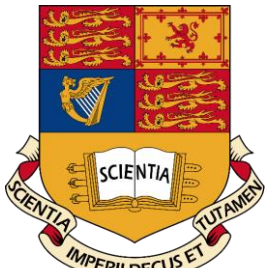
02:16 p.m. - 02:24 p.m.
Saturday, April 28, 2019
Presentation Theater 1, level 1

Ticagrelor monotherapy in GLOBAL LEADERS and TWILIGHT: Interpretation and Clinical Implication

Patrick W. Serruys, MD. PhD.
Imperial College London, London, UK
on behalf of the Investigators



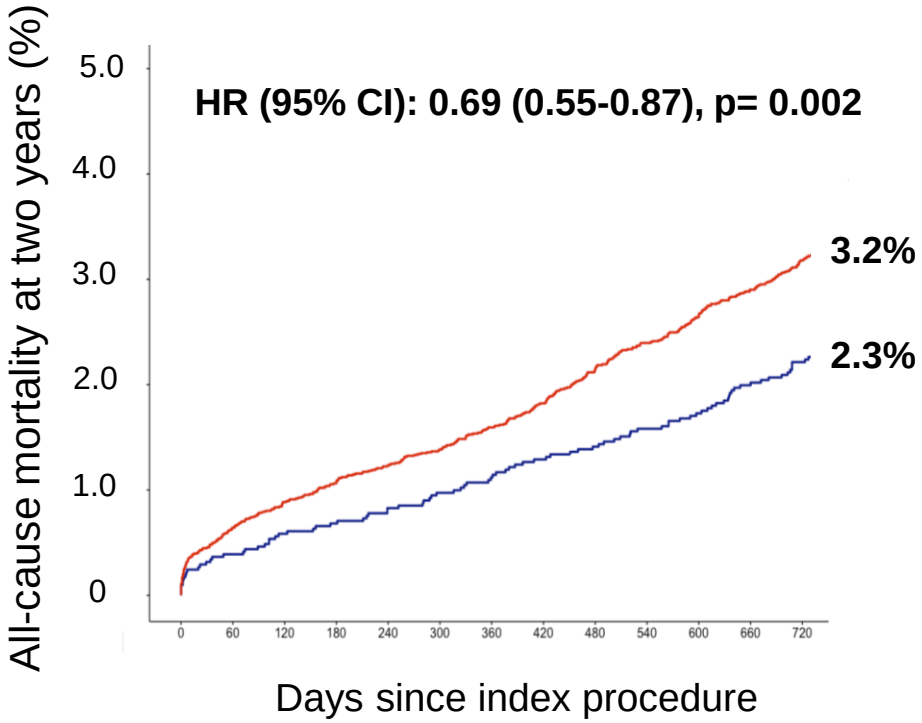
GENERAL WARNING

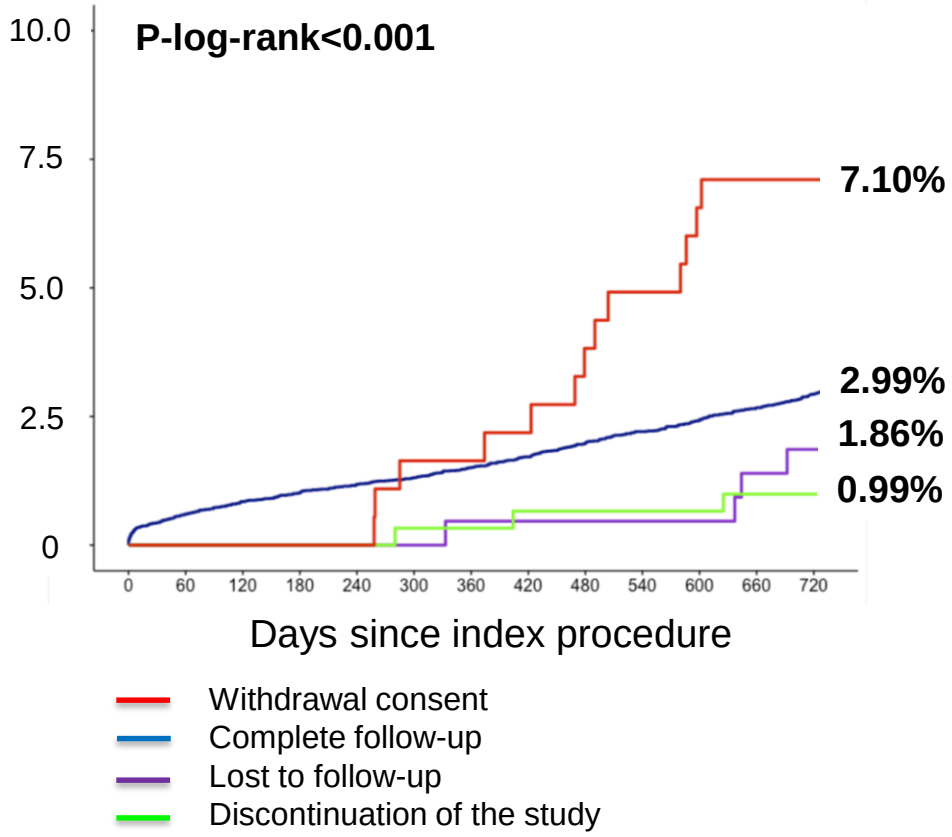
The preliminary clinical implications that I will suggest are derived from post hoc, exploratory, hypothesis-generating analyses, that can be fallacious or the play of chance due to multiple testing, in a trial that statistically failed to demonstate superiority

LESSON 1: for trialists, investigators and clinicians

✓ Be aware that in a "mega mammoth" trial the "high-recruiters" will have a higher rate of mortality.

✓ Be aware that in patients who withdraw from the study you have a higher rate of mortality

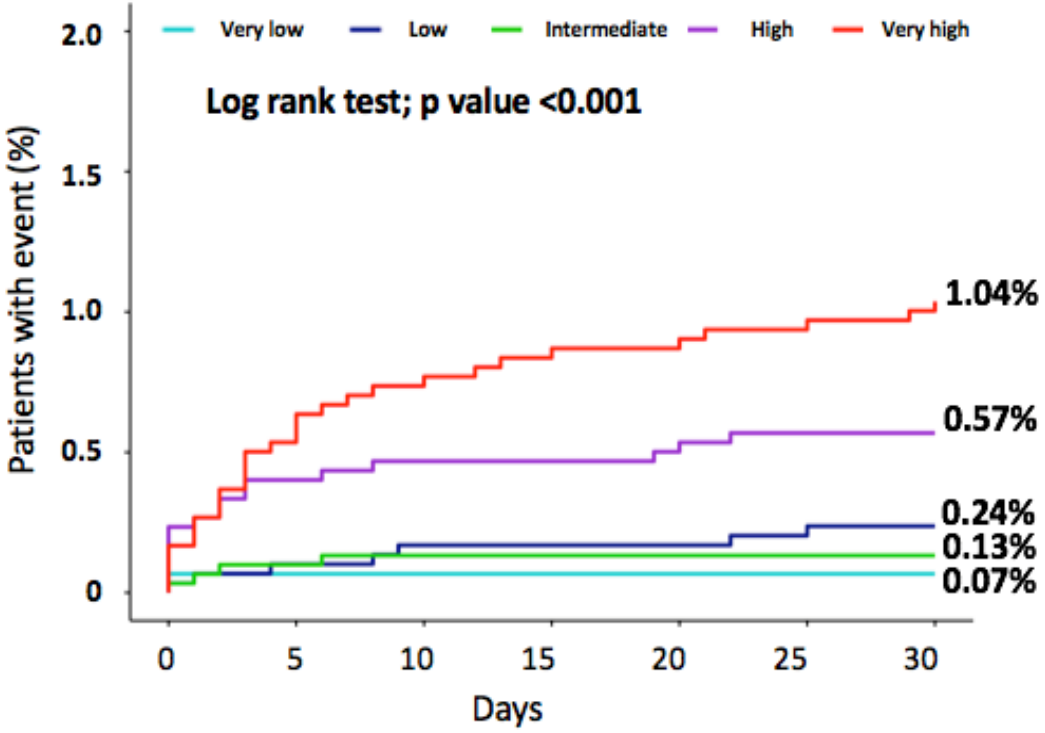




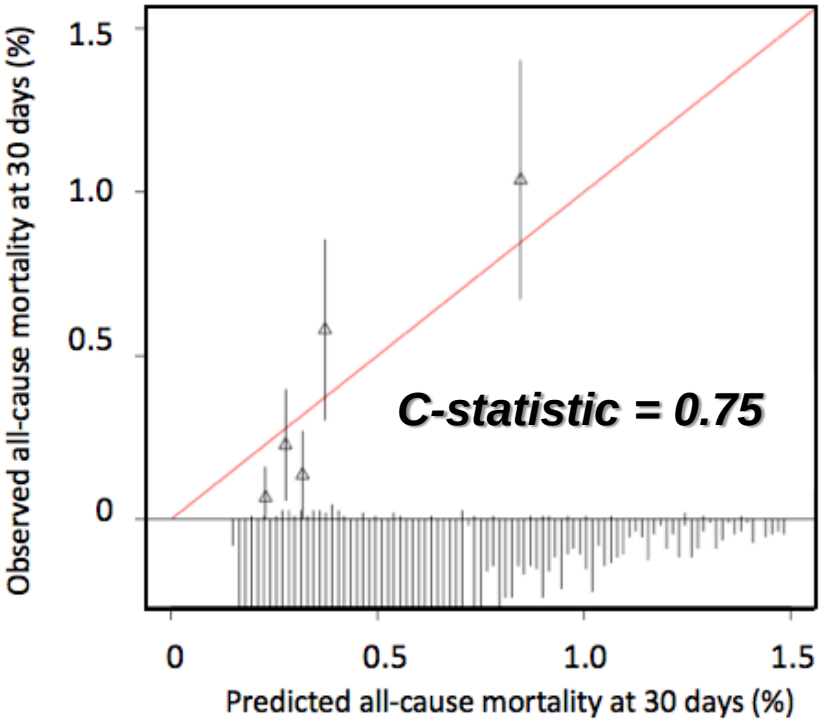
LESSON 2: for trialists, investigators and clinicians

✓ Simple parsimonious score (ACEF: age, creatinine clearance, ejection fraction) identified patients at high cardiovascular risk.
✓ This is the proper way to "enrich" a population.

30-day all-cause mortality and ACEF score quintiles



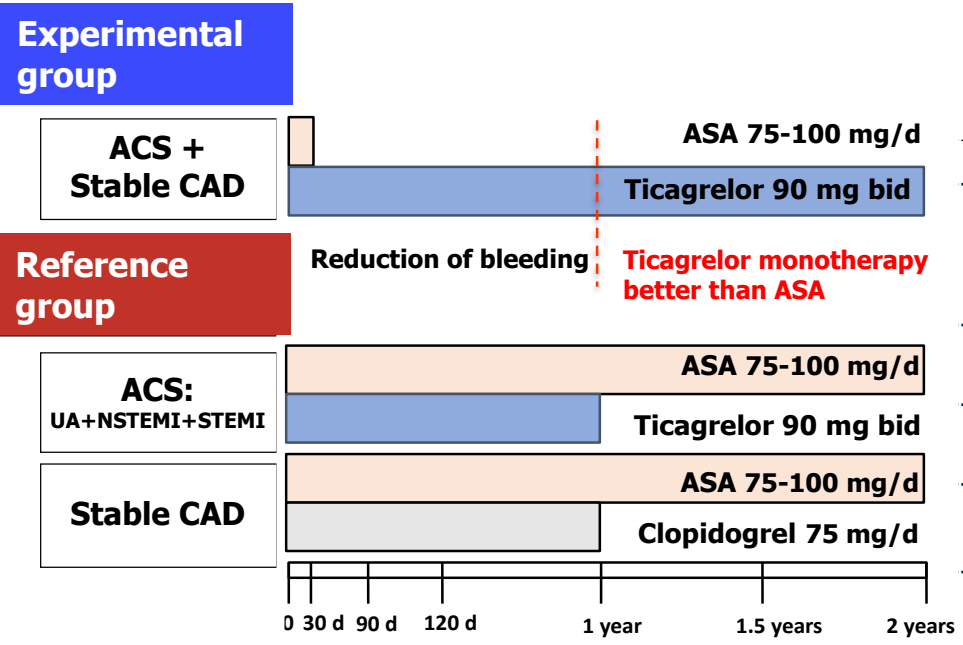
Recalibrated ACEF score in GL



Chichareon P, Modolo R, van Klaveren, PW Serruys et al. Int J Cardiol. 2019

LESSON 3: potential clinical implication of the trial

✓ If we had stopped the trial at 1 year, monotherapy with ticagrelor (beyond one-month after PCI), we would have been the "winner".
✓ To de-escalate ticagrelor to ASA at 1 year is probably the right approach.

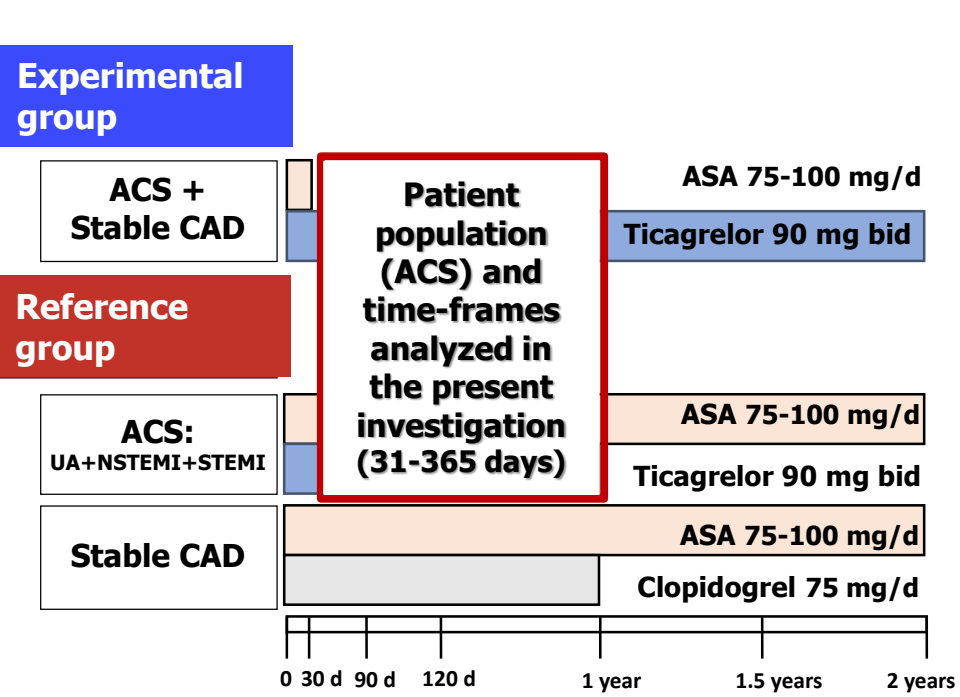


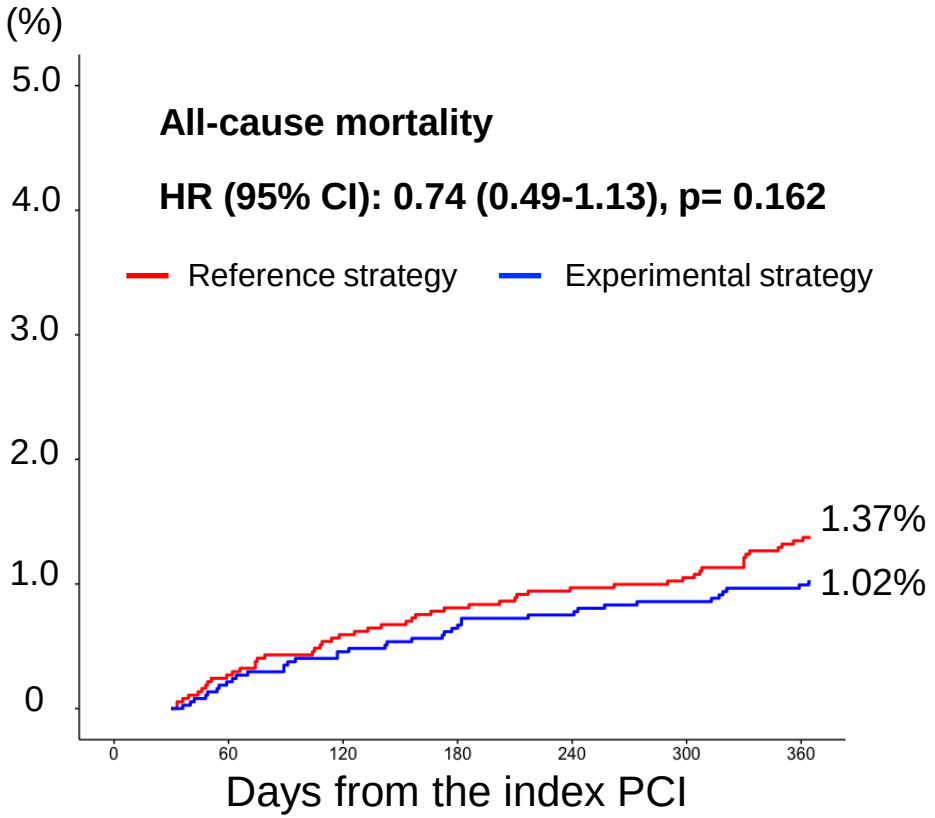
Clinical outcomes at 12 months	Experimental group	Reference group	Risk Ratio (95% CI)	p-value
Number of pts.	N=7980	N=7988		
All-cause mortality or new Q-wave MI*	**1.95** %, (156)	**2.47** %, (197)	**0.79** (0.64-0.98)	**0.028**
All-cause mortality	**1.35** % (108)	**1.64** % (131)	**0.82** (0.64-1.06)	0.138
New Q-wave MI	**0.60** % (48)	**0.86** % (69)	**0.70** (0.48-1.00)	0.052
BARC 3 or 5 Bleeding**	**1.47** %	**1.70** %	**0.86** (0.67-1.11)	0.243
BARC 5 Bleeding	**0.18** %	**0.20** %	**0.88** (0.43-1.80)	0.722
BARC 3 Bleeding	**1.34** %	**1.60** %	**0.84** (0.65-1.08)	0.179

Intention to treat analyses

LESSON 4: potential clinical implication of the trial

√ When ticagrelor monotherapy and ticagrelor + ASA are compared (between 31 and 365 days), the additional, beneficial and synergistic effect of ASA may be questioned.





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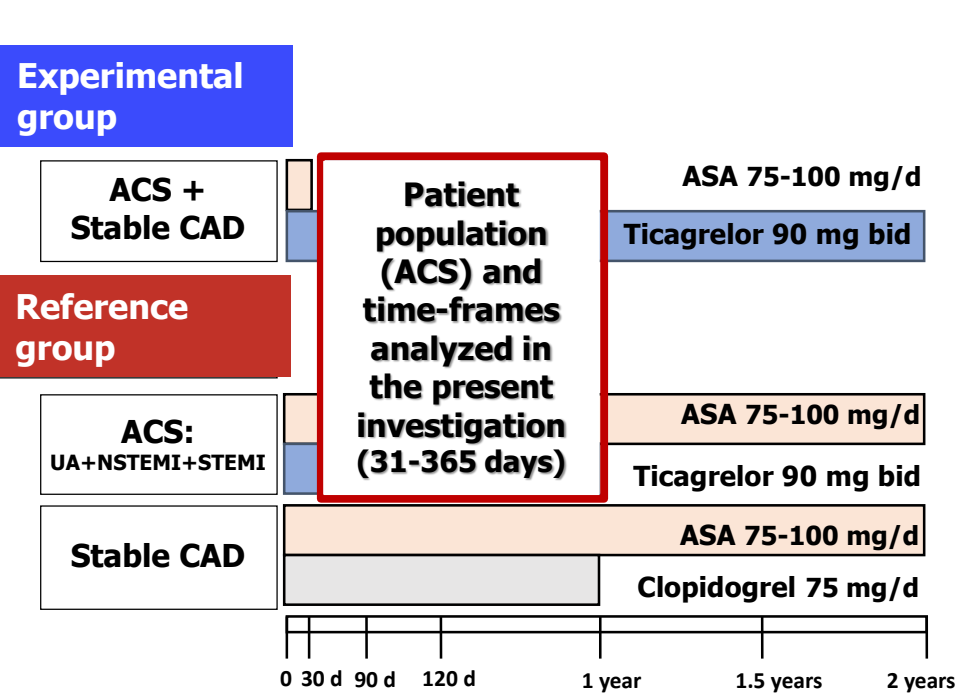
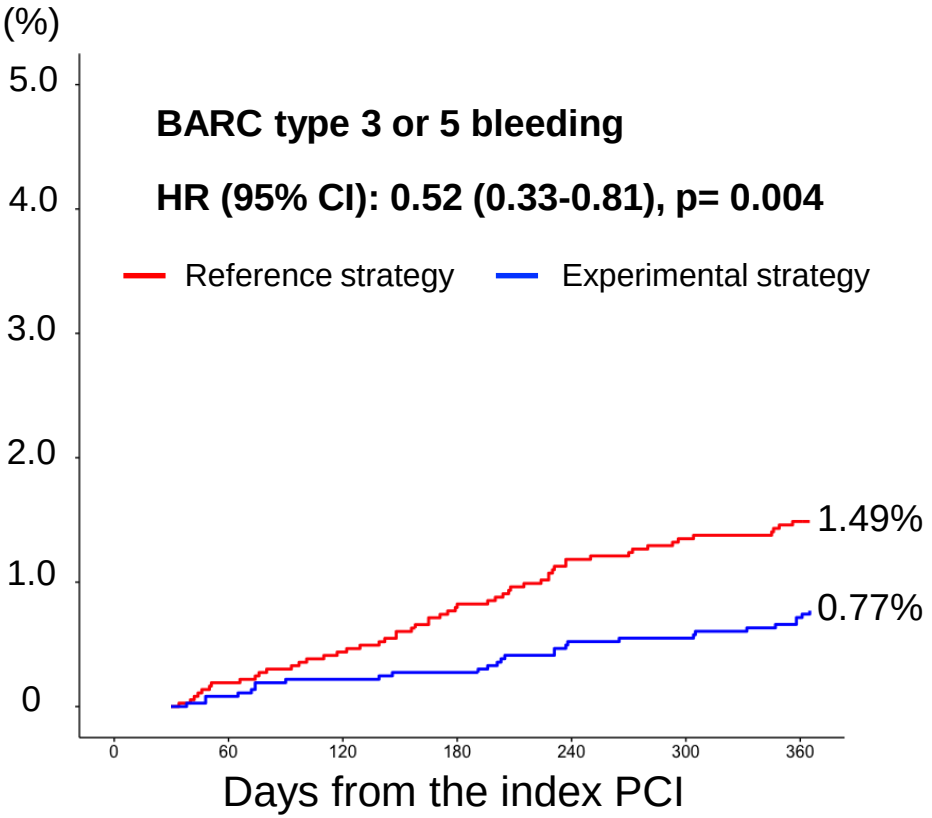
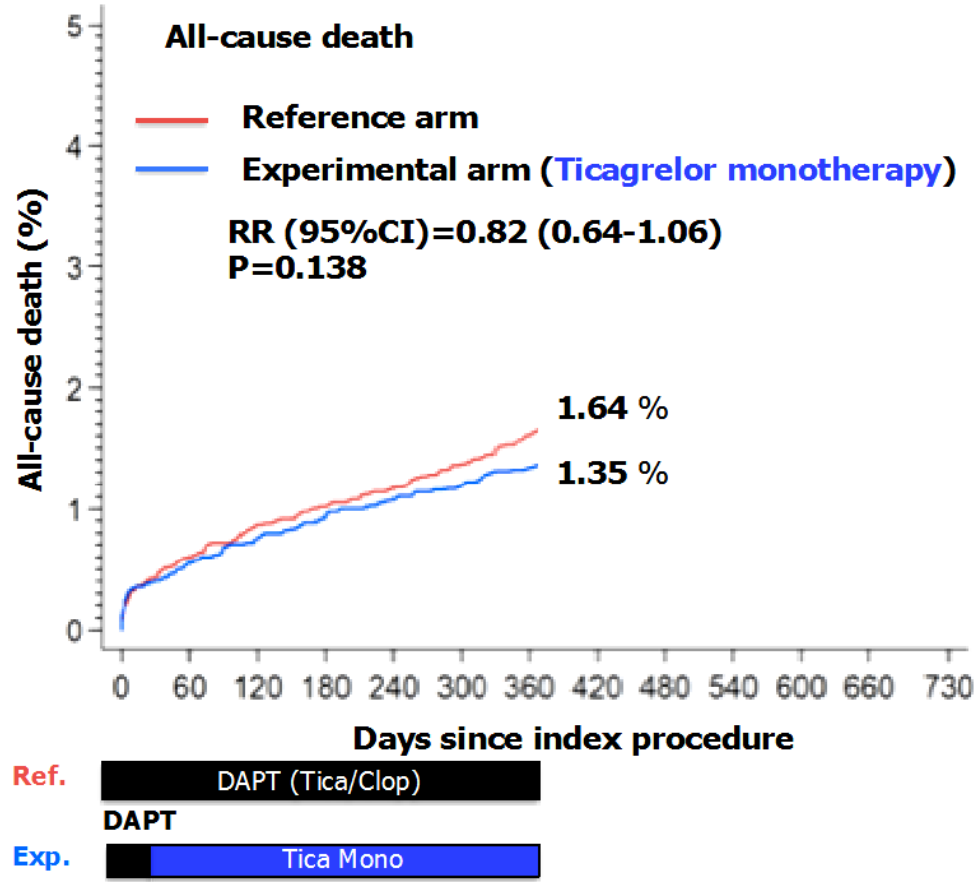


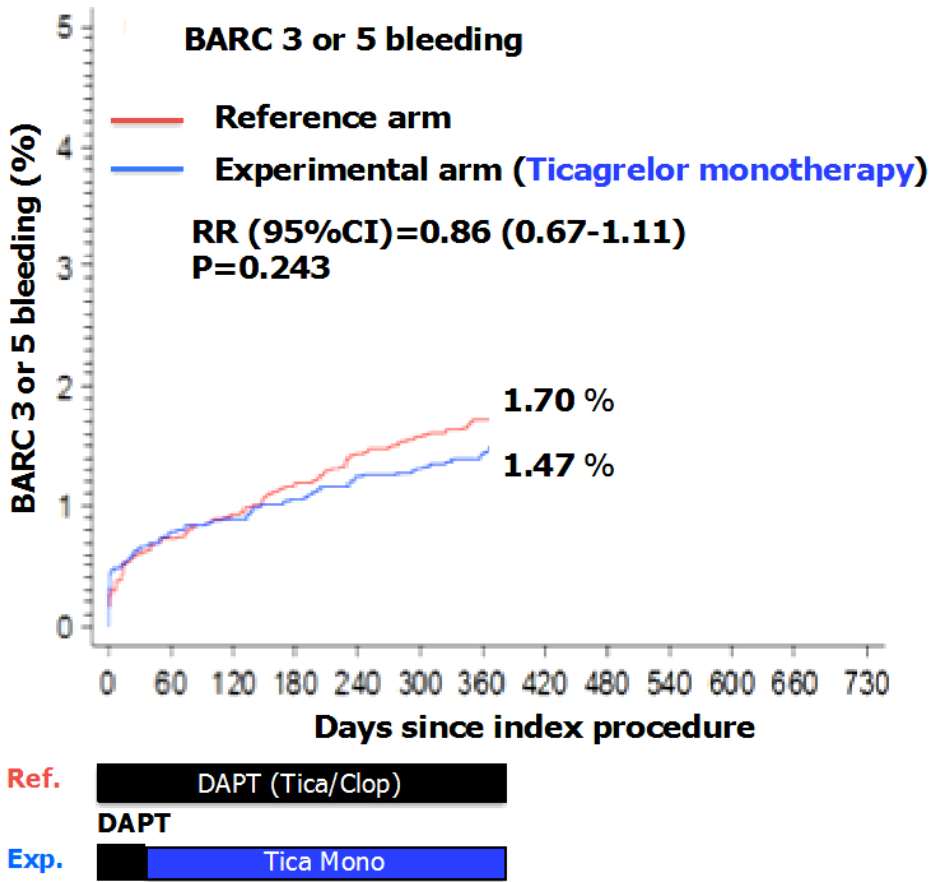


LESSON 5: potential clinical implication of the trial

✓ **Stopping ASA at 1 month is safe.**

✓ **The 1 year interval analysis and the 1 year landmark analysis show that discontinuation of ASA at 1 month is safe and that ticagrelor could be de-escalated to ASA at 1 year (no beneficial effect during the second year).**





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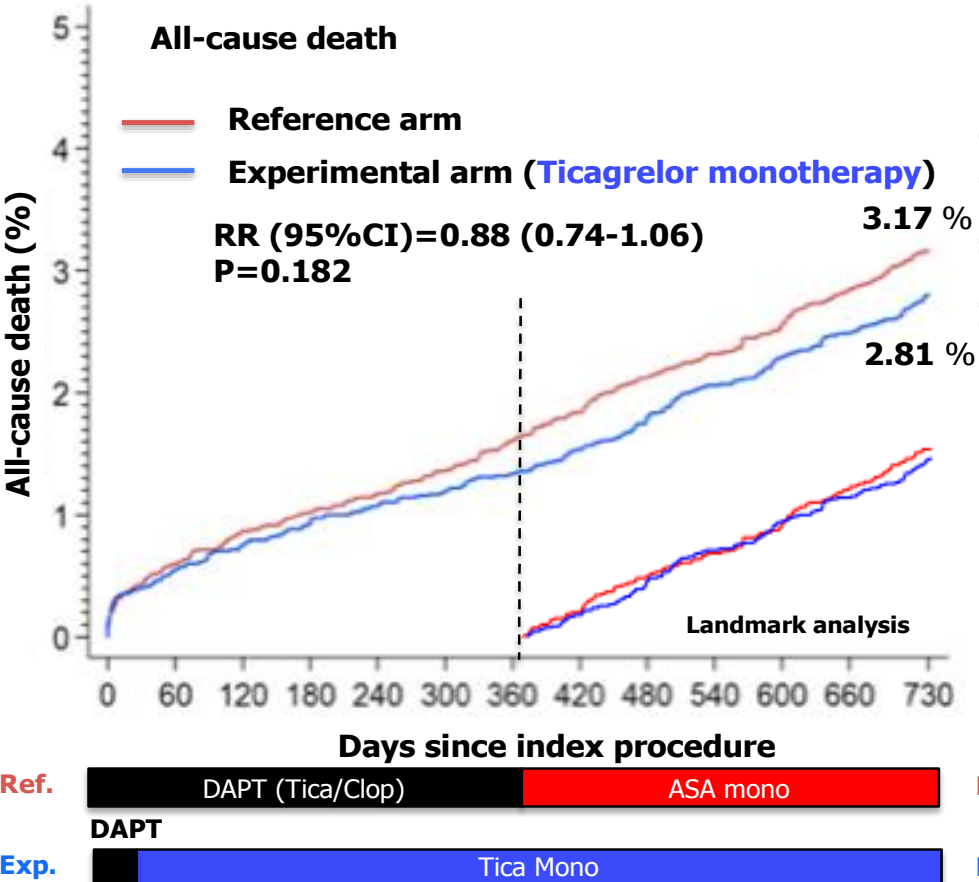
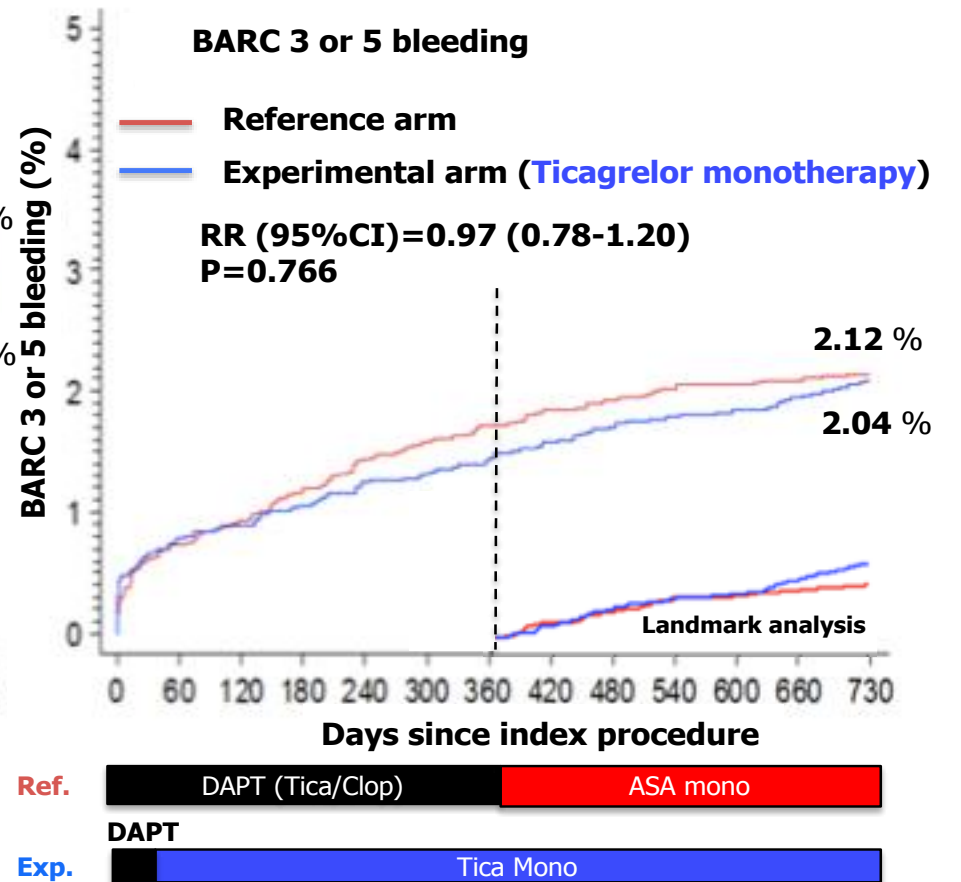
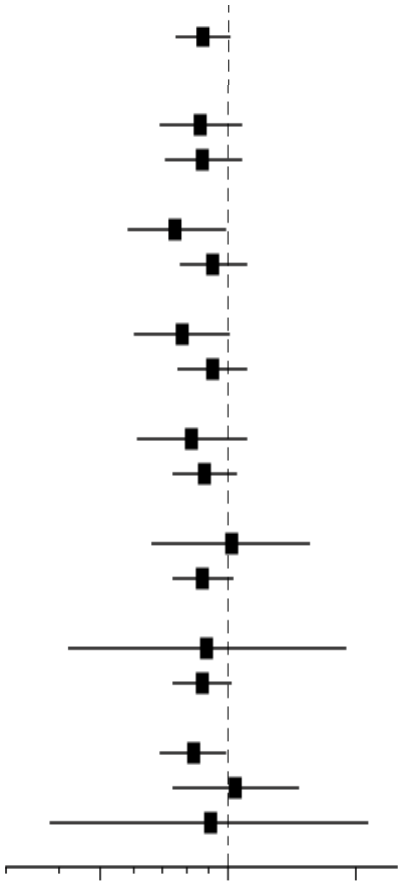




LESSON 6: potential clinical implication of the trial

At two-year the treatment effect is statistically non-detectable among various pre-specified clinical subgroups.

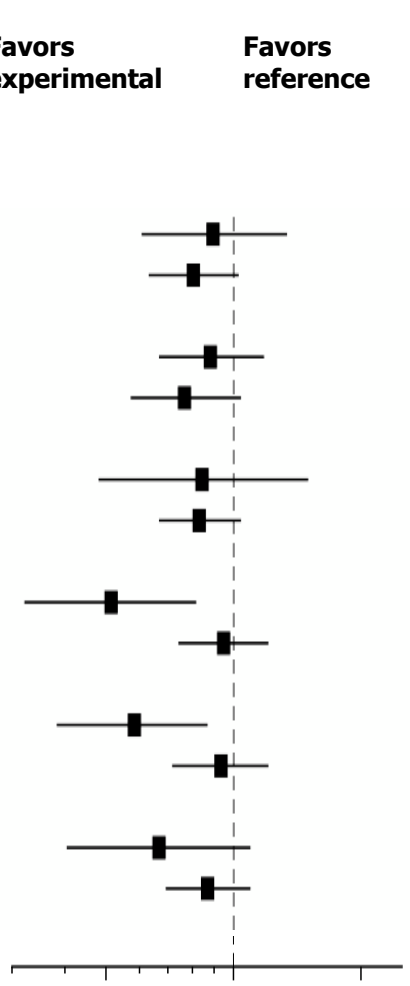
Pre-specified subgroups	Experimental Treatment Strategy	Reference Treatment Strategy	Risk Ratio [Exp/Ref] (95% CI)	p-value for interaction
Overall	**304/7980**	**349/7988**	**0.87 (0.75-1.01)**	
Indication				0.926
ACS	147/3750	169/3737	0.86 (0.69-1.08)	
Stable CAD	157/4230	180/4251	0.87 (0.71-1.08)	
Age				0.231
>75 years	**93/1292**	**120/1273**	**0.75 (0.58-0.99)**	
≤75 years	211/6688	229/6715	0.92 (0.77-1.11)	
Diabetes mellitus				0.326
diabetics	102/2049	126/1989	0.78 (0.60-1.01)	
non-diabetics	202/5925	222/5994	0.92 (0.76-1.11)	
Renal failure				0.680
Yes	79/1099	93/1072	0.82 (0.61-1.11)	
No	225/6881	256/6916	0.88 (0.74-1.05)	
PVD				0.521
Yes	40/476	44/529	1.02 (0.66-1.56)	
No	260/7428	295/7389	0.87 (0.74-1.03)	
Left main treated				0.950
Yes	13/197	14/190	0.89 (0.42-1.90)	
No	291/7783	335/7798	0.87 (0.74-1.02)	
Geographic area				0.488
Western Europe	**226/6156**	**273/6167**	**0.83 (0.69-0.99)**	
Eastern Europe*	68/1502	65/1500	1.04 (0.74-1.47)	
Rest of the world	10/322	11/321	0.91 (0.38-2.14)	



LESSON 7: potential clinical implication of the trial

At variance with clinical variables, extensive stenting and complex procedure may benefit from ticagrelor monotherapy.

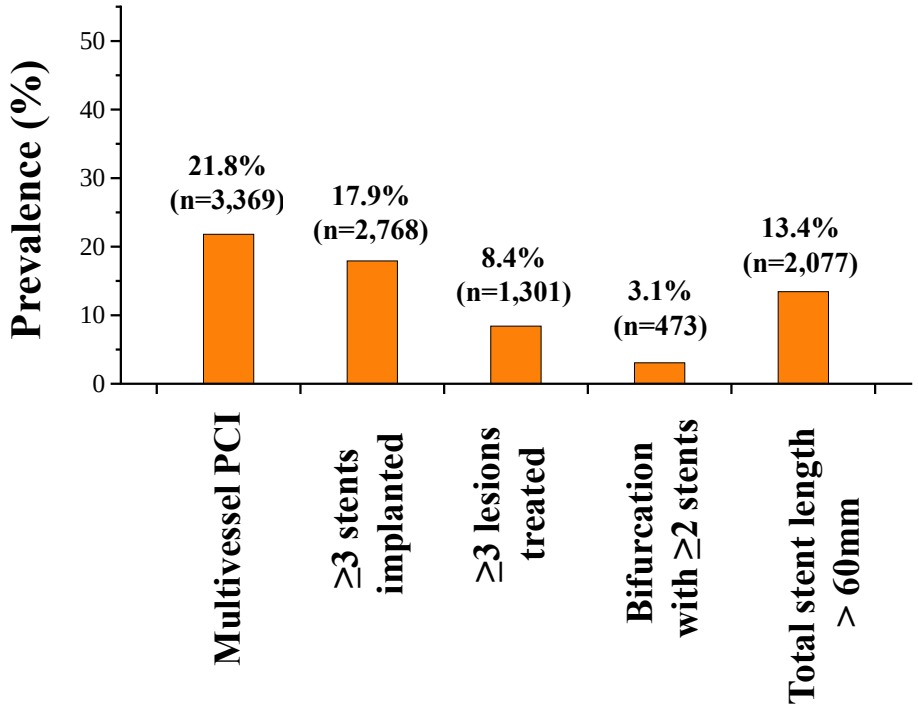
Clinical and procedural subgroups	Experimental Treatment Strategy	Reference Treatment Strategy	HR Ratio [Exp/Ref] (95% CI)	p-value for interaction
Gender*				0.638
Male	219/6115	258/6139	0.92 (0.69-1.24)	
Female	85/1865	91/1849	0.85 (0.71-1.02)	
BMI*				0.507
≥27	141/3502	169/3471	0.91 (0.74-1.13)	
<27	163/4477	180/4516	0.82 (0.66-1.03)	
COPD				0.952
Yes	40/407	47/425	0.88 (0.58-1.35)	
No	264/7573	302/7563	0.87 (0.74-1.03)	
Multivessel PCI				**0.020**
Yes	**55/1802**	**86/1774**	**0.61 (0.43-0.86)**	
No	247/6121	261/6148	0.96 (0.80-1.15)	
Long stenting				**0.042**
Yes	**73/1929**	**111/1955**	**0.67 (0.49-0.90)**	
No	218/5788	230/5778	0.95 (0.78-1.15)	
Bifurcation				0.343
Yes	50/1240	68/1258	0.74 (0.51-1.07)	
No	252/6683	279/6664	0.90 (0.76-1.07)	

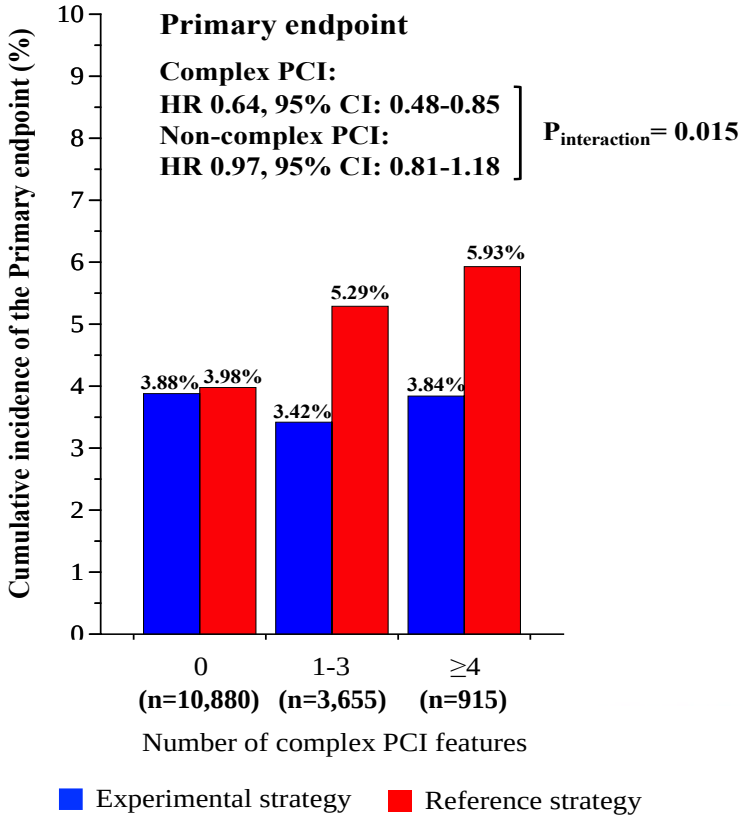


* Prespecified subgroup

LESSON 8: potential clinical implication of the trial

When complex PCI includes at least one of the following features; multivessel PCI, ≥ 3 stents implanted, ≥ 3 lesions treated, bifurcation PCI with ≥ 2 stents, and total stent length > 60 mm), long-term ticagrelor monotherapy could reduce the risk of the primary endpoint significantly.





Neumann et al. Eur Heart J. 2019 Jan 7;40(2):87-165.
Giustino et al. J Am Coll Cardiol. 2016 Oct 25;68(17):1851-1864.

LESSON 9: potential benefits in high risk group
(ACS patients with TWILIGHT-like criteria)

TWILIGHT (9000 pts)

Clinical criteria (must meet at least one)
Adult patients ≥ 65 years of age
Female gender
Troponin positive acute coronary syndrome
Established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization
Diabetes mellitus treated with medications (oral therapy or subcutaneous insulin)
Chronic kidney disease defined as an eGFR < 60 ml/min/1.73m2 or creatinine clearance < 60 ml/min
Angiographic criteria (must meet at least one)
Multivessel coronary artery disease
Target lesion requiring total stent length >30 mm
Thrombotic target lesion
Bifurcation lesions with Medina X,1,1 classification requiring at least 2 stents
Left main (≥ 50%) or proximal LAD (≥70%) lesion
Calcified target lesion (s) requiring atherectomy

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Diabetes mellitus
Chronic kidney disease (eGFR < 60 ml/min)
Angiographic criteria (must meet at least one)
Multivessel disease PCI
Total stent length >30 mm
Bifurcation PCI with at least 2 stents
Left main or proximal LAD PCI

UA, NSTEMI or STEMI patients (N = 2977) in GLOBAL LEADERS

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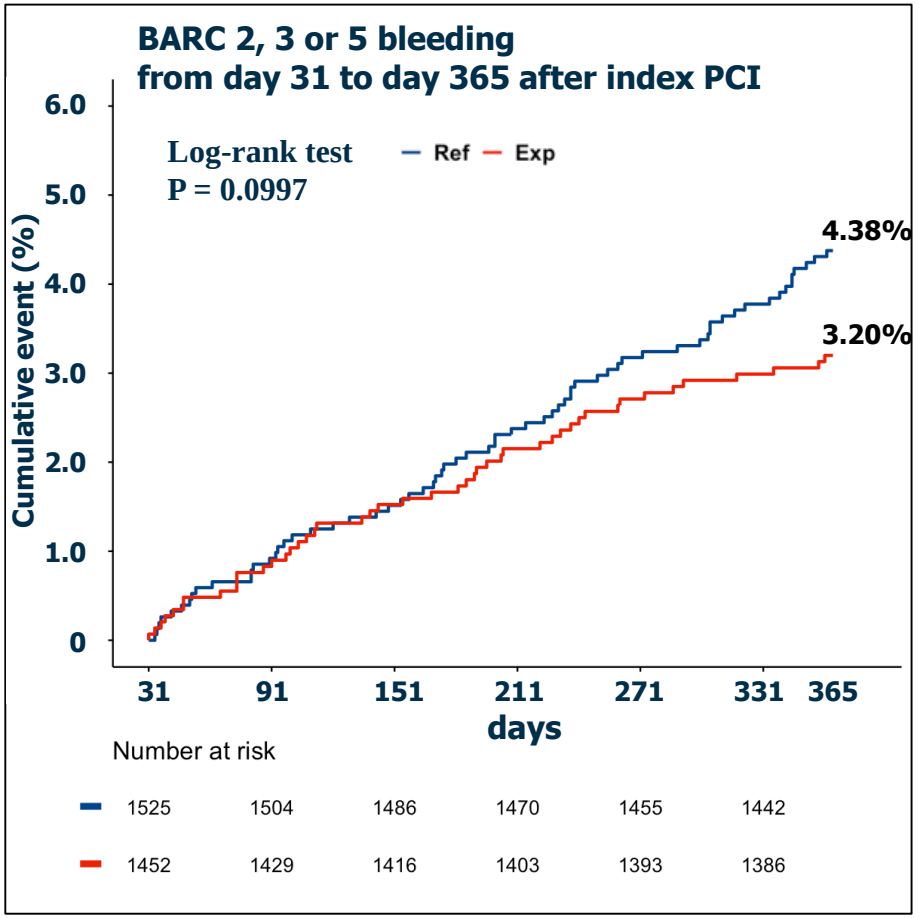

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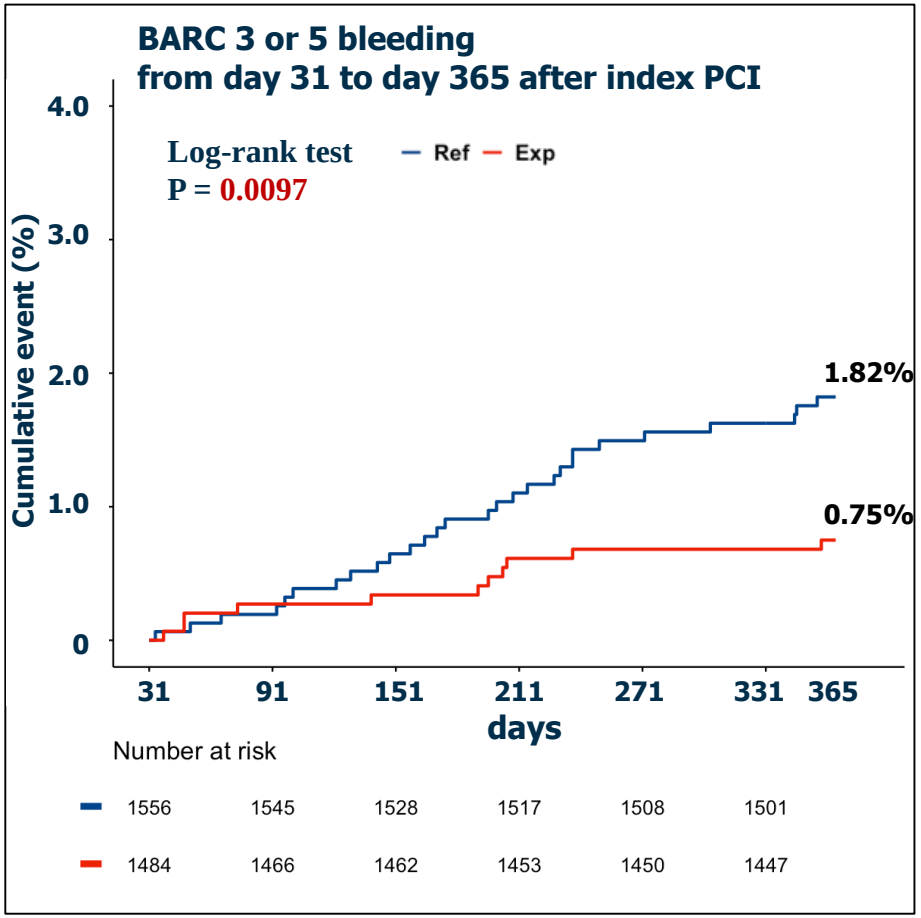

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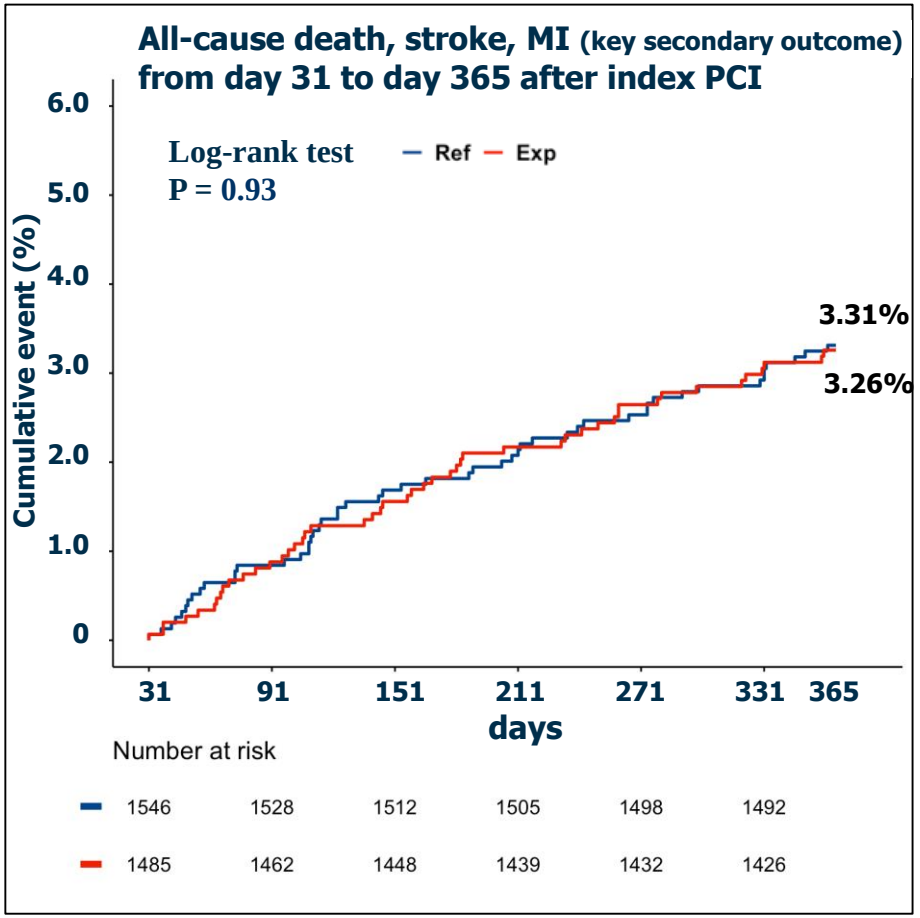

Conclusions

These "hypothesis-generating facts" will have to be demonstrated in a prospective, randomized, dedicated trial addressing the raised hypotheses…