Clinical evidence for high-risk cardiovascular medical devices

A systematic evaluation of the CORE-MD Consortium

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06 November 2023

FDA and NIH let clinical trial sponsors keep results secret and break the law – Missed Deadlines

NIH National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov

1506 31.6% **Not reported**	2130 44.7% **Reported on time or early**
1132 23.7% **Reported late**	

Science, 2020

Is the clinical evidence for medical devices published ?

Analyses performed in the USA

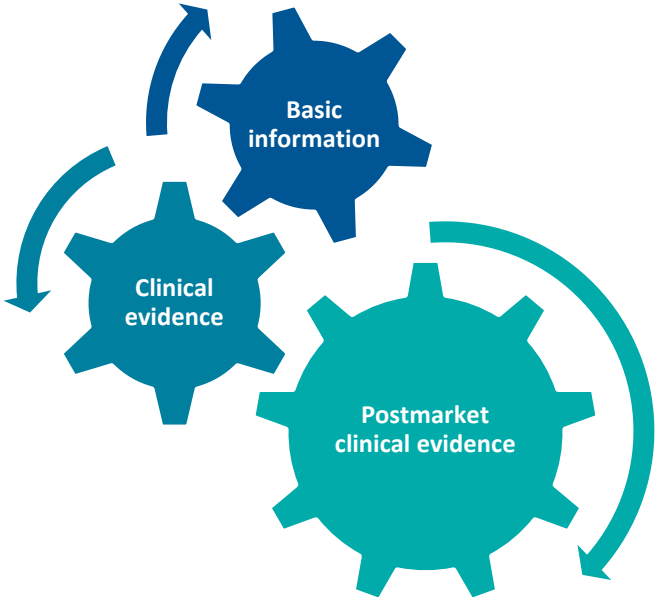
- **13,327 trials at ClinicalTrials.gov completed between 2008 and 2012 (79% drugs and 11% devices) → 13% reported summary results at 12 months**
  Anderson ML et al, NEJM 2015; 372: 1031

- **49% of studies of 177 new cardiovascular devices had been published up to 7 years after completion**
  Chang L et al, BMJ 2015; 350: h2613

- **92 mandated and completed post-approval studies → No clinical results published for 49%**
  Quesada O et al, JAMA Internal Medicine 2016: 176: 1221

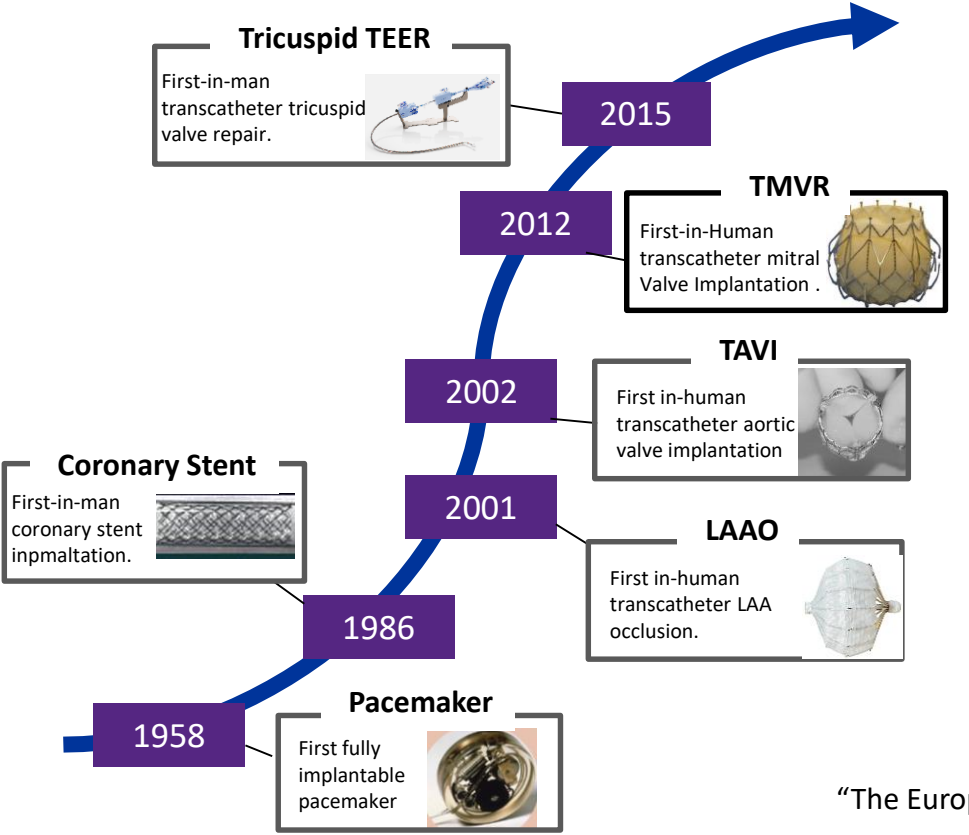
The need for transparency of clinical evidence for medical devices in Europe

Information that should be in the public domain for any approved high-risk medical device



Fraser A., et al. Lancet, 2018

Background: European medical device environment



- > 500,000 types of medical devices and IVDs on the market
- > 800,000 employees
- 150 billion EUR
- Active role of small and medium-sized enterprises
- Regulatory framework to ensure a high-level of protection of health for patients and users

"The European Medical Technology Industry in Figures", MedTech Europe, 2022

High risk devices

- **The classification of medical devices in use by the EU medical device legislation is a risk-based system taking into account the vulnerability of the human body and the potential risks associated with the devices***
  - Class I
  - Class IIa
  - Class IIb
  - **Class III (heart, central circulatory, central nervous system, total or partial joint replacement, spinal disc replacement, resorbable implants, …)**

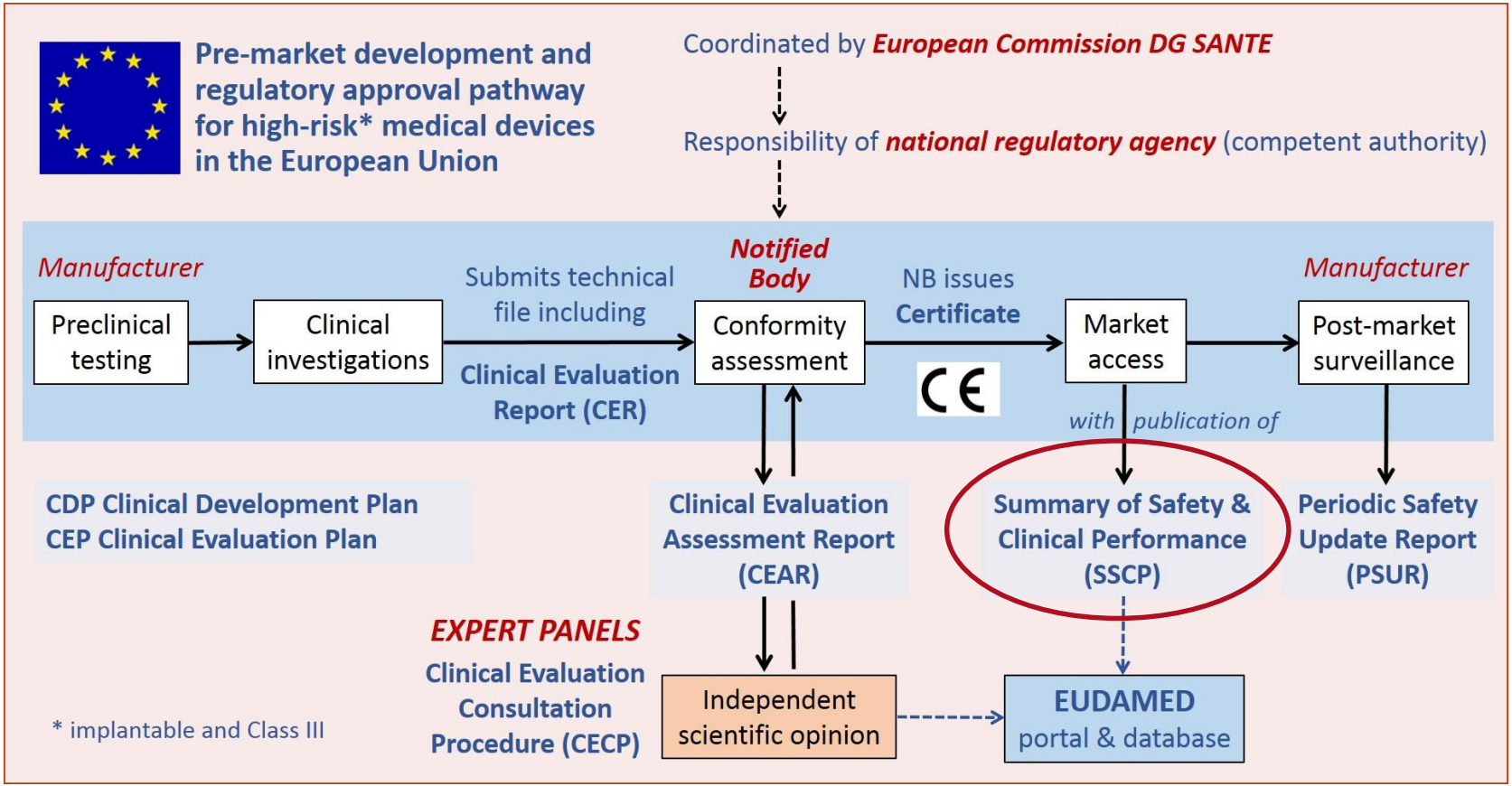
*) Medical Device Coordination Group Document 2021-24

Study design recommendations in guidance documents

- **Legally binding for market approval in the EU**
- **ISO 14155:2020 Clinical investigation of medical devices for human subjects**

Pre market		Post market	
First-in human Feasibility clinical investigation	Pivotal clinical investigation	Post-market clinical investigation	Registry

- **Further guidance documents**
  - RCT for pivotal clinical investigation for heart valves and resorbable devices (ISO 5840, ISO 17137)
  - Multi-centre trials for stents, grafts, patches (ISO 7198, ISO 12417, ISO 25539)



Fraser AG et al, Eur Heart J. 2020; 41: 2589–96


FAILURE
SUCCESS

A withdrawn cardiovascular device –

The bioresorbable scaffolds !

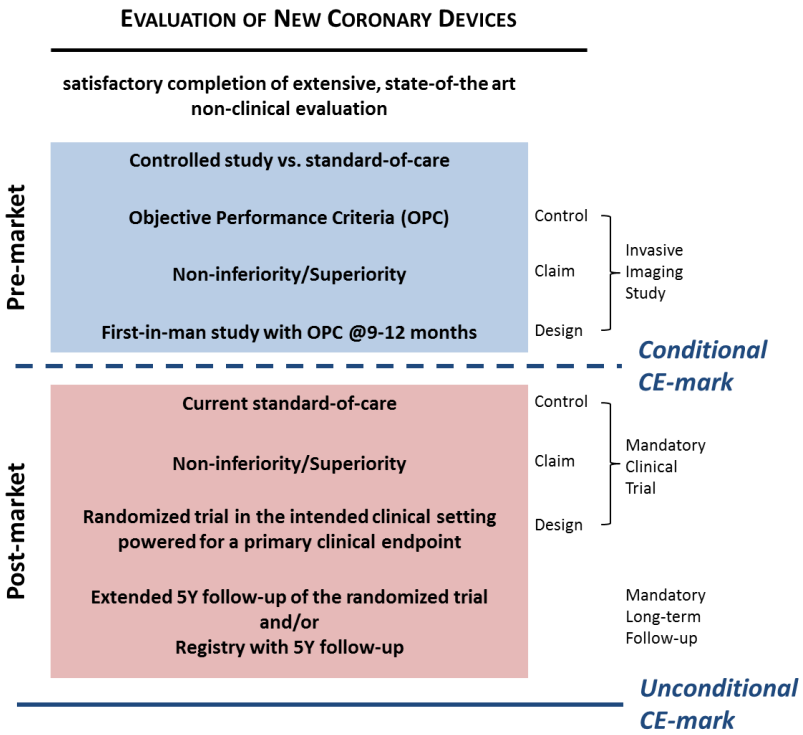
Evaluation of coronary stents in Europe

Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary

Robert A. Byrne[1], Patrick W. Serruys[2], Andreas Baumbach[3], Javier Escaned[4], Jean Fajadet[5], Stefan James[6], Michael Joner[7], Semih Oktay[8], Peter Jüni[9], Adnan Kastrati[1], George Sianos[10], Giulio G. Stefanini[11], William Wijns[12], and Stephan Windecker[11]*

Eur Heart J, 2015

ESC-EAPCI Task Force on Coronary Stents



Systematic review of 158 RCTs

Eur Heart J, 2015

ESC-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds for PCI

Report of an ESC-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds for percutaneous coronary intervention: executive summary

Robert A. Byrne[1,2], Giulio G. Stefanini[3], Davide Capodanno[4], Yoshinobu Onuma[5], Andreas Baumbach[6], Javier Escaned[7], Michael Haude[8], Stefan James[9], Michael Joner[1,2], Peter Jüni[10], Adnan Kastrati[1,2], Semih Oktay[11], William Wijns[12,13], Patrick W. Serruys[14,15], and Stephan Windecker[16]*

Eur Heart J, 2018

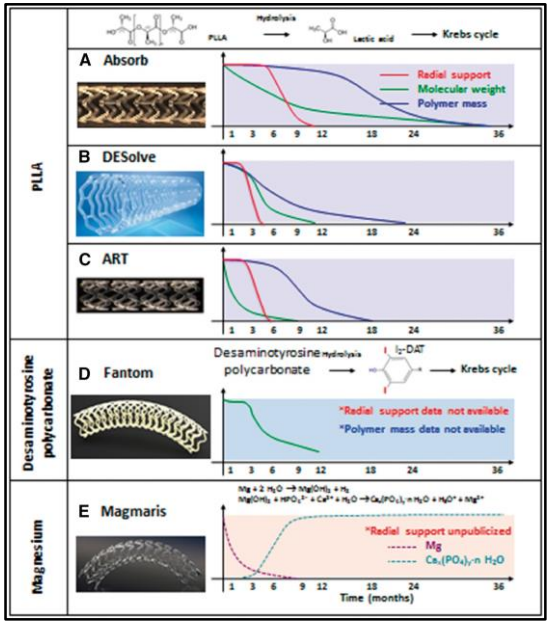
Bioresorbable scaffolds for PCI – Potential advantages?

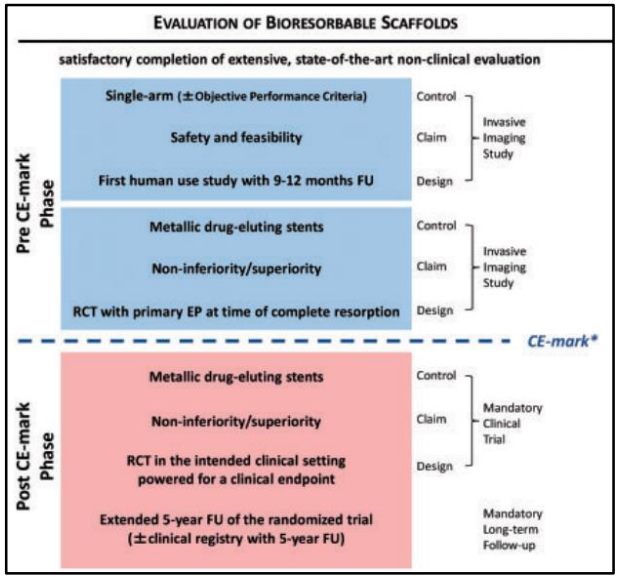
→ Address late stent failure

→ Potentially eliminate the risk of late adverse stent-related events

→ Restoration of physiological vasomotion

ESC-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds for PCI

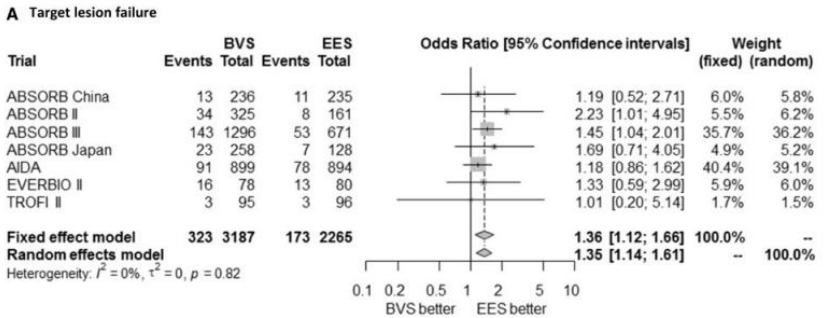




Eur Heart J, 2018

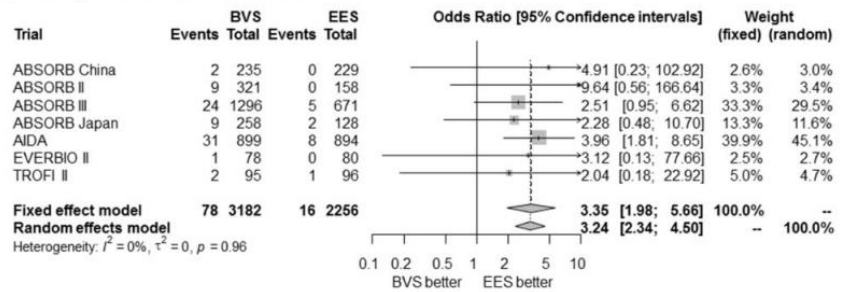
ESC-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds for PCI

Target lesion failure



Favors DES

Scaffold thrombosis



Favors DES

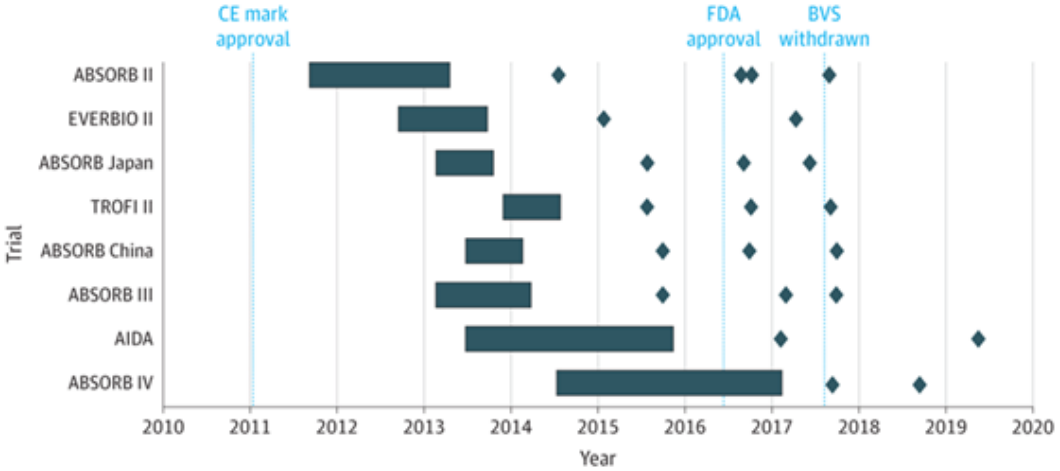
Eur Heart J, 2018

JAMA Network | Open™

Research Letter | Statistics and Research Methods

Evaluation of Cumulative Meta-analysis of Rare Events as a Tool for Clinical Trials Safety Monitoring

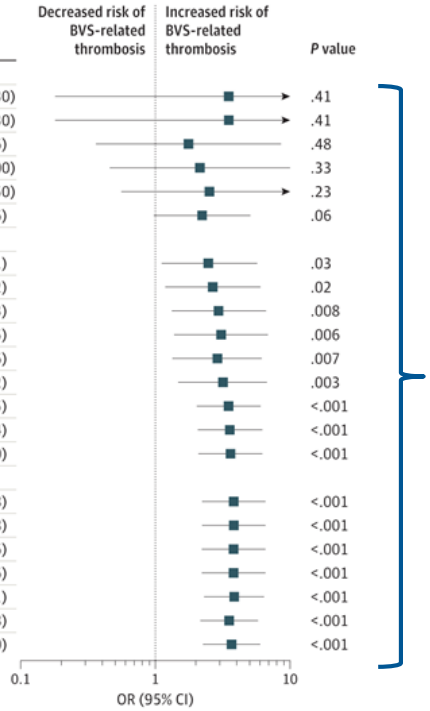
George C. M. Siontis, MD, PhD; Adriani Nikolakopoulou, PhD; Orestis Efthimiou, PhD; Lorenz Räber, MD, PhD; Stephan Windecker, MD; Peter Jüni, MD



- 22 reports describing 8 RCTs
- 8180 patients randomized to BVS (4553 patients) or everolimus-eluting stents (3627 patients)
- Patient recruitment took place over 6 years, with considerable overlap of recruitment periods

Cumulative Evidence & Clinical Trials Safety Monitoring

	Trial	Length of follow-up	Publicly available	Patients, No.	Events, No.	OR (95% CI)
CE-mark approval →	CE mark approval (January 2011)					
	ABSORB II	1 y	September 14, 2014	501	3	3.51 (0.18-68.30)
	EVERBIO II	1 y	March 3, 2015	659	3	3.51 (0.18-68.30)
	ABSORB Japan	1 y	September 1, 2015	1057	9	1.76 (0.36-8.56)
	TROFI II	1 y	September 24, 2015	1248	10	2.14 (0.46-10.00)
	ABSORB China	1 y	October 12, 2015	1723	11	2.53 (0.56-11.50)
	ABSORB III	1 y	October 12, 2015	3731	36	2.22 (0.97-5.06)
FDA approval →	FDA approval (July 2016)					
	ABSORB Japan	2 y	September 18, 2016	3731	40	2.52 (1.12-5.71)
	ABSORB II	2 y	October 20, 2016	3731	42	2.67 (1.19-6.02)
	ABSORB II	3 y	October 30, 2016	3731	46	2.96 (1.32-6.63)
	ABSORB China	2 y	October 31, 2016	3731	47	3.07 (1.38-6.85)
	TROFI II	2 y	October 31, 2016	3731	49	2.87 (1.34-6.16)
	ABSORB III	2 y	March 18, 2017	3731	53	3.15 (1.48-6.72)
	AIDA	2 y	March 29, 2017	5576	92	3.50 (2.03-6.05)
	EVERBIO II	2 y	May 12, 2017	5576	93	3.56 (2.06-6.14)
	ABSORB Japan	3 y	May 16, 2017	5576	94	3.60 (2.09-6.20)
BVS withdrawn →	BVS withdrawn (September 2017)					
	ABSORB III	3 y	October 20, 2017	5576	100	3.82 (2.22-6.58)
	ABSORB China	3 y	October 22, 2017	5576	100	3.82 (2.22-6.58)
	ABSORB II	4 y	October 31, 2017	5576	100	3.82 (2.22-6.56)
	TROFI II	3 y	October 31, 2017	5576	100	3.81 (2.22-6.56)
	ABSORB IV	30 d	October 31, 2017	8180	110	3.84 (2.30-6.41)
	ABSORB IV	1 y	September 25, 2018	8180	113	3.53 (2.16-5.78)
	AIDA	3 y	May 23, 2019	8180	116	3.68 (2.25-6.00)



Increasing PRECISION over time

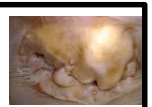
Siontis GC., et al. JAMA Netw Open, 2020

A “successful” cardiovascular device – TAVI !

Historical Background - VHD interventions

1920s

First surgical attempts to palliate MS in the US and UK.

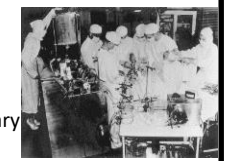


1940s

Brock, Bailey, and Harken introduced a "finger-fracture" valvuloplasty to treat rheumatic MS.

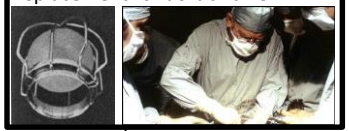
1952

John Gibbon introduced the heart-lung machine for cardiopulmonary bypass.



1953

Dwight Harken performed first valve replacement for aortic valve.

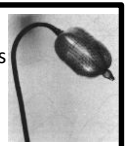


1960

Hufnagel and Harvey implanted the first cardiac prosthesis, a ball valve made of methyl methacrylate, in a patient's descending aorta to treat AR.

1982

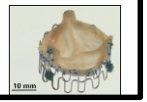
Kanji Inoue developped transseptal percutaneous mitral balloon valvuloplasty.



Nina Braunwald performed first successful mitral valve replacement.

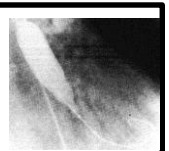
1985

Henning Andersen developed a stent-valve for implantation into the native aortic valve



1989

Alain Cribier performed percutaneous balloon aortic valvuloplasty

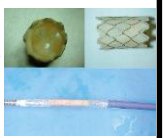


2000

Alain Cribier performed the first TAVI in an inoperable patient with severe native AS.

2002

Philipp Bonhoeffer performed first transcatheter pulmonary valve implantation in 12-year-old boy with pulmonary atresia and VSD.



2003

First-in-man transcatheter mitral edge-to-edge repair by Condado.

2006

First-in-human results of the CoreValve experience.

2012

First-in-Human Transfemoral Mitral Valve Implantation by Lars Søndergaard

2015

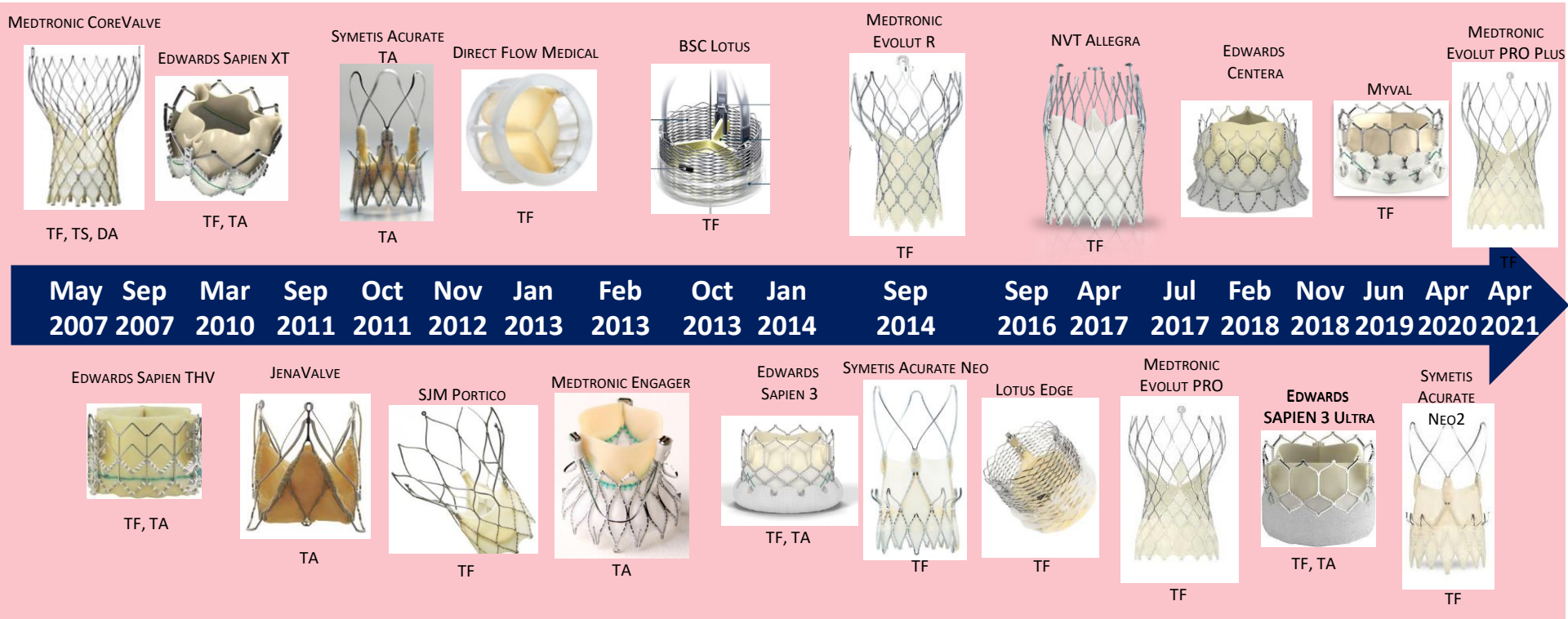
First-in-man transcatheter tricuspid valve repair by using MItraClip system.

2017

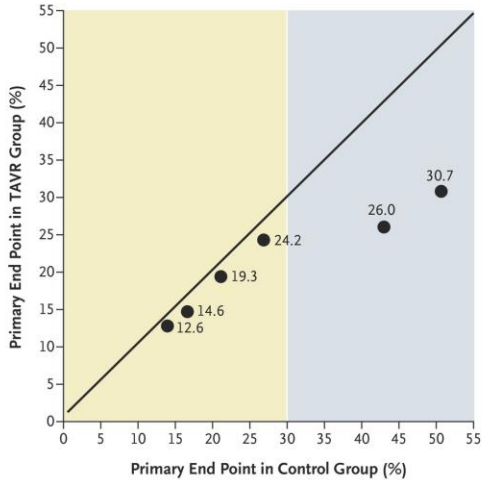
Transcatheter tricuspid valve replacement was first performed with GATE bioprosthesis.

Transcatheter aortic valve implantation systems

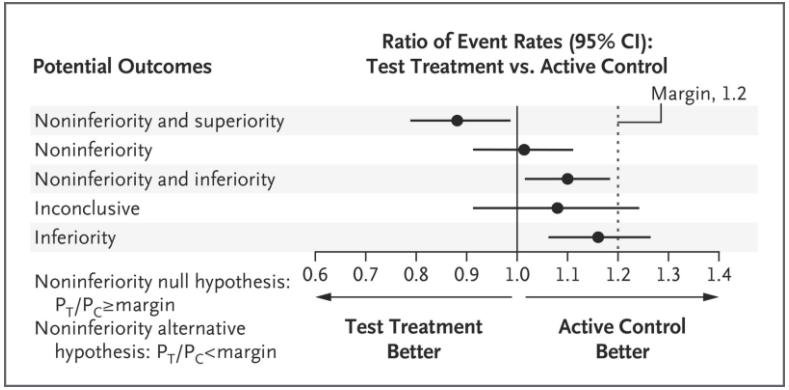
Devices and respective CE-mark date



TAVI: From superiority to non-inferiority trials



Trial	Study and Year	TAVR %	Control %	Primary End Point	Surgical Risk of Death at 30 Days
Superiority of TAVR vs. medical therapy	PARTNER[15] 2010	30.7	50.7	Death at 1 yr	Not suitable, ≥50%
	CoreValve[16] 2014	26.0	43.0	Death or stroke at 1 yr	Extreme, ≥50%
Noninferiority of TAVR vs. SAVR	PARTNER[17] 2011	24.2	26.8	Death at 1 yr	High, >10%
	PARTNER 2A[18] 2016	19.3	21.1	Death or disabling stroke at 2 yr	Intermediate, ≥4% and ≤8%
	SURTAVI[19] 2017	12.6	14.0	Death or disabling stroke at 2 yr	Intermediate, 3–15%
	PARTNER 3[20] 2016	14.6	16.6	Death, stroke, or rehospitalization at 1 yr	Low, <4%
	CoreValve[21] 2017	—	—	Death or stroke at 2 yr	Low, <3%

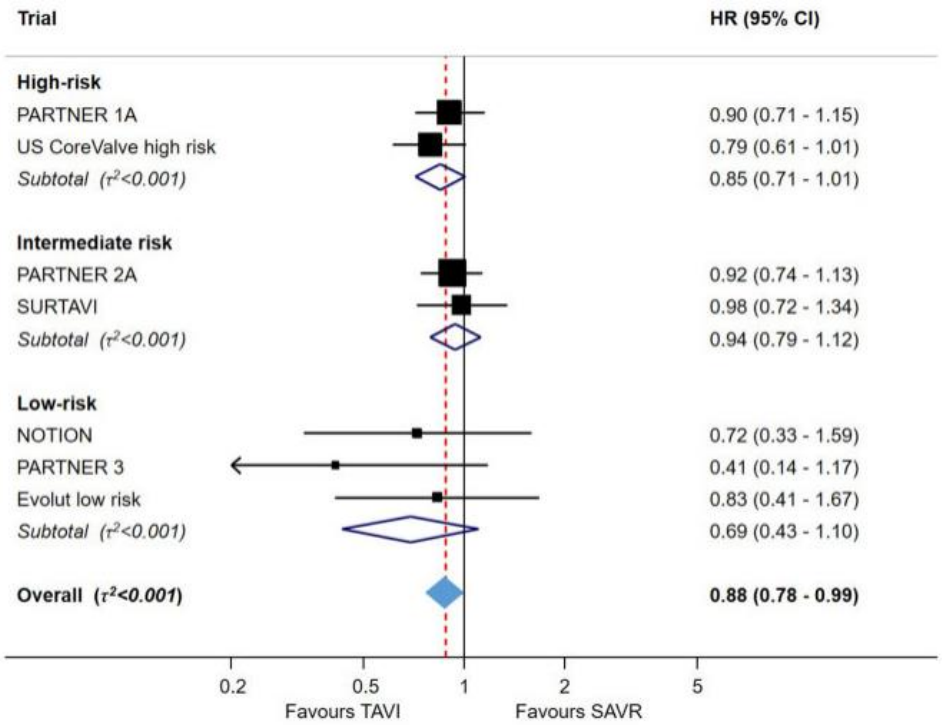


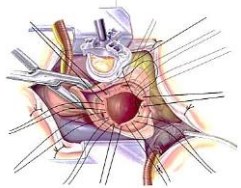
Mauri L., et al. New Eng J Med, 2017

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 3143–3153
doi:10.1093/eurheartj/ehz275

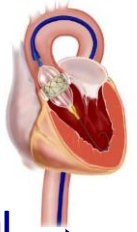
Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis

George C.M. Siontis[1†], Pavel Overtchouk[1†], Thomas J. Cahill[2†], Thomas Modine[3], Bernard Prendergast[4], Fabien Praz[1], Thomas Pilgrim[1], Tatjana Petrinic[5], Adriani Nikolakopoulou[6], Georgia Salanti[6], Lars Søndergaard[7], Subodh Verma[8], Peter Jüni[9], and Stephan Windecker[1*]





TAVI – Blueprint for Successful Innovation and Evidence Generation



PARTNER 1B
PARTNER 1A
CoreValve HR
PARTNER 2
NOTION
SURTAVI
PARTNER 3
Evolut LOW RISK
UK TAVI Trial

2008 2010 2011 2014 2016 2017 2019 2021 2022

2012 ESC Guidelines
2017 ESC Guidelines
2021 ESC Guidelines

1,057 (2 RCTs)
5,910 (6 RCTs)
8,378 (8 RCTs)
9,291 (9 RCTs)

ESC European Society of Cardiology
EACTS European Association For Cardio-Thoracic Surgery
American Heart Association.
American College of Cardiology

Extreme risk	I	B
High-risk	IIa	B

Extreme risk	I	B
Increased risk	I	B

Age ≥75 years	I	A
Patients according to individual characteristics	I	B

Prohibitive risk	I	B
High-risk	IIa	B

Prohibitive risk	I	A
High risk	I	A
Intermediate risk	IIa	B-R

Age 65-80 years	I	A
Age >80 years	I	A
High/prohibitive risk	I	A

Standardizing clinical research

- **VARC initiative: selecting appropriate clinical endpoints and standardizing endpoint definitions to optimally conduct clinical research in the field of aortic valve disease.**

VARC

Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium†

Martin B. Leon*, Nicolo Piazza, Eugenia Nikolsky, Eugene H. Blackstone, Donald E. Cutlip, Arie Pieter Kappetein, Mitchell W. Krucoff, Michael Mack, Roxana Mehran, Craig Miller, Marie-angèle Morel, John Petersen, Jeffrey J. Popma, Johanna J.M. Takkenberg, Alec Vahanian, Gerrit-Anne van Es, Pascal Vranckx, John G. Webb, Stephan Windecker, and Patrick W. Serruys

Columbia University Medical Center, Center for Interventional Vascular Therapy, 173 Fort Washington Avenue, Heart Center, 2nd floor, New York, NY 10032, USA.

Received 8 July 2010; revised 30 September 2010; accepted 6 October 2010

Published:
06 October 2010

VARC-2

Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document†

A. Pieter Kappetein*, Stuart J. Head, Philippe Généreux, Nicolo Piazza, Nicolas M. van Mieghem, Eugene H. Blackstone, Thomas G. Brott, David J. Cohen, Donald E. Cutlip, Gerrit-Anne van Es, Rebecca T. Hahn, Ajay J. Kirtane, Mitchell W. Krucoff, Susheel Kodali, Michael J. Mack, Roxana Mehran, Josep Rodés-Cabau, Pascal Vranckx, John G. Webb, Stephan Windecker, Patrick W. Serruys, and Martin B. Leon

Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands

Received 28 June 2012; revised 24 July 2012; accepted 26 July 2012

Published:
01 October 2012

VARC-3

Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research

VARC-3 WRITING COMMITTEE: Philippe Généreux[1], Nicolo Piazza[2], Maria C. Alu[3], Tamim Nazif[3], Rebecca T. Hahn[3], Philippe Pibarot[4], Jeroen J. Bax[5], Jonathon A. Leipsic[6], Philipp Blanke[6], Eugene H. Blackstone[7], Matthew T. Finn[3], Samir Kapadia[8], Axel Linke[9], Michael J. Mack[10], Raj Makkar[11], Roxana Mehran[12], Jeffrey J. Popma[13], Michael Reardon[14], Josep Rodes-Cabau[4], Nicolas M. Van Mieghem[15], John G. Webb[16], David J. Cohen[17] and Martin B. Leon[3]*

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Leon et al. Eur Heart J 2011;32(2):205-17; Kappetein et al. Eur Heart J 2012;33(19):2403-18; VARC-3: Généreux P et al. Eur Heart J 2021;42(19):1825-1857.

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 853–855
https://doi.org/10.1093/eurheartj/ehac635

EDITORIAL

Transcatheter aortic valve implantation: a blueprint for evidence-based evaluation of technological innovation

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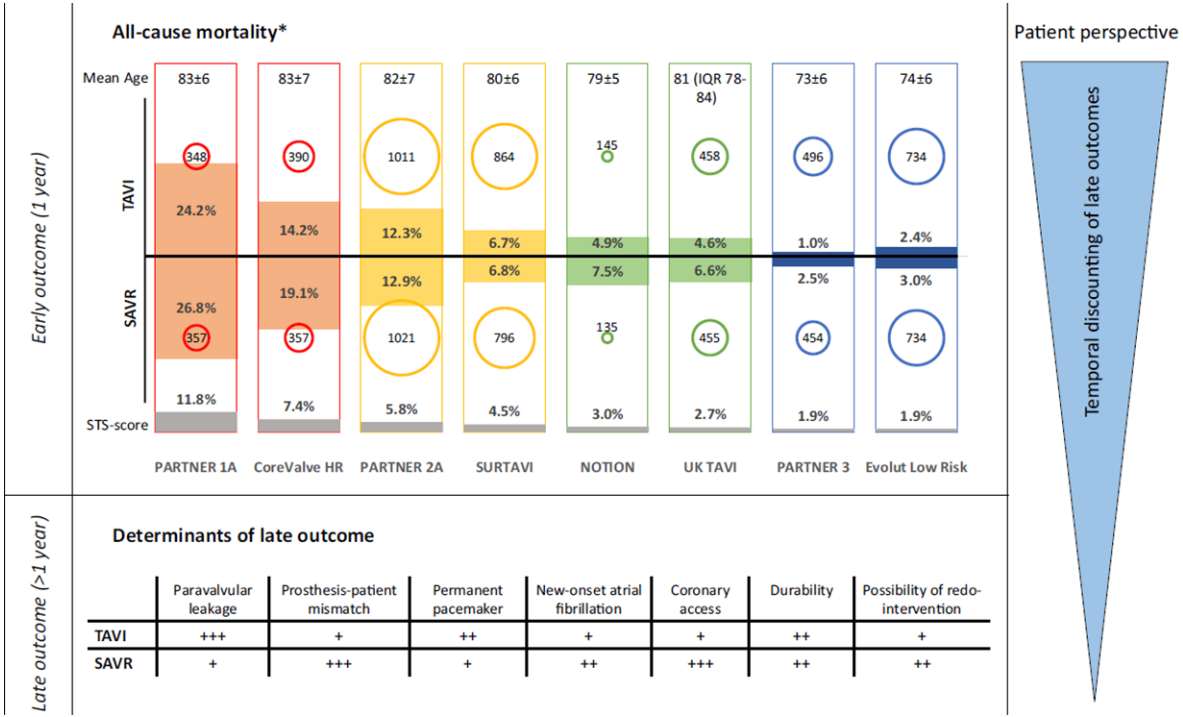

ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2021) **8**, 249–258
https://doi.org/10.1093/ehjqcco/qcab059

REVIEW

Improved clinical investigation and evaluation of high-risk medical devices: the rationale and objectives of CORE-MD (Coordinating Research and Evidence for Medical Devices)

A.G. Fraser [1,*], R.G.H.H. Nelissen [2], P. Kjærsgaard-Andersen [3], P. Szymański [4], T. Melvin [5] and P. Piscoi [6,†], on behalf of the CORE-MD Investigators (see appendix)

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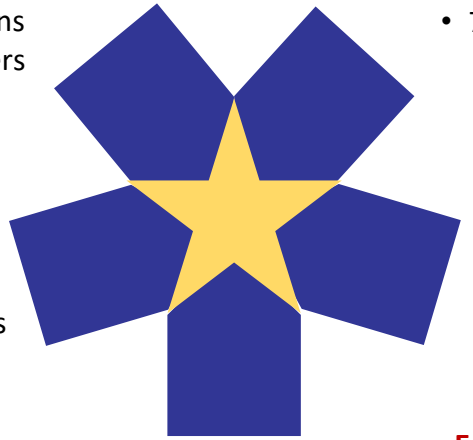
The CORE–MD Consortium

Physicians and healthcare professionals

- 4 European medical associations
- Biomedical Alliance 36 members
  - 9 academic institutions

European Patients Forum

- 75 patients' organisations

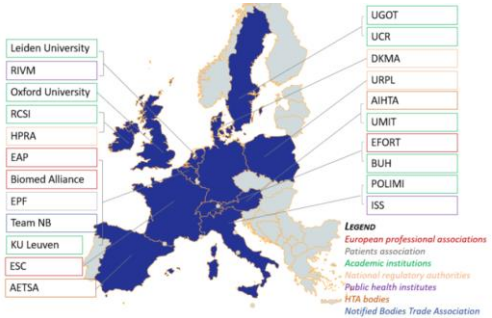


Public health authorities

- 2 National Public Health Institutes
- 2 Health technology assessment bodies

Medical device regulators

- 3 EU National regulatory agencies
- Competent Authorities for Medical Devices



Notified Bodies

- TEAM-NB has 27 members

European Commission DG SANTE

- Unit B6 / D3 – Medical devices, Health Technology Assessment
  - Clinical Investigation and Evaluation Working Group
  - New & Emerging Technologies Working Group
  - *European Medicines Agency*

- **Academic collaborators and volunteers**
- **Advisory Board**
- **Industry trade associations**

The CORE-MD Consortium

1. Trial designs, evidence, & regulatory guidance

- cardiovascular, orthopaedic, diabetic
- statistical methods
- patient-reported outcomes

2. Developing methods for evaluation

- early phase studies
- registry-based RCTs
- artificial intelligence
- devices in children

3. Real-world evidence

www.core–md.eu

Quality and transparency of clinical evidence for high-risk cardiovascular medical devices

→ **We aimed to:**

a) systematically review publicly available clinical investigations used in the evaluation of high-risk (Class III) cardiovascular medical devices mostly under the previous EU Medical Device Directive 93/42/EEC

b) identify differences in study designs before and after CE-mark approval during the period 2000-2021.

Study protocol pre-registration

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

George Siontis, André Frenk, Bernadette Coles, Joanna Bartkowiak, Laurna McGovern, Jonas Häner, Daijiro Tomii, Roberto Galea, Andreas Häberlin, Fabien Praz, Stephan Windecker. Clinical evidence for high-risk medical devices in cardiology: a protocol for a systematic review and meta-epidemiological investigation. PROSPERO 2022 CRD42022308593 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022308593

CORE-MD
Coordinating Research and Evidence for Medical Devices

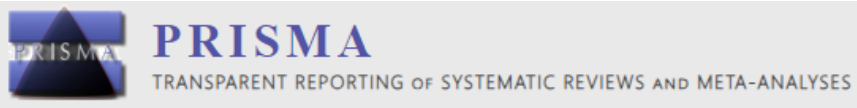
www.core-md.eu

CORE-MD protocol for a systematic review of methodologies

Under the leadership of the Department of Cardiology, Bern University Hospital, CORE-MD partners work on...

Information sources, search strategies, study eligibility criteria & data abstraction

→ MEDLINE, EMBASE and the CENTRAL with device-specific search algorithms



→ Peer-reviewed reports of trials of any prospective design (non-randomized or randomized clinical trials) for 1 of the devices of interest.

→ Information relating to study design, study population, intervention(s), comparators, and the evaluated outcomes.

Data analysis

→ Key dates in our analysis: date of publicly available report & CE-mark date

→ Multiple reports of the same study were jointly considered

→ Data-driven approaches to evaluate the distribution of study characteristics before and after CE-mark.

→ We did not aim to provide any comparative effectiveness analysis of the selected devices within a class!

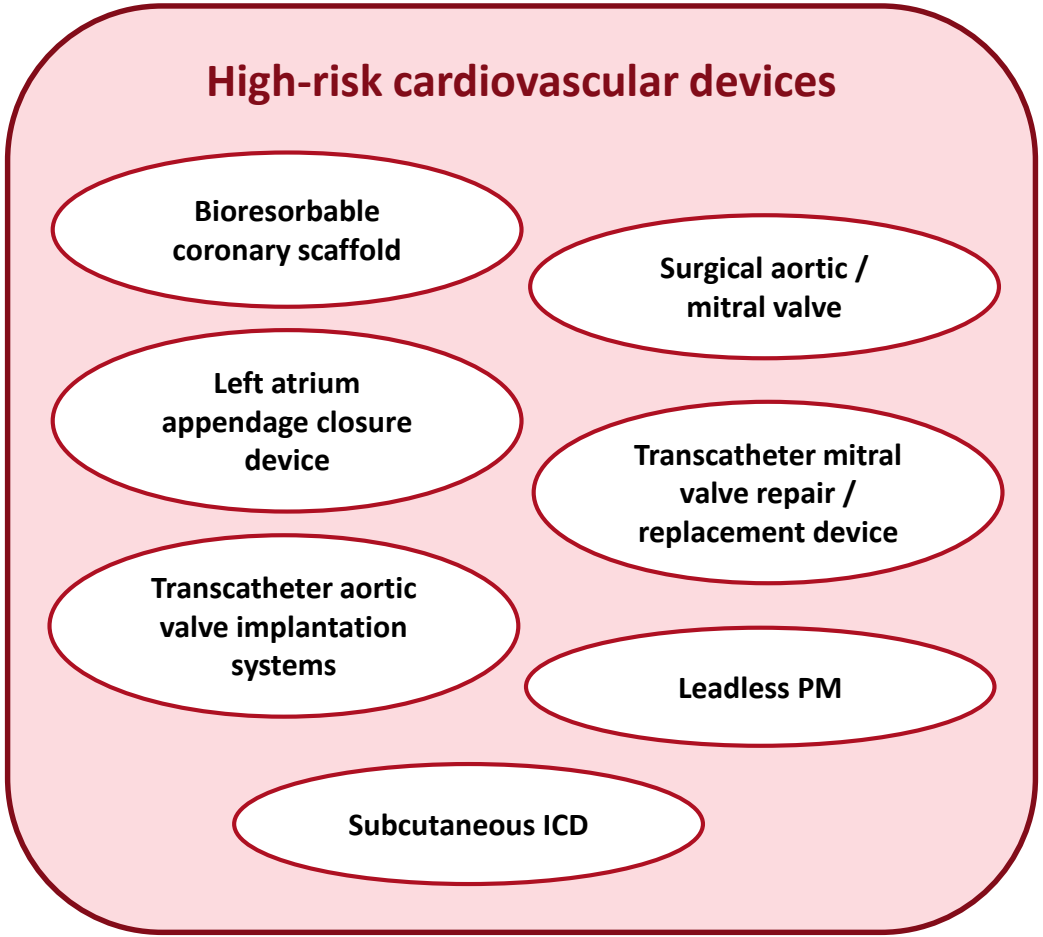
Methods

We predefined 7 groups of Class III cardiovascular devices, encompassing 71 long-term implantable devices put on the EU market since the year 2000

Drug-eluting coronary artery stents were excluded:

- **Well established**
- **Clinical evidence already reviewed with recommendations for study design leading to regulatory approval***

*) Byrne R et al. Eur Heart J 2015



Methods

- **71 high risk cardiovascular devices grouped in 7 classes**
- **Search period 2000-2021**
- **Device-sensitive search algorithms**
- **Study protocol pre-registration**
- **Databases**

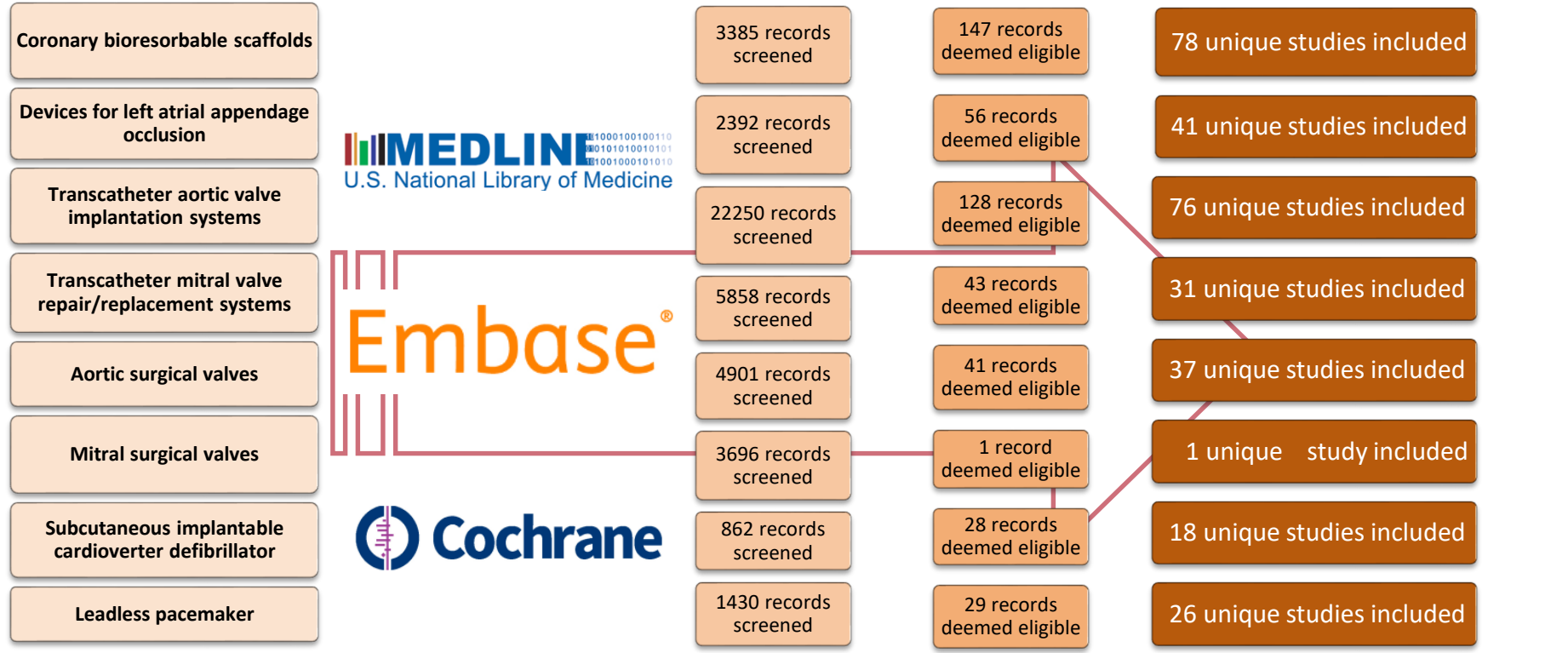
MEDLINE
U.S. National Library of Medicine

Embase®

Cochrane

Main Inclusion / Exclusion criteria

+ Trials that defined a prospective design (RCT and non-RCT)
+ Evaluated at least one of the devices of interest
- RCTs aimed to investigate other medical interventions
- Studies of non-prospective design

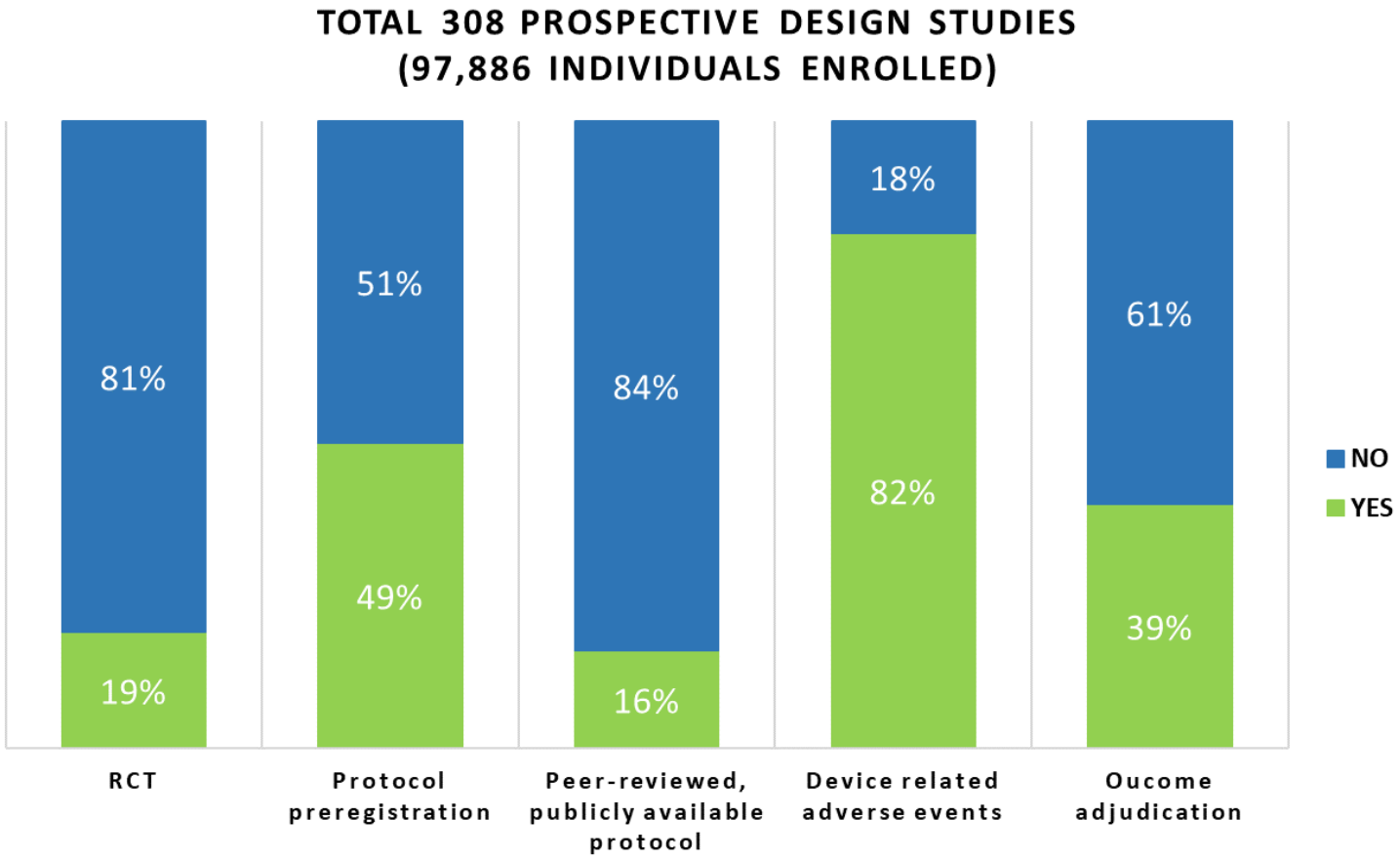


7 classes of CV devices

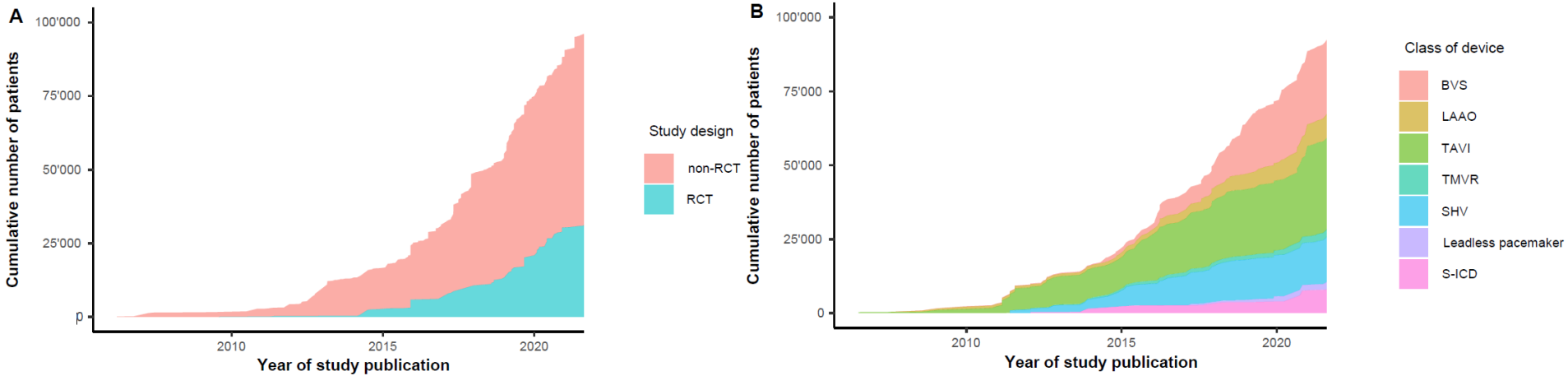
44,774 studies evaluated

308 studies across all classes of devices

Results - Clinical trial characteristics

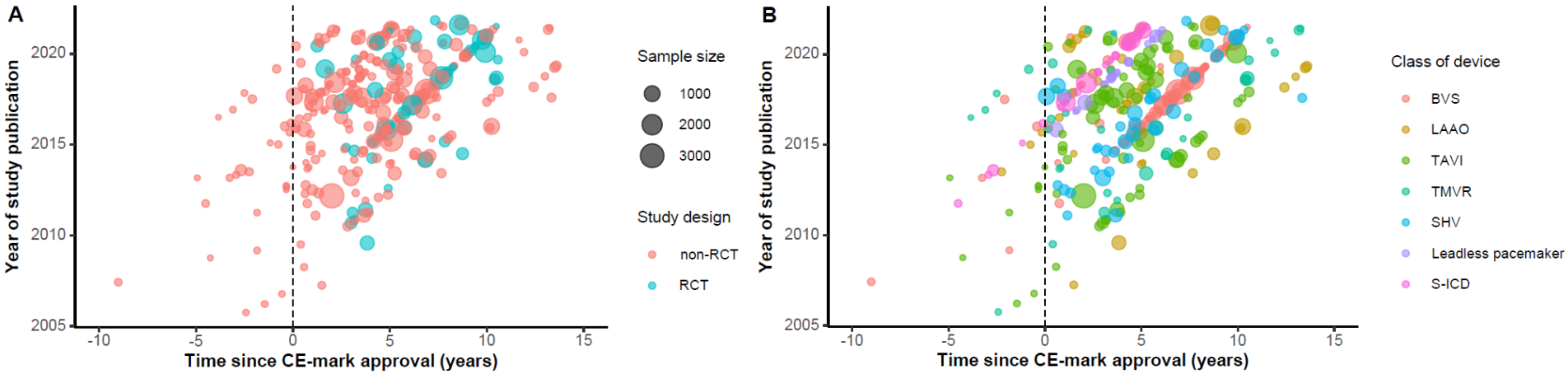


Cumulative number of patients recruited in prospective clinical trials evaluating high-risk cardiovascular devices between 2000-2021



Accumulated sample of 97’886 individuals
Mean sample size 120

Time lag between study publication and CE-mark



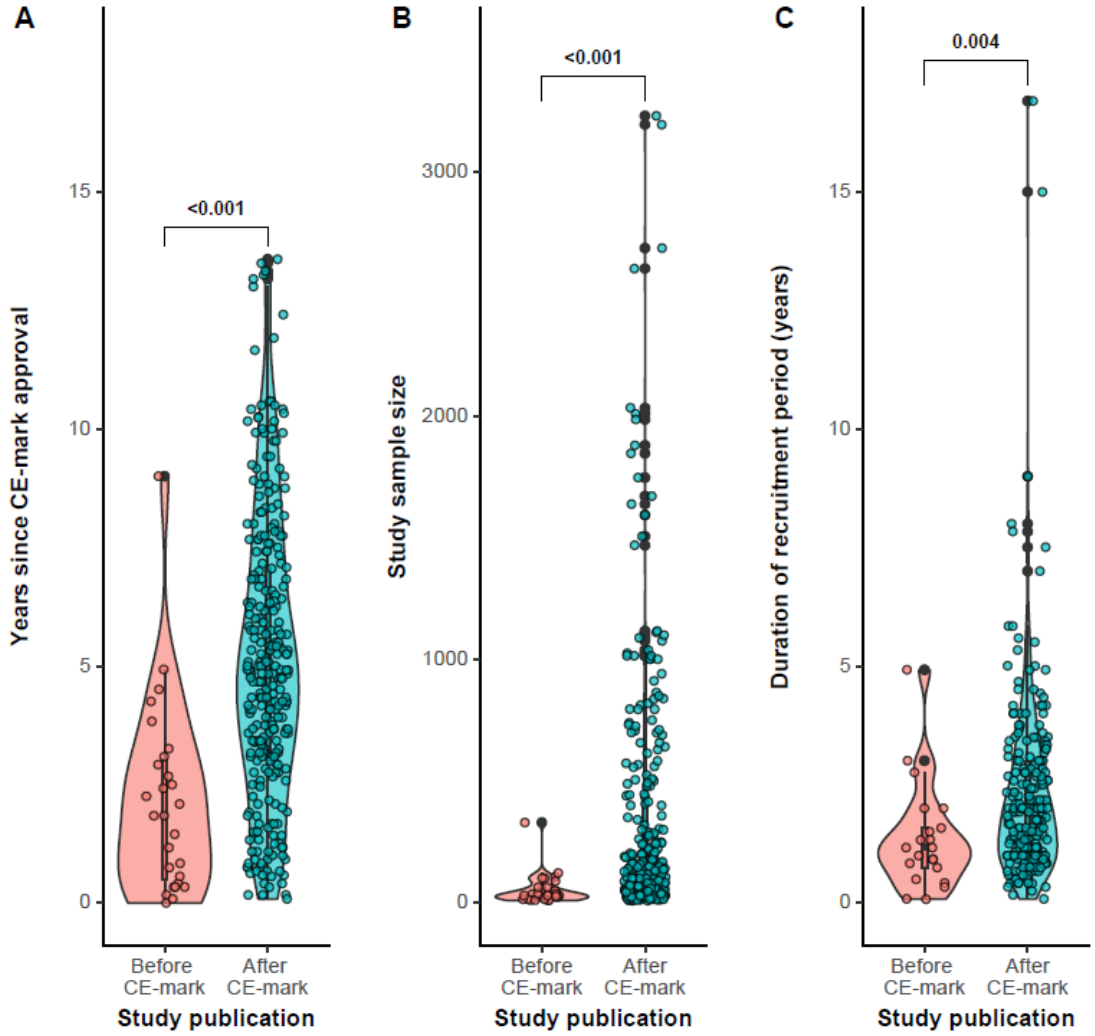
No RCT published before CE-mark approval for any of the 71 CV devices

Non-randomized trials were predominantly published after CE-mark approval (89%, 224/251)

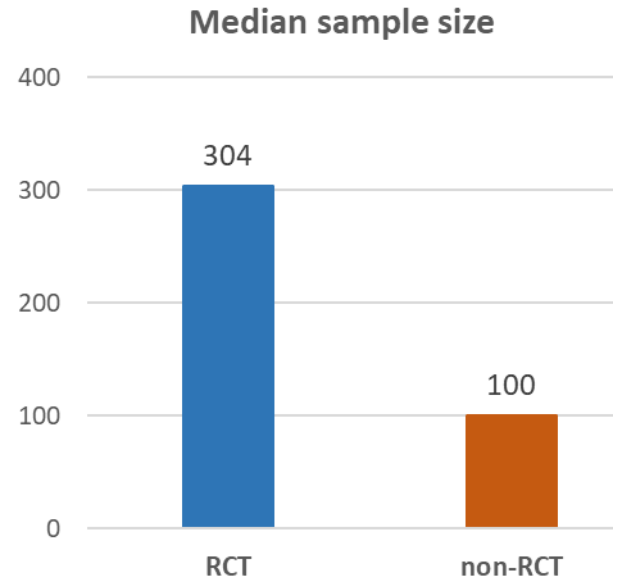
Clinical trials with larger sample sizes (>50 individuals) and longer recruitment periods

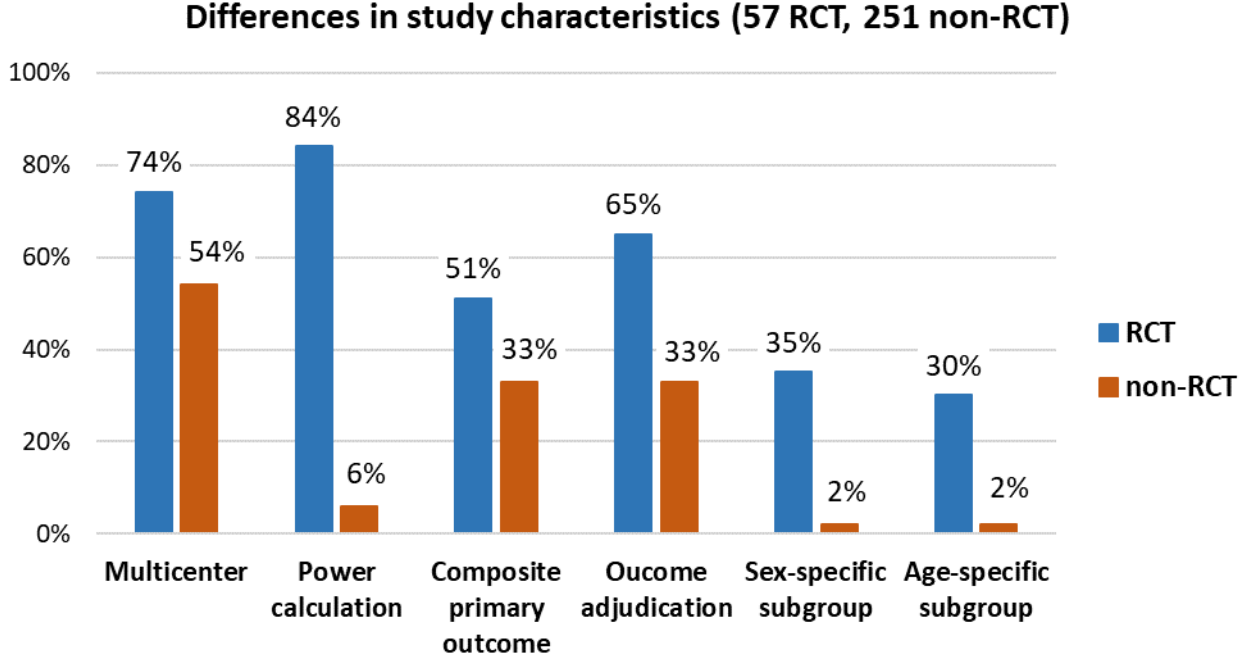
- likely to be published after CE-mark approval
- more frequent during the period 2016-2021

Characteristics of trials performed before and after CE-mark



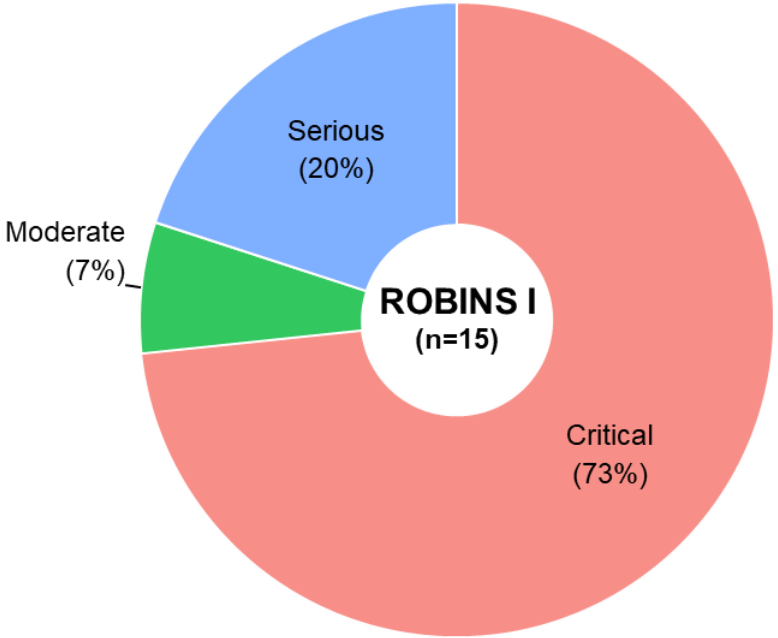
Differences between RCT and non-RCT



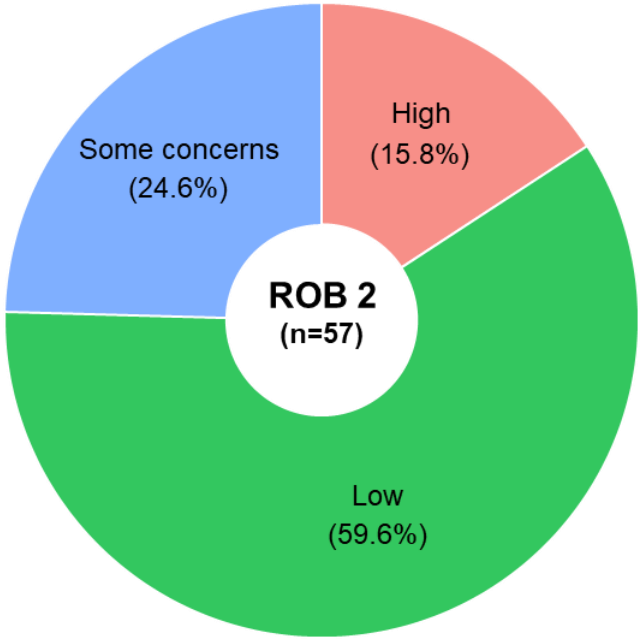


Risk-of-bias assessment

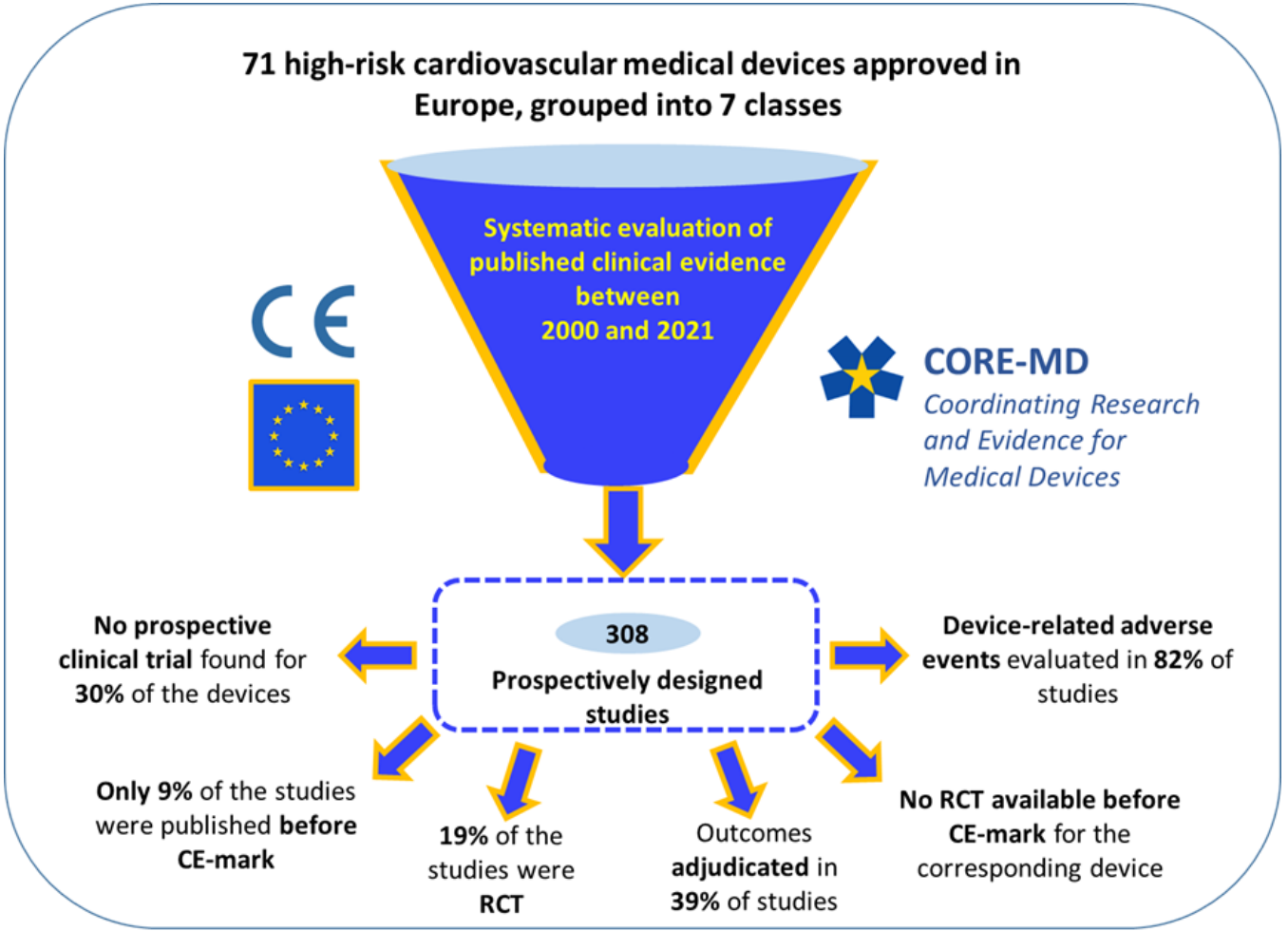
Non-randomized trials comparing health effects of two or more interventions (n=15)



Randomized Clinical Trials (n= 57)



Summary


71 high-risk cardiovascular medical devices approved in Europe, grouped into 7 classes
Systematic evaluation of published clinical evidence between 2000 and 2021
CE
CORE-MD
Coordinating Research and Evidence for Medical Devices
308
Prospectively designed studies
No prospective clinical trial found for 30% of the devices
Device-related adverse events evaluated in 82% of studies
Only 9% of the studies were published before CE-mark
19% of the studies were RCT
Outcomes adjudicated in 39% of studies
No RCT available before CE-mark for the corresponding device

Conclusions

- **The quantity and quality of publicly available data from prospective clinical investigations, before and after CE approval during the period 2000-2021, was deemed insufficient.**

- **The majority of studies were non-randomized, with increased risk of bias, and performed in small populations with limitations in reporting.**

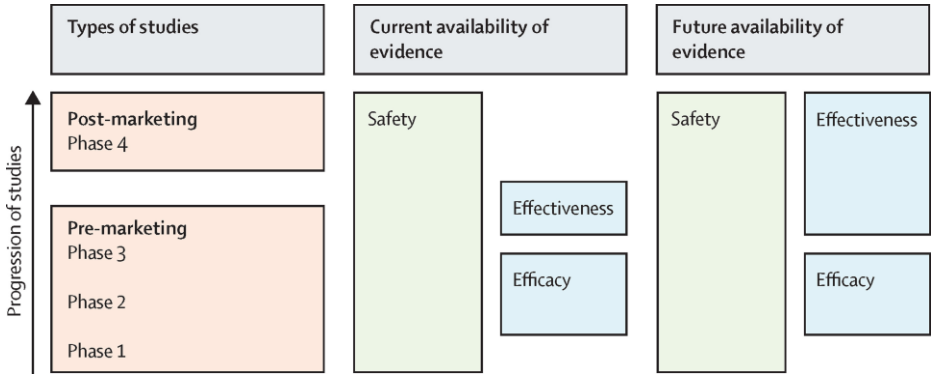
- **None of the reviewed devices had randomized trial results published prior to CE mark certification.**

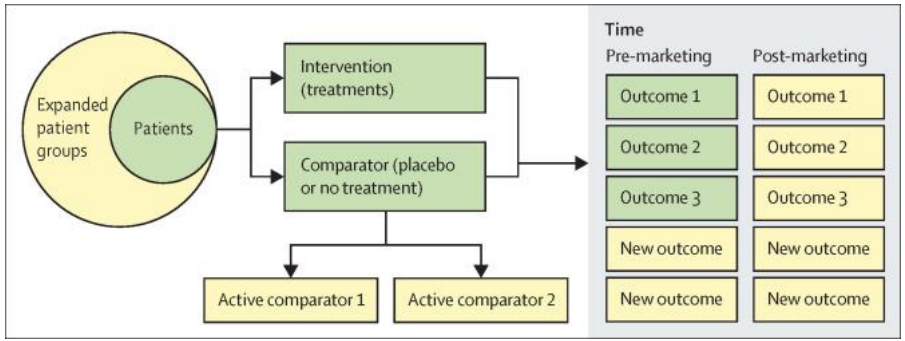
What is next?

→ New devices should undergo systematic non-clinical testing prior to evaluation in clinical studies.

→ Post-marketing studies should be designed hierarchically → priority at product's net clinical benefit in RCTs compared with current known effective therapy

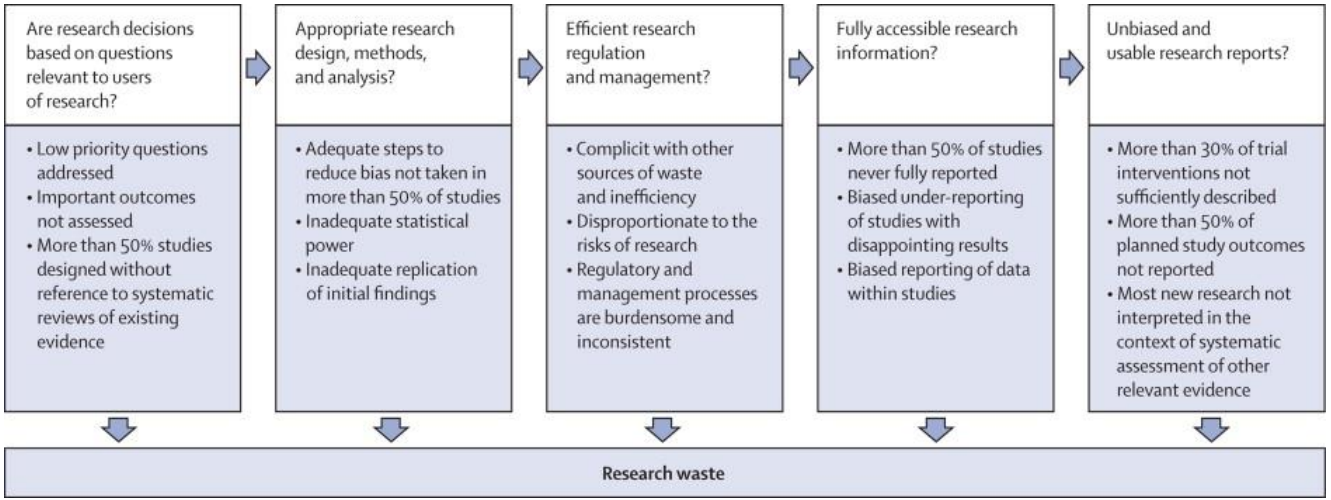
→ Post-marketing studies should incorporate active comparators and long-term follow-up as appropriate





Cipriani A., et al. Lancet, 2020

Biomedical research: increasing value, reducing waste

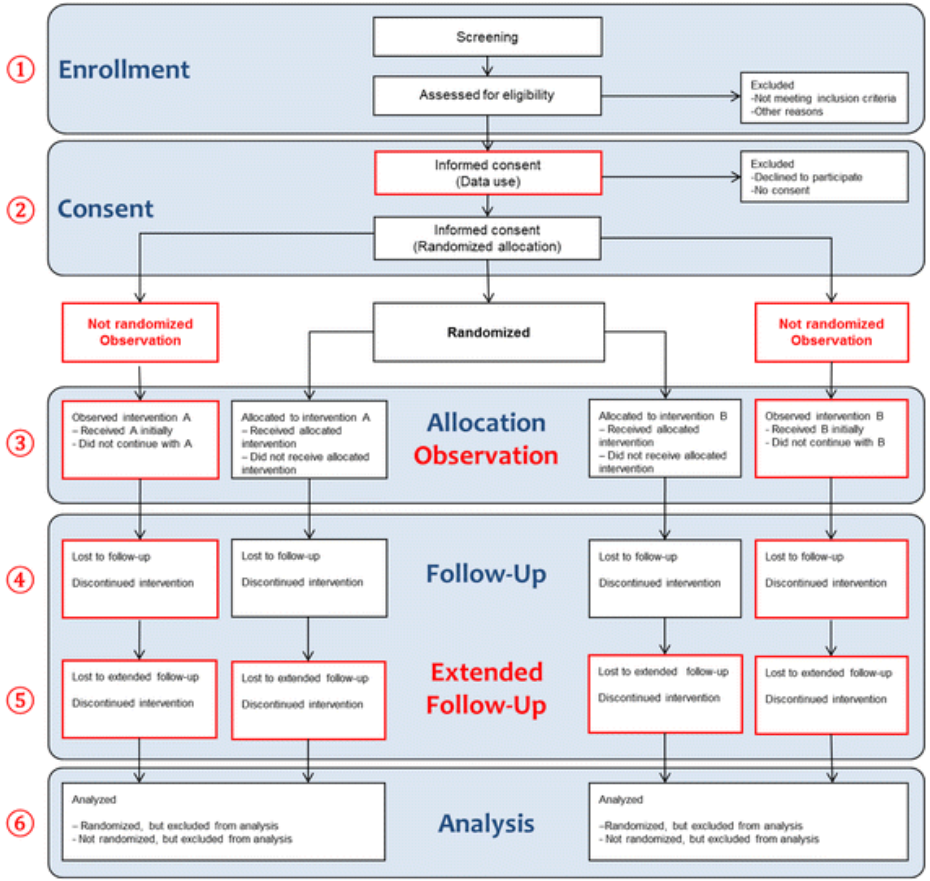


Continuously updated quantitative evidence synthesis is important for rare adverse events and novel devices.

Knowledge gained over the last decade should be considered in the future evaluation of devices.

Historical data to design future trials and avoid unnecessary exposure of patients to risks.

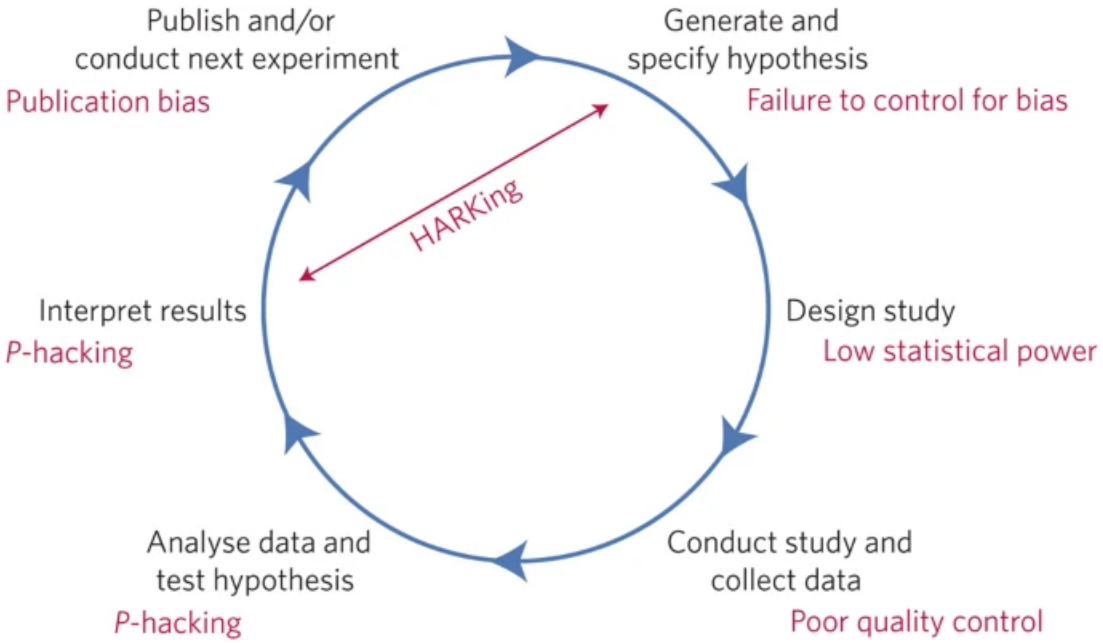
Macleod M., et al. Lancet, 2014



Routinely collected health data in RCTs !

McCord KA., et al. Trials, 2018

Quality <-> Transparency <-> Reproducibility

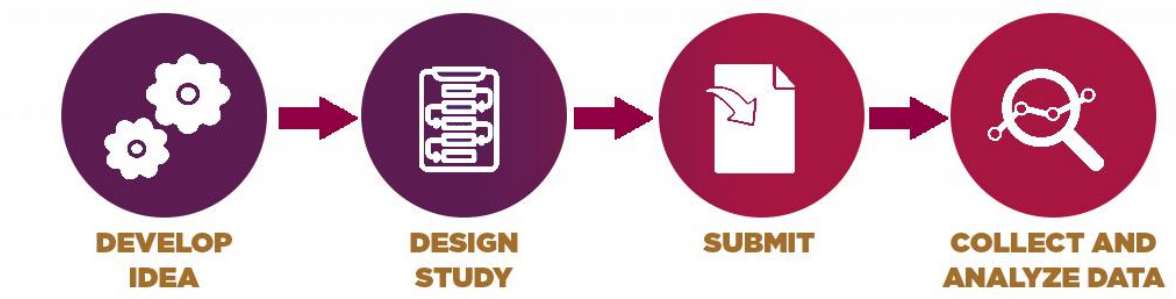


Munafo MR., et al. Nature Hum Behav, 2017

Preregistration

Preregistration is the practice of formally depositing a study design in a repository—and, optionally, submitting it for peer review at a journal—*before* conducting a scientific investigation.

Open Access Preprints Open Data Open Methods Published Peer Review History Credit



ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–17
https://doi.org/10.1093/eurheartj/ehad567

Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD consortium

George C.M. Siontis [1], Bernadette Coles[2], Jonas D. Häner[1], Laurna McGovern [3], Joanna Bartkowiak[1], J.J. Coughlan[3,4], Alessandro Spirito[5], Roberto Galea[1], Andreas Haeberlin [1], Fabien Praz [1], Daijiro Tomii[1], Tom Melvin[6], André Frenk[1], Robert A. Byrne[3], Alan G. Fraser[7], and Stephan Windecker [1]* for the CORE-MD Investigators