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Original Article

Real-world data on the effectiveness of TYRX and TauroPace for preventing CIED infections

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Abstract: Background: The implantation of cardiac implantable electronic devices (CIEDs) carries a known risk of infection. Two devices (TYRX and TauroPace) have been proposed to reduce this risk. Methods: The aim of our study was to compare the effectiveness of TauroPace and TYRX. Real-world comparative studies were included. Data analysis was based on reconstruction of individual patient data from Kaplan-Meier curves using an artificial intelligence algorithm. The endpoint was CIED infection or systemic infection. Statistical tests included heterogeneity assessment, superiority testing, and non-inferiority testing. The primary outcome measure was the hazard ratio (HR) with confidence interval (CI). Results: Our literature search identified two real-world studies suitable for our analysis. Follow-up was 12 months for TauroPace (654 patients) and 60 months for TYRX (872 patients), with a total of 2,083 controls. There was no heterogeneity among controls. Compared to the pooled control group, patients treated with TYRX or TauroPace had fewer CIED infections (HR, 0.3892; 95% CI, 0.2042-0.7419; P=0.00414; HR, 0.3313; 95% CI, 0.1005-1.0925; P=0.06958, respectively). When testing for non-inferiority of TauroPace vs. TYRX, the comparison yielded a HR of 0.8494 (in favor of TYRX) with a 90% CI of 0.27-2.63; this CI of TauroPace did not meet the non-inferiority criterion set at HR>0.75 (i.e., relative difference ≤25%). Conclusions: Both treatments had some important drawbacks. Regarding TYRX, more selective use in higher-risk patients should be advocated to improve its cost-effectiveness, but robust evidence is still lacking. Regarding TauroPace, our analysis testing for a non-inferiority margin of ≤25% did not meet this demonstration.

Keywords: TYRX, TauroPace, taurolidine, CIED infection

Introduction

Each year, approximately 1.2 to 1.4 million patients worldwide receive a cardiac implantable electronic device (CIED) [1-3]. CIED infection rates have been reported to be increasing for a variety of reasons, including CIED patients having more comorbidities, receiving more complex systems, living longer, and requiring revision procedures. The major complications of CIED include failure of the device to perform as expected and the development of infection. Regarding infection, preventive measures have been proposed, such as TauroPace and TYRX, and in fact the present study was specifically designed to compare these two devices. In addition, among the complications that may occur in the long term (e.g., after 5 years), the need to replace the device or its battery is an important factor. Finally, another factor influencing complications is the type of CIED: while traditional transvenous pacemakers have long been the standard, leadless pacemakers are increasingly being used, and their complication profile differs significantly from that of transvenous pacemakers. With respect to TauroPace and TYRX, there are studies that have monitored the occurrence of infections after more than 6 months and, in some cases, evaluated the long-term efficacy of these devices; however, the cause-and-effect relationship of these preventive measures in the long term remains controversial because the TYRX envelope may not have a significant long-term effect as the device is resorbed after 9 weeks, and a long-term effect of TauroPace is also unlikely.

In the field of interventions to reduce the risk of CIED infection, the WRAP-IT trial, published in

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the New England Journal of Medicine in 2019 [4], was a milestone in demonstrating that an antimicrobial envelope (developed under the proprietary name TYRX) significantly reduced the risk of CIED infection. The randomized design was the major strength of this study; on the other hand, the high price of TYRX has subsequently been the main barrier to widespread use of this device [5]. Numerous cost-effectiveness studies and national and international guidelines [1, 2] have suggested that more selective use of this device in patients at higher risk of infection could significantly improve the otherwise borderline or clearly unfavorable cost-effectiveness profile of TYRX. In an analysis conducted in the Region of Tuscany (Italy) by the regional HTA body for medical devices, the value-based price of TYRX was estimated at €621, compared to the current market price of over €1,000 [6].

TauroPace™ is an antimicrobial solution designed to remove bacterial contamination from the surface of CIEDs [2, 3]. The active ingredient is taurolidine, an amine derived from the amino acid taurine, which provides broad-spectrum and long-lasting activity. According to the device's instructions for use, the surface of the CIED should be moistened with the TauroPace solution prior to implantation to create a hostile environment for microbial proliferation. Specifically, the TauroPace™ solution should be applied to the entire surface of the CIED and its components by wiping with sterile, product-soaked gauze pads, taking care to keep them moist prior to implantation.

From the perspective of evidence-based methods used in comparative analyses [7-11], the use of appropriate statistical techniques is particularly relevant, especially when the clinical material is based on long-term follow-up. Here, we conducted the present comparative analysis using a new artificial intelligence technique (called the "IPDfromKM" method or the Shiny method [7-11]) to review the current literature and compare the incidence of post-implant CIED infections in patients treated with TYRX or TauroPace in a real-world setting. Only real-world comparative studies evaluating these two devices were included in the analysis. This decision to focus exclusively on real-world studies, as opposed to randomized trials, was made with the understanding that no randomized study of TauroPace has been conducted to date.

The IPDfromKM method is a new artificial intelligence tool that reconstructs individual patient data from the graph of Kaplan-Meier curves and allows cross-study comparisons based on reconstructed patients [7-11]. It is a relatively new method for generating original clinical evidence and is particularly suitable for indirect comparisons of time-to-event endpoints, especially those with long follow-up. An advantage of the method is that it takes into account the time at which each event occurred, whereas a standard binary meta-analysis ignores this information. In addition, the IPDfromKM method presents an easy-to-understand summary of the results by generating a typical multi-curve plot containing the Kaplan-Meier curves of reconstructed patients (where all patients who received the same treatment are pooled together). In other words, the Forest plot typical of standard binary meta-analysis is replaced by a survival plot with as many Kaplan-Meier curves as there are treatments being compared. Treatments are compared statistically using standard parameters such as hazard ratio (HR) and confidence interval (CI). In an IPDfromKM analysis, the value of the HR is influenced by the time course of the curves projected over the entire follow-up period. Thanks to the unique approach associated with the IPDfromKM method, in the present report we provide an original comparative analysis between TYRX and TauroPace based on the real-world efficacy data published in recent years. Finally, as the cost of TauroPace is significantly lower than that of TYRX, our statistical analysis was also designed to test the non-inferiority of TauroPace compared to TYRX.

Materials and methods

Study design

After selecting relevant real-world comparative studies from Pubmed, we used the IPDfromKM method to reconstruct individual patient data by analyzing the Kaplan-Meier plots reported in the included studies. To determine efficacy, the endpoint was the occurrence of post-implant CIED infection or systemic infection. After reconstructing the TauroPace-treated real-world cohort and the TYRX-treated real-world cohort, we generated the pooled Kaplan-

Meier plot showing the time course of infections occurring in the cohorts treated with these two devices; this result is often referred to as a multi-treatment Kaplan-Meier curve plot based on reconstructed patients. In this report, our main analysis included a superiority assessment, an assessment of heterogeneity between trials, and a non-inferiority comparison.

Literature search

We searched the PubMed database to identify all comparative trials that were eligible for our analysis (last search on April 20, 2024). The following search terms were used: "taurolidine OR tyrx OR tauropace". The main inclusion criteria for our analysis were: (a) real-world setting; (b) non-randomized comparative study including either TYRX or TauroPace or both; (c) endpoint defined as post-implant CIED infection or systemic infection; (d) publication of results as a Kaplan-Meier curve of event-free survival where the event was the endpoint described in (c).

The reason why only two-arm trials (and not single-arm trials) were included is that in the IPDfromKM method, the consistency of the pooling process across different studies needs to be verified by determining the level of heterogeneity across all included control arms; if this heterogeneity is low, the treatment arms can be more reliably compared with each other, and vice versa.

The selection process of articles in our literature search was managed according to the PRISMA algorithm [10], which recorded the reasons for inclusion and exclusion of each study; after elimination of duplicates, the final list of included studies was determined in the last step of the PRISMA flow.

For each included study, we recorded the Kaplan-Meier curve together with the number of patients enrolled and the number of events according to the specific treatment. To avoid duplicate inclusion of patients from the same trial, only the most recent publication was included.

Reconstruction of individual patient data

Patient-level data were reconstructed from Kaplan-Meier curves using the IPDfromKM method, as previously described [7-9]. The IPDfromKM method includes a first phase in which the graph of the Kaplan-Meier curve (which is a time-to-event curve) is digitized; in a second phase, the full text of the article is evaluated to determine how many events were found in each time-to-event curve; finally, the information derived from the above two phases is analyzed by an artificial intelligence algorithm that reconstructs individual patient data; the information for each patient consists of the length of follow-up and whether or not the event occurred on the last follow-up date. Numerous reports have confirmed the high reliability of this individual patient data reconstruction procedure.

In recent years, the use of this method has expanded considerably, especially in oncology and cardiology [7-9]. Curves were digitized using Webplotdigitizer (version 4.5 online; URL https://apps.automeris.io/wpd/, accessed January 10, 2024); the individual patient data reconstruction tool of the Shiny software was used according to version 1.2.3.0.

Statistical analysis

Event-free survival (EFS) based on reconstructed individual patients was estimated for the two devices and controls; HR with 95% CI and medians with 95% CI were also calculated. The likelihood ratio test was used to assess heterogeneity of results between studies. In addition, indirect comparisons between treatments were assessed using the Cox model with four specific packages of the R platform (version 4.2.1) for statistical analysis: survival, survRM2, survminer, and ggsurvplot (https://www.R-project.org/, accessed December 18, 2023).

Assessment of non-inferiority

We used the methods described by Walker and Novacki [11]. Accordingly, we first determined the non-inferiority margin applied to the endpoint and expressed according to the HR. This non-inferiority margin, applied to the database of all reconstructed patients and based on the primary endpoint of our analysis, was set at a relative increase in the endpoint of ≤25%. We then assessed whether non-inferiority of TauroPace vs. TYRX (estimated from the two pooled populations receiving the specific treatment) was met using a Forest plot showing both the margin and the incremental benefit (expressed as HR) with 90% CI for the two devices. The use of 90% CI versus 95% CI in

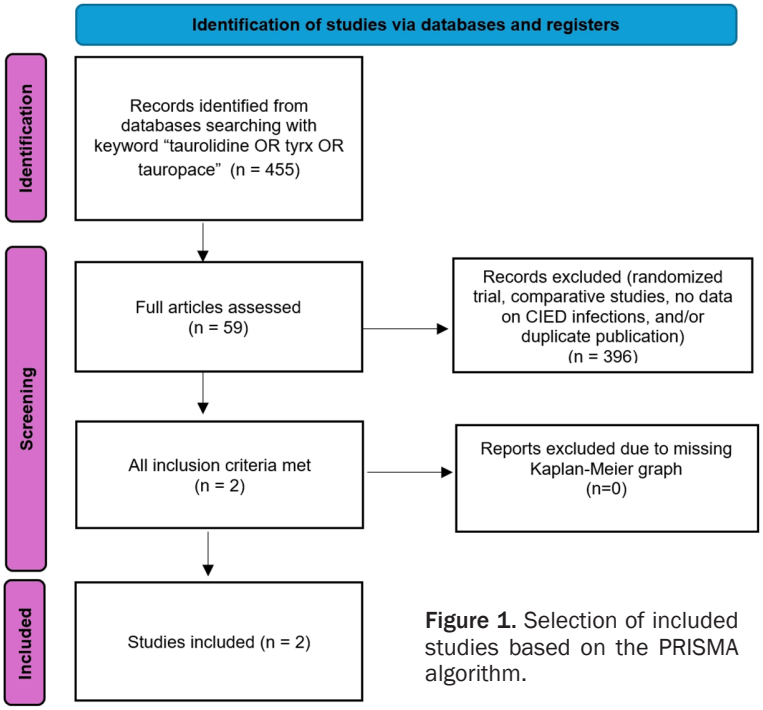

Figure 1. Selection of included studies based on the PRISMA algorithm.

non-inferiority trials is discussed in the article by Walker and Novacki [11].

Results

Literature search

Our literature search, which included only non-randomized real-world studies, is summarized in **Figure 1**. A total of two real-world studies [1, 5] were selected and included in our analysis. Their follow-up were 12 months for TauroPace and 60 months for TYRX. The endpoint was the occurrence of CIED infection or systemic infection. None of the studies used a composite endpoint. In the TauroPace study, although many patients were followed beyond 12 months, no systematic information on CIED infections could be collected after this time. In total, there were 654 patients treated with TauroPace and 872 patients treated with TYRX; there were 2,083 controls, but in this latter figure, the control patients were double counted in the propensity-matched analysis because they were a selection from the TYRX real-world study (**Table 1**).

Heterogeneity analysis

As mentioned above, the heterogeneity analysis was the first step of our comparative study because it served to appropriately design our subsequent main analysis. In fact, most IPDfromKM studies rely on this preliminary heterogeneity analysis to better design the subsequent main analysis.

Figure 2 shows this heterogeneity analysis, in which the 2,083 controls were compared according to the clinical material of their origin (**Table 1**): a) the TauroPace real-world study (N=551); b) the TYRX real-world study (N=947); c) a propensity-matched analysis based on a selection of the same patients enrolled in (b) (N=585). The presence of heterogeneity in these three patient groups remained far from the level of statistical significance (likelihood ratio test =0.12 on 2 df, P=0.90; Wald test =0.12 on 2 df, P=0.90). Based on this result, and in order to prioritize the real-world nature of our clinical material, we decided to exclude (c) for our main analysis and to pool (a) and (b) into a single control group of 1,498 pts. Finally, when comparing (from 0 to 12 months) the real-world controls of TauroPace (**Figure 2**, blue curve; n=551) and the real-world controls of TYRX (**Figure 2**, green curve; n=947), pooling these two curves into a single control group appears to be an acceptable choice given the lack of heterogeneity. According to **Figure 3**, the selection of 585 propensity-matched controls made by Ziacchi et al. [4] seems to identify a subgroup with slightly more favorable characteristics.

Main analysis

Figure 3 summarizes the results of our main analysis, which compared the 872 patients in the TYRX real-world study, the 654 patients in the TauroPace real-world study and the 1,498 controls (selected using the previously described process). Specifically, the 12-month endpoint rates estimated from the reconstructed patient data were 1.24% for TYRX and 1.88% for TauroPace.

When reviewing **Figures 2** and **3**, it is important to note that the y-axis is reported over the interval from y=90% to y=100%; this greatly ampli-

Table 1. Main characteristics of the included studies

Reference	Description	Follow-up (months)	Patients, treatments and events		
			TYRX	TauroPace	Controls
Ziacchi et al., 2023 [5]	Real world consecutive patients treated with TYRX (N=654) or not treated with TYRX (N=551)	60	7/872	-----	23/947
			HR§=0.34 (0.14 to 0.80; P=0.010)		
Ziacchi et al., 2023 [5]	Propensity score matching between 585 given TYRX vs. 585 controls	60	4/585	-----	19/585
			HR§=0.28 (0.09 to 0.82; P=0.014)		
Borov et al., 2023 [3]	Real-world consecutive patients treated with TauroPace (N=654) or not treated with TauroPace (N=551)	12	-----	(0+3)=3/654	(6+9)=15/551
			HR§=*		

Notes: §These values are those reported in the original publication and are based on real patients; our results section reports the values of HR estimated from reconstructed patients. *Published values of HR were reported separately for the period 0-3 months vs. >3 months.

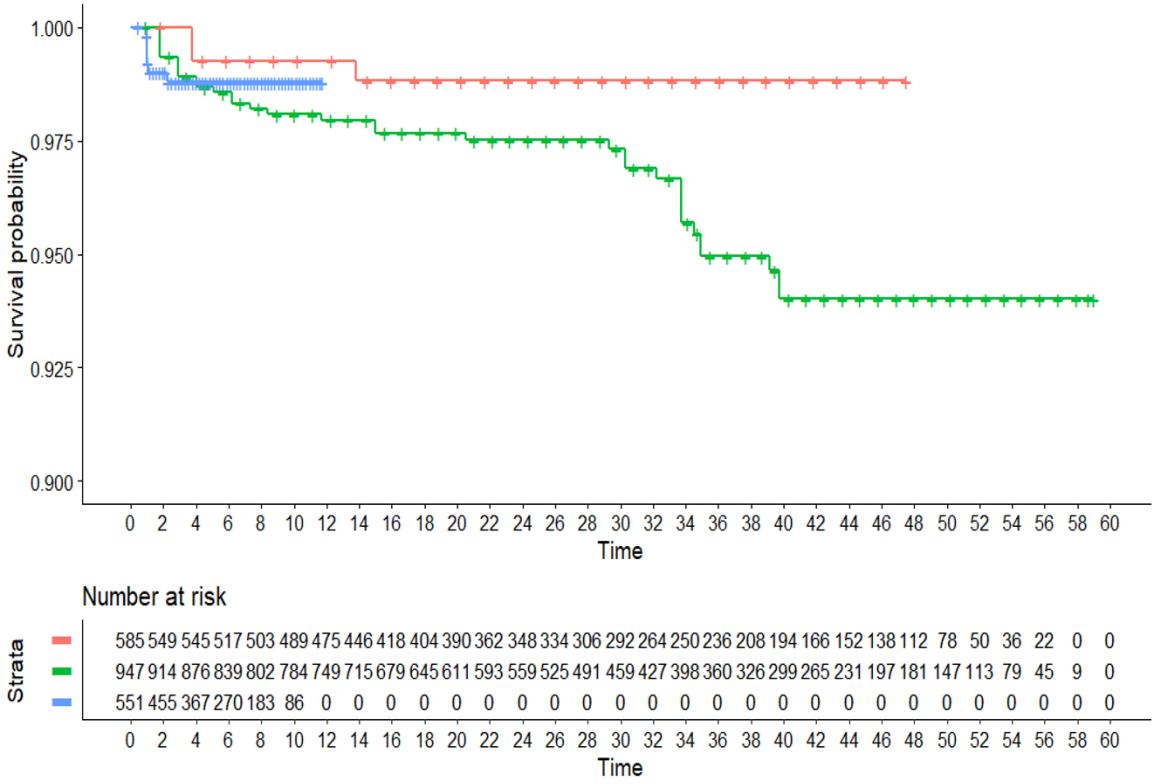

Figure 2. Heterogeneity analysis. In this comparison across three control groups (in red: propensity-matched group of 585 controls reported by Ziacchi et al.; in green: 947 controls of the TYRX real-world study by Ziacchi et al.; in blue: 551 controls of the TauroPace real-world study), the heterogeneity between trials is virtually absent (P=0.90). Endpoint: CIED infection or systemic infection; time in months, individual patient data reconstructed by the IPDfromKM method.

fies the perception of possible differences between these 3 curves. On the other hand, in a graph with y-values from y=0% to y=100% (data not shown), the three curves are largely superimposed and the better trend of the TYRX or TauroPace curves compared to the controls is difficult to discern. More importantly, when the two curves of TauroPace vs. TYRX are examined from 0 to 12 months, they are very much superimposed.

The values of HR for the two devices in comparison with the controls were the following: 1. TYRX vs. controls: HR=0.3892 (95% CI, 0.2042 to 0.7419; P=0.00414); 2. TauroPace vs. controls: HR=0.3313 (95% CI, 0.1005 to 1.0925; P=0.06958).

According to these results, TYRX was significantly more effective than the controls; by contrast, TauroPace was numerically more effec-

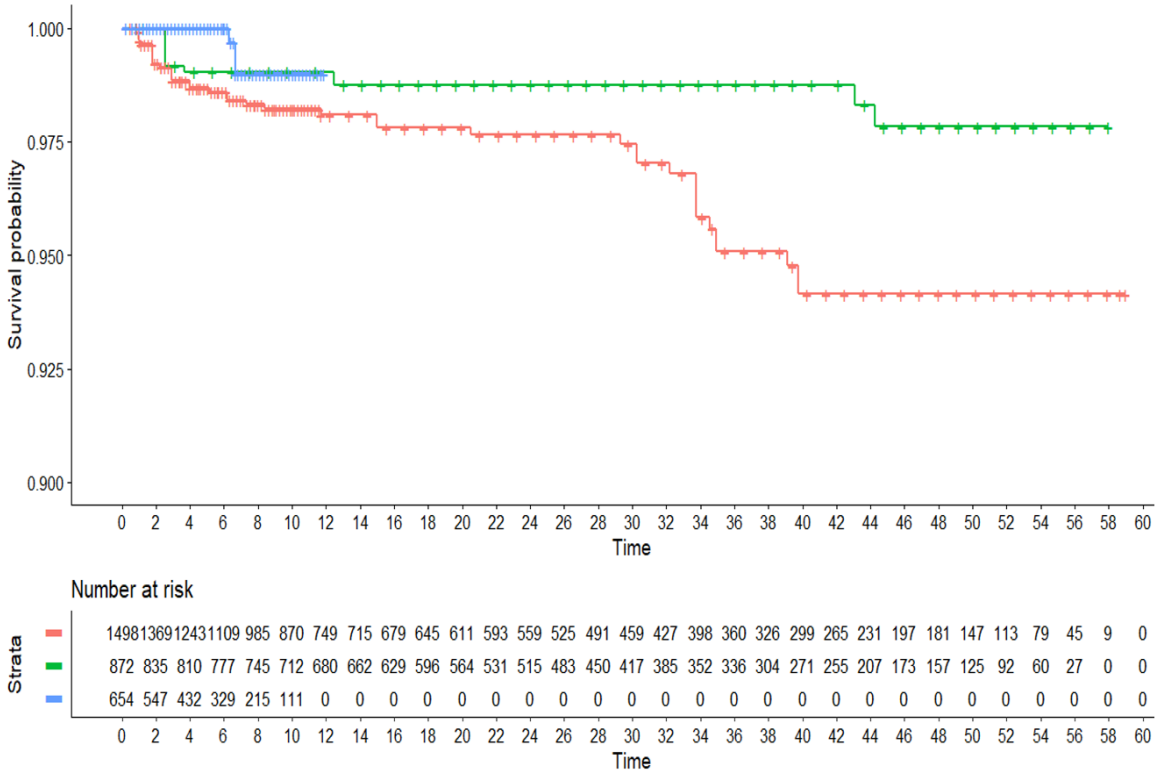

Figure 3. Main analysis. Two groups receiving device-based antimicrobial prevention are compared with a pooled control group. In red: pooled group of 1,498 controls; in green: 872 patients of the TYRX real-world study; in blue: 654 patients of the TauroPace real-world study. Endpoint: CIED infection or systemic infection; time in months, individual patient data reconstructed by the IPDfromKM method.

tive than the controls, but the difference did not reach statistical significance. Likewise, in the indirect comparison of TauroPace vs. TYRX, the results remained far from statistical significance (HR=1.177; 95% CI, 0.303 to 4.567; P=0.82).

Non-inferiority analysis

Figure 4 shows a Forest plot that summarizes the results of our non-inferiority analysis. In this graph, the comparison of TYRX vs. TauroPace is based on 90% CI, yielding a point-estimate at 0.8496 (equal to the reciprocal of 1.177) with an interval from 0.27 to 2.63. Considering the margin set at HR=0.75 (percent difference in favor of TYRX of ≤25%), these results clearly show that TauroPace fails to meet the non-inferiority criterion set by our analysis.

Discussion

This study has two major strengths. First, the methodology of this research is relevant because it is the first report to use the IPDfromKM method to perform a non-inferiority analysis. On the other hand, the results of our main analysis, together with the heterogeneity assessment, underscore an important potential role for these two devices (TYRX and TauroPace) in the management of patients receiving a CIED implant. Regarding the selection of clinical trials, since our objective was to compare TauroPace and TYRX, we excluded randomized trials because we knew that no randomized trial was available for TauroPace. As a result, we specifically focused our analysis on real-world comparative data in which the experimental group could receive either TYRX or TauroPace and the controls did not receive any preventive measure beyond current standards of care. In this context, the result of our heterogeneity analysis of the included studies (which evaluated the TauroPace controls versus the TYRX controls) is particularly important because such an analysis demonstrated the absence of heterogeneity.

As far as TYRX is concerned, since the current real-world results essentially confirm those

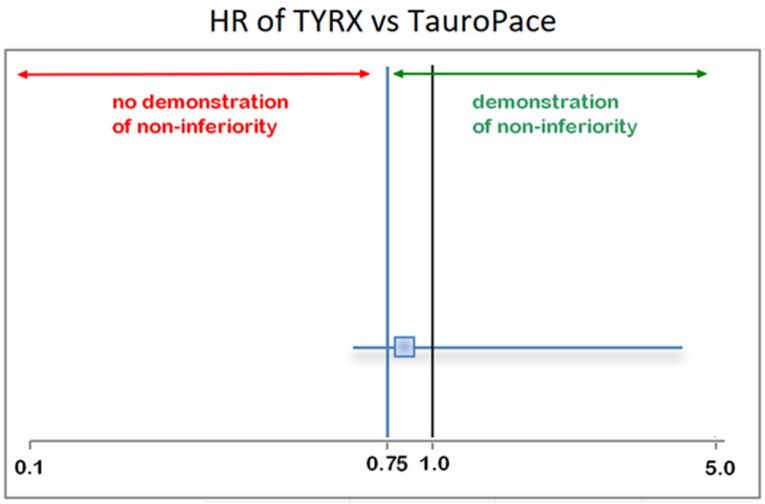

Figure 4. Results of the non-inferiority analysis of TauroPace (654 patients) vs. TYRX (872 patients). In this graph, the comparison is presented as the HR of TYRX vs. TauroPace (with 90% CI), yielding a point-estimate of 0.8496 (equal to the reciprocal of 1.177) with an interval from 0.27 to 2.63. Considering the margin set at HR=0.77 (percent difference in favor of TYRX of ≤23%), TauroPace fails to meet the non-inferiority criterion.

published in the randomized WRAP-IT trial [4] (including its long-term results [12]), the question of the poor cost-effectiveness of TYRX remains crucial and is reiterated in the same terms as in recent reports [1]. In addition to the already known literature on this subject, in our introduction we mentioned the HTA report [6] published by our regional institution (HTA Centro Operativo of the Tuscany Region) in Italy; its results suggest a value-based price of €621 for TYRX [13], estimated from the willingness-to-pay threshold of €60,000/QALY adopted in Tuscany since 2022 [13]. Unfortunately, the current price of the device is more than €1,000 (both in Tuscany and in Europe), so the question of cost-effective acquisition of this device remains unresolved. More selective use of the TYRX could significantly improve its cost-effectiveness profile and has been advocated in some authoritative guidelines [1]; however, a cost-effectiveness evaluation of the current price of the TYRX based on more selective use of the device is not currently available. In this context, the incremental effectiveness of TYRX (compared to controls not given the envelope) and the cost-effectiveness ratio of TYRX are closely related.

The clinical literature on the efficacy of TYRX is extensive, but there is only one randomized controlled trial evaluating this device and, more importantly, there are few well-conducted comparative studies. In this context, the propensity-matched analysis published by Ziacchi et al. was considered as our source of comparative data between TYRX and TauroPace, mainly because of its real-world nature. To complete our review of published data on this topic, another propensity-matched study (published by Chaudhry et al. [14]) deserves mention. The incremental benefit of TYRX found by Chaudhry et al. was less pronounced than that reported by Ziacchi et al.; consequently, the cost-effectiveness profile determined by Chaudhry et al. was less favorable than that reported in both the analyses published by Ziacchi et al. [5] and Regione Toscana [6].

In summary, TauroPace can be considered as a potential alternative to TYRX mainly because of its low and very attractive price (around €200 in Italy according to the HTA website of the Tuscany region [12]). However, on the clinical evidence side, our analysis shows that the approach based on this device is promising, but efficacy data showing non-inferiority of TauroPace versus TYRX are not currently available (as shown in our analysis in **Figure 4**). Therefore, further studies on TauroPace are needed, especially if based on a randomized design or, alternatively, conducted over many years of follow-up.

Regarding the limitations of the present study, it can be emphasized that the message resulting from our analysis, although unfortunately not conclusive, highlights an important methodological point (the cost-effectiveness of TYRX) that has already been underlined by a number of reviews or meta-analyses published in the recent literature [5, 6, 10, 14]. Thus, the main merit of the present study is the originality of the method used, which combines the IPDfromKM method with the well-known but complex principles of a non-inferiority analysis.

Finally, the inclusion criterion of our analysis, based exclusively on real-world studies, selected two studies with homogeneous characteristics, but these two studies are objectively few considering the numerous reports published on this topic, especially on TYRX. Finally, some studies are ongoing on both TYRX and TauroPace [15], and their results will hopefully help to clarify the relative roles of these two devices in the management of these patients.

Limitations

Due to the lack of randomized trials (WRAP-IT remains the only one), our analysis focused on real-world evidence, but only two large observational studies were found. Regarding TYRX, more selective use in higher-risk patients is often advocated, but there are currently no robust data to estimate the cost-effectiveness of such selective use.

Regarding our decision to focus our analysis exclusively on real-world data, this may be controversial as we consequently excluded the WRAP-IT trial and thus our design was influenced by the lack of randomized trials on TauroPace. Nevertheless, the two included clinical trials had an acceptable level of consistency across trials (as documented by our heterogeneity analysis) and, unlike the WRAP-IT trial, were both representative of a real-world setting. Another issue not addressed by our analysis is the distinction between early wound infection and late wound complications; in any case, primary data on this point were lacking in the included trials.

Conclusions

The use of specific devices to prevent CIED infections remains controversial. This report reviews the real-world evidence and identifies two main alternatives. First, TYRX, which has known characteristics, is expensive, and is supported by robust clinical evidence; its currently unfavorable cost-effectiveness ratio could be improved by selective use of this device in high-risk patients, but adequate clinical data are not available to support this option. Second, TauroPace, which does not pose a significant cost issue, is currently supported only by preliminary evidence. Interestingly, our original analysis reported in **Figure 4** failed to demonstrate non-inferiority of TauroPace versus TYRX.

While our analysis provides a synthesis of the real-world effectiveness data currently available for these two devices, other studies on this topic with different aims have recently been reported and deserve mention. Kranick et al. [16] published a survey of antibiotic use during the insertion of cardiovascular implantable devices, demonstrating that, at least in the United States, intraprocedural and postprocedural antibiotic use varies widely between institutions and requires further standardization. Similarly, Woodard et al. [17] studied the use of an antibacterial CIED envelope (TYRX or CanGaroo from Aziyo Biologics) versus no envelope in 455 patients from a single center in the United States and identified some criteria that predicted whether the envelope was used or not. On the other hand, Macleal et al. [18] described a novel tool (the BLISTER score) for predicting cardiac implantable electronic device infections and discussed its cost-utility implications; the BLISTER score is more complex than the PADIT score in that it includes more parameters.

Interestingly, the meta-analysis by Pranata et al. [19], including 6 studies, confirmed that the antibiotic envelope was associated with a reduction in CIED infections, especially for high-power devices. On the other hand, Ellis et al. [20] published a randomized controlled trial that enrolled patients undergoing CIED procedures with ≥2 risk factors for infection; the control arm (N=505) received standard chlorhexidine skin preparation, intravenous antibiotics, and the TYRX envelope, while the study arm (N=505) received pocket wash (500 mL antibiotic solution) and postoperative antibiotics for 3 days along with the prophylactic control measures; Despite the above-mentioned selection of high-risk patients, the CIED infection rate was low in both groups and the two respective rates were very similar (1.0% in the control arm vs. 1.2% in the study arm). Finally, regarding the adverse effects of TYRX, it is interesting to note the report by Wang et al. [21], which highlights the possibility of an inflammatory response to TYRX mimicking infection.

In conclusion, the current state of the art on this topic is likely to remain unchanged until new randomized trials are published or new cost-effectiveness analyses are available to evaluate the use of TYRX in high-risk patients.

These economic analyses should be based on actual clinical data, as opposed to the weak model-based simulations that have been published to date [22]. The results recently reported by Ellis et al. [21] are of particular interest because they show that even in high-risk patients, CIED infection rates are consistently below 2%, confirming the results of our real-world analysis. Therefore, in this overall framework, we conclude that the evidence of efficacy for this clinical problem remains uncertain.

Disclosure of conflict of interest

None.

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