NCT01813435

Ticagrelor Monotherapy Beyond One Month Versus Conventional Therapy On Adjudicated Ischemic And Bleeding Endpoints Following Drug Eluting Sent Implantation. Primary Results of the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY)

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on behalf of GLASSY Investigators

Declaration of Interest

Dr. Valgimigli reports grants and personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from Astrazeneca, personal fees from Biosensors, personal fees from Idorsia, outside the submitted work.

Background

- Dual antiplatelet therapy (DAPT) mitigates the risks of cardiac and, to lesser extent, cerebrovascular ischemic events.
- However, prolonged DAPT carries a heightened major bleeding risk.
- $P2Y_{12}$ inhibitor monotherapy might limit bleeding risk and retain the ischemic benefits of prolonged DAPT and provide long-term greater ischemic protection than aspirin alone.
- In GLOBAL LEADERS ticagrelor with 1-mo aspirin did not reduce the composite of death or Q-MI as compared to 1-year DAPT followed by aspirin*.

*: Vranckx et al, Lancet 2018

Background ii

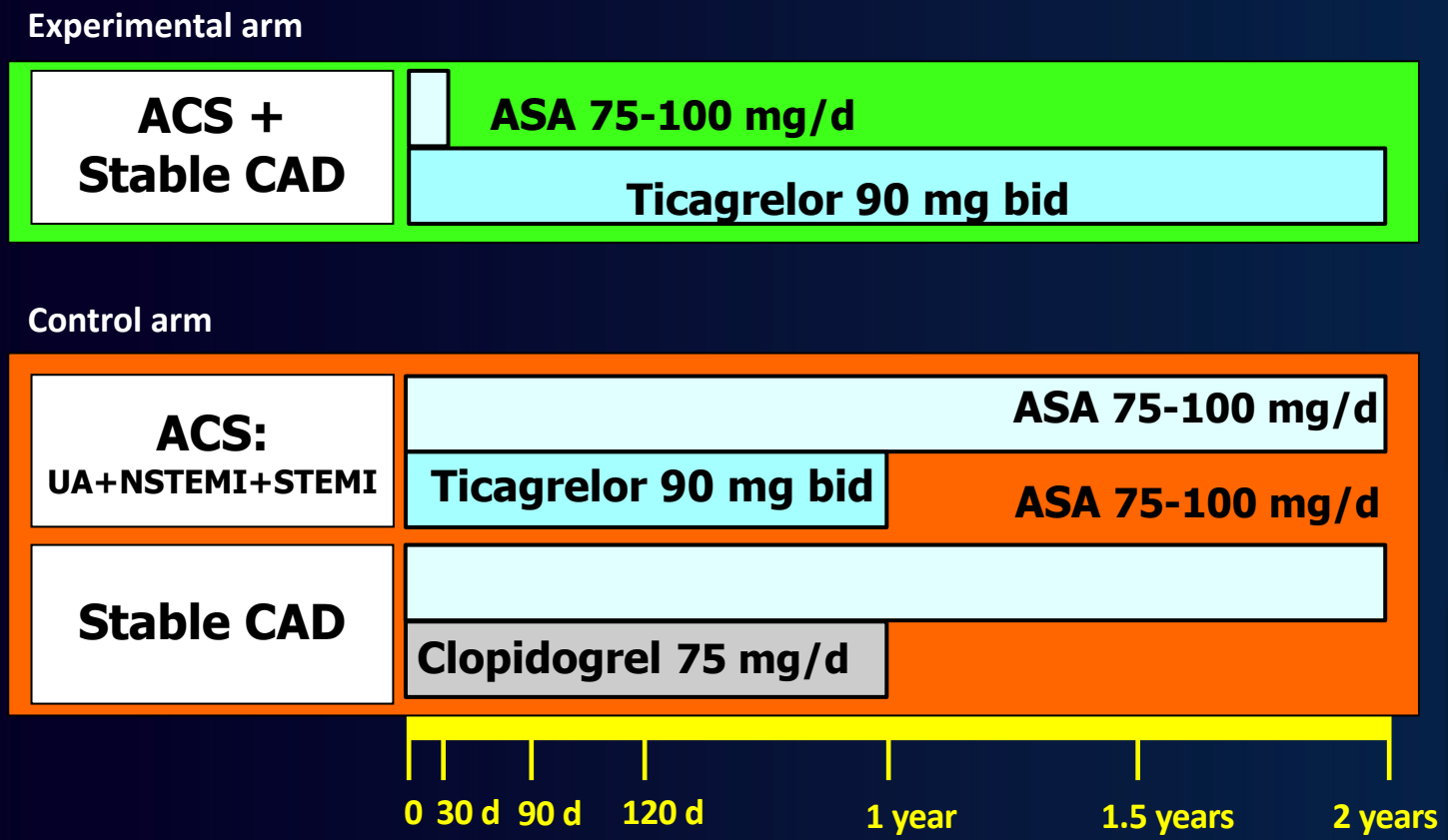
- By design, all clinical endpoints in the GLOBAL LEADERS study were investigator reported (IR) without central adjudication.

  *"The FDA considers the adjudication process to be a critically important component of good clinical study practice"**

- The current study was designed to prospectively implement an independent central adjudication process of both reported events and potential unreported event triggers to further assess the impact of this novel experimental treatment in a large stratified sample of patients included in the GLOBAL LEADERS trial.

*: *Andrew Farb, Bram D. Zuckerman Am Heart J.* 2017 Sep;191:62-64

GLOBAL LEADERS design



"All-comers" PCI population
N = 15,991
1:1 Randomisation, open-label design, 130 centers worldwide

Any type of lesions: Left main, SVG, CTO bifurcation, ISR, etc.

Unrestricted use of DES (number, length)

Randomization was also stratified by site

GLASSY – OBJECTIVES

To assess the comparative effectiveness of the experimental treatment strategy as compared to conventional 12-month DAPT followed by aspirin on the:

- **Primary efficacy EP of CEC-adjudicated all-cause death, non-fatal MI, non-fatal stroke or urgent TVR**
  (*non-inferiority* and if met *superiority*)

- **Primary safety EP of CEC-adjudicated BARC 3 or 5 bleeding**
  (*superiority*)

Leonardi S. et al, BMJ Open 2019

GLASSY – Statistical Considerations

Under the assumptions that the co-primary *Efficacy* and *Safety EPs* would occur, respectively at 11% and 5% in the control group, *7,186* patients would yield:

> 85% power to detect non-inferiority for the co-primary efficacy EP with a NI margin at 1.22 on a relative scale (≈ 2.4% ARD), 1-sided type I error of 2.5%.

80% power to assess the superiority for the co-primary efficacy EP, assuming 20% RRR with two-sided alpha of 2.5%.

> 80% power to detect a 33% RRR in the experimental arm for the co-primary safety endpoint (BARC 3 or 5 bleeding) with two-sided alpha error at 2.5%.

Leonardi S. et al, BMJ Open 2019

GLASSY – Participating sites and funds

The study was sponsored by the European Institute of Clinical Research (ECRI), a nonprofit organization, and received grant support from the department of cardiology at Bern university hospital, Bern, Switzerland and from the Swiss National Science Foundation (SNSF) Project number: IZSEZ0_180403.

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GLASSY – Study Design

GLASSY
7,585

Global Leaders Trial
15,991

CRF based screening
Investigator reported events
Event triggers based on prespecified logics

Source documents collection/translation

CEC process
Formal adjudication of IR and triggered EPs

Chair:
E. Mc Fadden
Co-chair:
S. Leonardi
Member:
R. Piccolo
Project Leader:
A. Franzone

Leonardi S. et al, BMJ Open 2019

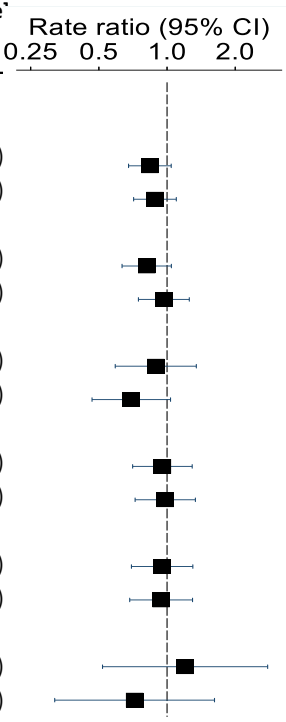
GLASSY – PARTICIPANTS VS NON PARTICIPANTS

Clinical characteristics	Glassy (20 sites) N=7,585	Not Glassy (110 sites) N= 8,383	P-value*
Age	64.9±10	64.2±10	0.41
Female sex	1799 (23.7)	1915 (22.8)	0.33
Hypertension	5492 (73)	6223 (74)	0.70
Diabetes mellitus	1822 (24)	2216 (26)	0.47
Renal failure (eGFR < 60 ml/min)	1005 (13)	1166 (14)	0.83
Peripheral Vascular disease	553 (7)	452 (5)	0.03
Current smoker	2186 (29)	1983 (24)	0.007
Previous MI	1762 (23)	1948 (23)	0.91
Previous PCI	2522 (33)	2699 (32)	0.53
Previous CABG	443 (6)	500 (6)	0.62
Stable CAD	3745 (49)	4736 (56)	0.048
Multivessel treatment	1098 (14)	1248 (15)	0.65
Previous major bleeding	48 (0.6)	50 (0.6)	0.78
Statin at dis.	6954 (92)	7747 (93)	0.78
Heart failure with ACEi or ARB at dis.	469 (84)	465 (83)	0.51
Heart failure with betablocker at dis.	130 (83)	181 (82)	0.88

*: Mixed-models p-values, accounting for a random effect of hospital identifier

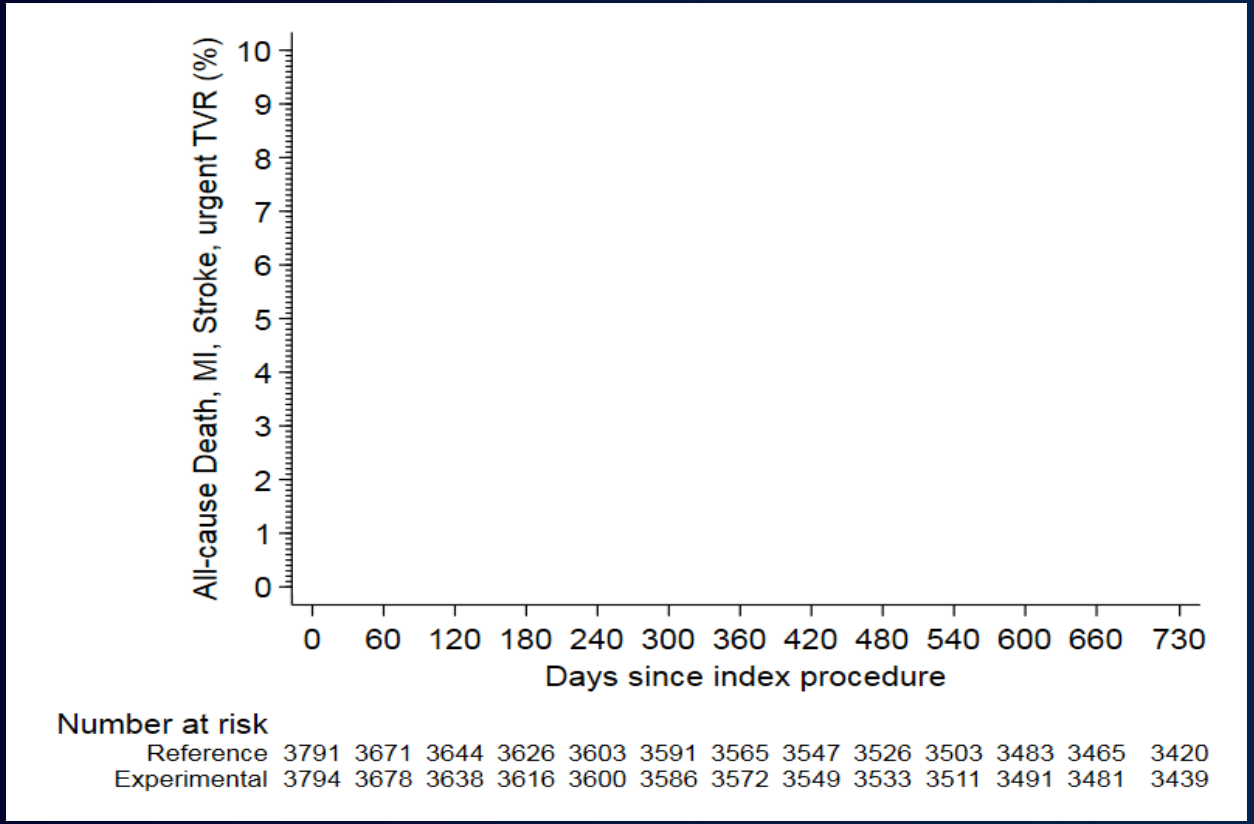
Clinical outcomes according to GLASSY inclusion

Subgroups	Experimental Intervention Group N = 7980	Control Group N = 7988	Rate Ratio [Exp./Reference] (95% CI)	p-value	p-value for interaction
All-cause mortality or New Q-wave MI or equivalent LBBB					0.741
GLASSY	151/3794	179/3791	0.84 (0.68-1.04)	0.114	
No GLASSY	154/4186	174/4197	0.88 (0.71-1.10)	0.266	
All-cause mortality					0.343
GLASSY	111/3794	136/3791	0.81 (0.63-1.04)	0.105	
No GLASSY	113/4186	117/4197	0.97 (0.75-1.25)	0.805	
New Q-wave MI or equivalent LBBB					0.395
GLASSY	43/3794	48/3791	0.89 (0.59-1.35)	0.585	
No GLASSY	41/4186	59/4197	0.70 (0.47-1.04)	0.072	
BARC 3 or 5 Bleeding					0.896
GLASSY	82/3794	86/3791	0.95 (0.70-1.29)	0.760	
No GLASSY	81/4186	83/4197	0.98 (0.72-1.33)	0.907	
BARC 3 bleeding					0.965
GLASSY	77/3794	81/3791	0.95 (0.70-1.30)	0.753	
No GLASSY	73/4186	78/4197	0.94 (0.68-1.30)	0.712	
BARC 5 bleeding					0.388
GLASSY	12/3794	10/3791	1.20 (0.52-2.78)	0.668	
No GLASSY	10/4186	14/4197	0.72 (0.32-1.62)	0.424	



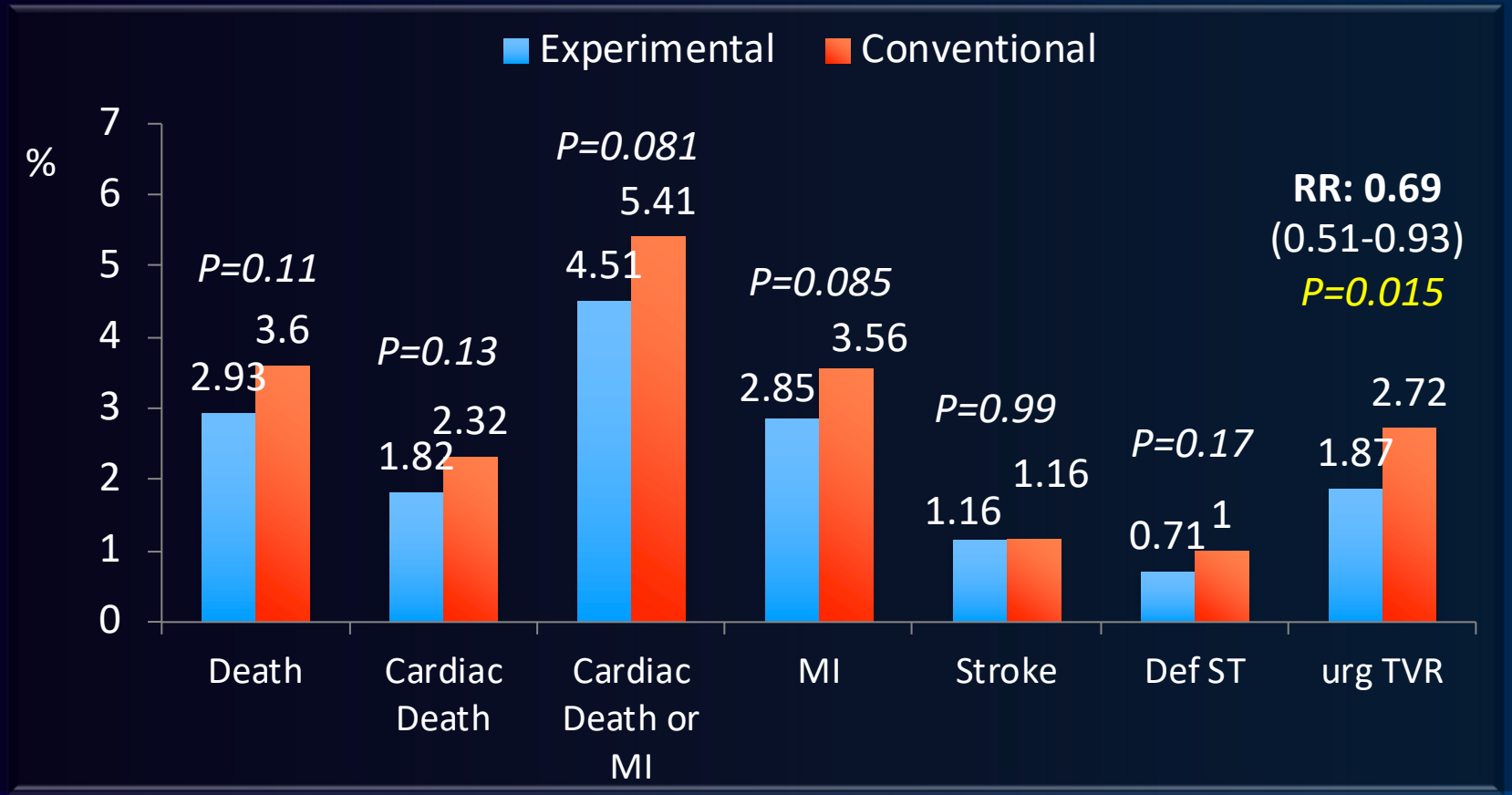
Leonardi S. et al, BMJ Open 2019

GLASSY – Co-primary Efficacy EP



GLASSY

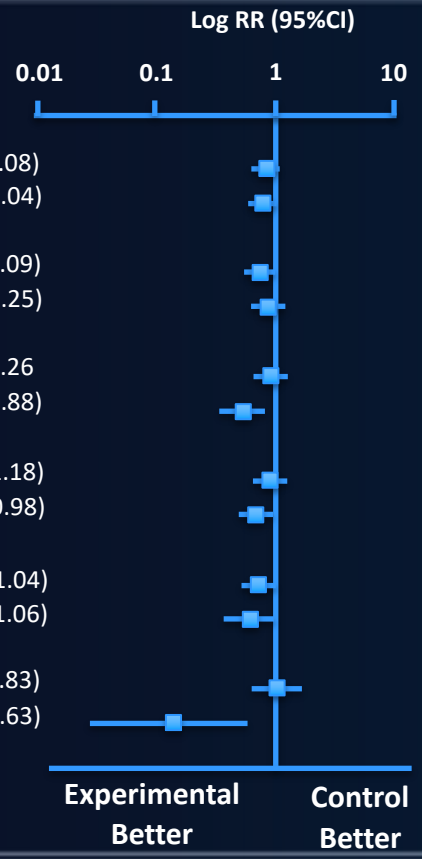
Secondary Efficacy Eps @ 2-years



GLASSY

Landmark Analysis @ 1-year

	Experimental Group	Control Group	Rate Ratio (95%CI)	P-value for interaction
All-cause death, MI, stroke or urgent TVR				
From 0 to 1-year	175 (4.61)	199 (5.25)	0.88 (0.72-1.08)	0.57
After 1-year	96 (2.69)	120 (3.37	0.80 (0.61-1.04)	
All-cause death				
From 0 to 1-year	54 (1.42)	71 (1.87)	0.76 (0.53-1.09)	0.58
After 1-year	57 (1.55)	65 (1.76)	0.88 (0.62-1.25)	
Myocardial infarction				
From 0 to 1-year	83 (2.19)	89 (2.35)	0.93 (0.69-1.26	0.062
After 1-year	25 (0.69)	46 (1.27)	0.54 (0.33-0.88)	
CV death or MI				
From 0 to 1-year	120 (3.16)	131 (3.46)	0.92 (0.72-1.18)	0.196
After 1-year	51 (1.41)	74 (2.05)	0.69 (0.48-0.98)	
Urgent TVR				
From 0 to 1-year	50 (1.32)	69 (1.82)	0.72 (0.50-1.04)	0.63
After 1-year	21(0.58)	34 (0.94)	0.62 (0.36-1.06)	
Definite ST				
From 0 to 1-year	25 (0.66)	24 0.63)	1.04 (0.59-1.83)	0.007
After 1-year	2(0.05)	14 (0.38)	0.14 (0.03-0.63)	

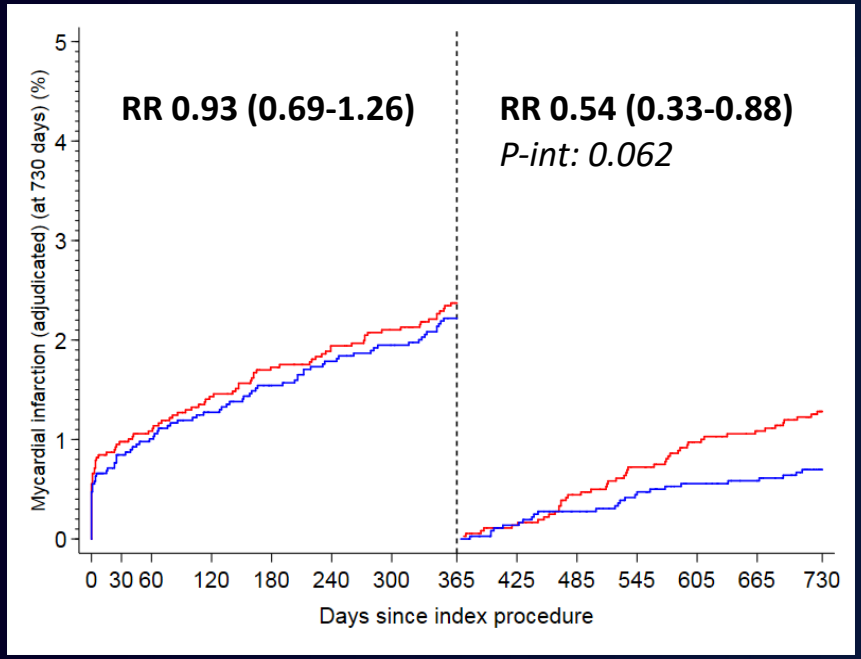


GLASSY

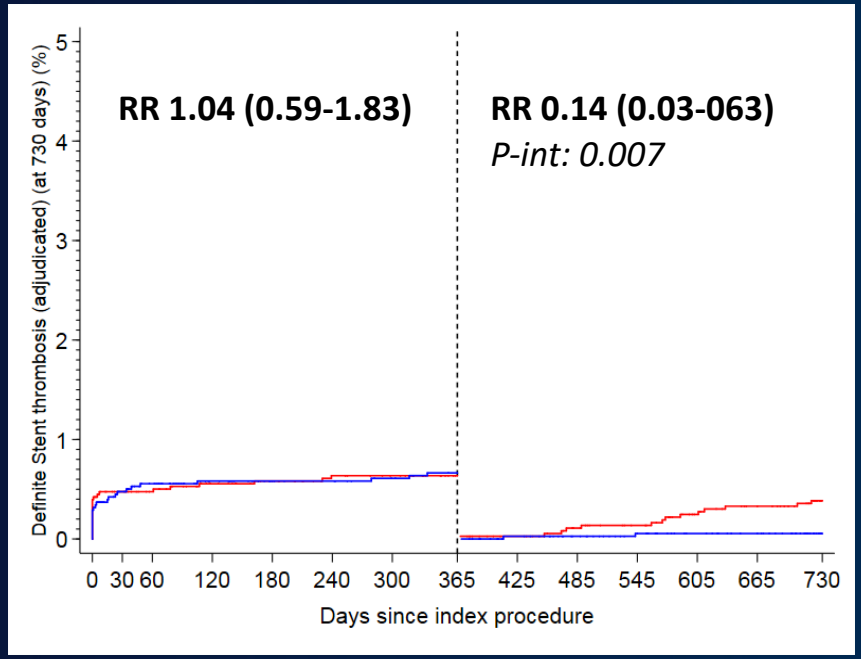
Landmark Analysis @ 1-year

Experimental arm Conventional arm

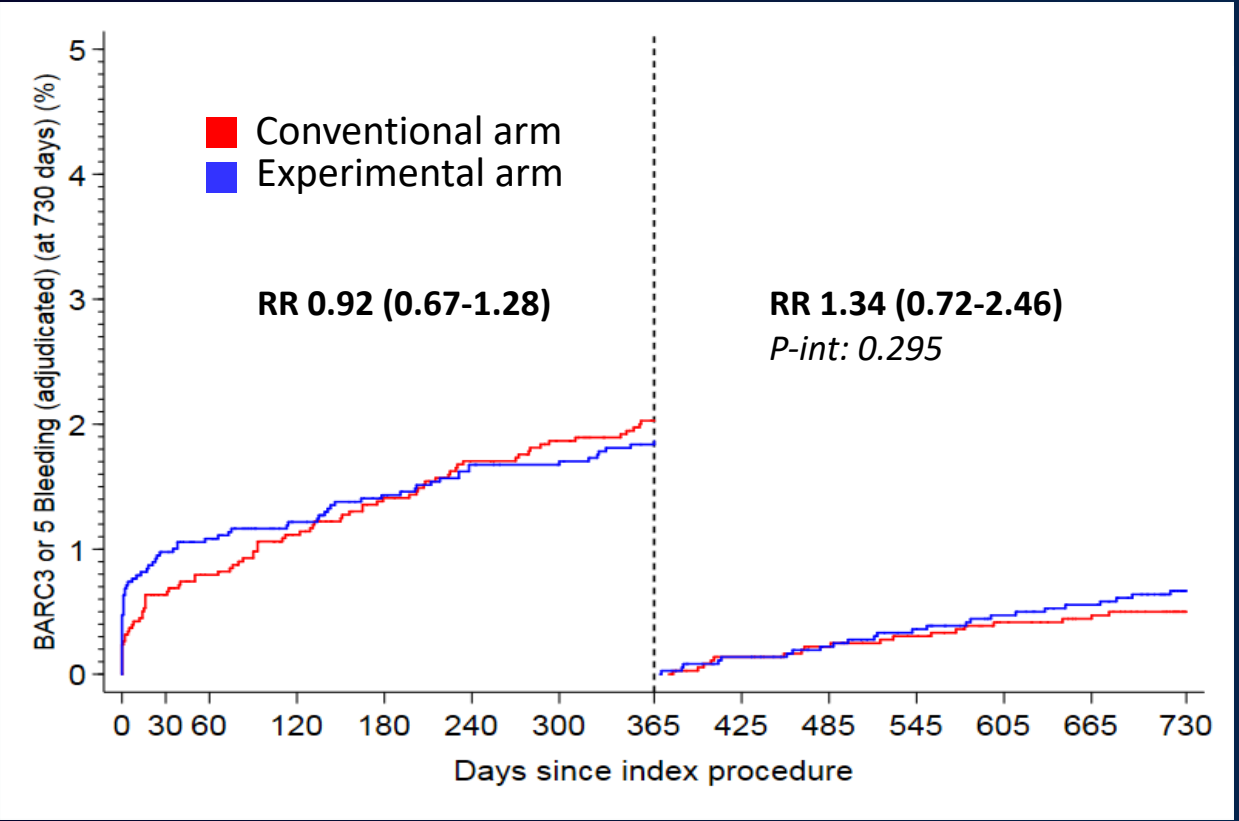
Myocardial Infarction



Definite Stent thrombosis



GLASSY – Co-primary safety EP



Summary

- Ticagrelor monotherapy after 1-month DAPT was non-inferior to conventional DAPT in the prevention of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or urgent target-vessel revascularization at 2 years.
- Our results provide new evidence that discontinuation of aspirin after 30 days while continuing ticagrelor alone does not expose patients to a higher ischemic risk as compared to a standard DAPT for 1 year and may reduce the rates of MI and stent thrombosis as compared to aspirin alone.
- Furthermore, the experimental treatment did not increase the risk of major bleeding.

1-year landmark: Global leaders vs GLASSY