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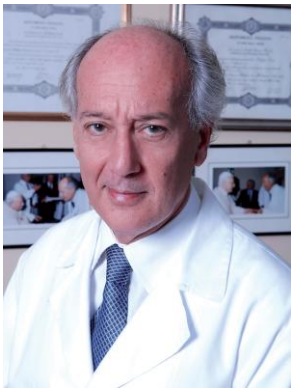
Focus on interventional cardiology: the need for quality and transparency of evidence for implantable cardiovascular medical devices



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This Focus Issue on interventional cardiology contains the Fast Track Clinical Research contribution '**Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD consortium**' by George Siontis from the University of Bern, and colleagues.[1] The authors note that 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. Pre-specified strategies were applied to identify published studies of prospective design evaluating 71 high-risk cardiovascular devices in seven different classes. 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. At least one prospective clinical trial was identified for 70% of the pre-specified devices. Overall, 473 reports of 308 prospectively designed studies were deemed eligible, including 81% prospective non-randomized clinical trials and 19% randomized clinical trials. Pre-registration of the study protocol was available for 49% of studies, and 16% had a peer-reviewed publicly available protocol. Device-related adverse events were evaluated in 82% of studies. An outcome adjudication process was reported in 39% of the studies. Sample size was larger for randomized in comparison with 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%). Sample sizes were smaller for studies published before than after 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.

Siontis *et al.* conclude that 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, are insufficient. The majority of studies are 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. The contribution is accompanied by an **Editorial** by Piotr Szymański from the National Institute of Medicine MSWiA in Warsaw, Poland, and Rita Redberg from the UCSF Division of Cardiology in San Francisco, CA, USA.[2] The authors note that 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 marketing of medical devices. 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.

The functional assessment of epicardial stenosis plays a key role in planning revascularization procedures.[3–8] In another Fast Track Clinical Research article entitled **'Coronary flow capacity and survival prediction after revascularization: physiological basis and clinical implications'**, Lance Gould from the University of Texas Health Science Center in Houston, TX, USA, and colleagues note that stress myocardial perfusion (mL/min/g) and coronary flow reserve (CFR) per pixel were quantified in ~7000 coronary artery disease

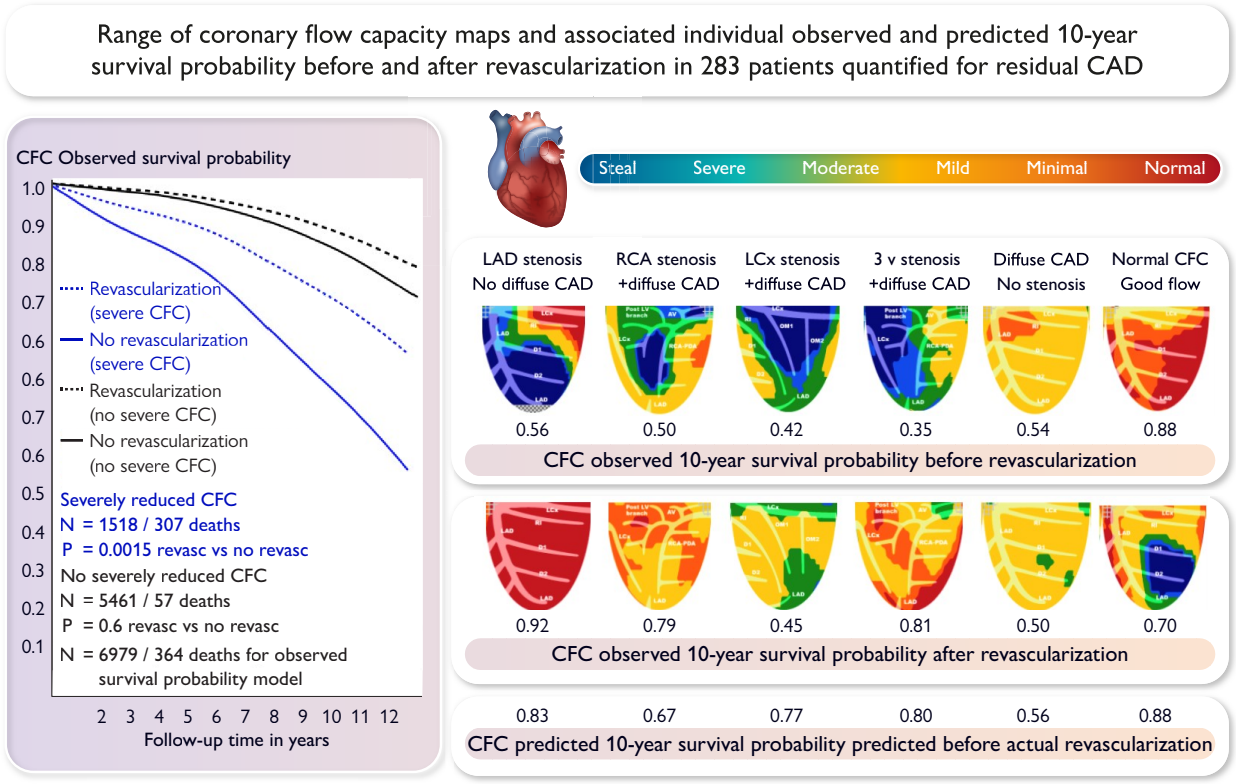

Figure 1 Coronary flow capacity (CFC) and survival prediction after revascularization: physiological basis and clinical implications. CFC maps in one view before (upper row) and after revascularization (lower row) show residual diffuse coronary artery disease (CAD), stenosis, and incomplete or inappropriate revascularization as examples from 283 pre- and post-revascularization positron emission tomography (PET) pairs. The 10-year survival probability is determined as a fraction of one for normal CFC (all red) by the proportional distribution of regional size–severity CFC abnormalities. The individual observed survival probabilities for each CFC map before and after actual coronary revascularization are listed below each CFC map. The virtual survival probability predicted for the baseline CFC map after virtual theoretical ideal complete revascularization is listed in the lowest (third) row for each case. The plots show the observed survival probability of 6979 PET cases with and without severely reduced CFC with and without non-randomized revascularization followed over 12 years as the database from which individual survival probability is determined by multivariable CFC components by Cox regression modelling. LAD, left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.[9]

(CAD) subjects using Rb-82 positron emission tomography (PET) to obtain coronary flow capacity (CFC) maps of artery-specific size–severity abnormalities expressed as a percentage of the left ventricle with prospective follow-up to define survival probability per decade as a fraction of 1.0.[9] Severely reduced CFC in 6979 subjects predicted low survival probability that improved by 42% after revascularization compared with no revascularization for comparable severity ($P = .0015$). For 283 pre- and post-procedure PET pairs, severely reduced regional CFC-associated survival probability improved heterogeneously after revascularization ($P < .001$), more so after bypass surgery than after percutaneous coronary interventions ($P < .001$), but normalized in only 5.7%. Non-severe baseline CFC or survival probability did not improve compared with severe CFC ($P = .00001$). Observed CFC-associated survival probability after actual revascularization was lower than virtual ideal hypothetical complete post-revascularization survival probability due to residual CAD or failed revascularization ($P < .001$) unrelated to gender or microvascular dysfunction. Severely reduced CFC in 2552 post-revascularization subjects associated with low survival probability also improved after repeat revascularization compared with no repeat procedures ($P = .025$) (*Figure 1*).

The authors conclude that severely reduced CFC and associated observed survival probability improved after first and repeat revascularization compared with no revascularization for comparable CFC severity. Non-severe CFC showed no benefit. Discordance between observed actual and virtual hypothetical post-revascularization survival probability revealed residual CAD or failed revascularization. The contribution is accompanied by an **Editorial** by Viviany Taqueti from Harvard Medical School in Boston, MA, USA.[10] Taqueti notes that the time has come to move beyond simplistic paradigms of obstructive focal anatomic-driven and flow-limiting regional ischaemia-driven strategies for revascularization in chronic coronary disease to incorporate global coronary flow-guided approaches in high-quality randomized clinical trials. To move the field forward, we must ask and rigorously test what this dynamic physiological tool, combined readily with assessments of diffuse atherosclerotic plaque burden and myocardial fibrosis, can potentially tell us about pathophysiology and appropriate patient selection—not only for invasive interventions—but also for novel and increasingly available preventive cardiometabolic therapies?

Transcatheter valve implantation plays a key role in the current treatment of heart valve disease.[11–17] Transcatheter pulmonary valve

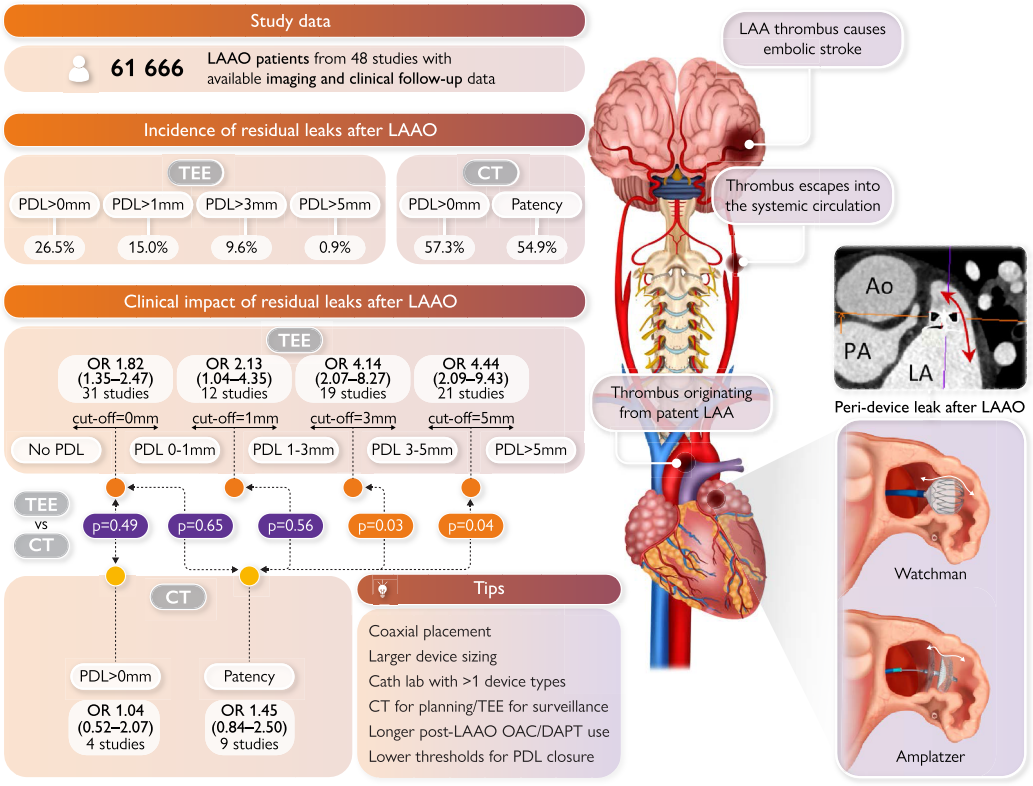

Figure 2 Incidence and clinical impact of residual leaks after left atrial appendage occlusion across different leak size thresholds and imaging modalities. Ao, aorta; CT, computed tomography; DAPT, dual antiplatelet therapy; LA, left atrium; LAA, left atrial appendage; LAAO, left atrial appendage occlusion; OAC, oral anticoagulation; OR, odds ratio; PA, pulmonary artery; PDL, peri-device leak; TEE, transoesophageal echocardiography.[20]

implantation (TPVI) is indicated to treat right ventricular outflow tract (RVOT) dysfunction related to congenital heart disease (CHD). In a Clinical Research article entitled **'Outcomes of transcatheter pulmonary SAPIEN 3 valve implantation: an international registry'**, Sebastien Hascoët from the Hospital Clinic de Barcelona in Le Plessis Robinson, France, and colleagues investigated outcomes of TPVI with the SAPIEN 3 valve that are insufficiently documented in the EUROPULMS3 registry of SAPIEN 3-TPVI.[18] Patient-related, procedural, and follow-up outcome data were retrospectively assessed in this observational cohort from 35 centres in 15 countries. Data for 840 consecutive patients treated in 2014–21 at a median age of 29 years were obtained. The most common diagnosis was conotruncal defect (70%), with a native or patched RVOT in 51% of all patients. Valve implantation was successful in 98% of patients. Median follow-up was 20 months. Eight patients experienced infective endocarditis; 11 required pulmonary valve replacement, with a lower incidence for larger valves ($P = .009$), and four experienced pulmonary valve thrombosis, including one who died and three who recovered with anticoagulation. Cumulative incidences of complications 6 years after TPVI were as follows: infective endocarditis 3.8%, pulmonary valve replacement 8%, and pulmonary valve thrombosis 0.7%.

Hascoët *et al.* conclude that outcomes of SAPIEN 3-TPVI are favourable in patients with CHD, half of whom have native or patched RVOTs. The contribution is accompanied by an **Editorial** by Jamil Aboulhosn from the University of California Los Angeles in the USA.[19] Aboulhosn concludes that the EUROPULMS3 registry results are encouraging, specifically regarding short- and intermediate-term outcomes in a real-world environment and in patients with conduits and bioprosthetic valves. Concerns remain regarding the complication rates and outcomes of SAPIEN S3 transcatheter pulmonary valve replacement in native RVOT patients.

Residual leaks are not infrequent after left atrial appendage occlusion. However, there is still uncertainty regarding their prognostic implications. In an article entitled **'Residual leaks following percutaneous left atrial appendage occlusion and outcomes: a meta-analysis'**, Athanasios Samaras from the Aristotle University of Thessaloniki in Greece, and colleagues evaluated the impact of residual leaks after left atrial appendage occlusion.[20] A literature search was conducted up to 19 February 2023. Residual leaks comprised peri-device leaks (PDLs) on transoesophageal echocardiography (TEE) or computed tomography (CT), as well as left atrial appendage patency on CT. Random effects meta-analyses were performed to assess the clinical impact of residual leaks. Overall, 48 eligible studies (44 non-randomized/observational and 4 randomized studies) including ~62 000 patients with atrial fibrillation who underwent left atrial appendage occlusion were analysed. Peri-device leak by TEE was present in 26% of patients. CT-based left atrial appendage patency and PDL were present in 55% and 57% of patients, respectively. TEE-based PDL (i.e. any reported PDL regardless of its size) was significantly associated with a higher risk of thrombo-embolism [pooled odds ratio (pOR) 2.04], all-cause mortality (pOR 1.16), and major bleeding (pOR 1.12), compared with no reported PDL. A positive graded association between PDL size

and risk of thrombo-embolism was noted across TEE cut-offs. Neither left atrial appendage patency nor PDL by CT was associated with thrombo-embolism (*Figure 2*).

The authors conclude that PDL detected by TEE is associated with adverse events, primarily thrombo-embolism. Residual leaks detected by CT are more frequent but lack prognostic significance. This manuscript is accompanied by an **Editorial** by Ole De Backer from the Copenhagen University Hospital in Denmark and Philippe Garot from the Hôpital Jacques Cartier in Massy, France.[21] The authors note that this meta-analysis contributes to a better understanding of the clinical importance and implications of residual leaks after transcatheter LAA closure. TEE-detected PDLs after LAA closure are associated with adverse clinical events, primarily thrombo-embolism, and should be avoided or at least kept to an absolute minimum. Moreover, this meta-analysis uncovers that screening for 'LAA patency' at follow-up cardiac CT is not sufficient and that 'LAA patency' at post-procedural cardiac CT is not associated with worse clinical outcomes. This is an important finding as an increasing number of sites are nowadays relying on cardiac CT for both pre- and post-procedural LAA imaging. Clearly, more research is warranted to determine the optimal detection method and cut-off value(s) for clinically relevant PDL across different protocols and imaging modalities.

Obstructive hypertrophic cardiomyopathy (oHCM) is an inherited myocardial disease, caused by mutations in genes encoding sarcomere (or sarcomere-related structures) proteins.[22,23] In a Rapid Communications article entitled **'Transcoronary radiofrequency ablation for obstructive hypertrophic cardiomyopathy: a feasibility study'**, Xiangshu Long from the Guizhou Provincial People's Hospital in China, and colleagues enrolled 13 consecutive hospitalized oHCM patients, who remained symptomatic in spite of maximally tolerated negative inotropic medications (beta-blockers, non-dihydropyridine calcium channel blockers).[24] Inclusion criteria were defined as a maximal end-diastolic wall thickness of ≥15 mm in an asymmetric hypertrophied septum in the short-axis view of transthoracic echocardiography, a resting peak left ventricular outflow gradient (LVOTG) ≥50 mmHg, New York Heart Association functional classes III–IV, and age ≥18 years. The left main coronary artery ostium was engaged with a 6 F suitable guiding catheter, and subsequent contrast echocardiography was performed to identify one or more target septal-perforating arteries and main branches perfusing the hypertrophic septum. A 0.014 inch coronary guidewire was advanced into the distal segment of the selected septal artery. According to the calibre of the vessel and its main branches, an appropriate size over-the-wire balloon or microcatheter was positioned in the proximal segment of the branch via the guidewire for insulation to prevent damage to non-target coronary arteries. The distal tip 5–15 mm of the guidewire was exposed for ablation. The extracorporeal end of the guidewire was connected to a radiofrequency ablation catheter. Finally, unipolar radiofrequency ablation with a power setting of 30 W and impedance <300 Ω was undertaken until auto cut-off. The procedure was repeated 3–5 times in the same branch. If an LVOTG reduction of <50% was not achieved, the next target septal artery was identified and ablated further. Compared with baseline, the invasive and non-invasive LVOTG decreased by 73.0 and 63.3 mmHg immediately post-procedure; the non-invasive LVOTG decreased by 45 mmHg pre-discharge and by 56.9 mmHg after 3 months, achieving 92.3% technical success and 84.6% clinical success.

The issue is also complemented by a Discussion Forum contribution. In a commentary entitled '**Nickel hypersensitivity as the cause of atrial fibrillation after patent foramen ovale closure: fact or myth?**', Anastasios Apostolos, Konstantinos Toutouzas, and Constantina Aggeli from the National and Kapodistrian University of Athens in Greece comment on the recent publication **'Long-term risk of atrial fibrillation or flutter after transcatheter patent foramen ovale closure: a nationwide Danish study'** by Christian Valdemar Skibsted from the Aarhus University Hospital in Denmark.[25,26]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

Dr. Crea reports speaker fees from Abbott, Amgen, Astra Zeneca, BMS, Chiesi, Daiichi Sankyo, Menarini outside the submitted work.

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