ITALIC

American Heart Association
Learn and Live

Chicago 2014

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

Disclosure Information

- Consulting / Advisory board:

Boston Scientific, Astra Zeneca, Daiichi Sankyo, Lilly
Bayer, Abbott Vascular, Terumo, Direct Flow, Edwards, Guerbet, GE

- Lectures:

Boston Scientific, Biotronik, Medtronic,
St. Jude Medical, Terumo, Edwards, GE, Astra Zeneca, Daichii Sankyo, Lilly

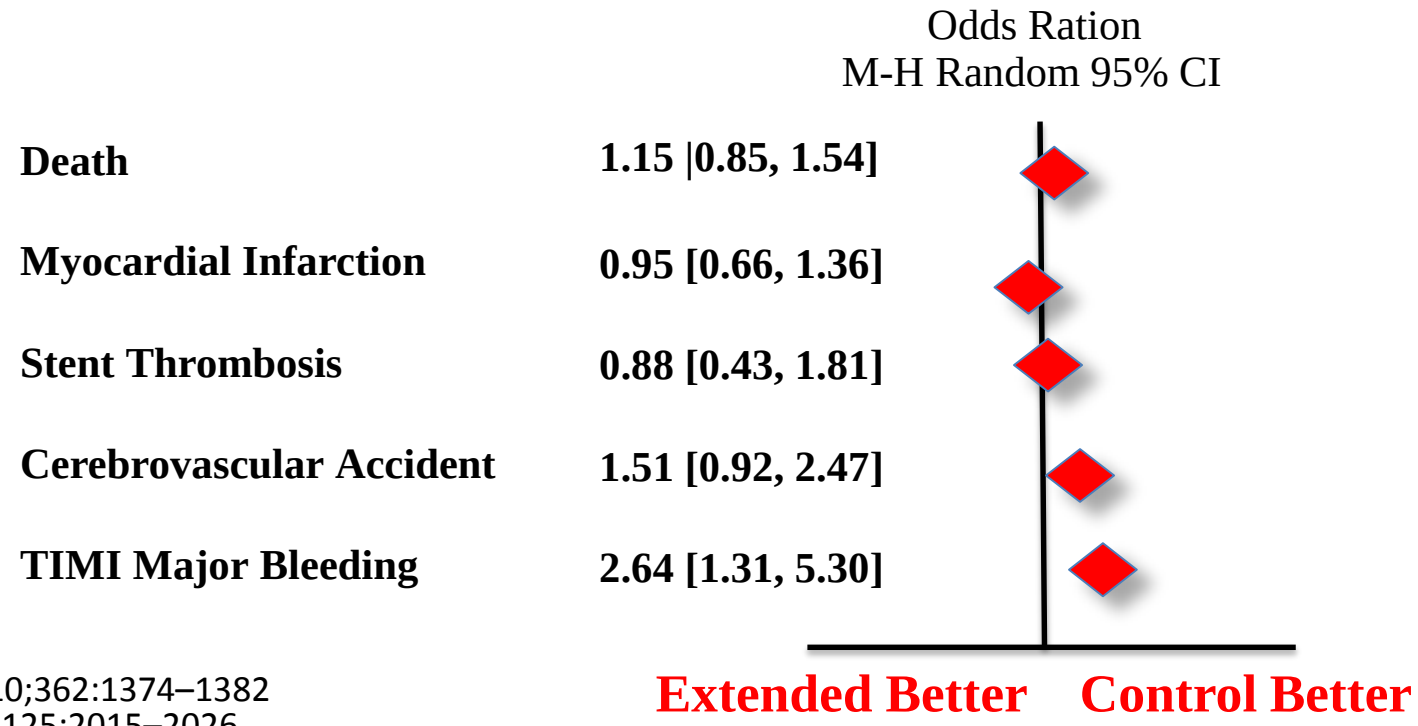
Background

The currently recommended duration of DAPT after DES implantation is 12 months, to reduce the risk of late stent thrombosis, particularly in acute coronary syndrome.

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

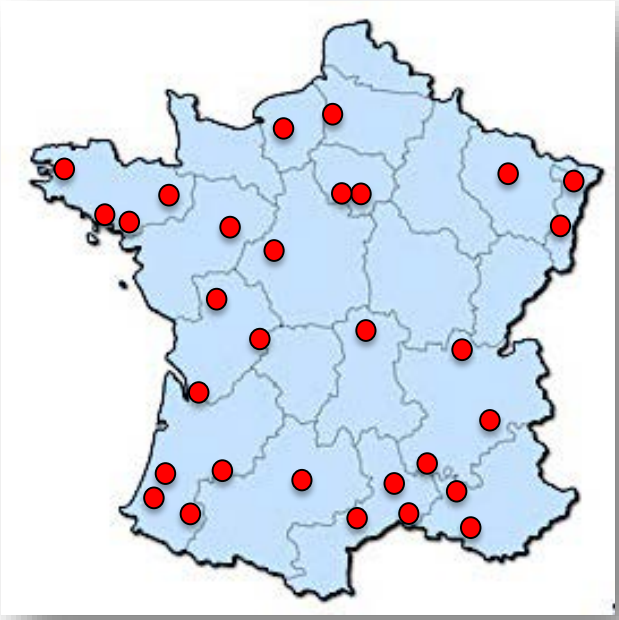
To be sure that patients would be protected by their antiplatelet therapy in either situation, **patients resistant to aspirin were excluded**

Methods

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

48 French sites (ITALIC)

11- 2008 to 12-2010



7 European - Middle East sites (ITALIC +)

01- 2012 to 11-2013

Methods

Recruiting centers

Dr Arif AL NORYANI	Al Qassimi Hospital Shariah UAE
Dr Hussam A NOOR	Bahrain Defence Force West Riffa
Dr Talib MAJWAL	Dubai Hospital UAE
Dr Paul Barragan	Poly Les Fleurs, Ollioules France
Dr Thomas Hovasse	ICPS, Massy France
Dr Jacques Boschat	CHU Brest,France
Dr Michel Schneeberger	Hôpital Albert Schweitzer, Colmar France
Dr Luc Maillard	CI Axium, Aix en Provence France
Dr Laurent Ledain	CH Saint Louis, La Rochelle France
Dr Erwan Bressollette	Nantes NCN, Nantes France
Pr Jaroslaw WOJCIK Co PI Marek ANKIEWIECZ Dr Nicolas Delarche	Klinika Kardiologii SPSK4 Lublin Poland CH Mitterrand, Pau France
Dr Didier Blanchard	Clinique St Gatien, Tours France
Dr Bernard Jouve	CH du Pays d'Aix, Aix en Provence France
Dr Olivier Ormezzano	CHU Grenoble, Grenoble France
Dr Franck Paganelli	CHU Hôpital Nord, Marseille France
Dr Gilles Levy	Clinique du Millénaire, Montpellier France
Dr Joël Sainsous	Clinique Rhône Durance, Avignon France
Pr Didier Carrié	CHU Rangueil, Toulouse France
Pr Alain Furber	CHU Angers, Angers France
Dr Jacques Berland	Clinique St Hilaire, Rouen France
Dr Olivier Darremont	Clinique Saint Augustin, Bordeaux France
Dr Hervé Le Breton	CHU Rennes, Rennes France
Dr Anne Luycx-Bore	CH Compiègne, Compiègne France
Dr Antoine Gommeaux	Polyclinique de Bois Bernard, Bois Bernard France
Dr Claude Cassat	CHU Limoges, Limoges France

Study organisation

Conduct by the French Society of Cardiology

Management of the trial

Clinical Event Committee: L. Belle, C Tron, C Caussin, G Helft

Funding: Abbott Vascular Devices, Santa Clara, California

Methods

Inclusion criteria

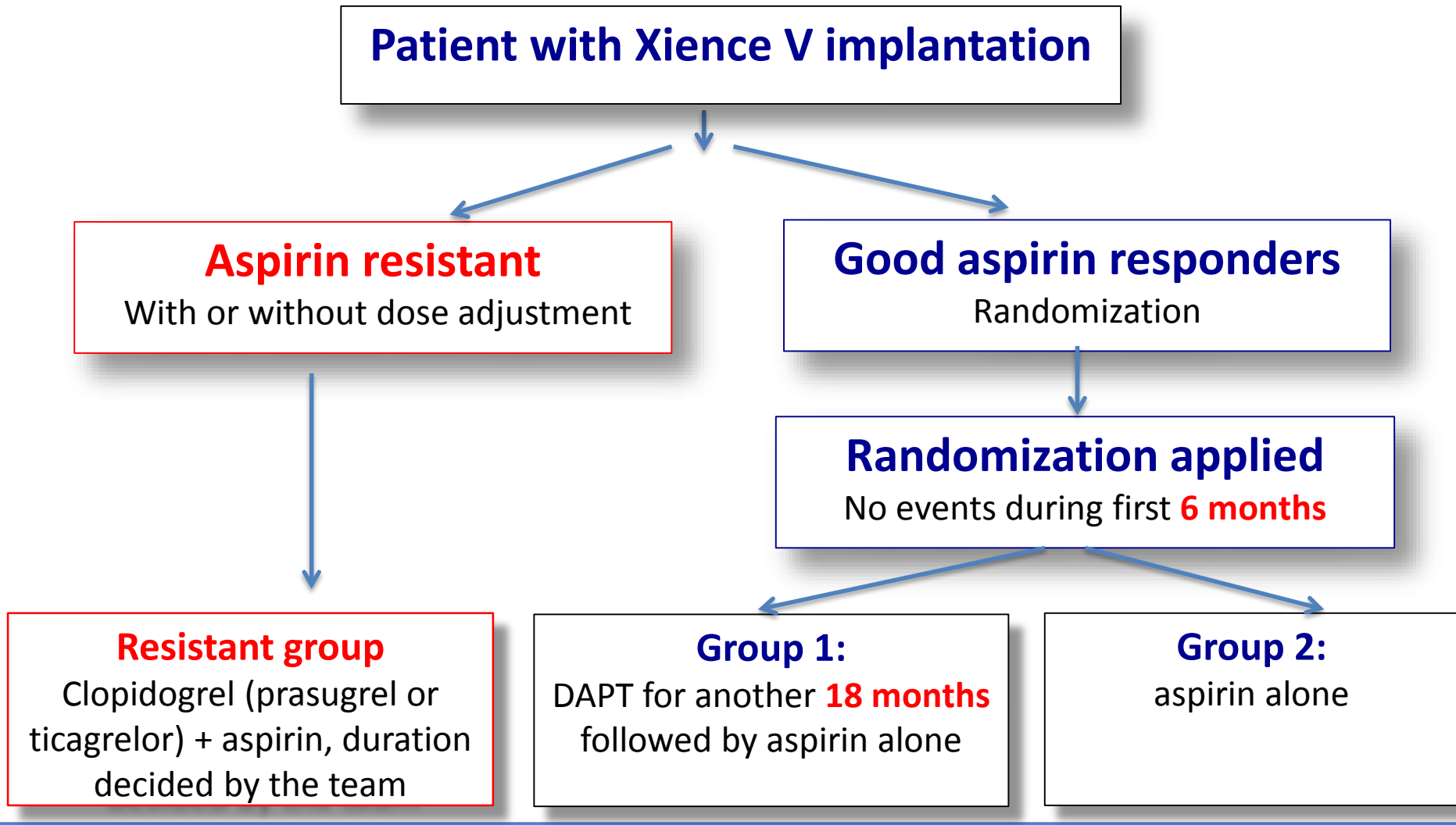
- Patients aged 18 years or over, eligible for PCI
- At least one **Xience V DES** (Abbott Vascular Devices) implanted
- Patients were not pre-treated with abciximab during hospital stay.
- **Aspirin resistance was tested**.
- Patients were pre-treated with aspirin + clopidogrel (prasugrel or ticagrelor)

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:
DAPT for another 18 months followed by aspirin alone
Group 2:
aspirin alone

Methods

Aspirin Resistance Tests: 3

Patient aspirin responder :

PFA-100: epinephrine-collagen cartridge closure time >165 s

Multiplate electrical impedance aggregometry: ≥ 30% reduction in platelet aggregation

VerifyNow Aspirin: ≥ 550 aspirin reaction units.

The type of test depends of the centre

Methods

Endpoints

Academic Research Consortium criteria

Primary endpoint : **Composite of** 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)

Statistical analysis

The expected rate of events was 3% and the non-inferiority margin was set at 2%, leading to inclusion of 900 patients per arm, for a type-I error of alpha=5%.

Sample size was calculated consideting an alpha=5% but to be compliant with the most recent guidelines the non-inferiority confidence interval has been performed finally at 97.5%

Results

Patient with Xience V implantation
2031 pts

Aspirin resistant group
137 pts

Good aspirin responders
1894 pts

44 patients: randomization not apply
- Death = 13
- MI = 10
- TVR = 2
- Other = 19 (7 with no consent validated)

6 months

Randomization applied
1850 pts

Resistant group
FU: 131 pts at 1-Y

Group 1: 24 months
924
FU: 910 at 1-Y

Group 2: 6 months
926
FU: 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
Target 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
Total no. of 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 stent per 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
At least 1 restenotic lesion, n (%)	5 (3.8%)	51 (5.6%)	54 (5.9%)	0.772

Results

DAPT duration

In the short-DAPT arm:

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

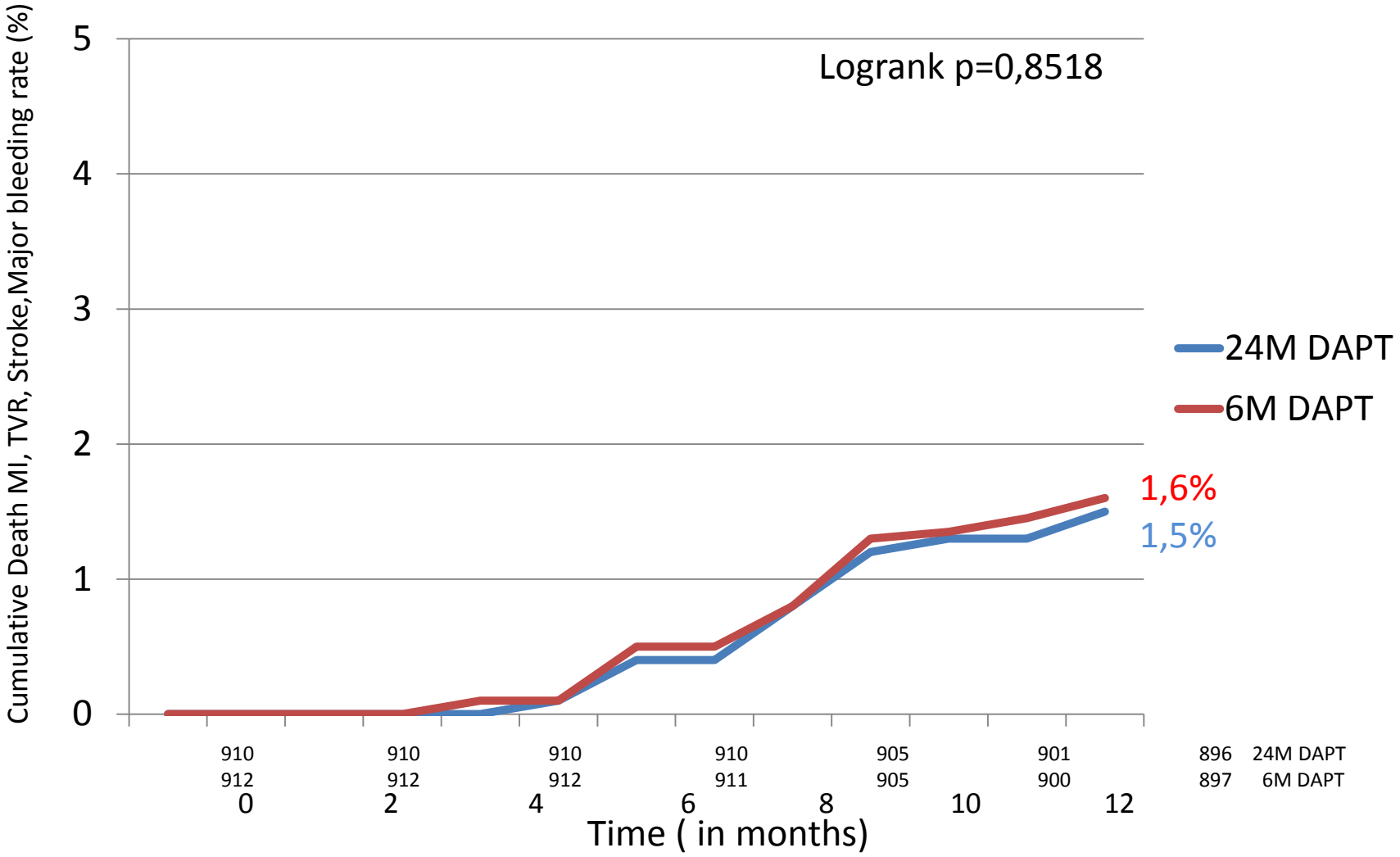
83 patients (8.9%) continuing treatment longer

In the long-DAPT arm:

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

Results

End Point @ 1 year



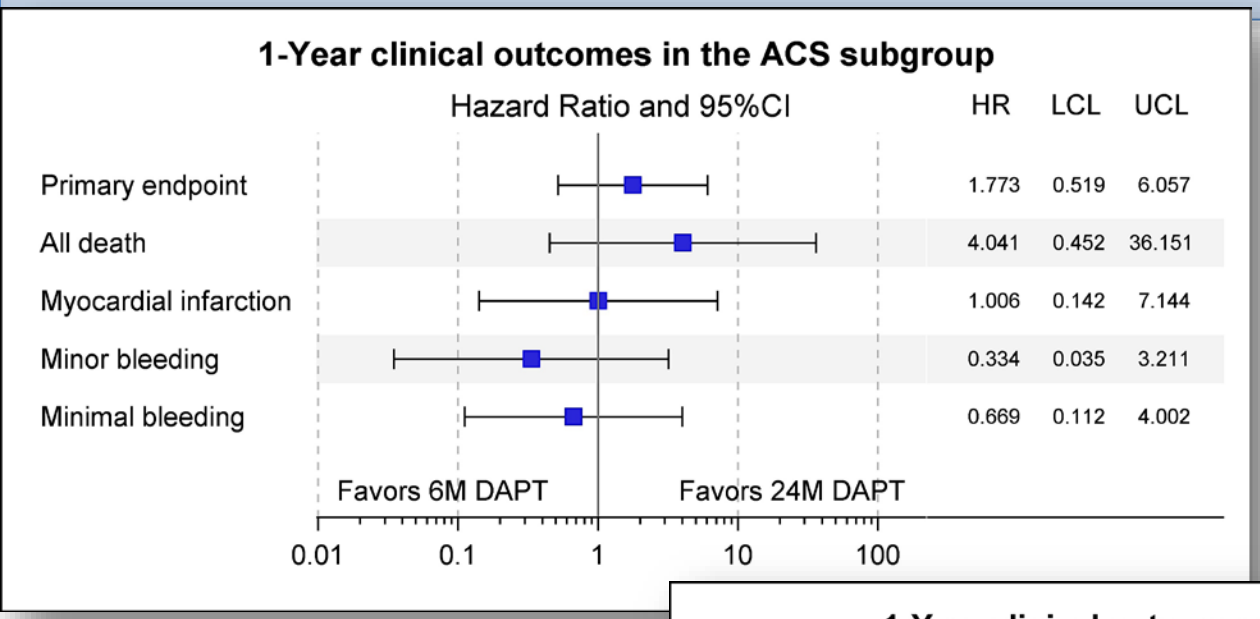
Results

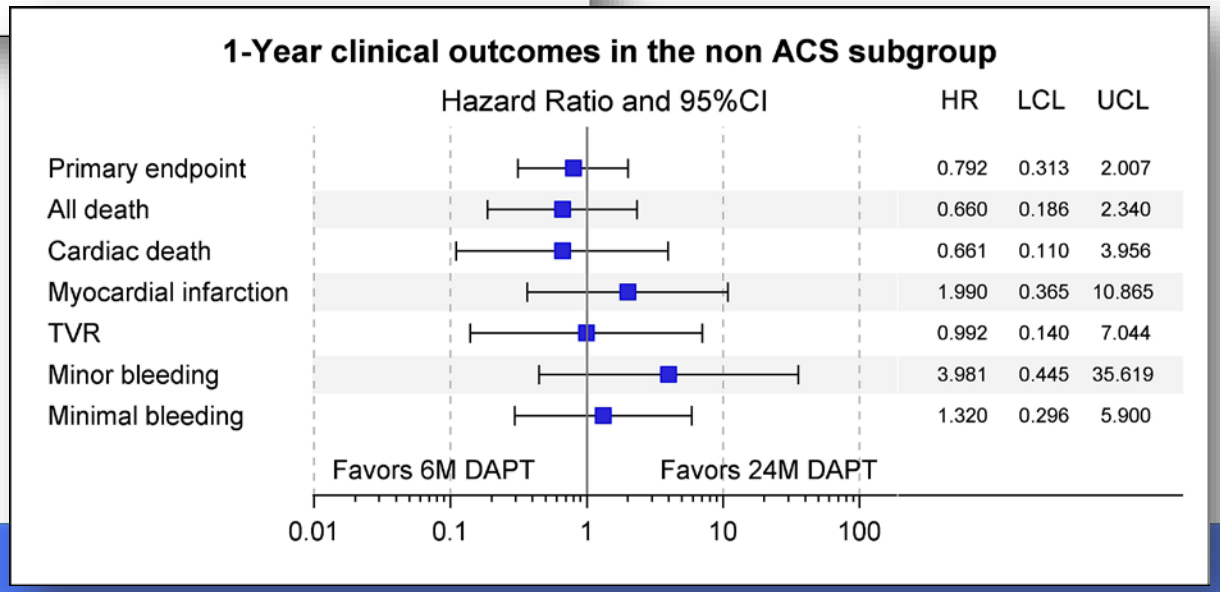
1-year clinical outcomes in the intention-to-treat study population

	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

The significance of the test was confirmed by the lower limit of the 1-tailed 97.5% CI(-1.04%) being greater than the non-inferiority margin (-2%)

Study limitations

Relatively small sample size

However:

A single type of second-generation DES, to minimize variation in efficacy and safety

Low event rate in our study population

However:

A better outcome than BMS or first-generation DES

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 seems to be observed in the subgroup of unstable patients.
Larger trials are needed to assess the effect of antiplatelet duration in ACS patients.

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Accepted Manuscript

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

Martine Gilard , MD, PhD, Paul Barragan , MD, Arif AL. Noryani , MD, Hussam A. Noor , MD, Talib Majwal , MD, Thomas Hovasse , MD, Philippe Castellant , MD, Michel Schneeberger , MD, Luc Maillard , MD, PhD, Erwan Bressolette E , MD, Jaroslaw Wojcik , MD, Nicolas Delarche , MD, Didier Blanchard , MD, Bernard Jouve , MD, Olivier Ormezzano , MD, Franck Paganelli , MD, Gilles Levy , MD, Joël Sainsous , MD, Didier Carrie , MD, Alain Furber , MD, PhD, Jacques Berland , MD, Oliver Darremont , MD, Hervé Le Breton , MD, Anne Lyuycx-Bore , MD, Antoine Gommeaux , MD, Claude Cassat , MD, Alain Kermarrec , MD, Pierre Cazaux , MD, Philippe Druelles , MD, Raphael Dauphin , MD, Jean Armengaud , MD, Patrick Dupouy , MD, Didier Champagnac , MD, Patrick Ohlmann , MD, Knut Endresen K , MD, Hakim Benamer , MD, Robert Gabor Kiss , MD, Imre Ungi , MD, Jacques Boschat J , MD, Marie-Claude Morice , MD