Standardizing the Language on Bleeding and Ischemic Risks: Insights on ARC, BARC, VARC, and Others

Pieter C. Smits MD, Ph.D, FESC
Rotterdam, The Netherlands
&
CERC, Massy, France

Disclosure

In the last 3 years I received,

- Institutional research grants from Abbott Vascular and Sahajanad Medical Technologies (SMT)
- Consultancy and speakers fees from Abbott Vascular, Abiomed, Microport, Terumo and SMT, and
- I’m CERC shareholder (minor)

Academic Research Consortium (ARC)

- The Academic Research Consortium (ARC) is an international collaborative forum across medical device stakeholders that includes academics, clinical trialists, regulatory bodies and industry.

The ARC Board includes representatives from:

- Baim Institute for Clinical Research (Boston, USA)
- Cardialysis & European Cardiovascular Research Institute - ECRI (Rotterdam, The Netherlands)
- Cardiovascular Research Foundation (New York, USA)
- Duke Clinical Research Institute (Raleigh, USA)
- CERC - Cardiovascular European Research Center (Massy, France)
- United States Food and Drug Administration (Advisory role)

Academic Research Consortium (ARC)

- The purpose of the ARC is to create a dynamic, transparent and collaborative forum for stakeholders to develop consensus definitions and standard nomenclature in pivotal clinical trials of medical devices and to disseminate such definitions and recommended processes into the public domain.
    - Universal language
    - Comparison between device, drugs, strategies and trials
    - Facilitates clinicians
    - Facilitates regulatory
    - Facilitates industry stakeholders
    - In the end…patients will benefit

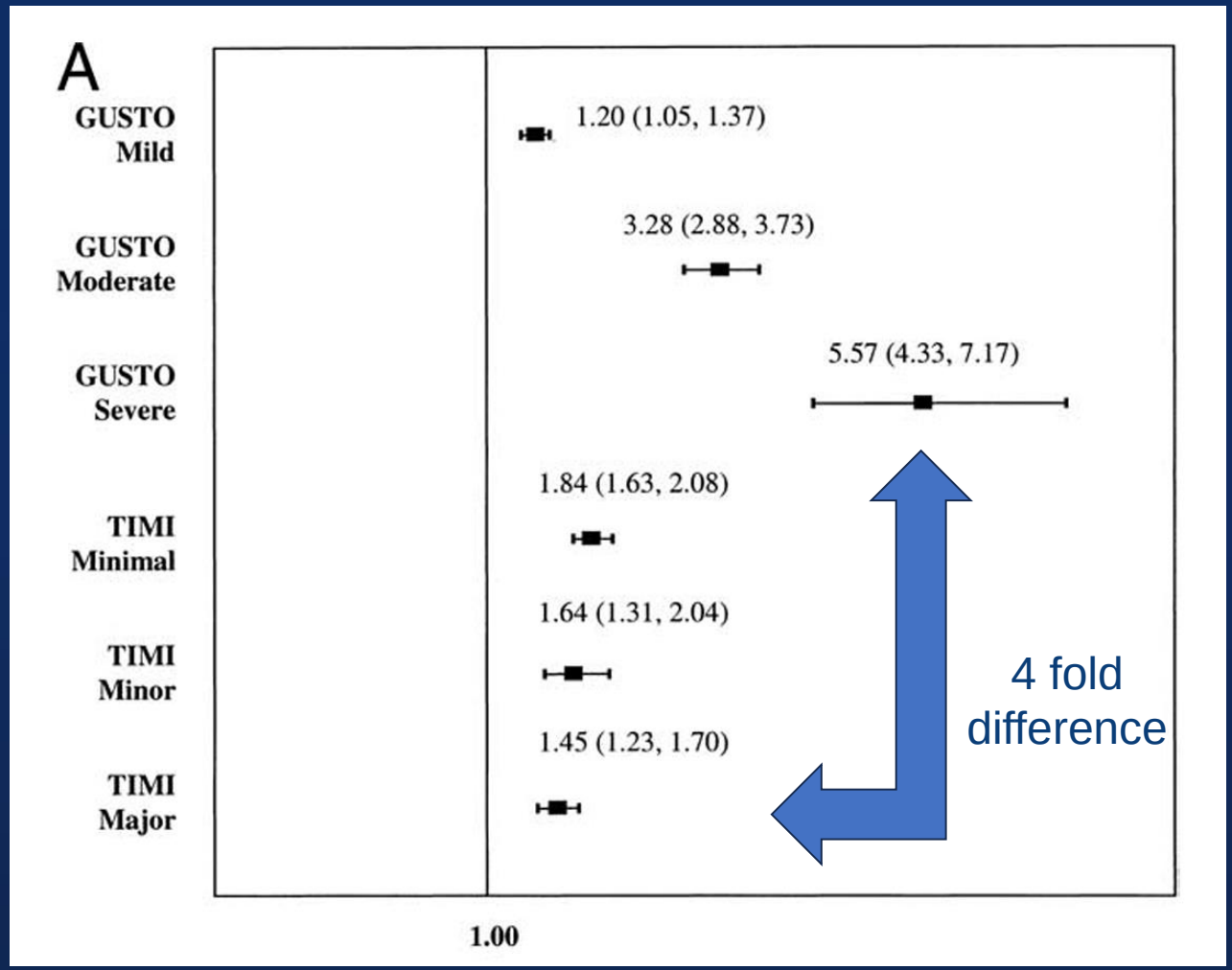
Impact of two bleeding criteria in the same ACS population (15.000 pts)

TIMI Bleeding Classification (7)*

Major	Intracranial hemorrhage or a ≥5 g/dl decrease in the hemoglobin concentration or a ≥15% absolute decrease in the hematocrit
Minor	Observed blood loss: ≥3 g/dl decrease in the hemoglobin concentration or ≥10% decrease in the hematocrit No observed blood loss: ≥4 g/dl decrease in the hemoglobin concentration or ≥12% decrease in the hematocrit
Minimal	Any clinically overt sign of hemorrhage (including imaging) that is associated with a <3 g/dl decrease in the hemoglobin concentration or <9% decrease in the hematocrit

GUSTO Bleeding Classification (8)

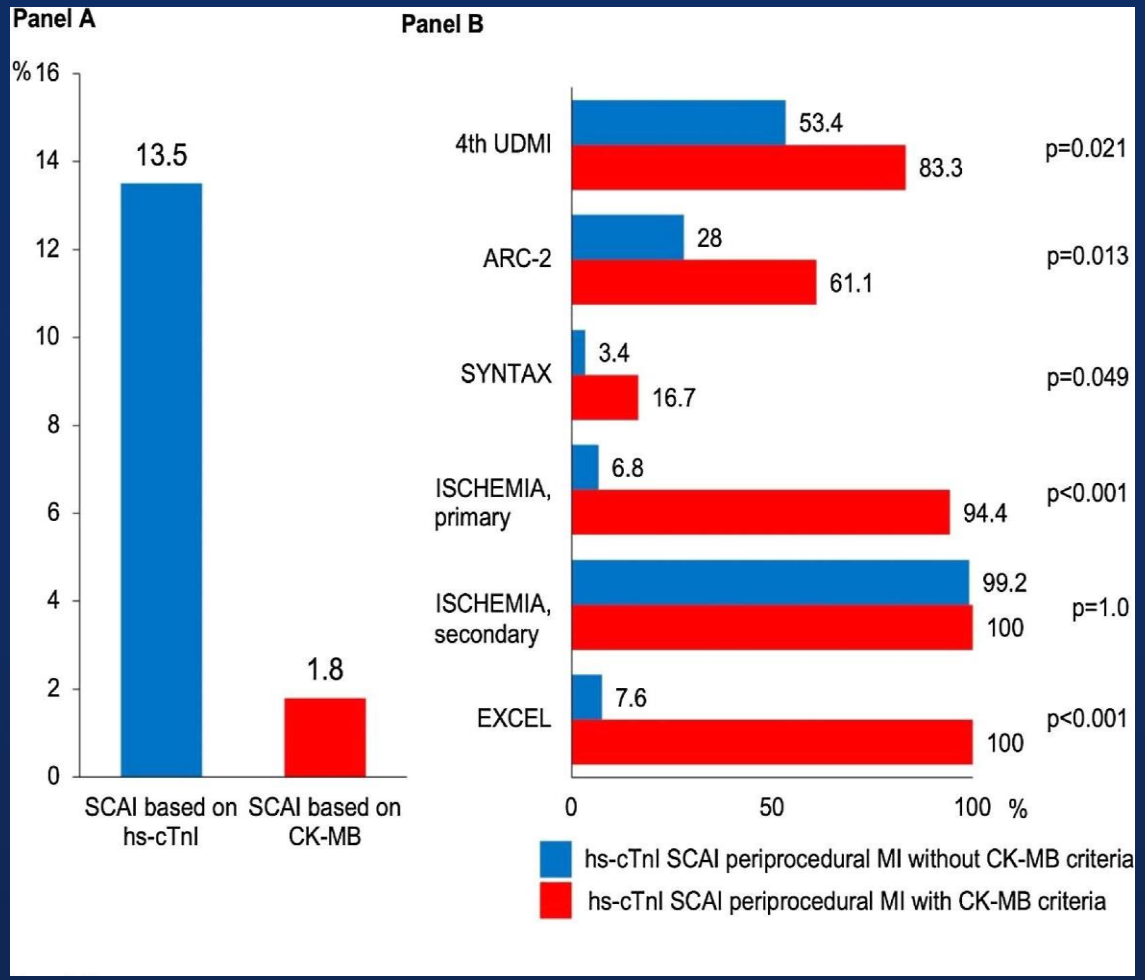
Severe or life-threatening	Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in hemodynamic compromise
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding

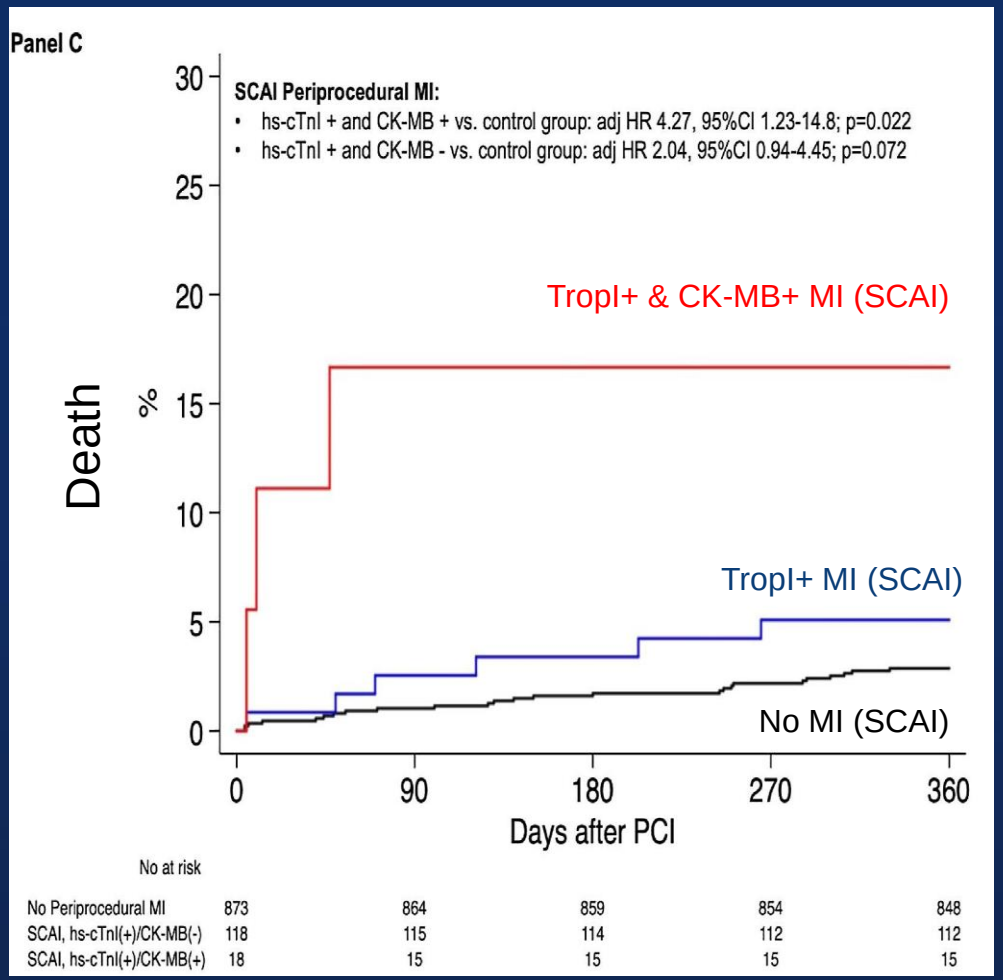


Rao et al. JACC 2006

HR for MI and Death at 30days

Impact of different peri-procedural MI criteria in the same PCI population (1010 pts)





Piccolo et al. European Heart Journal- Quality of Care and Clinical Outcomes (2023)

Coronary artery disease

Bleeding Events

Neurological events

Aortic Valve Disease

Mitral Valve Disease

Peripheral Artery Disease

High bleeding risk

Coronary bifurcations

ESC European Society of Cardiology
European Heart Journal (2018) 39, 2192–2207
doi:10.1093/eurheartj/ehy223

SPECIAL ARTICLE
Interventional cardiology

Standardized End Point Definitions for Coronary Intervention Trials

The Academic Research Consortium-2 Consensus D

Hector M. Garcia-Garcia, MD[1,2], Eugène P. McFadden, MD[3], A
Roxana Mehran, MD[5], Gregg W. Stone, MD[6], John Spertus, M
Yoshinobu Onuma, MD[1], Marie-angèle Morel, BSc[1], Gerrit-A
Bram Zuckerman, MD[*4], William F. Fearon, MD[8], David Tag
Arie-Pieter Kappetein, MD[10], Mitchell W. Krucoff, MD[11], Pas
Stephan Windecker, MD[13], Donald Cutlip, MD[14] and Patrick
On behalf of the Academic Research Consortium

Special Report

Standardized Bleeding Definitions for Cardiovascular Clinical Trials

A Consensus Report From the Bleeding Academic Research Consortium

Roxana Mehran, MD; Sunil V. Rao, MD; Deepak L. Bhatt, MD, MPH; C. Michael Gibson, MS, MD;
Adriano Caixeta, MD, PhD; John Eikelboom, MD, MBBS; Sanjay Kaul, MD;
; Eugenia Nikolsky, MD, PhD;
i, MD, PhD; Pascal Vranckx, MD;
E. Cutlip, MD; Mitchell W. Krucoff, MD;
MD; Harvey White, MB, ChB, DSc

ESC European Society of Cardiology
European Heart Journal (2018) 39, 1687–1697
doi:10.1093/eurheartj/ehx037

CURRENT OPINION
Thrombosis and antithrombotic therapy

Proposed standardized neurological endpoints for cardiovascular clinical trials

An academic research consortium initiative

Alexandra J. Lansky[1,2,3], Steven R. Messé[4], Adam M. Brickman
H. Bart van der Worp[7], Ronald M. Lazar[5], Cody G. Pietras[1,2],
Eugene McFadden[9], Nils H. Petersen[10], Jeffrey Browndyke[11], B
Vivian G. Ng[1,2], Donald E. Cutlip[13], Samir Kapadia[14], Mitchell
Axel Linke[16], Claudia Scala Moy[17], Joachim Schofer[18], Gerrit-A

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© PUBLISHED ON BEHALF OF THE EUROPEAN SOCIETY OF CARDIOLOGY. ALL RIGHTS RESERVED. © THE AUTHOR(S) 2021.
VOL. 77, NO. 21, 2021

SPECIAL ARTICLE
VALVULAR HEART DISEASE

Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research

VARC-3 WRITING COMMITTEE: Philippe Généreux,[a] Nicolo Piazza,[b] Maria C. Alu,[c] Tamim Nazif,[c]
Rebecca T. Hahn,[c] Philippe Pibarot,[d] Jeroen J. Bax,[e] Jonathon A. Leipsic,[f] Philipp Blanke,[f]
Eugene H. Blackstone,[g] Matthew T. Finn,[c] Samir Kapadia,[h] Axel Linke,[i] Michael J. Mack,[j] Raj Makkar,[k]
Roxana Mehran,[l] Jeffrey J. Popma,[m] Michael Reardon,[n] Josep Rodes-Cabau,[o] Nicolas M. Van Mieghem,[c]
John G. Webb,[p] David J. Cohen,[q] Martin B. Leon[c]

European Heart Journal (2015) 36, 1851–1877
doi:10.1093/eurheartj/ehv281

CURRENT OPINION

Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair a replacement: part 1: clinical trial design princip

A consensus document from the mitral valve academic research consortium

Gregg W. Stone[1,2*], Alec S. Vahanian[3], David H. Adams[4], William T. Abraham[5],
Jeffrey S. Borer[6], Jeroen J. Bax[7], Joachim Schofer[8], Donald E. Cutlip[9],

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Evaluation and Treatment of Patients With Lower Extremity Peripheral Artery Disease

Consensus Definitions From Peripheral Academic Research Consortium (PARC)

Manesh R. Patel, MD,[a] Michael S. Conte, MD,[b] Donald E. Cutlip, MD,[c] Nabil Dib, MD,
William Gray, MD,[d**] William R. Hiatt, MD,[e†] Mami Ho, MD, PhD,[f†] Koji Ikeda, PhD,[g]
Michael R. Jaff, DO,[¶] W. Schuyler Jones, MD,[a] Masayuki Kawahara, MD,[f] Robert A.

ESC European Society of Cardiology
European Heart Journal (2019) 40, 2632–2653
doi:10.1093/eurheartj/ehz372

CURRENT OPINION

Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk

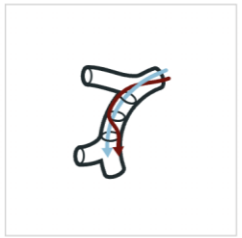
Philip Urban[1,2*], Roxana Mehran[3], Roisin Colleran[4],
Dominick J. Angiolillo[5], Robert A. Byrne[4], Davide Capodanno[6,7],
Thomas Cuisset[8], Donald Cutlip[9], Pedro Eerdmans[10], John Eikelboom[11],
Andrew Farb[12], C. Michael Gibson[13,14], John Gregson[15], Michael Haude[16],
Stefan K. James[17], Hyo-Soo Kim[18], Takeshi Kimura[19], Akihide Konishi[20],

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Definitions and Standardized Endpoints for Treatment of Coronary Bifurcations

Mattia Lunardi, MD, MSc,[a,b] Yves Louvard, MD,[c] Thierry Lefèvre, MD,[c] Goran Stankovic, MD, PhD,[d]
Francesco Burzotta, MD, PhD,[e] Ghassan S. Kassab, PhD, MSc,[f] Jens F. Lassen, MD, PhD,[g] Olivier Darremont, MD,[h]
Scot Garg, MD, PhD,[i] Bon-Kwon Koo, MD, PhD,[j] Niels R. Holm, MD, PhD,[k] Thomas W. Johnson, MD,[l]
Manuel Pan, MD, PhD,[m] Yiannis S. Chatzizisis, MD, PhD,[n] Adrian Banning, MD, PhD,[o] Alaide Chieffo, MD,[p]
Dariusz Dudek, MD, PhD,[q] David Hildick-Smith, MD,[r] Jérome Garot, MD, PhD,[s] Timothy D. Henry, MD,[t]
George Dangas, MD, PhD,[i] Gregg W. Stone, MD,[i] Mitchell W. Krucoff, MD,[u] Donald Cutlip, MD,[v] Roxana Mehran, MD,[i]
William Wijns, MD, PhD,[w,x] Faisal Sharif, MD, PhD,[y] Patrick W. Serruys, MD, PhD,[z,x] Yoshinobu Onuma, MD, PhD,[z]
on behalf of the Bifurcation Academic Research Consortium and European Bifurcation Club

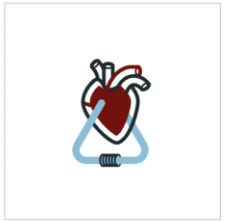


Coronary chronic total occlusions

Paravalvular leaks

Hypertension

Heart failure



Mechanical circulatory support

Medical therapies

Tricuspid valve disease

Cardiogenic shock

Circulation

FRONTIERS

Definitions and Clinical Trial Desig for Coronary Artery Chronic Total Therapies

CTO-ARC Consensus Recommendations

ABSTRACT: Over the past 2 decades, chronic total occlusion (CTO) percutaneous coronary intervention has developed into its own subspecialty of interventional cardiology. Dedicated terminology, techniques, devices, courses, and training programs have enabled progressive advancements. However, only a few randomized trials have been performed to evaluate the safety and efficacy of CTO percutaneous coronary intervention. Moreover, several published observational studies have shown conflicting data. Part of the paucity of clinical data stems from the fact that prior studies have been suboptimally designed and performed. The absence of standardized end points and the discrepancy

Circulation

FRONTIERS

Clinical Trial Design Principles and Outcomes Definitions for Device-Based Therapies for Hypertension: A Consensus Document From the Hypertension Academic Research Consortium

David E. Kandzari, MD; Felix Mahfoud, MD; Michael A. Weber, MD; Raymond Townsend, MD; Gianfranco Parati, MD; Naomi D.L. Fisher, MD; Melvin D. Lobo, MD; Michael Bloch, MD; Michael Böhm, MD; ... MD; Aloke V. Finn, MD; ... MD; Mitchell W. Krucoff, MD; ... MD

ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

CONSENSUS STATEMENT

Updated definitions of adverse events for trials and registries of mechanical circulatory support: A consensus statement of the mechanical circulatory support academic research consortium

Robert L. Kormos, MD, ... Daniel J. Goldstein, MD, ... Randall C. Starling, MD, ...

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Tricuspid Valve Academic Research Consortium Definitions for Tricuspid ...gitation and Trial Endpoints

... MD, Matthew K. Lawlor, MD, MS, Charles J. Davidson, MD, Vinay Badhwar, MD, ... MD, PhD, Ernest Spitzer, MD, Philipp Lurz, MD, PhD, Brian R. Lindman, MD, MSCI, ... MD, Suzanne J. Baron, MD, MSc, Scott Chadderdon, MD, Omar K. Khalique, MD, ... MD, MSc, MBA, Maurizio Taramasso, MD, PhD, Paul A. Grayburn, MD,

ESC European Society of Cardiology

European Heart Journal (2016) **37**, 2627–2644
doi:10.1093/eurheartj/ehw115

REVIEW

Clinical update

Adjudicating paravalvular leaks of tra... aortic valves: a critical appraisal

Mohammad Abdelghani[1], Osama I.I. Soliman[2,3], Carl Schultz[4,5], and Patrick W. Serruys[2,7]*

[1]Academic Medical Center, Amsterdam, The Netherlands; [2]Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Card... Management, Rotterdam, The Netherlands; [4]Cardiology Department, Royal Perth Hospital, Perth, Australia; [5]School of Medicine and Phar... Perth, Australia; [6]Cardiology Department, Bichat University Hospital, Paris, France; and [7]International Centre for Circulatory Health, NH...

Received 7 August 2015; revised 8 January 2016; accepted 1 March 2016; online publish-ahead-of-print 13 April 2016

MINI-FOCUS: CLINICAL TRIAL CONSIDERATIONS

JACC: HEART FAILURE EXPERT PANEL PAPER

Standardized Definitions for Evaluation of Heart Failure Therapies: Scientific Expert Panel From the Heart Failure Collaboratory and Academic Research Consortium

William T. Abraham, MD, Mitchell A. Psotka, MD, PhD, Mona Fiuzat, PharmD, Gerasimos Filippatos, MD, JoAnn Lindenfeld, MD, Roxana Mehran, MD, Amrut V. Ambardekar, MD, PhD, Peter E. Carson, MD, Richard Jacob, James L. Januzzi, Jr, MD, Marvin A. Konstam, MD, Mitchell W. Krucoff, MD, Eldrin F. Lewis, MD, MPH, Jonathan P. Piccini, MD, MHS, Scott D. Solomon, MD, Norman Stockbridge, MD PhD, John R. Teerlink, MD, Ellis F. Unger, MD, Emily P. Zeitler, MD, MHS, Stefan D. Anker, MD, PhD, Christopher M. O'Connor, MD

Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC)

Marco Valgimigli[1]*, Hector M. Garcia-Garcia[2], Bernard Vrijens[3], Pascal Vra... Eugène P. McFadden[6], Francesco Costa[1,7], Karen Pieper[8], David M. Vock[9], Min Zhang[10], Gerrit-Anne Van Es[11], Pierluigi Tricoci[8], Usman Baber[12],

European Heart Journal (2019) **40**, 2070–2085
doi:10.1093/eurheartj/ehy377

SPECIAL ARTICLE
Disease management

Circulation

IN DEPTH

Standardized Definitions for Cardiogenic Shock Research and Mechanical Circulatory Support Devices: Scientific Expert Panel From the Shock Academic Research Consortium (SHARC)

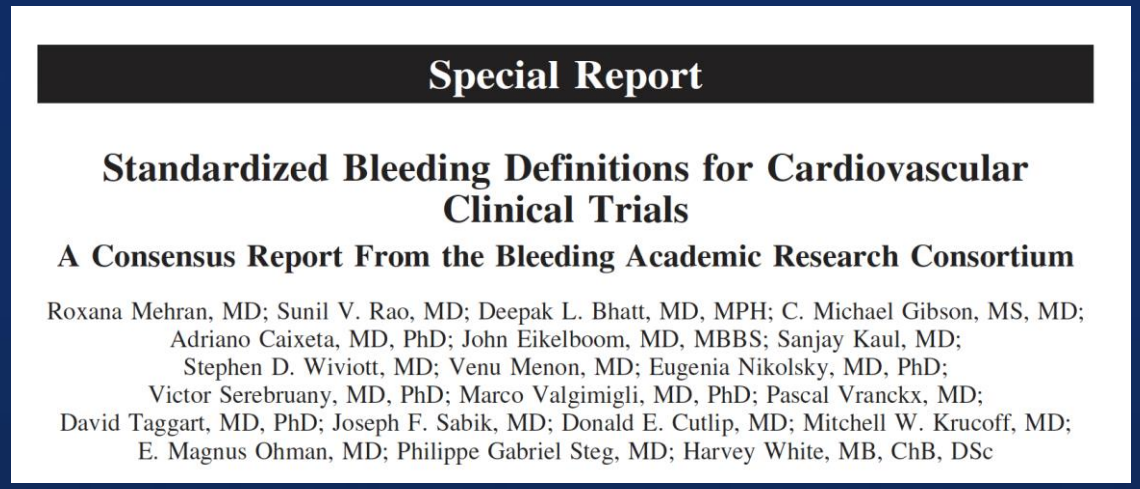
Ron Waksman, MD; Mohit Pahuja, MD; Sean van Diepen, MD, MSc; Alastair G. Proudfoot, MBChB, PhD; David Morrow, MD, MPH; Ernest Spitzer, MD; Graham Nichol, MD, MPH; Myron L. Weisfeldt, MD; Mauro Moscucci, MD, MBA, MPH; Patrick R. Lawler, MD, MPH; Alexandre Mebazaa, MD, PhD; Eddy Fan, MD, PhD; Neal W. Dickert, MD, PhD; Marc Samsky, MD; Robert Kormos, MD; Ileana L. Piña, MD, MPH; Bram Zuckerman, MD; Andrew Farb, MD; John S. Sapirstein, MD; Charles Simonton, MD; Nick E.J. West, MD; Abdulla A. Damluji, MD, PhD; Ian C. Gilchrist, MD; Uwe Zeymer, MD; Holger Thiele, MD; Donald E. Cutlip, MD; Mitchell Krucoff, MD; William T. Abraham, MD

Bleeding classification

Comprehensive bleeding classification should address:

- Cause (procedural, spontanenous)
- Site
- Severity
- Correlation with prognosis
- Easyness to use
- Guide treatment

Circulation 2011



Special Report

Standardized Bleeding Definitions for Cardiovascular Clinical Trials

A Consensus Report From the Bleeding Academic Research Consortium

Roxana Mehran, MD; Sunil V. Rao, MD; Deepak L. Bhatt, MD, MPH; C. Michael Gibson, MS, MD; Adriano Caixeta, MD, PhD; John Eikelboom, MD, MBBS; Sanjay Kaul, MD; Stephen D. Wiviott, MD; Venu Menon, MD; Eugenia Nikolsky, MD, PhD; Victor Serebruany, MD, PhD; Marco Valgimigli, MD, PhD; Pascal Vranckx, MD; David Taggart, MD, PhD; Joseph F. Sabik, MD; Donald E. Cutlip, MD; Mitchell W. Krucoff, MD; E. Magnus Ohman, MD; Philippe Gabriel Steg, MD; Harvey White, MB, ChB, DSc

Type 0: No bleeding

Type 1: Non-actionable bleeding

Type 2: Actionable, non-invasive intervention

Type 3a: Transfusion / Hb drop <5 mg/dl

3b: Tamponade / HB drop >5 mg/dl

3c: Intracranial and intra-oculair

Type 4: CABG related

Type 5a: Probable fatal

5b: Definite fatal

ARC HBR consensus:
Factors associated with increased bleeding risk

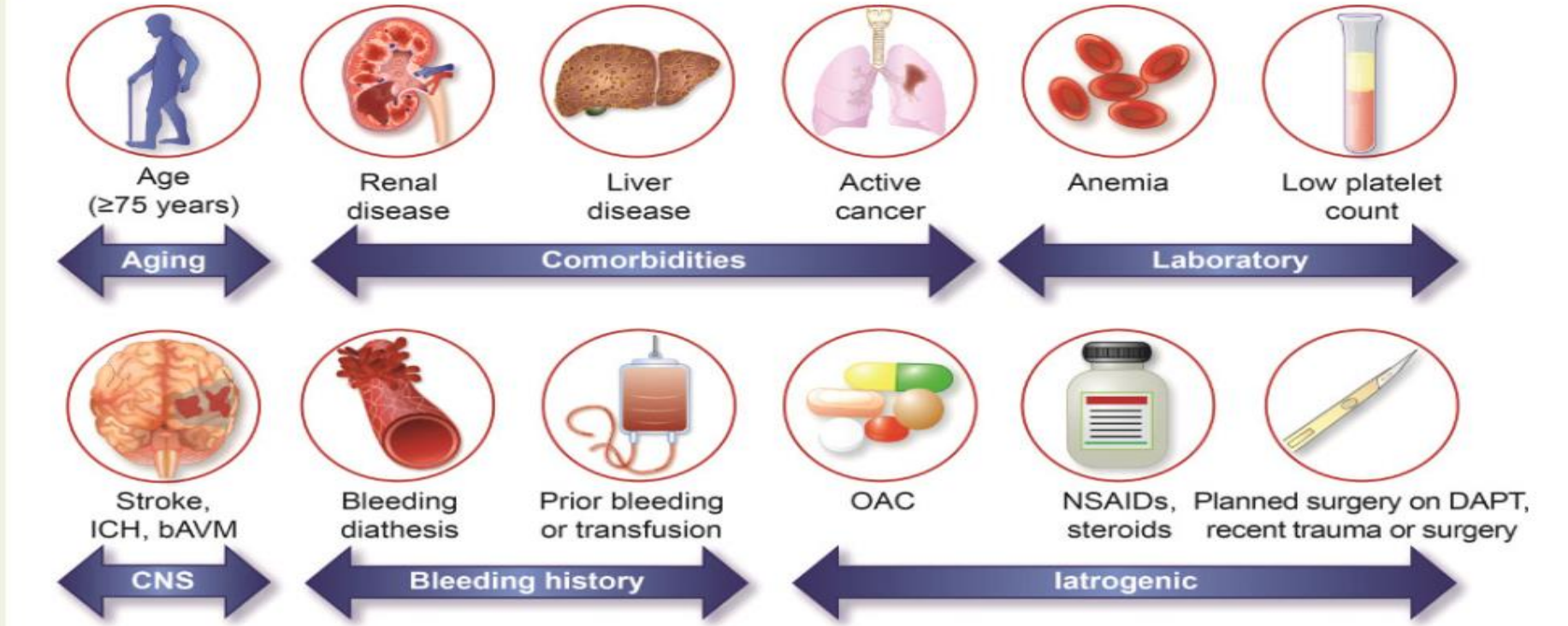


Figure Factors associated with an increased bleeding risk after percutaneous coronary intervention. bAVM indicates brain arteriovenous malformation; CNS, central nervous system; DAPT, dual antiplatelet treatment; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and OAC, oral anticoagulation.

Urban P et al. *Eur Heart J.* 2019;pii: ehz372
Urban P et al. *Circulation.* 2019;**140**:240-261

ARC HBR consensus

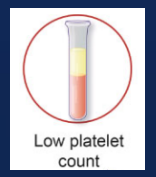
10 major HBR criteria

Anticipated use of long-term **oral anticoagulation**

Major criterion:
1. Risk BARC bleed 3 or 5 risk ≥ 4%
and/or
2. Risk ICH ≥ 1% <12 months post PCI

Hemoglobin <11 g/dL (<6.8 mmol/l)

Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent



Moderate or severe **baseline thrombocytopenia†** (platelet count <100 109/L)

Chronic bleeding diathesis

with
nsion

Active malignancy (excluding non-melanoma skin cancer)
within the past 12 mo

ARC-HBR criteria for HBR patient if ≥1 major or 2 minor criteria are met

within the past 6 mo

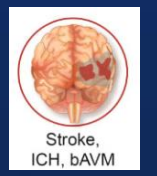
Nondeferrable major surgery on DAPT
Recent major surgery or major trauma within 30 d before PCI

6 minor HBR criteria

Age ≥75 years

Minor criterion:
1. Risk BARC bleed 3 or 5 < 4%
and/or
2. Risk ICH < 1% <12 months post PCI

11–11.9 g/dL women



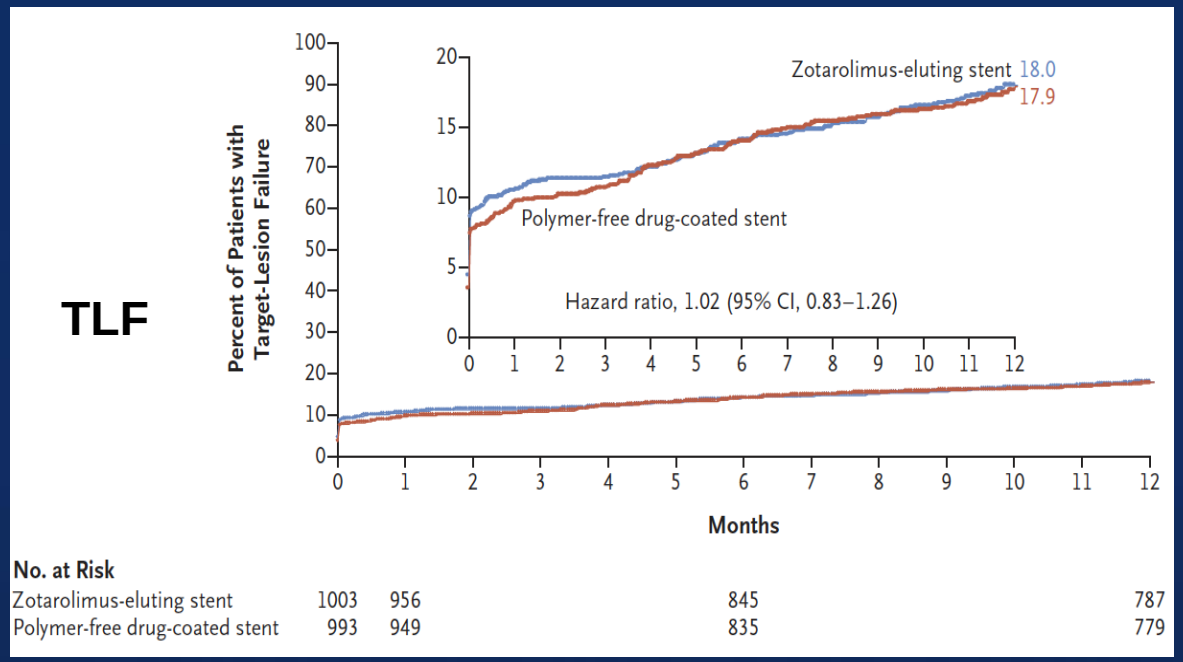
Any **ischemic stroke** at any time *not meeting the major criterion*

Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months

Long-term use of oral NSAIDs or steroids

Same language ischemic risk?

ONYX-ONE
Resolute Onyx *versus* BioFreedom

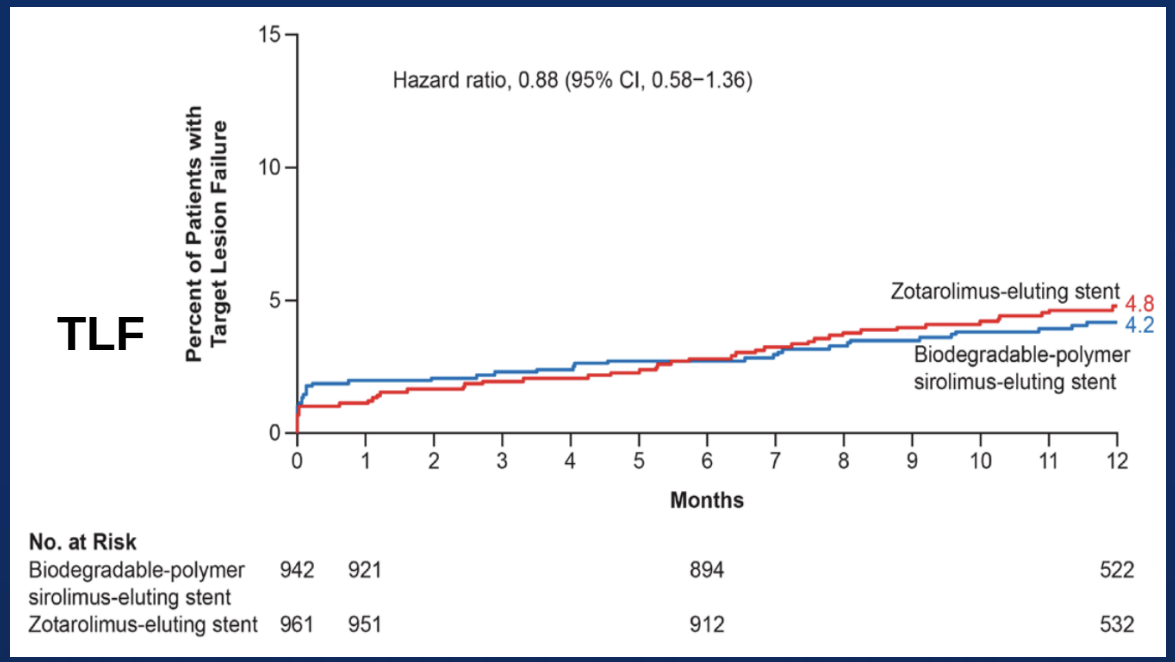


HBR patients (ACS&CCS) with 1 month DAPT

NEJM 2021

MI according to 3rd UDMI

Bioflow-DAPT
Osiro *versus* Resolute Onyx



HBR patients (ACS&CCS) with 1 month DAPT

Circulation 2023

MI according to ARC-2

Conclusion

- ARC initiative has created a unique platform for standardization of trial endpoints
- Facilitating research and regulatory work, making outcomes and comparisons of devices and medical strategies better interpretable
- Consensus on bleeding endpoints and identifying patients at high bleeding risk, though ischemic endpoints – specifically peri-procedural MI – remains to be better defined or represented