INVITED EDITORIAL COMMENTING ON THE ARTICLE:

Schrage B, Lund LH, Benson L, Dahlström U, Shadman R, Linde C, Braunschweig F, Levy WC, Savarese G. Predictors of primary prevention implantable cardioverter-defibrillator use in heart failure with reduced ejection fraction: impact of the predicted risk of sudden cardiac death and all-cause mortality. Eur J Heart Fail. 2022 May 3. doi: 10.1002/ejhf.2530. Epub ahead of print. PMID: 35502681.

Implantable cardioverter defibrillators for primary prevention of sudden cardiac death: what are the barriers to implementation in the "real world"?

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In the 1960s, Mirowski conceived that an implantable cardioverter-defibrillator (ICD) could prevent sudden, arrhythmic death. Despite criticism, scepticism and ostracism in the scientific community, Mirowski and Mower first reported ICD implantation in humans in 1980 (1). International guidelines, based on randomized, controlled trials, have since firmly established indications for primary ICD implantation in patients with left ventricular systolic dysfunction and heart failure and broader patient populations (2--5). However, implementation of ICD therapy for primary prevention is still challenging for a series of reasons and prominent amongst these are low referral rates and financial issues. (2, 4).

In this issue of *The European Journal of Heart Failure,* Schrage et al. (6) provide a subanalysis of the SwedeHF registry, undertaken from 2011-2018. They have assessed rates of ICD implantations according to guideline indications, taking into account the Seattle Proportional Risk and the Seattle HF Models to predict the proportional SCD and all-cause mortality risks, respectively. Whilst the cut-offs of left ventricular ejection fraction of 30% and 40% were used, rather than the generally accepted cut-off <35%, the study is of interest with regard to the implementation of ICD therapy in the "real world". Important aspect of this analysis are the barriers to ICD implantation in patients who satisfy the indications of clinical guidelines. Essentially, only 15.5% of 13,475 heart failure patients were implanted with an ICD. Predictors of non-use of ICDs were: follow-up in primary vs. specialty care, a higher comorbidity burden, older age, female sex and lower socioeconomic status. At 3 years, ICD use was associated with lower mortality in patients with higher predicted SCD and lower mortality risk (3-year relative risk reduction of 34% for all-cause mortality and of 37% for cardiovascular mortality). However, in these subgroups, underuse of ICD was 81.8%. Essentially, patients with a predicted high risk of SCD associated with a low all-cause mortality risk did not receive ICD therapy. As a matter of fact, it appears that estimates on the expected role of SCD as a determinant of outcome, versus other competing risks of death, did not substantially influence the complex process of decision making about ICD implant. In terms of ideal targeting, ICD should be a primary option, without hesitance, in patients with a predicted high risk of SCD associated with a low absolute mortality risk, but this option was largely underused in the Swedish registry (6).

The authors should be commended for addressing an issue that is important to ICD implantation practice worldwide and which is not addressed in clinical guidelines. In this context, the Atlas published by the European Society of Cardiology (7) showed a wide

variation in ICD implantation rates across Europe (**Figure**). Such variations may be due to a bad perceptions of the cost of ICD therapy, which is a high upfront cost, differently from the costs of medical therapy, which tend to be spread, or diluted over time (8). We know that, despite its up-front costs, ICD therapy is cost-effective in appropriately selected patients and that its economic profile is in line with widely accepted standards for willingness to pay. In essence it is a sound investment for healthcare systems (2, 4, 8, 9).

As the authors argue, any analysis of ICD and cardiac resynchronization therapy (CRT) with defibrillation (CRT-D) implant rates has to consider the DANISH trial, in which patients with non-ischemic cardiomyopathy did not derive a survival benefit from devices with defibrillator capabilities (10). Despite that the DANISH trial has not influenced clinical guidelines, it may have influenced ICD and CRT-D implantation rates (11).

Other organizational issues, not all of which are specific to cardiology, may explain variations in ICD implantation rates (**Table**). A survey of Swedish physicians in the fields of cardiology, internal medicine, and family medicine identified substantial awareness gaps with regard to evidence-based indications for ICD implantation (12). Such gaps may account for the low referral rates to specialized centres, where heart failure units and electrophysiologists work hand-in-hand. The increased use of telemedicine that we saw during the COVID-19 pandemic may improve contacts between referring clinicians and specialist centres (13). Increased access to specialist units through telemedicine may be useful the training and support required to ensure a more uniform access to ICD therapy,.

The decision as to whether to implant a ICD in a patient with heart failure and reduced ejection fraction is not easy. Whilst guidelines are invaluable, a decision on an individual patient may be influenced by age, sex, frailty, as well as patient beliefs and concerns (**Table)** (3, 5, 10), none of which is addressed in guidelines. The lower use of ICDs in women observed in Sweden appears unjustified, particularly as women appear to have a better outcome than men, in terms of lower risk of appropriate shocks and death, in case of ICD implant (6).

The past two decades has seen an improved armamentarium of pharmacological treatments for heart failure (14). Whilst some authorities have taken the position that drugs and devices are alternative treatments, the greatest clinical benefit is seen in patients who are treated with both pharmacological and device therapy (15, 16). We should consider that delays in delivering device therapy may lead to SCD, even after optimal medical therapy (15).

In summary, Schrage et al. (6) highlight the importance of a detailed assessment of patients who satisfy the guidelines criteria for ICD implantation. Their findings highlight the need to collect data on actual implementation and associated outcomes for patients implanted with ICDs and CRT-D in routine clinical practice (17-19).

Whilst under-use of ICDs in elderly patients and those with significant co-morbidities is understandable, underuse in women and patients with a lower socio-economic status does not seem justifiable.

In the field of ICD therapy, all we can hope for is that patients do not succumb to a SCD before dying from another cause (competing risks). A multidisciplinary approach geared towards individual patient characterisation is crucial for targeting ICD therapy to the right patients (5, 8). The balance between the competing risks of SCD and all-cause mortality needs to be addressed at an individual, personalised level.

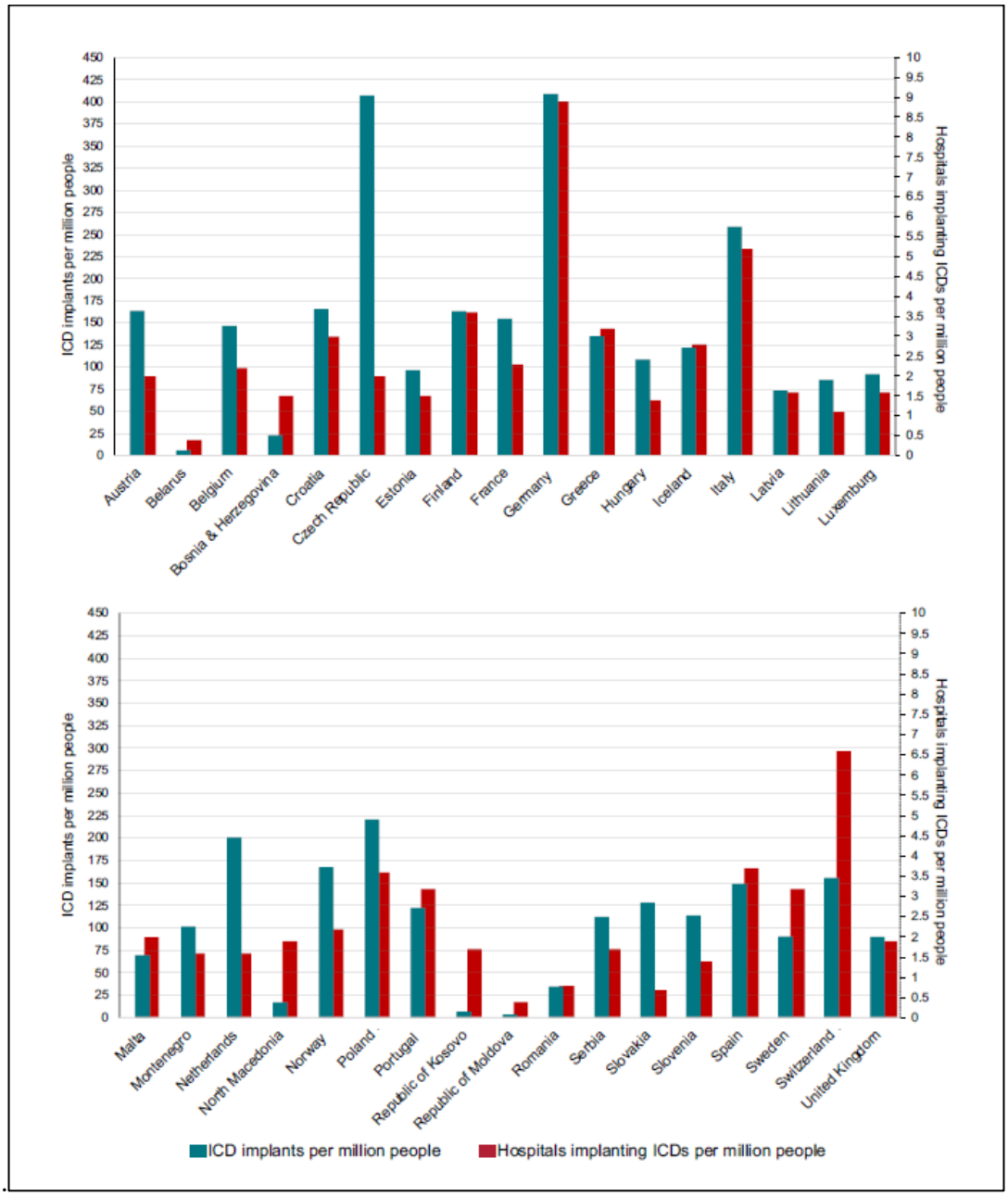
Conflict of interest

GB reported speaker's fees of small amounts from Bayer, Boston and Daiichi outside the submitted work. FL has served as a consultant for and has received research funding from Medtronic, Boston Scientific, Abbott, Microport, and Biotronik, outside the submitted work. MV reported no conflicts to disclose.

Table. Barriers that may limit a full implementation of ICD therapy in primary prevention, as a strategy for improving patient survival through a reduction of SCD. Legend: CRT-P: cardiac resinchronization therapy with a pacemaker; ICD= implantable cardioverter-defibrillator; LV: left ventricular; SCD: sudden cardiac death.

Barriers at the level of eligible patients
• Inertia in the presence of stable cardiac conditions • Difficulty in understanding the risk of SCD in the absence of previous events (primary prevention) • Concerns on quality of life in relationship with inappropriate shocks • Concerns on device/leads reliability at long term (knowledge of prior device/lead recalls) • Concerns about the restrictions for driving licence • Uncertainty about the net benefit of ICD therapy • Psychological problems • Depression • Cultural barriers
Barriers at the level of referring physicians
• Lack of confidence on risk stratification for SCD • Difficulty in understanding the risk of ventricular tachyarrhythmias in the absence of previous events (primary prevention) • Underestimation of the risk of SCD in patients with heart failure with reduced LV ejection fraction • Clinical inertia related to patient clinical stability despite depressed LV ejection fraction • Concerns about the translation of clinical trial results to patients in daily real-world practice in terms of net benefit • Therapeutic nihilism • Limited organization of pathways for referral to specialized centres for ICD implant and for shared decision-making • Concerns on patient quality of life in relationship with inappropriate shocks • Concerns on device/leads reliability at long term (knowledge of prior device/lead recalls) • Difficulties in assessing the risk of non-cardiovascular death due to comorbidities and age and the risk of non-sudden cardiovascular death • Difficulties in predicting life expectancy, particularly in the elderly • Need for validation of better and more specific tools for risk-stratification and patient selection for ICD • Delay in referral of potential candidates to ICD implant related to extension of the time for pharmacological therapy optimization (waiting for improvement in LV ejection fraction) • Lack of knowledge/confidence on guidelines for ICD implantation • Lack of confidence on the benefit of ICD therapy in non-ischemic cardiomyopathy • Preference for implant of a CRT-P device, that may reduce SCD through LV reverse remodeling • Lack of interest on the potential impact of remote monitoring on patient management • Personal biases
Barriers at the level of regulators/payers/health care system
• Relatively low level of priority for SCD prevention as a major goal • High upfront cost of ICD therapy with delayed benefits • Silo-budgeting for health care resources with competition among different non-pharmacological treatments • Concerns about the methods for risk stratification and selection of candidates for ICD therapy (resulting in high number of potentially eligible patients) • Concerns about potential selection as candidates to ICD therapy of elderly patients with multiple comorbidities, with expected marginal benefit or no benefit

Figure. Implant rates (per million inhabitants) and number of centres implanting ICDs across Europe, according to data reported in the ESC Atlas (7). Legend: Number of ICD implants per million people from Denmark, Bulgaria, Ireland and Cyprus were not available. ICD= implantable cardioverter-defibrillator



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