Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	TYRX™ Absorbable Antibacterial Envelope for patients at risk of Cardiac Implantable Electronic Device (CIED) migration, erosion and infection
Topic exploration report number:	TER297

Introduction and aims

The TYRX™ Absorbable Antibacterial Envelope was developed for use with Cardiac Implantable Electronic Devices (CIEDs), including Implantable Cardioverter Defibrillators (ICDs) and pacemakers. It is designed to prevent device migration and erosion, and to reduce the incidence of infection. The latter is one of the most serious complications experienced with CIEDs and it is associated with significant mortality, morbidity, and healthcare costs. The TYRX™ Absorbable Antibacterial Envelope consists of a multifilament knitted mesh with a polymer coating containing the antibiotics rifampicin and minocycline, and is fully absorbed after 9 weeks.

Health Technology Wales (HTW) researchers searched for evidence on the clinical and cost-effectiveness of the TYRX™ Absorbable Antibacterial Envelope in patients at risk of CIED migration, erosion and infection.

Summary of evidence

Recommendations/guidelines

The European Heart Rhythm Association (EHRA) has recommended that antibacterial envelopes are used as a preventative measure for CIED infections in high risk situations, as defined in the World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT; Tarakji et. al. 2019) and detailed in the EHRA international consensus document (Blomström-Lundqvist et. al. 2020). It is advised that consideration is also given to the local incidence of CIED infections. The EHRA recommendation is based on the TYRX™ Absorbable Antibacterial Envelope and they state that the use of other 'envelopes' (bioscaffold or pericardium patches) for stabilization, antibiotic soaked gauze, etc. has not been rigorously studied and cannot be supported.

Systematic reviews and meta-analyses

HTW identified systematic reviews and meta-analyses of antibacterial envelopes in the prevention of CIED infections. Four of these were peer-reviewed papers and included a randomised controlled trial (RCT; WRAP-IT [Tarakji et. al. 2019]) and are discussed further in this report. Meta-analysis patient numbers were between 11,897 and 32,329.

Kumar, Doshi and Shariff (2020) reported that antibacterial envelopes reduced the risk of all infections (relative risk [RR]: 0.41, [0.31, 0.54], p <0.05, I^2 = 75%, χ^2 p <0.05) and major infections (RR: 0.48, [0.32, 0.70], p <0.05, I^2 = 60%, χ^2 p=0.04). Further meta-analyses in 2020 also reported a lower risk of major infection with antibacterial envelope use: Pranata et. al. (odds ratio [OR] 0.42 [0.19, 0.97], p=0.04; I^2: 58% and hazard ratio [HR] 0.52 [0.32, 0.85], p=0.009; I^2: 80%); Ullah et. al. (OR 0.34, [0.13, 0.86], p=0.02). Asbeutah et. al. (2020) reported that no significant reduction in major infections was observed among patients with any risk for infection (RR: 0.53 [0.06, 4.52]; p=0.56). However, they observed a 74% RR reduction in major infections in the subpopulation deemed to be high risk for infection. The incidence of infection is also reported to be lower in patients receiving high-power devices (OR 0.44 [0.27, 0.73], p=0.001; I^2 = 0%), but not those receiving low-power devices (Pranata et. al. 2020).

No statistically significant difference in mortality was identified in any of the meta-analyses, although Ullah et. al. (2020) reported numerically lower (45%) odds of mortality if the antibacterial envelopes were used in conjunction with the standard infection prevention protocol.

Key primary research

The WRAP-IT multicentre RCT (Tarakji et. al. 2019) included patients who were perceived to be at increased risk for CIED infection (based on historical studies in the literature), and randomised a total of 6,983 patients. The TYRX™ Absorbable Antibacterial Envelope was successfully implanted in 99.7% of procedure attempts and no increase in procedure-related or system-related complications were observed as compared to the standard infection-control group. There were significantly less major infections within 12 months in the antibacterial envelope group (30 major infections in 25 patients) compared to the control group (45 major infections in 42 patients); 12-month Kaplan–Meier estimated event rate, 0.7% and 1.2%, respectively; HR 0.60; [0.36, 0.98]; P=0.04). The authors reported that the beneficial effects of the envelope in preventing major CIED infection in 12 months were more pronounced in patients with high-power devices than in those with low-power devices.

Economic evaluations

Prior to publication of data from the WRAP-IT RCT, Kay et. al. (2018) assessed the cost-effectiveness of the TYRX™ Absorbable Antibacterial Envelope compared to standard of care from a UK NHS perspective, stratified by device type implanted. The antibacterial envelope was less costly and more effective than standard of care in patients with an ICD or cardiac resynchronization therapy defibrillator (CRT-D) over a 12-month time horizon. When utilised in patients with an implantable pulse generator (IPG) or cardiac resynchronization therapy pacemaker (CRT-P), incremental cost-effectiveness ratios (ICERs) of £46,548 and £21,768 per QALY gained were reported, respectively. The antibacterial envelope was cost-effective at a £30,000 threshold at baseline probabilities of infection exceeding 1.65% (CRT-D), 1.95% (CRT-P), 1.87% (IPG), and 1.38% (ICD).

Boriani et. al. (2020) subsequently published a cost-effectiveness analysis based on the WRAP-IT RCT in the context of European healthcare systems, including England (incorporating a current risk-share agreement between manufacturer and hospitals). The antibacterial envelope had the most favourable ICERs over a lifetime horizon when patients had previously experienced CIED infection, had a history of immunosuppressive therapy, or had a Prevention of Arrhythmia

Device Infection Trial (PADIT) score indicating high risk of infection (scores ≥6) at a cost-effectiveness threshold of £30,000 per QALY in England. Probabilistic sensitivity analysis indicated that the antibacterial envelope was likely to be cost-effective in patients with other risk factors (including replacement of high power CIEDs, generator replacement with lead modification, and PADIT scores indicating intermediate risk of infection) when used with some device types and in some countries. Sensitivity analysis indicated that the baseline risk of infection required for the antibacterial envelope to be cost-effective in England was approximately 3.6% across all device types. Boriani et. al. (2020) concluded that cost-effectiveness would be likely in subgroups of high-risk patients with observed infection rates above these thresholds who were not included in their model. They suggested this might include patients with renal failure (particularly those receiving dialysis), patients receiving chronic immunosuppressive therapy or undergoing "early" or "delayed" CIED re-implantation.

In line with the above results, a retrospective based cost analysis carried out by Burnhope et. al. (2019) to consider potential trust-level savings showed the TYRX™ Absorbable Antibacterial Envelope to be cost-saving for heart failure patients undergoing ICD and CRT device procedures (estimated cost-saving of £624 per patient). Further studies from the perspectives of the US (Wilcoff et. al. 2020) and Canadian (Rennert-May et. al. 2020) healthcare systems concluded the antibacterial envelope was cost-effective compared to standard of care, although only where baseline infection was increased to 6% in the latter study.

Areas of uncertainty

TYRX™ Absorbable Antibacterial Envelope is for patients at risk of CIED migration, erosion and infection. Evidence appears to focus on the risk of CIED infection rather than device migration and erosion. Furthermore, evidence that antibacterial envelopes reduce the risk of CIED infection appears to be stronger for patients deemed at high risk for infection. Clarification of the exact patient group most likely to experience improved outcomes from the technology would be beneficial.

Current evidence compares antibacterial envelopes to standard of care, including aseptic surgical technique and pocket irrigation. Additional evidence comparing to Collatamp G would be helpful as this is sometimes wrapped around CIEDs before implantation to reduce the rate of surgical site infections and is therefore a relevant comparator. CanGaroo G may also be a relevant comparator.

There is an ongoing NICE Single Technology Appraisal (Guidance in development [GID-TA10370]). HTW would not duplicate NICE's work, however NICE's schedule has been impacted by COVID-19 and, at the time of writing, there is no expected publication date.

Conclusions

The EHRA has recommended that antibacterial envelopes are used as a preventative measure for CIED infections in high risk situations (noting that other non-TYRX™ versions have not been rigorously studied and cannot be supported). The consensus document also states that consideration should be given to local CIED infection levels.

Systematic reviews which include an RCT suggest that the TYRX™ Absorbable Antibacterial Envelope reduces the risk of infection (particularly major infection) in patients receiving CIEDs, especially in patients deemed to be at high risk of infection and those receiving high-

power devices. The TYRX™ Absorbable Antibacterial Envelope also appears to be cost-effective, with the most favourable ICERs observed in patients at high risk of CIED infection.

NICE Guidance on this technology is in development [GID-TA10370]; timelines are not known at the time of writing, but if this appraisal proceeds, HTW will not undertake their own appraisal. We are publishing these findings interim to full appraisal.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	Evidence/guidance relevant to the disease area was identified, but does not make any specific recommendations about TYRX Absorbable Antibacterial Envelope.
Health Technology Assessment Group	Evidence/guidance relevant to the disease area was identified, but does not make any specific recommendations about TYRX Absorbable Antibacterial Envelope.
Health Information and Quality Authority	We did not identify any relevant evidence from this source
EUnetHTA	TYRX absorbable antibacterial envelope for cardiac implantable electronic devices. EUnetHTA Prioritisation List for Medical Devices and In-Vitro Diagnostics: https://eunethta.eu/assessments/eunethta-prioritisation-list-epl-other-technologies/
International HTA Database	AIGISRx® Antibacterial Envelope for preventing infection in implanted cardiac devices. International HTA database (2012): https://database.inahta.org/article/12792 AIGISRx® Antibacterial Envelope for preventing infection in implanted cardiac devices. NIHR Horizon Scanning Centre (2012): http://www.io.nihr.ac.uk/wp-content/uploads/migrated/2275.dcc8725a.TyRxAIGISRxAntibacterialEnvelopeexpert.pdf
UK guidelines and guidance	
SIGN	Evidence/guidance relevant to the disease area was identified, but does not make any specific recommendations about TYRX Absorbable Antibacterial Envelope.
NICE	TYRX Absorbable Antibacterial Envelope for preventing infection from cardiac implantable electronic devices [ID1440] In development [GID-TA10370]: https://www.nice.org.uk/guidance/indevelopment/gid-ta10370 TYRX Absorbable Antibacterial Envelope for preventing infection from pacemakers and implantable defibrillators. Batch 62 block scoping report: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Block-scoping-reports/batch-block-scoping-report-B62.pdf Additional evidence/guidance relevant to the disease area was identified, but does not make any specific recommendations about TYRX™ Absorbable Antibacterial Envelope.
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	Ali, S., Kanjwal, Y., et. al. (2017) A meta-analysis of antibacterial envelope use in prevention of cardiovascular implantable electronic device infection. *Ther. Adv. Infect. Dis.*; 4(3): 75-82: https://doi.org/10.1177/2049936117702317 Asbeutah, A., Salem, M. H., et. al. (2020) The role of an antibiotic envelope in the prevention of major cardiac implantable electronic device infections: A systematic review and meta-analysis. *Medicine*; 99(26): e20834: http://dx.doi.org/10.1097/MD.0000000000020834

	Khan, M. U., Lone, A. N., et.al. (2020) A meta analysis of antibiotic envelope use to prevent cardiac implantable electronic device infections. *Circ. Cardiovasc. Qual. Outcomes*; 13 (Suppl. 1) https://doi.org/10.1161/hcq.13.suppl_1.103 Koerber, S. M., Turagam, M. K., et. al. (2018) Use of antibiotic envelopes to prevent cardiac implantable electronic device infections: A meta-analysis. *Journal of cardiovascular electrophysiology*; 29(4): 609-615: https://doi.org/10.1111/jce.13436 Kumar, A., Doshi, R. and Shariff, M. (2020) Role of antibiotic envelopes in preventing cardiac implantable electronic device infection: A meta-analysis of 14 859 procedures. *J. Arrhythmia*; 36(1): 176-179: http://dx.doi.org/10.1002/joa3.12262 Pranata R., Vania R., et. al. (2020) Antibiotic envelope is associated with reduction in cardiac implantable electronic devices infections especially for high-power device—Systematic review and meta-analysis. *J. Arrhythmia*; 36(1): 166-173: https://doi.org/10.1002/joa3.12270 Ullah, W., Nadeem, N., et. al. (2020) Efficacy of antibacterial envelope in prevention of cardiovascular implantable electronic device infections in high-risk patients: A systematic review and meta-analysis. *Int. J. Cardiol.*; 315: 51-56: http://dx.doi.org/10.1016/j.ijcard.2020.03.042
https://www.tripdatabase.com/	Asbeutah A. (2020). Letter to Editor "Role of antibiotic envelopes in preventing cardiac implantable electronic device infection: A meta-analysis of 14 859 procedures". J. Arrhythmia; 36(2): 377: https://doi.org/10.1002/joa3.12302 Kawamura M. (2019). Editorial to "Antibiotic envelope is associated with reduction in cardiac implantable electronic devices infections especially for high-power device-Systematic review and meta-analysis". J. Arrhythmia; 36(1): 174–175: https://doi.org/10.1002/joa3.12289 Kumar, A., Doshi, R. and Shariff, M. (2020). Reply "Role of antibiotic envelopes in preventing cardiac implantable electronic device infection: A meta-analysis of 14 859 procedures". *J. Arrhythmia*; 36(3): 544–545: https://doi.org/10.1002/joa3.12327 Tarakji, K.G., Ellis, C.R., et. al. (2016) Cardiac Implantable Electronic Device Infection in Patients at Risk. *Arrhythm. Electrophysiol. Rev.*; 5(1): 65-71: https://doi.org/10.15420/aer.2015.27.2 Wilkoff, B. L., Boriani, G., et. al. (2020) Cost-effectiveness of an antibacterial envelope for cardiac implantable electronic device infection prevention in the US healthcare system from the WRAP-IT Trial. Circulation: arrhythmia and electrophysiology; 12: 1073-1082: https://doi.org/10.1161/CIRCEP.120.008503 Wilkoff, B. L., Boriani, G., et. al. (2020) Impact of Cardiac Implantable Electronic Device Infection: a Clinical and Economic Analysis of the WRAP-IT Trial. Circulation: arrhythmia and electrophysiology; 13(5): e008280: https://doi.org/10.1161/CIRCEP.119.008280 Zhu, Y., Bi, Y. and Wu, Y. (2020) A meta-analysis on the prevention of cardiovascular implantable electronic device infection by antibacterial envelope. PROSPERO 2020 CRD42020160670: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020160670

Cochrane library	Boriani, G., Kennergren, C., et. al. (2020) MT1 Cost-Effectiveness Analyses of an Absorbable Antibacterial Envelope for Use in Patients at Increased Risk of Cardiac Implantable Electronic Device Infection in Three European Countries. *Value in health*; 23: s405-S406: https://doi.org/10.1016/j.jval.2020.08.051
Medline (via Ovid or Pubmed)	Burnhope, E., Rodriguez-Guadarrama, Y., et.al. (2019) Economic impact of introducing TYRX amongst patients with heart failure and reduced ejection fraction undergoing implanted cardiac device procedures: a retrospective model based cost analysis. *J. Med. Econ.*; 22(5): 464-470: https://doi.org/10.1080/13696998.2019.1581621 Kay, G., Eby, E.L., et. al. (2018) Cost-effectiveness of TYRX absorbable antibacterial envelope for prevention of cardiovascular implantable electronic device infection. *J. Med. Econ.*; 21(3): 294-300: https://doi.org/10.1080/13696998.2017.1409227 Rennert-May, E., Raj, S. R., et. al. (2020). Economic evaluation of an absorbable antibiotic envelope for prevention of cardiac implantable electronic device infection. *Europace*; euaa291 Epub ahead of print. PMID: 33554239: https://doi.org/10.1093/europace/euaa291 Xiang, K., Catanzaro, J. N., et. al. (2021). Antibiotic-Eluting Envelopes to Prevent Cardiac-Implantable Electronic Device Infection: Past, Present, and Future. *Cureus*; 13(2), e13088: https://doi.org/10.7759/cureus.13088
Key primary research	
Medline (via Ovid or Pubmed)	Tarakji, K., Mittal, S, et. al. (2019) Antibacterial Envelope to Prevent Cardiac Implantable Device Infection. *N. Engl. J. Med.*; 380: 1895-1905: https://www.nejm.org/doi/full/10.1056/NEJMoa1901111
Ongoing primary or secondary research	
PROSPERO database	Jubb, A., Bartlett, C., et. al. (2019) Systematic review of the cost-effectiveness of TYRX for the prevention of cardiac implantable electronic device (CIED) infections. PROSPERO 2019 CRD42019121429: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019121429 Jubb, A., Wilson, K., et. al. (2019) Systematic review of the cost-effectiveness of TYRX for the prevention of cardiac implantable electronic device (CIED) infections. PROSPERO 2019 CRD42019121140: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019121140 Zhu, Y., Bi, Y. and Wu, Y. (2020) A meta-analysis on the prevention of cardiovascular implantable electronic device infection by antibacterial envelope. PROSPERO 2020 CRD42020160670: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020160670
Other	
Additional evidence provided by topic proposer and/or identified through other references	Blomström-Lundqvist, C., Traykov, V. et. al. (2020) European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections—endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Europace 22(4): 515-549: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7132545/

	Sandoe, J.A.T., Barlow, G., et al. (2015) Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE), Journal of Antimicrobial Chemotherapy, vol 70, pp325-359: https://doi.org/10.1093/jac/dku383

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Concepts used:	Absorbable antibacterial envelope, AIGISRx, antibiotic envelope, antimicrobial, arrhythmia, CanGaroo-G, cardiac implantable electronic device, cardiac resynchronization therapy, CIED, Collatamp G, CRT-D, CRT-P, erosion, heart failure, implantable cardioverter defibrillator, implantable pulse generator, ICD, infection, IPG, migration, pacemaker, TYRX.