ESC European Society of Cardiology

European Heart Journal (2024) **45**, 178–180
https://doi.org/10.1093/eurheartj/ehad786

EDITORIAL

Epidemiology, prevention, and health care policies

Quality and transparency of clinical evidence for high-risk cardiovascular medical devices: a long way to go

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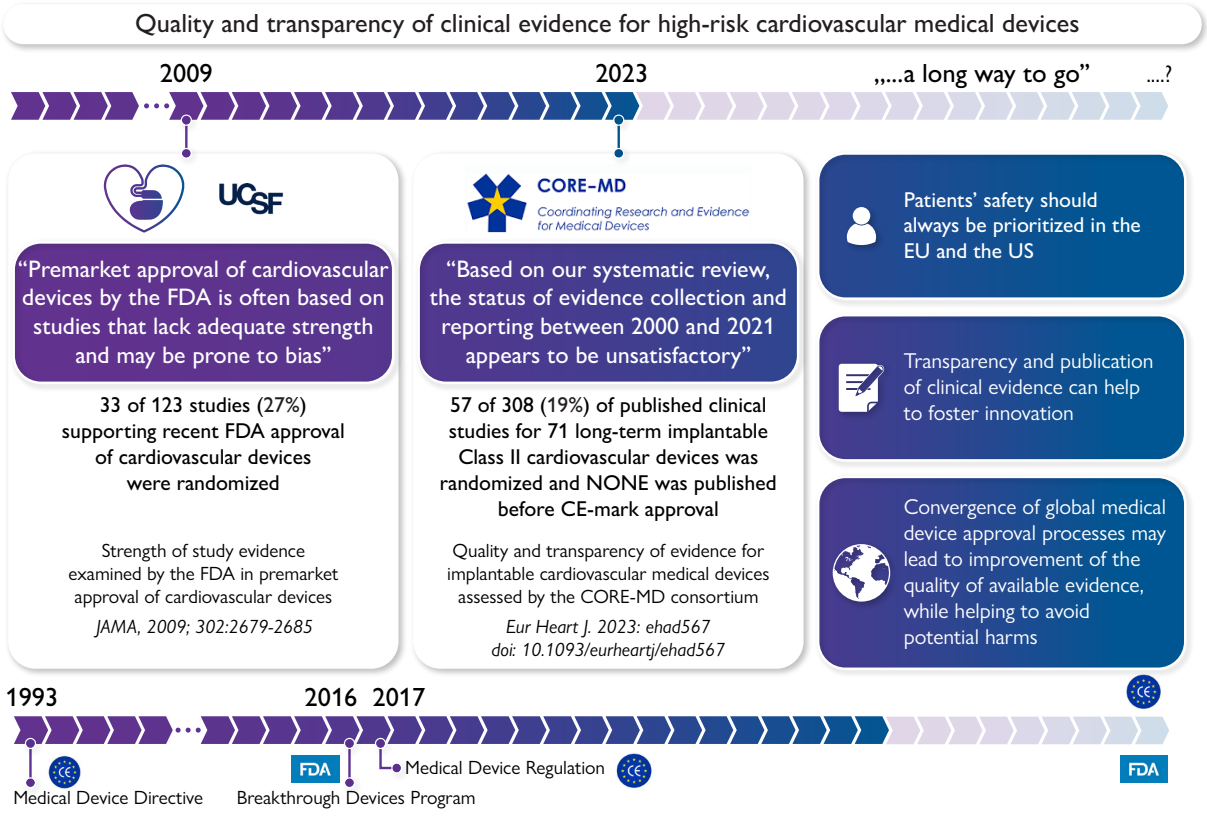
Online publish-ahead-of-print 30 November 2023

This editorial refers to 'Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD Consortium', by G.C.M. Siontis *et al.*, https://doi.org/10.1093/eurheartj/ehad567.

Graphical Abstract



Persistently missing evidence of clinical benefits for high-risk medical devices.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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What has been will be again, what has been done will be done again
—Eclesiastes
History (…) gives life to recollection and guidance to human existence
—Cicero

In November 2018, a group of 252 journalists from 36 countries led by the Pulitzer prize-winning International Consortium of Investigative Journalists (ICIJ) concluded in their 'Implant Files' report that 'Millions of people's lives have been saved or made better by implanted medical devices, but information about the safety of devices can be hard to find … even for 250 journalists'.[1]

A systematic evaluation of that important statement was underaken by the CORE-MD Consortium in a study published in the current issue of the *European Heart Journal*.[2] In a review of all high-risk cardiovascular medical devices that gained access to the European market between 2000 and 2021, Siontis *et al*. found that evidence to support clinical benefit remains sparse and largely hidden.[2] In spite of the 2005 International Committee of Medical Journal Editors (ICMJE) requirement that all prospective trials involving human participants be registered prior to the beginning of study enrolment in order to be considered for publication in member journals, pre-registered study protocols were available only for the half of published clinical trials that supported approval of these high-risk devices. Only a small proportion (19%) of clinical studies underpinning Conformitee Europeanee (CE) mark certification were randomized, and none of the reviewed devices had randomized trial results published prior to market access. For nearly a third of approved devices, no prospective clinical trial was dentified in a rigorous literature search.

The lack of high-quality (or sometimes any) evidence of clinical benefit is disturbing. It is concerning that no improvements have been seen since the prior reports of a similar lack of evidence almost two decades ago—with several reports demonstrating that no more than half of completed clinical trials are published (*Graphical Abstract*).[3] Almost 15 years ago, a systematic review of the evidence to support pre-market approval (PMA)—the most stringent US Food and Drug Administration (FDA) review process—found that approximately a quarter of studies used to support approval were randomized clinical trials and 7% were blinded.[4] Empirical studies and common sense tell us that less and lower quality information on the potential benefits and harms of new devices threatens patients' safety. A lower evidence bar for approval under the previous EU framework for regulating medical devices [Medical Devices Directive (93/43/EEC or 'MDD')] translated into a higher number of post-marketing safety alerts and recalls under European as compared with US regulation.[5]

Several significant regulatory changes relevant to medical devices occurred during the 20 year period studied by the CORE-MD consortium, including the adoption of a Medical Devices Regulation in 2017 (Regulation 2017/745 or 'MDR') replacing 'MDD'.[6] Although the 2017 legislation does not refer specifically to clinical efficacy, it has increased the need for clinical evidence. MDR Article 2.44 defines clinical evaluation as 'a systematic and planned process to continuously generate, collect, analyse, and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits', defined as 'the positive impact of a device on the health of an individual, expressed in terms of meaningful, measurable, patient-relevant clinical outcome(s)' (MDR Article 2.53). Every manufacturer must include the results of clinical investigations requesting a conformity assessment for implantable and Class III medical devices. However, since MDR became only partly applicable in 2021, it had no direct effect on the results of the analysis. Unfortunately other preliminary data show no improvement in the clinical evidence for high-risk devices generated under the MDR.[7]

While in 2017 the EU launched more rigorous medical device legislation, in contrast, the US FDA introduced the Breakthrough Devices program as part of the 20th Century Cures Act of 2016 which superseded Priority Review program of the FDA, and lowered evidence standards for medical devices. The traditional PMA pathway had already raised concerns about its common reliance on a single non-randomized, non-blinded pivotal study, with surrogate endpoints.[4] The Priority Review, which placed emphasis on post-approval studies, elicited similar concerns on lack of evidence for clinical benefit prior to approval of permanently implanted devices and was associated with an increasing number of recalls.[8] The latest iteration of accelerated approval, the Breakthrough Devices program, allows the FDA to 'accept a greater degree of uncertainty of the benefit–risk profile for these devices if the uncertainty is sufficiently balanced by other factors […] and adequate postmarket controls to support premarket approval.'[9] However, prior work has shown that few (13%) post-approval studies are completed up to 5 years after FDA approval.[10] The Breakthrough Devices program is growing almost exponentially.[11] As US and European medical devices markets are closely intertwined,[12] it is important to understand how regulatory changes in the USA impacted the quality of evidence used for the approval process in Europe and patient safety.

The current analysis did not examine whether the time lag between publication of a clinical trial and the corresponding CE mark varied with funding source. Reasons for delays in or failure of publication include: business-related confidentiality issues and varying timelines of approval processes in different jurisdictions, as well as academic reasons unrelated to regulatory processes.[13] Difference in timing of European and US approvals may potentially lead to withholding publication of certain sets of data prior to regulators decisions. This phenomenon, regardless of the specific causes, significantly affects patients' safety.

Recent improvements in the regulatory system in Europe will help ensure better quality and quantity of clinical evidence for high-risk medical devices and improve patient safety. The CORE MD report confirms the urgent need for such reform. Yet MDR opponents argue that stronger evidence requirements would increase cost to industry for developing and maintaining medical devices, and it will negatively impact innovations.[14] In attempts to maintain a delicate balance between safety and innovation, patients' safety should always be prioritized in the European Union and the USA. There is a strong argument to accelerate harmonization of international medical device regulatory standards as one of the strategic goals. For example, device names and Unique Device Identifiers should be global, and not vary from country to country.[15]

Transparency and publication of clinical evidence can help to foster innovation. Convergence of global medical device approval processes may lead to improvement in the quality of available evidence, while helping to avoid potential harms, and be good for patients. Mutual recognition of publicly reported high-quality evidence may speed up the regulatory processes, increase patient safety, and decrease the number of future recalls, thus decreasing rather than increasing the total costs of medical devices marketing. The exhaustive and careful review of almost 45 000 records by the CORE MD investigators shines a light on the path to transparency and patient safety, and will facilitate such work.[2]

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

References

1. Lenzer J; ICIJ reporters. Medical device industry: international investigation exposes lax regulation. *BMJ* 2018;**363**:k4997. https://doi.org/10.1136/bmj.k4997.
2. Siontis GC, Coles B, Häner JD, McGovern L, Bartkowiak J, Coughlan JJ, *et al.* Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD consortium. *Eur Heart J* 2024:**45**:161–77. https://doi.org/10.1093/eurheartj/ehad567
3. Chan AW, Song F, Vickers A, Jefferson T, Dickersin K, Gøtzsche PC, *et al.* Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014;**383**:257–66. https://doi.org/10.1016/S0140-6736(13)62296-5
4. Dhruva SS, Bero LA, Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. *JAMA* 2009;**302**:2679–85. https://doi.org/10.1001/jama.2009.1899
5. Hwang TJ, Sokolov E, Franklin JM, Kesselheim AS. Comparison of rates of safety issues and reporting of trial outcomes for medical devices approved in the European Union and United States: cohort study. *BMJ* 2016;**353**:i3323. https://doi.org/10.1136/bmj.i3323
6. Fraser AG, Byrne RA, Kautzner J, Butchart EG, Szymański P, Leggeri I, *et al.* Implementing the new European regulations on medical devices—clinical responsibilities for evidence-based practice: a report from the regulatory affairs committee of the European Society of Cardiology. *Eur Heart J* 2020;**41**:2589–96. https://doi.org/10.1093/eurheartj/ehaa382
7. Hulstaert F, Pouppez C, Primus-de Jong C, Harkin K, Neyt M. Gaps in the evidence underpinning high-risk medical devices in Europe at market entry, and potential solutions. *Orphanet J Rare Dis* 2023;**18**:212. https://doi.org/10.1186/s13023-023-02801-7
8. Jones LC, Dhruva SS, Redberg RF. Assessment of clinical trial evidence for high-risk cardiovascular devices approved under the Food and Drug Administration priority review program. *JAMA Intern Med* 2018;**178**:1418–20. https://doi.org/10.1001/jamainternmed.2018.3649
9. U.S. Food & Drug Administration. Breakthrough devices program draft guidance for industry and Food and Drug Administration staff. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm581664.pdf. Issued 25 October 2017. (24 September 2023).
10. Rathi VK, Krumholz HM, Masoudi FA, Ross JS. Characteristics of clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving FDA premarket approval in 2010 and 2011. *JAMA* 2015;**314**:604–12. https://doi.org/10.1001/jama.2015.8761
11. Johnston JL, Dhruva SS, Ross JS, Rathi VK. Early experience with the FDA's breakthrough devices program. *Nat Biotechnol* 2020;**38**:933–8. https://doi.org/10.1038/s41587-020-0636-7
12. Fudim M, Abraham WT, von Bardeleben RS, Lindenfeld J, Ponikowski PP, Salah HM, *et al.* Device therapy in chronic heart failure: jACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:931–56. https://doi.org/10.1016/j.jacc.2021.06.040
13. Zarin DA, Fain KM, Dobbins HD, Tse T, Williams RJ. 10-Year update on study results submitted to ClinicalTrials.gov. *N Engl J Med* 2019;**381**:1966–74. https://doi.org/10.1056/NEJMsr1907644
14. MedTech Europe Survey Report—Analysing the availability of Medical Devices in 2022 in connection to the Medical Device Regulation (MDR) implementation. (https://www.medtecheurope.org/wp-content/uploads/2022/07/medtech-europe-survey-report-analysing-the-availability-of-medical-devices-in-2022-in-connection-to-the-medical-device-regulation-mdr-implementation.pdf) (24 September 2023).
15. Rathi VK, Ross JS, Redberg RF. Unique device identifiers—missing in action. *JAMA Intern Med* 2023;**183**:1049–50. https://doi.org/10.1001/jamainternmed.2023.3561