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

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See the editorial comment for this article 'Quality and transparency of clinical evidence for high-risk cardiovascular medical devices: a long way to go', by P. Szymański and R. Redberg, https://doi.org/10.1093/eurheartj/ehad786.

Abstract

Background and Aims The European Union Medical Device Regulation 2017/745 challenges key stakeholders to follow transparent and rigorous approaches to the clinical evaluation of medical devices. The purpose of this study is a systematic evaluation of published clinical evidence underlying selected high-risk cardiovascular medical devices before and after market access in the European Union (CE-marking) between 2000 and 2021.

Methods Pre-specified strategies were applied to identify published studies of prospective design evaluating 71 high-risk cardiovascular devices in seven different classes (bioresorbable coronary scaffolds, left atrial appendage occlusion devices, transcatheter aortic valve implantation systems, transcatheter mitral valve repair/replacement systems, surgical aortic and mitral heart valves, leadless pacemakers, subcutaneous implantable cardioverter-defibrillator). The search time span covered 20 years (2000–21). Details of study design, patient population, intervention(s), and primary outcome(s) were summarized and assessed with respect to timing of the corresponding CE-mark approval.

Results At least one prospective clinical trial was identified for 70% (50/71) of the pre-specified devices. Overall, 473 reports of 308 prospectively designed studies (enrolling 97 886 individuals) were deemed eligible, including 81% (251/308) prospective non-randomized clinical trials (66 186 individuals) and 19% (57/308) randomized clinical trials (31 700 individuals). Pre-registration of the study protocol was available in 49% (150/308) studies, and 16% (48/308) had a peer-reviewed publicly available protocol. Device-related adverse events were evaluated in 82% (253/308) of studies. An outcome adjudication process was reported in 39% (120/308) of the studies. Sample size was larger for randomized in comparison to non-randomized trials (median of 304 vs. 100 individuals, $P < .001$). No randomized clinical trial published before CE-mark approval for any of the devices was identified. Non-randomized clinical trials were predominantly published after the corresponding CE-mark approval of the device under evaluation (89%, 224/251). Sample sizes were smaller for studies published before (median of 31 individuals) than after (median of 135 individuals) CE-mark approval ($P < .001$). Clinical trials with larger sample sizes (>50 individuals) and those with longer recruitment periods were more likely to be published after CE-mark approval, and were more frequent during the period 2016–21.

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Conclusions The quantity and quality of publicly available data from prospective clinical investigations across selected categories of cardiovascular devices, before and after CE approval during the period 2000–21, were deemed insufficient. The majority of studies was non-randomized, with increased risk of bias, and performed in small populations without provision of power calculations, and none of the reviewed devices had randomized trial results published prior to CE-mark certification.

Structured Graphical Abstract

Key Question

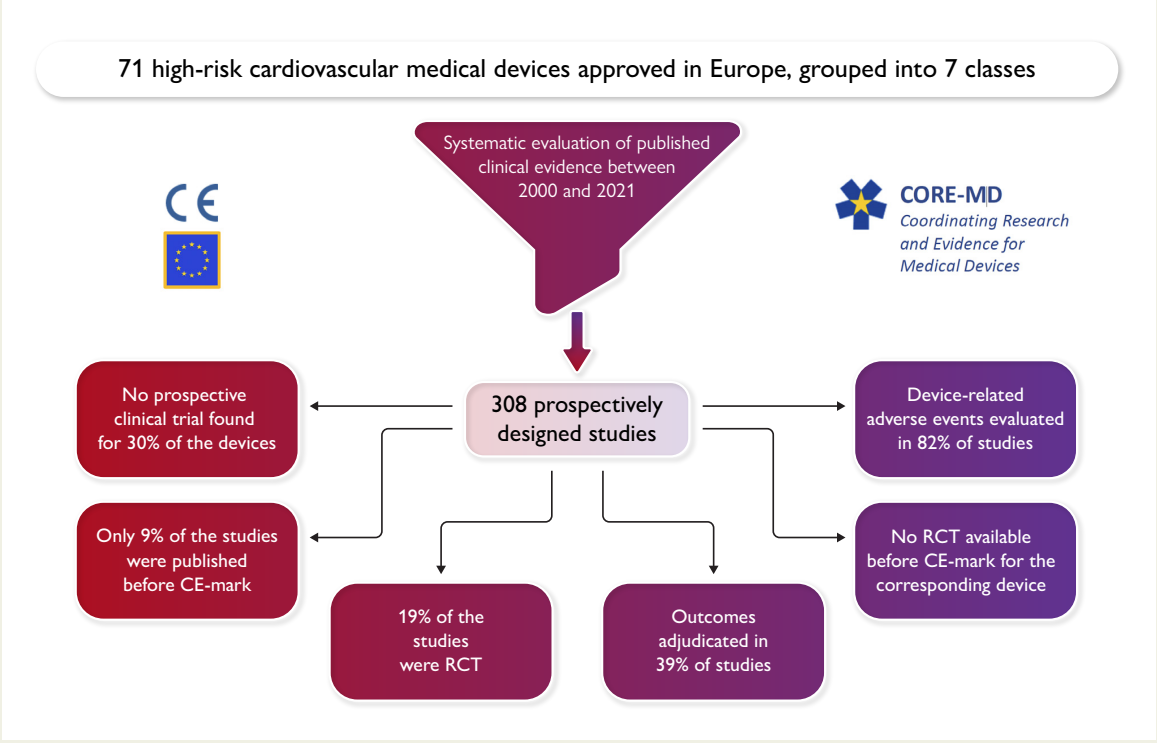
What is the published clinical evidence for high-risk (Class III) cardiovascular medical devices before and after market access in the European Union (CE marking) during the period 2000-2021?

Key Finding

No randomized clinical trial (RCT) of 71 widely-used cardiovascular devices had been conducted and reported prior to the date of CE-mark approval between 2000 and 2021. The vast majority of prospective studies were non-randomized in design and were published predominantly after CE-mark.

Take Home Message

The essential preconditions for evidence-based medicine are the conduct of high quality clinical trials with clinical data published irrespective of the results. Larger and better-designed clinical trials of high-risk cardiovascular devices should be conducted and reported timely.



Systematic evaluation of published clinical trials with prospective design for 71 high-risk cardiovascular devices during the period 2000–21.

Keywords High-risk medical devices • Class III medical devices • Implantable devices • Cardiovascular devices • Conformité Européenne • Medical Device Regulation • European Union

Introduction

A primary goal of the Medical Device Regulation (MDR) enacted in the European Union in 2017 [(EU) 2017/745] is to increase the quantity and improve the quality of clinical evidence to support the use of new high-risk medical devices. The previous medical device directives required manufacturers to demonstrate safety and performance of their devices, with a positive ratio of benefit to risk, but there were few specific requirements relating to methods for clinical evaluation.

Some insights have been obtained from studies of medical devices submitted for regulatory approval by the Food and Drug Administration (FDA) in the USA. For example, during the period 2000 to 2007 only 31% of 78 pre-market approvals were supported by evidence from more than one randomized clinical trial (RCT).[1] This contrasts with new drugs which are usually approved only after

evidence of their safety and efficacy has been established in large randomized trials. Until recently, approval of high-risk medical devices in the EU was granted on the basis of limited data related to proof of their mechanism of action, with a reliance on post-market surveillance to identify safety or efficacy issues.[2–4]

An overview of clinical trial characteristics and methodologies underlying the approval of high-risk medical devices in the EU under the previous Medical Device Directive (93/42/EEC) may be useful to better understand practices applied in the past and to provide a platform on which to consider recommendations during implementation of the MDR. As part of the Coordinating Research and Evidence for Medical Devices (CORE-MD) consortium,[5] we aimed to: (i) systematically review published clinical investigations of a pre-specified selection of 71 high-risk (Class III) cardiovascular medical devices before and after CE-mark approval—mostly under the previous EU Medical Device Directive 93/42/EEC—in order to assess the quality and quantity of published clinical data around the milestone of CE-mark approval and during post-market surveillance; and (ii) identify differences in study designs before and after CE-mark approval during the period 2000–21.

Methods

The study was performed according to a pre-specified protocol registered in PROSPERO (CRD42022308593) and available on the website of the CORE-MD consortium (www.core-md.eu). We reported as recommended by the PRISMA and SWiM reporting guidelines (Preferred Reporting Items for Systematic Review and Meta-Analysis protocols[6]; and Synthesis Without Meta-analysis in systematic reviews[7]).

High-risk cardiovascular medical devices

We aimed to evaluate a representative sample of classes of devices widely used in the EU for the management of common medical cardiovascular conditions. The included devices of interest all received CE-mark approval during the last 20 years. The final list of devices was defined in consensus with members of the CORE-MD consortium from different disciplines. We selected the groups of devices based on the incidence of the disease and resulting market volume, the impact of the device on the corresponding medical conditions, and devices that respond to an unmet need. We did not include coronary drug-eluting stents because a comprehensive systematic review was performed in 2015 under the auspices of the European Society of Cardiology (ESC), in response to a request by the Clinical Investigation and Evaluation Working Group of the European Commission. This review was published with recommendations for future clinical trial methodology.[8]

We systematically reviewed published clinical evidence for 71 long-term implantable devices from seven types of Class III devices in the field of cardiovascular medicine including as follows: bioresorbable vascular scaffolds (BVS) for percutaneous treatment of coronary artery disease; left atrial appendage occlusion (LAAO) devices for thromboembolic stroke prevention; transcatheter aortic valve implantation (TAVI) systems for the treatment of severe symptomatic stenosis of native aortic valves; transcatheter mitral valve repair/replacement (TMVR) devices for the treatment of native mitral valve regurgitation; surgical heart valve replacement devices for native aortic and mitral valve pathologies; leadless pacemakers; and subcutaneous implantable cardioverter-defibrillator (S-ICD). A summary of the pre-specified devices of interest along with the respective manufacturer and the CE-mark approval dates is provided in supplementary data online, *Appendix S1*. Device modifications resulting in relabelling or expanded indications were captured along the lifecycle of a given device.

Information sources, search strategies, and study eligibility criteria

Individual search strategies for each device category (class) were adapted to retrieve available peer-reviewed publications of interest from different online bibliographic databases. We searched MEDLINE (OVID), EMBASE (OVID), and the Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley) with device-sensitive search algorithms and considering each iteration of a specific device separately. The detailed search algorithms are provided in supplementary data online, *Appendix S2*. For each device of interest and subsequent device iterations we considered the date of the first CE-mark approval (see supplementary data online, *Appendix S1*), which was defined from press releases available online, information provided by regulatory sources such as notified bodies, and by personal communications with the corresponding manufacturers. The time span of our searches was 20 years (from 1 January 2000 to 31 August 2021), enabling a review of both the contemporary body of clinical evidence available for each device around the milestone of CE-mark approval and the evidence relevant to post-market surveillance.

We summarized trials of any prospective design (non-randomized or randomized clinical trials) in humans. We included reports of trials that defined a prospective design and studies that clarified the evaluation of the indexed device by protocol before patients were recruited and after ethics committee approval had been obtained. Eligible trials either evaluated at least one of the devices of interest in comparison to any control group [active intervention, sham-procedure, or no intervention (medical therapy)] or evaluated the device(s) of interest in a single-arm prospective study. Clinical trials of any sample size were considered. Different reports of the same prospective study were identified and jointly considered, only if the corresponding sub-analysis was pre-specified. For devices related to heart valve interventions, we included clinical trials evaluating the device of interest only in native anatomical valve structures. Studies reporting the results of combined interventions with one or more of the devices of interest were not considered. We excluded RCTs which aimed to investigate other medical interventions in patients that received one of the medical devices of interest in the absence of randomization/clinical investigation on device level. We also excluded case reports including case series, compassionate use reports, reviews, systematic reviews, meta-analyses, and expert opinion documents. We did not apply any language restrictions.

Initial eligibility assessment at the title and abstract level was performed by a single reviewer. A second reviewer independently checked the initially identified reports for eligibility. After screening at a title and abstract level, full texts of potentially relevant articles were obtained in order to finally determine eligibility. The initial reviewer retrieved the potentially eligible studies in full text, and a list of eligible studies was set. The full texts of all potentially eligible studies at title/abstract level were reviewed by a second reviewer. The list of finally eligible studies was also reviewed by the second reviewer. Whenever uncertainty occurred in any step of the review process, a third reviewer was consulted and the final decision was made based on consensus.

Data abstraction, processing, and risk-of-bias assessment

Data abstraction from eligible studies was performed at a study level in pre-specified forms, which were calibrated as appropriate due to the heterogeneity of eligible studies, after pilot data extraction of 5% of the eligible studies from each class of devices. We extracted information relating to study design, study population, intervention(s), comparators, and evaluated outcomes. A detailed list of extracted items is provided in supplementary data online, *Appendix S3*. Different eligible reports of the same study (i.e. different reports of the same prospective clinical study or different reports of the same RCT) were treated as a single entity for data extraction purposes. We assessed the risk of bias in the results of non-randomized and randomized studies that evaluated the indexed device and at least another intervention, by using the dedicated tools of Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I)[9] and Risk of Bias (RoB) 2,[10] respectively.

Data analysis

Reports of different timepoints of follow-up that corresponded to the same study population were considered as a single entity for the purposes of this analysis. Using descriptive statistics, we summarized study characteristics for the overall sample of studies and for each class of device separately. Nominal data were summarized using counts with percentages. The distribution of the continuous variables was assessed by quantile vs. quantile plots. Normally distributed continuous data were reported as mean and standard deviations (SDs). Non-normally distributed continuous data were reported as medians and interquartile ranges (IQRs). Cross-tabulations were used to evaluate differences in characteristics between studies of different design and studies published before and after CE-mark approval. The above comparisons between independent groups of studies were performed with Fisher's exact test for categorical data of unpaired samples, Mann–Whitney *U* test for continuous data, and Kruskal–Wallis analysis of variance for more than two groups of comparison. Finally, multivariable logistic regression models for the entire sample of studies addressed the relationship of study sample size (>50 individuals), multicentre studies, year of publication, duration of recruitment period, and pre-registration in dedicated platforms adjusted for study design and funding source (industry or other sources), with the study publication date after CE-mark approval of the corresponding device as binary dependent variable. All data wrangling and analyses were performed using R 4.2.3 (R Core Team, www.R-project.org/). *P*-values are two-tailed. All *P*-values were considered significant at the conventional nominal level of <.05.

Patient involvement

No information on individual patients was considered in the current analysis. Another task within the CORE-MD consortium will address issues related to patient involvement in clinical evaluations of high-risk medical devices.

Funding and data sharing process

The project is supported by a grant from the European Union (CORE-MD, Grant Agreement 965246, European Union Horizon 2020 project) and institutional grants from Bern University Hospital, Inselspital, Bern, Switzerland. The abstracted information from the included studies is publicly available, and is provided as supplementary material data online to this manuscript.

Results

Eligible clinical trials across all classes of devices

The detailed study-selection flowchart across all classes of high-risk cardiovascular devices is provided in supplementary data online, *Appendix S4*. A total of 44 774 records were scrutinized by title and abstract level. Some clinical reports used the terminology 'prospective' in the absence of clear documentation such as protocol availability prior to patient inclusion, ethics committee approval, trial registration, protocol publication, or pre-defined patient selection criteria highlighting suboptimal reporting of clinical trials. Finally, 473 reports of 308 unique prospectively designed studies were deemed eligible for inclusion (see supplementary data online, *Appendix S4*). We identified at least one prospective study for 70% (50 out of the 71) of the pre-specified devices. The classes of devices with the largest number of included trials were coronary bioresorbable scaffolds (78 unique trials) and TAVI systems (76 unique trials). The number of included trials for the five remaining classes of devices ranged from 18 (leadless pacemaker) to 41 (devices for LAAO) (see supplementary data online, *Appendices S5, S6 and S7*). Within each class of device, trials of one or two landmark devices were dominant.

Characteristics of eligible clinical trials

Summary characteristics are provided for the whole sample of 308 clinical trials, and for each class of high-risk cardiovascular device separately, in *Table 1*. Detailed study-level characteristics are available in supplementary data online, *Appendices S7 and S8*. We identified 251 (81%) reports of prospective non-randomized trials and 57 (19%) reports of RCTs that evaluated at least one of the pre-specified high-risk cardiovascular devices. For the class leadless pacemaker, we found no randomized clinical trial. Although we chose devices that had undergone EU conformity assessment and obtained their CE-mark throughout a period of 20 years (2000–21), the vast majority of eligible prospective trials was published during the last 5 years [215 trials out of 308 (70%) between 2016 and 2021].

The median (IQR) sample size of the eligible trials was 120 (45–344), with a range from 9 to 3231 individuals. The accumulated sample of individual patients was 97 886 (66 186 for non-randomized trials and 31 700 for RCTs), and ranged from 2740 for the class of leadless pacemaker to 32 069 for the class of TAVI devices (*Figure 1*). The majority of the included clinical trials [57% (175 out of 308)] was conducted in Europe and 11% (33 out of 308) of studies were conducted solely in North America. The median (IQR) duration of recruitment was 1.8 (1.0–2.8) years. Half of the trials (52%) were funded solely by industry. Pre-registration of the study protocol was available in 49% of included studies, and 16% provided a peer-reviewed publicly available protocol. A prospective design was claimed by the authors for the remaining clinical trials (51% of the entire study sample), without a pre-registered study protocol being available/reported. The most reported method for analysis and interpretation of the findings was using a frequentist framework.

The primary outcome was a clinical endpoint in 67%, and a composite endpoint in 37% of the clinical trials. A surrogate outcome was considered as a single outcome, or component of a composite outcome, in 23% of studies. Different scales of quality of life measurements were reported in 7% of included clinical trials (*Table 1*). Device-related adverse events were reported in 253 out of 308 (82%) of the primary study reports. Sex- and age-specific subgroup analyses were provided in 8% and 7% of studies, respectively. An outcome adjudication process was reported in 39% of included clinical trials.

Risk-of-bias assessment for the clinical trials comparing at least two interventions is provided in *Figure 2* and supplementary data online, *Appendix S9*. Seventy-three per cent of the non-randomized studies of interventions were judged to be at a critical level of risk, and 16% of the RCTs were judged to be at a high risk of bias. Among the 308 clinical trials, we identified 10 that were terminated early. The reasons for early termination of these studies reported by their authors are provided in supplementary data online, *Appendix S10*. All were randomized trials, and in 7 of the 10 studies the index device was the Absorb BVS, which was withdrawn by the manufacturer due to safety and performance concerns (increased risk of scaffold-related thrombosis).[2]

Differences between prospective randomized and non-randomized clinical trials

Randomized clinical trials were larger than non-randomized studies in our sample [median (IQR) sample sizes 304 (120–750) vs. 100 (39–222), $P < .001$], and they were more often multicentre (74% vs. 54%) ($P = .022$) (*Table 2*). Pre-registered or published peer-reviewed study protocols were more often available for randomized clinical trials ($P < .001$ for both characteristics). Power calculations were reported

Table 1 Summary of study characteristics for the different classes of high-risk cardiovascular devices

	Overall ($n = 308$)	Coronary bioresorbable scaffolds ($n = 78$)	Devices for left atrial appendage occlusion ($n = 41$)	Transcatheter aortic valve implantation systems ($n = 76$)	Transcatheter mitral valve repair/ replacement systems ($n = 31$)	Surgical heart valves ($n = 38$)	Leadless pacemaker ($n = 18$)	Subcutaneous implantable cardioverter-defibrillator ($n = 26$)
Study characteristics								
Study design, *n* (%)								
Prospective non-randomized trials	251 (81)	52 (67)	37 (90)	59 (78)	27 (87)	34 (89)	18 (100)	24 (92)
Randomized clinical trials	57 (19)	26 (33)	4 (10)	17 (22)	4 (13)	4 (11)	0	2 (8)
Sample size								
Median (IQR)	120 (45–344)	111 (35–234)	107 (55–201)	150 (60–595)	49 (30–114)	288 (151–681)	51 (24–118)	67 (37–251)
Min/max	9/3231	9/3231	19/1878	10/3195	11/614	11/1110	14/795	15/1984
Multicentre, *n* (%)	177 (57)	42 (54)	22 (54)	55 (72)	21 (68)	25 (66)	4 (22)	8 (31)
Geographic area, *n* (%)								
Europe	175 (57)	52 (67)	22 (54)	32 (42)	18 (58)	23 (61)	10 (56)	18 (69)
North America	33 (11)	0	5 (12)	14 (19)	3 (10)	6 (16)	0	5 (19)
Asia-Pacific	28 (9)	10 (13)	5 (12)	7 (9)	0	2 (5)	4 (22)	0
Multiple/other	72 (23)	16 (20)	9 (22)	23 (30)	10 (32)	7 (18)	4 (22)	3 (12)
Publication year (Epub)								
2000–05	1 (0)	0	0	0	1 (3)	0	0	0
2006–10	13 (4)	2 (3)	2 (5)	8 (11)	1 (3)	0	0	0
2011–15	79 (26)	15 (19)	9 (22)	27 (35)	9 (29)	15 (39)	0	4 (15)
2016–21	215 (70)	61 (78)	30 (73)	41 (54)	20 (65)	23 (61)	18 (100)	22 (85)
Duration of recruitment period (years)								
Median (IQR)	1.8 (1.0–2.8)	1.3 (0.9–2.0)	2.0 (0.9–3.3)	1.5 (0.9–2.1)	2.0 (1.0–3.0)	3.0 (2.1–5.2)	2.0 (1.3–2.6)	1.6 (1.2–4.0)
Min/max	0.1/17	0.2/4.9	0.3/5.0	0.1/4.3	0.1/7.0	0.8/17	0.9/4.5	0.4/5.8
Funding source, *n* (%)								
Industry	161 (52)	42 (54)	11 (27)	55 (72)	19 (61)	25 (66)	3 (17)	6 (23)
Non-industry	72 (24)	21 (27)	7 (17)	9 (12)	1 (3)	2 (5)	15 (83)	17 (65)

Continued

Table 1 *Continued*

	Overall ($n = 308$)	Coronary bioresorbable scaffolds ($n = 78$)	Devices for left atrial appendage occlusion ($n = 41$)	Transcatheter aortic valve implantation systems ($n = 76$)	Transcatheter mitral valve repair/ replacement systems ($n = 31$)	Surgical heart valves ($n = 38$)	Leadless pacemaker ($n = 18$)	Subcutaneous implantable cardioverter-defibrillator ($n = 26$)
Both	10 (3)	5 (6)	2 (5)	2 (3)	1 (3)	0	0	0
None declared	65 (21)	10 (13)	21 (51)	10 (13)	10 (32)	11 (29)	0	3 (12)
Pre-registered protocol in dedicated platform, *n* (%)	150 (49)	39 (50)	14 (34)	51 (67)	18 (58)	19 (50)	3 (17)	6 (23)
Published peer-reviewed protocol, *n* (%)	48 (16)	12 (15)	13 (32)	10 (13)	3 (10)	4 (11)	3 (17)	3 (12)
Follow-up duration (primary publication) (months)								
Mean (SD)	13 (18)	13 (11)	16 (17)	9 (8)	9 (16)	27 (35)	6 (7)	9 (14)
Min/max	1/204	1/60	1/79	1/36	1/72	1/204	1/22	1/49
Intention-to-treat analysis in randomized trials, *n* (%)[a]	47 (82)	20 (80)	4 (100)	17 (100)	4 (100)	1 (25)	0	1 (50)
Power calculations available, *n* (%)	63 (21)	25 (32)	4 (10)	24 (32)	5 (17)	2 (5)	1 (6)	2 (8)
Interim analysis planned, *n* (%)	15 (5)	6 (8)	3 (7)	4 (5)	0	1 (3)	1 (6)	0
Final statistical analysis, *n* (%)[b]								
Frequentist	301 (98)	78 (100)	39 (95)	73 (96)	31 (100)	37 (97)	17 (94)	26 (0)
Bayesian	6 (2)	0	2 (5)	3 (4)	0	1 (3)	0	0
Both	1 (0)	0	0	0	0	0	1 (6)	0
Early termination, *n* (%)	10 (33)	7 (10)	0	2 (3)	0	1 (3)	0	0
Interventions/comparators								
Type of comparator, *n* (%)								
Medical therapy	14 (5)	3 (4)	4 (10)	1 (1)	2 (7)	0	0	4 (15)
Medical device	34 (11)	1 (1)	3 (7)	16 (21)	2 (7)	6 (16)	2 (11)	4 (15)
Drug-delivery device	24 (8)	24 (31)	0	0	0	0	0	0
No comparison	236 (76)	50 (64)	34 (83)	59 (78)	27 (87)	32 (84)	4 (89)	18 (69)

Continued

Table 1 *Continued*

	Overall ($n = 308$)	Coronary bioresorbable scaffolds ($n = 78$)	Devices for left atrial appendage occlusion ($n = 41$)	Transcatheter aortic valve implantation systems ($n = 76$)	Transcatheter mitral valve repair/ replacement systems ($n = 31$)	Surgical heart valves ($n = 38$)	Leadless pacemaker ($n = 18$)	Subcutaneous implantable cardioverter-defibrillator ($n = 26$)
Outcomes								
Primary outcome, *n* (%)[c]								
Composite outcome	113 (37)	38 (49)	26 (63)	23 (30)	15 (48)	33 (87)	6 (33)	2 (8)
Binary outcome(s)	240 (78)	49 (63)	40 (98)	69 (91)	28 (90)	30 (79)	10 (56)	14 (54)
Surrogate outcome(s)	69 (23)	32 (41)	3 (7)	8 (11)	12 (39)	14 (37)	0	0
Quality of life metric	20 (7)	8 (10)	0	8 (11)	0	2 (5)	0	2 (8)
Risk prediction score	0	0	0	0	0	0	0	0
Device-related complication(s) evaluated, *n* (%)	253 (82)	58 (74)	38 (93)	69 (91)	24 (77)	36 (95)	15 (83)	13 (50)
Sex-specific subgroup, *n* (%)								
Analysis provided	25 (8)	5 (6)	3 (7)	10 (14)	3 (10)	0	1 (6)	3 (12)
Claimed difference	4 (1)	1 (1)	1 (2)	1 (1)	0	0	0	1 (4)
Age-specific subgroup, *n* (%)								
Analysis provided	22 (7)	3 (4)	3 (7)	9 (12)	3	0	1 (6)	3 (12)
Claimed difference	1 (0)	0	0	0	1	0	0	0
Outcome adjudication, *n* (%)	120 (39)	47 (60)	6 (15)	35 (46)	16 (52)	14 (37)	0	2 (8)

IQR, interquartile range shown as Q1–Q3; SD, standard deviation; Epub, electronic publication.
The number in parenthesis under each group of high-risk cardiovascular device indicates the number of unique prospective studies included in each group. The sum of observations does not always correspond to the total sum in each group because of missing information.
[a]Only for the 57 RCTs. The percentages have been calculated for this group of studies.
[b]For the primary report of the study.
[c]Correspond to the primary outcome of the main report either as single or as any component of the composite endpoint.

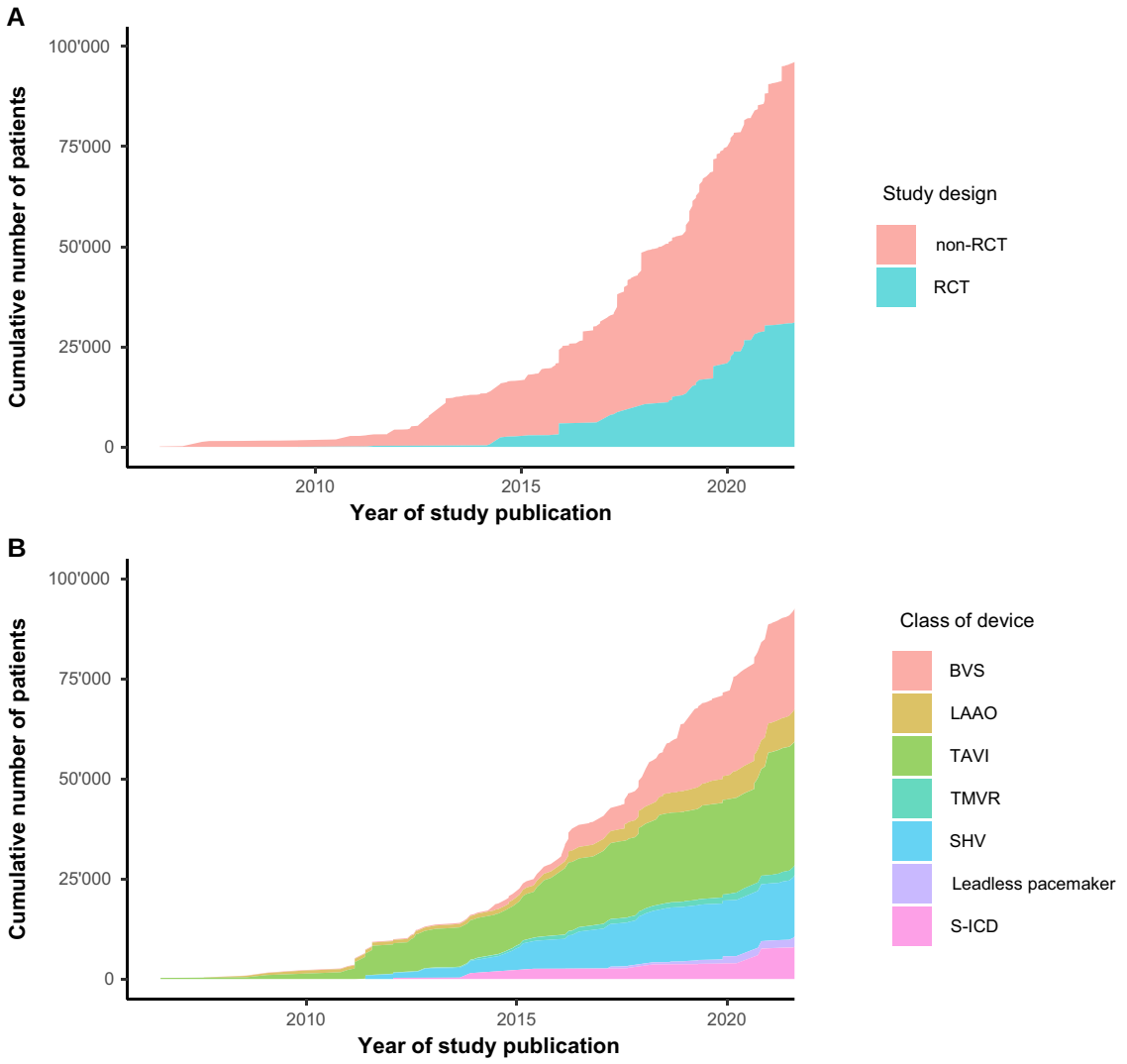


Figure 1 Cumulative number of patients recruited in prospective clinical trials evaluating 71 high-risk cardiovascular devices over the period of 20 years and included in our evaluation. Panel *A* shows the cumulative number of patients recruited between 2000 and 2021 in prospective studies of high-risk cardiovascular devices, with cumulative sample of 66 186 individuals and 31 700 individuals for prospective non-randomized studies and randomized clinical trials, respectively. Panel *B* shows the cumulative number of patients recruited between 2000 and 2021 in prospective studies of high-risk cardiovascular devices stratified according to the class of devices (cumulative sample of 25 262 individuals for BVS, 10 360 individuals for LAAO devices, 32 069 individuals for TAVI devices, 3543 individuals for TMVR devices, 15 630 individuals for surgical heart valves, 2740 individuals for leadless pacemaker, 8282 individuals for S-ICD). Each colour represents a different class of high-risk devices as indicated in the labels. RCT, randomized clinical trials; BVS, bioresorbable vascular scaffolds; LAAO, left atrial appendage occlusion; TAVI, transcatheter aortic valve implantation; TMVR, transcatheter mitral valve repair/replacement; SHV, surgical heart valve; S-ICD, subcutaneous implantable cardioverter-defibrillator

for 84% of randomized trials compared with 6% of non-randomized clinical trials ($P < .001$).

The two groups of study design were comparable in terms of geographic area, year of publication, and duration of recruitment period. Industry-related funding was disclosed in 70% of randomized clinical trials and in 48% of non-randomized clinical trials ($P = .002$ for industry-related vs. other resources).

Composite primary endpoints were chosen more often in randomized compared to non-randomized clinical trials (51% vs. 33%, $P = .033$). Surrogate endpoints were considered either as single outcomes or as component of composite endpoints in 36% of the randomized and 19% of the non-randomized clinical trials ($P = .005$). Device-related adverse events were commonly evaluated in both study design groups (82% for non-randomized vs. 84% for randomized clinical trials) ($P = .848$). Sex- and age-subgroup analyses were provided more often in randomized than in non-randomized clinical trials ($P < .001$ for both characteristics). Outcome adjudication was reported more frequently in RCTs compared to non-randomized studies ($P < .001$), but was only reported in 65% (37 out of 57) of the randomized studies (*Table 2*).

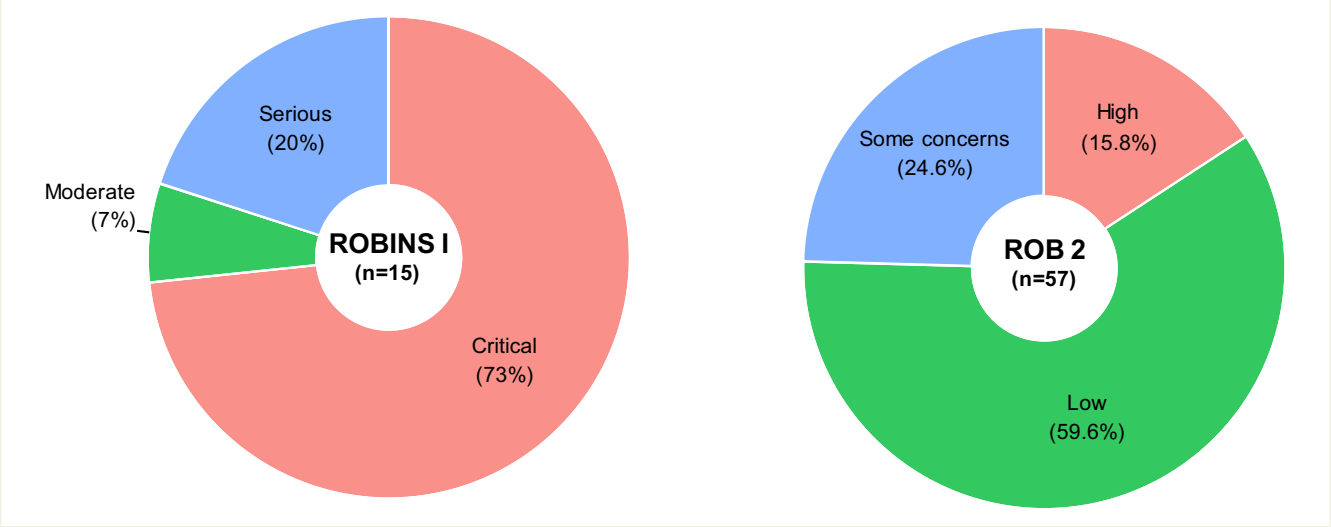


Figure 2 Risk-of-bias assessment for non-randomized and randomized clinical trials. Circular statistical graphics to illustrate the numerical proportions of different levels of risk of bias in trials that compared two or more interventions, as it has been quantified by the ROBINS-I tool for non-randomized trials[9] and by the RoB 2 tool for randomized clinical trials.[10] Study level assessment is available in supplementary data online, *Appendix S9*. In each pie chart, the arc length of each slice (and consequently its central angle and area) is proportional to the quantity it represents

Evidence accumulated before and after CE-mark approval

We did not identify any RCT published before any of the 71 devices had received CE-mark approval. Among the included studies, non-randomized prospective clinical trials were also published mostly after approval of the device under evaluation (224 out of 251 studies) (*Table 3*, *Figure 3*). Studies conducted before approval were generally published shortly before the date of CE-marking [median (IQR) of 1.84 (0.49–3.0) years] whereas studies published after CE-marking continued to be published over a long time period after the date of CE-marking [4.84 (3.08–7.06) years] ($P < .001$ for comparison) (*Figs. 3 and 4*).

The distribution of sample sizes differed considerably between studies published before [median (IQR) of 31 (20–64)], and after [135 (51–436)], CE-mark approval ($P < .001$). The number of prospective clinical trials of any design increased after the corresponding CE-mark approval, especially during the last five years (2016–21) of the 20-year period of interest (*Table 3*, *Figure 4*). The duration of the recruitment period was longer for studies published after the CE-mark timepoint [1.9 (1.0–3.0) vs. 1.2 (0.7–1.6) years] ($P = .004$). We found no differences in other study characteristics, assessed outcomes, and interventions.

In multivariable logistic regressions, reports of clinical trials that were published after CE-mark approval were likely to be larger [>50 participants, odds ratio (95% confidence interval) 6.5 (2.7–16.4), $P < .001$] and to have been reported during the last quartile (2016–21) of the study time span [8.3 (1.2–53.1), $P < .027$]. Compared with single-centre studies and studies without pre-registered protocols, multicentre studies [1.24 (0.42–3.55), $P = .692$] and studies with pre-registered protocols [1.27 (0.41–3.45), $P = .642$] did not have higher odds for publication after the corresponding CE-mark approval date.

Discussion

The lack of transparency about regulatory decisions within Europe has made it difficult to disprove the perception that high-risk medical devices have been approved on the basis of limited clinical evidence. The present study has suggested that assertion may indeed be true. Assuming that the published literature accurately (even if incompletely) reflects what is known, then our systematic review has demonstrated that no RCT of 71 widely used cardiovascular devices had been conducted and reported prior to their CE-marked dates of approval between 2000 and 2021. The results of the vast majority of prospective studies, which were mostly non-randomized in design, became publicly available only after the devices had been approved. Even then, no prospectively designed studies were identified for nearly one-third of the high-risk cardiovascular devices that we investigated (*Structured Graphical Abstract*).

Accumulation and transparency of data for high-risk medical devices

The essential preconditions for evidence-based medicine are that clinical data irrespective of the results must be collected and published.[4,11,12] In this systematic review, we could not determine the clinical evidence that had been collected by manufacturers and submitted for approval of their new devices, given that this information is confidential, but we could assess all prospective studies that had been published (usually after CE-marking).

In the EU, the procedure for approving a new high-risk medical device is known formally as a Conformity Assessment, and it is conducted by an inspection company that has been designated ('notified') by its national competent authority to perform that task.[3,4] If the data in the file that is submitted by the manufacturer are considered to satisfy the requirements set by EU legislation and international standards, then the notified body will issue a 'certificate of conformity' which is a prerequisite for the manufacturer to market its device in the EU market. In this paper we have used the term 'CE-marking' to refer to this whole process. As independent commercial organisations the notified bodies are exempted from EU laws requiring freedom of public access to information.[4] Moreover, the previous Medical Device Directive (93/42/EEC) applied a presumption of confidentiality which prevented notified bodies from disclosing information submitted by manufacturers, and that provision has been retained in the new regulation. The non-availability

Table 2 Differences in study characteristics between prospective non-randomized and randomized clinical trials

	Prospective non-randomized clinical trials ($n = 251$)	Randomized clinical trials ($n = 57$)	*P*-value for difference
Study characteristics			
CE-mark approval, *n* (%)			
Published before CE-mark approval	27 (11)	0	0.004
Published after CE-mark approval	224 (89)	57 (100)	.004
Sample size			
Median (IQR)	100 (39–222)	304 (120–750)	<.001
Min/max	9/3231	13/2604	
Multicentre, *n* (%)	135 (54)	42 (74)	.022
Geographic area, *n* (%)			.507
Europe	147 (59)	28 (49)	
North America	25 (10)	8 (14)	
Asia-Pacific	23 (9)	5 (9)	
Multiple/other	56 (22)	16 (28)	
Publication year (Epub)			.671
2000–05	1 (0)	0	
2006–10	11 (4)	2 (4)	
2011–15	65 (26)	14 (25)	
2016–21	174 (70)	41 (71)	
Duration of recruitment period (years)			
Median (IQR)	1.7 (1.0–2.8)	2.0 (1.1–2.9)	.326
Min/max	0.1/16.9	0.2/5.8	
Funding source, *n* (%)			<.001[a]
Industry	121 (48)	40 (70)	
Non-industry	61 (24)	11 (19)	
Both	5 (2)	5 (9)	
None declared	64 (25)	1 (2)	
Pre-registered protocol in dedicated platform, *n* (%)	103 (41)	47 (82)	<.001
Published peer-reviewed protocol, *n* (%)	25 (10)	23 (40)	<.001
Follow-up duration (primary publication) (months)			
Mean (SD)	13 (19)	13 (10)	.066
Min/max	1/204	1/49	
Intention-to-treat analysis in randomized trials, *n* (%)[b]	0	47 (82)	nc
Power calculations available, *n* (%)	15 (6)	48 (84)	<.001
Interim analysis planned, *n* (%)	7 (3)	8 (14)	.002
Final statistical analysis, *n* (%)[c]			
Frequentist	249 (99)	52 (91)	.001
Bayesian	1 (0.5)	5 (9)	
Both	1 (0.5)	0	

Continued

Table 2 ***Continued***

	Prospective non-randomized clinical trials ($n = 251$)	Randomized clinical trials ($n = 57$)	*P*-value for difference
Early termination, *n* (%)	0	10 (18)	<.001
Interventions/comparators			
Type of comparator, *n* (%)			.213[d]
Medical therapy	4 (2)	10 (18)	
Medical device	9 (4)	25 (44)	
Drug-delivery device	2 (1)	22 (38)	
No comparison	236 (94)	0	
Outcomes			
Primary outcome, *n* (%)[e]			
Composite outcome	84 (33)	29 (51)	.033
Binary outcome(s)	204 (81)	36 (63)	<.001
Surrogate outcome(s)	47 (19)	22 (36)	.005
Quality of life metric	15 (6)	5 (9)	.555
Risk prediction score	0	0	nc
Device-related complication(s) evaluated, *n* (%)	205 (82)	48 (84)	.848
Sex-specific subgroup, *n* (%)			
Analysis provided	5 (2)	20 (35)	<.001
Claimed difference	2 (1)	2 (4)	.166
Age-specific subgroup, *n* (%)			
Analysis provided	5 (2)	17 (30)	<.001
Claimed difference	0	1 (2)	.999
Outcome adjudication, *n* (%)	83 (33)	37 (65)	<.001

IQR, interquartile range shown as Q1–Q3; SD, standard deviation; Epub, electronic publication; nc, not computed.
The number in parenthesis under the group of studies before and after CE-mark approval indicates the number of unique prospective studies included in each group.
[a]$P = .002$ for the comparison of industry-funded vs. other.
[b]Only for the 57 RCTs. The percentages have been calculated for this group of studies.
[c]For the primary report of the study.
[d]After excluding the 232 single arm intervention non-randomized studies.
[e]Corresponds to the primary outcome of the main report either as single or as any component of the composite endpoint.

of the Clinical Evaluation Report submitted by a manufacturer to its notified body, and of the Clinical Evaluation Assessment Report prepared by the notified body, continues to impede independent analyses of the clinical evidence submitted in the EU in support of applications for approval of new high-risk medical devices.

During the period of our study, medical devices were certified under the previous EU Medical Device Directive 93/42/EEC[13] rather than the new Medical Device Regulation (EU) 2017/745.[14] The directives allowed for a device to be approved if its manufacturer could establish equivalence to similar devices that had already been CE-marked. The use of that route for approval may explain in part why we could find no published clinical studies relating to some of the devices that were included in this review. The new MDR will provide limited public information about the evidence available, through the publication of Summaries of Safety and Clinical Performance (SSCP)[4] and it introduces restrictions with respect to the use of data from equivalent devices for the purpose of market entry, with a contract now being required between the respective manufacturers for full sharing of data [MDR, Article 61(5)]. Following CE-mark approval, post-market surveillance and clinical follow-up studies are mandatory. Although manufacturers are able to submit clinical evidence collected independently by academic bodies or medical associations, specific standards are required to ensure the quality and reliability of such data and to establish methods for sharing data.[15–17] It is expected that this will result in more trials being performed and reported for a higher proportion of devices.

Based on our systematic review, the status of evidence collection and reporting between 2000 and 2021 appears to be unsatisfactory. On average, sample sizes were too small, follow-up durations too short, and the timing of publications was far from ideal. Cumulatively, these factors resulted in a dearth of available high quality evidence when new devices were introduced. In the future, the SSCP will be released to coincide with the approval of all new high-risk medical devices. This will be provided in the new European database for medical devices (EUDAMED) and will improve the transparency of the existing clinical

Table 3 Differences in study characteristics published before and after the corresponding CE-mark approval date

	Prospective studies before CE-mark approval ($n = 27$)	Prospective studies after CE-mark approval ($n = 281$)	*P*-value for difference
Study characteristics			
Study design, *n* (%)			
Non-randomized trials	27 (100)	224 (80)	.004
Randomized clinical trials	0	57 (20)	.004
Sample size			
Median (IQR)	31 (20–64)	135 (51–436)	<.001
Min/max	10/330	9/3231	
Multicentre, *n* (%)	16 (59)	161 (57)	.999
Geographic area, *n* (%)			.074
Europe	11 (41)	164 (58)	
North America	2 (7)	31 (11)	
Asia-Pacific	2 (7)	26 (9)	
Multiple/Other	12 (44)	60 (21)	
Publication year (Epub)			<.001
2000–05	1 (4)	0	
2006–10	5 (18)	8 (3)	
2011–15	13 (48)	66 (23)	
2016–21	8 (30)	207 (74)	
Duration of recruitment period (years)			
Median (IQR)	1.2 (0.7–1.6)	1.9 (1.0–3.0)	.004
Min/max	0.1/4.9	0.1/16.9	
Funding source, *n* (%)			.267
Industry	16 (59)	145 (52)	
Non-industry	3 (11)	69 (25)	
Both	0	10 (4)	
None declared	8 (30)	57 (20)	
Pre-registered protocol in dedicated platform, *n* (%)	12 (44)	138 (49)	.691
Published peer-reviewed protocol, *n* (%)	1 (4)	47 (17)	.095
Follow-up duration (primary publication) (months)			
Mean (SD)	8.3 (6)	13.5 (18)	.316
Min/max	1/36	1/204	
Intention-to-treat analysis in randomized trials, *n* (%)[a]	0	47 (82)	nc
Power calculations available, *n* (%)	3 (11)	60 (21)	.316
Interim analysis planned, *n* (%)	0	15 (5)	.378
Final statistical analysis, *n* (%)[b]			.999
Frequentist	27 (100)	274 (97)	
Bayesian	0	6 (2)	
Both	0	1 (1)	

Continued

Table 3 ***Continued***

	Prospective studies before CE-mark approval ($n = 27$)	Prospective studies after CE-mark approval ($n = 281$)	*P*-value for difference
Early termination, *n* (%)	0	10 (4)	.999
Interventions/comparators			
Type of comparator, *n* (%)			.123
Medical therapy	0	14 (5)	
Medical device	1 (4)	33 (12)	
Drug-delivery device	0	24 (8)	
No comparison	26 (96)	210 (75)	
Outcomes			
Primary outcome, *n* (%)[c]			
Composite outcome	10 (37)	103 (37)	.827
Binary outcome(s)	23 (85)	217 (77)	.203
Surrogate outcome(s)	3 (11)	66 (24)	.311
Quality of life metric	1 (4)	19 (7)	.999
Risk prediction score	0	0	nc
Device-related complication(s) evaluated, *n* (%)	24 (89)	229 (81)	.437
Sex-specific subgroup, *n* (%)			
Analysis provided	0	25 (9)	.146
Claimed difference	0	4 (1)	.999
Age-specific subgroup, *n* (%)			
Analysis provided	0	22 (8)	.237
Claimed difference	0	1 (0.4)	.999
Outcome adjudication, *n* (%)	11 (41)	109 (39)	.839

IQR, interquartile range shown as Q1–Q3; SD, standard deviation; Epub, electronic publication; nc, not computed.
The number in parenthesis under the group of studies before and after CE-mark approval indicates the number of unique prospective studies included in each group.
[a]Only for the 57 RCTs. The percentages have been calculated for this group of studies.
[b]For the primary report of the study.
[c]Corresponds to the primary outcome of the main report either as single or as any component of the composite endpoint.

evidence. However, this will not address the need for those studies to be well conducted and will potentially introduce new hurdles that may delay the timely approval of devices addressing unmet needs.[18]

Quality of trials for cardiovascular devices

High-quality clinical trials are adequately powered to answer the question that is posed.[18–21] Power calculations were reported for only 20% of the studies included in this systematic review, and the sample size was on average relatively small. Randomized clinical trials sit atop the hierarchy of clinical trial methodologies, but only 19% of the studies that we identified had a randomized design. An overview of the trends in the total numbers of patients being recruited into studies suggests that the proportion of patients enrolled in RCTs is not increasing (see *Figure 1A*).

Prospectively designed clinical trials were available for about two-thirds (70%) of the included high-risk cardiovascular devices, but these were mostly non-randomized studies and as a consequence their risk of bias was judged to be high. None of the 15 non-randomized studies that compared at least two interventions were deemed to have no risk of bias, and in the majority of those studies (73%) the risk of bias was determined to be critical, for example due to issues with the selection of patients (see supplementary data online, *Appendix S8*). In comparison, the risk of bias in the 57 included RCTs was judged to be high in just 16%, a finding that was potentially related in part to selective reporting.

A critical appraisal of the practices applied during the last 20 years is essential in order to plan how to improve the quality of clinical trials.[18,21] Our systematic evaluation has provided robust evidence in terms of the publicly available and prospectively designed studies, but it has also raised questions that can be answered only with full transparency with respect to the totality of the evidence for the included devices.

Introduction of innovative medical devices

Our review covering the first two decades of the 21st century indicates that a majority of the studies was performed in Europe. Concerns have been raised that the new EU regulatory environment may negatively impact innovation, by slowing approval of new devices due to the limited capacity of notified bodies and increased requirements for clinical evidence.[22,23] However, high-risk medical devices that were approved first

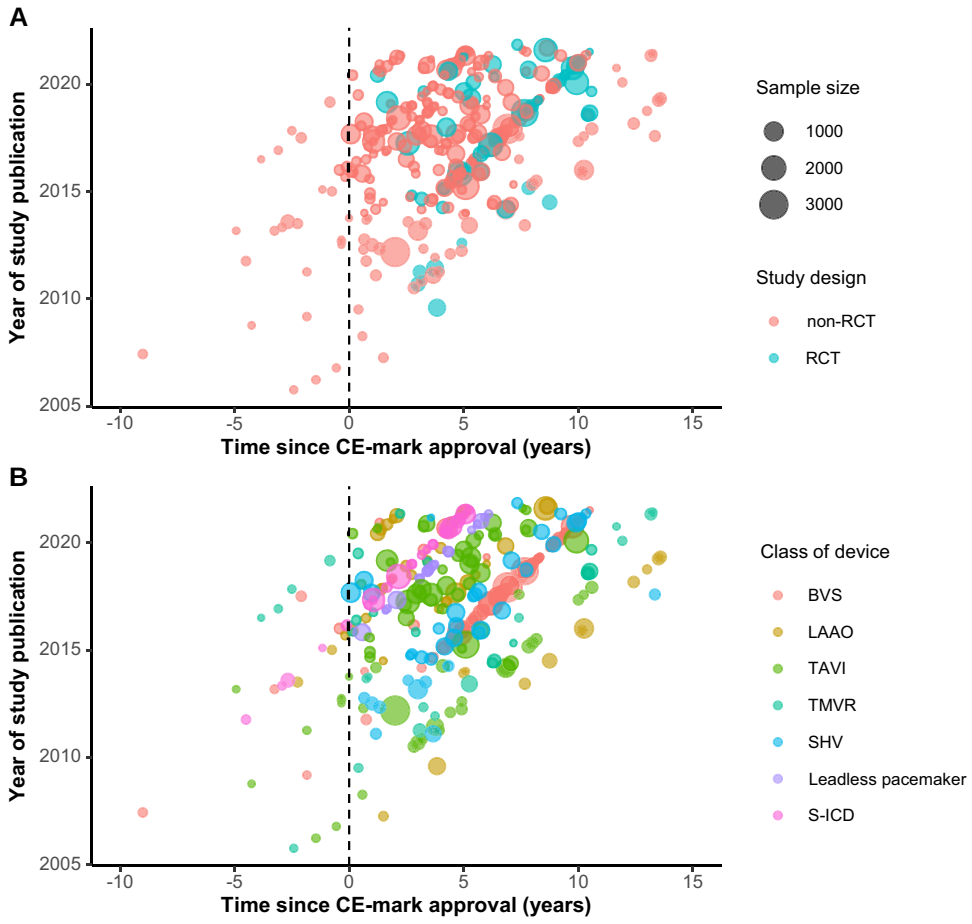


Figure 3 Accumulation of prospective clinical trials over time and indication of time lag between publication and corresponding CE-mark approval time point. Each circle represents a single report of the primary studies included in the analysis. Panel *A* depicts each single report as published relative to CE approval time point. The size of each circle is indicative of the sample size of each study and stratified by study design. Panel *B* depicts each single report according to class of device as published relative to CE approval time point. The size of each circle is indicative of the sample size in each study and stratified by class of device. The *x*-axis shows the time lag since CE-mark approval for the corresponding device; negative values indicate publication of the study prior to the provision of CE-mark approval. The *y*-axis shows the date of study publication (electronic publication was considered). CE, Conformité Européenne; RCT, randomized clinical trials; BVS, bioresorbable vascular scaffolds; LAAO, left atrial appendage occlusion; TAVI, transcatheter aortic valve implantation; TMVR, transcatheter mitral valve repair/replacement; SHV, surgical heart valves; S-ICD, subcutaneous implantable cardioverter-defibrillator

in the EU under the previous directives (with their lower level of requirements), rather than in the USA, were associated with a higher rate of recalls.[24] More recently, the US FDA has introduced a scheme for the accelerated assessment of new devices that has increased the number of first-in-man studies conducted in the USA[25]—but it has been reported that high-risk devices approved under their early feasibility programme have also had higher recall rates and shorter times on the market before serious recalls, in comparison to devices approved by standard processes.[26] Most orthopaedic devices have been approved in the USA by their 510(k) pathway, using evidence from equivalent or 'predicate' devices with limited clinical trials data, and this has been associated with a 12-times greater risk of recall.[27] There are some reasons why it is not always possible to evaluate new implantable medical devices in standard RCTs. In the case of genuine advances for independently defined unmet needs it may be appropriate for market access to be granted on more limited evidence. Risks should therefore be transparent and shared, and limited evidence should still be published and then supported by rigorous post-market surveillance.

Limitations of this study

This review was restricted to selected high-risk cardiovascular devices and to published reports of prospective studies; other documents were not publicly available. The ascertainment of evidence supporting a claim for a prospective design may have been unreliable in some cases, since no study protocol with a record of changes over time was published in many cases. Because a prospective design and conduct of a specific non-randomized study was not always clearly documented, this may have led to the rejection of some published clinical studies due to suboptimal reporting. It is likely that we were unable to identify and therefore assess every high-risk cardiovascular device that was available with CE-mark approval within each class. The classes of devices were dominated by one or two landmark devices within a class. Due to the limited number of studies for the majority of the devices within a class, we were unable to assess intercorrelations separately for each class of specific devices in the different study populations. Notwithstanding, the

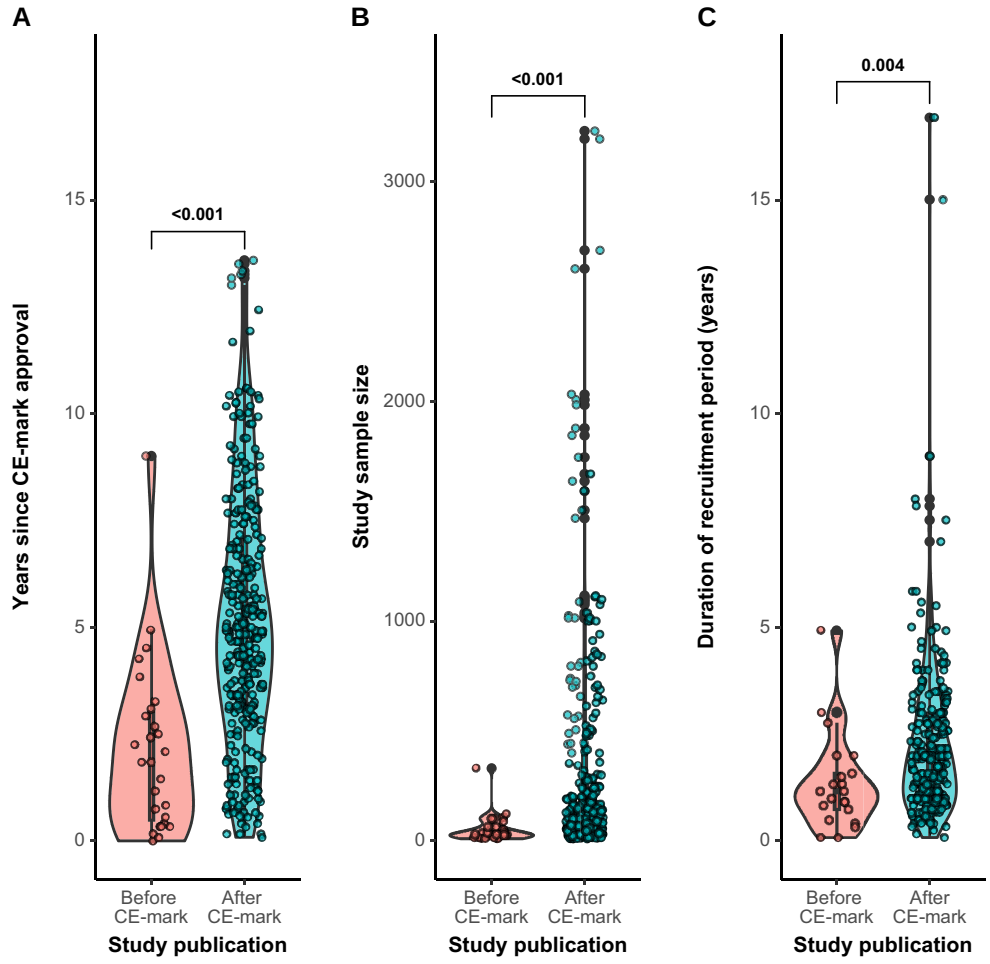


Figure 4 Distributions of time lag of study publication since CE-mark approval date, sample size on study level, and duration of recruitment period stratified by time of publication before and after CE-mark approval. Panel *A* shows the distribution of observed time intervals between study publication and CE-mark approval; panel *B* the distribution of study sample sizes; and panel C the duration of the recruitment period reported in individual studies. Densities are accompanied by an overlaid boxplot, with the rectangle showing the ends of the first and third quartiles and central dot the median. The black points are determined to be 'outliers'. Wider sections of the violin plots represent a higher probability that units of the sample will take on the given value; the skinnier sections represent a lower probability. CE, Conformité Européenne

current analysis did not aim to provide conclusions about the comparative effectiveness of the selected devices within a class.

In the absence of protocol specifications or contextual factors, it was impossible to review if learning curves and operator experience had been adequately reported.

Extrapolating from the results of this systematic review should be done only with caution, but it is possible nonetheless to offer some wider conclusions.

Implications for regulatory science and practice

Our systematic review has provided objective confirmation that revision of the EU system of regulation was warranted in order to improve the quality and quantity of clinical evidence particularly for high-risk medical devices. The political decision that was taken to retain notified bodies and to preserve their legal duty of confidentiality, however, makes it uncertain if the reformed system can deliver the standards of clinical evidence and transparency that physicians, guideline committees, and patients would expect. It will be necessary to provide more specific EU guidance on clinical trial methodologies, appropriate endpoints, comparators, and follow-up and to develop systems for demonstrating concordance of regulatory judgements between notified bodies.

The results of the present study raise some more general questions about the EU system for approval of new high-risk medical devices that are beyond the scope of this discussion which is focused on the specific issues of the quantity, quality, and transparency of evidence from formal clinical investigations. The prerequisite for considering any new regulatory pathways or even more wide-ranging regulatory reform must be to understand how the current system is operating, and the goal of this systematic review was to quantify and evaluate the quality of published evidence from clinical investigations prior to and after CE approval for a pre-specified selection of high-risk (Class III) cardiovascular medical devices. It is the first study to formally assess the clinical evidence when new devices were approved by notified bodies in the EU mostly under the previous EU Medical Device Directive 93/42/EEC and before the implementation of MDR. The increased costs and delays of 'conformity assessments' (by the notified bodies) under the EU MDR

are caused at least in part by the absence of a system for early consultation with the regulatory authorities, so manufacturers are unable to clarify in advance what clinical evidence will be needed for their device. There are several new initiatives by regulators in Europe to address this deficiency. Ultimately, global regulatory convergence of standards, with full transparency of evidence, and mutual recognition agreements, would be preferable.

Ideally, larger and better-designed clinical trials of high-risk devices will be conducted and reported more quickly. For new devices in well-established classes, an early feasibility study could establish non-inferiority or benefit as compared to a defined objective performance criterion (OPC).[8] Data assembled within this systematic review could serve as an inventory of studies that could be used to define OPCs[28,29] for each of the seven different classes of devices. Thereafter, an RCT should be performed for each new high-risk device against an active comparator and with adequate statistical power.

Any special provisions for innovative devices will need to be balanced by surveillance through comprehensive device registries that are run independently by academic bodies. Following CE-mark approval, post-market surveillance and clinical follow-up studies are mandatory; specific standards are required to ensure the quality and reliability of such data and to establish methods for sharing data.[15–17] As part of the CORE-MD project, a systematic review reporting on the quality and utility of European cardiovascular and orthopaedic registries for the regulatory evaluation of medical device safety and performance across the implant lifecycle has been conducted and recently published.[30] The main findings suggest that current registries do not (yet) fulfil their full potential due to substantial heterogeneity and limitations related to their structure and methodology to provide the data that regulators and manufacturers require for post-market surveillance and clinical follow-up.

Scientific and clinical experts should advise how high-risk medical devices should be investigated so that regulators can undertake an objective evaluation of the safety, performance, and clinical efficacy of individual medical devices. The Clinical Investigation and Evaluation Working Group (CIE), composed of medical device regulators from EU member states with the European Commission, has recently embarked on a revision of the EU guidance on clinical evaluation of medical devices that dates from 2016 (MEDDEV 2.7/1, revision 4).[31] A working group of the International Standardization Organisation has recently started to prepare a new horizontal standard on the 'Clinical Evaluation of Medical Devices' (which will become ISO 18969).[32] Insights from this study by the CORE-MD consortium will be submitted to both of these working groups, and it is hoped that the development and implementation of new recommendations will be an important step towards similar standards in all medical device jurisdictions.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

A.H. has received travel fees/educational grants from Abbott, Biotronik, Boston Scientific, and Medtronic and serves as a consultant for Medtronic and Biotronik without impact on his personal remuneration. He has received research grants from the Swiss Innovation agency Innosuisse and the Swiss Heart Foundation. T.M. has engaged in paid clinical training for the National Standards Authority of Ireland, he is previous co-chair of the Clinical Investigation and Evaluation Working Group, and he is member of the medical device expert panel of the European Commission. He is previously unpaid advisory board member of Pumpinheart Ltd. R.A.B. reports research or educational grants to the institution(s) of employment from Abbott Vascular, Biosensors, Boston Scientific, and Translumina not affecting personal remuneration. A.G.F. is Chairman of the Regulatory Affairs Committee of the Biomedical Alliance in Europe. S.W. reports research, travel, or educational grants to the institution without personal remuneration from Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, BBraun, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Cordis Medical, Corflow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Farapulse, Fumedica, GE Medical, Guerbet, Idorsia, Inari Medical, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medalliance, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pfizer, Pharming Tech, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed, Terumo, Vifor, and V-Wave. S.W. served as consultant for Medtronic with payments to the institution; he served as advisory board member and/or member of the steering/executive group of trials funded by Abbott, Abiomed, Boston Scientific, Biotronik, Edwards Lifesciences, MedAlliance, Medtronic, Polares, Recardio, Sinomed, Terumo, and V-Wave with payments to the institution but no personal payments. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. He is Vice-President ESC and Associate Editor of JACC CV Interventions. All other authors have nothing relevant to disclose.

Data Availability

All data are available in the appendix of the main manuscript. Any further required information is available upon request.

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Ethical Approval

Ethical approval was not required.

Pre-registered Clinical Trial Number

Not applicable, because it is not clinical trial. But this study was performed according to a pre-specified protocol registered in PROSPERO (CRD42022308593) and available on the website of the CORE-MD consortium (www.core-md.eu).

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