CORE-MD

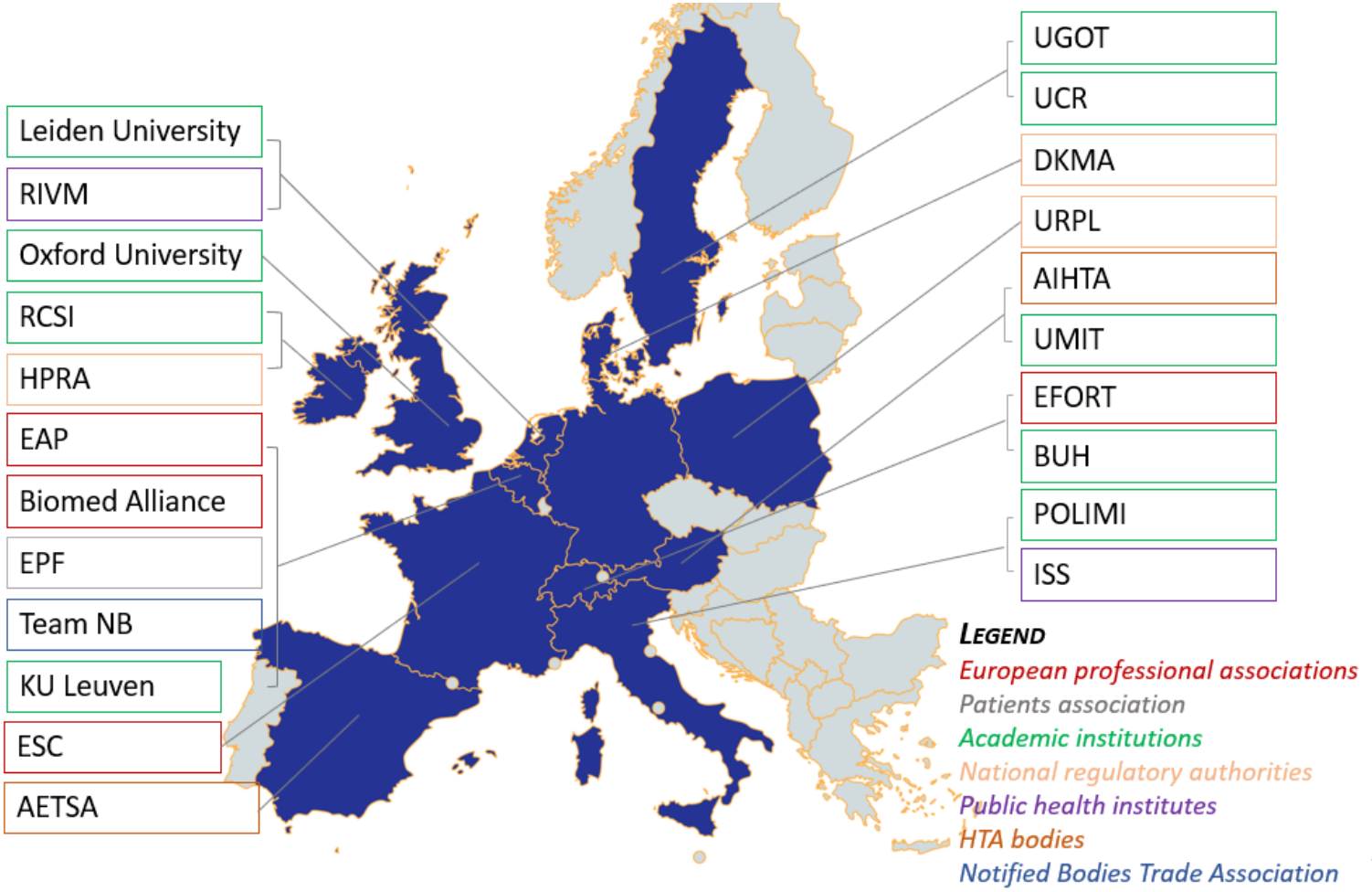
Coordinating Research and Evidence for Medical Devices

Clinical evaluation & transparency of evidence for high-risk medical devices

Prof. Robert A. Byrne | Royal College of Surgeons in Ireland

CORE-MD

Coordinating Research and Evidence for Medical Devices


Leiden University
RIVM
Oxford University
RCSI
HPRA
EAP
Biomed Alliance
EPF
Team NB
KU Leuven
ESC
AETSA
UGOT
UCR
DKMA
URPL
AIHTA
UMIT
EFORT
BUH
POLIMI
ISS
LEGEND
European professional associations
Patients association
Academic institutions
National regulatory authorities
Public health institutes
HTA bodies
Notified Bodies Trade Association

Clinical evaluation & transparency of evidence for high-risk medical devices

1. INTRODUCTION
2. CARDIOVASCULAR DEVICES
3. ORTHOPAEDIC DEVICES
4. DEVICES FOR Mx OF DIABETES MELLITUS
5. REPRESENTATION & INCLUSION

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

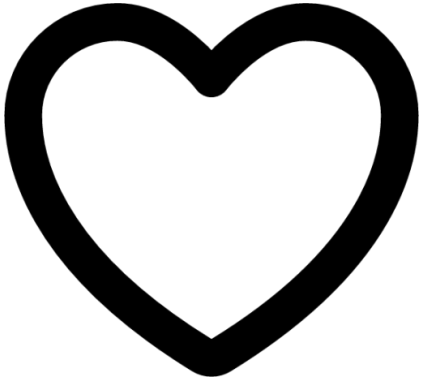
www.core–md.eu

WP1: Systematic literature review

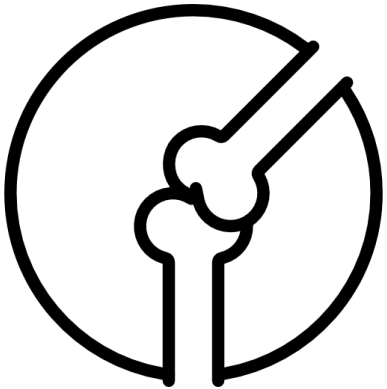
We aimed to:

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

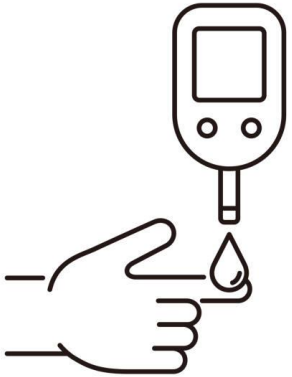
High Risk Medical Device Systematic Reviews



Cardiovascular



Orthopaedics



Diabetes

CORE-MD

Coordinating Research and Evidence for Medical Devices

EFORT open reviews

GENERAL ORTHOPAEDICS | 8:11 | 781–791

Clinical investigations to evaluate high-risk orthopaedic devices: a systematic review of the peer-reviewed medical literature

Anne Lübbeke[1,2], Christophe Combescure[3], Christophe Barea[1], Amanda Inez Gonzalez[1], Keith Tucker[4], Per Kjærsgaard-Andersen[5], Tom Melvin[6], Alan G Fraser[7], Rob Nelissen[8] and James A Smith[9,10]

Open access Protocol

BMJ Open

Clinical evidence for high-risk medical devices used to manage diabetes: protocol for a systematic review and meta-analysis

Arjola Bano [1,2] Markus Laimer,[3] Faina Wehrli,[3] Juri Kunzler,[3] Tania Rivero,[4] Alan G Fraser,[5] Christoph Stettler,[3] Roman Hovorka,[6] Lia Bally [3]

ESC European Society of Cardiology

European Heart Journal (2024) 45, 161–177
https://doi.org/10.1093/eurheartj/ehad567

FASTTRACK CLINICAL RESEARCH
Clinical trials

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

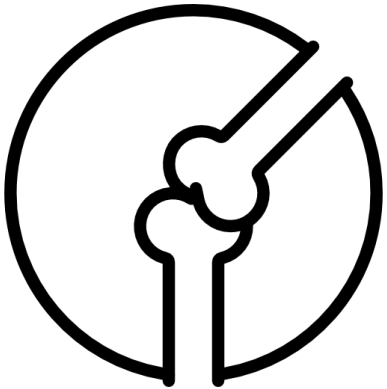
George C.M. Siontis [1], Bernadette Coles[2], Jonas D. Häner[1], Laurna McGovern [3], Joanna Bartkowiak[1], J.J. Coughlan[3,4], Alessandro Spirito[5], Roberto Galea[1], Andreas Haeberlin [1], Fabien Praz [1], Daijiro Tomii[1], Tom Melvin[6], André Frenk[1], Robert A. Byrne[3], Alan G. Fraser[7], and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

CORE-MD

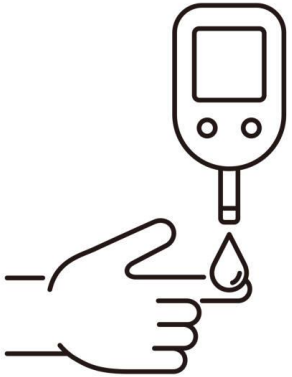
Coordinating Research and Evidence for Medical Devices

High Risk Medical Device Systematic Reviews

Cardiovascular



Orthopaedics



Diabetes

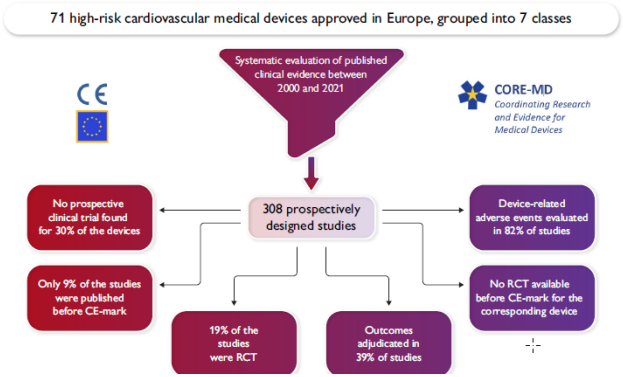
CORE-MD

Coordinating Research and Evidence for Medical Devices

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

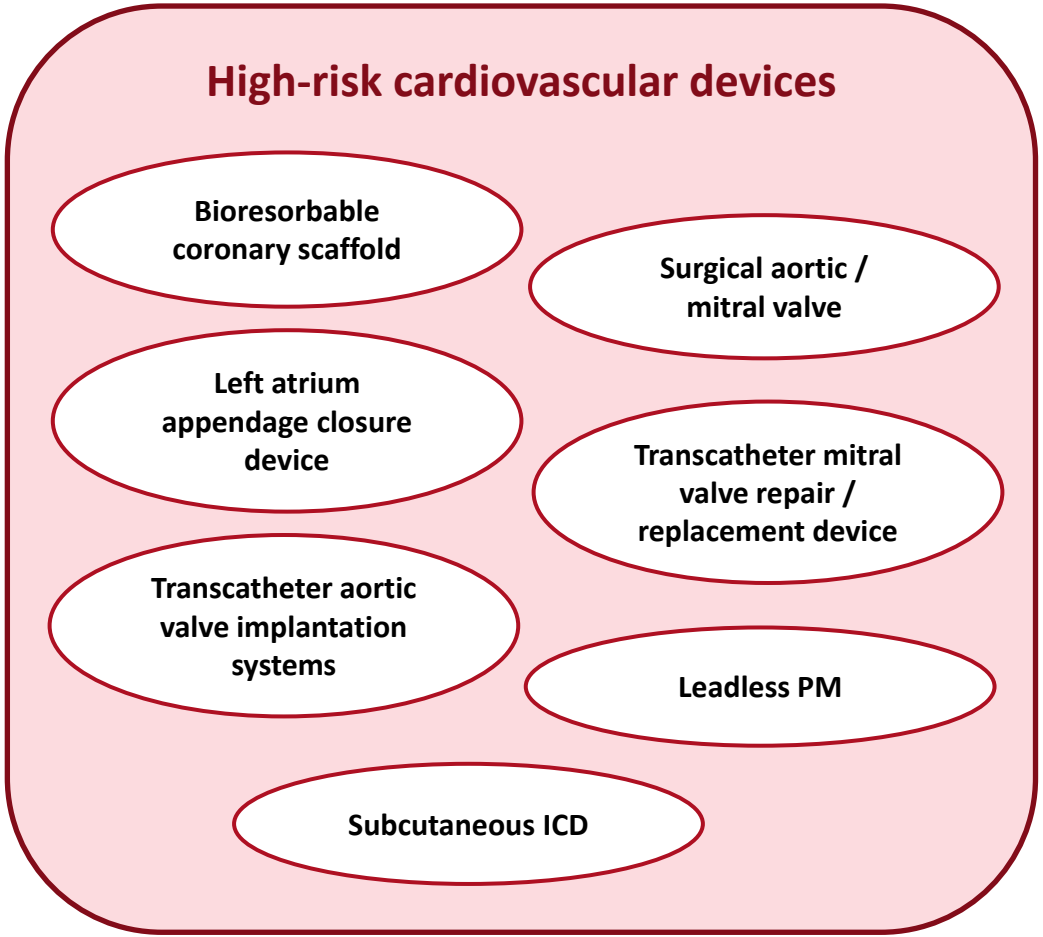


Methods

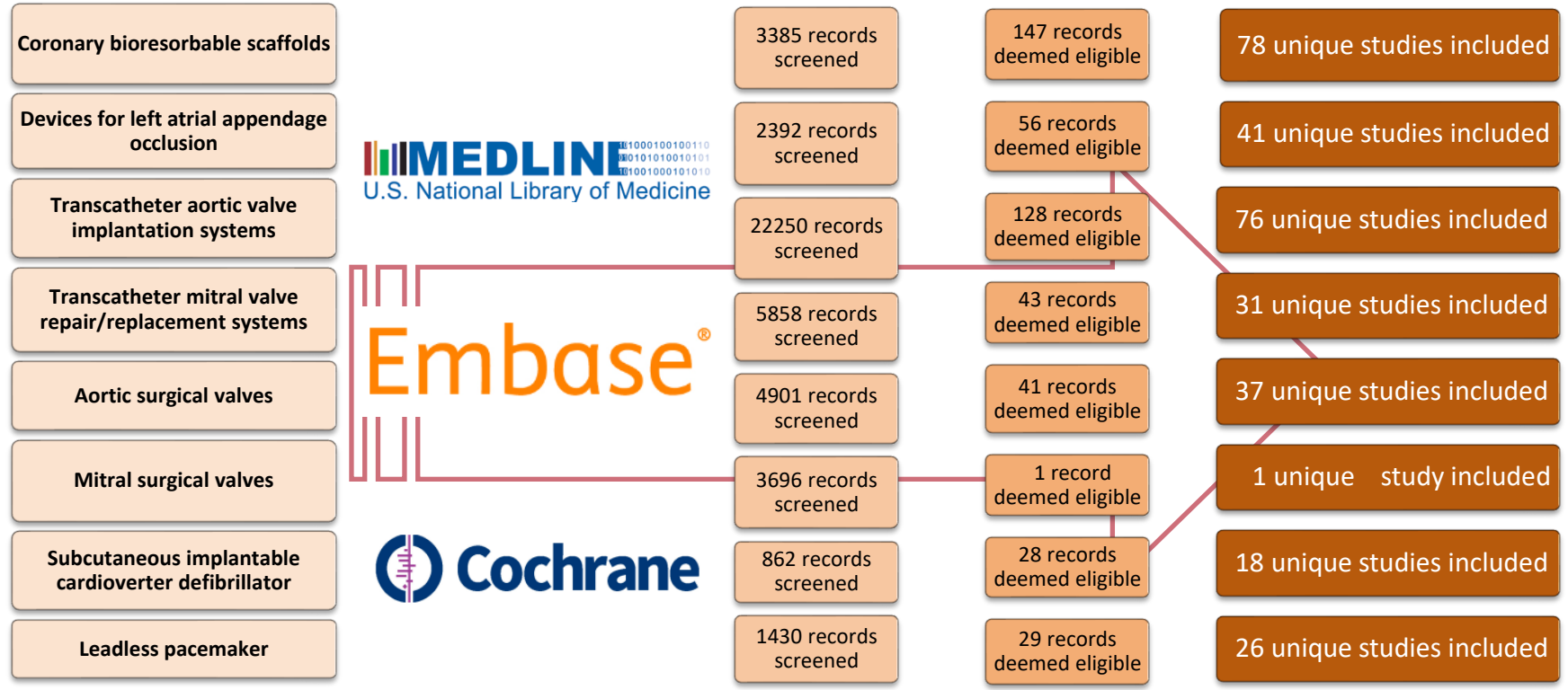
We predefined 7 groups of Class III cardiovascular devices, encompassing 71 long-term implantable devices put on the EU market since the year 2000

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



7 classes of CV devices

44,774 studies evaluated

308 studies across all classes of devices

Siontis et al. Eur Heart J 2023

Catalogue of Included Surgical Heart Valves

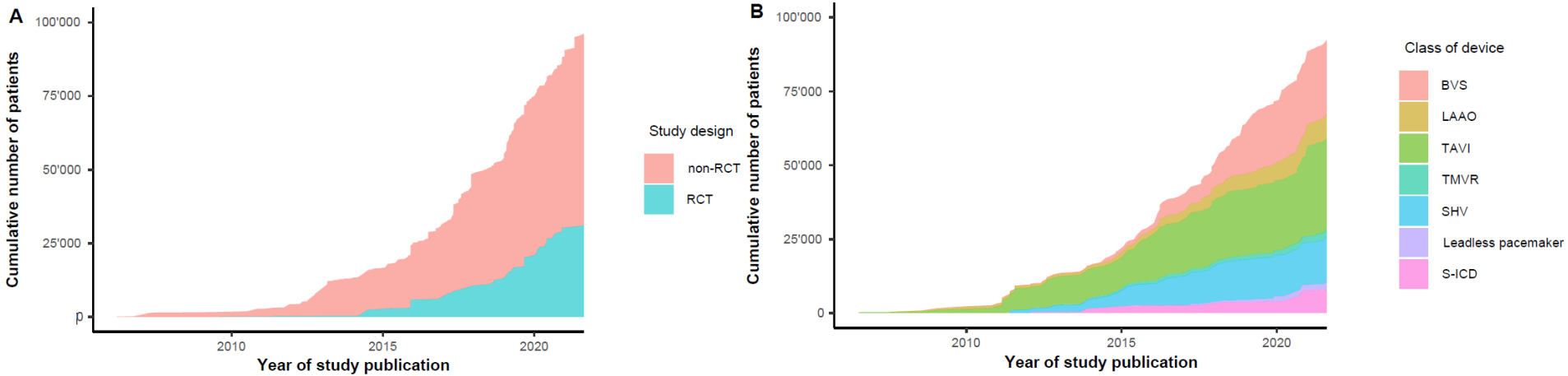
No publicly accessible listing of devices with CE mark approval

Company	Name	CE mark
AORTIC BIOPROSTHETIC		
Edwards Lifesciences	Perimount Magna (model 3000 TFX)	2004
	Perimount Magna Ease (model 3300 TFX)	12/2006
	Inspiris Resilia	09/2016
	Intuity	02/2012
	Intuity Elite	06/2014
Sorin/Livanova/Corcym	Mitroflow PRT	07/2011
	Crown PRT	07/2014
	Solo Smart	11/2013
	Perceval	01/2011
	Perceval Plus	07/2020
Medtronic	Avalus	08/2017
	3F Enable	12/2009
St Jude/Abbott	Epic Aortic	06/2007
	Trifecta	03/2010
	Biocor Aortic	06/2007

Company	Name	CE mark
AORTIC MECHANICAL		
Cryolife	Aortic ON-X with Conform-X sewing ring	2002
	Aortic ON-X with anatomic sewing ring	2012
MITRAL BIOPROSTHETIC		
Edwards Lifesciences	Perimount Plus (model 6900 PTFX)	04/2004
	Magna Mitral Ease (model 7300 TFX)	08/2010
St Jude/Abbott	Epic Mitral	06/2007
	Biocor Mitral	06/2007

McGovern et al. ESC Congress 2023

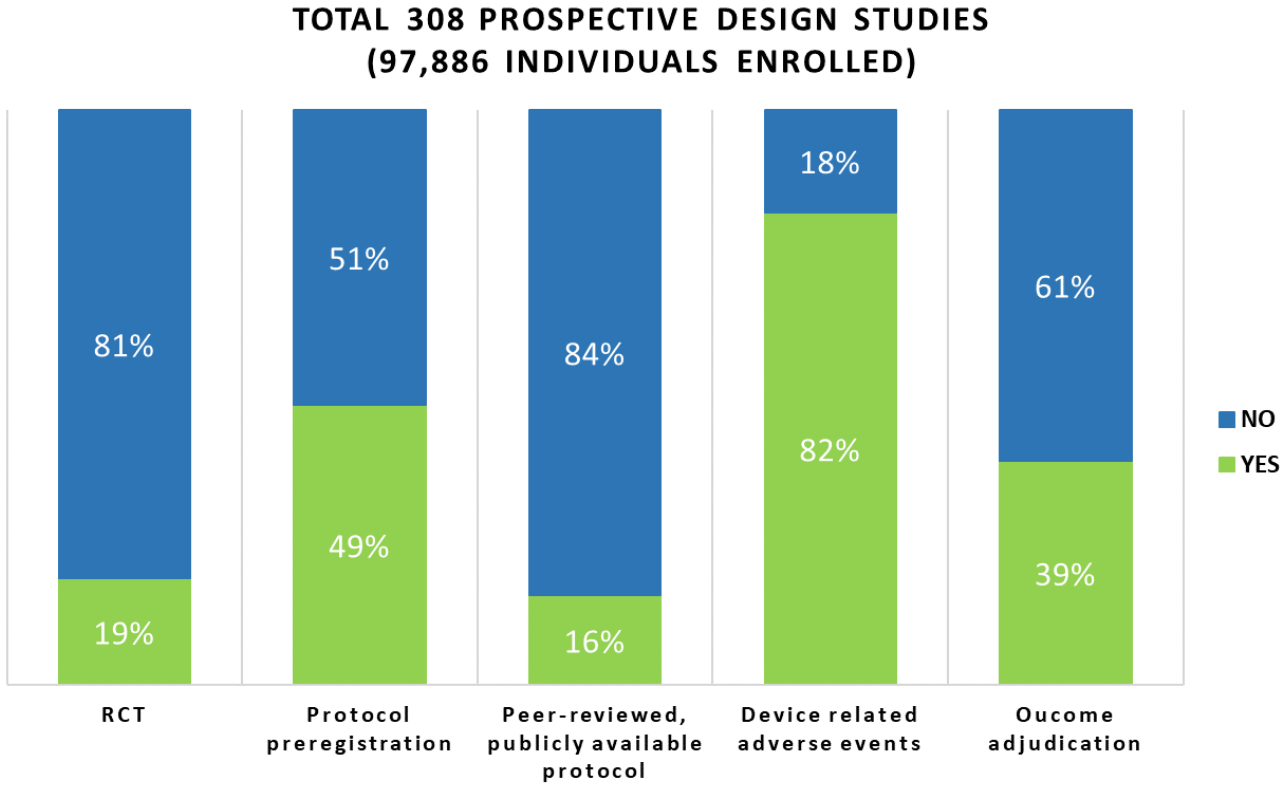
Cumulative number of patients recruited in prospective clinical trials evaluating high-risk cardiovascular devices between 2000-2021



Accumulated sample of 97,886 individuals | Mean sample size 120

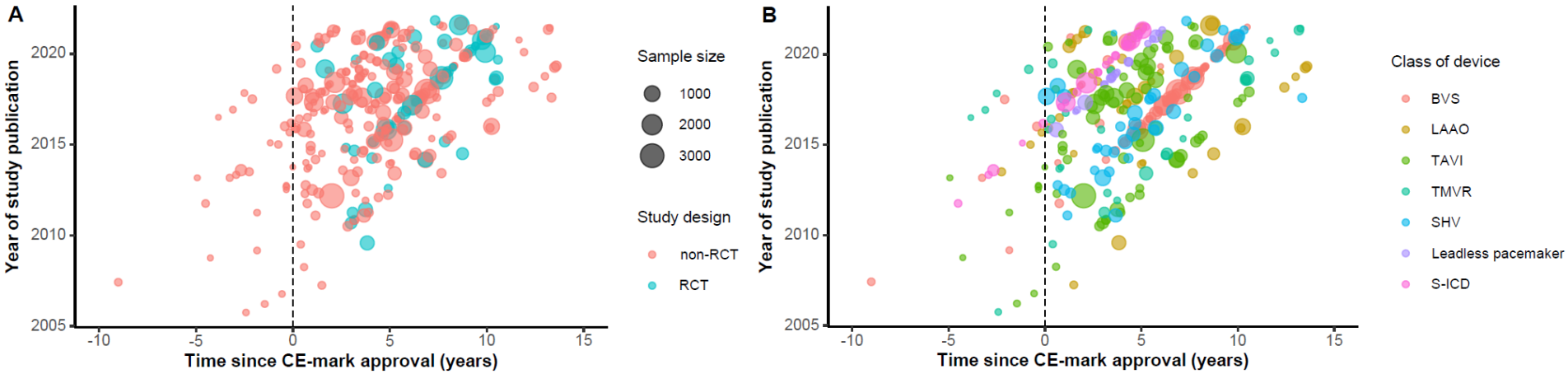
Siontis et al. Eur Heart J 2024

Results - Clinical trial characteristics



Siontis et al. Eur Heart J 2024

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)

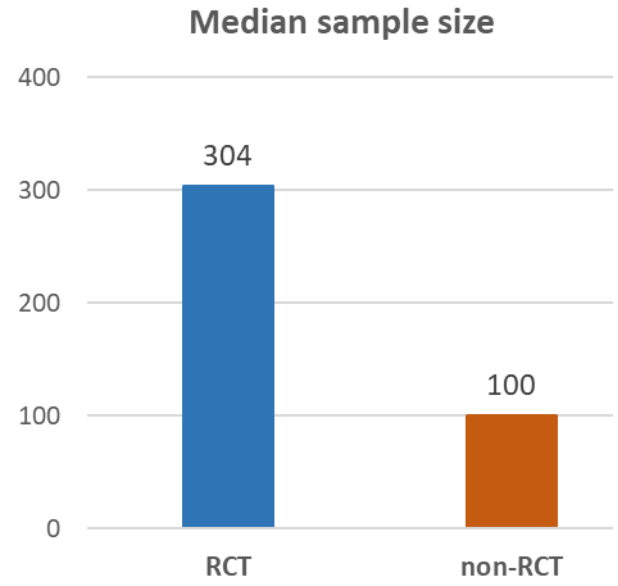
Clinical trials with larger sample sizes (>50 individuals) and longer recruitment periods

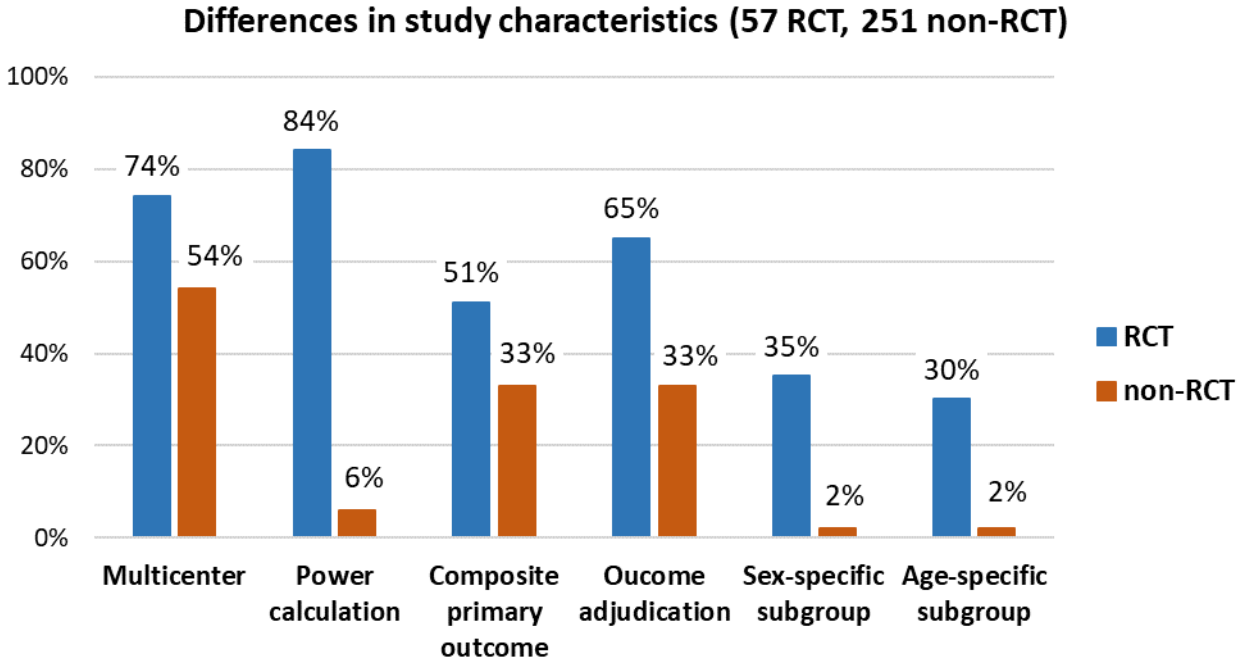
–likely to be published after CE-mark approval

–more frequent during the period 2016-2021

Siontis et al. Eur Heart J 2024

Differences between RCT and non-RCT

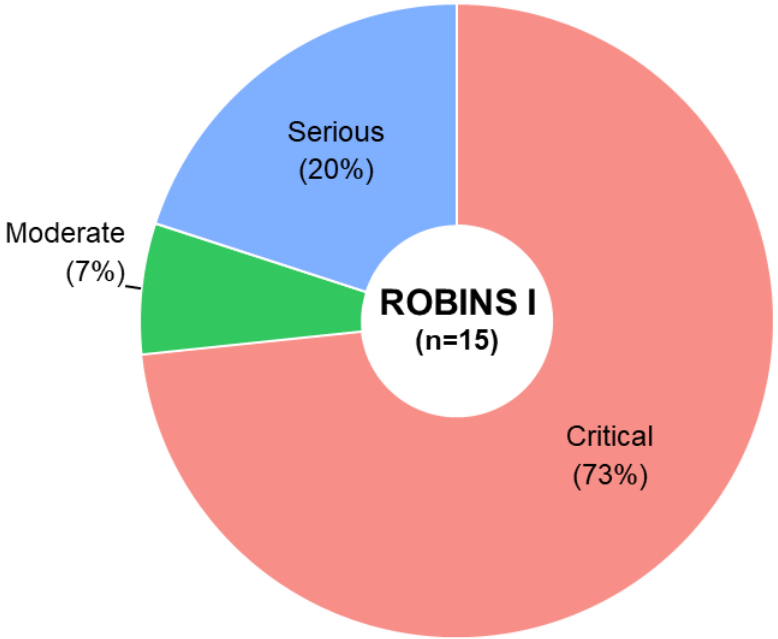




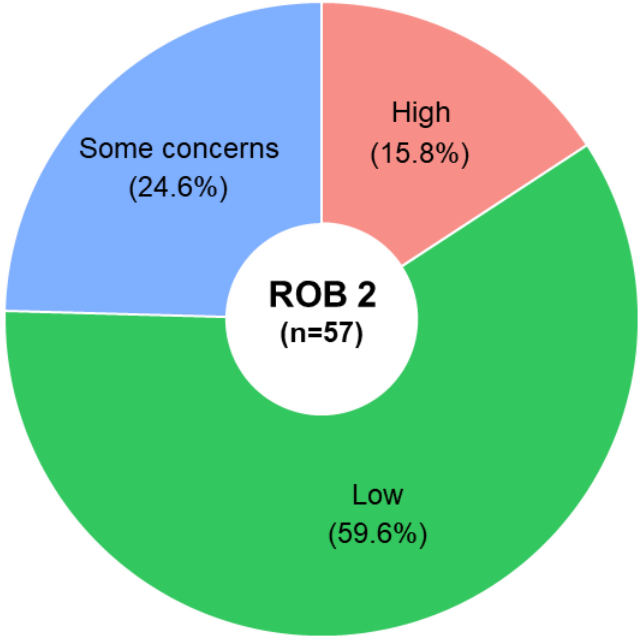
Siontis et al. Eur Heart J 2024

Risk-of-bias assessment

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

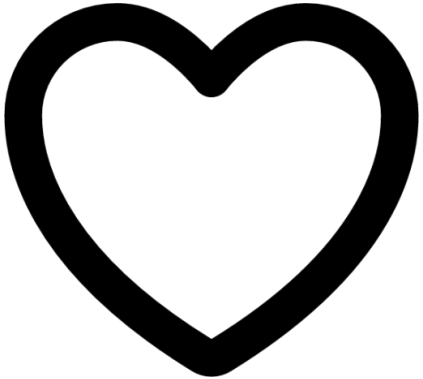


Randomized Clinical Trials (n= 57)

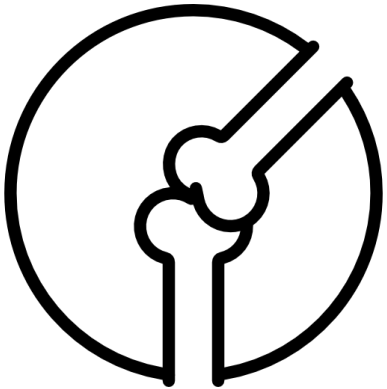


Siontis et al. Eur Heart J 2024

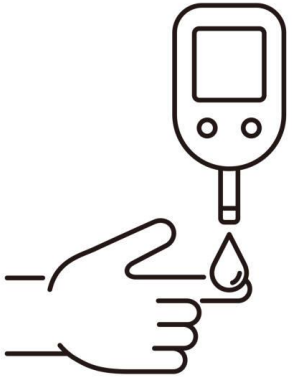
High Risk Medical Device Systematic Reviews



Cardiovascular



Orthopaedics



Diabetes

CORE-MD

Coordinating Research and Evidence for Medical Devices

Methods – Literature methodology and outcomes

- **Random selection of 30 (in total) hip and knee devices from ODEP* and registry reports from European countries for inclusion in systematic review**
- For each device, identification of year of first CE-marking & FDA approval
- 30 systematic literature searches to identify peer-reviewed literature available for each device 10 years before and 20 years after CE-marking
- Reporting according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[3] statement
- Protocol registered on open science framework (https://osf.io/6gmyx)

*Orthopaedic data evaluation panel

Lubbeke et al. Effort Open Rev 2023

Search strategy - Literature methodology and outcomes

Search strategy and articles screened

Total N articles: 2901

Search terms

Device name AND hip/knee AND date range AND Humans[MeSH Terms]

Date range = 10 years before to 20 years after CE marking

Implant type	Embase	PubMed	Web of science	N after deduplication*	N other sources*	N studies included
Hip stem	408	238	293	751	9	63
Hip cup	199	50	137	302	1	34
Knee	825	399	352	1078	1	54
Total	**1432**	**687**	**782**	**2131**	**11**	**151**

Lubbeke et al. Effort Open Rev 2023

Results – Literature methodology and outcomes

	Hip stems (N=63)	Hip cups (N=34)	Knees (N=54)	All (N=151)
Publication period	1995-2021	2007-2021	2002-2021	1995-2021
Location EU/America/Asia/Other	66.7/23.8/1.6/7.9%	70.6/0/23.5/11.8%	61.1/29.6/9.3/1.9%	**63.6**/19.9/9.3/5.3%
Study type				
Case report	3.2%	11.8%	1.9%	4.6%
Case-control	-	-	5.6%	2%
Cohort registry-bas.	7.9%	11.8%	18.5%	12.6%
Other cohorts	84.1%	67.6%	59.3%	**71.5%**
Retrospective*	83.0%	56.5%	62.5%	72.2%
RCT	4.8%	8.8%	14.8%	9.3%
Comparator groups yes	41.3%	20.6%	59.3%	43%

CORE-MD
Coordinating Research and Evidence for Medical Devices

Results – Literature methodology and outcomes

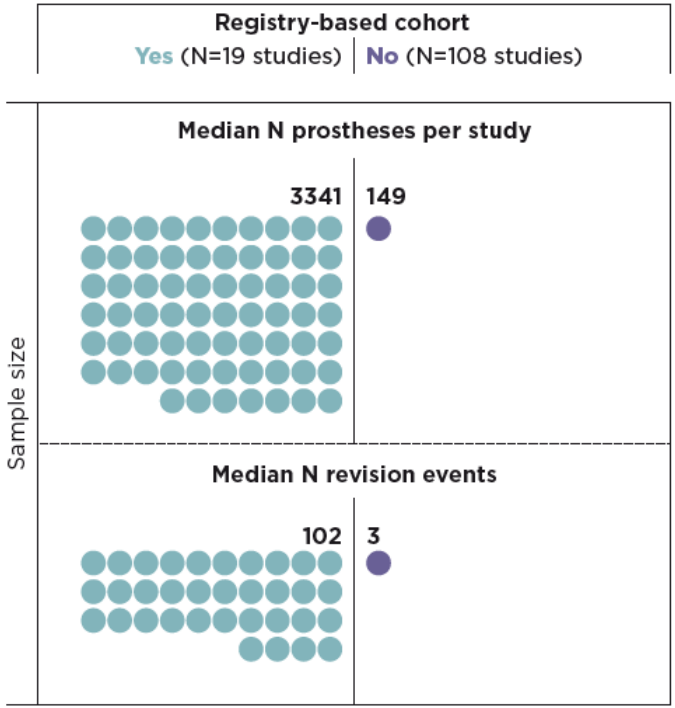
	Hip stems (N =63)	Hip cups (N =34)	Knees (N =54)	All (N =151)
N° prostheses included, mean-median(range)	615-139(1-14'147)	613-95(1-14'147)	1460-180(1-27'193)	917-139(1-27'193)
Inclusion period, median years	3	2	3	3
Follow-up, median years, range	5.5(0.1-17.8)	5.0(0.3-15.0)	3.4(1-13.4)	4.6(1-17.8)
First inclusion date to publication in years, median, range	10(4-22)	9(2-21)	11(3-20)	**10(2-22)**
CE-mark date to first publication in years, median, range	9(3-13)	10(7-12)	7(5-10)	**9(3-13)**
FDA approval to first publication in years, median, range	5(-8)-10)	2(1-3)	5(-3)-8)	5(-8)-10)

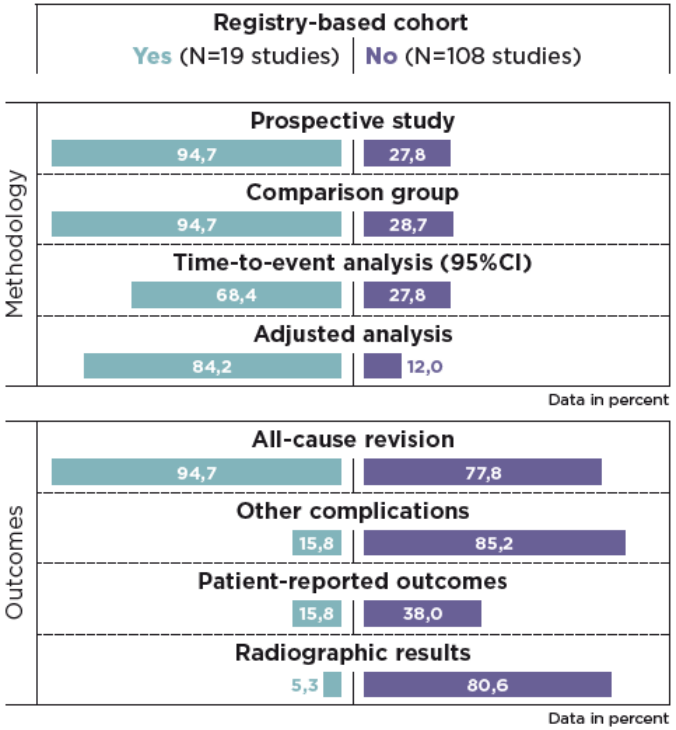
CORE-MD
Coordinating Research and Evidence for Medical Devices

No study published before CE-mark date

Results – Literature methodology and outcomes

Comparison of cohort studies conducted yes or no within a registry (median follow-up 5 years)





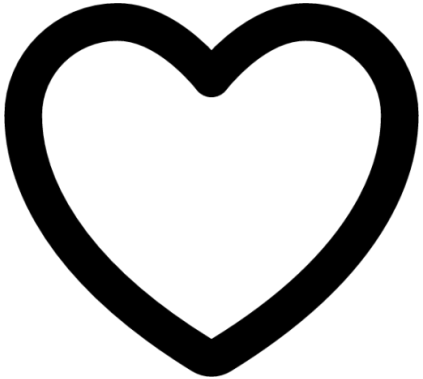
CORE-MD
Coordinating Research and Evidence for Medical Devices

Summary - Literature methodology and outcomes

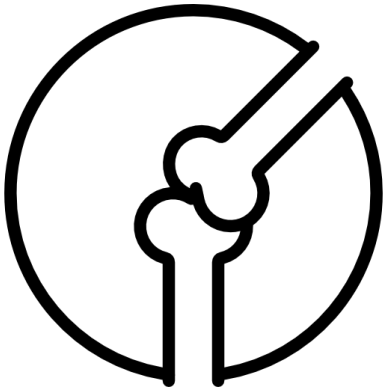
- **No pre-CE-marking clinical investigations in peer-reviewed literature for the 30 randomly selected implants**
- On average 5 publications within 20 yrs. after CE-marking
- Majority cohort studies - conducted in academic institutions – 2/3 in EU
- On average 9 yrs. from CE-mark date to first publication
- Main outcome all-cause revision - PROs increasing – Imaging surrogate
- Registry-based studies: more efficient - higher quality – Revision & PROs

Lubbeke et al. Effort Open Rev 2023

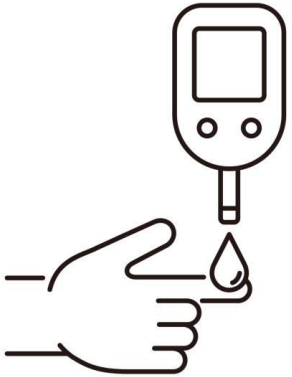
High Risk Medical Device Systematic Reviews



Cardiovascular



Orthopaedics



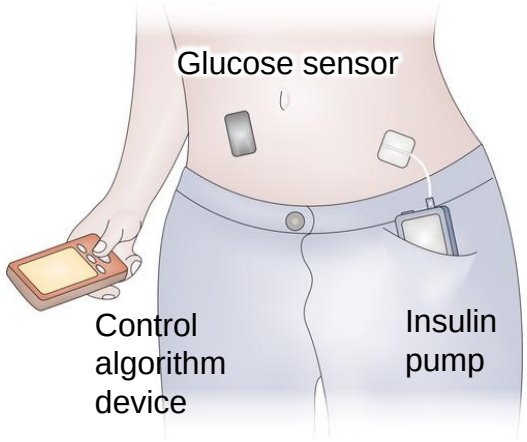
Diabetes

CORE-MD

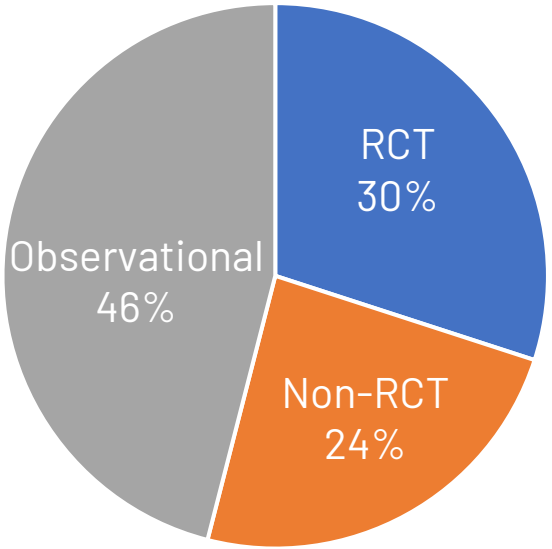
Coordinating Research and Evidence for Medical Devices

Classes of Devices

- Implantable continuous glucose monitoring systems (CGM)
- Implantable insulin pumps
- Automated insulin delivery systems (AID)
  -Hybrid closed loop systems
  -Fully closed loop systems



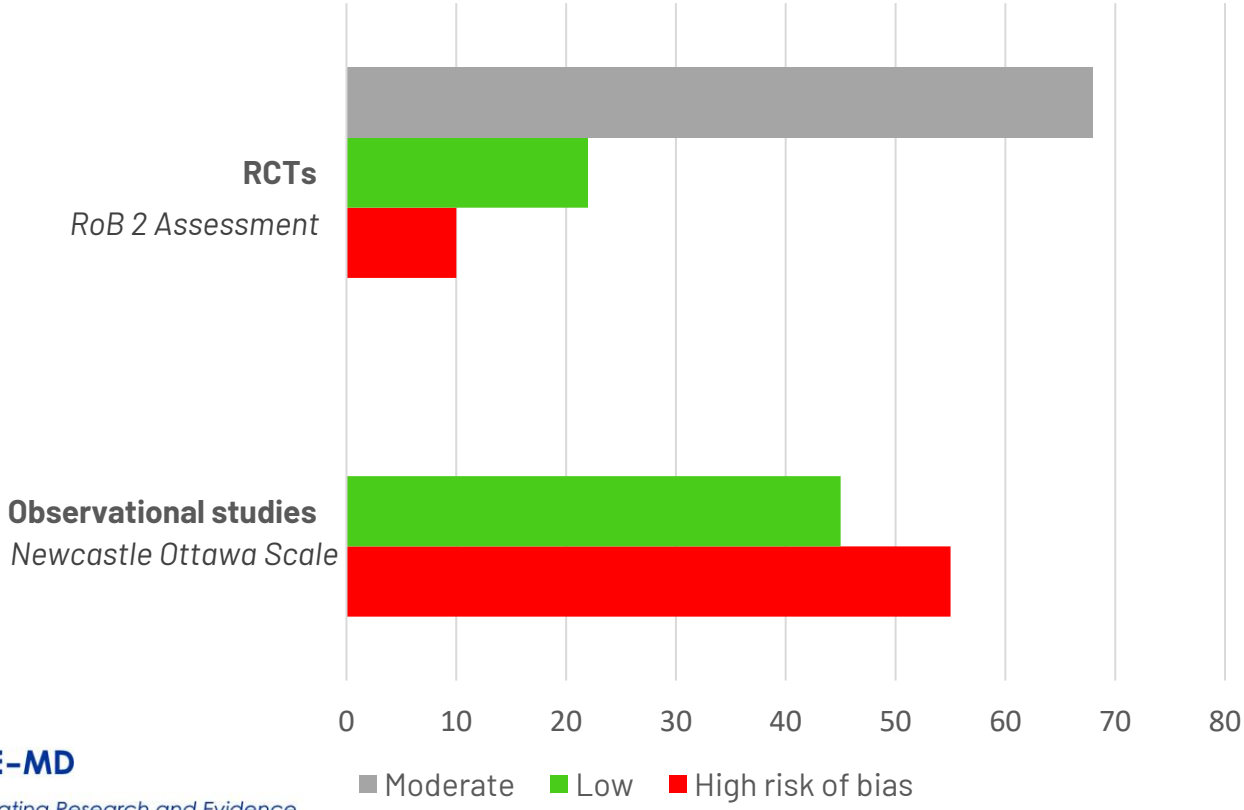
Study designs



- Studies published 2009-2022
- 41% industry funding
- **27% of studies were published before the dates of regulatory approval (CE-mark)**

- **Median sample size: 52 participants (IQR: 25-115)**
- Predominantly type 1 diabetes
- Predominantly aged ≥18 years
- Median max follow-up: 13 weeks (IQR: 4-26)
- **47% of studies had a comparator group**

Risk of Bias Assessment



CORE-MD
Coordinating Research and Evidence for Medical Devices

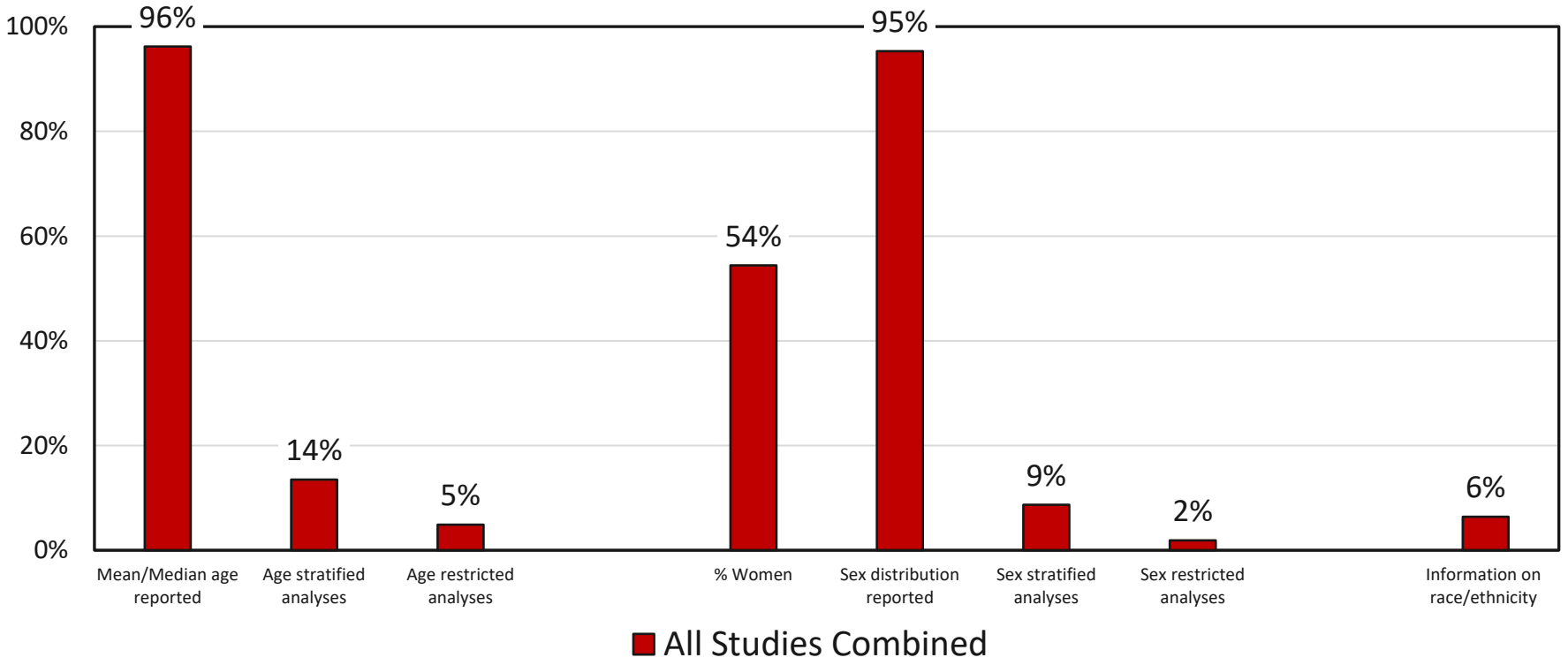
Potential Groups of Interest

Older adults

Female

Ethnic/Racial Groups

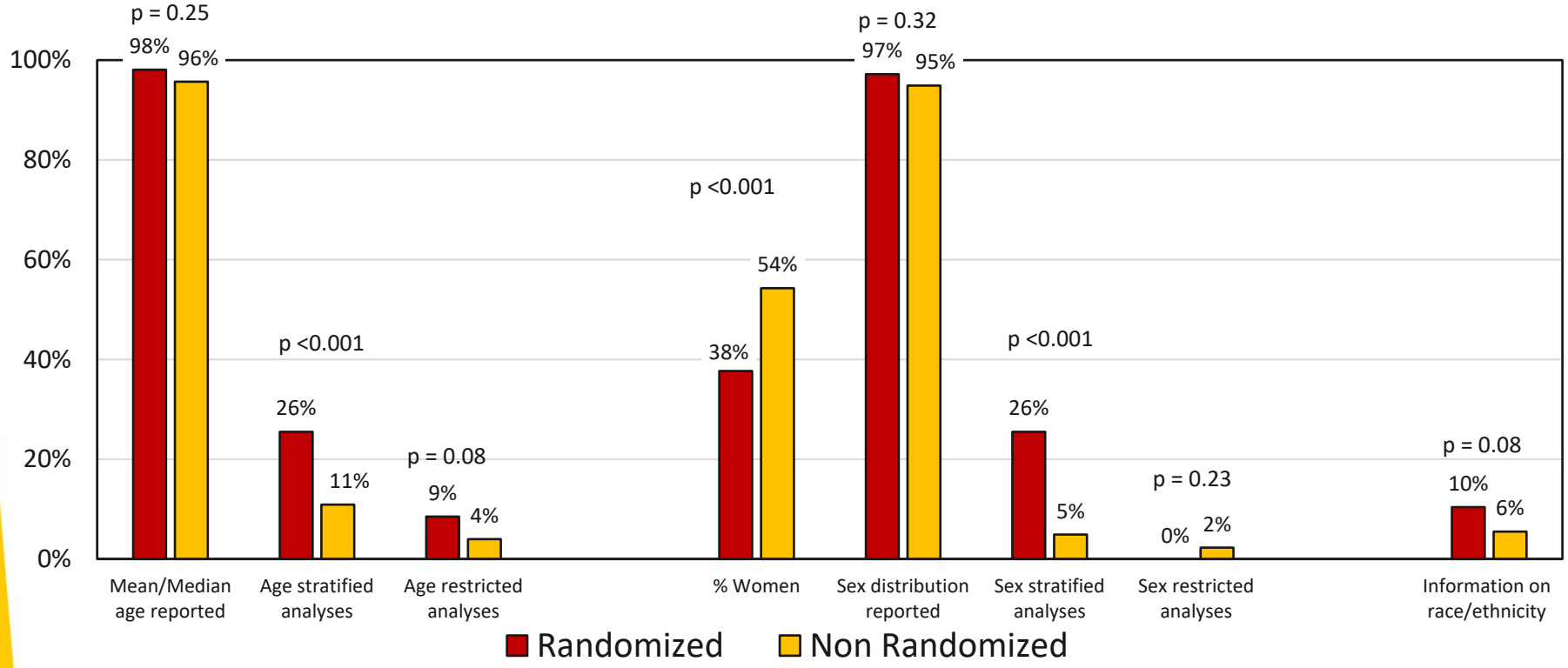
Age, sex & ethnicity in prospective studies of hi-risk MDs



CORE-MD

Coordinating Research and Evidence for Medical Devices

Age, sex & ethnicity in randomized versus non-randomized studies of hi-risk MDs



CORE-MD

Coordinating Research and Evidence for Medical Devices

Conclusions: CORE-MD systematic literature review

1. Significant issues with quality and transparency of evidence for high-risk medical devices before CE mark approval was identified in all three surveyed domains (CV, ortho, diabetes)
2. Published studies were frequently characterized by small sample size, were mostly non-randomized and often reported without comparator
3. There was considerable variability of quality of clinical evidence from published studies across devices from the same class, between different classes of devices, and between devices from different medical fields
4. Evidence of cohort-specific outcomes in subgroups of treated patients according to age, sex & ethnicity was limited across the literature surveyed

EFORT open reviews

GENERAL ORTHOPAEDICS | 8:11 | 781–791

Clinical investigations to evaluate high-risk orthopaedic devices: a systematic review of the peer-reviewed medical literature

Anne Lübbeke[1,2], Christophe Combescure[3], Christophe Barea[1], Amanda Inez Gonzalez[1], Keith Tucker[4], Per Kjærsgaard-Andersen[5], Tom Melvin[6], Alan G Fraser[7], Rob Nelissen[8] and James A Smith[9,10]

Open access Protocol

BMJ Open

Clinical evidence for high-risk medical devices used to manage diabetes: protocol for a systematic review and meta-analysis

Arjola Bano [1,2] Markus Laimer,[3] Faina Wehrli,[3] Juri Kunzler,[3] Tania Rivero,[4] Alan G Fraser,[5] Christoph Stettler,[3] Roman Hovorka,[6] Lia Bally [3]

ESC European Society of Cardiology

European Heart Journal (2024) 45, 161–177
https://doi.org/10.1093/eurheartj/ehad567

FASTTRACK CLINICAL RESEARCH
Clinical trials

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

CORE-MD

Coordinating Research and Evidence for Medical Devices

Thank you

CORE-MD

Coordinating Research and Evidence for Medical Devices

CORE-MD

Coordinating Research and Evidence for Medical Devices