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EDITORIAL

REINFORCING the clinical utility of an antibacterial envelope to prevent infection following a cardiac implantable electronic device implant procedure

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This editorial refers to 'REducing INFectiOns thRough cardiac device envelope: insight from real world data. The REINFORCE Project' by M. Ziacchi *et al.*, https://doi.org/10.1093/eupace/euad224.

Infection of cardiac implantable electronic devices (CIEDs) remains an important ongoing issue in clinical practice.[1] Once it occurs, treatment typically requires explantation of the implanted hardware; the infection as well as the treatment contributes to morbidity and mortality. Thus, attention has recently focused on strategies at time of device implantation to *prevent* CIED infection. Towards that end, availability of an antibacterial envelope has been an important advance in the fight against CIED infection.

A series of initial observational studies suggested that an antibacterial envelope reduced CIED infection.[2–6] The first-generation envelope was non-absorbable; once an absorbable envelope became available (TYRX^{TM}, Medtronic, Minneapolis, MN, USA), the envelope was formally tested in a randomized clinical trial. The Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) was a multi-centre, randomized, controlled, prospective, single-blind, post-marketing, interventional clinical trial that compared the incidence of major CIED infections through 12 months after implantation among patients who received an absorbable antibacterial envelope with the incidence among patients who did not receive the envelope.[7] Patients who were undergoing a CIED pocket revision, generator replacement, or system upgrade or an initial implantation of a cardiac resynchronization therapy defibrillator were randomly assigned, in a 1:1 ratio, to receive the envelope or not. Standard-of-care strategies to prevent infection were used in all patients. A total of 6983 patients underwent randomization: 3495 to the envelope group and 3488 to the control group. The primary endpoint occurred in 25 patients in the envelope group and 42 patients in the control group [12-month Kaplan–Meier estimated event rate, 0.7 and 1.2%, respectively; hazard ratio, 0.60; 95% confidence interval (CI), 0.36–0.98; $P = 0.04$]. Additional analyses have confirmed the safety and efficacy of the envelope in short-term and long-term follow-up, identified risk factors and microbiology of infection, the relationship between pocket haematoma and infection, and the cost-effectiveness of the envelope.[8–12]

Despite the results of WRAP-IT, several unresolved issues have remained. The first is whether the data can be extrapolated to patients not enrolled in this trial, such as those undergoing *de novo* pacemaker or defibrillator implantation. The second is whether high-risk patients can be identified who may most benefit from an antibacterial envelope; this issue is largely driven by concerns about the cost of the envelope. The third is whether the findings can be replicated in 'real-world' use. In this issue of *Europace*, Ziacchi *et al.*[13] attempt to answer these questions.

This study enrolled consecutive patients undergoing a CIED procedure using a Medtronic device at 11 Italian centres between August 2016 and May 2022. The authors describe the characteristics of the patients in whom an antibacterial envelope was used as well as the impact of the envelope in preventing infection-related events. The decision on whether to use or not use the envelope was left to the discretion of the operator.

Overall, 1819 patients were enrolled; an envelope was used in 872 (48%) patients. Two-thirds of patients underwent a *de novo* procedure, which was a pacemaker in 53% and a defibrillator in 47%. During a mean follow-up of 1.4 ± 1.7 years, there were 27 pocket and 3 systemic infections. Patients who received an envelope had a significantly lower likelihood of infection (0.8 vs. 2.4%, $P = 0.007$); as in WRAP-IT, the impact of the envelope was largely in preventing pocket infections. Although not statistically significant, likely due to the sample size and lower infection rate in this group, there was also a numerically lower rate of infection in patients undergoing a *de novo* procedure who received an envelope (0.8 vs. 1.9%, $P = 0.130$). Notably, a favourable impact of other interventions such as use of antibiotic pocket irrigation and post-operative oral antibiotics was not observed in another study that included *de novo* patients, where all patients were deemed high-risk and received an antibacterial envelope.[14] The study by Ziacchi *et al.*[13] and the WRAP-IT trial suggest that the CIED major infection rate can be reduced to <1% with use of an antibacterial envelope.

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

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Since most patients undergoing a CIED implant will not develop an infection and because of the inherent costs of the antibacterial envelope, there has been a great risk interest in identifying the patients at highest risk. Risk factors are related to patient, procedure, and device characteristics; using these, a variety of risk scores have been proposed.[15,16] Ziacchi *et al.*[13] used the PADIT risk score, which encompasses the following risk factors: (P) prior procedures, (A) age, (D) depressed renal function, (I) immunocompromised, and (T) procedure type. The score ranges from 0 to 15; patients with a score 0–4 are classified as low risk, 5–6 as intermediate risk, and 7 or more as high risk. Patients with a high-risk PADIT score were three times more likely to receive an envelope in this study. In the control group, the infection rate was 1.7, 2.9, and 5.6% in the low, intermediate, and high-risk PADIT risk groups; the envelope reduced the infection rate by a similar magnitude in all three groups. Since the 'low-risk' group still had a clinically significant rate of infection and since the envelope reduced the infection rate in all risk groups, it does not appear that a risk score alone can be used to withhold the envelope in patients.

The last point is that 'real-world' evidence is very much needed once the benefit of any therapy is suggested in a randomized clinical trial. The study by Ziacchi *et al.*[13] is very reassuring that the favourable impact of the antibacterial envelope observed in the WRAP-IT trial was also observed in their experience. Importantly, the protective benefit of the envelope appeared to persist for up to 5 years of follow-up. This finding has implications for the ultimate cost-effectiveness of a strategy of using an antibacterial envelope at the time of a CIED implant procedure.

The European Heart Rhythm Association international consensus document on how to prevent, diagnose, and treat CIED infections recommends the use of an antibacterial envelope in high-risk patients, defined as those included in WRAP-IT and those with other high-risk features.[17] The findings by Ziacchi *et al.*[13] provide further support for these recommendations and extend the findings to patients undergoing a *de novo* pacemaker or defibrillator procedure but raise question about our ability to identify truly 'low-risk' patients based on a risk score alone. Till additional studies emerge, available data REINFORCE the clinical utility of an antibacterial envelope as a very important strategy for the prevention of CIED infections.

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