Supplemental Table S6. Evidence linking *CYP2C19* genotype with clopidogrel response.

Type of Experimental Model	Major Findings	References	Level of Evidence*
In vitro	*CYP2C19*2* (c.681G>A; rs4244285) is a common polymorphism that results in a splicing defect and non-functional CYP2C19 protein.	de Morais, *et al*. 1994 (96)	High
In vitro	The *CYP2C19*3* - **8* variant alleles result in loss-of-function.	de Morais, *et al*. 1994 (97), Xiao, *et al*. 1997 (98), Ferguson, *et al*. 1998 (99), Ibeanu, *et al*. 1998 (100), Ibeanu, *et al*. 1998 (101), Ibeanu, *et al*. 1999 (102)	High
In vitro/In vivo	*CYP2C19*17* (c.-806C>T; rs12248560) is a common polymorphism that results in increased activity as a consequence of enhanced transcription.	Sim, *et al*. 2006 (103), Rudberg, *et al*. 2008 (104), Li-Wan-Po, *et al*. 2010 (105)	High
In vitro	CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 are involved in the hepatic metabolism of clopidogrel.	Savi, *et al*. 1992 (107), Savi, *et al*. 2000 (108), Clarke, *et al.* 2003 (109), Farid, *et al*. 2007 (110), Kazui, *et al*. 2010 (111), Abell and Liu, 2011 (112)	High
In vitro	CYP2C19 contributes substantially to both oxidative steps of clopidogrel metabolism during the formation of its active metabolite.	Kazui, *et al*. 2010 (111)	High
Clinical	*CYP2C19*2* is associated with reduced formation of active metabolites (pharmacokinetics) in healthy subjects treated with clopidogrel.	Brandt, *et al.* 2007 (32), Kim, *et al*. 2008 (82), Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2), Simon, *et al.* 2011 (57), Gong, *et al.* 2012 (52),	High

		Kelly, *et al.* 2012 (113)	
Clinical	*CYP2C19*2* is associated with reduced formation of active metabolites (pharmacokinetics) in ACS/PCI patients treated with clopidogrel.	Varenhorst, *et al*. 2009 (84), Collet, *et al.* 2011 (114)	High
Clinical	*CYP2C19*2* is associated with higher on-treatment platelet reactivity (pharmacodynamics) in healthy subjects treated with clopidogrel.	Hulot, *et al.* 2006 (1), Brandt, *et al.* 2007 (32), Fontana, *et al*. 2007 (115), Chen, *et al*. 2008 (116), Kim, *et al*. 2008 (82), Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2), Shuldiner, *et al.* 2009 (3), Simon, *et al.* 2011 (57)	High
Clinical	*CYP2C19*2* is associated with higher on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Giusti, *et al.* 2007 (73), Frere, *et al.* 2008 (33), Geisler, *et al.* 2008 (31), Trenk, *et al.* 2008 (30), Jinnai, *et al*. 2009 (117), Shuldiner, *et al.* 2009 (3), Varenhorst, *et al*. 2009 (84), Harmsze, *et al*. 2010 (41), Hochholzer, *et al*. 2010 (118), Jeong, *et al*. 2010 (119), Kang, *et al*. 2010 (120), Sibbing, *et al*. 2010 (106), Bouman, *et al.* 2011 (121), Collet, *et al.* 2011 (114), Cuisset, *et al.* 2011 (122), Gurbel, *et al.* 2011 (36), Hwang, *et al*. 2011 (123), Jeong, *et al*. 2011 (124), Maeda, *et al*. 2011 (125), Ono, *et al.* 2011 (126),	High

		Park, *et al.* 2011 (127), Rideg, *et al.* 2011 (128), Yamamoto, *et al.* 2011 (129), Bonello, *et al.* 2012 (130), Harmsze, *et al.* 2012 (131), Kassimis, *et al.* 2012 (132), Kim, *et al.* 2012 (133), Kreutz, *et al.* 2012 (78), Oh, *et al.* 2012 (134), Price, *et al.* 2012 (56), Tang, *et al.* 2012 (135), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	
Clinical	*CYP2C19*2* is associated with adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS/PCI patients treated with clopidogrel.	Trenk, *et al.* 2008 (30), Collet, *et al.* 2009 (28), Giusti, *et al*. 2009 (138), Mega, *et al.* 2009 (2), Shuldiner, *et al.* 2009 (3), Sibbing, *et al.* 2009 (4), Simon, *et al.* 2009 (5), Harmsze, *et al*. 2010 (139), Malek, *et al*. 2010 (140), Cayla, *et al.* 2011 (10), Jeong, *et al*. 2011 (124), Marcucci, *et al.* 2011 (141), Rideg, *et al.* 2011 (128), Yamamoto, *et al.* 2011 (129), Delaney, *et al.* 2012 (80), Oh, *et al.* 2012 (134), Teixeira, *et al.* 2012 (142), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is	Kim, *et al*. 2008 (82),	High

	associated with lower formation of active metabolites (pharmacokinetics) in healthy subjects treated with clopidogrel.	Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2), Kelly, *et al.* 2012 (113)	
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with higher on-treatment platelet reactivity (pharmacodynamics) in healthy subjects treated with clopidogrel.	Chen, *et al*. 2008 (116), Kim, *et al*. 2008 (82), Umemura, *et al*. 2008 (83), Mega, *et al.* 2009 (2)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with higher on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Jinnai, *et al*. 2009 (117), Lee, *et al*. 2009 (143), Jeong, *et al*. 2010 (119), Kang, *et al*. 2010 (120), Hwang, *et al*. 2011 (123), Jeong, *et al*. 2011 (124), Maeda, *et al*. 2011 (125), Ono, *et al.* 2011 (126), Park, *et al.* 2011 (127), Yamamoto, *et al.* 2011 (129), Kim, *et al.* 2012 (133), Tang, *et al.* 2012 (135), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	High
Clinical	*CYP2C19*3* (and possibly other loss-of-function alleles) is associated with adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) in ACS/PCI patients treated with clopidogrel.	Collet, *et al.* 2009 (28), Mega, *et al.* 2009 (2), Simon, *et al.* 2009 (5), Harmsze, *et al*. 2010 (139), Jeong, *et al*. 2011 (124), Yamamoto, *et al.* 2011 (129), Wu, *et al.* 2012 (136), Zou, *et al.* 2012 (137)	High
Clinical	*CYP2C19*17* is associated with lower on-treatment platelet reactivity (pharmacodynamics) in ACS/PCI patients treated with clopidogrel.	Frere, *et al*. 2009 (144), Sibbing, *et al*. 2010 (29), Sibbing, *et al*. 2010 (106), Harmsze, *et al.* 2012 (131),	Moderate

		Li, *et al*. 2012 (35), Sorich, *et al*. 2012 (37), Subraja, *et al*. 2012 (145)	
Clinical	*CYP2C19*17* is associated with enhanced clopidogrel response and an increased bleeding risk in ACS/PCI patients treated with clopidogrel.	Sibbing, *et al*. 2010 (29), Tiroch, *et al*. 2010 (146), Harmsze, *et al.* 2012 (131), Li, *et al*. 2012 (35), Sorich, *et al*. 2012 (37)	Moderate
Clinical	*CYP2C19* loss-of-function alleles are not associated with adverse cardiovascular outcomes in coronary patients with low frequencies of PCI and with other indications (e.g., atrial fibrillation) treated with clopidogrel.	Pare, *et al*. 2010 (88), Wallentin, *et al*. 2010 (9)	High
Clinical	ACS/PCI patients with *CYP2C19* reduced metabolizer genotypes have reduced risks of primary outcome with prasugrel compared to clopidogrel. However, for *CYP2C19* EMs, the risks with prasugrel and clopidogrel are not significantly different.	Sorich, *et al*. 2010 (147)	High
Clinical	ACS/PCI patients with *CYP2C19* reduced metabolizer genotypes have reduced risks of primary outcome with ticagrelor compared to clopidogrel, which was less significant among *CYP2C19* EMs and most pronounced among patients undergoing PCI.	Wallentin, *et al*. 2010 (9), Hulot, *et al*. 2011 (90)	High

ACS: acute coronary syndrome; EM: extensive metabolizer; PCI: percutaneous coronary intervention
* See above for description of '**Levels of Evidence Linking Genotype to Phenotype**'.