Definition and Optimal Antithrombotic and PCI Strategies in HBR Patients:
Updated Consensus of the ARC-HBR Group

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La Tour hospital
Geneva, Switzerland
Conflicts of interest

• Consulting for Biosensors, Morges, Switzerland
• Honoraria from Edwards Lifesciences
• Stockholder of MedAlliance, Nyon, Switzerland
• Stockholder of CERC, Massy, France (Centre for European Research in Cardiovascular medicine)
# Trials of HBR have varying inclusion criteria

<table>
<thead>
<tr>
<th></th>
<th>LEADERS FREE</th>
<th>ZEUS</th>
<th>SENIOR</th>
<th>ONYX ONE</th>
<th>MASTER DAPT</th>
<th>TARGET SAFE</th>
<th>EVOLVE SHORT DAPT</th>
<th>XIENCE 90 SHORT DAPT</th>
<th>XIENCE 28 GLOBAL</th>
<th>POEM</th>
<th>COBRA REDUCE</th>
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<td>Bleeding score cut-off</td>
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<td>Female &amp; ACS</td>
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<td>CHF &amp; LVEF 30-50%</td>
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<tr>
<td>Experimental DAPT</td>
<td>1 month</td>
<td>~1 month</td>
<td>1-6 months</td>
<td>1 month</td>
<td>1 month</td>
<td>1 month</td>
<td>3 months</td>
<td>3 months</td>
<td>1 month</td>
<td>1 month</td>
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</table>
The ARC–HBR Initiative

• Compliant with the ARC Charter, organized by CERC Europe
• Non-profit initiative, sponsored by 22 pharma and device companies
• 31 experts from Europe, USA, Japan and South Korea
• Two meetings in 2018 - Washington (US), April 13-14 and Paris (FR), October 19-20
In isolation, confers:

1) BARC 3 or 5 bleeding risk of ≥ 4% at one year
2) risk of ICH of > 1% at one year

In isolation confers increased bleeding risk, but:

- risk of BARC 3 or 5 bleeding of <4% at one year
- risk of ICH < 1%

HBR = BARC 3 or 5 bleeding risk of ≥ 4%
and/or risk of intracranial hemorrhage (ICH) ≥ 1%
within 1 year after PCI

HBR status conferred if:

- 1 major criterion
- 2 minor criteria
Eur Heart J 2019; 40: 2632-2653
Circulation 2019; 140: 240-261
Design Principles for Clinical Trials in Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention

**Device**
- Cardiovascular death
- Myocardial infarction (target vessel)
- Target lesion revascularization (clinically driven)

**Drug**
- Cardiovascular death
- Myocardial infarction (any)
- Ischemic stroke
- ± systemic arterial embolism, any revascularization
- BARC type 3 bleeding
- BARC type 5 bleeding
- ± BARC type 2 bleeding

Capodanno D. et al. JACC 2020 (accepted for publication)
Validation of ARC-HBR criteria
Validation of ARC–HBR criteria in PCI Patients

Ueki Y et al. EuroIntervention 2020, published online

- 12121 patients in the Bern PCI registry
- Bleeding = BARC 3 or 5
- Ischemia = cardiac death, TV-MI, and TLR
- Follow-up for 1 year

![Pie chart showing 39% ARC-HBR and 61% non-ARC-HBR]
Validation of ARC–HBR criteria in PCI Patients
Ueki Y et al. EuroIntervention 2020, published online

Bleeding and ischaemic events

<table>
<thead>
<tr>
<th>Category</th>
<th>ARC-HBR</th>
<th>non-ARC-HBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC 3 or 5</td>
<td>6.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Cardiac death, TV-MI or TLR</td>
<td>12.5</td>
<td>6.1</td>
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</tbody>
</table>
Prevalence of ARC–HBR patients in PCI registries

2. EuroIntervention 2020
3. JACC 2020 (in press)

- Ueki et al ²: 39.4\% ARC HBR, 60.6\% non-HBR
- Natsuaki et al ¹: 43\% ARC HBR, 57\% non-HBR
- Cao et al ³: 44.4\% ARC HBR, 55.6\% non-HBR
Bleeding and ischaemic risks for HBR patients


Natsuaki et al. Circ Cardiovasc Interv. 2019
Ueki et al. EuroIntervention 2020
Cao et al. JACC 2020 (in press)
The thrombosis vs bleeding trade-off

- Anemia
- Prior bleeding
- OAC
- Cancer
- Planned surgery
- Renal insufficiency
- etc...

- ACS
- Diabetes
- Prior MI
- Complex PCI
- Prior ST
- Renal insufficiency
- etc...
Assessing the trade-off

- We assessed 12517 patients enrolled in 6 PCI studies and focused on 6641 of them who satisfied at least 1 major or 2 minor ARC-HBR criteria.

- After excluding peri-procedural events, we identified independent predictors of BARC 3-5 bleeding and MI/ST (myocardial infarction and/or stent thrombosis) using Cox proportional hazards modeling.

- A scatterplot of the 6641 patients for BARC 3-5 bleeding vs. MI/ST risks was generated, and excess mortality risks associated with each type of adverse event were determined.

- Validation of the model was obtained with 1458 ARC-HBR patients enrolled in the ONYX ONE trial.
6 studies for the derivation cohort

- **LEADERS FREE**: 86.8% (ARC-HBR), 13.2% (non ARC-HBR)
- **LEADERS FREE II**: 85.6% (ARC-HBR), 14.4% (non ARC-HBR)
- **SENIOR**: 73.2% (ARC-HBR), 26.8% (non ARC-HBR)
- **ZEUS**: 58.6% (ARC-HBR), 41.4% (non ARC-HBR)
- **PARIS**: 29.2% (ARC-HBR), 70.8% (non ARC-HBR)
- **CENTURY II**: 23.5% (ARC-HBR), 76.5% (non ARC-HBR)
Essential results

*peri-procedural events excluded

1 year event rates*

- ARC-HBR (n=6641):
  - BARC 3-5: 5.7
  - MI/ST: 5.3

- non-ARC-HBR (n=5876):
  - BARC 3-5: 1.2
  - MI/ST: 2.5

Adapted criteria for 6641 ARC-HBR patients:

- Age > 75 years: 64.1%
- renal insufficiency: 43.3%
- anemia: 28.5%
- OAC: 40.2%
- planned surgery: 9.9%
- cancer < 3 years: 8.7%
- ICH/stroke < 1 year: 7.7%
- platelets < 100,000/mm³: 3.0%
- steroids/NSAIDs: 2.0%
- severe liver disease: 0.9%
## Multivariate predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>BARC 3-5 bleeding</th>
<th>MI/ST</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
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<tr>
<td>OAC at discharge</td>
<td>2.00 (1.62, 2.48)</td>
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<tr>
<td>Liver disease, cancer or planned surgery</td>
<td>1.63 (1.27, 2.09)</td>
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<tr>
<td>Age ≥65 years</td>
<td>1.50 (1.08, 2.08)</td>
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<tr>
<td>COPD</td>
<td>1.39 (1.05, 1.83)</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>-</td>
<td>1.89 (1.52, 2.35)</td>
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<tr>
<td>NSTEMI or STEMI presentation</td>
<td>-</td>
<td>1.82 (1.46, 2.25)</td>
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<tr>
<td>Diabetes</td>
<td>-</td>
<td>1.56 (1.26, 1.93)</td>
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<tr>
<td>Bare metal stent</td>
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<td>1.53 (1.23, 1.89)</td>
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<tr>
<td>Hemoglobin (g/L)</td>
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<tr>
<td>&gt;130</td>
<td>reference group</td>
<td>&lt;0.0001</td>
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<td>110-129</td>
<td>1.69 (1.30, 2.20)</td>
<td>1.27 (0.99, 1.63)</td>
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<tr>
<td>&lt;110</td>
<td>3.99 (3.06, 5.20)</td>
<td>1.50 (1.12, 1.99)</td>
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<tr>
<td>Estimated GFR (mL/min)</td>
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<td>&gt; 60</td>
<td>reference group</td>
<td>0.02</td>
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<td>30-59</td>
<td>0.99 (0.79, 1.24)</td>
<td>1.30 (1.03, 1.66)</td>
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<tr>
<td>&lt;30</td>
<td>1.43 (1.04, 1.96)</td>
<td>1.69 (1.20, 2.37)</td>
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<td>Current smoker</td>
<td>1.47 (1.08, 1.99)</td>
<td>1.48 (1.09, 2.01)</td>
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<td>Complex procedure</td>
<td>1.32 (1.07, 1.61)</td>
<td>1.50 (1.21, 1.85)</td>
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<td>C-statistic=0.68</td>
<td>C-statistic=0.69</td>
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<td>Validation: ARC-HBR ONYX-ONE patients</td>
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C-statistic=0.74 | C-statistic=0.74
Predicted risks for 6641 individual patients

equal trade-off

mortality-weighted equal trade-off

Excess mortality with MI/ST and BARC 3-5

<table>
<thead>
<tr>
<th>Event</th>
<th>Background Risk</th>
<th>Excess Mortality Risk Associated with MI/ST</th>
<th>Excess Mortality Risk Associated with BARC 3-5</th>
<th>Ratio of Excess Risk</th>
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<tr>
<td>MI/ST</td>
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<td>HR 6.07 (95% CI = 4.8 – 7.7)</td>
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<td>5.1/2.7 = 1.90</td>
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<tr>
<td>BARC 3-5</td>
<td>background</td>
<td>HR 3.7 (95% CI = 2.9 – 4.8)</td>
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</table>
Patient 1:
56 year-old diabetic woman, active smoker
Presents with NSTEMI
Prior MI 2 years ago
On long term ibuprofen for osteoarthritis
Hemoglobin 120 g/L, e-GFR 40 ml/min
Treated by complex PCI (4 DES)
discharged on ticagrelor + aspirin

Patient 2:
79 year-old man with atrial fibrillation on OAC
Presents with grade 3 stable angina
Ex-smoker (stopped 2 years ago) with COPD
Hemi-colectomy for cancer 6 month ago
Hemoglobin 105 g/L, e-GFR 70 ml/min
Treated with a single DES to the proximal
LAD discharged on clopidogrel and OAC
Conclusions

- Patients at increased risk of bleeding have received considerable attention over the past few years.

- The ARC-HBR consensus-based criteria are designed to help better define this population and allow consistent and comparable trial results. They have been validated in several clinical series from Japan, Europe, and the US.

- Using 12 readily available predictors, the respective risks of bleeding and MI/ST can be estimated and further modulated by the associated mortality risk for individual HBR patients.