Identification of HBR patients

the ARC-HBR project

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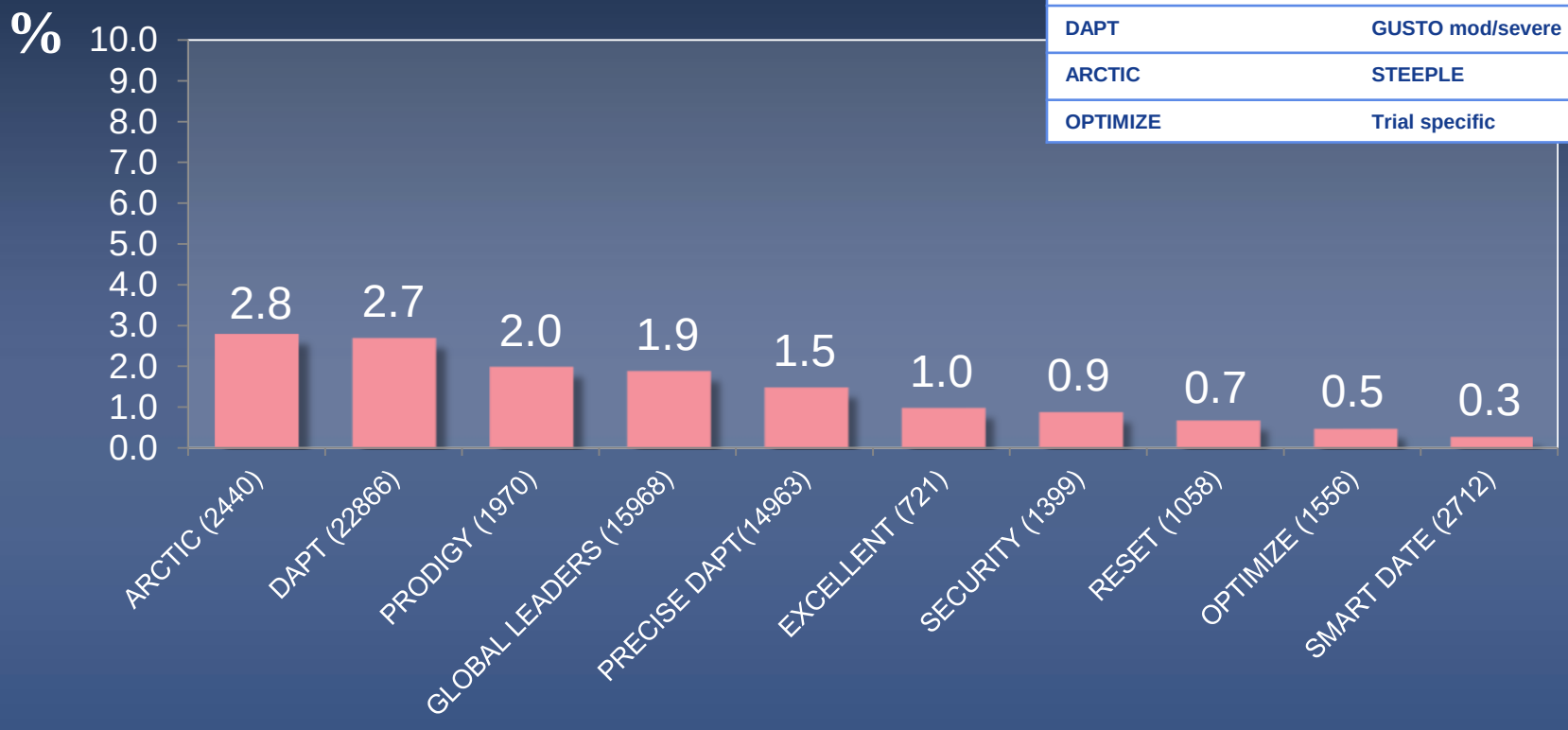
Geneva, Switzerland

Conflicts of Interest

- I am a consultant for Biosensors
- I have received honoraria as a speaker, and/or for DSMB or CEC activities from: Edwards Life Sciences, Abbott Vascular and Terumo
- I am medical co-director and shareholder of CERC, a CRO based in Massy, France

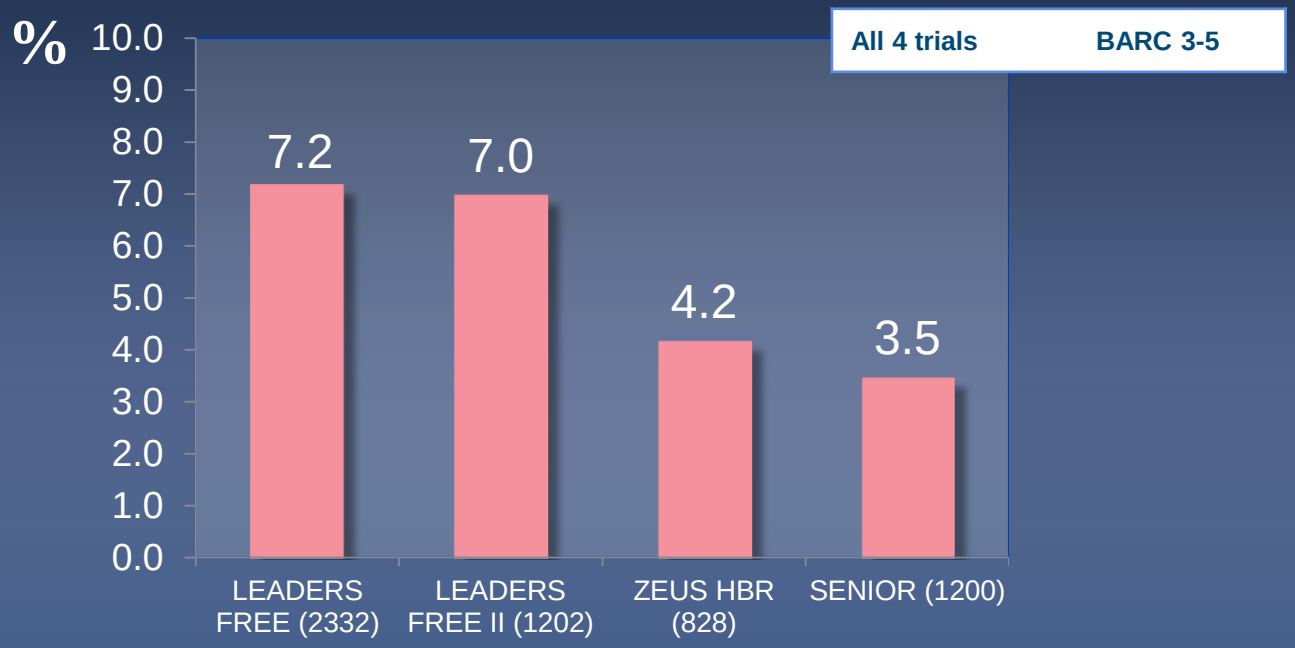
1 year bleeding rates in DAPT trials

PRODIGY, SECURITY, SMART- DATE, GLOBAL LEADERS	BARC 3-5
RESET, EXCELLENT, PRECISE DAPT	TIMI major/minor
DAPT	GUSTO mod/severe
ARCTIC	STEEPLE
OPTIMIZE	Trial specific



HBR patients excluded or under-represented

1 year bleeding rates in trials of patients selected for their increased bleeding risk



Identifying patients at High Bleeding Risk (HBR)

- LEADERS FREE
- What inclusion criteria do HBR trials use?
- Expert assessment of bleeding risk
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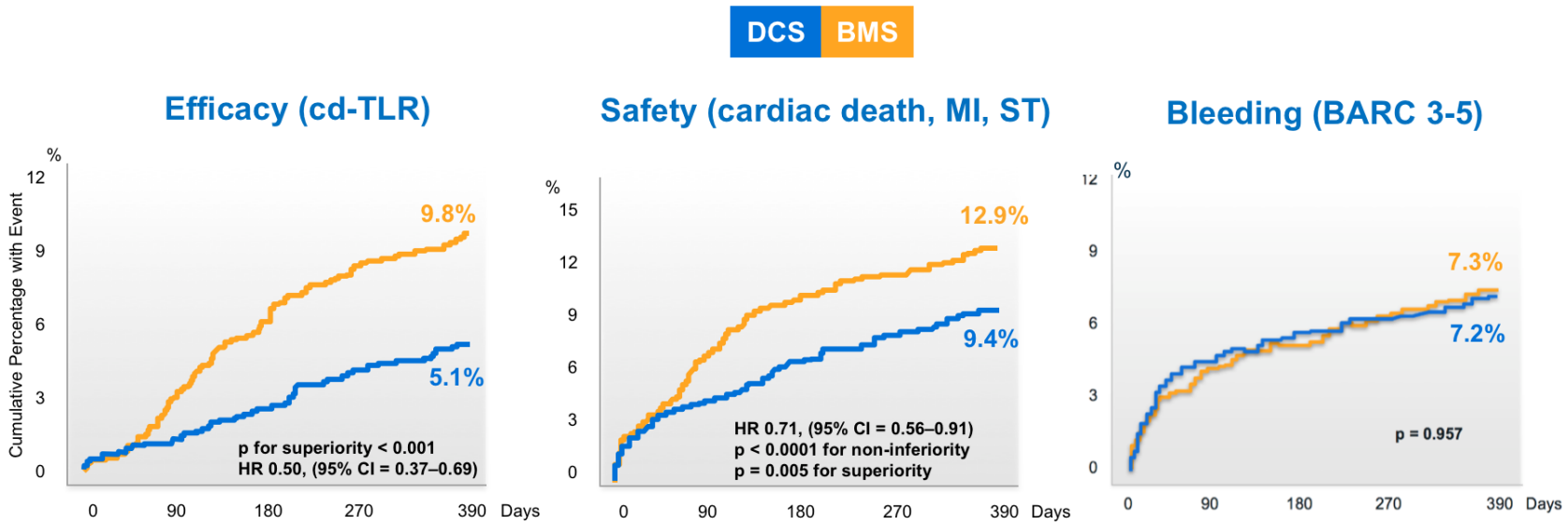
LEADERS FREE

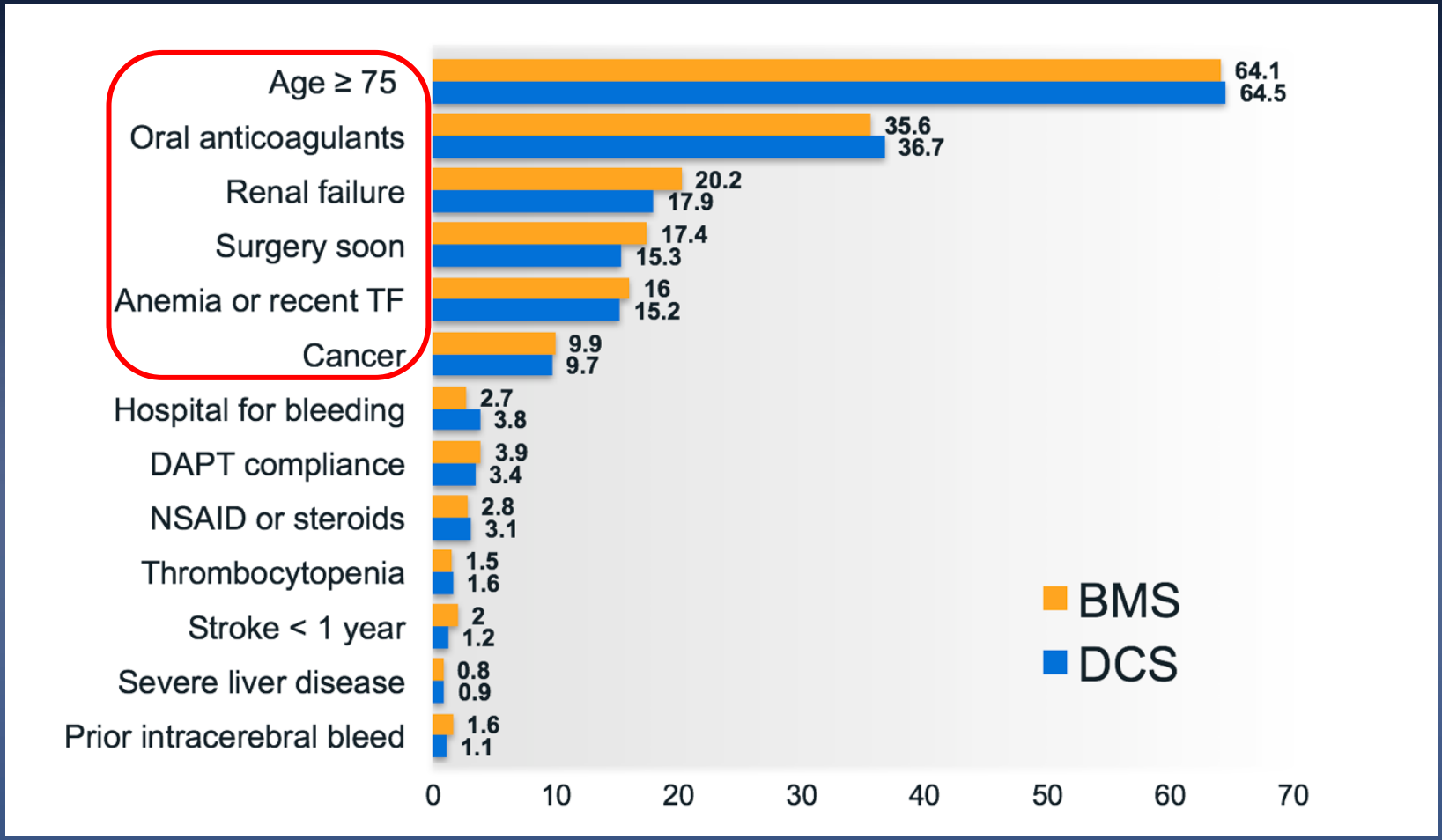
2466 HBR patients randomised to BA-9 DCS or BMS
One month DAPT only for all

Primary Endpoints and Major Bleeding at 1 Year

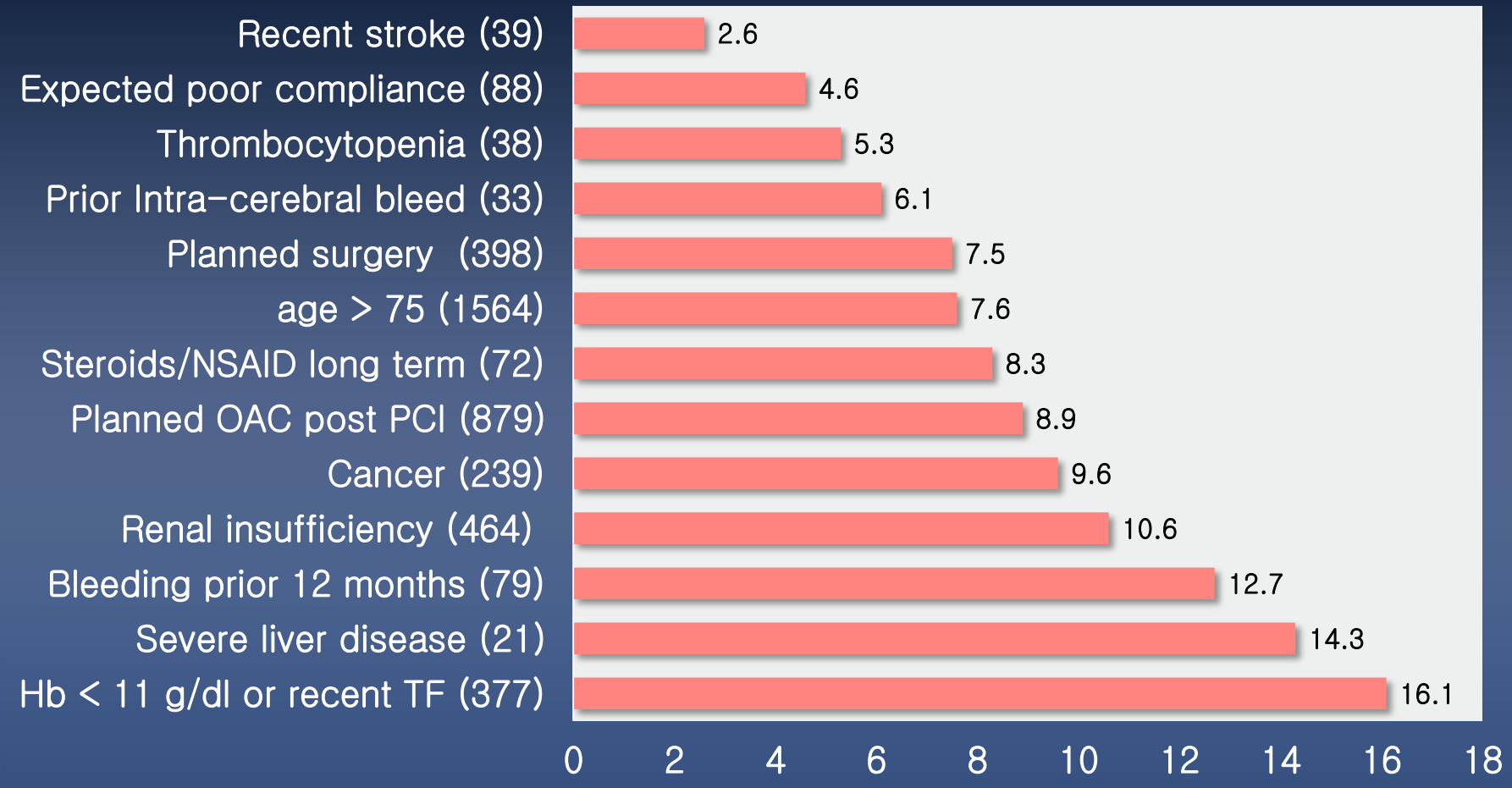


Urban P et al. N Engl J Med 2015;373:2038-47

Inclusion Criteria Applied (1.7 criteria / patient)



First major bleeding bleeding event (BARC 3-5) according to inclusion criteria (1 year FU)



Biosensors, data on file

LEADERS FREE

*DCS and BMS analysed together, periprocedural (<48h) events excluded

CVRF

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10 ongoing trials of ≤ 3 months DAPT for HBR patients

	Trial	stent	type	limus kinetics	patients	experimental arm DAPT	control arm	Status September 2018
randomized	ONYX ONE	Resolute Onyx DES vs. BioFreedom DCS	Permanent polymer vs. polymer-free	slow vs. fast	2000 HBR	1 month	1 month	follow-up
	COBRA-REDUCE	Cobra PzF	Polyzene-F nanocoating	na	840 on AVK or NOAC	2 weeks	EES or R-ZES & 6 months DAPT	enrolling
	MASTER DAPT	Ultimaster SES	2nd G BD polymer	slow	4300 HBR	1 month	guidelines	enrolling
	TARGET SAFE	Firehawk	Biodegradable polymer	slow	1700 HBR	1 months DAPT	6 months DAPT	planned
single arm	EVOLVE SHORT DAPT	Synergy EES	2nd G BD polymer	slow	2000 HBR	3 months	single arm trial	follow-up
	POEM	Synergy EES	2nd G BD polymer	slow	1023 HBR	1 month	single arm trial	enrolling
	XIENCE 90 (Xience Short DAPT)	Xience EES	Permanent polymer	slow	2000 HBR	3 months	single arm trial	enrolling
	XIENCE Global 28	Xience EES	Permanent polymer	slow	800 HBR	1 month	single arm trial	enrolling
	ONYX ONE CLEAR	Resolute Onyx DES	Permanent polymer	slow	800 HBR	1 month	Single arm trial	enrolling
	LEADERS FREE III	CoCr BioFreedom	Polymer-free	fast	1200 HBR	1 month	DCS arm of LEADERS FREE	enrolling

Inclusion criteria in HBR trials (completed & ongoing)

	LEADERS FREE I, II, and III	ZEUS HBR*	SENIOR	MASTER DAPT	ONYX ONE	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	●			●	●					●	
Prior stroke/ICH	●			●	●	●	●	●	●	●	
Liver disease	●				●					●	
NSAIDs/steroids	●	●		●	●	●				●	
BLEEDING SCORE				●		●					
Female and/or ACS						●					
CHF & LVEF 30-50%						●					
Experimental DAPT	1 month	1 month	1 or 6 months	1 month	1 month	1 month	3 months	3 months	1 month	1 month	2 weeks

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Bleeding post-PCI: expert opinion vs. the PRECISE-DAPT & PARIS scores

Philip Urban, C. Michael Gibson, Usman Baber, Samuel Copt, Mitch Krucoff, Roxana Mehran, Sarah Sadozai Slama, Marco Valgimigli, and Marie-Claude Morice

- Random selection of 100 patients enrolled in the LEADERS FREE trial and followed for 1 year (days 3-365)
  - 20 with a major bleeding episode (BARC 3 or 5)
  - 80 without a major bleeding episode
- Selection of 5 experienced interventionists in 5 countries
  - France
  - Japan
  - Korea
  - Switzerland
  - USA

Expert clinical bleeding prediction

- Jean-Louis Bonnet (F)
- Philippe Gaspard (F)
- Martine Gilard (F)
- Jean-Pierre Monassier (F)
- Thomas Hovasse (F)

- Ken Kozuma (J)
- Yuji Ikari (J)
- Yoshihisa Nakagawa (J)
- Masahiro Natsuaki (J)
- Hiroki Shiomi (J)

- Soon-Jun Hong (K)
- Young-Hoon Jeong (K)
- Moo-Hyun Kim (K)
- Keun-Ho Park (K)
- Kyung-Woo Park (K)

- Stephane Cook (CH)
- Raban Jaeger (CH)
- Giovanni Pedrazzini (CH)
- Thomas Pilgrim (CH)
- Hans Rickli (CH)

- Usman Baber (US)
- Emmanuel Brilakis (US)
- Bimmer Claessen (US)
- Timothy Henry (US)
- Binita Shah (US)

Expert clinical bleeding prediction

Each expert was asked to score 20 patients for their 1 year post-discharge bleeding risk

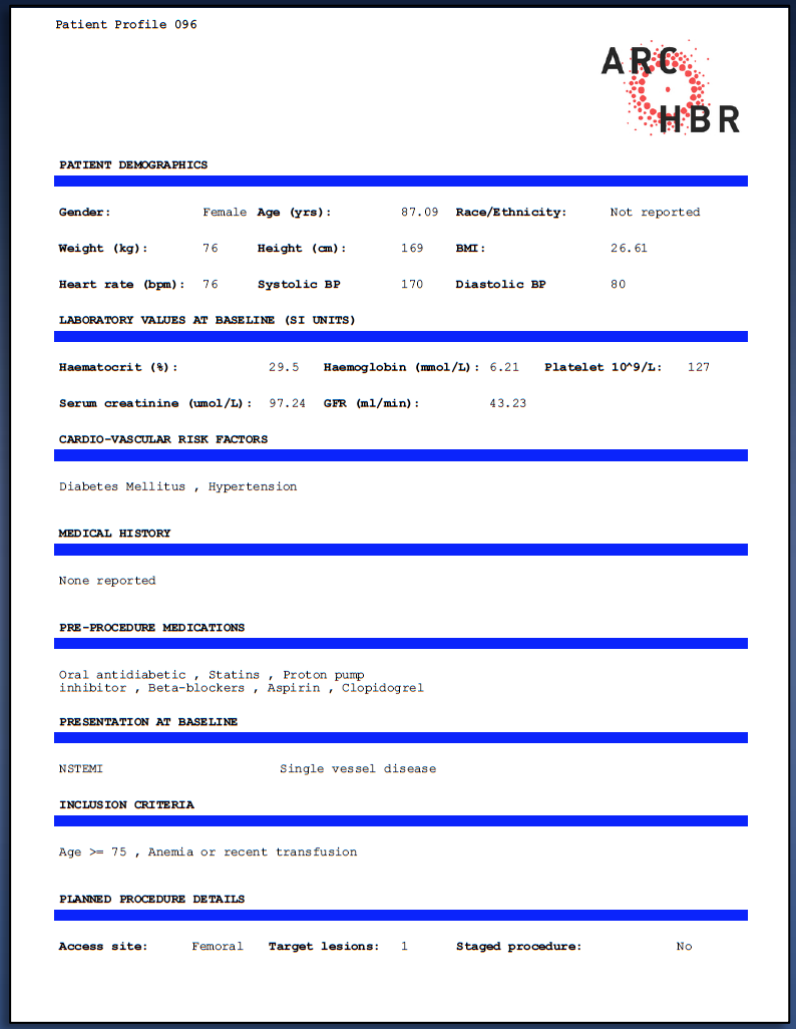
- Low (<3%)
- Intermediate (3-7%)
- High (>7%)

The bleeding rate between days 3 and 365 in LEADERS FREE was 5.95% (95% CI= 5.01-6.90)

Expert clinical bleeding prediction

Available data

- Baseline demographics
- Lab values (Hb, thrombocytes, creatinine clearance)
- Medical history and CVRF
- Pre-procedure medication
- LEADERS FREE trial inclusion criteria applied
- Number of diseased vessels
- PCI procedure (vascular access site, number of target lesions, planned staging)



Patient Profile 096

ARC HBR

PATIENT DEMOGRAPHICS

Gender:	Female	**Age (yrs):**	87.09	**Race/Ethnicity:**	Not reported
Weight (kg):	76	**Height (cm):**	169	**BMI:**	26.61
Heart rate (bpm):	76	**Systolic BP**	170	**Diastolic BP**	80

LABORATORY VALUES AT BASELINE (SI UNITS)

Haematocrit (%):	29.5	**Haemoglobin (mmol/L):**	6.21	**Platelet 10^9/L:**	127
Serum creatinine (umol/L):	97.24	**GFR (ml/min):**	43.23		

CARDIO-VASCULAR RISK FACTORS

Diabetes Mellitus , Hypertension

MEDICAL HISTORY

None reported

PRE-PROCEDURE MEDICATIONS

Oral antidiabetic , Statins , Proton pump inhibitor , Beta-blockers , Aspirin , Clopidogrel

PRESENTATION AT BASELINE

NSTEMI Single vessel disease

INCLUSION CRITERIA

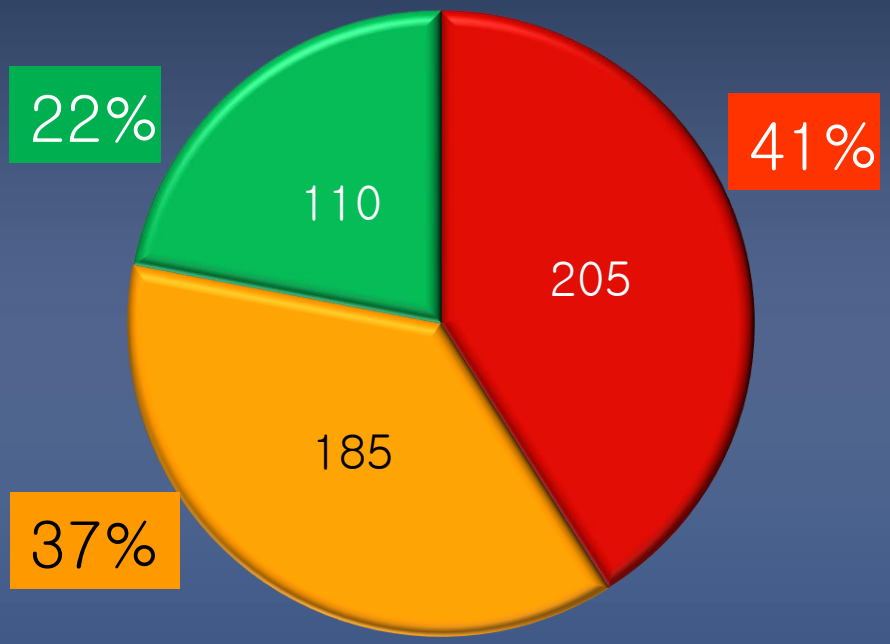
Age >= 75 , Anemia or recent transfusion

PLANNED PROCEDURE DETAILS

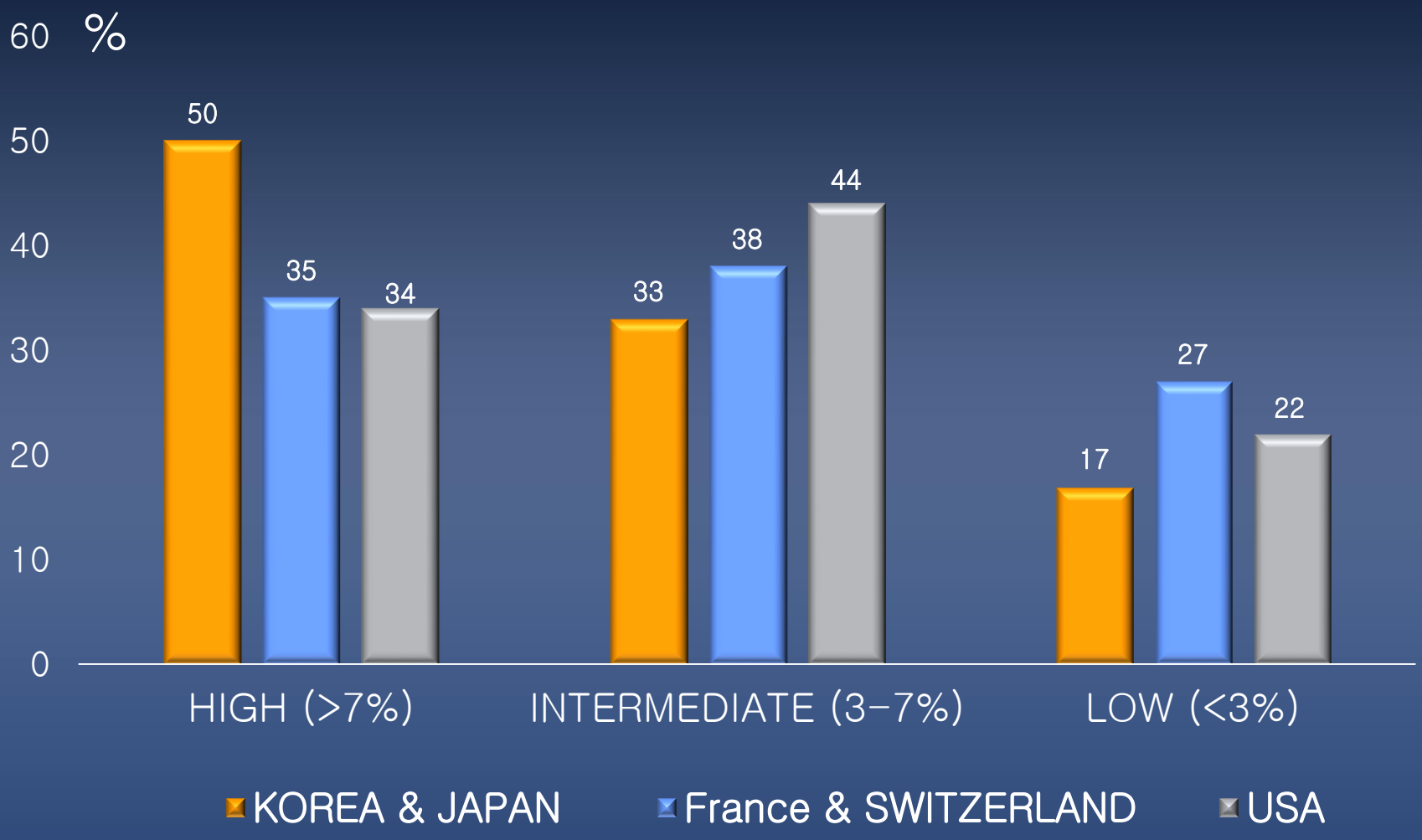
Access site:	Femoral	**Target lesions:**	1	**Staged procedure:**	No

Expert clinical bleeding prediction

500 scores for 100 cases

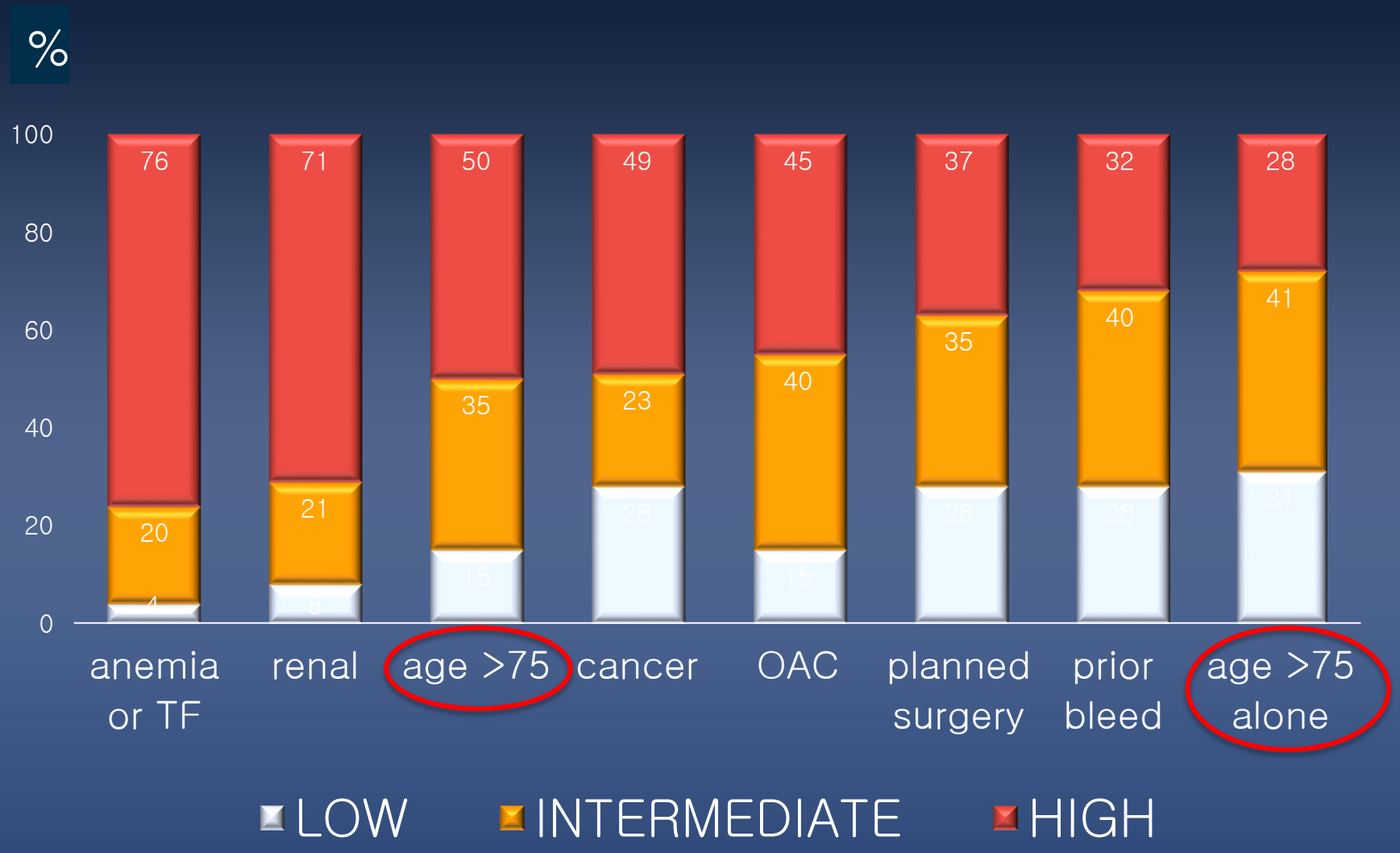


Scoring per region

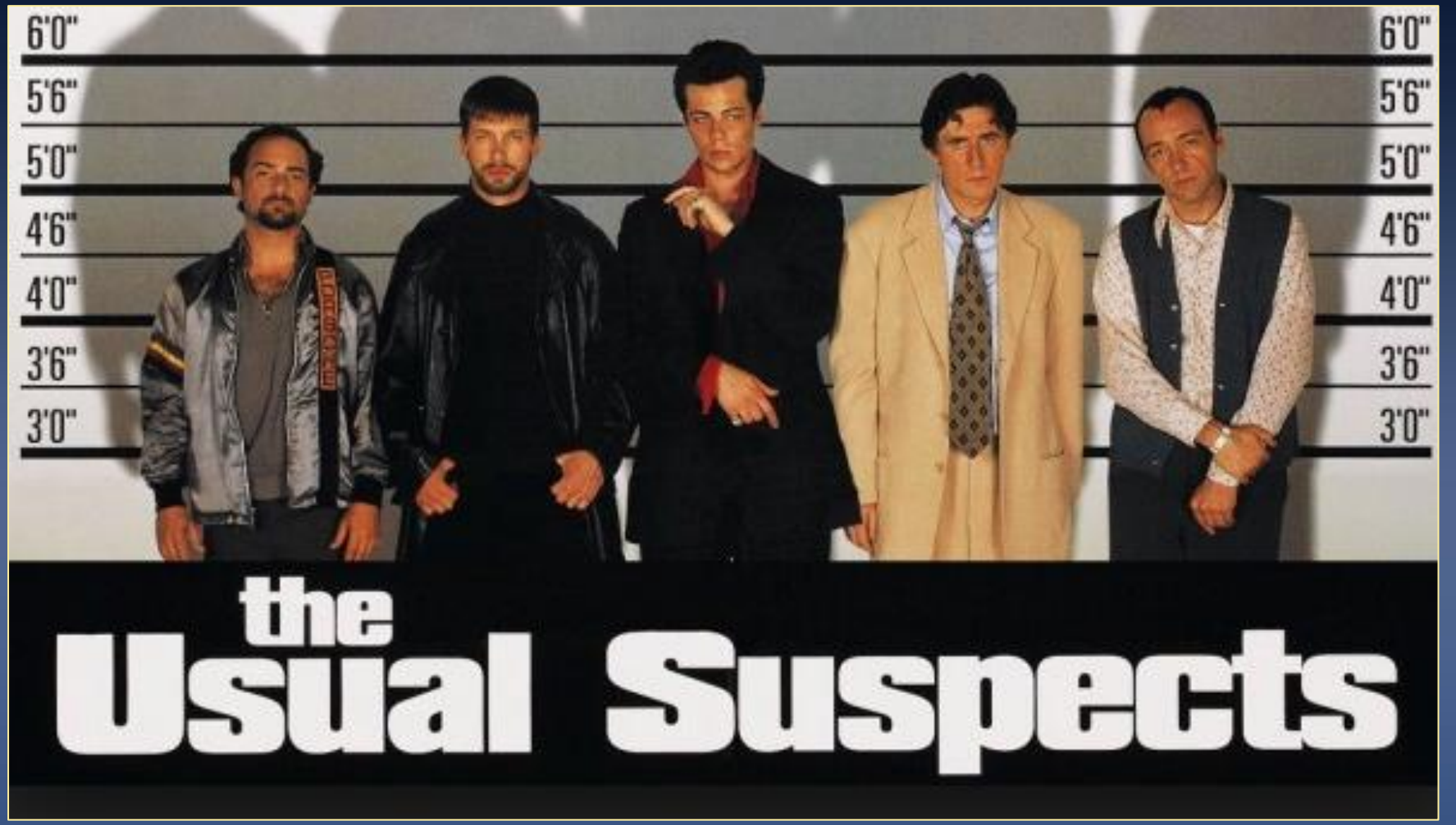


The same 100 patients were graded in each of the 5 countries

LEADERS FREE inclusion criteria vs. expert scoring



1.7 inclusion criteria/patient


6'0"
5'6"
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4'6"
4'0"
3'6"
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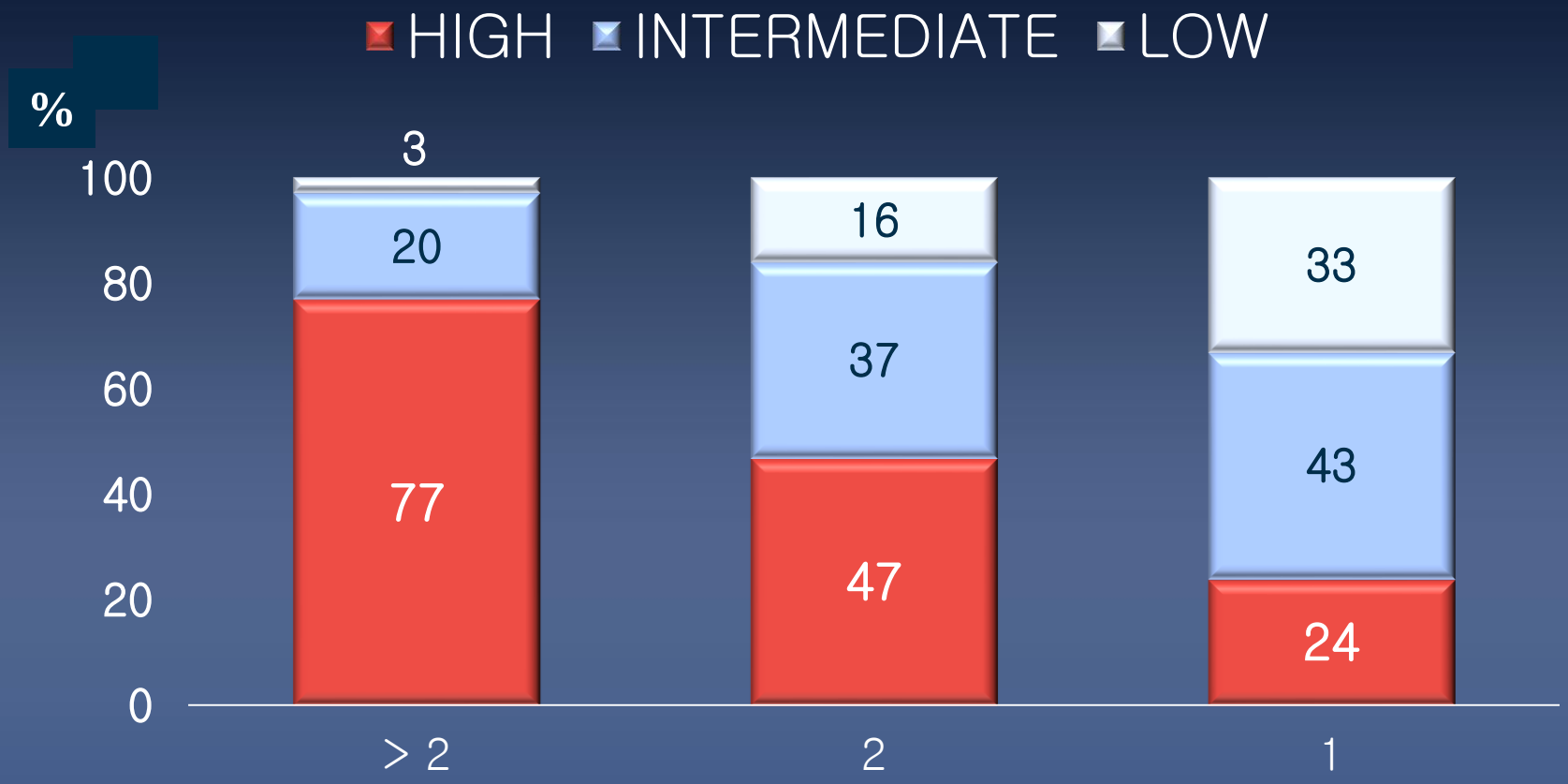
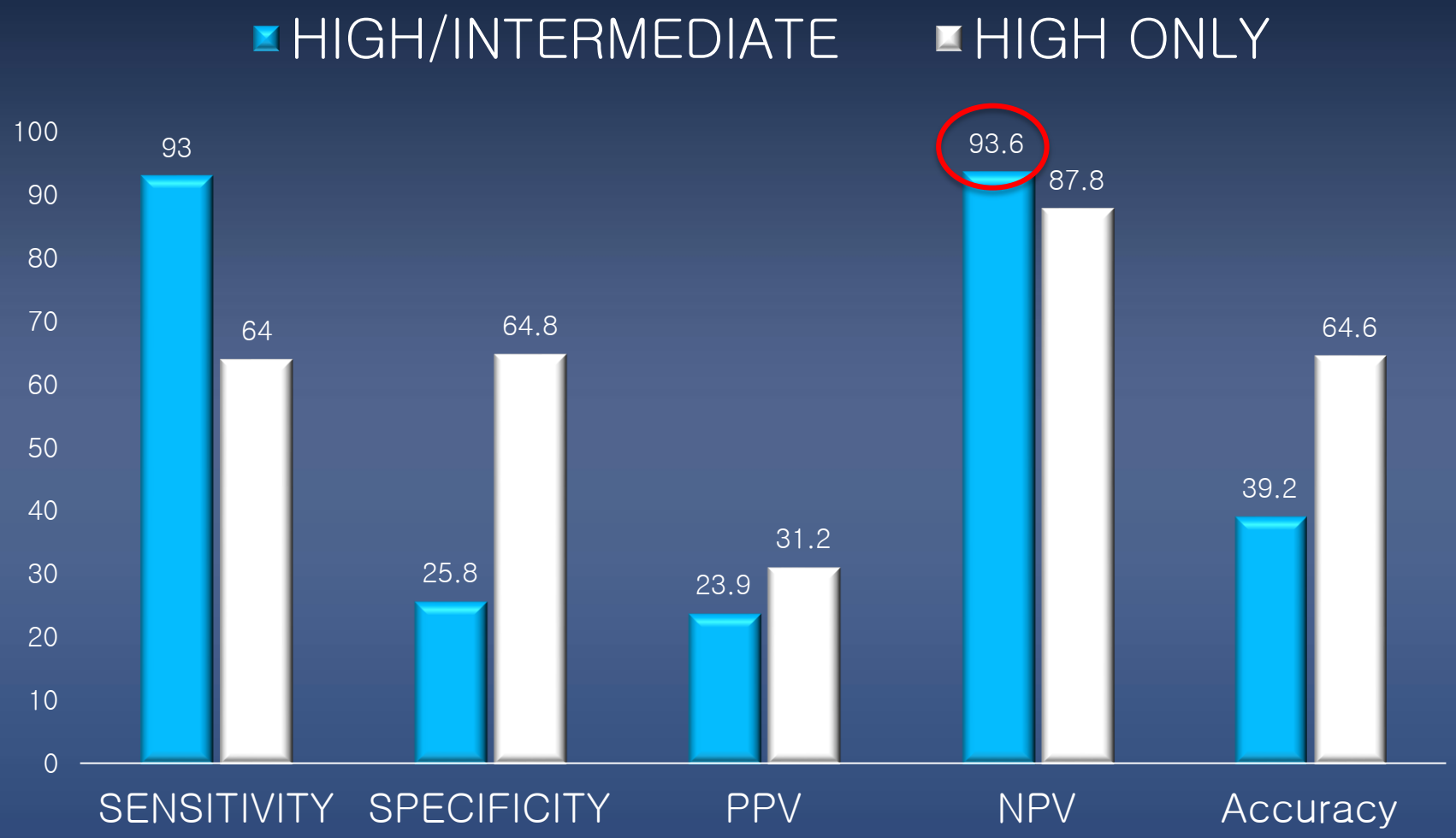
the
Usual Suspects

Number of LF inclusion criteria vs. scoring



Nb of patients	15	39	46

Sensitivity & specificity for BARC 3–5



The “lower risk HBR”

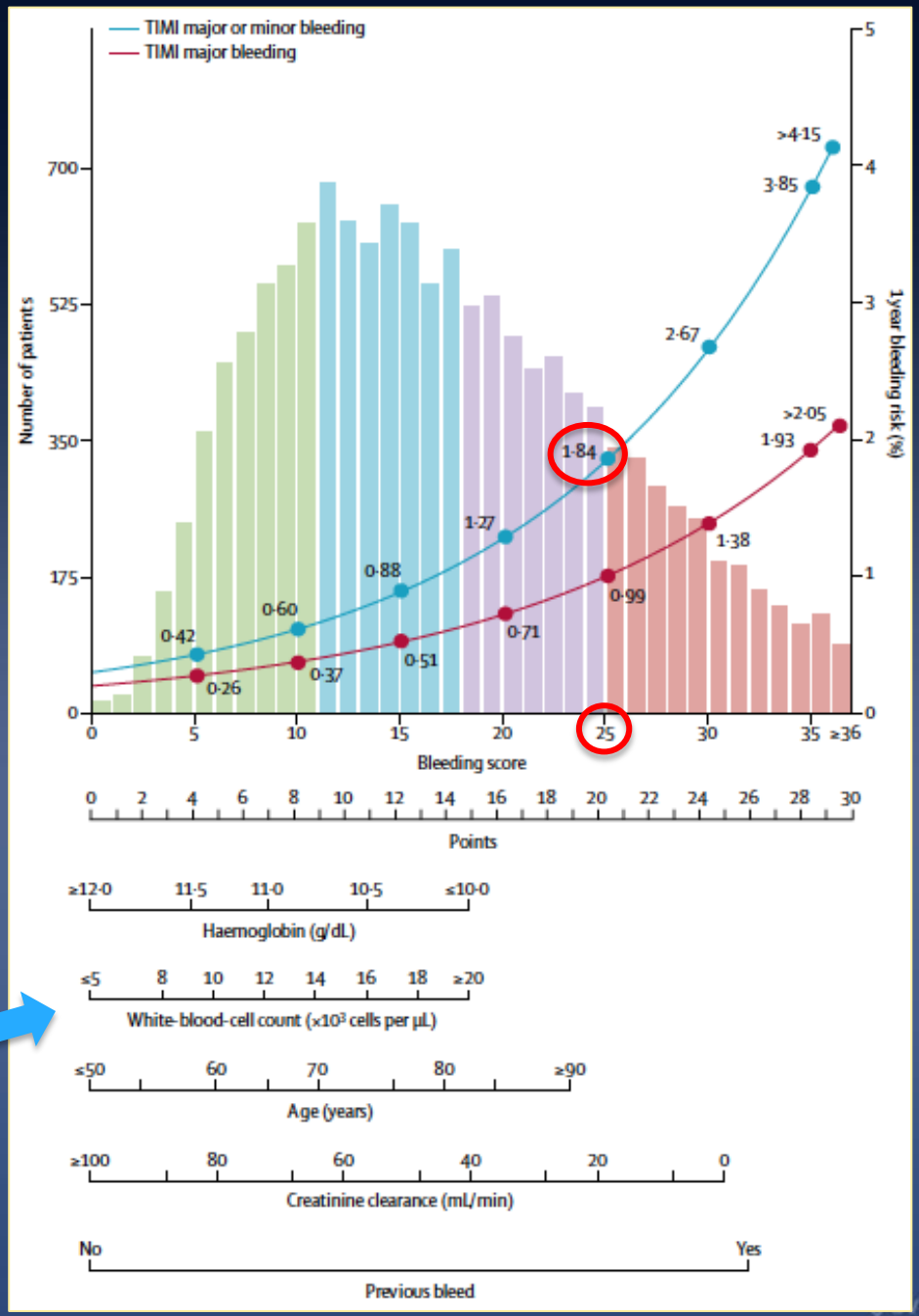
Experts vs. scores

- PRECISE DAPT

- PARIS

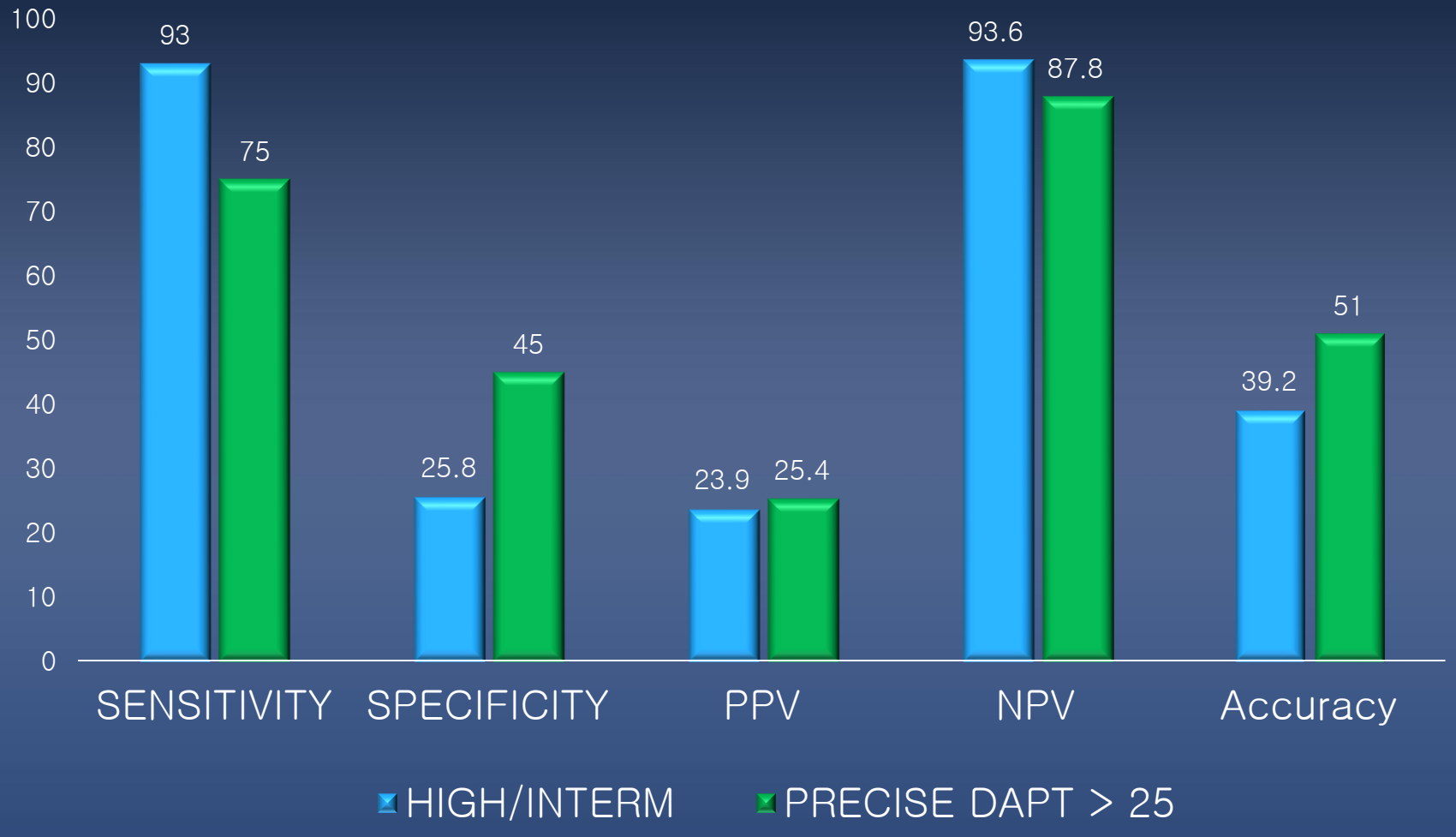
PRECISE-DAPT

Costa F et al Lancet 2017; 389: 1025–34



C stat for TIMI major or minor = 0.73

Sensitivity & specificity for BARC 3–5: PRECISE DAPT vs. experts



Based on the alternative version for PRECISE DAPT, without white cell counts

Experts vs. scores

- PRECISE DAPT

- PARIS

PARIS score Baber U et al. JACC 2016; 67: 2224–34

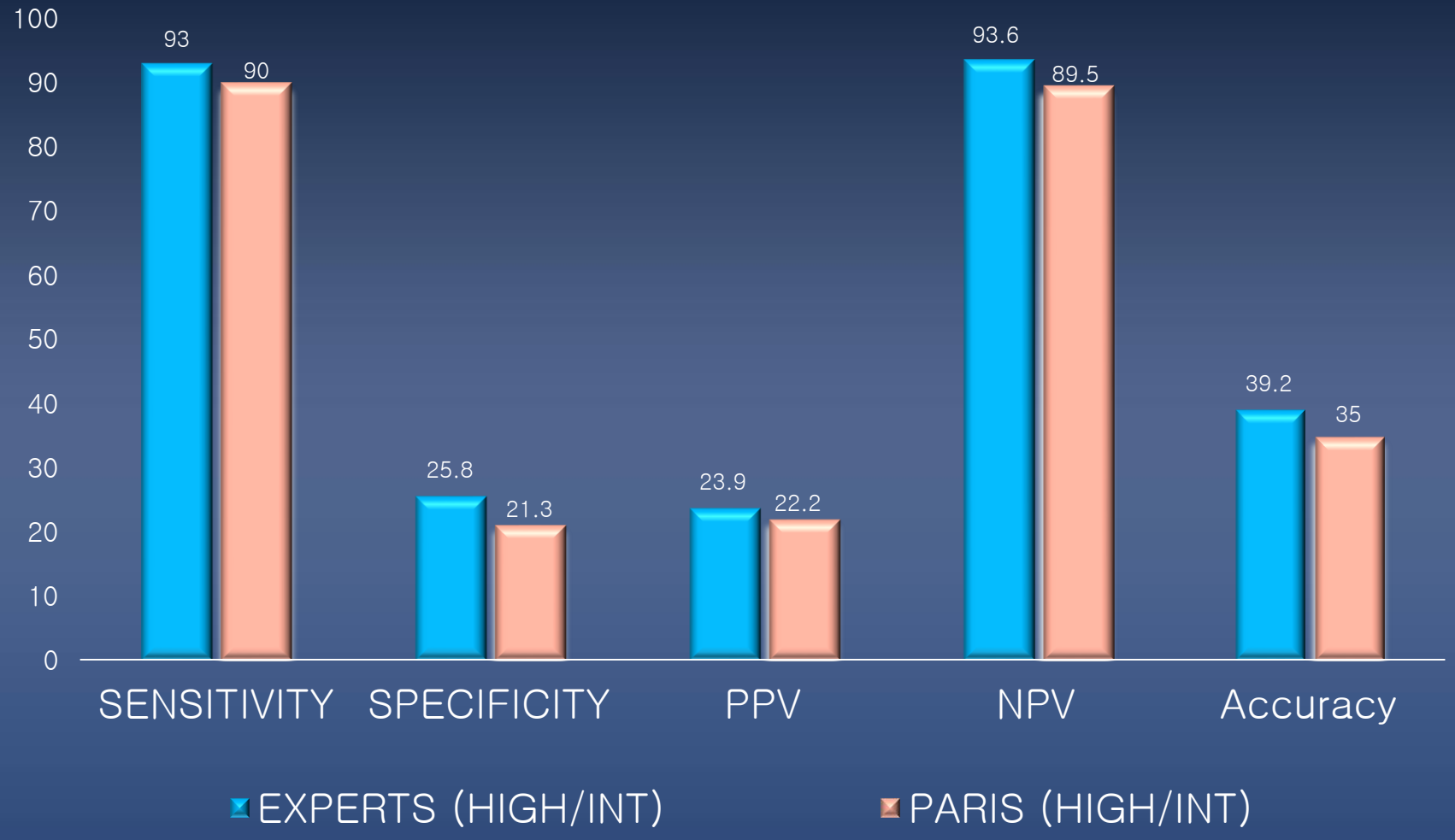
TABLE 4 Integer Risk Score for Major Bleeding

Parameter	Score
Age, yrs	
<50	0
50-59	+1
60-69	+2
70-79	+3
≥80	+4
BMI, kg/m^2	
<25	+2
25-34.9	0
≥35	+2
Current smoking	
Yes	+2
No	0
Anemia	
Present	+3
Absent	0
CrCl <60 ml/min	
Present	+2
Absent	0
Triple therapy on discharge	
Yes	+2
No	0

Registry
4190 all-comers
Successful PCI

C stat 0.72

Sensitivity & specificity for BARC 3-5 PARIS vs. experts



Experts vs. scores

- Even experienced interventionists have only limited ability to predict major bleeding after PCI
- Within a group of HBR patients, experts appear to be best at identifying those with a lower bleeding risk
- When considering the NPV for HBR patients, experts are only marginally superior to both PRECISE-DAPT and to PARIS

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The ARC Focus Group on HBR

- In accordance with the ARC Charter (JACC Cardiovasc Interv 2011; 4: 595–6)
- 31 experts from Europe, USA, Japan and Korea
- Non-profit initiative, sponsored by 22 pharma and device companies
- Organised by CERC (Massy, France)
- Two meetings in 2018 (Washington in April and Paris in October)
- Literature-based pragmatic consensus definition of HBR criteria

ACC INTERVENTIONAL SCIENTIFIC COUNCIL: NEWS AND VIEWS

The Academic Research Consortium Governance Charter

Mitchell W. Krucoff, MD,* Roxana Mehran, MD,† Gerrit-Anne van Es, PhD,‡ Ashley B. Boam, MSBE,§ Donald E. Cutlip, MD‖

Durham, North Carolina; New York, New York; Rotterdam, the Netherlands; Silver Spring, Maryland; and Boston, Massachusetts

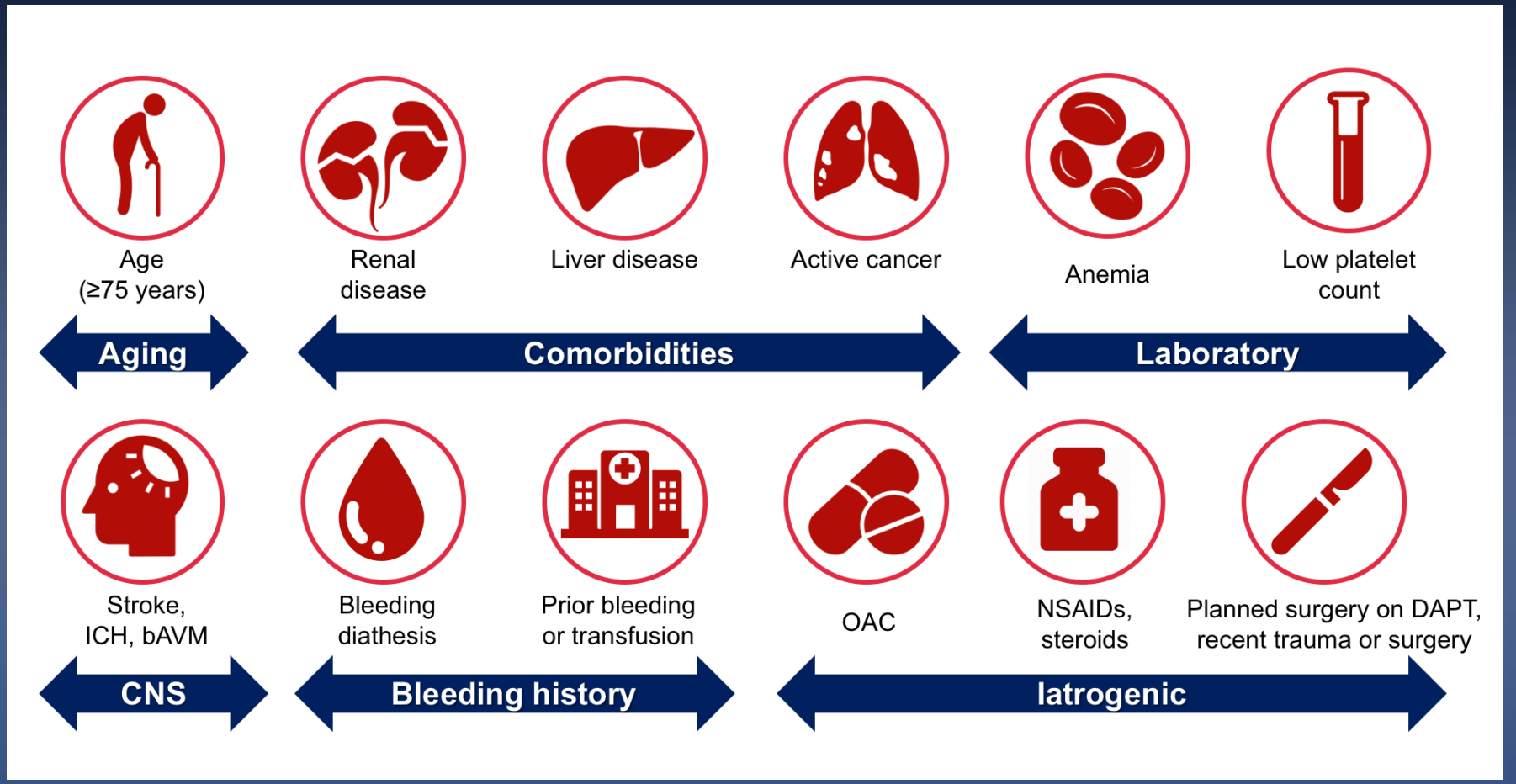
Evaluation of new medical devices and demonstration of their conformity to essential principles of safety and effectiveness frequently require clinical trials in human subjects. For many cardiovascular devices, in particular implantable or invasive devices, ethical, clinical, and logistical constraints must be integrated into the balance of how best to encourage innovation and brisk access to better therapies with potential safety concerns and their evaluation. As device manufacturing and adoption progress throughout the total product life cycle, the ability to aggregate data across individual clinical trials, patient subgroups, or device models adds critical knowledge, in particular with regard to safety. One of the most fundamental barriers to meaningful data aggregation is the use of different nomenclature and definitions of key descriptors and endpoints from 1 trial to another, or from 1 manufacturer to another. Thus, the eventuation of robust, practical consensus definitions and nomenclature represents a manageable and important advance in the quality, speed, and cost of research and development pathways for new devices.

Controversies around optimal definitions for clinical more "right or wrong" than may be available using other options. The consistent use of well-considered consensus definitions throughout the life cycle of a medical device, however, has unique value to scientific, clinical, regulatory, and industry stakeholders and most importantly, to protection of the public health, well beyond the limitations of relative degrees of accuracy or inaccuracy.

Definitions per se are not self-sufficient, but are dependent on how they are used. Thus, optimal consensus definitions and nomenclature may be crafted differently for different purposes. Professional societies or expert panels developing consensus definitions to support practice guidelines, for instance, may prefer different constructs of evidence than a clinical events committee or a data and safety monitoring committee might require for a clinical trial.

The purpose of the Academic Research Consortium (ARC) is to create a dynamic, open-ended, transparent, collaborative forum across stakeholders, whose objective is to develop consensus definitions and nomenclature and related processes, optimized for application in pivotal clinical trials of specific classes of new medical devices, and to disseminate such definitions and recom-

Criteria for High Bleeding Risk (HBR)



Courtesy of Davide Capodanno and the ARC-HBR group

Conclusions

- Identifying and defining HBR patients is important for:
  - **Clinicians**: selecting a stent, defining revascularisation strategy and optimizing antithrombotic treatment
  - **Trialists**: to design future trials, render them comparable, allow for pooling and metanalysis
  - **Industry & regulators**: to develop, evaluate and approve devices and drug regimens appropriate for HBR patients
- The ARC-HBR consensus will be presented and published in May at Euro-PCR in Paris. It is hoped that it will be widely adopted and serve as a common language for the interventional community

Thank you!