Cardiac Devices Enveloped with an Ounce of Prevention

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Infections involving cardiac implantable electronic devices (CIEDs) are challenging to treat. Primary infections, mostly pocket infections occurring at the time of implantation, usually require removal of the device, thus adding to the cost and morbidity associated with CIEDs. Secondary infections, resulting from bacteremia from a remote source, often lead to endocarditis with additional devastating outcomes. Despite the effectiveness of current standard strategies for prevention of CIED infections (i.e., sterile surgical techniques and the timely administration of preoperative antibiotics), the potential to achieve further reductions in infection rates exists.

In this issue of the *Journal*, Tarakji et al. report the results of the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT). This industry-sponsored, postmarketing, multicenter, prospective, single-blind, randomized, interventional trial evaluates the effect of an absorbable multifilament mesh envelope that surrounds a CIED and improves its stability in the subcutaneous pocket. The envelope elutes the antibiotics minocycline and rifampin, aiming to achieve sufficient concentrations in surrounding tissues to prevent infection with bacterial flora residing on the skin. Did the antibiotic-eluting envelope protect against CIED infections? The answer is clear: the use of this envelope, in addition to standard procedures, significantly reduced the incidence of major infection without increasing other complications. The results of WRAP-IT enhance the findings from a meta-analysis of observational studies, which supports the use of antibiotic envelopes to prevent CIED infections.

In WRAP-IT, approximately 7000 participants were enrolled at 181 centers in 25 countries within North America, Europe, Asia, and South America. The intervention and control groups had an equivalent risk of CIED infection, including an age of approximately 70 years and similar rates of previous device infection, anticoagulant use, and coexisting conditions such as diabetes mellitus, although patients in the control group were slightly more likely to be receiving immunosuppressive treatments.

The primary end point, major CIED infection (defined as infection requiring device removal or revision or resulting in prolonged antibiotic therapy or death) within 12 months after the procedure, was observed in 25 patients (0.7%) in the intervention group and 42 patients (1.2%) in the control group. Between-group differences in major CIED infections were mostly at the expense of pocket infections (which occurred in 22 fewer patients in the intervention group than in the control group), thus avoiding removal or revision of the device. Overall, 40% fewer patients who received a device with the antibiotic-eluting envelope had major infections. By our estimate, 200 patients needed to receive the intervention to avoid one major infection within 12 months after device placement. As expected, patients who received intracardiac defibrillators, as opposed to pacemakers, had both a higher risk of infection and a more pronounced benefit from receiving a device with an antibiotic-eluting envelope.

The secondary safety end point, CIED procedure-related or system-related complications within 12 months after implantation, was observed in 201 patients in the envelope group and 236 patients in the control group. This finding helps to allay concerns that the larger incision and tis-
sue dissection required to accommodate the envelope may result in hematoma formation or other complications. Other secondary end points were also favorable in the group receiving devices with the antibiotic-eluting envelope: 25 fewer patients had major or minor CIED infections within 12 months after implantation and 19 fewer patients had major CIED infections during 3 years of follow-up. This is a remarkable observation, given that the envelope is thought to be absorbed in approximately 2 months. The number of cases of bacteremia or endocarditis was higher in the intervention group than in the control group. This finding regarding bacteremia or endocarditis in the envelope group requires careful follow-up, especially in light of the increasing rates of cardiac device–related endocarditis in recent years.4

It is not an accident that the components of the antibiotic-eluting envelope, minocycline and rifampin, were effective. Both have potent antistaphylococcal activity as well as activity against a broad spectrum of bacteria potentially involved in CIED infections. Given this advantage, these antibiotics have been used in other applications, and there is evidence suggesting that central venous catheters impregnated with minocycline–rifampin are effective in preventing catheter-related bloodstream infections.5 An analysis of the microbiology of CIED infections that were documented in WRAP-IT shows a reduction in infections related to coagulase-negative staphylococci, whereas infections caused by Staphylococcus aureus appeared to have shifted from pocket-related to bacteremia and endocarditis, another finding that requires careful follow-up. In addition, the antimicrobial-resistance patterns of breakthrough infections will need to be monitored because this approach might select for organisms resistant to rifampin and minocycline.

It is notable that instances of methicillin-resistant S. aureus (MRSA) infection were not recorded. Implementation of decolonization with intranasal antibiotics and chlorhexidine baths may be of benefit in patients undergoing implantation of cardiac devices who are carriers of S. aureus (not only MRSA).6 In the WRAP-IT cohort, strategies for infection prevention and control, including prophylactic antibiotic use, were not uniformly administered. Although almost all the patients received periprocedural antibiotics, an essential intervention to prevent CIED infection, many patients also received additional antibiotics after the procedure and pocket washes. Despite their broad application, a recent cluster-randomized, controlled trial does not show an advantage of these approaches over conventional preoperative antibiotics.7

The findings from WRAP-IT support the local application of minocycline and rifampin as an adjuvant to prevent infection at the surgical site at the time of device placement. In many ways, antibiotic-eluting envelopes provide “an ounce of prevention.”

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Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Medical Service, Veterans Affairs Northeast Ohio Healthcare System, Case Western Reserve University Veterans Affairs Center for Antimicrobial Resistance and Epidemiology (Case VA CARES), and the Department of Medicine, University Hospitals Cleveland Medical Center — all in Cleveland.


DOI: 10.1056/NEJM ea1905678

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