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Is There A LIfe for DES after discontinuation of Clopidogrel

Six-month versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients non-resistant to aspirin: ITALIC, a randomized multicenter trial

Gilard M, Barragan P, AL Noryani A, Noor H AMajwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, §Carrie D, Furber Berlan J, Darremont O, Le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D, Ohlmann P, Endresen K, Ben Amer H, Kiss R G,; Ungi I, Boschat J, Morice MC

Background

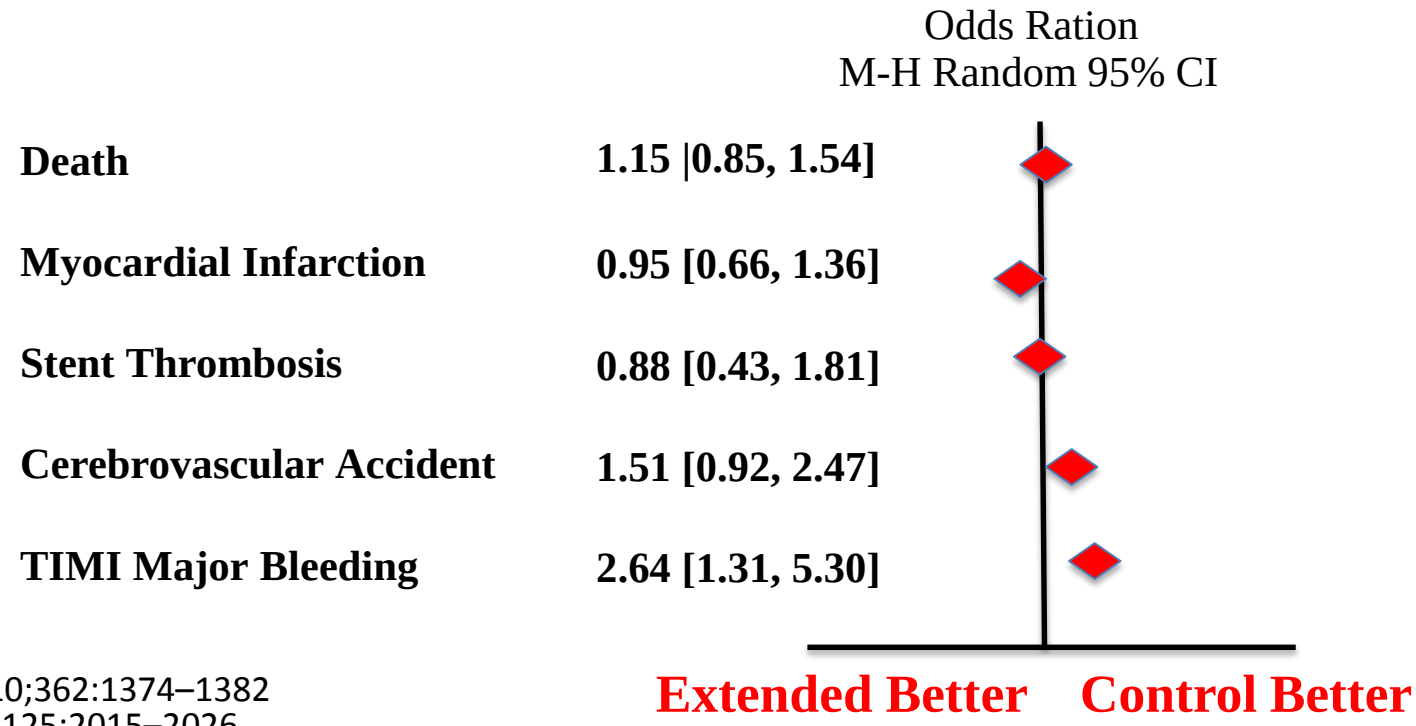
Background. The currently recommended duration of dual antiplatelet therapy (DAPT) in drug-eluting stent (DES) recipients is 12 months, to reduce the risk of late stent thrombosis, particularly in acute coronary syndrome.

Objectives: It was hypothesized that antiplatelet treatment with DAPT for 6 versus may be non-inferior to DAPT for 24 months in aspirin-sensitive patients

Background

Clinical Impact of Extended DAPT after PCI

A metanalysis of Randomized trials (n=8231)



N Engl J Med 2010;362:1374–1382
Circulation 2012;125:2015–2026
Circulation 2012;125:505–513.
J Am Coll Cardiol. 2012 Oct 9;60(15):1340-8.

Cassese et al European Heart Journal 2012; 33: 3078-3087

Objectives

It was hypothesized that antiplatelet treatment with DAPT for 6 versus may be **non-inferior** to DAPT for 24 months

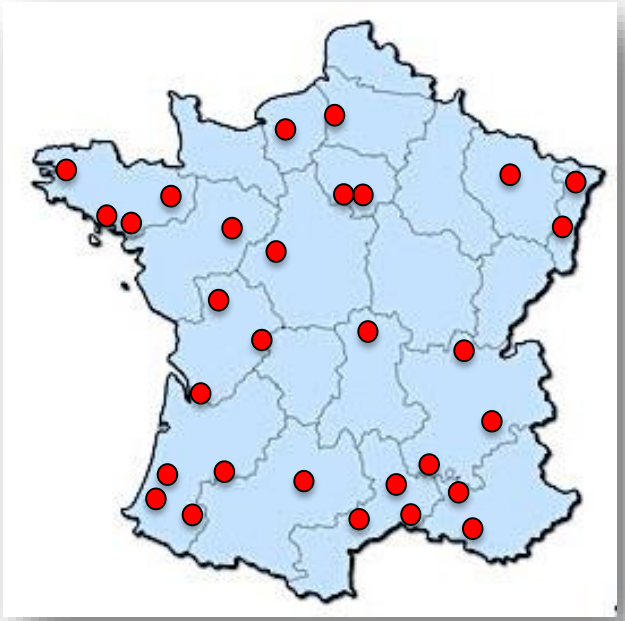
To be sure that patients would be protected by their antiplatelet therapy in either situation, **patients resistant to aspirin were excluded**

Methods

A prospective open-label randomized trial
70 sites in Europe and the Middle East.

48 French sites

11- 2008 to 12-2010



7 European - Middle East sites

11- 2008 to 12-2010

Methods

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Dr Jacques Berland	Clinique St Hilaire, Rouen France
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Dr Hervé Le Breton	CHU Rennes, Rennes France
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Methods

Inclusion criteria

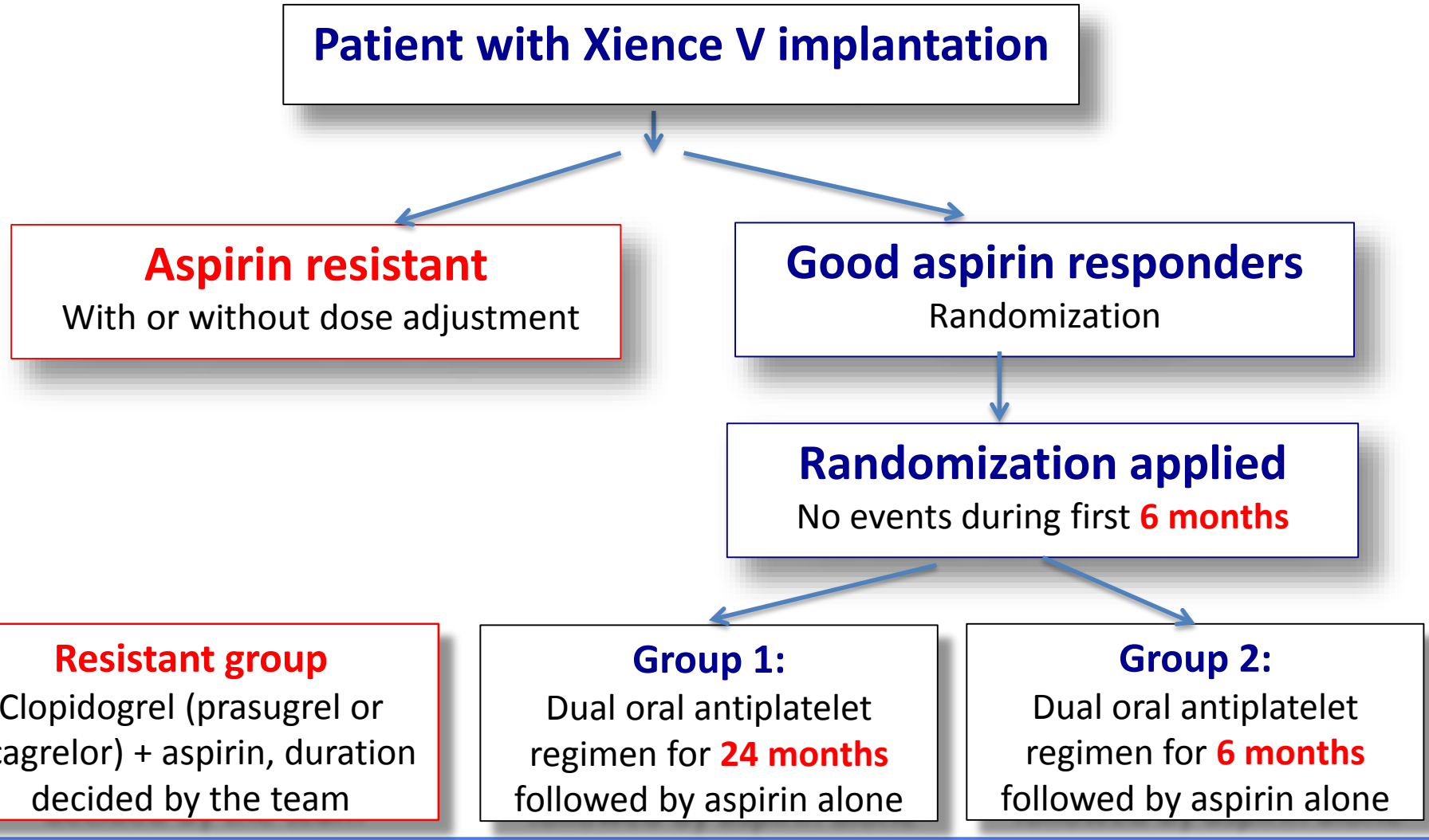
- Patients aged 18 years or over, eligible for PCI
- At least one Xience V DES (Abbott Vascular Devices) implanted
- Patients were not pre-treated with abciximab during hospital stay.
- Aspirin resistance was checked.
- Patients were pre-treated with aspirin + clopidogrel (prasugrel or ticagrelor)

Methods

Exclusion criteria

- Known platelet level less than 100,000/µl or known hemorrhagic diathesis
- Oral anticoagulation therapy
- Contraindications to aspirin or clopidogrel (prasugrel or ticagrelor)
- Major surgery within the preceding 6 weeks
- Evidence of active gastrointestinal or urogenital bleeding
- Severe liver failure; any surgery scheduled during the year after enrolment
- Severe concomitant disease with less than 2 years' life expectancy
- **Prior DES implantation within 1 year**
- **Primary PCI for acute myocardial infarction**
- **Treatment of the left main artery**

Methods


Patient with Xience V implantation
Aspirin resistant
With or without dose adjustment
Good aspirin responders
Randomization
Randomization applied
No events during first 6 months
Resistant group
Clopidogrel (prasugrel or ticagrelor) + aspirin, duration decided by the team
Group 1:
Dual oral antiplatelet regimen for 24 months followed by aspirin alone
Group 2:
Dual oral antiplatelet regimen for 6 months followed by aspirin alone

Methods

Aspirin Resistance Tests: 3

Patient aspirin responder :

PFA-100 >165 seconds

Multiplate electrical impedance aggregometry ≥30%

VerifyNow Aspirin ≥ 550 aspirin reaction units.

The type of test depends of the centre

Methods

Endpoints

Academic Research Consortium criteria

Primary endpoint : death, MI, emergency TVR, stroke or major bleeding according to the TIMI criteria within 12 months

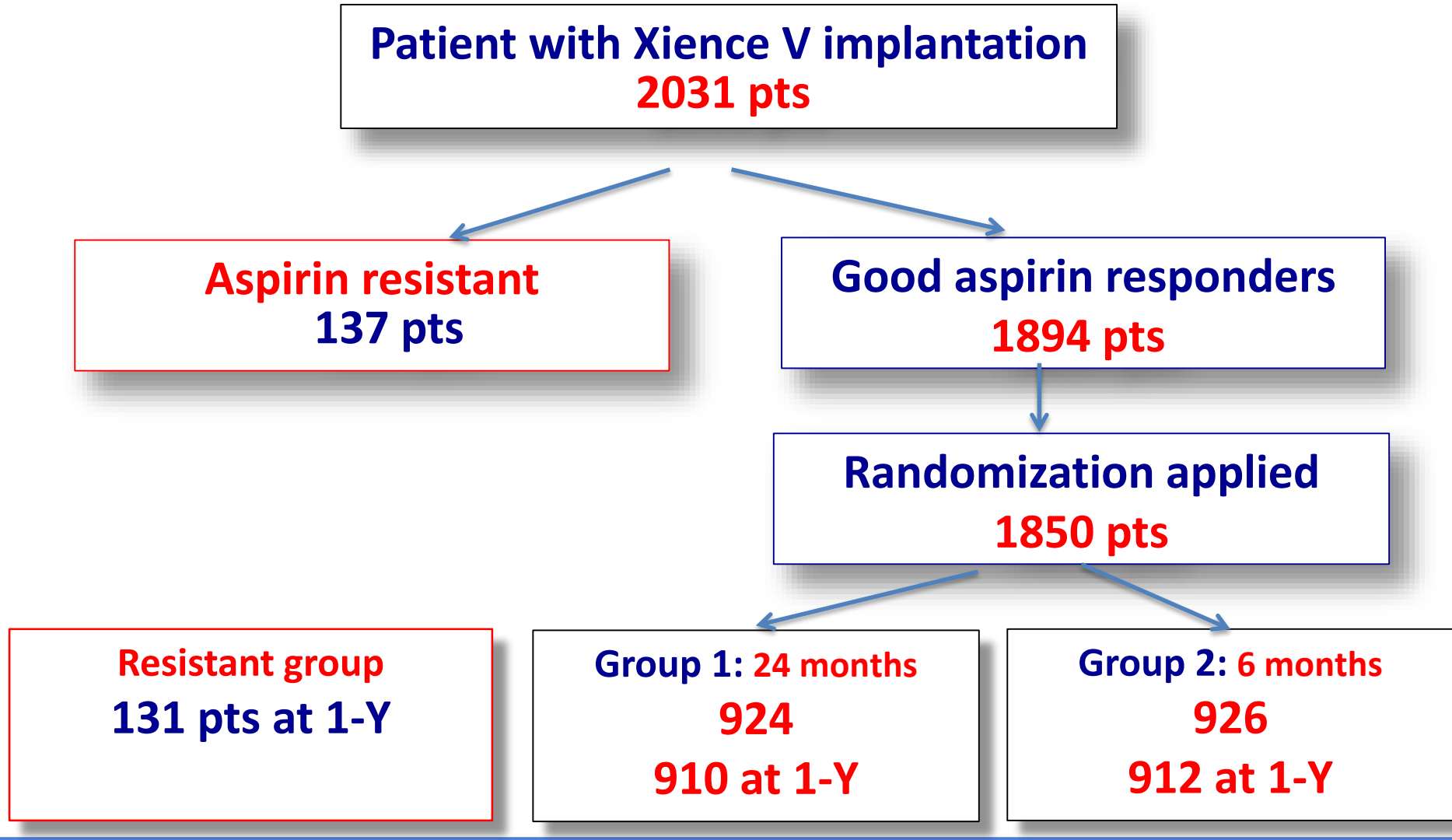
Secondary endpoints :

Same composite endpoint at 24 and 36 months

Individual endpoints used in the composite major

Incidence of minor and minimal bleeding complications (TIMI criteria)

Results


Patient with Xience V implantation
2031 pts
Aspirin resistant
137 pts
Good aspirin responders
1894 pts
Randomization applied
1850 pts
Resistant group
131 pts at 1-Y
Group 1: 24 months
924
910 at 1-Y
Group 2: 6 months
926
912 at 1-Y

Results

Baseline Characteristics

	Resistant Group n=131	24-month DAPT n=910	6-Month DAPT n=912	P
Age, yrs	62.6 (10.8)	61.5 (11.1)	61.7 (10.9)	0.792
Male gender, n (%)	106 (80.9%)	721 (79.2%)	737 (80.8%)	0.399
Body Mass Index (kg/m^2)	27.5 (4.2)	27.1 (4.7)	27.0 (4.6)	0.549
Type-2 diabetes, n (%)	42 (32.1%)	344 (37.8%)	331 (36.3%)	0.505
Hypertension, n (%)	76 (58.0%)	589 (64.7%)	595 (65.2%)	0.817
Hyperlipidemia, n (%)	84 (64.1%)	611 (67.1%)	612 (67.1%)	0.986
Smoker, n (%)	69 (52.7%)	480 (52.7%)	464 (50.9%)	0.424
Family history, n (%)	50 (38.2%)	325 (35.7%)	322 (35.3%)	0.856
Previous MI, n (%)	36 (27.5%)	134 (14.7%)	142 (15.6%)	0.615
Previous PCI, n (%)	39 (29.8%)	205 (22.5%)	220 (24.1%)	0.421
Previous CABG, n (%)	6 (4.6%)	45 (4.9%)	61 (6.7%)	0.111
Previous stroke, n (%)	6 (4.6%)	26 (2.9%)	25 (2.7%)	0.881
Renal insufficiency	4 (3.1%)	25 (2.7%)	28 (3.1%)	0.682

Results

Baseline Characteristics

	Resistant Group n=131	24-month DAPT n=910	6-Month DAPT n=912	P
Ejection fraction				0.321
< 31%	1 (0.8%)	20 (2.2%)	29 (3.2%)	
31 to 50%	21 (16.0%)	151 (16.6%)	162 (17.8%)	
> 50%	65 (49.6%)	514 (56.5%)	482 (52.9%)	
Unknown	44 (33.6%)	225 (24.7%)	239 (26.2%)	
Clinical presentation, n (%)				0.911
Stable angina	53 (40.5%)	378 (41.5%)	375 (41.1%)	
Silent ischemia	18 (13.7%)	183 (20.1%)	185 (20.3%)	
Unstable angina	23 (17.6%)	149 (16.4%)	143 (15.7%)	
NSTEMI	9 (6.9%)	65 (7.1%)	67 (7.3%)	
STEMI	0	3 (0.3%)	1 (0.1%)	
Antiplatelet therapy associated				
Clopidogrel	129 (98.5%)	895 (98.4%)	902 (98.9%)	
Prasugrel	2 (1.5%)	16 (1.8%)	15 (1.6%)	
Ticagrelor	0	0	1 (0.1%)	

Results

Procedural Characteristics

Characteristic	Resistant Group n=131	24-Month DAPT n=910	6-Month DAPT n=912	p
Procedural success, n (%)	130 (99.2%)	901 (99.0%)	895 (98.1%)	0.112
lesion coronary artery, n (%)				
Left main	4 (3.1%)	8 (0.9%)	14 (1.5%)	0.197
Left anterior descending	96 (73.3%)	658 (72.3%)	669 (73.4%)	0.615
Left circumflex	59 (45.0%)	436 (47.9%)	456 (50.0%)	0.373
Right coronary artery	62 (47.3%)	474 (52.1%)	489 (53.6%)	0.513
Bypass graft	5 (3.8%)	39 (4.3%)	59 (6.5%)	0.038
lesion treated/patient, n (%)				0.239
1 lesion treated	77 (58.8%)	494 (54.3%)	459 (50.3%)	
2 lesions treated	38 (29.0%)	252 (27.7%)	275 (30.2%)	
3 of more lesions treated	16 (12.2%)	164 (18.0%)	178 (19.5%)	
Number of XienceV / patient,n(%)	1.6 (0.8)	1.7 (1.0)	1.7 (1.0)	0.497
Total stent length, mean ± SD	33.2 (22.7)	37.8 (26.1)	38.6 (25.6)	0.533
Stent diameter, mean ± SD	3.0 (0.2)	3.1 (0.3)	3.1 (0.3)	0.113
Rotablator, n (%)	4 (2.9%)	12 (1.3%)	15 (1.6%)	0.553
1 restenotic lesion, n (%)	5 (3.8%)	51 (5.6%)	54 (5.9%)	0.772

Results

In the short-DAPT arm:

221 patients (24.2%) did not respect the 6-month TTT

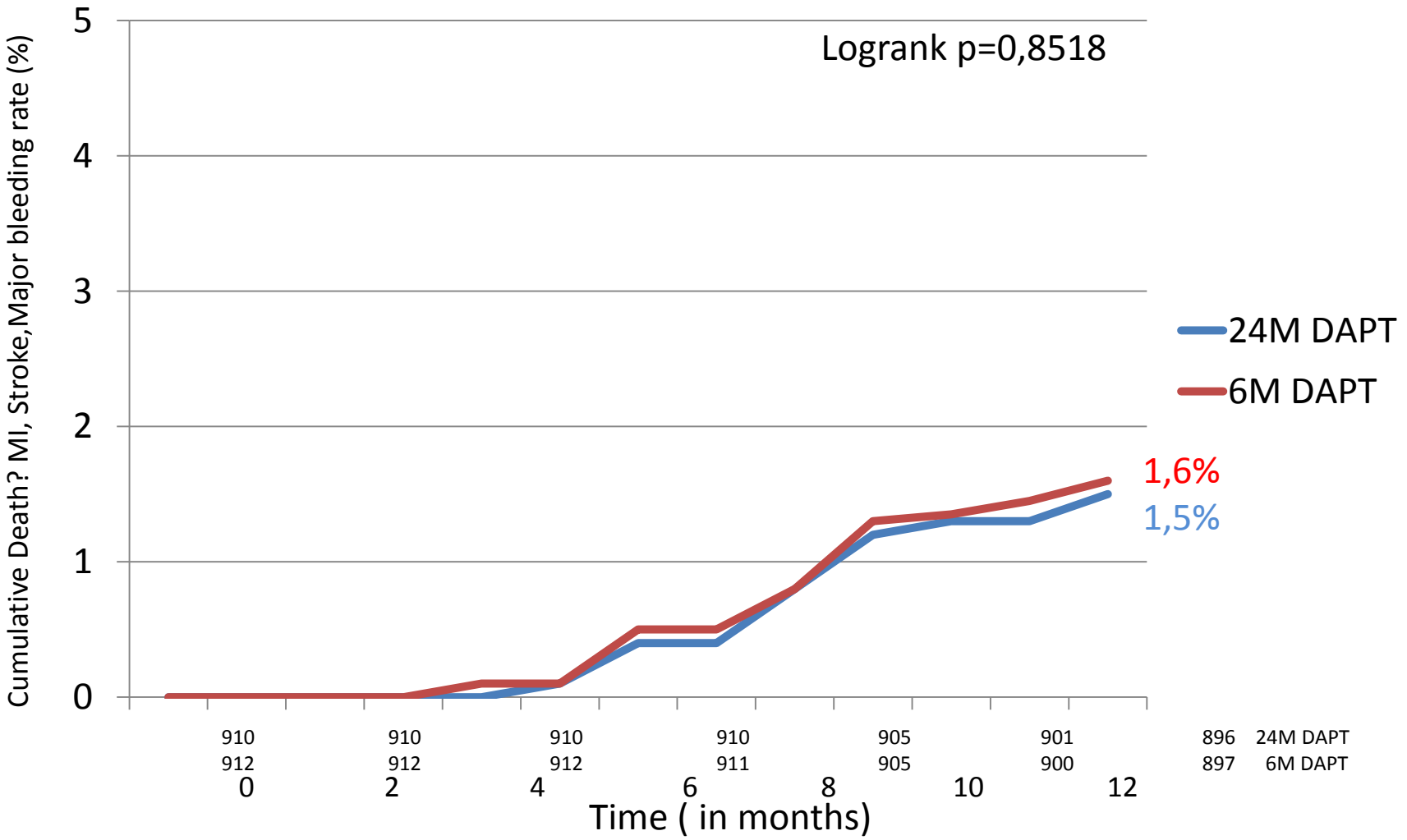
83 patients (8.9%) continuing treatment longer

In the long-DAPT arm:

49 patients (5.4%) discontinued TTT before 24 months.

Results

End Point @ 1 year



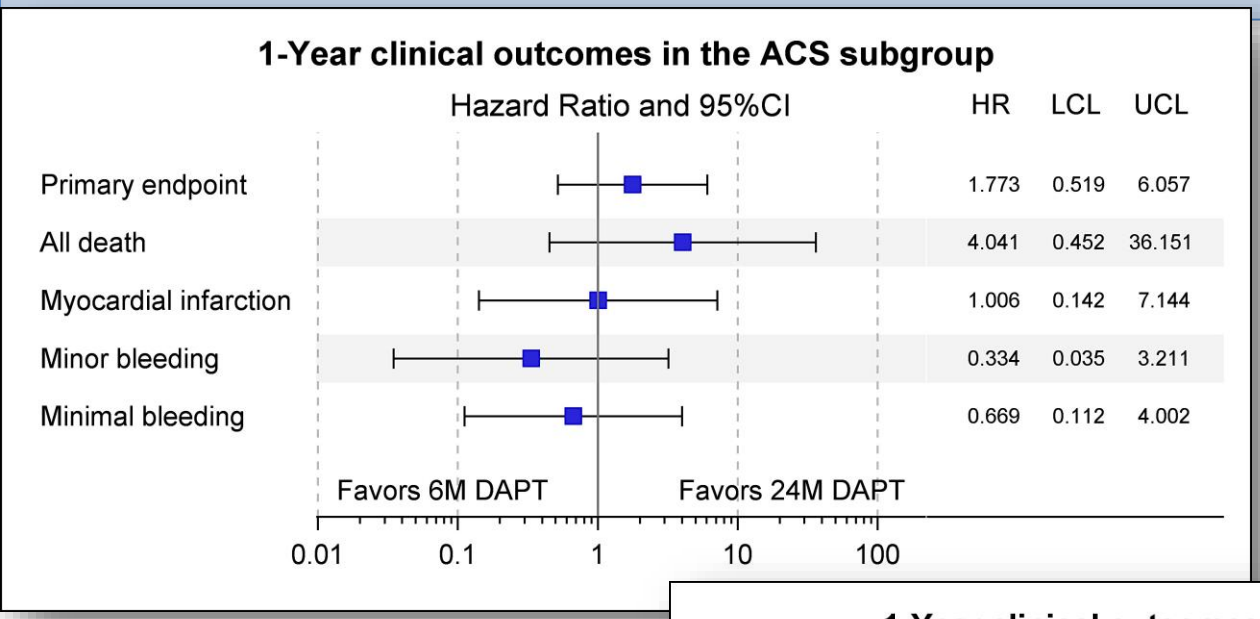
Results

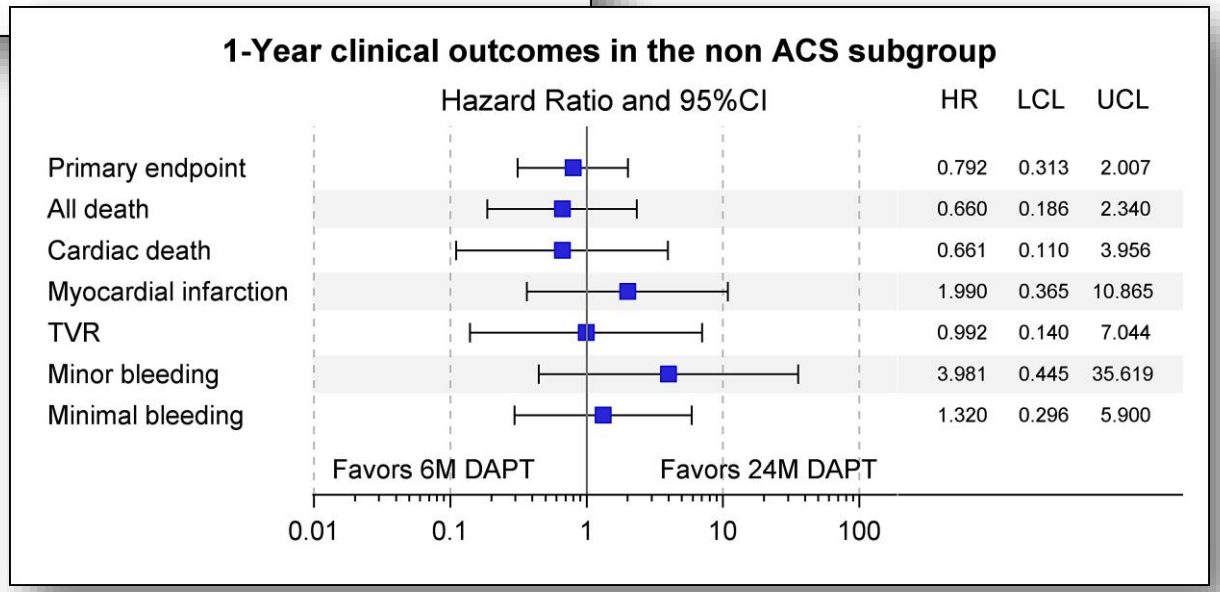
1-year clinical outcomes in the intention-to-treat study

	Resistant Group n=131	24-month DAPT n=910	6-Month DAPT n=912	Hazard Ratio [95% CI]	p
Primary end point, n (%)					
Death from any cause, MI*, stroke, TVR†, major bleeding	2 (1.5%)	14 (1.5%)	15 (1.6%)	1.072 (0.517 - 2.221)	0.85
Secondary end point, n (%)					
Minor bleeding	0	4 (0.4%)	5 (0.5%)	1.247 (0.335 - 4.643)	0.74
Minimal bleeding	1 (0.8%)	6 (0.7%)	6 (0.7%)	0.997 (0.321 - 3.090)	0.99
Death, n (%)					
All deaths	1 (0.8%)	7 (0.8%)	8 (0.9%)	1.143 (0.414 -3.152)	0.80
Cardiac death	0	3 (0.3%)	5 (0.5%)	1.667 (0.398 - 6.974]	0.48
Myocardial infarction, n (%)	0	4 (0.4%)	6 (0.7%)	1.500 (0.423 - 5.317)	0.53
Stroke, n (%)	0	4 (0.4%)	0	N/A	
TVR, n (%)	1 (0.8%)	2 (0.2%)	5 (0.5%)	2.499 (0.485 - 12.882]	0.27
Stent thrombosis	0	0	3 (0.3%)	N/A	
Major bleeding, n (%)	0	3 (0.3%)	0	N/A	

*MI: myocardial infarction; †TVR: urgent target vessel revascularization

Results


1-Year clinical outcomes in the ACS subgroup
Hazard Ratio and 95%CI
HR LCL UCL
Primary endpoint 1.773 0.519 6.057
All death 4.041 0.452 36.151
Myocardial infarction 1.006 0.142 7.144
Minor bleeding 0.334 0.035 3.211
Minimal bleeding 0.669 0.112 4.002
Favors 6M DAPT
Favors 24M DAPT
0.01 0.1 1 10 100


1-Year clinical outcomes in the non ACS subgroup
Hazard Ratio and 95%CI
HR LCL UCL
Primary endpoint 0.792 0.313 2.007
All death 0.660 0.186 2.340
Cardiac death 0.661 0.110 3.956
Myocardial infarction 1.990 0.365 10.865
TVR 0.992 0.140 7.044
Minor bleeding 3.981 0.445 35.619
Minimal bleeding 1.320 0.296 5.900
Favors 6M DAPT
Favors 24M DAPT
0.01 0.1 1 10 100

Results

Non-inferiority was established
for 6-month versus 24-month DAPT

0.11% (95% CI: -1.04 to 1.26; p for non-inferiority = 0.0002)

The trial was prematurely terminated due to problems with recruitment. However:

Rate of events of 1.5% (compared to 3% expected)

Far from the boundary

Conclusion

ITALIC showed that rates of bleeding and thrombotic events were not significantly different between the 6- and 24-month DAPT groups after PCI with new-generation DES

6-month DAPT was non-inferior to 24-month DAPT in good aspirin responders.

Non-inferiority was also observed in the subgroup of unstable patients (one half of patients).

Larger trials are needed to assess the effect of antiplatelet duration in ACS patients.