Use of Antibiotic Envelopes to Prevent Cardiac Implantable Electronic Device Infections: A Meta-Analysis

Scott M Koerber, DO*; Mohit K. Turagam, MD^; Jeffery Winterfield, MD*; Sandeep Gautam, MD**; Michael R. Gold* MD, PhD

From the *Medical University of South Carolina, Charleston, SC; ^Mount Sinai Medical Center, NY; **University of Missouri-Columbia, Columbia, MO

Address for correspondence:

Michael R. Gold, MD, PhD, Division of Cardiology, Medical University of South Carolina

114 Doughty Street - MSC 592, Charleston, SC 29425-5920

Tel: 843-876-4760, Fax: 843-876-4990, Email: goldmr@musc.edu

Dr. Gold reports clinical trials and consultant to Medtronic and Boston Scientific. Other authors: No disclosures.

Abstract

Introduction

The rates of cardiac implantable electronic device (CIED) infections have risen over the past decade and are associated with increased hospitalizations and mortality. A number of

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jce.13436

preventative strategies have been developed including an antibiotic coated envelope, but it has yet to gain widespread use.

Methods

A meta-analysis was performed on controlled studies of the antibiotic envelope. PubMed and Google Scholar were searched for studies comparing infection rates with and without the use of an antibiotic envelope. Studies including both new implants and pulse generator replacements were included in the analysis.

Results

Five studies were included in the meta-analysis. A total of 4,490 patients underwent CIED implantation, 1798 with an antibiotic envelope and 2,692 without an envelope. In the pooled cohort, the envelope was associated with a 69% relative risk reduction in CIED infection (0.31[0.17,0.58]CI 95%, p=0.0002). Propensity matched data from 3 studies were analyzed to ensure accurate comparison. In the risk-matched cohort, infections were significantly lower in the envelope group (3 vs 26, p< 0.0003).

Conclusion

The use of antibiotic envelopes in CIED implant is associated with a significantly lower rate of infection.

Introduction

Cardiac implantable electronic devices (CIED) have been shown to improve both survival and quality of life in selective patient populations. [1, 2] [3], [4] As the indications for CIEDs continue to expand, the number of implantations continues to rise, with over 600,000 annually worldwide [5, 6] Despite the benefits of these devices, both short- and long-term complications remain common. CIED infection is one of the most serious complications that not only increases

mortality, but also has a significant financial impact on the health care system. [7], [8] The estimated annual prevalence of CIED infection is 2-4% [9]. The American College of Cardiology/American Heart Association current guideline recommend perioperative parenteral antibiotics as a class I recommendation for prevention of CIED infections. [10] Despite these evidence based recommendations, the rate of CIED infections continues to rise [5].

An antibiotic envelope (TYRX^{TM} Medtronic, Inc., Minneapolis, MN,USA) was developed in an effort to reduce device infections and was approved by the FDA in 2008. The first generation envelope was a non-resorbable, antibiotic eluting polypropylene mesh coated in rifampin and minocycline, with the aim to prevent local contamination and inflammation with CIED implantation. A newer, bio-absorbable generation envelope is now commercially available, and is coated with the same antibiotics as the non-resorbable envelope. Despite low prevalence of CIED infections reported from multiple studies [11-13], it has yet to gain standardized, widespread use among implanting physicians. To better quantify the efficacy of using an antibiotic envelope at implantation, we performed a systematic review and meta-analysis of all the studies comparing the antibiotic envelop in prevention of CIED infections.

Methods

Search strategy

A comprehensive literature search was performed on clinicaltrials.gov, PubMed, Cochrane central registry and Google Scholar using the search terms "cardiac implantable electronic device infection with antibiotic envelope", "antibiotic envelope for CIED infection", and "cardiac implantable electronic device infections." All observational, retrospective cohort and randomized control trials that compared CIED infections with and without the use of an antibiotic envelope Jan 1, 2008 to October 10, 2017 were evaluated for inclusion in the meta-analysis.

Study Selection

Studies were excluded if a control arm was not reported in the study. Both bio-absorbable and non-resorbable envelopes were included in this analysis. Baseline characteristics were reviewed to ensure study cohorts were statistically similar. Risk factors for CIED infections have been previously reported and include presence of ≥ 3 leads, anticoagulation use, fever/leukocytosis, renal insufficiency, corticosteroid use, pacemaker dependence, prior CIED infection, and early pocket reentry. [9, 14-16] Risk factors were reviewed in each cohort to ensure that groups had similar risk scores.

Data extractions and Quality appraisal

Two investigators (SK and MT) independently performed the literature search and screened the relevant studies that met inclusion criteria. Any discrepencies between the two investigators were resolved by mutual consensus. The primary outcome was infection rate with and without the use of an antibiotic envelope.

Statistical analysis

After data were reviewed, statistical analyses were performed using Cochrane RevMan version 5.3. Results were expressed as odds ratio (OR) for dichotomous outcomes. P values < 0.05 were considered statistically significant. Mantel-Haenszel risk ratio (RR) random effects model (DerSimonian and Laird method) was used to summarize data across the groups. Heterogeneity of effects among the included studies was assessed by Higgins I-squared (I^2) statistic. The degree of heterogeneity was defined using the I2 statistic value, with low values being $< 50\%$.

Results

Search Results and Study Selection

The initial search strategy returned 1090 articles. The titles and abstracts were reviewed applying the inclusion/exclusion criteria, which resulted in 9 articles meeting criteria for further review. After reviewing each manuscript, 5 studies were identified which compared the use of an antibiotic envelope to a control cohort without the envelope. (Figure 1) One study was excluded due to significant overlap of patients in a subsequent study. Studies using external databases as the infection rate for the control group were excluded. If baseline characteristic were statistically different between original cohorts (control vs envelope), data from a propensity matched cohort study were used.

Study Characteristics

The study and patient characteristics of the 5 cohort studies are summarized in Table 1. A total of 4490 patients underwent CIED implantation, with 1,798receiving an antibiotic envelope at implant and 2,692 in the control group. As noted above major CIED risk factors previously reported include generator replacement or device upgrade, diabetes mellitus, renal insufficiency, systemic oral anticoagulation, chronic corticosteroid use, prior CIED infection, fever/leukocytosis at time of implant, presence of greater the 2 leads, and early pocket reentry [9, 10, 14, 16, 17] were documented. For the primary endpoint of CIED infection, 2 analyses were performed. First, the entire pooled cohort was included. In the second analysis, only propensity-matched cohorts were used in order to ensure individual CIED infection risk factors were similar between groups. (Table 1) The Citadel study results were not included in this analysis since no site-matched controls were present.

Infection Analysis

In the pooled cohort analysis, a total of 4,490 patients underwent CIED implantation, 1,798 with an antibiotic envelope at implant and 2,692 in the control group. The envelope was associated with a 69% relative risk reduction in CIED infection (0.31[0.17,0.58] 95% CI, p=0.0002). The individual study Odds Ratios and pooled analysis results are shown in Figure 2.

Propensity matched data from three studies included a total of 1909 patients (Envelope: 956, Control: 953). CIED risk factors were similar between groups as part of the propensity matching process. In this analysis, the use of an antibiotic envelope was associated with an 86% reduction (OR 0.14 [0.05, 0.41] 95% CI, p =0.0003) in the risk of a CIED infection. (Figure 3) Low

heterogeneity was present as demonstrated by an I^2 statistic value of 0. Of note, Kolek et al was the only study to include bio-aborbable envelopes. They reported no significant difference in CIED infections between the first generation, non-resorbable envelope with the newer, bio-absorbable version in 488 patients. [18]

Examination of Study Population

To ensure the study population represented a typical patient population including high risk characteristics, and to examine the effect of the envelope in such patients, we examined the infection rates with various procedure types, device types, and other known CIED infection risk factors.

Impact of Early Pocket Reentry on CIED infection

Early pocket reentry (EPR), generally defined as entry into a device pocket within 2 weeks of initial implant, has been described as a significant risk factor for CIED infection. In this meta-analysis, no significant difference in infection rates was observed when comparing patients with established infections with and without early pocket reentry. In three of the studies, a total of 120 patients underwent EPR, with 4 subjects developing subsequent CIED infections (3.33%). Among patients that did not undergo EPR the rate was 1.62% (61 infections in 3766 cases), with no statistical difference observed between groups (OR 2.11[0.80, 5.56] 95% CI, p=0.13). (Figure 4a) One possible explanation for this finding is that one study (Kolek 2015) included patients with an ABX envelope in this analysis. In this study, over 75% of the patients that underwent EPR also had an ABX envelope placed. To examine the impact of EPR on CIED infections

independent of envelope use, this study was removed from the comparison. (Figure 4b) When only using patients without an ABX envelope, a significant increase in CIED infection risk associated with EPR was observed (OR 6.54 [2.22, 19.24] 95% CI, p=0.0007).

Impact of type of device on infection

Two of the studies included a breakdown of CIED infections according to device type, cardiac resynchronization therapy (CRT), implantable defibrillator (ICD) or pacemaker (PPM). In order to examine the impact of device type on CIED infections, all patients included in this analysis did not have an ABX envelope placed. CRTs and ICDs were associated with a significant increase in infection risk compared with PPM (OR 3.36 [1.65, 6.86] 95% CI, p= 0.0008). Further analysis showed that ICDs were associated with a 55% lower risk for CIED infection compared to CRTs (OR 0.45 [0.22, 0.91] 95% CI, p=0.03).

Impact of procedure type on CIED infection

The type of procedure being performed has been reported to impact the device infection risk, with initial implants representing the lowest risk of infection and device upgrades and pulse generator replacements incurring higher infection risks. [12] In this meta-analysis, no statistical difference in infection risk was observed between de novo implants and upgrades/replacements in patients without an ABX envelope (OR 0.94[0.50, 1.78] 95% CI, p= 0.85). However, device upgrades were associated with higher infections risk compared to pulse generator replacements (OR 4.16[1.39, 12.47] 95% CI, p=0.01).

Discussion

The main findings of this meta-analysis were a significant reduction in the risk of CIED infection with the use of antibiotic envelopes. The pooled and propensity matched cohorts were associated with a 69% and 86% relative risk reduction for CIED infection, respectively. Moreover, a reduction of infection with the envelope was observed in with a variety of device types, procedures, and in patients with multiple CIED infection risk factors.

The most common pathogens associated with CIED infections are staphylococcal.[10] In a review of 189 cases admitted for CIED infection at Mayo Clinic, coagulase-negative staphylococci and Staphylococcus aureus accounted for the majority of pathogens. [15] TYRX^{TM} is coated with two antibiotics with different mechanisms of action, but both with activity against staphylococci. [19] The bioabsorbable envelope releases these antibiotics over time and is fully resorbed around 9 weeks post procedure. [20]

In the pooled analysis, the entire cohorts were included, which demonstrated a significant reduction in CIED infection with use of the antibiotic envelope. On further review of the cohorts included in this analysis, there were significant differences in the predefined CIED infection risk factors. In the study of Hassoun et al[21], the antibiotic envelope group had significantly higher CIED risk factors, including higher corticosteroid use, higher rates of revisions/upgrades, and a higher percentage of patients with >2 leads. In addition, the Centurion results were site-matched controls, but differed in the number of risk factors between groups.

In order to examine the impact of the ABX envelope on CIED infection more accurately, further analysis was performed using propensity-matched data to ensure risk factors were comparable between groups. This analysis revealed an even greater relative risk reduction for CIED infection than the pooled cohort (86% vs 69%). A low degree of heterogeneity was demonstrated by a Cochran I-q statistic (I^2=0).

Results from the recently published Citadel study showed a significantly lower CIED infection rate with use of an envelope compared to a previously reported rates without an envelope (0.4% vs 2.2%, p=0.0023). [22] Although these data were not included in our analysis due to the use of only a benchmark control infection rate being used as a control, the results support the findings of our meta-analysis.

Numerous studies have demonstrated a significant increase in mortality and health care costs associated with CIED infection. [7, 23] In a retrospective analysis of patients undergoing a CIED implant at a single center, Shariff et al reported a substantial increase in the 6-month mortality rate among patients with a CEID infection (15.7%) compared to those without an infection (4.5%). [23] Furthermore, Sohail et al reported a long-term mortality increase in patients with CIED infections for as long as 2-3 years post infection. [7] Greenspon et al reported a significant increase in health care costs for treatment of CIED infections. In that study, inpatient hospital charges for CIED infections rose from $75K in 1993 to $146K in 2008, corresponding to an increase of 47% per decade.[6] The currently approved envelope (Tyrx) has been reported to be cost effective.[5, 23] Ellis et al reported the number needed to treat to prevent one infection using an antibiotic envelope was 40 patients. [5]

Currently, limited controlled trial data exist comparing infection rates with and without the use of an envelope, and none of these are randomized control trials. A wide variation in practice patterns exist among implanting physicians on which patients receive an antibiotic envelope, with some centers not using them on any patients and others using in every implant. As the cost of the envelope may factor into the decision, further data are needed to determine which patient benefits the most with use of an envelope as the incidence of CIED infection is influenced by a number of factors. These include type of implanted device, number of leads present, performing lead revisions, device upgrades, and early pocket reentry. By identifying higher risk cohorts for CIED infection, selective patient selection may improve its cost effectiveness. Multiple risk scoring criteria have been established to help identify those at highest risks of CIED infection. [13, 24] Shariff et al found the total cost of treating the 19 CIED infections in their study was over 1 million dollars, with an average cost of almost $55K per patient. [23] Furthermore, they found that patients with preoperative CIED infection risk scores $\geq$3 had greater cost efficiency with use of an antibiotic envelope. Mittal et al found similar results, with the greatest effect of the antibiotic envelope seen in the highest risk patients. [25]

To help identify high-risk cohorts, a number of subgroups were studied. Pacemakers were associated with a lower infection risk compared to CRT and ICD devices. When comparing ICD to CRT implants, ICDs had a 55% relative risk reduction in CIED infection (p=0.03). Surprisingly, in the overall cohort, no significant difference in CIED infection was observed with early pocket reentry. On further review of the studies, over 75% of patients in one study (Kolek 2015) received an antibiotic envelope which likely account for this result as a marked effect was noted when this study was excluded (p=0.007). De novo implants have been previously reported

to have a lower risk of CIED infection compared to non-de novo procedures. [9] In the present analysis, no significant difference was observed between de novo implants and a combination of pulse generator replacements and device upgrades. When comparing pulse generator replacements to device upgrades, device upgrades were associated with a significant increase in CIED infection risk (p=0.01). This implies that generator replacements incur similar risks as de novo implants, which has been supported by previous studies. [25]

The Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) is a large, prospective, multicenter, industry sponsored randomized control trial is currently ongoing which is designed to test the efficacy and cost effectiveness of the TYRX^{TM} envelope in various patient groups undergoing de novo CIED implant, revision or upgrade. [26] This study is fully enrolled and in the follow-up phase. These data will provide much needed information to help guide device implanting physicians.

Study Limitations

The present study should be interpreted in light of several limitations. First, the majority of studies to date have either been retrospective in nature or prospective but lacking a control arm. Second, further analysis is restricted by the limited data examining the efficacy of antibiotic envelopes in specific subgroups. Additionally, the antibiotic envelope used in practice today is the bio-absorbable version. The majority of the studies in this meta-analysis used the first generation, non-resorbable envelope.

Conclusion

The present meta-analysis showed a significant risk reduction in CIED infection with use of an antibiotic envelope and suggests that this therapy is likely underutilized in clinical practice. Patients at highest risk for CIED infection include those undergoing CRT implant, device upgrade/lead revision and early pocket reentry after initial implant. Additional data examining cost effectiveness in various CIED infection risk cohorts is needed to better identify which patient populations are most appropriate for the use of an antibiotic envelope.

References

1. Moss, A.J., et al., *Cardiac-resynchronization therapy for the prevention of heart-failure events.* N Engl J Med, 2009. **361**(14): p. 1329-38.
2. *A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias.* N Engl J Med, 1997. **337**(22): p. 1576-83.
3. Bardy, G.H., et al., *Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure.* N Engl J Med, 2005. **352**(3): p. 225-37.
4. Cleland, J.G., et al., *The effect of cardiac resynchronization on morbidity and mortality in heart failure.* N Engl J Med, 2005. **352**(15): p. 1539-49.
5. Christopher Ellis MD and Matthew Kolek, *Rising Infection Rate in Cardiac Electronic Device Implantation; the Role of the AIGISRx ® Antibacterial Envelope in Prophylaxis.* Comb Prod Ther, 2011. **I**.
6. Arnold Greenspon MD, et al., *16-Year Trends in the Infection Burden for Pacemakers and Implantable Cardioverter-Defibrillators in the United States.* Journal of the American College of Cardiology 2011. **58**(10): p. 1001-1006.
7. Rizwan Sohail, M., et al., *Increased long-term mortality in patients with cardiovascular implantable electronic device infections.* Pacing Clin Electrophysiol, 2015. **38**(2): p. 231-9.

8. Sohail, M.R., et al., *Mortality and cost associated with cardiovascular implantable electronic device infections.* Arch Intern Med, 2011. **171**(20): p. 1821-8.

9. Klug, D., et al., *Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study.* Circulation, 2007. **116**(12): p. 1349-55.

10. Baddour, L.M., et al., *Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association.* Circulation, 2010. **121**(3): p. 458-77.

11. Mittal, S., et al., *Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AigisRx antibacterial envelope.* Heart Rhythm, 2014. **11**(4): p. 595-601.

12. Matthew Kolek MD, et al., *Use of Antibacterial Envelope is Associated with Reduced Cardiac Implantable Electronic Device Infections in High-Risk Patients.* Pacing Clin Electrophysiol, 2013. **36**(3): p. 354-361.

13. Shariff, N., et al., *Cardiovascular Implantable Electronic Device Infections: Risk Scoring and Role of Antibiotic Envelope in Prevention.* Recent Adv Cardiovasc Drug Discov, 2015. **10**(1): p. 70-6.

14. Lekkerkerker, J.C., et al., *Risk factors and time delay associated with cardiac device infections: Leiden device registry.* Heart, 2009. **95**(9): p. 715-20.

15. Sohail, M.R., et al., *Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections.* J Am Coll Cardiol, 2007. **49**(18): p. 1851-9.

16. Bloom, H., et al., *Renal insufficiency and the risk of infection from pacemaker or defibrillator surgery.* Pacing Clin Electrophysiol, 2006. **29**(2): p. 142-5.

17. Sohail, M.R., et al., *Risk factor analysis of permanent pacemaker infection.* Clin Infect Dis, 2007. **45**(2): p. 166-73.

18. Matthew Kolek MD, et al., *Efficacy of a Bio-Absorbable Antibacterial Envelope to Prevent Cardiac Implantable Electronic Device Infections in High-Risk Subjects.* J Cardiovasc Electrophysiol 2015. **26**:1111-1116.

19. Segreti, J., L.C. Gvazdinskas, and G.M. Trenholme, *In vitro activity of minocycline and rifampin against staphylococci.* Diagn Microbiol Infect Dis, 1989. **12**(3): p. 253-5.

20. Marye Gleva and Jeanne Poole, *Prevention of Cardiac Implantable Electronic Device Infections: Update and Evaluation of the Potential Role for Capsulectomy or the Antibiotic Pouch.* Journal of Atrial Fibrillation 2017. **9**(5): p.

21. Hassoun, A., et al., *Retrospective comparative analysis of cardiovascular implantable electronic device infections with and without the use of antibacterial envelopes.* J Hosp Infect, 2017. **95**(3): p. 286-291.

22. Henrikson, C.A., et al., *Antibacterial Envelope Is Associated With Low Infection Rates After Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Therapy Device Replacement.* Results of the Citadel and Centurion Studies, 2017.

23. Nasir Shariff MD, et al., *Journal of Cardiovascular Electrophysiology* 26, 2015. **7**: p. 783-789.

24. Sohail, M.R., et al., *Predicting risk of endovascular device infection in patients with Staphylococcus aureus bacteremia (PREDICT-SAB).* Circ Arrhythm Electrophysiol, 2015. **8**(1): p. 137-44.

25. Suneet Mittal MD, et al., *Cardiac Implantable Electronic Device Infections: Incidence, Risk Factors, and the Effect of the AigisRx Antibacterial Envelope.* Heart Rhythm, 2013. **11**(4): p. 595-601.

26. Tarakji, K.G., et al., *Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT).* Am Heart J, 2016. **180**: p. 12-21.

FIGURE LEGENDS

Figure 1. Study selection flow chart

Table 1. Study characteristics

Figure 2. Pooled Cohort CIED Infection Analysis

Figure 3. Propensity-Matched Cohort CIED Infection Analysis

Figure 4. a. Early Pocket Reentry Analysis, **b.** Early Pocket Reentry Without use of Envelope Analysis

Figure 1.

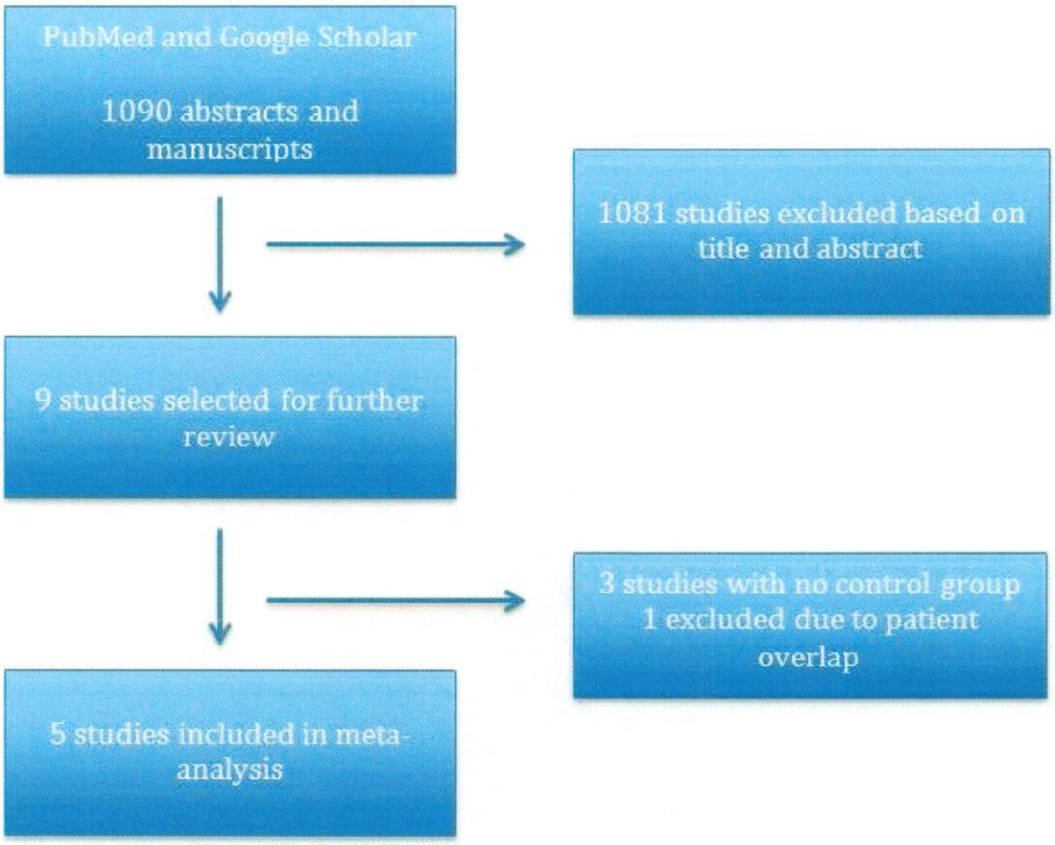

Table 1.

Study	Type of Envelope (Non or Abs)	Number of Patients N (%)	Minimum follow-up	Age (Mean ± SD) or median (95% CI)	Male Gender N, (%)	DM N (%)	Generator replacement or upgrade N (%)	Oral Anticoagulation N (%)
Mittal et al. 2014*	Non							
- **Envelope**		275	180 days	75 ± 11	199 (72)	137 (50)	130 (47.3)	NR
- **Control**		275		74 ± 12	209 (76)	135 (49)	115 (41.8)	NR
Shariff et al. 2015	Non							
- **Envelope**		365	180 days	71 ± 12	221 (61)	102 (28)	237 (64.9)	177 (49)
- **Control**		1111		67 ± 16	735 (66)	351 (32)	367 (33)	394 (36)
Kolek et al. 2015								
- **Envelope Abs**	Abs	135	300 days	67 (63.5-70.5)^	92 (68.1)	55 (40.7)	90 (66.7)	77 (57)
Non	Non	353		69 (67-71)^	242 (68.6)	148 (41.9)	180 (51)	204 (57.8)
- **Control**		636		70 (68-71)^	400 (62.9)	344 (54.1)	215 (33.8)	433 (68.1)
Henrikson et al. 2017	Non							
-Envelope		578	12 months	72.2 ± 10.7	444 (76.8)	242 (41.9)	578 (100)	283 (49)
- Site-matched control		578		71.5 ± 10.9	434 (75.1)	193 (33.4)	578 (100)	249 (43.1)

Hassoun et al. 2017	Abs						
- **Envelope**	92	9 months	69	52 (57)	NR	51.1%	28 (30)
- **Control**	92	(mean)	73	58 (63)	NR	8.7%	27 (29)

*= propensity matched cohort study data; NR= not reported; ^= median (95% CI), Non=non-resorbable, Abs=bio-absorbable,

Figure 2.

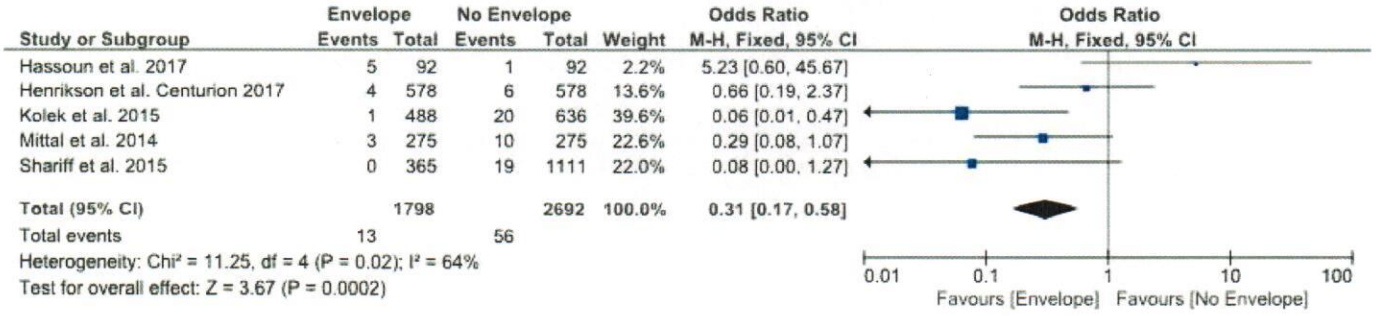

Figure 3.

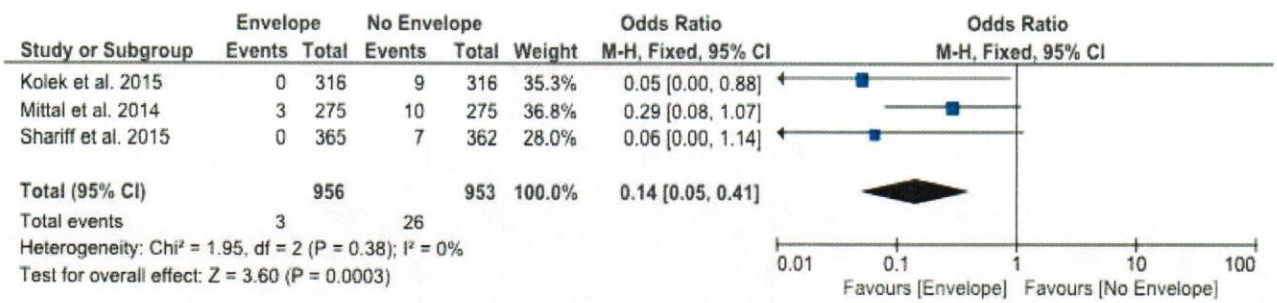

Figure 4a.

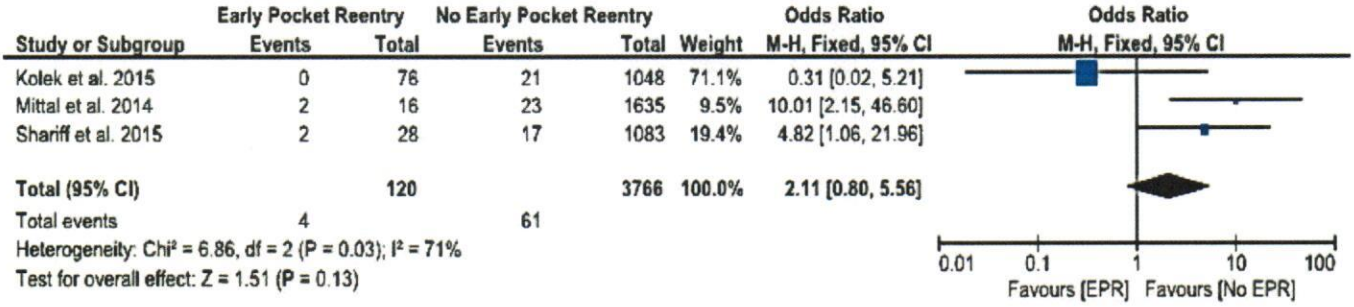

Figure 4b.