COMMENTARY

# ICD early after myocardial infarction: it is really necessary to wait 40 days before implantation?

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Graphical Abstract

ESC Guidelines don't recommend ICD implantation within 40 days after MI, on the basis of old evidence with several limitations. However, a significant number of patients remain at high risk of arrhythmic death also in the early period after ACS, in these patients early ICD implantation or LifeVest may be use with benefit on survival.
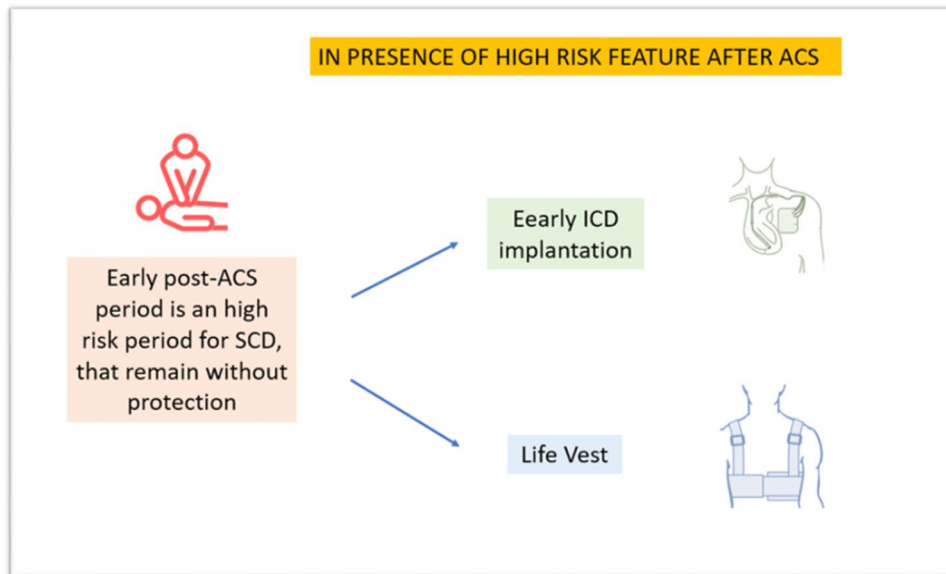
Gianmarco Arabia takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Although the prevalence of ventricular arrhythmias (VAs) after acute coronary syndrome (ACS) has decreased in the era of percutaneous coronary intervention (PCI), almost 5% of patients affected by myocardial infarction (MI) still experience VAs. Unlike early post-MI VAs, late VAs occur 48 h after MI and do not tend to disappear with the resolution of ischemia. Late VAs are linked to the formation of an irreversible arrhythmogenic scar substrate, are monomorphic and reproducible by electrophysiologic study (EPS) and constitute an indication to implantable cardioverter-defibrillator (ICD) implantation in secondary prevention. The rate of arrhythmic death due to late VAs is highest during the first 30 days after MI, with a post-discharge general incidence of 0.12 to 2.0%. Despite that the European Society of Cardiology (ESC) recommend that primary prevention ICD implantation should be withheld for at least 40 days after ACS on the basis of the results of the two only large randomized trials on the topic, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) [1] and the Immediate Risk Stratification Improves Survival (IRIS) [2]. In these trials, early ICD implantation was linked to reduced arrhythmic death and total mortality in the first period post-MI but not in the long-term follow up, because of an inflation of non-cardiac and cardiac non-arrhythmic deaths in the implanted patients [1, 2]. Of note, trials' authors report that these results could not be easily linked to the implantation because no deaths were related to complications of the procedure in the DINAMIT (and only 1 death in the IRIS), the pacing rate was low because of the device programming (device lower rate was 40-55 bpm in the DINAMIT and 40 bpm in the IRIS), and furthermore the patients' left ventricular ejection fraction did not recover in the follow-up [1, 2]. The most probable explanation hypothesized by the authors was that the patients "saved" from an arrhythmia-related death by ICD therapy were also at high risk for death from other cardiac causes [1, 2]. However, there are other possible reasons. In the DINAMIT trial, for example, the control group mortality at 24 months was significantly lower (< 15%) than in positive ICD trials, such as the Dutch, MADIT, MUSTT and MADIT II, which had reached mortality rates between 20 and 35%. Moreover, the percentage of SCD was significantly lower in the IRIS (19%) [2] and the DINAMIT (34%) [1] than in MADIT (35%) and the MUSTT (55%), and there was an excess of non-cardiac deaths in implanted patient group. These discrepancies were probably due to the high crossover rate from the ICD group to the control group (10.1% in the IRIS, 6.6% in the DINAMIT), to the artefacts created during the non-blinded determination of the cause of death, and above all to the selection criteria of the trial population. For example, patients enrolled in the IRIS trial had LVEF < 40% or TVns (regardless of LVEF) as a result of STEMI or non-STEMI [2], and so, they constituted a very different population from that of the DINAMIT

or of the MADIT, which respectively had LVEF < 35% and < 30% as a result of STEMI [1]. Interestingly, in the subgroup of patients with New York Heart Association class (NYHA) III or IV of the IRIS, the benefit of the ICD implantation was almost significant [2]. Moreover, both in the DINAMIT and in the IRIS trials, the prevalence of non-cardiovascular pathologies was not analysed (except for Diabetes Mellitus 2, which were significantly more prevalent in the implanted group of the IRIS), but one can hypothesize that they were probably different on the basis of non-cardiac mortality rate [1, 2]. Finally the different incidence of ischemic and decompensation events during follow up in the DINAMIT and the different prevalence of left bundle branch block (LBBB) in the IRIS suggest that the implanted group had more severe coronary artery disease [2]. However, the major limitation of these trials remains the fact that they date back to the thrombolysis era, when cardiologic treatments were very different than today [1, 2]. Indeed, the trials' population received no treatment for the index MI, thrombolysis (of note with a completely different long-term prognosis) [1, 2] or PCI with old generation coronary stents, without complete revascularization [1, 2] and optimal medical treatment [1, 2], so probably, ICD implantation saved patients form early arrhythmic death but, on the long term, patients died all the same because of mechanical heart failure derived from severe not optimally treated ischemic heart disease. In the last years, the treatment of ACS improved with reduction of late VAs and more frequent LVEF recovery; however, a significant post-MI risk, albeit lower, of malignant arrhythmias persists with a post-discharge general incidence of out-of-hospital post-MI cardiac arrest of 0.12% to 2.0%, highest in case of ST-elevation myocardial infarction (STEMI), or reduced LVEF. Despite these changes, only few recent trials have been conducted on early post-MI implantation of ICD in primary prevention. The Defibrillator After Primary Angioplasty (DAPA) trial was the most important; it highlighted the need to anticipate the ICD implantation at 30 days after MI to protect high-risk patients in the time window at high risk of SCD. High-risk features were defined as at least one of the following: primary ventricular fibrillation (VF), LVEF < 30%, Killip class ≥ 2 or TIMI flow < 3 after primary PCI [3]. Other interesting evidence comes from the use of the electrophysiological study (EPS) early post ACS; for example, Zaman et al. showed benefit of ICD implantation in primary prevention in presence of inducible VAs at EPS in patients with STEMI treated with PCI and LVEF < 40%. Of note, there was not an increase in mortality during follow-up and not implanted patients with reduced LVEF have no arrhythmic deaths during the 2 years of follow up [4]. A similar trial, conducted by Kumar et al., showed long-term outcome benefits of electrophysiology-guided ICD implantation, 9 days after STEMI, in 360 patients with LVEF < 40% [5]. Other studies have been

conducted on alternative means of temporary protection from SCD. The Vest Prevention of Early Sudden Death Trial (VEST) evaluated the wearable cardioverter-defibrillators (LifeVest, ZOLL Medical Corporation, Chelmsford, MA) in 2302 patients with LVEF < 35%, without proving a statistically significant reduction of arrhythmic death at 90 days, probably because of the low patients' adherence; consequently, ESC Guidelines indicate to consider LifeVest in the early phase after MI in selected patients. Finally, even the few available registry data are in favour of an earlier ICD implantation: the Danish Cardiac Arrest Registry reported that, of the total patient population between 2001 and 2012 that suffered from out-of-hospital cardiac arrest caused by myocardial infarction (974 patients), 13% received ICD implantation earlier than recommended by the guidelines, presumably as primary prevention and early implantation was significantly associated with a long-term survival benefit [6]. A similar result was reported by Solomon et al. and other large retrospective studies. Moreover, in a recent large-scale, prospective, multicentre registry analysis of 10,103 patients, Choi et al. confirm a significant residual risk of death in the subacute stage (within 90 days) after ACS. Authors report that patients were successfully treated and stabilized after the acute event and successfully discharged, so they argue that the proportion of deaths due to fatal pump failure would not be high; instead, the deaths were probably arrhythmic and preventable with an early ICD implantation. The incidence of early cardiac death was also quantified according to the number of some risk factors added to LVEF criteria; it was 3.03% for patients with 0 factors, 8.11% for 1 factor and 9.16% for ≥ 2 factors of Killip class ≥ 3, chronic kidney disease stage ≥ 4, severe anaemia, cardiopulmonary support usage, no dual antiplatelet therapy at discharge [7]. In conclusion, the risk of SCD in early post MI period is substantial, and the optimal timing of ICD implantation in MI survivors remains a debated argument. The ESC Guidelines Class III recommendations about ICD implantation within 40 days after MI is based on old evidence with several limitations, and newer data confirm that early ICD implantation could lead to long-term benefit. So, ideally, better stratification of the patients' risk for earlier ICD implantation together with the use of new means of protection should be foreseen in the future in a comprehensive and personalized approach to reduce SCD rate in this high-risk time window.

Declarations

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