



**Impact of CYP2C19 and ABCB1 SNPs
on outcomes with ticagrelor versus
clopidogrel in acute coronary syndromes:
a PLATO genetic substudy**

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for the PLATO investigators

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Background:

Genetic variability of P2Y₁₂ inhibitor response

- CYP2C19 (and ABCB1?) are main genetic determinants of clopidogrel PK/PD variability



- CYP2C19 gene is polymorphic in populations, affecting enzyme activity
 - Caucasians: 72% EMs (WT/WT); 25% IMs (WT/LOF); ~2–3% PMs (LOF/LOF)
- Recent data indicate that CYP2C19 ‘LOF carriers’ have more clinical events
- FDA warning about poor metabolisers of clopidogrel (March 2010)
- No known genetic regulation of ticagrelor PK/PD or response

LOF = loss of function; EM = extensive metaboliser; IM = intermediate metaboliser; PM = poor metaboliser

PLATO study design



**NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomized within 24 hours of index event
(N=18,624)**

Clopidogrel

**If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)**

Ticagrelor

**180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)**

6–12-month exposure

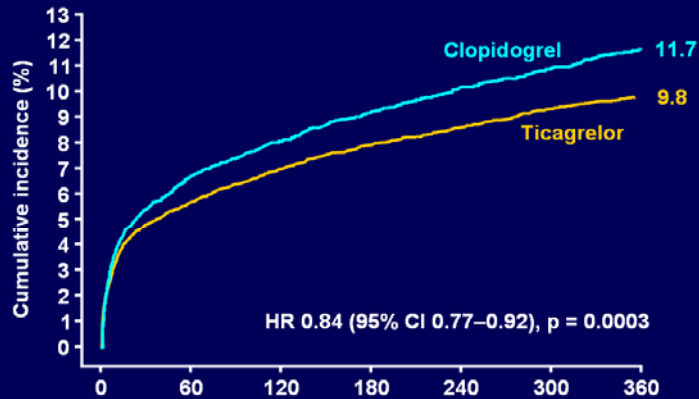
**Primary endpoint: CV death + MI + stroke
Primary safety endpoint: Total major bleeding**

ASA = acetylsalicylic acid; CV = cardiovascular; MI = myocardial infarction;
PCI = percutaneous coronary intervention; TIA = transient ischemic attack

Background: Primary outcomes of the main PLATO trial



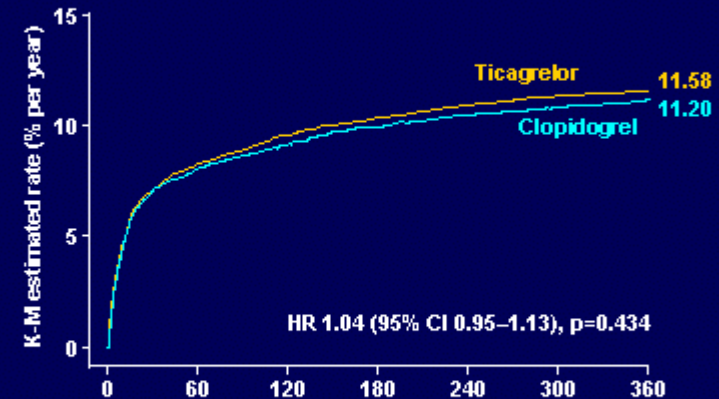
KM estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



No. at risk	Days after randomization						
	0	60	120	180	240	300	360
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,650	5,096	4,047

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Time to major bleeding – primary safety event



No. at risk	Days from first IP dose						
	0	60	120	180	240	300	360
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

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Ticagrelor vs clopidogrel
 – Less CV death, MI, stroke
 – Less stent thrombosis

Ticagrelor vs clopidogrel
 – Similar total major bleeding
 – More non-CABG-related bleeding

Objectives of the genetic substudy



- Primary
 - Investigate if CYP2C19 and/or ABCB1 polymorphisms influence primary efficacy outcome when comparing treatments with ticagrelor versus clopidogrel in PLATO
- Secondary
 - Explore the role of the CYP2C19 and ABCB1 polymorphisms regarding other efficacy and safety outcomes both between and within the ticagrelor and clopidogrel arms in PLATO

- Genetic analysis
 - 10,285 patients in the PLATO study provided samples for DNA analysis at randomization
 - Genotyping: 7 CYP2C19 LOF alleles and 1 GOF allele; ABCB1 SNP
 - ~95,000 genotypes (2 weeks)
- Statistical analysis
 - Data-guided decision as to appropriate genotype groupings within each arm for each outcome
 - Assessment of impact of genotype on outcomes for each drug
 - Application of these and literature precedent (any versus no LOF allele) groupings to between-arms analysis
 - Compare outcomes between ticagrelor and clopidogrel groups

SNP = single nucleotide polymorphism

Selected baseline characteristics

Characteristic	Ticagrelor n=5,137	Clopidogrel n=5,148
Age, mean (SD)	62.5 (11)	62.5 (11)
Age ≥75 years	760 (15%)	835 (16%)
Female	1,577 (31%)	1,577 (31%)
Caucasian	5,057 (98%)	5,058 (98%)
Weight, mean kg (SD)	81.9 (15)	81.8 (16)
Body mass index ≥30 kg/m ²	1,560 (30%)	1,520 (30%)
Habitual smoker	1,796 (35%)	1,829 (36%)
Diabetes mellitus	1,177 (23%)	1,189 (23%)
PPI use (at randomization)	2,154 (42%)	2,083 (40%)
Statin use (at randomization)	4,079 (79%)	4,059 (79%)
Aspirin use (at randomization)	4,962 (97%)	4,946 (96%)
Open-label clopidogrel	2467 (48%)	2,486 (48%)
Planned invasive treatment	3,403 (66%)	3,375 (66%)
Troponin positive	4,149 (81%)	4,199 (82%)

Data are n (%) unless otherwise stated. BMI = body mass index; PPI = proton pump inhibitor; SD = standard deviation

Predicted CYP2C19 phenotype and genotype by treatment

	Ticagrelor n=5,137 (%)	Clopidogrel n=5,148 (%)
CYP2C19 predicted phenotype, n (%)		
Extensive metaboliser (*1/*1)	1,849 (36%)	1,862 (36%)
Intermediate metaboliser (*2/*2–*8)	894 (17%)	935 (18%)
Poor metaboliser (*2–*8/*2–*8)	121 (2%)	125 (2%)
Poor/rapid het metaboliser (*2–*8/*17)	369 (7%)	328 (6%)
Rapid het metaboliser (*1/*17)	1,437 (28%)	1,386 (27%)
Ultra rapid metaboliser (*17/*17)	268 (5%)	268 (5%)
CYP2C19 LOF category, n (%)		
No LOF	3,554 (72%)	3,516 (72%)
Any LOF	1,384 (28%)	1,388 (28%)

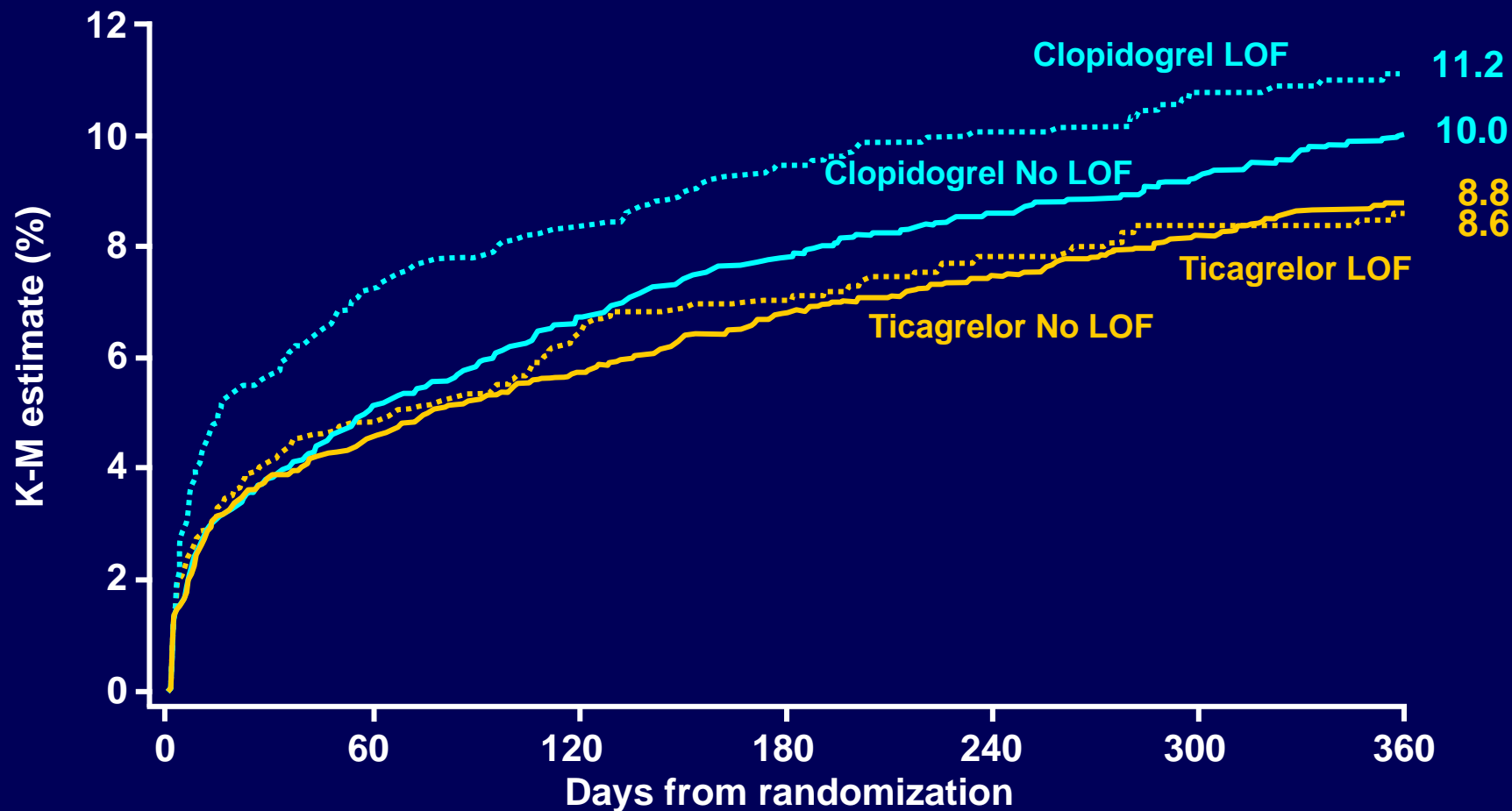
Data were missing for 199 and 244 patients in the ticagrelor and clopidogrel groups, respectively. Het = heterozygote

ABCB1 genotype by treatment

ABCB1 predicted phenotype	Ticagrelor n=5,137 (%)	Clopidogrel n=5,148 (%)
High expression (C/C)	1,167 (22.7%)	1,195 (23.2%)
Intermediate expression (C/T)	2,570 (50.0%)	2,518 (48.9%)
Low expression (T/T)	1,349 (26.3%)	1,386 (26.9%)

Data were missing for 51 and 49 patients in the ticagrelor and clopidogrel groups, respectively

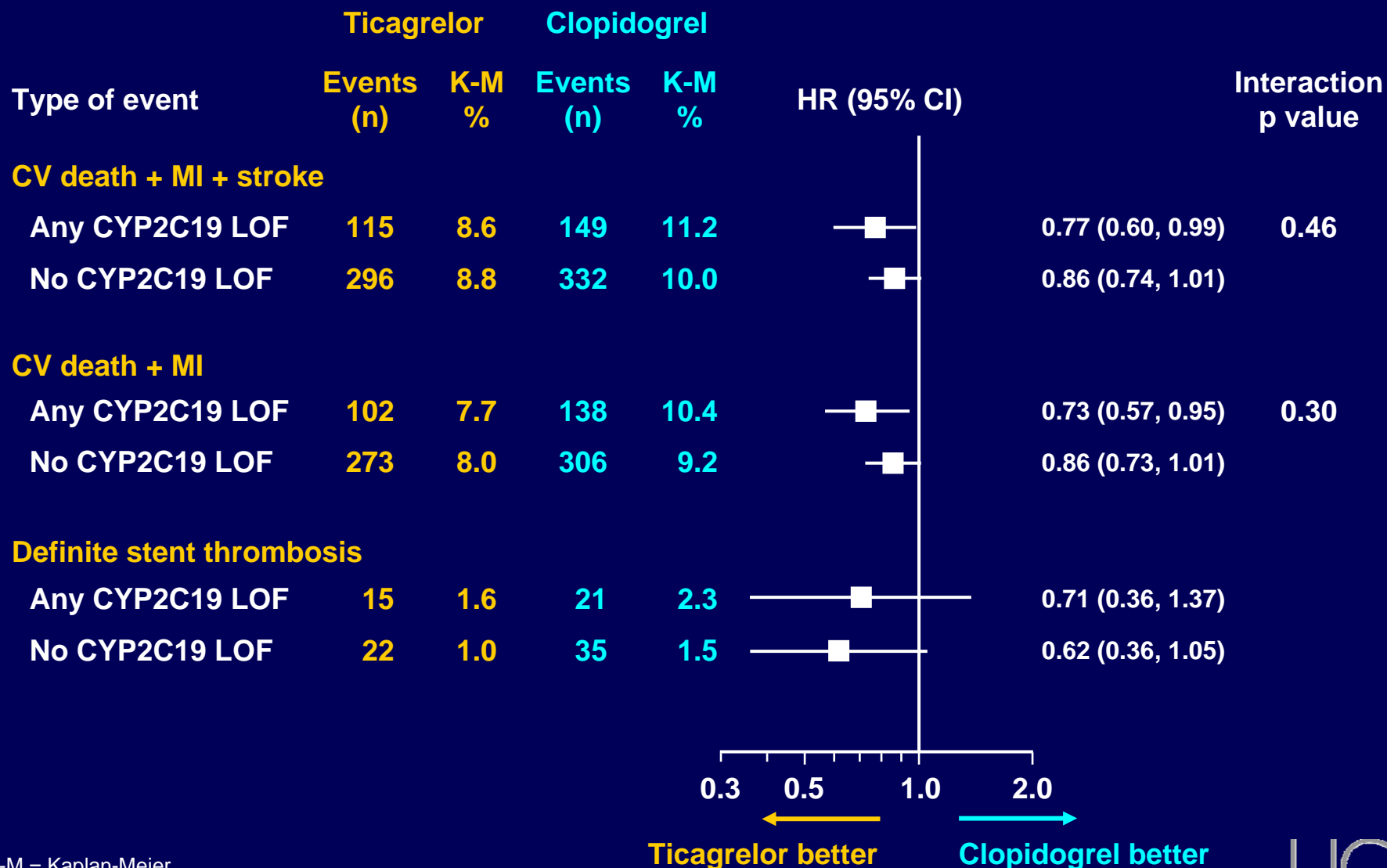
K-M estimate of the primary endpoint in relation to any CYP2C19 LOF allele



No. at risk

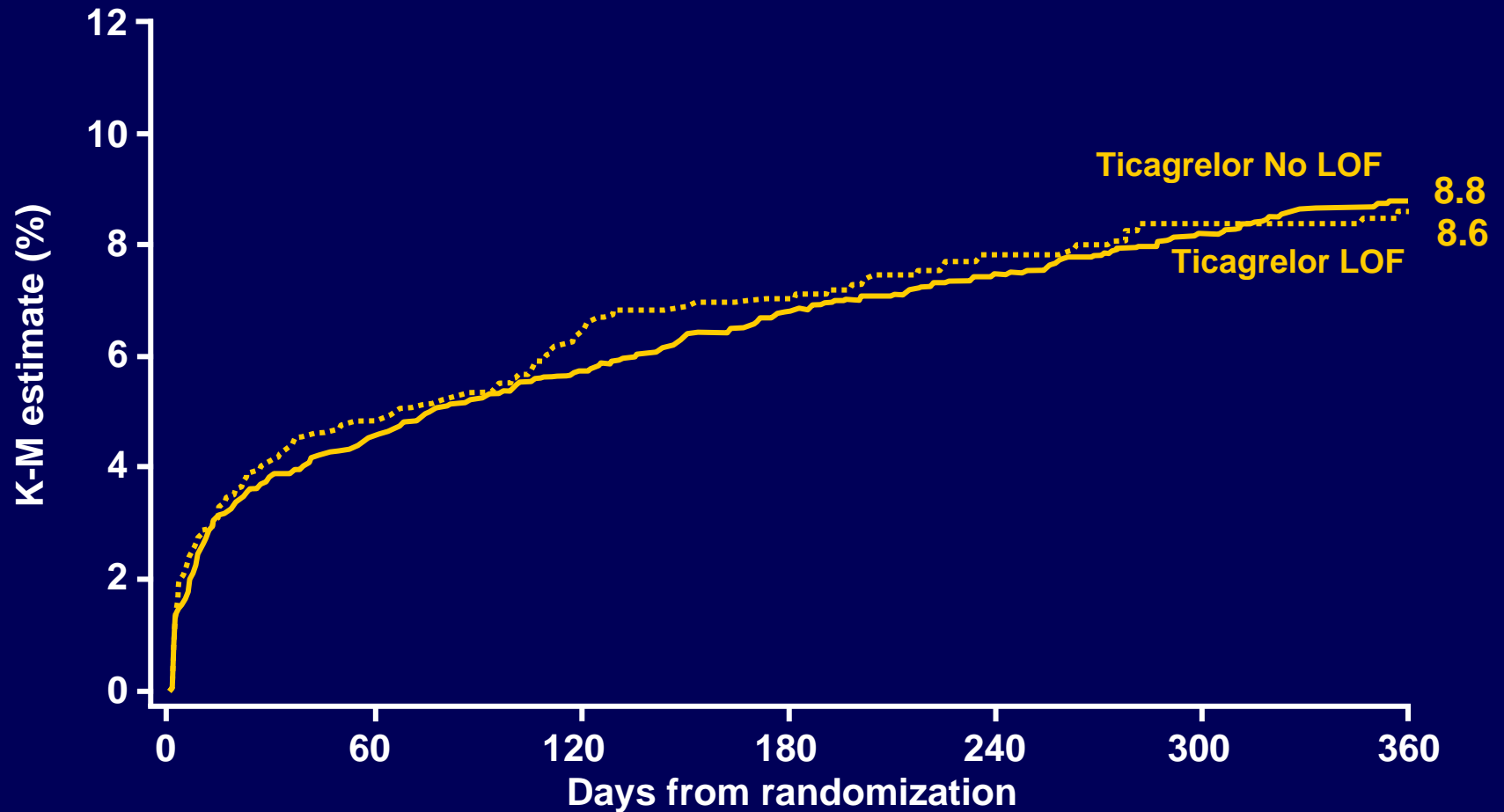
Clopidogrel LOF	1,388	1,275	1,259	1,226	1,027	801	658
Clopidogrel No LOF	3,516	3,321	3,256	3,186	2,691	2,123	1,757
Ticagrelor LOF	1,384	1,305	1,274	1,250	1,053	834	683
Ticagrelor No LOF	3,554	3,352	3,301	3,222	2,718	2,127	1,761

Efficacy outcomes in relation to CYP2C19 genetics



K-M = Kaplan-Meier

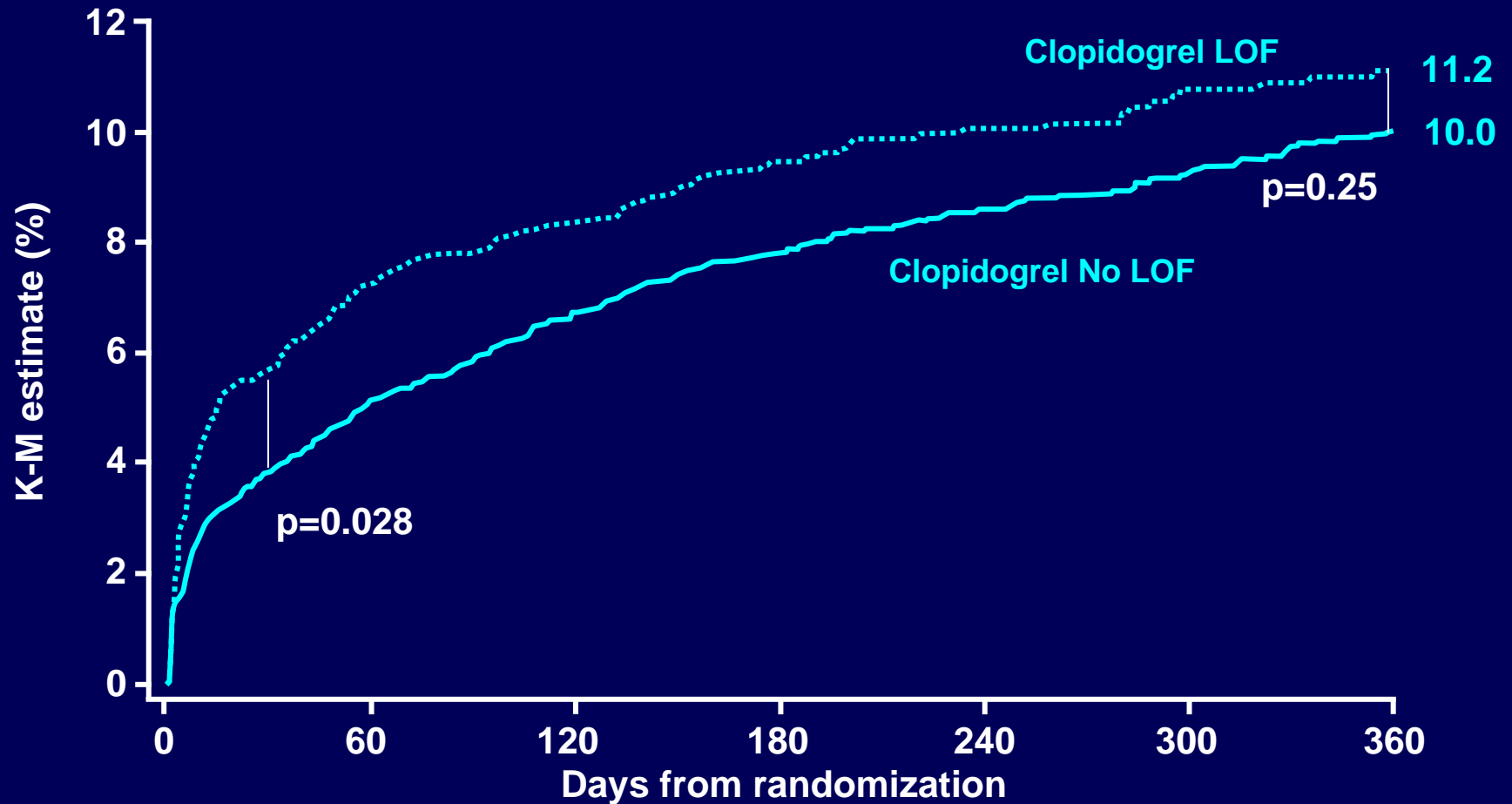
Primary endpoint in the ticagrelor group in relation to any CYP2C19 LOF allele (K-M estimate)



No. at risk

Ticagrelor LOF	1,384	1,305	1,274	1,250	1,053	834	683
Ticagrelor No LOF	3,554	3,352	3,301	3,222	2,718	2,127	1,761

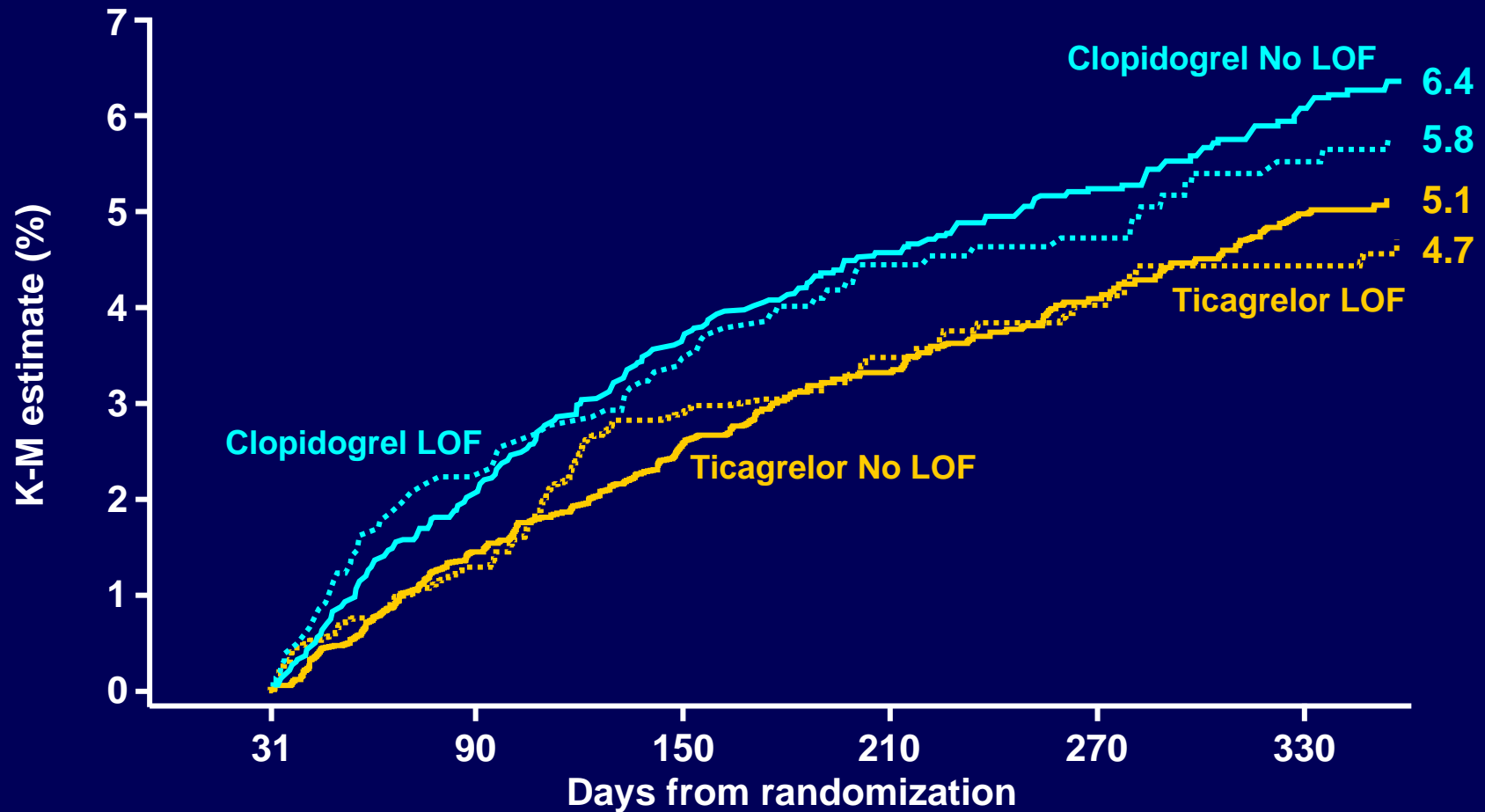
Primary endpoint in the clopidogrel group in relation to any CYP2C19 LOF allele (K-M estimate)



No. at risk

Clopidogrel LOF	1,388	1,275	1,259	1,226	1,027	801	658
Clopidogrel No LOF	3,516	3,321	3,256	3,186	2,691	2,123	1,757

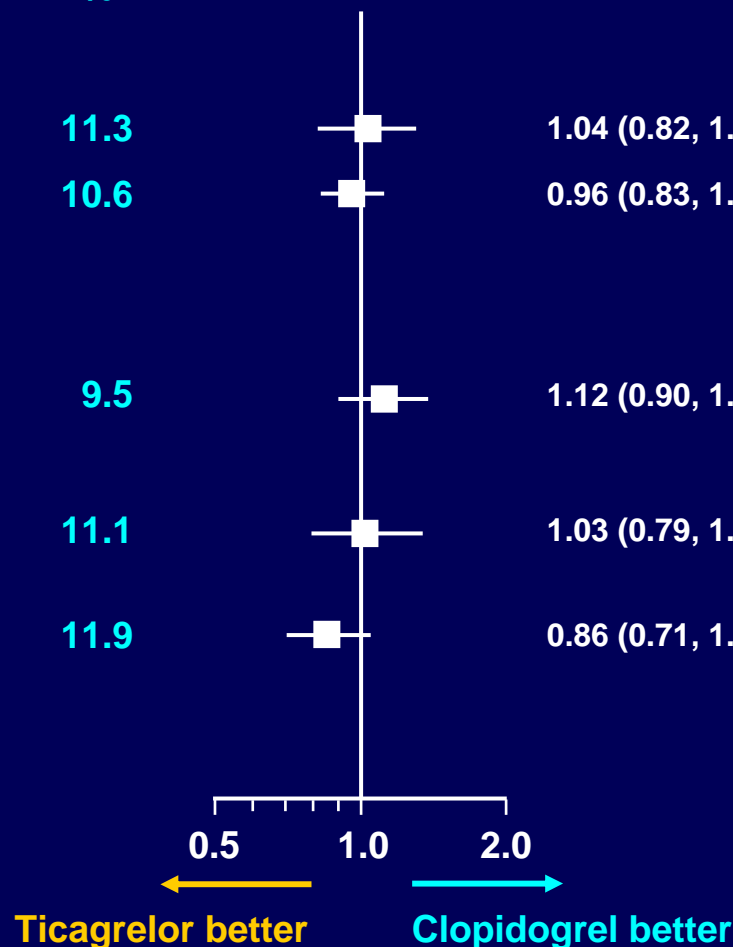
K-M estimate of the rate of primary efficacy events in relation to CYP2C19 genotype as a 'landmark analysis' from day 31



No. at risk	31	90	150	210	270	330
Clopidogrel LOF	1,302	1,266	1,247	1,066	996	771
Clopidogrel No LOF	3,370	3,291	3,228	2,756	2,600	2,027
Ticagrelor LOF	1,320	1,296	1,267	1,082	1,028	800
Ticagrelor No LOF	3,393	3,324	3,276	2,803	2,615	2,035

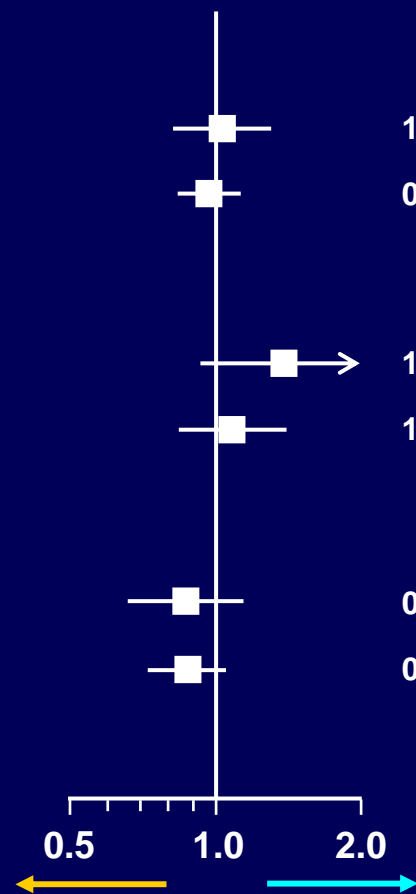
Safety outcomes in relation to CYP2C19 GOF allele

Type of event	Ticagrelor		Clopidogrel		HR (95% CI)	Interaction p value
	Events (n)	K-M %	Events (n)	K-M %		
Major bleeding/LOF						
Any CYP2C19 LOF	149	11.8	143	11.3	1.04 (0.82, 1.30)	0.60
No CYP2C19 LOF	331	10.3	340	10.6	0.96 (0.83, 1.12)	
Major bleeding/GOF						
No CYP2C19 LOF or GOF	176	10.5	161	9.5	1.12 (0.90, 1.38)	0.19
Any CYP2C19 LOF, no GOF	108	11.6	108	11.1	1.03 (0.79, 1.34)	
Any CYP2C19 GOF	196	10.5	214	11.9	0.86 (0.71, 1.05)	



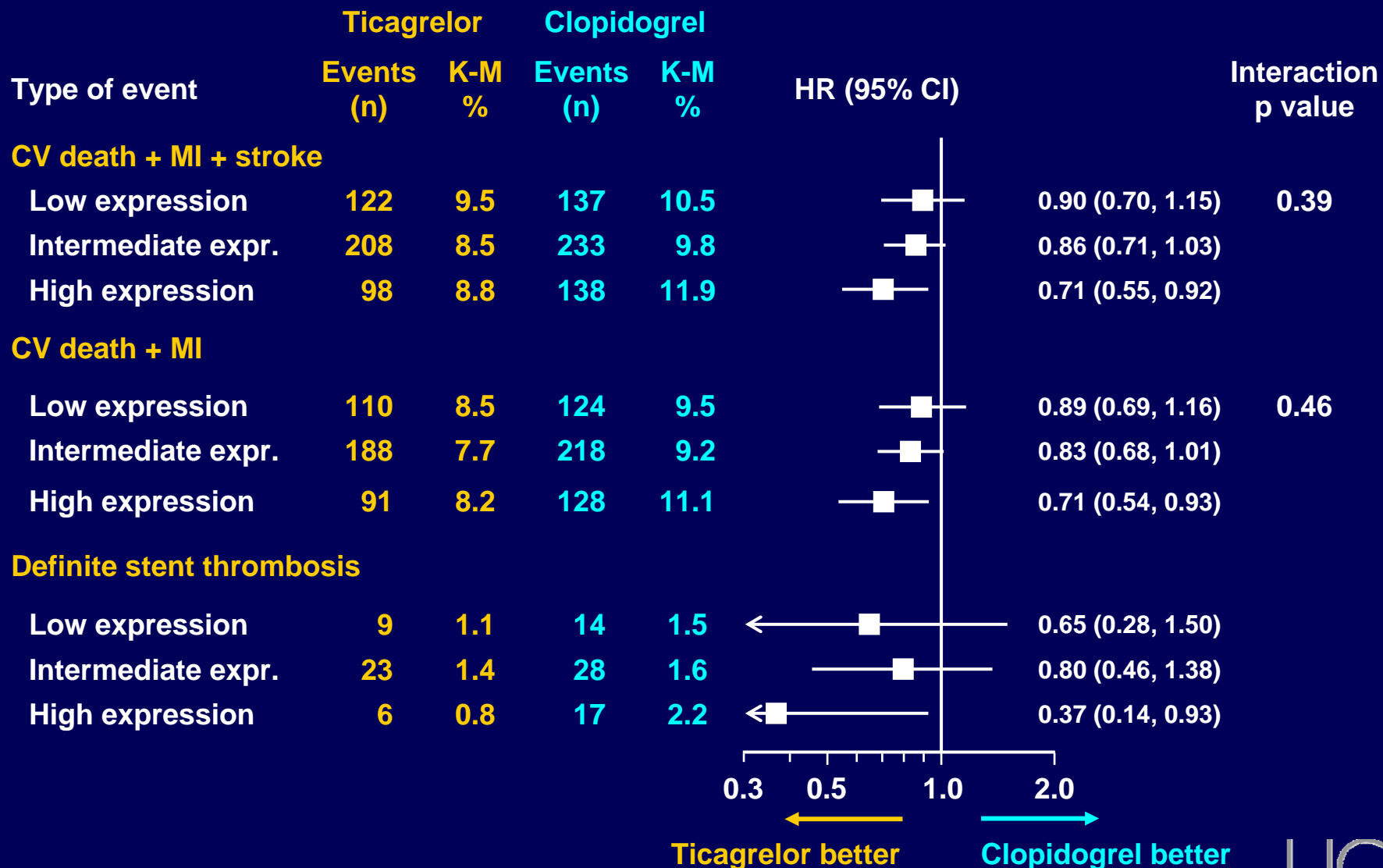
Safety outcomes in relation to CYP2C19 LOF alleles

Type of event	Ticagrelor		Clopidogrel		HR (95% CI)	Interaction p value
	Events (n)	K-M %	Events (n)	K-M %		
Major bleeding						
Any CYP2C19 LOF	149	11.8	143	11.3	1.04 (0.82, 1.30)	0.60
No CYP2C19 LOF	331	10.3	340	10.6	0.96 (0.83, 1.12)	
Major non-CABG bleeding						
Any CYP2C19 LOF	56	4.6	41	3.2	1.39 (0.93, 2.08)	0.31
No CYP2C19 LOF	121	3.9	110	3.6	1.08 (0.84, 1.40)	
Major CABG bleeding						
Any CYP2C19 LOF	96	7.6	107	8.6	0.87 (0.66, 1.14)	0.93
No CYP2C19 LOF	218	6.8	246	7.7	0.88 (0.73, 1.05)	



CABG = coronary artery bypass graft

Efficacy outcomes in relation to ABCB1 genetics



Conclusions

In a broad, global population with ACS:

- **ticagrelor vs clopidogrel** superior for prevention of CV death, MI and stroke regardless of CYP2C19 and ABCB1 genotype
- **ticagrelor vs clopidogrel** benefits on ischemic events appear earlier in carriers of any CYP2C19 LOF allele
- **ticagrelor vs clopidogrel** bleeding comparisons are unaffected by CYP2C19 and ABCB1 genotypes
- **with clopidogrel**, carriers of CYP2C19 LOF allele have higher ischemic event rates early, but not later, after start of treatment
- **with clopidogrel**, carriers of CYP2C19 GOF allele have higher bleeding rates
- **with ticagrelor**, no variation in rates of ischemic or bleeding events in relation to CYP2C19 or ABCB1 genotype

Ticagrelor is a more efficacious treatment for acute coronary syndromes than is clopidogrel, irrespective of *CYP2C19* and *ABCB1* polymorphisms.

Use of ticagrelor instead of clopidogrel eliminates the need for presently recommended genetic testing before dual antiplatelet treatment.

Wallentin L et al Lancet 2010: 376, Online Aug 29, 2010

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