacy of Clopidogrel for Prevention of Stroke Based on CYP2C19 Allele Status in the POINT Trial. *Stroke* **51**, 2058-65 (2020).
(296) Yi, X., Zhou, Q., Wang, C., Lin, J. & Chai, Z. Aspirin plus clopidogrel may reduce the risk of early neurologic deterioration in ischemic stroke patients carrying CYP2C19*2 reduced-function alleles. *J Neurol* **265**, 2396-403 (2018).
(297) Lyu, S.Q. *et al.* The efficacy and safety of CYP2C19 genotype-guided antiplatelet therapy compared with conventional antiplatelet therapy in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials. *Platelets* **31**, 971-80 (2020).
(298) Kheiri, B. *et al.* CYP2C19 pharmacogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with coronary artery disease: A meta-analysis of randomized clinical trials. *Catheter Cardiovasc Interv* **93**, 1246-52 (2019).
(299) Kheiri, B. *et al.* Personalized antiplatelet therapy in patients with coronary artery disease undergoing percutaneous coronary intervention: A network meta-analysis of randomized clinical trials. *Catheter Cardiovasc Interv* **94**, 181-6 (2019).
(300) Hou, X., Shi, J. & Sun, H. Gene polymorphism of cytochrome P450 2C19*2 and clopidogrel resistance reflected by platelet function assays: a meta-analysis. *Eur J Clin Pharmacol* **70**, 1041-7 (2014).
(301) *Clopidogrel Pathway, Pharmacokinetics* <https://www.pharmgkb.org/pathway/PA154424674>. Accessed June 14 2021.