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A Roadmap for Reducing Cardiac Device Infections: a Review of Epidemiology, Pathogenesis, and Actionable Risk Factors to Guide the Development of an Infection Prevention Program for the Electrophysiology Laboratory

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Abstract
Purpose of Review Cardiovascular implantable electronic device (CIED) infections are highly morbid, common, and costly, and rates are increasing (Sohail et al. Arch Intern Med 171(20):1821–8 2011; Voigt et al. J Am Coll Cardiol 48(3):590–1 2006). Factors that contribute to the development of CIED infections include patient factors (comorbid conditions, self-care, microbiome), procedural details (repeat procedure, contamination during procedure, appropriate pre-procedural prep, and antimicrobial use), environmental and organizational factors (patient safety culture, facility barriers, such as lack of space to store essential supplies, quality of environmental cleaning), and microbial factors (type of organism, virulence of organism). Each of these can be specifically targeted with infection prevention interventions.
Recent Findings Basic prevention practices, such as administration of systemic antimicrobials prior to incision and delaying the procedure in the setting of fever or elevated INR, are helpful for day-to-day prevention of cardiac device infections. Small single-center studies provide proof-of-concept that bundled prevention interventions can reduce infections, particularly in outbreak settings. However, data regarding which prevention strategies are the most important is limited as are data regarding the optimal prevention program for day-to-day prevention (Borer et al. Infect Control Hosp Epidemiol 25(6):492–7 2004; Ahsan et al. Europace 16(10):1482–9 2014).
Summary Evolution of infection prevention programs to include ambulatory and procedural areas is crucial as healthcare delivery is increasingly provided outside of hospitals and operating rooms. The focus on traditional operating rooms and inpatient care leaves the vast majority of healthcare delivery—including cardiac device implantations in the electrophysiology laboratory—uncovered.

Keywords Cardiac device infection · Infection prevention and control · Surveillance · Quality improvement

Introduction—Scope of the Problem

Over 14.4 million people suffer from cardiac arrhythmias worldwide and more than 1 million new cardiovascular implantable electronic devices (CIEDs), such as pacemakers and implantable cardioverter defibrillators (ICDs), are placed annually [1]. At least 2% of patients over the age of 65 have a CIED, and the number of new implantation procedures is increasing rapidly [2, 3••, 4], nearly doubling during the period from 1995–1999 to 2005–2009 [3••, 4]. Simultaneous with the rise in device implantations, the rate of infectious complications is increasing by an estimated 5% per year [5]. These device infections are a major cause of morbidity and mortality in patients with implantable devices, resulting in higher rates of mortality and readmission that persists for at least 3 years following a device implantation procedure [6–9]. Among patients with pacemakers, mortality rates are 53.8% (with an infection) vs 33% (without an infection), $p < 0.001$; among patients with implantable cardioverter defibrillator (ICD) infections, mortality rates are 47.7% (with an infection) vs 31.6% (without an infection), $p < 0.001$; and among patients

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with resynchronization devices, mortality rates are 50.8% (with an infection) vs 36.5% (without an infection), $p < 0.001$ [10]. Preventable CIED infections are estimated to cost over US$500 million per year worldwide [8, 9].

Pathogenesis

The Infectious Diseases Society of America/American Heart Association divides CIED infections into superficial infections that involve the device pocket and deep infections in which deeper portions of the device and leads are contaminated [11]. Deep infections can be associated with bloodstream infections and evidence of endovascular infection. Superficial infections have lower risk of mortality and lower management costs than deep infections [12••, 13].

CIED infections occur via two major mechanisms: (1) Contamination of the device at the time of the procedure and/or incisional breakdown shortly after the procedure and (2) hematogenous seeding of the device unrelated to device insertion or manipulation [14•]. Because most infections are related to device contamination and skin breakdown, the majority of infections are caused by skin organisms, such as Staphylococcal species [14•]. Infections that are related to device contamination can be targeted with specific prevention interventions during the peri-procedural period, whereas infections that are caused by hematogenous seeding following a bloodstream infection from another source are unpredictable and generally are not avoidable with traditional prevention programs.

Procedure-related infections generally occur within 6 months after implantation and most commonly within a 90-day window [15]. In a large prospective cohort study of 3918 VA patients receiving a first ICD implantation, 20/74 (27%) of infections occurred in the first 30-day post-procedure, 19/74 (25.7%) occurred 30–90 days post-procedure, and 7/74 (9.5%) occurred 90 days to 1 year post-procedure. Only 28/74 occurred more than 1 year post-procedure [15]. In this cohort, 49/74 (66.2%) infections were superficial, 7/74 (9.5%) were pocket erosions (i.e., the device eroded through the skin), and 18/74 (24.3%) were deep with evidence of endovascular infection.

Risk Factors: Patient, Procedure, Provider, and Device; Actionable and Non-actionable

Patient, procedural, and pathogen factors all contribute to cardiac device infections [16••]. In a systematic review and meta-analysis, patient-level variables that increased risk included diabetes mellitus (odds ratio (OR) 2.08, 95% confidence interval (CI) 1.62–2.67), end-stage renal disease (OR 8.73, 95% CI, 3.42–22.31), chronic kidney disease (OR 3.02, 95% CI, 1.38–6.64), chronic obstructive pulmonary disease (OR 2.95, 95% CI, 1.78–4.90), corticosteroid use (OR 3.44, 95% CI, 1.62–7.32), malignancy (OR 2.23, 95% CI, 1.26–3.95), heart failure (OR 1.65, 95% CI, 1.14–2.39), and skin disorders (OR 2.46, 95% CI, 1.04–5.80). History of previous device infection was also a strong predictor (OR 7.84, 95% CI, 1.94–31.60). Procedure-related risk factors included post-operative hematoma (OR 8.46, 95% CI, 4.01–17.86), re-intervention for lead dislodgement (OR 6.37, 95% CI, 2.93–13.82), device replacement or revision procedure (OR 1.98, 95 CI, 1.46–2.70), lack of pre-procedural antimicrobial prophylaxis (OR 0.32, 95% CI 0.18–0.55), temporary pacing prior to placement of a permanent device (OR 2.31, 95% CI, 1.36, 3.92), inexperienced operator placing the device (OR 2.85, 95% CI, 1.23–6.58), and procedure duration (mean difference in length, 9.89 min, 95% CI, 0.52–19.25). Device-related factors associated with infection included placement of device in the abdominal area (OR 4.01, 95% CI, 2.48–6.49), placement of epicardial leads (OR 8.09, 95% CI, 3.46–18.92), placement of two or more leads (OR, 2.02, 95% CI, 1.11–3.69) and dual chamber systems (OR 1.45, 95% CI, 1.02–2.05). Additional risk factors included pre-procedural fever (OR 4.27, 95% CI, 1.13–16.12) and anticoagulant use at the time of the procedure (OR 1.59, 95% CI, 1.01–2.48).

Some of these risk factors are actionable—they can be specifically targeted in order to reduce rates of infection—and others are non-actionable because there are no available interventions to mitigate them. Examples of actionable risk factors include elevated international normalized ratio (INR) at the time of procedure and presence of a fever prior to device intervention. In these cases, a simple and straightforward intervention—delaying the procedure—can reduce risk. If procedural delay is not possible, patients with elevated INR can receive compression vests to reduce the risk of hematoma, which in turn reduces the risk of both repeat procedure and device infection [17•]. Examples of patient-level non-actionable risk factors include patient age, end-stage renal disease, chronic immunosuppression, and cancer diagnosis [16••]. Infection prevention interventions cannot change these factors, but these patients may derive more absolute benefit from more aggressive prevention strategies than lower-risk patients. Procedural risk factors also contribute and some of these factors can be specifically targeted. Emerging technology includes leadless CIEDs; because these devices do not include leads that are inserted into the heart, there is no risk of lead infection and reduced overall risk of infection. A secondary benefit is that implanting these devices is simpler and thus the duration of the procedure is shorter. Thus, these technologically advanced devices can target two procedural risk factors simultaneously.

Prevention Strategies

The chain of infection is a general model that considers essential factors that interact to cause a procedure-related infection,

such as a CIED infection (Fig. 1). Major elements in the chain are (1) susceptible host, (2) infectious agent, (3) source of exposure, (4) mode of transmission, and (5) portal of entry. The chain of infection model can be used to frame the development and evaluation of infection prevention interventions; by breaking up key interactions, procedure-related infections can be avoided. Infection prevention interventions, such as hand hygiene programs, use of protective equipment, environmental screening, and prophylaxis, target different links in the chain. A review of current prevention strategies, and the evidence supporting them, follows.

Procedural Checkpoints/Stops

Cardiac devices are placed underneath the skin; the area where the device resides is often termed the "device pocket." Patients with elevated INR or anticoagulant use—common in the population of patients receiving CIEDs—are at increased risk of developing device pocket hematomas. Pocket hematomas are a well-recognized risk factor for infection [17]. A recent study found that a compression vest significantly reduces the incidence of pocket hematomas in patients receiving anticoagulant or antiplatelet therapy (0 vs 30%, $p = 0.02$). Although the study was small and the data quality was low, this is a relatively simple intervention with little downside that may reduce risk of complications in the subset of patients at high risk of bleeding complications.

Skin Preparations

Reducing bacterial colonization on the skin reduces the chances of device contamination and therefore future infection. Different types of antiseptic solutions have been evaluated for pre-operative skin sterilization; the two most commonly used are iodine and chlorhexidine-based preparations. Using a pre/post design, one study evaluated povidone-iodine vs chlorhexidine and found a 1.1% incidence of CIED infections in both groups, $p = 0.95$ [18]. Notably, while pre-incision cleaning of the surgical site reduces infection, administration of topical antimicrobials after wound closure has not been shown to impact rates of device infections [19].

Perioperative Antimicrobial Prophylaxis

Appropriate pre-operative antibiotic prophylaxis can reduce surgical site infections (SSI) by over 50% [20]; marked reductions in CIED infections have also been demonstrated for pre-procedural antibiotic prophylaxis prior to cardiac device procedures (RR, 0.13, 95% CI 0.05–0.36) [16••, 21, 22••]. However, despite strong data supporting the administration of antimicrobials prior to incision, clinical practice continues to vary widely [23, 24]. Many centers do not administer *pre*-incision antimicrobials, and administration of systemic antibiotics *after* the procedure has been completed is *common*, despite data suggesting that prolonged use of systemic antimicrobials does not lower rates of CIED infections, but is associated with other harms, such as antimicrobial resistance, kidney injury, and *Clostridium difficile* infection in other clinical settings [21, 25–31].

Intraoperative Antimicrobial and/or Antiseptic Washes

A common practice is the use of antiseptic and/or antimicrobial-containing solutions to rinse the device pocket. However, single-center data suggest that routine use of solutions containing antimicrobials does not reduce the incidence of infection when compared to saline solutions [32]. In this pre/post study, infections occurred in 2/118 patients who received an antibiotic solution and 2/209 patients who received a saline wash alone ($p = 0.62$). Further studies evaluating this question are warranted, as antimicrobial and antiseptic solutions are commonly used in the electrophysiology laboratory despite a limited evidence base supporting their efficacy.

Antimicrobial Pockets

Several studies suggest that antimicrobial pockets, such as the TYRX-A bio-absorbable antimicrobial envelope, may be effective for reducing CIED infections [33]. The bio-absorbable envelope can also be used without embedded antimicrobials (TYRX). One single-center retrospective cohort study compared the rates of CIED infections in high-risk patients who received the TYRX-A device, the TYRX without antimicrobials, and standard of care. Similar rates of infection were found in patients who received the TYRX-A vs TYRX (0/135, 0% for TYRX-A vs 1/353, 0.3% for TYRX, $p = 1.0$). Control patients had higher rates of CIED infections (20/636, 3.1%, $p = 0.03$ for TYRX-A vs controls and $p = 0.002$ for TYRX vs controls). Another single-study retrospective study found that use of an antimicrobial envelope (AIGISRx) was associated with lower rates of CIED infections when compared to control cases (0/365 in the intervention group vs 19/1111 in the control group, $p = 0.0063$) [34]. These results are similar to other pre/post retrospective studies that measured the impact of antimicrobial pockets in high- and moderate-risk patients and found a significant reduction in the incidence of CIED infections [33, 35]. Notably, many of these studies did not include an arm with receipt of a pocket without antimicrobials. In combination with the data demonstrating no benefit to antimicrobial washes over saline rinses, this raises the question of whether the local antimicrobial treatments are beneficial, or if all of the benefit is derived from the presence of the absorbable pocket or rinsing of the pocket, both to minimize bacterial contamination at the time of the procedure. The high costs of these antimicrobial pockets also raise questions about the best way to deploy them. Because some

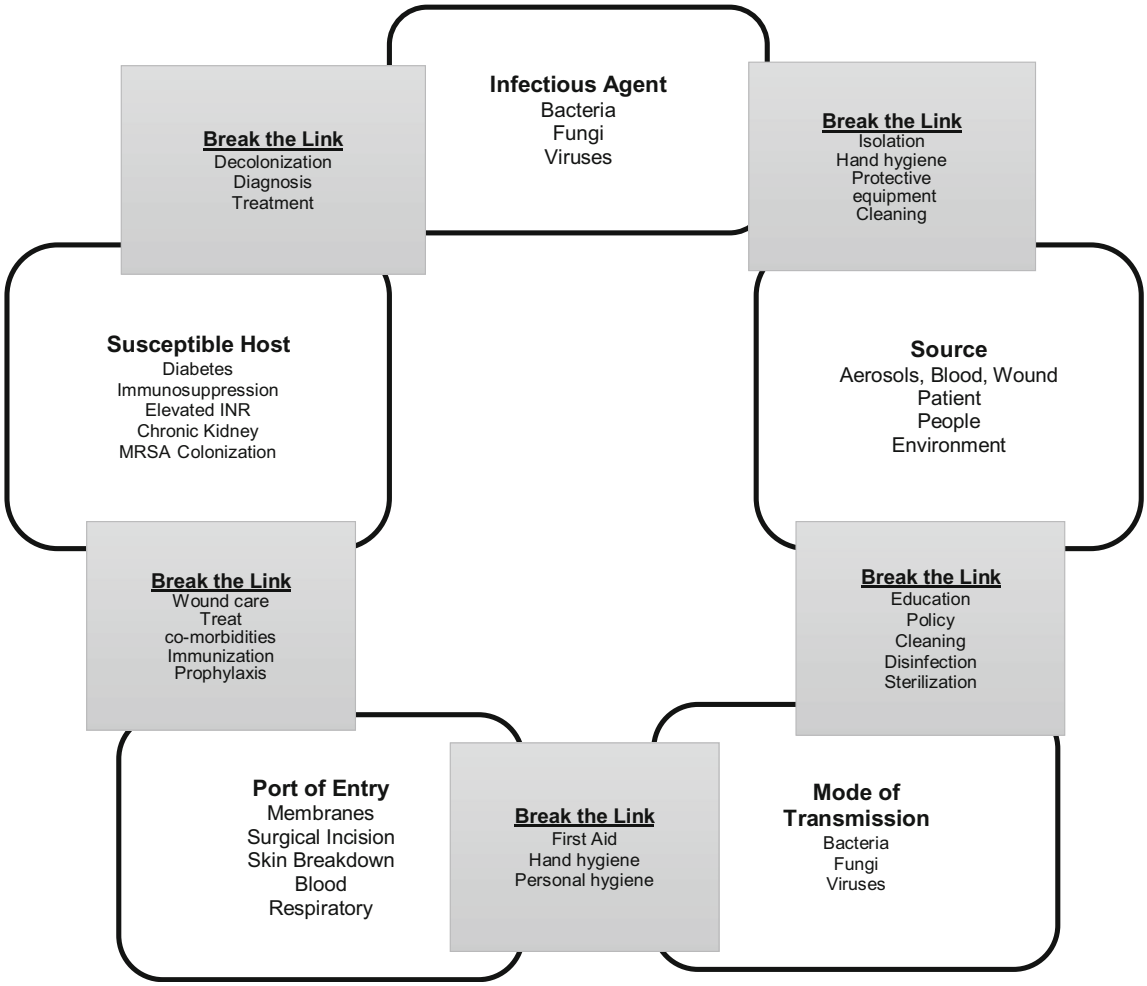

Fig. 1 The chain of cardiac device infection

patients are at inherently higher risk of infection due to multiple factors, scoring systems have been developed to identify and target patients who might benefit from more aggressive prevention strategies, such as the use of pockets, with or without impregnated antimicrobials [36].

Bundled Approaches

Although checklists have not been widely implemented to reduce CIED infections, there is strong evidence supporting their utility for reducing other HAIs, including surgical site infections, central line-associated bloodstream infections [37] and ventilator-associated pneumonias [38]. Surgical checklists and timeouts are an evidence-based method for improving perioperative care and outcomes [39–42]. One center reported low rates of CIED infections (0.26% overall) in the setting of an aggressive prevention bundle that included skin preparation with alcohol followed by povidone-iodine, administration of antimicrobials prior to incision and continuing for 5 days after incision, pocket washing with povidone-iodine solution, and skin closure with absorbable sutures [43]. However, incidence of CIED infections in this hospital without the bundled intervention is not reported, and the contribution of individual elements of the bundle cannot be delineated. Further, the comorbidity index of the patient population was not presented. Therefore, while this center does report an overall low rate of infections, determining which aspects contributed to the low rate is not possible. Another center used a pre/post design to measure the impact of an infection prevention bundle including antimicrobial prophylaxis, antimicrobial prophylaxis, systematic glycemic control, and skin closure techniques [44]. This single-center retrospective study found a 54% reduction in CIED infections in the period following introduction of the bundle (1.3 to 0.6%, $p < 0.03$), although teasing out the individual impact of each bundle element was again not possible.

Data from Cardiac Surgery

In the absence of strong data to support best practices in the electrophysiology laboratory, many strategies aimed at reducing CIED infections are based on data from cardiac surgery.

These include skin antisepsis with chlorhexidine-based solutions, antimicrobial prophylaxis prior to incision and MRSA screening and decolonization with mupirocin and/or intranasal iodine; each is designed to reduce the bacterial burden on the skin and to prevent contamination of the surgical site. Additional interventions that are effective for reducing surgical site infections include smoking cessation programs and excellent wound care; both of these interventions benefit patients in other ways—including reducing cardiovascular disease in the case of smoking cessation—and so are reasonable to implement around the time of cardiac device procedures despite limited specific data regarding impact on rates of CIED infections.

Surveillance and Feedback

Surveillance is a strategy that can be used to identify infections; surveillance programs led to sustained reductions in SSI by providing direct feedback to surgeons, including information about their individual infection rates benchmarked to their colleagues' rates. Clinical research demonstrates that simply having a surveillance system and providing feedback to providers can lead to reductions in SSI, perhaps due to the Hawthorne effect seen with other infection prevention interventions [45, 46]. Infection prevention programs can also use SSI surveillance reports to target interventions, such as appropriate antibiotic use, to improve practice and reduce infections. Ongoing surveillance can be used to assess the effectiveness of interventions. However, despite the potential benefits of systematic surveillance in the electrophysiology laboratory, a recent study found that implementation of a systematic surveillance program for identifying cardiac device infections and providing feedback to providers is rare [24]. While several centers reported passive surveillance, there was limited information about the number of procedures performed in a facility, so determination of facility rates and identification of clusters was limited. Boggan et al. recently reported that automated algorithms using a combination of International Classification of Disease coding and microbiology results may be an effective means of expanding surveillance programs to include electrophysiology laboratory procedures [47]. Additional work is warranted to see if surveillance can be used to improve peri-procedural care in the electrophysiology laboratory.

Emerging Technologies

Examples of intriguing new technologies include the development of leadless pacemakers and completely subcutaneous implantable cardioverter defibrillators [48]. These devices reduce the chances of infection by limiting the amount of implanted foreign material, the invasiveness of the procedure, and the duration of the procedure. Another emerging technology is the use of blood plasma-based biomaterials integrated with antimicrobials to reduce infections. In vitro and animal studies have found that these materials can be used to elute local antimicrobial treatments over a 6-day period and demonstrated lower rates of pocket infections in rabbits with devices directly contaminated with *Staphylococcus aureus* [49]. In this rabbit model, 100% of the animals who received *S. aureus* contamination but not the biomaterial developed culture-positive purulent infection, compared to 0% of the animals who received the biomaterial injection (0%, $p < 0.001$). An in vitro study measured the impact of antimicrobial and antiseptic impregnated platelets on bacterial adhesion and found that these coatings can significantly reduce biofilm formation on pacemakers [50]. Thus, while these technologies are not ready for human use, they present intriguing strategies for future investigations.

Implementation, Scope of Quality Improvement Programs, and the Political Landscape

Although evidence defining the best prevention bundle is limited, strong data clearly support several simple measures, such as administration of systemic antimicrobial prophylaxis prior to incision and consideration to delay procedure in the setting of elevated INR and fever. However, a recent study by Mehrotra et al. found that systematic implementation of basic infection prevention practices in the electrophysiology laboratory is rare [24]. Surveillance is limited by lack of accurate data about number of procedures performed, making measurement of infection rates difficult. Delay of procedure if INR is over 1.5 or if temperature is over 100 degrees Fahrenheit is rarely implemented. Further, despite strong evidence, administration of prophylactic antibiotics prior to incision is not universally applied, with estimates of uptake ranging to 60 to 88% of facilities [24, 25] providing any peri-procedural antimicrobials. Additional studies have found that antimicrobials are commonly prescribed after the procedure—not before—and thus the significant benefit of antimicrobial prophylaxis is lost [51].

The lack of systematic prevention programs in the electrophysiology laboratory may be partially explained by the historical classification of these cardiac device implantations as "procedures" rather than "surgeries." Traditional surgeries that occur in an operating room setting fall under the umbrella of major quality improvement and surveillance initiatives, such as the Surgical Care Improvement Project (SCIP), the VA Surgical Quality Improvement Program, and the National Surgical Quality Improvement Program. Each of these programs highlights the importance of infection prevention. SCIP tracked appropriate pre-operative antimicrobial prophylaxis; this measurement led to marked improvements in antimicrobial use following traditional operating room surgeries. When these programs were initially envisioned and developed, procedures performed outside of the operating room

setting were rare. However, increasingly, care is delivered outside of these traditional settings; procedures and outpatient surgeries are increasingly common, and care in these settings is expected to increase exponentially [52]. This creates an urgent need for the evolution of traditional infection prevention and quality improvement programs to include a stronger focus on a wider variety of clinical settings, including the electrophysiology laboratory.

Limitations of Current Evidence and Future Directions

The majority of published reports of infection prevention programs designed to reduce cardiac device infections have been developed and implemented in an outbreak setting that required immediate action. These studies borrowed from data on preventing infections following cardiac surgery, but are based on limited high-quality data in the electrophysiology laboratory. Most have taken a "kitchen sink" approach to solving the problem. However, due to the nature of these interventions, there is unfortunately no strong data regarding which elements of the bundles are important for reducing infections and which were not. Furthermore, these studies probably overestimate the benefits of prevention programs, as there is always a tendency toward regression to the mean over time—and the reduction of infections if a cluster or outbreak is identified. Strong evidence from other areas of infection prevention demonstrates that simply shining light on a problem can lead to significant improvements, probably because of improved application of basic infection prevention practices, such as excellent hand hygiene and skin preparation, which may have been overlooked when strong oversight was not provided. These outbreak-driven interventions do, however, provide some important clues regarding how to address infections in the setting of an outbreak: Basic infection prevention interventions, including pre-procedural antimicrobial prophylaxis and delay of procedure in the setting of elevated INR and fever are highly effective measures [24]. If CIED infections continue to be a problem despite compliance with these basic interventions, additional considerations include MRSA screening and decolonization programs and use of pocket devices. Technological advancements, such as the use of leadless devices, will likely reduce infections in the future, independent of other specific infection prevention interventions.

Conclusions

CIED infections are highly morbid, common, and costly, and rates are increasing [6, 12]. Small single-center studies provide proof-of-concept that prevention interventions can reduce infections; however, data regarding which prevention strategies are the most important is limited [44, 53]. Basic practices, such as administration of systemic antimicrobials prior to incision and procedure stops, are helpful for day-to-day prevention. Bundled approaches are effective in outbreak settings, but the effectiveness of these aggressive measures for routine prevention is unknown. Evolution of infection prevention programs to include ambulatory and procedural areas is crucial as healthcare delivery is increasingly provided outside of hospitals and operating rooms. The focus on traditional operating rooms and inpatient care leaves the vast majority of healthcare delivery—including cardiac device implantations in the electrophysiology laboratory—uncovered.

Compliance with Ethical Standards

Conflict of Interest Westyn Branch-Elliman is supported by a Veterans Integrated Service Network (VISN)-1 Career Development Award and is the recipient of an American Heart Association Institute for Precision Cardiovascular Medicine Award no. 17IG33630052.

Dr. Branch-Elliman declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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