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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Swiss Cardiovascular Center Bern, Inselspital, Bern, Switzerland
on behalf of GLASSY Investigators

NCT01813435
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
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

Experimental arm
- ACS + Stable CAD
  - ASA 75-100 mg/d
  - Ticagrelor 90 mg bid

Control arm
- ACS: UA+NSTEMI+STEMI
  - Ticagrelor 90 mg bid
- Stable CAD
  - Clopidogrel 75 mg/d

Randomization was also stratified by site

“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)
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)
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
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.

20 Top enrolling sites (N= 7, 585 )

- Austria: Vienna, PI: K. Huber
- Italy: Pavia, PI: M. Ferrario; Ferrara, PI: C. Tumscitz; Terni, PI: M. Dominici; Arezzo, PI: L. Bolognese
- Poland: Chrzabow, PI: A. Zurakowski; Krakow, PI: K. Zmudka; Dabrowa Gornicza, PI: P. Buszan; PAKS Kozle, PI: J. Prokopczuk
- United Kingdom: Blackburn, PI: S. Gard
- Belgium: Hasselt, PI: E. Benit; Bonheiden, PI: L. Janssens; Chaleroi, PI: A. Aminian; Genk, PI: M. Vrolix
- Switzerland: Bern, PI: S. Windecker
- Germany: Bad Nauheim, PI: C. Hamm; Essen, PI: C. Naber
- The Netherlands: Rotterdam, PI: D. Diletti; Amsterdam, PI: T. Slagboom
- Netherlands: Rotterdam, PI: D. Diletti; Amsterdam, PI: T. Slagboom
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

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

*: Mixed-models p-values, accounting for a random effect of hospital identifier
Clinical outcomes according to GLASSY inclusion

Leonardi S. et al, BMJ Open 2019

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

Conventional arm
Experimental arm

Rate Ratio, 0.85
95% CI, 0.72-0.99
P<0.001 for non-inferiority
P=0.0465 for superiority
GLASSY

SECONDARY EFFICACY EPS @ 2-YEARS

<table>
<thead>
<tr>
<th>Event</th>
<th>Experimental</th>
<th>Conventional</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.93</td>
<td>3.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>1.82</td>
<td>2.32</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiac Death or MI</td>
<td>4.51</td>
<td>5.41</td>
<td>0.081</td>
</tr>
<tr>
<td>MI</td>
<td>2.85</td>
<td>3.56</td>
<td>0.085</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.16</td>
<td>1.16</td>
<td>0.99</td>
</tr>
<tr>
<td>Def ST</td>
<td>0.71</td>
<td>1</td>
<td>0.17</td>
</tr>
<tr>
<td>Urg TVR</td>
<td>1.87</td>
<td>2.72</td>
<td></td>
</tr>
</tbody>
</table>

RR: 0.69 (0.51-0.93)  
P = 0.015
GLASSY

LANDMARK ANALYSIS @ 1-YEAR

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

Myocardial Infarction

- Experimental arm: RR 0.93 (0.69-1.26), P-int: 0.062
- Conventional arm: RR 0.54 (0.33-0.88)

Definite Stent thrombosis

- Experimental arm: RR 1.04 (0.59-1.83), P-int: 0.007
- Conventional arm: RR 0.14 (0.03-0.63)
GLASSY – Co-primary Safety EP

7.14%  
8.41%  

Conventional arm
Experimental arm

Rate Ratio, 0.85  
95% CI, 0.72-0.99  
P<0.001 for non-inferiority  
P=0.0465 for superiority

2.46%  

Conventional arm
Experimental arm

Rate Ratio   (95% CI);     p-value
0-30d: 1.54 (0.92-2.58); 0.095
30-730d: 0.82 (0.58-1.16); 0.26

P-interaction= 0.043

RR 0.92 (0.67-1.28)  
RR 1.34 (0.72-2.46)

P-int: 0.295
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

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Conventional</th>
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</thead>
<tbody>
<tr>
<td>MI GL</td>
<td>0.36</td>
<td>0.46</td>
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<tr>
<td>MI Glassy</td>
<td>0.69</td>
<td>1.27</td>
</tr>
<tr>
<td>ST GL</td>
<td>0.60</td>
<td>0.43</td>
</tr>
<tr>
<td>ST Glassy</td>
<td>0.05</td>
<td>0.38</td>
</tr>
</tbody>
</table>

(0.51-1.41)  (0.33-0.88)  (0.89-2.19)  (0.03-0.63)