Individualized Decision Making between Percutaneous and Surgical Revascularization in Patients with Complex Coronary Artery Disease: Redevelopment and Validation of the SYNTAX score II 2020

In press in the LANCET
RCT’s are the gold standard for testing the effectiveness of novel treatment. Average treatment effect are typically reported in RCT’s. However, treatment effectiveness can vary across individual patients. Average treatment effect may be suboptimal for decision-making in individual patients. The SYNTAX score II (2013) derived from 2 angiographic and 6 clinical variables, provides an individualized decision-making based on 4-year all-cause death after either CABG or PCI. Using the data of the 10 years F/uP of SYNTAX Extended Survival (SYNTAXES), we sought to:

(i) update the SS II (version 2020) for prediction of 10-year Mortality and 5-year MACCE
(ii) to externally validate (FREEDOM,BEST,PRE-COMBAT) the SS II 2020 for its ability to predict treatment benefit in mortality and in MACCE.
Average Treatment Effect as a Summary Result for 10-year All-cause Death in the SYNTAXES

Based on the average treatment effect, should you send all your patients to surgery?

The answer is of course :no!

**HR 1.19, 95% CI (0.99-1.43), P = 0.066**
Decision Tools to Improve Personalized Care in Cardiovascular Disease
Moving the Art of Medicine Toward Science

A Average Treatment Effect Assessed in a Heterogeneous Population

B Identification of Heterogeneous Responses to Treatment

= expected to derive benefit from treatment
= expected to have an equivocal response
= expected to be harmed by treatment
= response in the “average”

Segregation of patient population based on treatment response
SYNTAX Score II (2013)

SYNTAX Score II was developed by applying a Cox proportional hazards model to the 4-year results of SYNTAX trial resulting in a combination of 6 clinical and 2 anatomical independent predictors of 4 years all-cause mortality:

- Age
- Cr Clearance
- Female
- PVD
- LVEF
- COPD

At four year follow-up, females randomized to CABG had a lower all-cause mortality than females randomized to PCI.

At ten years all-cause mortality rates in females (PCI or CABG) were identical.

In male (PCI vs CABG) all cause mortality started to diverge after 7 years.
SYNTAX Score II 2020 was redeveloped to predict 10-year mortality and 5-year MACE in the SYNTAX(ES) trial and externally validated in the FREEDOM, BEST, and PRECOMBAT trials:

\[
\text{Pr (10-year mortality)} = 1 - \exp(-0.243 \times \exp(0.99 \times (0.72 \times \text{Age}/10 - 0.07 \times \min(\text{CrCl}, 90)/10 - 0.31 \times \min(\text{LVEF}, 50)/10 + 0.48 \times \text{COPD} + 0.73 \times \text{PVD} + 0.20 \times \text{Medically treated diabetes} + 0.46 \times \text{on insulin} + 0.66 \times \text{Current smoking}) - 0.10 \times \text{LMCAD} - 0.40 \times \text{CABG} \times 3VD + 0.02 \times \text{CABG} \times \text{LMCAD} + 0.16 \times \text{PCI} \times \text{(SYNTAX Score - 29)/10 - 2.80}).
\]
SYNTAX Score II 2020 was redeveloped to predict \(10\)-year mortality and \(5\)-year MACE in the SYNTAX(ES) trial and externally validated in the FREEDOM, BEST, and PRECOMBAT trials:

\[
Pr\ (5\text{-year MACE}) = 1 - \exp(-0.175 \times \exp(0.74 \times (0.72 \times \text{Age}/10 - 0.07 \times \text{min(CrCl, 90)}/10 - 0.31 \times \text{min(LVEF, 50)}/10 + 0.48 \times \text{COPD} + 0.73 \times \text{PVD} + 0.2 \times \text{Medically treated diabetes} + 0.46 \times \text{On insulin} + 0.66 \times \text{Current smoking}) - 0.23 \times \text{LMCAD} - 0.48 \times \text{CABG} \times 3\text{VD} + 0.13 \times \text{CABG} \times \text{LMCAD} + 0.19 \times \text{PCI} \times (\text{SYNTAX Score} - 29)/10 - 2.00)).
\]
Cross validation of the 10 years mortality in the SYNTAXES (1,800 patients)

Difference in 10-year mortality called “Treatment benefit” of CABG vs. PCI for mortality

Observed treatment benefit of CABG vs. PCI

PCI BETTER

CABG BETTER

Slope= 0.96
intercept= 0.00

Slope= 0.99
intercept= -0.01
Cross validation of the 10 years mortality in the SYNTAXES (1800 patients)

Kaplan-Meier curves by quartiles

- **Predicted risk of 10-year mortality with PCI**
- **Predicted risk of 10-year mortality with CABG**

**Observed treatment benefit of CABG vs. PCI for mortality**

**Difference in 10-year mortality called**
“Treatment benefit” of CABG vs. PCI for mortality

- **PCI BETTER**
- **CABG BETTER**

**Predicted treatment benefit of CABG vs. PCI**

<table>
<thead>
<tr>
<th>Time since randomization (years)</th>
<th>Survival probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td>0.4 0.5 0.6 0.7 0.8 0.9 1.0</td>
</tr>
<tr>
<td>CABG</td>
<td>-0.2 -0.1 0.0 0.1 0.2 0.3</td>
</tr>
<tr>
<td>PCI</td>
<td>-0.2 -0.1 0.0 0.1 0.2 0.3</td>
</tr>
</tbody>
</table>

**Cross Validation of the 10 years mortality model**

- **EQUIPOISE**
- **DIFFERENCE :ARD**

- **11.4 %**
- **6.1 %**
- **0.3%**
- **-1.4%**

**Predicted treatment benefit of CABG vs. PCI**

- **PCI BETTER**
- **CABG BETTER**
External Validation of the 5-year MACE model in the FREEDOM, BEST, and PRECOMBAT trials (n=3,380 patients)

- Predicted 5-year MACE:
  - PCI:
    - Observed 5-year MACE: $c = 0.67$
    - Predicted 5-year MACE: $\text{Slope} = 0.86, \text{intercept} = 0.20$
  - CABG:
    - Observed 5-year MACE: $\text{Slope} = 0.95, \text{intercept} = -0.16$

- Difference in 5-year MACCE called “Treatment benefit” of CABG vs. PCI for rMACCE:
  - PCI BETTER
  - CABG BETTER
  - ABSOLUTE RISK DIFFERENCE: ARD
    - 9.4 %
    - 4.9 %
    - 6.5 %
    - -1.2 %

- Slope= 0.95
- intercept= -0.16

- Observed treatment benefit of CABG vs. PCI

- Predicted treatment benefit of CABG vs. PCI
SYNTAX Score II 2020
for Individualized Decision Making

Baseline characteristics at the time of decision-making

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td>74</td>
<td>59</td>
</tr>
<tr>
<td>Diabetes:</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>On insulin:</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CrCl (ml/min/1.73m²):</td>
<td>38.6</td>
<td>67.6</td>
</tr>
<tr>
<td>LVEF (%):</td>
<td>40</td>
<td>67</td>
</tr>
<tr>
<td>COPD:</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PVD:</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Current smoking:</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>3VD or LMCAD:</td>
<td>LMCAD</td>
<td>3VD</td>
</tr>
<tr>
<td>Anatomical SYNTAX score:</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

PCI
CABG
Treatment benefit

ABSOLUTE RISK (%)
Conclusions

- Using data from the randomized SYNTAX(ES) trial, we have updated and externally validated the SS II 2020, a personalized predictive model based on 7 prognostic factors and 2 pre-specified effect modifiers _disease type (3VD or LMCAD) and_ the anatomical SS to predict **10-year all-cause death** and 5-year MACE for patients treated with either PCI or CABG.

- By providing expected **probabilities of 5- and 10-year outcomes**, this model may improve the ability of the Heart Team to inform patients and their families regarding the risks and benefits of alternative treatments for complex CAD and support a **more transparent shared decision-making process**.
Limitations

- The **SYNTAX** trial was conducted between 2005 and 2007 with a default use of the first-generation DES for treatment with PCI, whereas the newer generation DES may improve outcomes. However, it is unavoidable that the findings from long-term follow-up data are inherently based on somewhat outdated technology and method of treatment, whereas evidence derived from implementation of contemporary technology and best practice can be derived only from short-term follow-up studies.

- The **SYNTAXES** study evaluated vital status up to 10 years and did not assess other outcomes, and thus a prediction model for MACE beyond 5 years could not be constructed.
Algorithm to guide the choice of revascularization procedure across major categories in patients with 3VD or LMCAD

Stable multivessel coronary artery disease with suitable anatomy for PCI and CABG and clinical eligibility for either PCI or CABG

Three-vessel CAD

SYNTAX score 0-22

No diabetes

PCI IA
CABG IA

Diabetes

PCI IIA
CABG IA

SYNTAX score >22

Left main CAD

SYNTAX score 0-22

PCI IA
CABG IA

SYNTAX score 23-32

PCI IIA
CABG IA

SYNTAX score >32

PCI IIIB
CABG IA
