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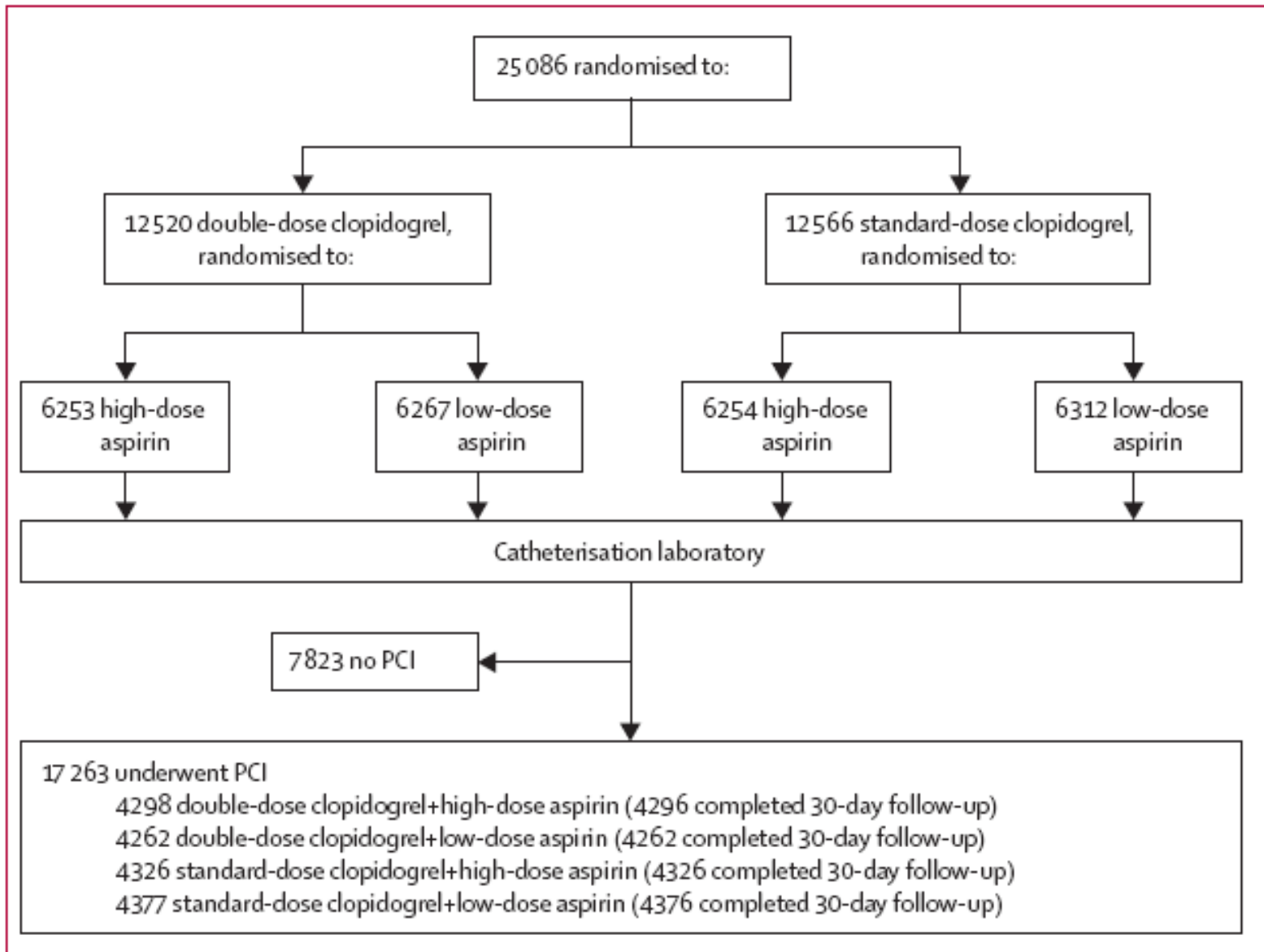
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Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial



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Méthodes

Etude 2x2

High dose clopidogrel vs **standard dose**

- Day1: 600mg 300mg
- Day2-7: 150mg 75mg
- Day 8-30: 75mg 75mg

Tous les patients reçoivent **aspirine** > 300mg
Day1

High dose aspirine vs **standard dose**

300 -325 mg 75-100mg

The primary outcome :

composite of
cardiovascular death
myocardial infarction
or stroke
to day 30

Patients

- juin 2006–juillet 2009
39 pays 597 centres
- SCA ST- et + éligible a une PCA < 72h
- Critères d'exclusions: CI au médicaments

	Clopidogrel dose		Aspirin dose	
	Double (N=8560)	Standard (N=8703)	High (N=8624)	Low (N=8639)
Demographics				
Age (years)	61.2 (11.7)	61.2 (11.6)	61.1 (11.6)	61.3 (11.7)
Age >75 years	1096 (12.8%)	1092 (12.5%)	1101 (12.8%)	1087 (12.6%)
Female sex	2051 (24.0%)	2183 (25.1%)	2149 (24.9%)	2085 (24.1%)
Admission diagnosis				
Unstable angina or NSTEMI	5379 (62.8%)	5520 (63.4%)	5469 (63.4%)	5430 (62.9%)
Time from randomisation to PCI (h)	3.1 (0.9-19.5)	3.3 (0.9-19.8)	3.2 (0.9-19.6)	3.2 (0.9-19.7)
STEMI	3181 (37.2%)	3183 (36.6%)	3155 (36.6%)	3209 (37.1%)
Time from randomisation to PCI (h)	0.5 (0.3-1.0)	0.5 (0.3-1.0)	0.5 (0.3-1.0)	0.5 (0.3-1.0)
Previous history				
Current smoker	3205 (37.5%)	3189 (36.6%)	3176 (36.8%)	3218 (37.3%)
Hypertension	5080 (59.4%)	5117 (58.8%)	5087 (59.0%)	5110 (59.2%)
Dyslipidaemia	3447 (40.3%)	3506 (40.3%)	3479 (40.4%)	3474 (40.2%)
Diabetes mellitus	1910 (22.3%)	1934 (22.2%)	1974 (22.9%)	1869 (21.6%)
Myocardial infarction	1474 (17.2%)	1459 (16.8%)	1473 (17.1%)	1460 (16.9%)
PCI	1251 (14.6%)	1264 (14.5%)	1280 (14.8%)	1235 (14.3%)
CABG	486 (5.7%)	499 (5.7%)	487 (5.6%)	498 (5.8%)
Raised biomarker	5762 (67.3%)	5839 (67.1%)	5709 (67.1%)	5810 (67.3%)
Clopidogrel ≤24 h before randomisation				
<300 mg	1443 (16.9%)	1443 (16.6%)	1403 (16.3%)	1483 (17.2%)
≥300 mg	296 (3.5%)	312 (3.6%)	292 (3.4%)	316 (3.7%)
Regular aspirin before randomisation				
Unfractionated heparin	7401 (86.5%)	7490 (86.1%)	7425 (86.1%)	7466 (86.4%)
Low-molecular-weight heparin	4319 (50.5%)	4301 (49.4%)	4333 (50.2%)	4287 (49.6%)
Fondaparinux	379 (4.4%)	400 (4.6%)	389 (4.5%)	390 (4.5%)
Bivalirudin	481 (5.6%)	479 (5.5%)	478 (5.5%)	482 (5.6%)
Glycoprotein IIb/IIIa inhibitor	3503 (40.9%)	3507 (40.3%)	3486 (40.4%)	3524 (40.8%)
Stent				
Bare-metal stent only	4688/8101 (57.9%)	4769/8222 (58%)	4709/8160 (57.7%)	4748/8163 (58.2%)
Drug-eluting stent	3413/8101 (42.1%)	3453/8222 (42.0%)	3451/8160 (42.31%)	3415/8163 (41.8%)
Vessels treated (per number of lesions)				
Left main	139/8771 (1.6%)	140/8900 (1.6%)	144 (1.6%)	135 (1.5%)
Left anterior descending	3077/8771 (35.1%)	3053/8900 (34.3%)	3097 (35.1%)	3033 (34.3%)
Left circumflex	2282/8771 (26.0%)	2374/8900 (26.7%)	2316 (26.2%)	2340/8837 (26.5%)
Right coronary artery	3037/8771 (34.6%)	3124/8900 (35.1%)	3057/34.6 (34.6%)	3104/8837 (35.1%)
Saphenous vein/arterial graft	236/8771 (2.7%)	209/8900 (2.3%)	220/8834 (2.5%)	225/8837 (2.5%)
Visible angiographic thrombus before PCI	2719/8276 (32.9%)	2747/8399 (32.7%)	2726/8349 (32.7%)	2740/8326 (32.9%)

Data are mean (SD), number (%), median (IQR), or n/N (%). NSTEMI=non-ST-segment elevation myocardial infarction. STEMI=ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft surgery.

Table 1: Baseline characteristics, drugs received, and invasive procedures in patients undergoing PCI



	Clopidogrel dose		Adjusted HR (95% CI)	p value
	Double (N=8560)	Standard (N=8703)		
CV death, MI, or stroke	330 (3.9%)	392 (4.5%)	0.86 (0.74-0.99)	0.039
CV death, MI, stroke, or recurrent ischaemia	363 (4.2%)	435 (5.0%)	0.85 (0.74-0.98)	0.025
CV death	160 (1.9%)	169 (1.9%)	0.96 (0.77-1.19)	0.71
MI	172 (2.0%)	226 (2.6%)	0.79 (0.64-0.96)	0.018
Stroke	30 (0.4%)	36 (0.4%)	0.87 (0.53-1.41)	0.56
Recurrent ischaemia	39 (0.5%)	48 (0.6%)	0.85 (0.56-1.31)	0.47
Total mortality	166 (1.9%)	179 (2.1%)	0.94 (0.76-1.16)	0.57
CURRENT-defined major bleed	139 (1.6%)	99 (1.1%)	1.41 (1.09-1.83)	0.009
CURRENT-defined severe bleed	96 (1.1%)	72 (0.8%)	1.34 (0.99-1.82)	0.060
TIMI-defined major bleed	81 (1.0%)	60 (0.7%)	1.36 (0.97-1.90)	0.074
Fatal bleed	6 (0.07%)	13 (0.2%)	0.46 (0.18-1.22)	0.12
Intracranial bleed	3 (0.04%)	4 (0.05%)	0.77 (0.17-3.43)	0.73
Red-cell transfusion ≥ 2 units	109 (1.3%)	77 (0.9%)	1.42 (1.06-1.91)	0.019
CABG-related bleed	10 (0.1%)	6 (0.07%)	1.70 (0.62-4.69)	0.30
Haemoglobin drop ≥ 50 g/L	47 (0.6%)	30 (0.3%)	1.60 (1.01-2.53)	0.045
Minor bleed	435 (5.1%)	368 (4.3%)	1.23 (1.07-1.41)	0.004
Events before PCI				
MI or stroke	25 (0.3%)	19 (0.2%)	1.34 (0.74-2.44)	0.33
MI	25 (0.3%)	17 (0.2%)	1.50 (0.81-2.78)	0.20
Stroke	0	2 (0.02%)
CURRENT-defined major bleed	9 (0.1%)	4 (0.04%)	2.31 (0.71-7.49)	0.16
CURRENT-defined severe bleed	5 (0.1%)	2 (0.02%)	2.55 (0.49-13.14)	0.26
TIMI-defined major bleed	5 (0.1%)	1 (0.01%)	5.09 (0.60-43.60)	0.14

Events after PCI

CV death, MI, or stroke	305 (3.6%)	373 (4.3%)	0.83 (0.71-0.96)	0.015
CV death, MI, stroke, or recurrent ischaemia	319 (3.7%)	397 (4.6%)	0.81 (0.70-0.94)	0.006
CV death	160 (1.9%)	169 (1.9%)	0.96 (0.77-1.19)	0.69
MI	147 (1.7%)	209 (2.4%)	0.72 (0.58-0.88)	0.002
Stroke	30 (0.4%)	34 (0.4%)	0.89 (0.55-1.46)	0.65
Recurrent ischaemia	20 (0.2%)	29 (0.3%)	0.70 (0.40-1.24)	0.23
Total mortality	166 (1.9%)	179 (2.1%)	0.94 (0.76-1.16)	0.55
CURRENT-defined major bleed	130 (1.5%)	95 (1.1%)	1.39 (1.07-1.81)	0.0141
CURRENT-defined severe bleed	91 (1.1%)	70 (0.8%)	1.32 (0.97-1.80)	0.080
TIMI-defined major bleed	76 (0.9%)	59 (0.7%)	1.31 (0.93-1.84)	0.12

Data are number (%), unless otherwise indicated. HR=hazard ratio. CV=cardiovascular. MI=myocardial infarction. TIMI=Thrombosis In Myocardial Infarction. CABG=coronary artery bypass graft surgery. PCI=percutaneous coronary intervention.

Table 2: Efficacy and safety outcomes for the clopidogrel dose comparison

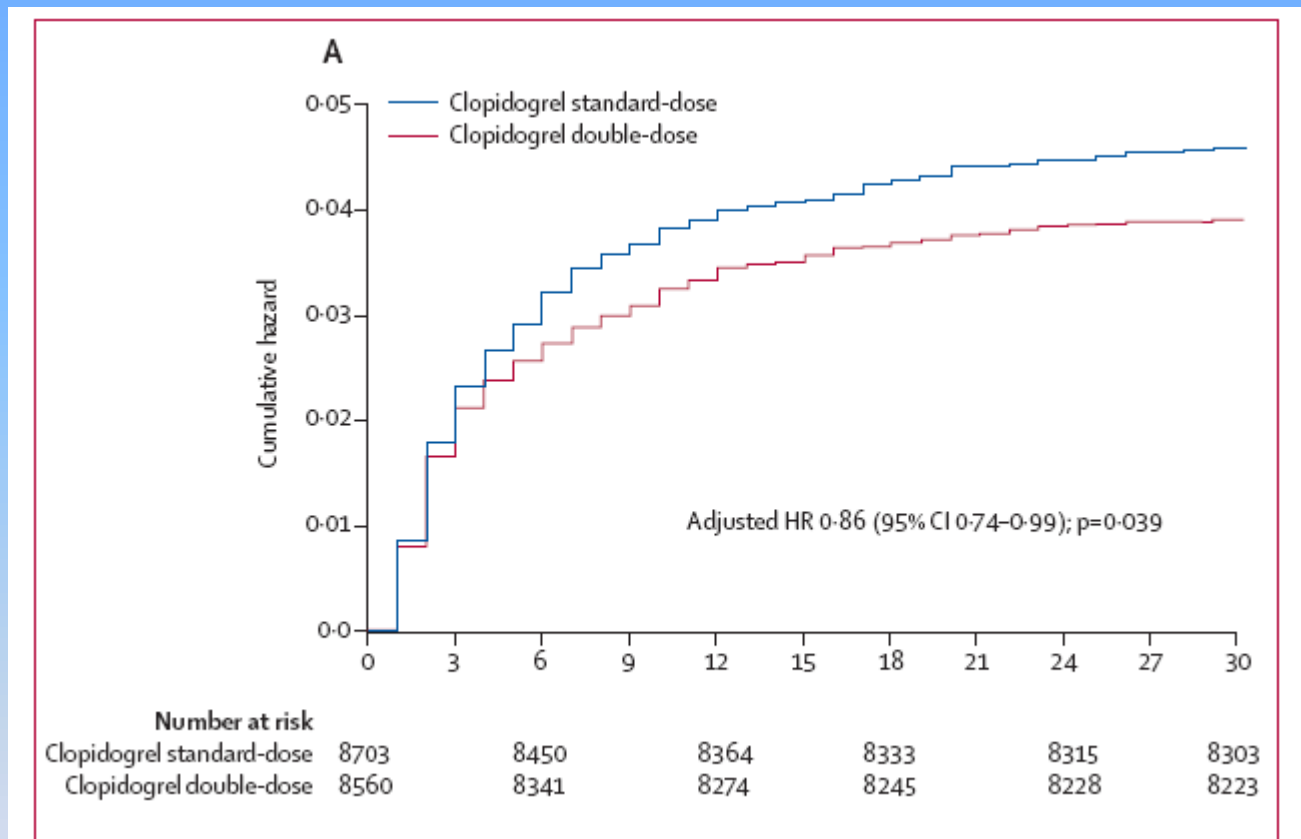


Figure 2: Kaplan-Meier curves for the primary outcome of cardiovascular death, myocardial infarction, or stroke, for the clopidogrel dose comparison (A) and the aspirin dose comparison (B)
HR=hazard ratio.

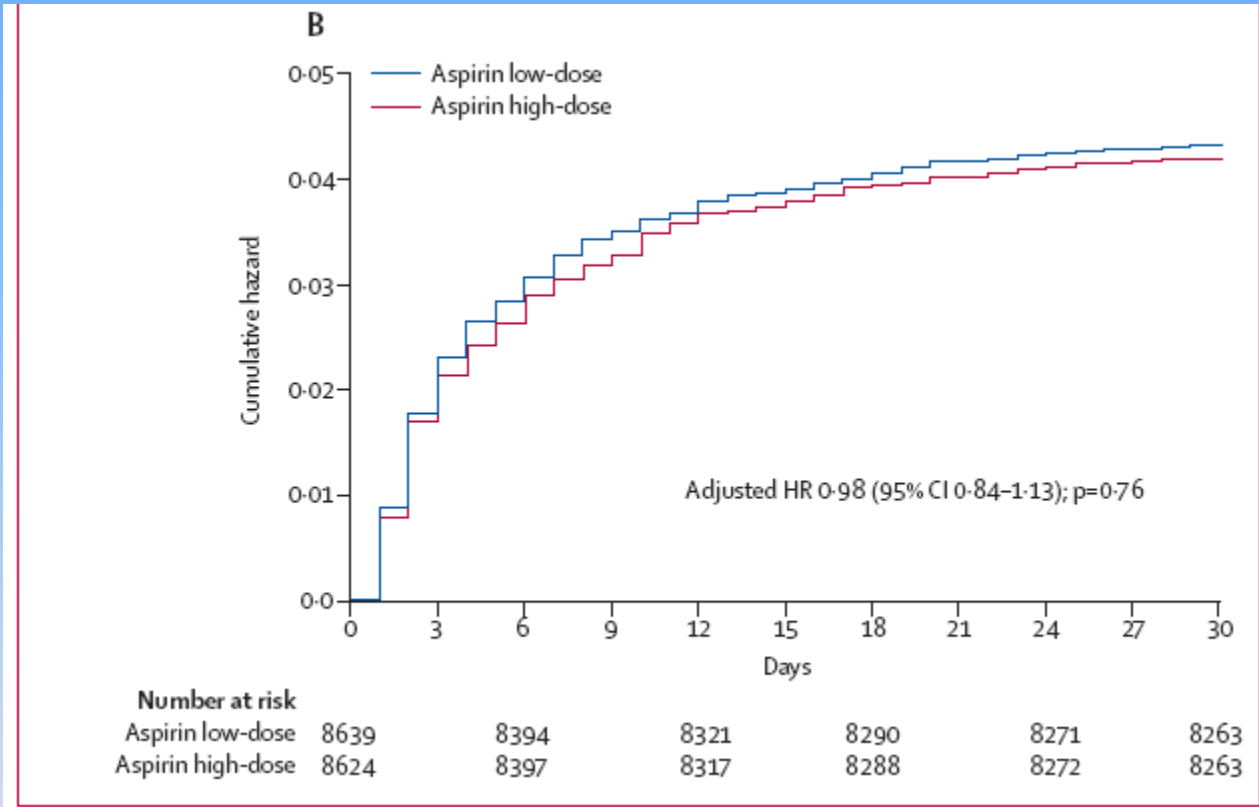
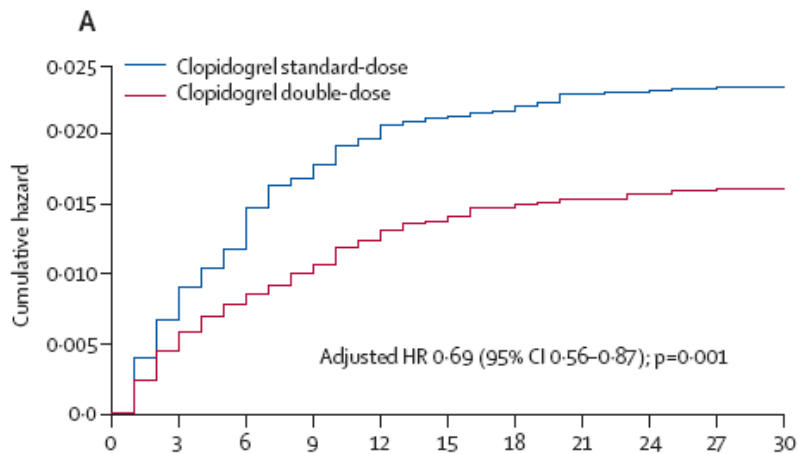
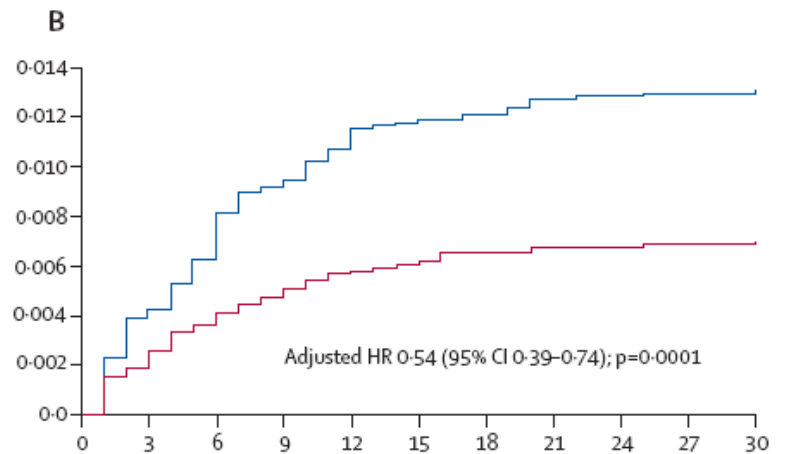


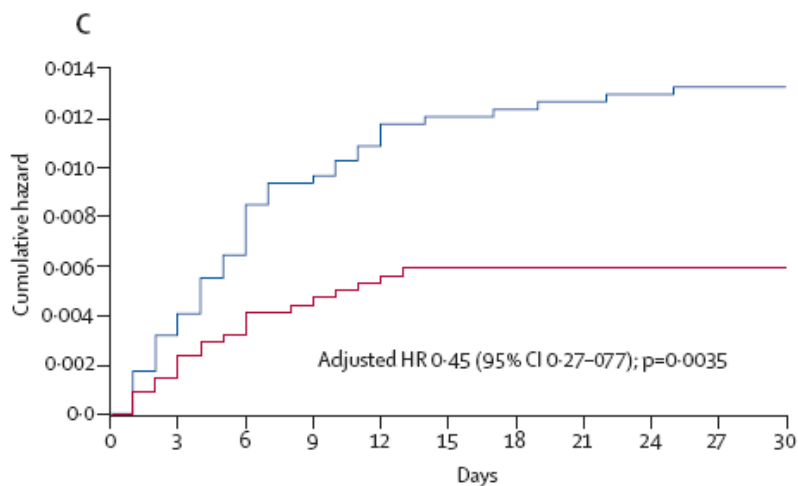
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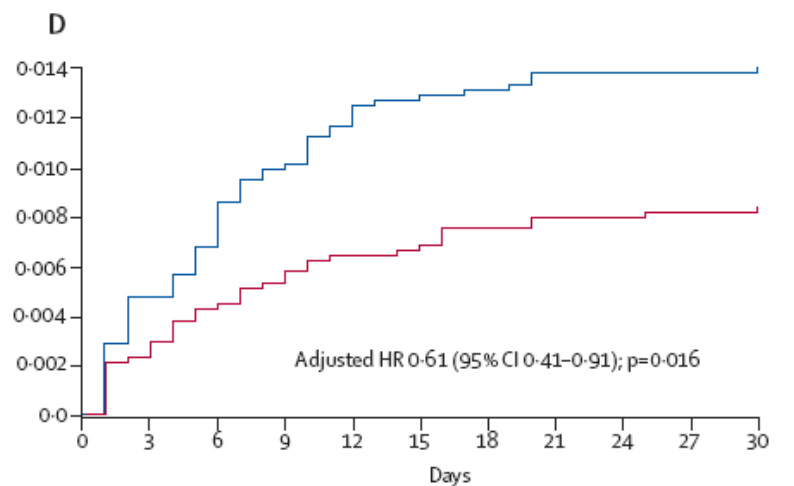
	0	3	6	9	12	15	18	21	24	27	30
Clopidogrel standard-dose	8703	8553	8470	8444	8428	8418					
Clopidogrel double-dose	8560	8442	8386	8363	8353	8343					



	0	3	6	9	12	15	18	21	24	27	30
Clopidogrel standard-dose	8703	8561	8482	8455	8438	8428					
Clopidogrel double-dose	8560	8444	8390	8366	8356	8347					



	0	3	6	9	12	15	18	21	24	27	30
Clopidogrel standard-dose	3453	3397	3367	3358	3352	3348					
Clopidogrel double-dose	3413	3378	3361	3354	3353	3350					



	0	3	6	9	12	15	18	21	24	27	30
Clopidogrel standard-dose	4769	4695	4649	4637	4624	4620					
Clopidogrel double-dose	4688	4617	4585	4568	4561	4554					

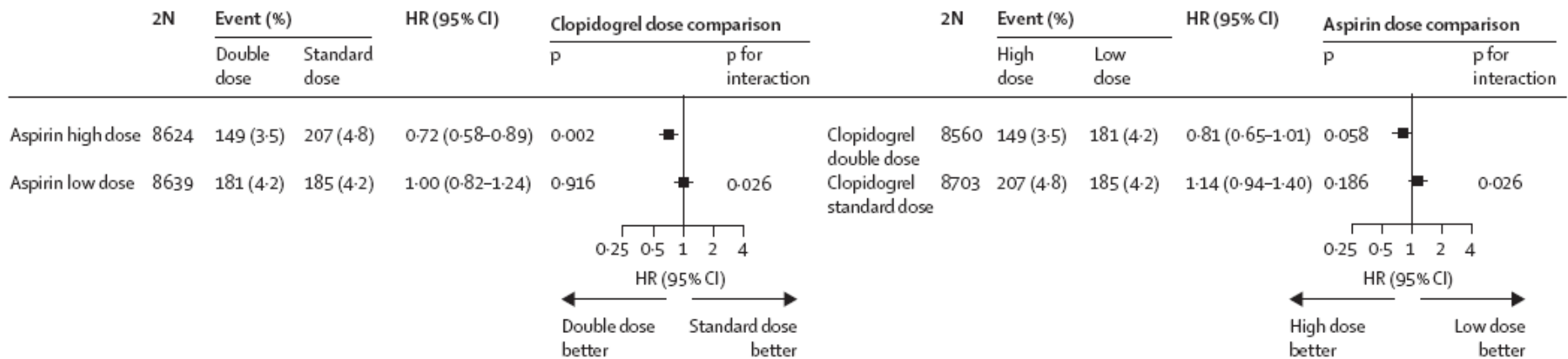
Figure 3: Kaplan-Meier curves for clopidogrel dose comparison for definite or probable stent thrombosis (A), definite stent thrombosis (B), definite stent thrombosis in patients receiving a drug-eluting stent (C), and definite stent thrombosis in patients receiving bare-metal stents (D)
HR=hazard ratio.

	Aspirin dose		Adjusted HR (95% CI)	p value
	High (N=8624)	Low (N=8639)		
CV death, MI, or stroke	356 (4.1%)	366 (4.2%)	0.98 (0.84-1.13)	0.76
CV death, MI, stroke, or recurrent ischaemia	381 (4.4%)	417 (4.8%)	0.92 (0.80-1.06)	0.23
CV death	156 (1.8%)	173 (2.0%)	0.90 (0.72-1.12)	0.35
MI	196 (2.3%)	202 (2.4%)	0.97 (0.80-1.19)	0.80
Stroke	37 (0.4%)	29 (0.3%)	1.26 (0.77-2.05)	0.36
Recurrent ischaemia	31 (0.4%)	56 (0.7%)	0.56 (0.36-0.88)	0.011
Total mortality	160 (1.9%)	185 (2.1%)	0.86 (0.70-1.07)	0.18
CURRENT-defined major bleed	128 (1.5%)	110 (1.3%)	1.18 (0.92-1.53)	0.20
CURRENT-defined severe bleed	92 (1.1%)	76 (0.9%)	1.22 (0.90-1.66)	0.20
TIMI-defined major bleed	79 (0.9%)	62 (0.7%)	1.29 (0.93-1.80)	0.13
Fatal bleed	10 (0.1%)	9 (0.1%)	1.12 (0.46-2.76)	0.80
Intracranial bleed	4 (0.05%)	3 (0.03%)	1.34 (0.30-5.98)	0.70
Red-cell transfusion ≥ 2 units	100 (1.2%)	86 (1.0%)	1.19 (0.89-1.59)	0.24
CABG-related bleed	8 (0.1%)	8 (0.1%)	0.99 (0.37-2.64)	0.99
Haemoglobin drop ≥ 50 g/L	43 (0.5%)	34 (0.4%)	1.27 (0.81-1.98)	0.30
Minor bleed	433 (5.0%)	370 (4.3%)	1.18 (1.03-1.36)	0.019
Events before PCI				
MI or stroke	23 (0.3%)	21 (0.2%)	1.09 (0.60-1.96)	0.78
MI	21 (0.2%)	21 (0.2%)	0.99 (0.54-1.82)	0.98
Stroke	2 (0.02%)	0 (0.0%)
CURRENT-defined major bleed	8 (0.1%)	5 (0.1%)	1.58 (0.52-4.84)	0.42
CURRENT-defined severe bleed	5 (0.1%)	2 (0.02%)	2.48 (0.48-12.78)	0.28
TIMI-defined major bleed	4 (0.05%)	2 (0.02%)	1.98 (0.36-10.81)	0.43
Events after PCI				
CV death, MI, or stroke	333 (3.9%)	345 (4.0%)	0.97 (0.83-1.13)	0.68
CV death, MI, stroke, or recurrent ischaemia	342 (4.0%)	374 (4.3%)	0.92 (0.79-1.06)	0.24
CV death	156 (1.8%)	173 (2.0%)	0.91 (0.73-1.13)	0.38
MI	175 (2.0%)	181 (2.1%)	0.97 (0.79-1.19)	0.75
Stroke	35 (0.4%)	29 (0.3%)	1.21 (0.74-1.98)	0.45
Recurrent ischaemia	15 (0.2%)	34 (0.4%)	0.44 (0.24-0.81)	0.0083
Total mortality	160 (1.9%)	185 (2.1%)	0.87 (0.70-1.08)	0.20
CURRENT-defined major bleed	120 (1.4%)	105 (1.2%)	1.14 (0.88-1.49)	0.32
CURRENT-defined severe bleed	87 (1.0%)	74 (0.9%)	1.18 (0.86-1.60)	0.30
TIMI-defined major bleed	75 (0.9%)	60 (0.7%)	1.25 (0.89-1.76)	0.20

Data are number (%), unless otherwise indicated. HR=hazard ratio. CV=cardiovascular. MI=myocardial infarction. TIMI=Thrombosis In Myocardial Infarction. CABG=coronary artery bypass graft surgery. PCI=percutaneous coronary intervention.

Table 3: Efficacy and safety outcomes for the aspirin dose comparison

A



B

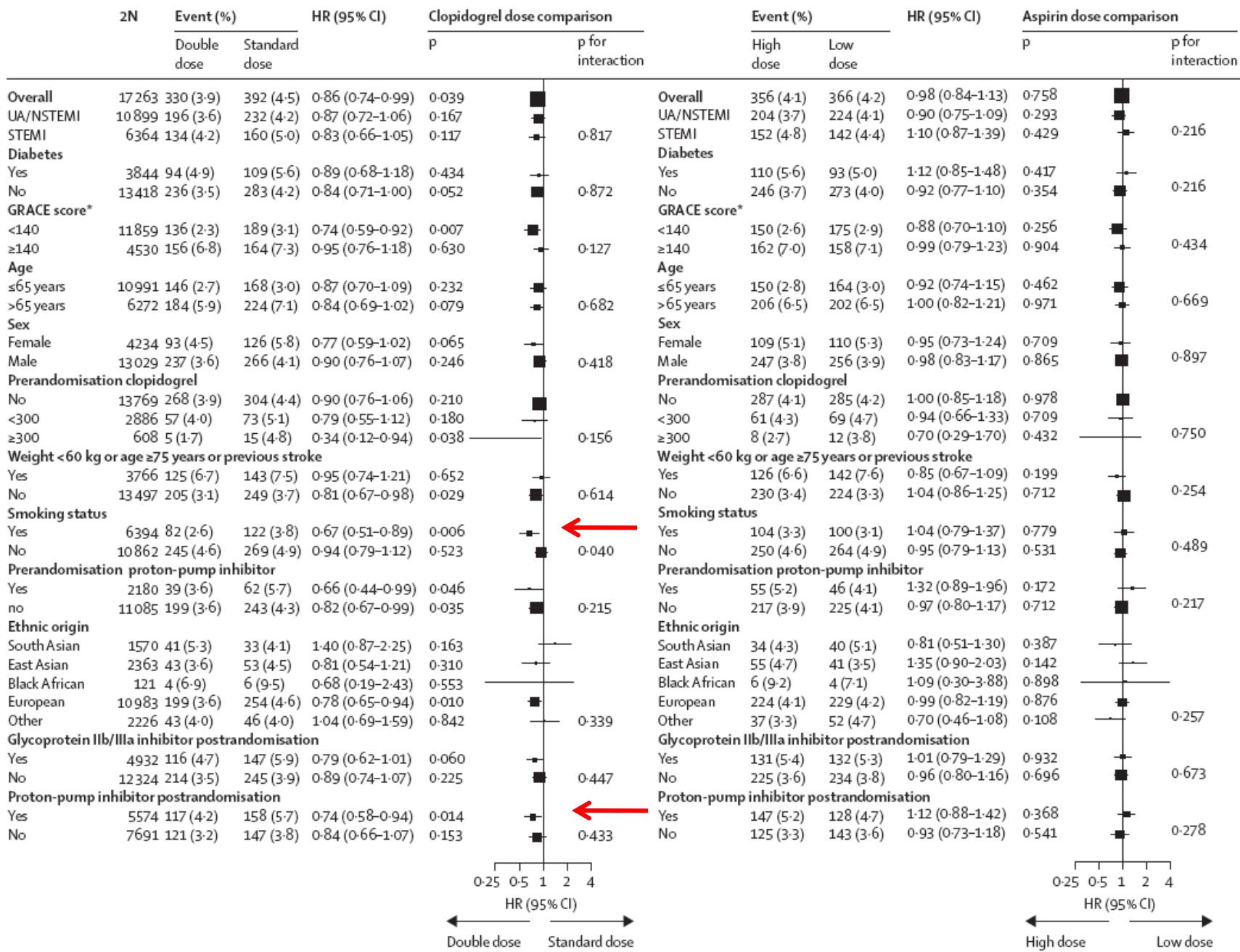


Figure 4: Primary outcome for clopidogrel and aspirin dose comparisons according to randomised factorial design (A), and subgroup analyses for primary outcome in subgroups for clopidogrel and aspirin dose comparisons (B)

Interpretation In patients undergoing PCI for acute coronary syndromes, a 7-day double-dose clopidogrel regimen was associated with a reduction in cardiovascular events and stent thrombosis compared with the standard dose. Efficacy and safety did not differ between high-dose and low-dose aspirin. A double-dose clopidogrel regimen can be considered for all patients with acute coronary syndromes treated with an early invasive strategy and intended early PCI.

Funding Sanofi-Aventis and Bristol-Myers Squibb.

CONCLUSION

- **In patients undergoing PCI for acute coronary syndromes, a 7-day double-dose clopidogrel regimen was associated with a reduction in cardiovascular events and stent thrombosis compared with the standard dose.**
- **Efficacy and safety did not differ between high-dose and low-dose aspirin.**
- **A double-dose clopidogrel regimen can be considered for all patients with acute coronary syndromes treated with an early invasive strategy and intended early PCI.**