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

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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

	LEADERS FREE	ZEUS	SENIOR	ONYX ONE	MASTER DAPT	TARGET SAFE	EVOLVE SHORT DAPT	XIENCE 90 SHORT DAPT	XIENCE 28 GLOBAL	POEM	COBRA REDUCE
Age ≥ 75 (or 80*)	•	•	•	•	•	•	•	•	•	•	
OAC	•	•		•	•		•	•	•	•	•
Renal failure	•			•		•	•	•	•	•	
Surgery soon	•			•		•				•	
Anaemia or TF	•	•		•	•	•		•	•	•	
Hospital for bleed	•	•		•	•					•	
Actionable bleed					•	•	•	•	•		
Thrombocytopenia	•	•		•	•	•	•	•	•	•	
Recent cancer	•			•	•					•	
Stroke/ICH	•			•	•	•	•	•	•	•	
Liver disease	•			•						•	
NSAID	•	•		•	•	•				•	
Bleeding score cut-off					•	•					
Female & ACS						•					
CHF & LVEF 30-50%						•					
Experimental DAPT	1 month	~1 month	1-6 months	1 month	1 month	1 month	3 months	3 months	1 month	1 month	2 weeks

The ARC-HBR Initiative

ARC HBR Focus Group, Washington April 13,14 2018

- 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

ARC-HBR criteria

consensus

HBR =

BARC 3 or 5 bleeding risk of ≥ 4%

and/or

risk of intracranial hemorrhage (ICH) ≥ 1%

within 1 year after PCI

so…

major criterion

In isolation, confers:

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

and/ or

2) risk of ICH of ≥ 1% at one year

and

minor criterion

In isolation confers increased bleeding risk, but:

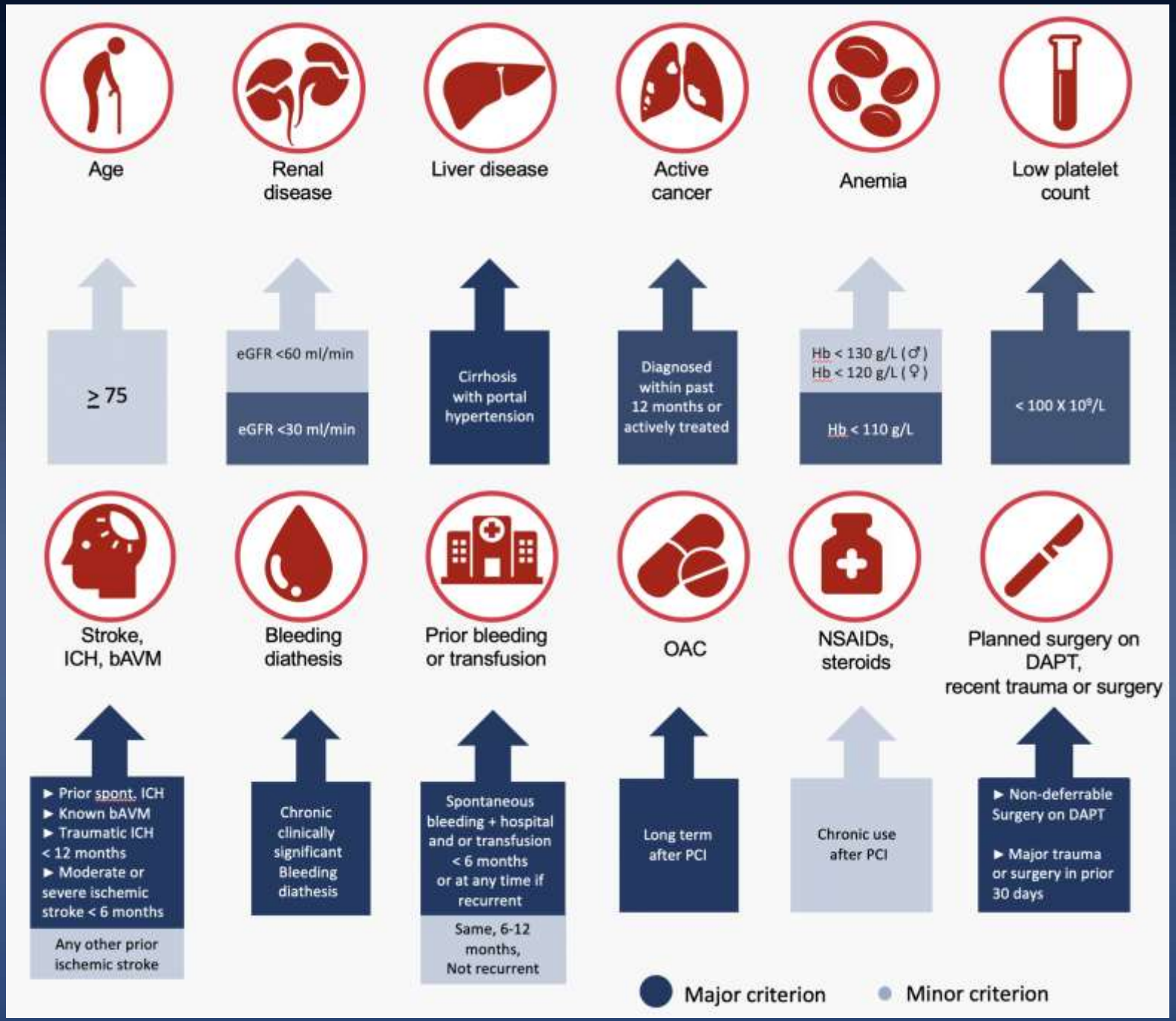
risk of BARC 3 or 5 bleeding of <4% at one year

and

risk of ICH < 1%

HBR status conferred if: ● 1 major criterion or ●● 2 minor criteria

ARC HBR

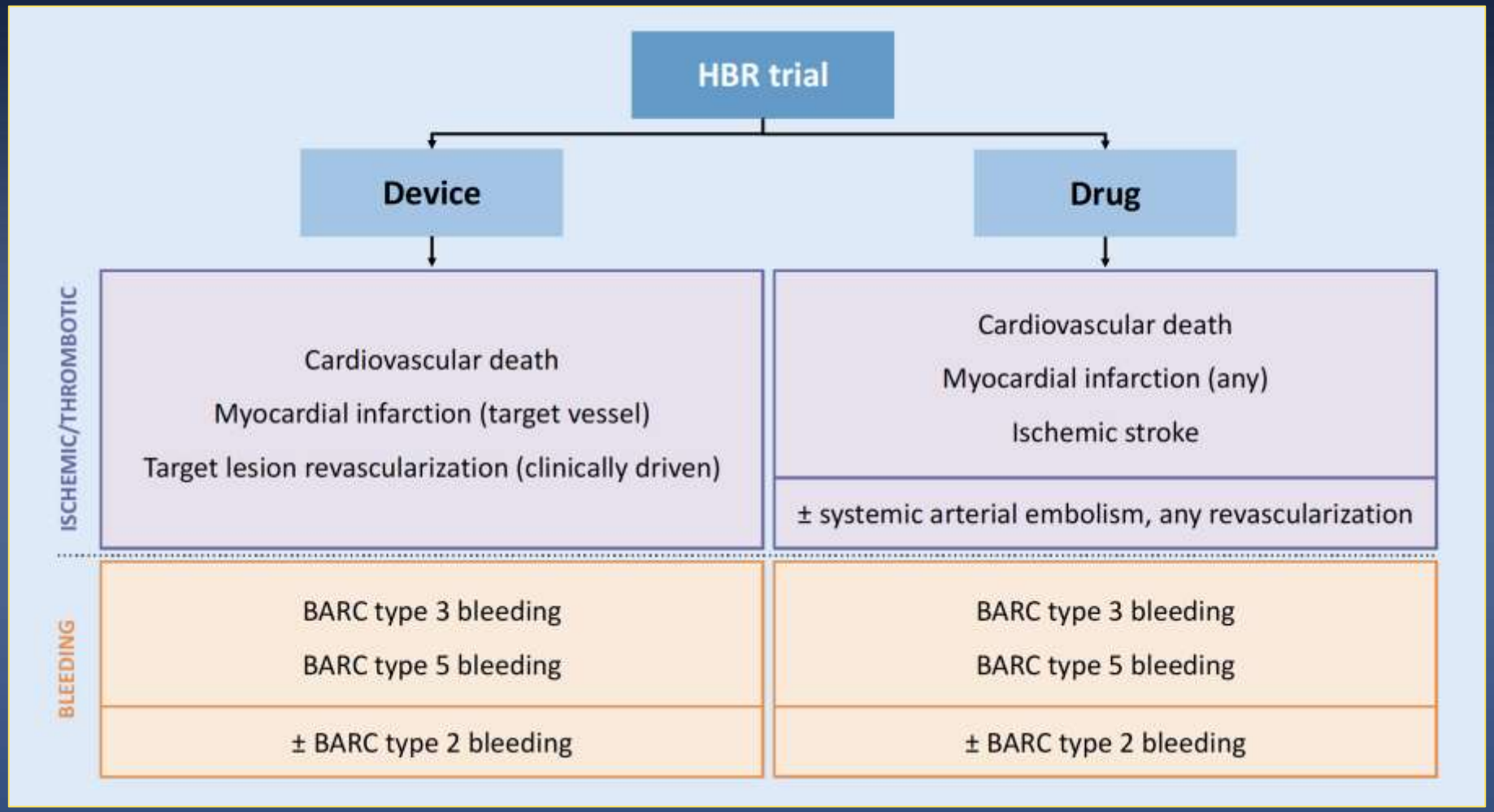

Age
≥ 75
Renal disease
eGFR <60 ml/min
eGFR <30 ml/min
Liver disease
Cirrhosis with portal hypertension
Active cancer
Diagnosed within past 12 months or actively treated
Anemia
Hb < 130 g/L (♂)
Hb < 120 g/L (♀)
Hb < 110 g/L
Low platelet count
< 100 X 10⁹/L
Stroke, ICH, bAVM
► Prior spont. ICH
► Known bAVM
► Traumatic ICH < 12 months
► Moderate or severe ischemic stroke < 6 months
Any other prior ischemic stroke
Bleeding diathesis
Chronic clinically significant Bleeding diathesis
Prior bleeding or transfusion
Spontaneous bleeding + hospital and or transfusion < 6 months or at any time if recurrent
Same, 6-12 months, Not recurrent
OAC
Long term after PCI
NSAIDs, steroids
Chronic use after PCI
Planned surgery on DAPT, recent trauma or surgery
► Non-deferrable Surgery on DAPT
► Major trauma or surgery in prior 30 days
Major criterion
Minor criterion

CVRF

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



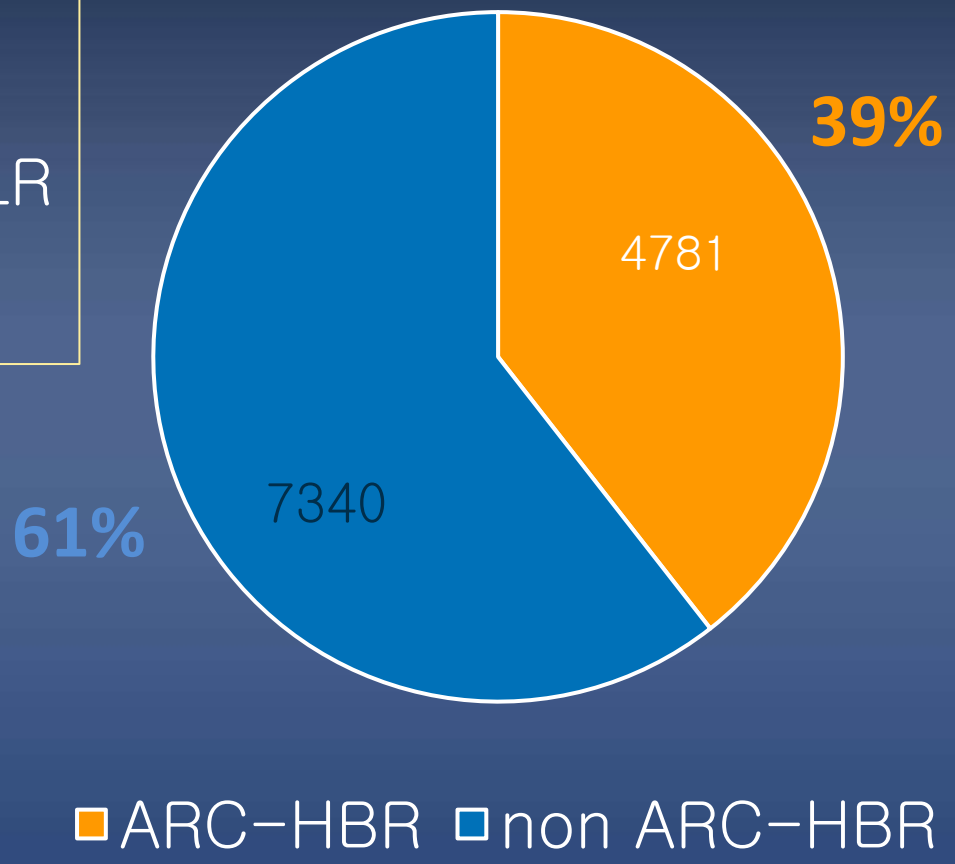
Capodanno D. et al. JACC 2020 (accepted for publication)

Validation of ARC-HBR criteria

Validation of ARC-HBR criteria in PCI Patients

Ueki Y et al. EuroIntervention 2020, published online

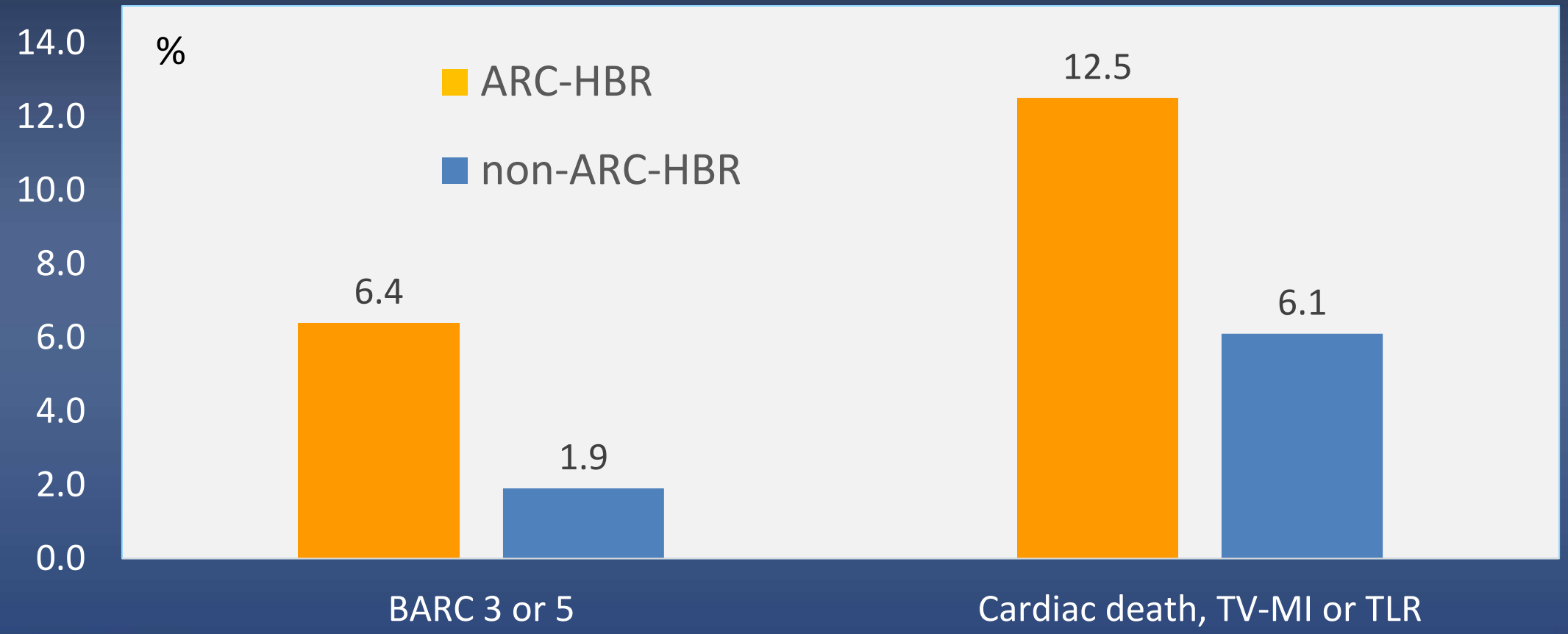
- 12121 patients in the Bern PCI registry
- Bleeding = BARC 3 or 5
- Ischemia = cardiac death, TV-MI, and TLR
- Follow-up for 1 year



Validation of ARC-HBR criteria in PCI Patients

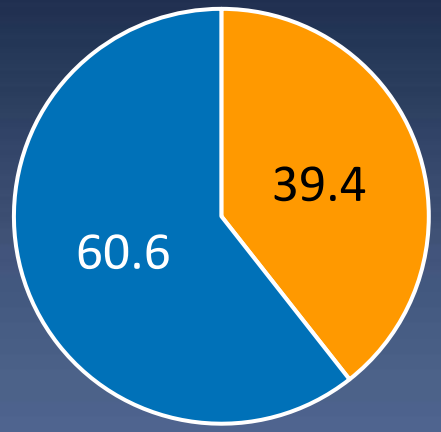
Ueki Y et al. EuroIntervention 2020, published online

Bleeding and ischaemic events

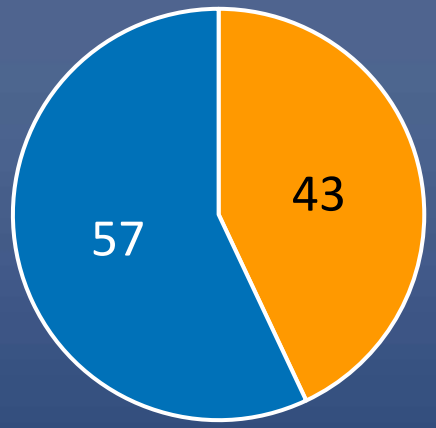


Prevalence of ARC-HBR patients in PCI registries

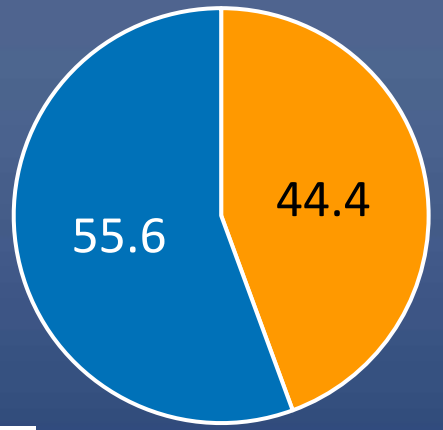
Ueki et al [2]



Natsuaki et al [1]



Cao et al [3]

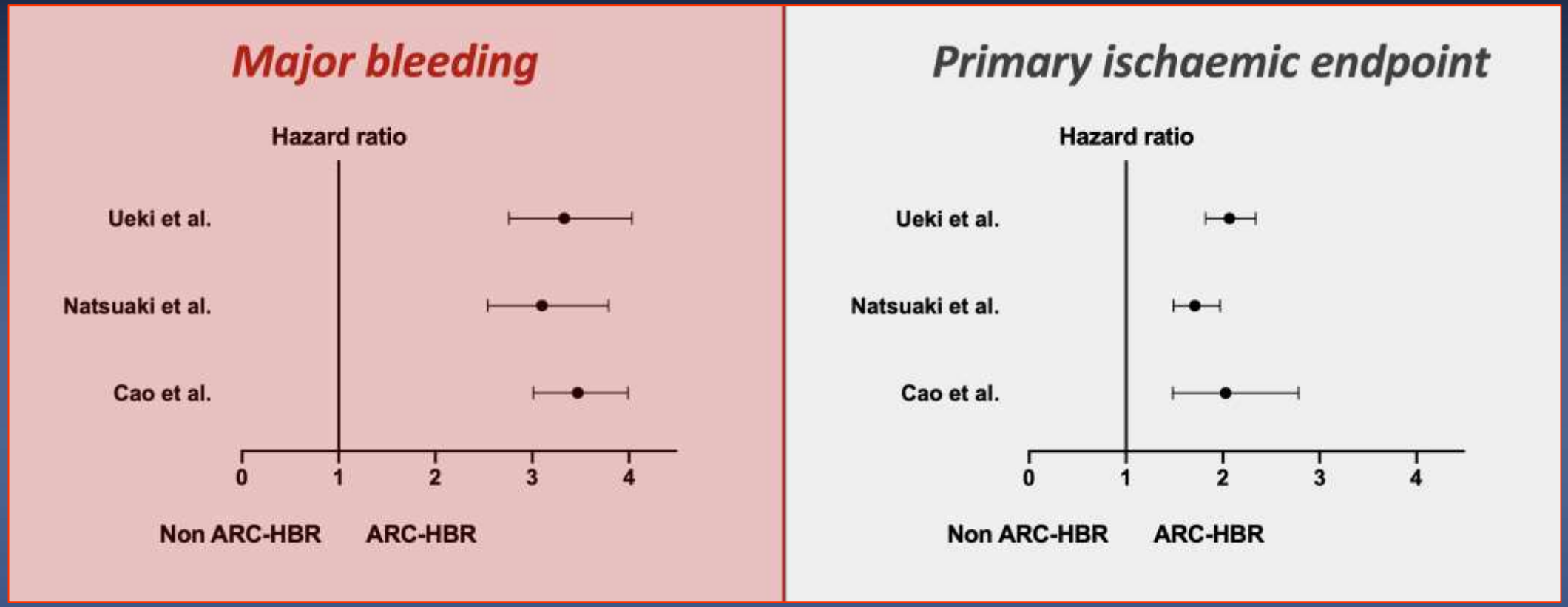


ARC HBR non-HBR

1. Circ Cardiovasc Interv. 2019
2. EuroIntervention 2020
3. JACC 2020 (in press)

Bleeding and ischaemic risks for HBR patients

Colleran R and Urban P. EuroIntervention 2020 (in press)



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

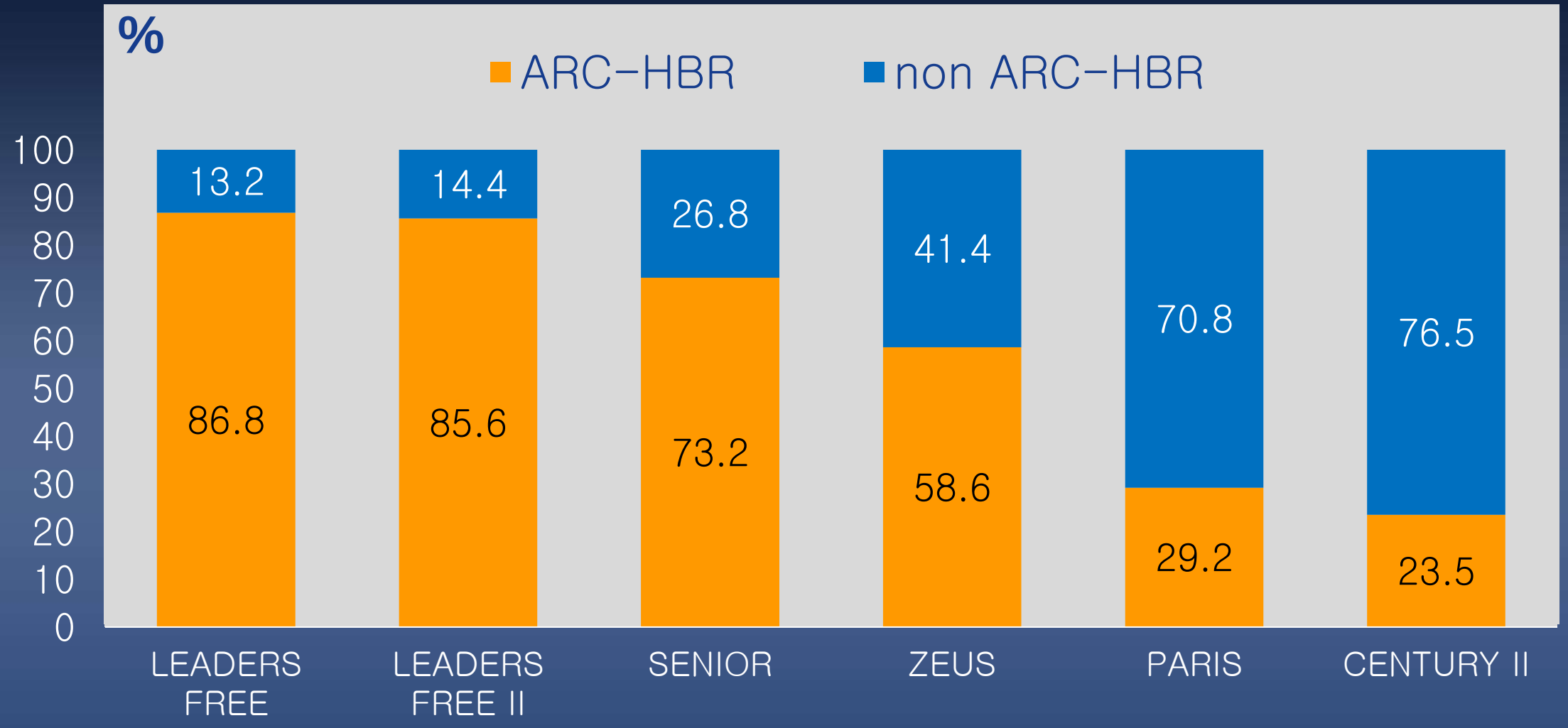
- Anemia
- Prior bleeding
- OAC
- Cancer
- Planned surgery
- Renal insufficiency
- etc…

- ACS
- Diabetes
- Prior MI
- Complex PCI
- Prior ST
- Renal insufficiency
- etc…

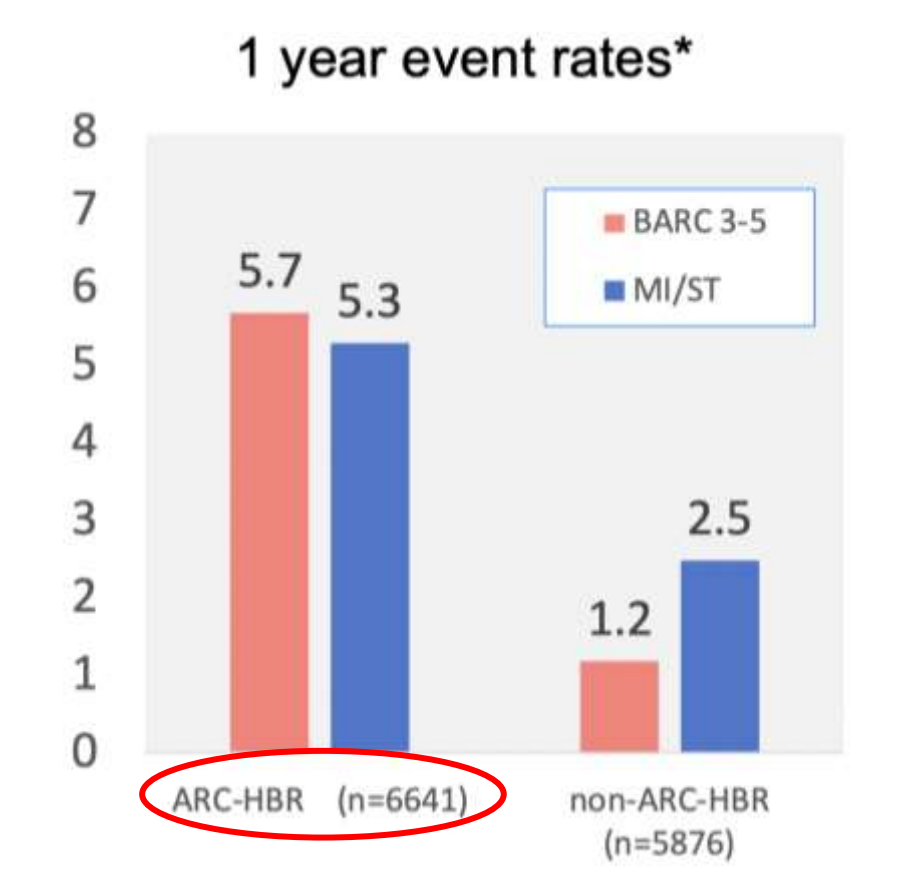
Assessing the trade-off

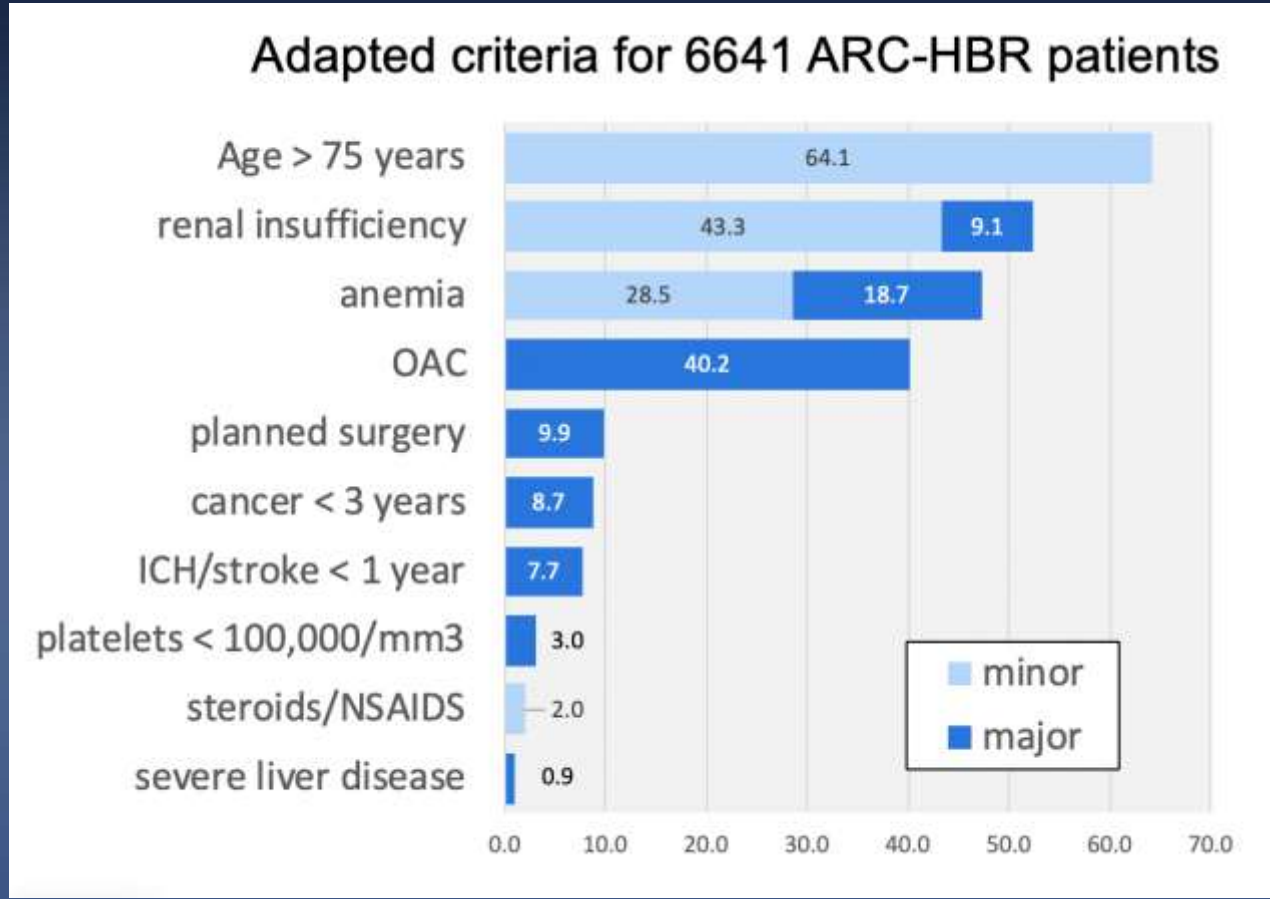
- We assessed 12517 patients enrolled in 6 PCI studies and focused on 6641 of them who satisfied at least 1 major or 2 minor ARC-HBR criteria
- After excluding peri-procedural events, we identified independent predictors of BARC 3-5 bleeding and MI/ST (myocardial infarction and/or stent thrombosis) using 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



Essential results



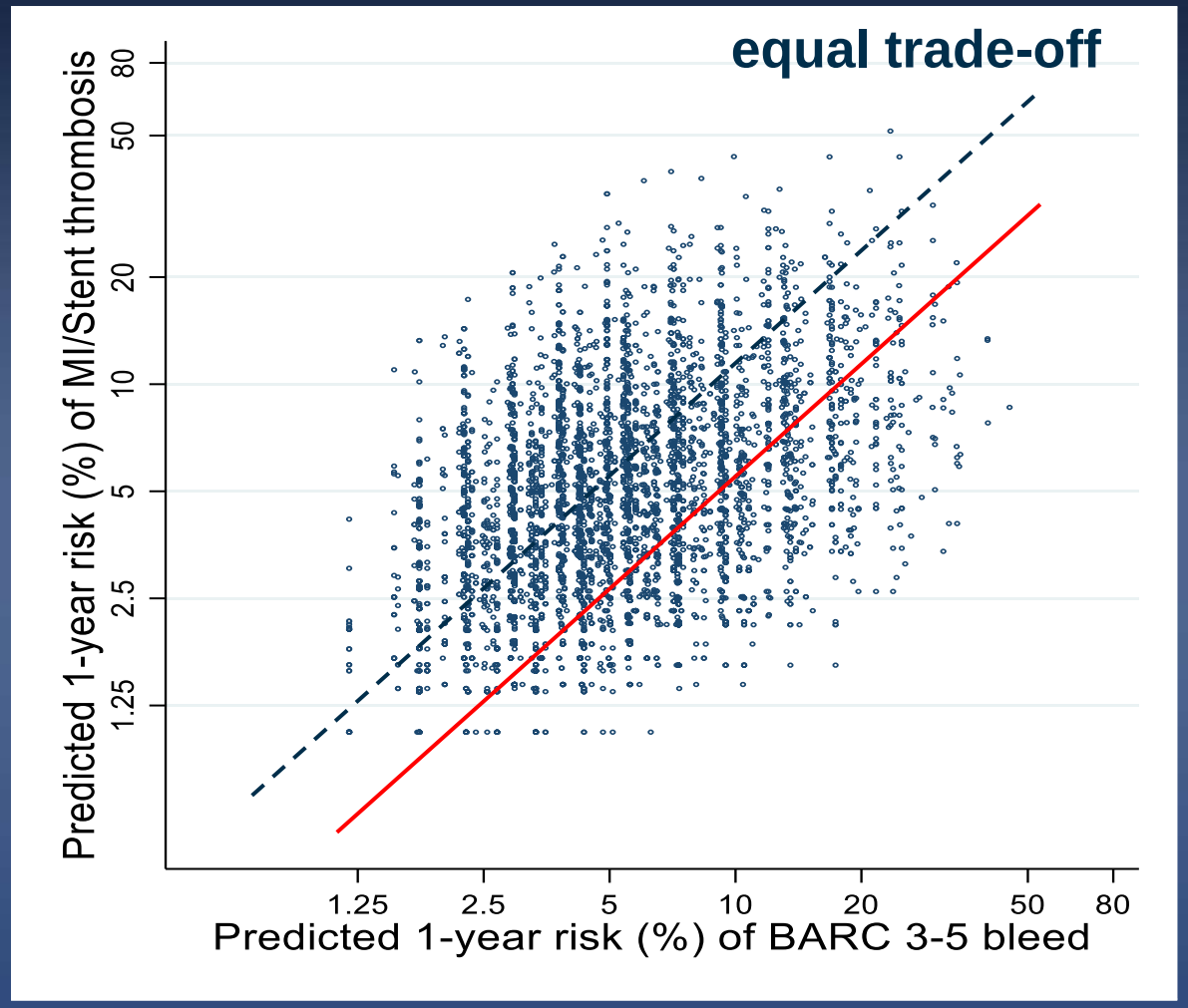


*peri-procedural events excluded

Multivariate predictors

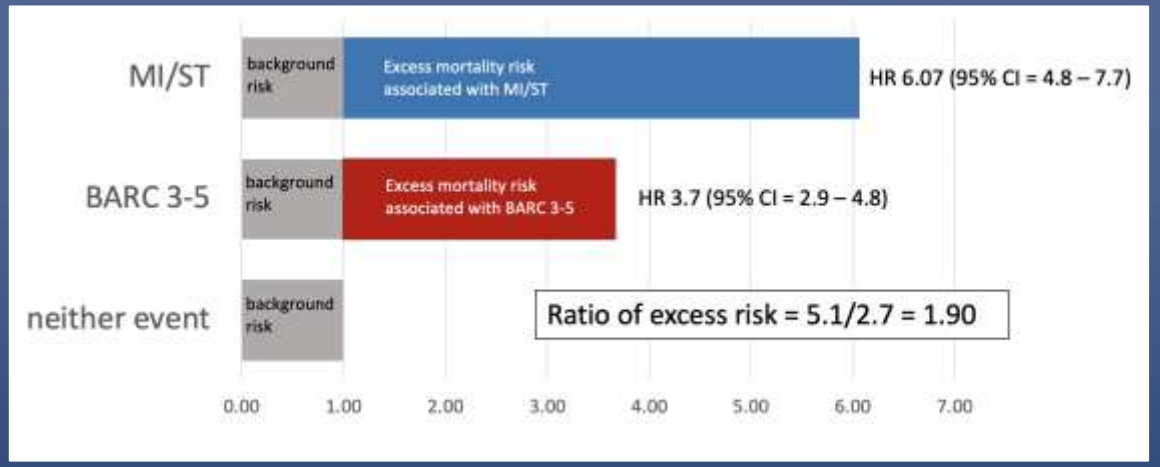
	BARC 3-5 bleeding		MI/ST	
	HR (95% CI)	P	HR (95% CI)	P
4 OAC at discharge	2.00 (1.62, 2.48)	<0.0001	-	
4 Liver disease, cancer or planned surgery	1.63 (1.27, 2.09)	0.0001	-	
4 Age ≥65 years	1.50 (1.08, 2.08)	0.01	-	
4 COPD	1.39 (1.05, 1.83)	0.02	-	
4 Prior myocardial infarction	-		1.89 (1.52, 2.35)	<0.0001
4 NSTEMI or STEMI presentation			1.82 (1.46, 2.25)	<0.0001
4 Diabetes	-		1.56 (1.26, 1.93)	<0.001
4 Bare metal stent	-		1.53 (1.23, 1.89)	<0.001
4 Hemoglobin (g/L)				
≥130	reference group	<0.0001	reference group	0.005
110-129	1.69 (1.30, 2.20)		1.27 (0.99, 1.63)	
<110	3.99 (3.06, 5.20)		1.50 (1.12, 1.99	
4 Estimated GFR (mL/min)				
≥ 60	reference group	0.02	reference group	0.001
30-59	0.99 (0.79, 1.24)		1.30 (1.03, 1.66)	
<30	1.43 (1.04, 1.96)		1.69 (1.20, 2.37)	
4 Current smoker	1.47 (1.08, 1.99)	0.01	1.48 (1.09, 2.01)	0.009
4 Complex procedure	1.32 (1.07, 1.61)	0.008	1.50 (1.21, 1.85)	<0.001
	C-statistic=0.68		**C-statistic=0.69**	
Validation: ARC-HBR ONYX-ONE patients	C-statistic=0.74		C-statistic=0.74	

Predicted risks for 6641 individual patients

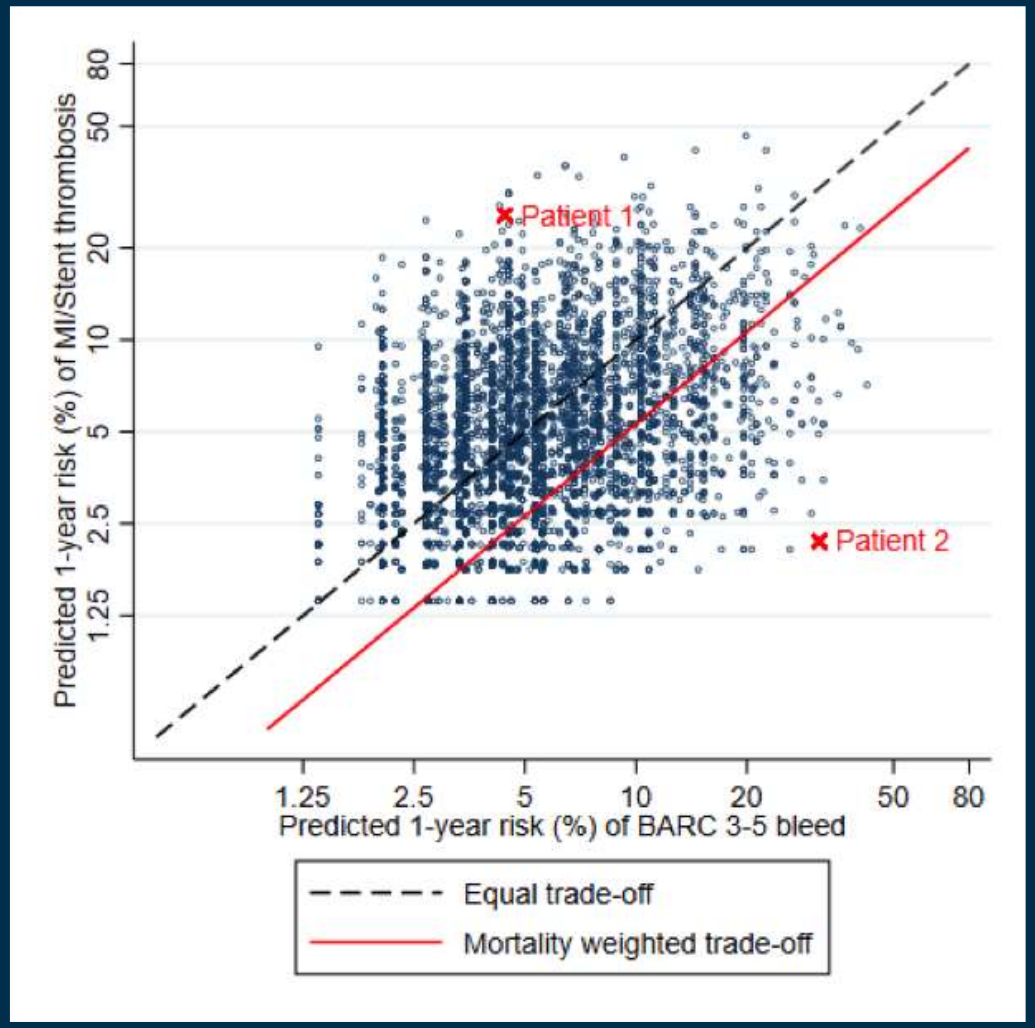


mortality-weighted equal trade-off

Excess mortality with MI/ST and BARC 3-5



Illustrative HBR cases



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