

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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**Supplemental Table 1. Healthy Subject Pharmacokinetic and Pharmacodynamic Studies**

<b>Study</b>	<b>Clopidogrel Doses</b>	<b># of Subjects</b>	<b>PK</b>	<b>PD</b>
Study 1	300 mg LD	28	28	28
Study 2	300 mg LD, 75 mg MD	26	26	26
Study 3	300 or 600 mg LD, 75 mg MD	28	28	28
Study 4	600 mg LD	39	0	39
Study 5	600 mg LD, 75 mg MD	24	24	24
Study 6	300 mg LD	17	17	16
<b>TOTAL</b>		<b>162</b>	<b>123</b>	<b>161</b>

Time points in the pharmacodynamic analyses included before first dose and 4 and 24 hours postdose for loading and maintenance dosing. LD denotes loading dose, MD maintenance dose, PD pharmacodynamics, PK pharmacokinetics.

**Supplemental Table 2. Baseline Characteristics of Clopidogrel Allocated Subjects in the TRITON-TIMI 38 Genetic Study and the Overall Trial**

	<b>Genetic Substudy</b>	<b>Overall Trial</b>
<b>Total (N)</b>	1477	6,795
<b>Age (y, mean ± SD)</b>	60.1±11.1	60.9±11.4
<b>Female (N, [%])</b>	433 (29.3)	1,818 (26.8)
<b>Body Weight (kg, mean ± SD)</b>	82.6±16.2	83.2±16.9
<b>Ethnicity (N, [%])</b>		
<b>Caucasian</b>	1,442 (97.6)	6,274 (92.3)
<b>Hispanic</b>	18 (1.2)	256 (3.8)
<b>African</b>	10 (0.7)	187 (2.8)
<b>Asian</b>	5 (0.3)	64 (0.9)
<b>Other</b>	2 (0.1)	14 (0.2)
<b>Region (N, [%])</b>		
<b>North America</b>	117 (7.9)	2,146 (31.6)
<b>South America</b>	27 (1.8)	264 (3.9)
<b>Western Europe</b>	310 (21.0)	1,774 (26.1)
<b>Eastern Europe</b>	949 (64.3)	1,665 (24.5)
<b>Other</b>	74 (5.0)	946 (13.9)
<b>Hypertension (N, [%])</b>	972 (65.8)	4,371 (64.3)
<b>Hypercholesterolemia (N, [%])</b>	725 (49.1)	3,790 (55.8)
<b>Diabetes mellitus (N, [%])</b>	322 (21.8)	1,570 (23.1)
<b>Tobacco Use (N, [%])</b>	562 (38.1)	2,583 (30.0)
<b>Prior MI</b>	240 (16.2)	1,208 (17.8)
<b>Prior TIA or Stroke (N, [%])</b>	51 (3.5)	160 (2.4)
<b>Creatinine Clearance &lt;60 ml/min</b>	163 (11.0)	773 (11.6)
<b>Index diagnosis (N, [%])</b>		
<b>UA/NSTEMI</b>	1,049 (71.0)	5,030 (74.0)
<b>STEMI</b>	428 (29.0)	1,765 (26.0)

Ethnicity was self-reported.

**Supplemental Table 3. Cytochrome P450 Genes and Measured Alleles**

<b>Gene</b>	<b>Star Alleles</b>
<b><i>CYP2C19</i></b>	*1A, *2A, *3, *4, *5A, *6, *7, *8, *9, *10, *12, *13, *14, *17 <sup>a</sup>
<b><i>CYP2C9</i></b>	*1A, *2A, *3A, *4, *5, *6, *8, *9, *10, *11A, *12
<b><i>CYP2B6</i></b>	*1A, *1C, *6, *8, *9, *11, *12, *13, *14, *15
<b><i>CYP3A5</i></b>	*1A, *3A, *3B, *3D, *3F, *6, *8, *9, *10
<b><i>CYP3A4</i></b>	*1A, *17, *18
<b><i>CYP1A2</i></b>	*1A, *1C, *1D, *1E, *1K, *1L, *7

<sup>a</sup> *CYP2C19*\*17 allele measured by conventional polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis. All remaining alleles genotyped by the Affymetrix Targeted Human DMET (Drug Metabolizing Enzymes and Transporters) 1.0 Assay (Affymetrix, Santa Clara, CA, USA). In the case of missing genotype data from the DMET chip, additional genotyping was conducted using bi-directional sequencing or exon-specific polymerase chain reaction amplification followed by restriction fragment length polymorphism gel electrophoresis.

**Supplemental Table 4. Genotyping Results in Clopidogrel Allocated Subjects by Gene and Predicted Metabolic Phenotype**

Gene	Dichotomous classification	Predicted Phenotype	Observed Genotypes <sup>a</sup>	Number of Subjects (%)	
				PK/PD	TRITON-TIMI 38
<i>CYP2C19</i>	Non-carrier	UM	*17/*17, *1A/*17	44 (30)	1064 (73) <sup>b</sup>
		EM	*1A/*1A	53 (36)	
	Carrier	IM	*1A/*2A, *1A/*3, *1A/*4, *1A/*8	43 (29)	357 (24)
		PM	*2A/*2A, *2A/*3, *2A/*4 *2A/*5A, *2A/*8	8 (5)	38 (3)
	n/a	Unknown <sup>c</sup>	*1A/*9, *1A/*10, *2A/*17, *6/*17	NI <sup>c</sup>	NI <sup>c</sup>
<i>CYP2C9</i>	Non-carrier	EM	*1A/*1A, *1A/*2A, *1A/*11A, *1A/*12	143 (89)	1226 (84)
	Carrier	IM	*1A/*3A, *2A/*2A, *2A/*3A, *2A/*11A, *2A/*12, *3A/*11A, *3A/*12, *6/*11A	17 (11)	221 (15)
		PM	*3A/*3A	0 (0)	9 (1)
	n/a	Unknown <sup>c</sup>	*1A/*5, *1A/*8, *1A/*9, *9/*9	NI <sup>c</sup>	NI <sup>c</sup>
<i>CYP2B6</i>	Non-carrier	EM	*1A/*1A, *1A/*1C, *1C/*1C	101 (65)	777 (68)
	Carrier	IM	*1A/*6, *1A/*9, *1C/*6 *1C/*9, *1C/*13, *6/*9	55 (35)	306 (27)
		PM	*9/*9	0 (0)	64 (6)
<i>CYP3A5</i>	Non-carrier	EM	*1A/*1A	9 (6)	7 (1)
		IM <sup>d</sup>	*1A/*3A, *1A/*6, *2A/*3A	31 (19)	144 (11)
	Carrier	PM	*3A/*3A, *3A/*3F, *3A/*6	121 (75)	1130 (88)
<i>CYP3A4</i>	Non-carrier	EM	*1A/*1A, *1A/*18	162 (100)	1392 (100)
	Carrier <sup>e</sup>	IM	None		
		PM	None		
<i>CYP1A2</i>	Non-carrier	EM	*1A/*1A, *1A/*1D, *1A/*1E, *1D/*1D, *1D/*1E, *1D/*1L, *1E/*1L, *1L/*1L	133 (86)	1099 (95)
		Carrier	IM	*1A/*1C, *1C/*1D, *1C/*1E	21 (14)
	PM		*1C/*1C	0 (0)	0 (0)
	n/a	Unknown <sup>c</sup>	*1A/*7	NI <sup>c</sup>	NI <sup>c</sup>

<sup>a</sup> The frequencies of CYP genotypes were similar to previous reports and within Hardy-Weinberg equilibrium.

<sup>b</sup> *CYP2C19*\*17 was not measured in TRITON-TIMI 38. Thus, ultra-rapid and extensive metabolizer status could not be distinguished and were combined as non-carriers of a reduced-function allele. In addition, \*2A/\*17, \*6/\*17 genotypes would be classified as heterozygous carriers of a reduced-function allele.

<sup>c</sup> The predicted metabolic phenotypes of these observed genotype combinations are unknown. They were therefore excluded from analyses.

<sup>d</sup> For *CYP3A5*, intermediate metabolizer genotypes confer near-normal activity and were therefore *a priori* combined with the extensive metabolizer genotypes.

<sup>e</sup> No associations with *CYP3A4* alleles were tested because no subjects carried the assayed alleles.

CYP denotes cytochrome P450, EM extensive metabolizer, IM intermediate metabolizer, NI not included in analyses, PK/PD pharmacokinetics/pharmacodynamics, PM poor metabolizer, UM ultra-rapid metabolizer.

**Supplemental Table 5. Baseline Characteristics of *CYP2C19* Carriers and Non-carriers in Clopidogrel Treatment Arm in TRITON-TIMI 38**

	<i>CYP2C19</i>	
	Carriers of Reduced-Function Allele	Non-carriers
<b>Total (N)</b>	395	1064
<b>Age (y, mean ± SD)</b>	60.5±11.0	60.0±11.1
<b>Female (N, [%])</b>	123 (31.1)	307 (28.9)
<b>Body Weight (kg, mean ± SD)</b>	81.8±16.6	83.0±16.1
<b>Ethnicity (N, [%])</b>		
<b>Caucasian</b>	385 (97.5)	1042 (97.9)
<b>Hispanic</b>	3 (0.8)	15 (1.4)
<b>African</b>	3 (0.8)	4 (0.4)
<b>Asian</b>	4 (1.0)	1 (0.1)
<b>Other</b>	0 (0.0)	2 (0.2)
<b>Region (N, [%])</b>		
<b>North America</b>	31 (7.8)	79 (7.4)
<b>South America</b>	6 (1.5)	20 (1.9)
<b>Western Europe</b>	75 (19.0)	232 (21.8)
<b>Eastern Europe</b>	260 (65.8)	683 (64.2)
<b>Other</b>	23 (5.8)	50 (4.7)
<b>Hypertension (N, [%])</b>	251 (63.5)	710 (66.7)
<b>Hypercholesterolemia (N, [%])</b>	203 (51.4)	510 (47.9)
<b>Diabetes mellitus (N, [%])</b>	84 (21.3)	235 (22.1)
<b>Tobacco Use (N, [%])</b>	147 (37.2)	409 (38.4)
<b>Prior Myocardial Infarction (N, [%])</b>	63 (15.9)	170 (16.0)
<b>Prior TIA or Stroke (N, [%])</b>	14 (3.5)	36 (3.4)
<b>Creatinine clearance &lt;60 ml/min</b>	50 (12.7)	112 (10.5)
<b>Index diagnosis (N, [%])</b>		
<b>UA/NSTEMI</b>	286 (72.4)	747 (70.2)
<b>STEMI</b>	109 (27.6)	317 (29.8)
<b>Statin (N, [%])</b>		
<b>CYP 3A4-metabolized (atorvastatin, simvastatin, fluvastatin, cerivastatin)</b>	353 (89.4)	957 (89.9)
<b>CYP 3C9-metabolized (fluvastatin)</b>	42 (10.6)	121 (11.4)
<b>Non CYP-metabolized (rosuvastatin, pravastatin)</b>	36 (9.1)	81 (7.6)

Ethnicity was self-reported.

**Supplemental Table 6. *CYP2C19* Genetic Effects on Pharmacokinetics ( $AUC_{0-t}$ ) and Pharmacodynamics ( $\Delta MP A$ ) Following Clopidogrel Loading Dose and Maintenance Dose, by Dose**

<b><i>CYP2C19</i> Classification</b>	<b>Percent Difference in <math>AUC_{0-t}</math></b>		
	<b>LD 300mg</b>	<b>LD 600mg</b>	<b>MD 75mg</b>
IM vs EM	-26.1	-29.9	-30.7
PM vs EM	-55.2	NA	-45.6
P Value	<0.001 (n= 89)	0.047 (n = 42)	0.0023 (n = 87)
<b><i>CYP2C19</i> Classification</b>	<b>Absolute Difference in <math>\Delta MP A</math></b>		
	<b>LD 300mg</b>	<b>LD 600mg</b>	<b>MD 75mg</b>
IM vs EM	-10.6	-6.3	-9.1
PM vs EM	-19.3	NA	-28.7
P Value	0.011 (n = 180)	0.024 (n = 155)	<0.001 (n = 197)

CYP denotes cytochrome P450, EM extensive metabolizer, IM intermediate metabolizer, LD loading dose, MD maintenance dose, n number of observations (subjects had observations at 4 and 24 hours after administration of clopidogrel), and PM poor metabolizer.

**Supplemental Figure 1. Schematic Representation of the Metabolic Activation Pathway for Clopidogrel**

