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Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive-Dental Procedures

Brief Title – Antibiotic Prophylaxis for Invasive-Dental Procedures

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Abstract (250/250 words)

Background:
Antibiotic prophylaxis (AP) before invasive dental procedures (IDP) is recommended to prevent infective endocarditis (IE) in those at high-IE-risk but there are sparse data supporting a link between IDP and IE or AP efficacy in IE-prevention.

Objectives:
To investigate any association between IDP and IE, and AP effectiveness in reducing this.

Methods:
We performed a case-crossover analysis and cohort study of the association between IDP and IE, and AP efficacy, in 7,951,972 US subjects with employer-provided Commercial/Medicare-Supplemental cover.

Results:
Time course studies showed that IE was most likely to occur within 4-weeks of an IDP. For those at high-IE-risk, case-crossover analysis demonstrated a significant temporal association between IE and IDP in the preceding 4-weeks (OR 2.00, 95%CI 1.59-2.52, p=0.002). This relationship was strongest for dental extractions (OR 11.08, 95%CI 7.34-16.74, p<0.0001) and oral-surgical procedures (OR 50.77, 95%CI 20.79-123.98, p<0.0001). AP was associated with a significant reduction in IE incidence following IDP (OR 0.49, 95%CI 0.29-0.85, p=0.01). The cohort study confirmed the associations between IE and extractions or oral surgical procedures in those at high-IE-risk and the effect of AP in reducing these associations (extractions: OR 0.13, 95%CI 0.03-0.34, p<0.0001; oral surgical procedures: OR 0.09, 95%CI 0.01-0.35, p=0.002).

Conclusions:
We demonstrated a significant temporal association between IDP (particularly extractions and oral-surgical procedures) and subsequent IE in high-IE-risk individuals, and a significant association between AP use and reduced IE incidence following these procedures. These data support American Heart Association, and other, recommendations that those at high-IE-risk should receive AP before IDP.

Keywords:
Infective endocarditis, antibiotic prophylaxis, dental procedures, guidelines, prevention, risk

Abbreviations:

ADA = American Dental Association
AHA = American Heart Association
AP = Antibiotic prophylaxis
CCI = Charlson Comorbidity Index
CPT = Current Procedural Terminology
CDT = Common Dental Terminology
ESC = European Society of Cardiology
HIPAA = Health insurance portability and accountability act
ICD = International Classification of Disease
IDP = Invasive dental procedures
IE = Infective endocarditis
IRB = Institutional review board
Non-IDP = Non-invasive dental procedures
OR = Odds ratio
STROBE = Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cohort studies.
UK = United Kingdom
US = United States of America

Introduction

Infective endocarditis (IE) has ~30% first-year mortality.[1,2] Although uncommon, many individuals with predisposing cardiac conditions are at increased risk of IE or adverse IE-outcome.[3] A causal link with invasive-dental procedures (IDP) has long been postulated to explain the 30-40% of IE cases caused by oral streptococci.[4] Consequently, the American Heart Association (AHA) has issued guidelines on antibiotic prophylaxis (AP) to prevent IE in patients undergoing IDP since 1955.[5]

Although AP became the worldwide standard of care for IE prevention, there has never been a clinical trial of AP efficacy in reducing IE-risk. Moreover, the link between IDP and IE has been questioned, and routine daily activities (e.g. toothbrushing, flossing, mastication) proposed as more likely causes of oral streptococcal-related IE, particularly in those with poor oral hygiene.[6,7] Accompanying concerns about adverse drug reactions and promoting antibiotic resistance led the AHA[8] and the European Society of Cardiology (ESC)[9] to restrict AP to those at highest IE-risk undergoing IDP. In the UK, it was recommended that AP cease completely.[10] The aim of this study, therefore, was to identify any temporal association between IDP and IE, and any effect of AP on IE incidence.

Methods

Data Source

The study was conducted in a US-healthcare population and reported following STROBE guidelines for cohort studies.[11] Data from the Commercial, Medicare-Supplemental (for retirees with employer-paid Medicare-Supplemental insurance), prescription benefits and Dental, IBM® MarketScan® databases (integrating unidentifiable patient-level data) were linked (see supplementary appendix for more details on these). Since MarketScan databases

are statistically de-identified in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and meet HIPAA limited-use dataset criteria they are not subject to IRB-review.[12] All enrollees ≥18 years with >16 months linked data (January 2000 - August 2015) were included. Data after 2015 was not included due to changes in the way diagnosis and procedure codes were recorded in the US after this date (see supplementary appendix for more details)

IE admissions and IE-risk stratification

IE-related hospital admissions were identified using primary or secondary ICD-9 discharge diagnostic codes 421.0, 421.1 or 421.9. Previously described methods were used to ensure single continuous IE episodes were only counted once.[13] New episodes were distinguished from re-admissions by excluding IE admissions <6 months apart.[14] ICD-9 or CPT diagnosis/procedural codes were used to identify individuals as previously being at high or moderate IE-risk (Table 1, and Supplemental Table S1 and S2), based on AHA guidelines,[8,15] using all available records back as far as January 2000. After IE-admission, enrollees were considered at high-risk of future IE. Remaining individuals were considered at low/unknown IE-risk.

Invasive Dental Procedures

American Dental Association (ADA) CDT or ICD-9 procedure codes were used to classify dental procedures into: (i) Invasive-dental procedures (IDP) – those dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa e.g. dental extractions, oral surgical procedures, scaling (supragingival or subgingival) and endodontic procedures, i.e. those dental procedures that the AHA guidelines recommend 'should' be covered by AP,[8,15] (ii) Intermediate-dental procedures e.g. most restorative dental procedures, that may require AP cover when gingival manipulation is

required to complete the procedure but do not require AP cover when the procedure can be completed without gingival manipulation. (iii) Non-IDP, e.g., routine dental examination, dental radiographs, placement of removable prosthodontic or orthodontic appliances, for which AP is not recommended (Table 2 and Supplemental Table S3).[8,15] The most invasive procedure was ascribed to each visit. When treatment involved multiple visits, each was evaluated separately for procedures performed and AP cover. IDP were also sub-analyzed using codes specific for dental extractions, oral surgical procedures, scaling and endodontic procedures (Table 2 and Supplemental Table S3).

Prescription benefits data were used to identify if AP was prescribed for each dental visit using previously validated methodology[16] (see also Supplemental Methods).

Cohort Study

The entire 7·95 million person cohort with linked medical/dental/prescription data was examined. Subjects were stratified by IE-risk (high-, moderate- or low/unknown-risk) and followed until study completion, expiry of linked data or death. Individuals could transition to a higher risk-group if new risk-related diagnoses or procedures arose.

For each risk-group, IE-incidence was quantified in the 30-day exposure period following dental-procedures, identified by plotting dental-procedure incidence over 16 months prior to IE-admission (see Case-Crossover methods). Analysis was repeated using a 4-month exposure period. IE incidence was compared between different IE risk-groups, different types of dental procedure, and procedures with or without AP cover. Crude incidence was adjusted for differences in age, sex and Charlson Comorbidity Index (CCI) between groups.[17] To address the rare outcome of interest (3,774 IE cases in 7,951,972 population), we applied Firth logistic regression - a penalized-likelihood statistical method. This method was introduced to address the possibility of rare outcomes causing small sample size bias

(particularly in some sub-analyses) when using traditional maximum likelihood logistic regression that can lead to the non-convergence of regression estimates.[18,19] The odds of IE following an IDP (including sub-types), or intermediate-dental procedure, were estimated by comparison with IE-incidence following non-IDP (the control group for this purpose) to test the null hypothesis that there is no increase in the incidence of IE in the 30-days (or 4-months) following an invasive dental procedure (the dental procedures model). We also compared IE-incidence following dental-procedures with or without AP cover to test the null hypothesis that AP does not reduce the incidence of IE in the 30-days (or 4-months) following a dental procedure (the antibiotic prophylaxis model). For both models we set a $p<0.05$ criterion for determining significance but we first applied a Bonferroni correction to the p values to account for situations where multiple comparisons were performed.

Case-Crossover Study

The monthly exposure of 3,774 subjects with IE-related hospital admission to different IDP was quantified over the 16 months before admission and plotted to identify the timing of any association with IE. Accordingly, incidence of IDP, extractions and surgical-procedures peaked in the 30-days before IE-admission in those at high IE-risk (Figures 1 and S1). Case-crossover analysis[20,21] comparing exposure to dental procedures during this 30-day case-period with the preceding 12-month control-period (months 2-13) was performed using conditional logistic regression (with fixed effects to control for time-invariant patient characteristics).[21] To permit comparison with previous case-crossover studies that used longer case-periods (3-4 months),[22-24] we performed further analyses using a 4-month case-period and 12-month control-period (months 5-16). A Bonferroni correction was also applied to p values where multiple comparisons were made.

Results

Cohort Study - *Dental Procedures Model*

Of 7,951,972 Commercial/Medicare enrollees, 3,774 (475 cases/million) were hospitalized with IE, 1,292 (34.2%) in individuals previously at high-IE-risk, 831 (22.0%) in those at moderate-IE-risk and 1,651 (43.8%) in those at low/unknown-IE-risk (Table 3). The overall adjusted IE-incidence within 30-days of a dental-procedure was 467.6, 24.2 and 3.8 per million procedures in those at high, moderate, and low/unknown IE-risk, respectively (Table 4).

The odds of developing IE were non-significantly higher following IDP compared to non-IDP procedures in high IE-risk patients (Table 4). However, sub-analysis of IDP demonstrated that the odds of IE were significantly increased following extractions (OR 9.22, 95% CI 5.54-15.88, p<0·0001) and other oral surgical procedures (OR 20.18, 95% CI 11.22-36.74, p<0·0001). Although smaller, the odds of IE were also significantly increased following extractions in individuals at moderate IE-risk, and extractions and other surgical-procedures in those at low/unknown IE-risk.

Cohort - *Antibiotic Prophylaxis Model*

AP was prescribed to cover 32.6%, 9.5% and 2.9% of IDP in those at high, moderate, and low/unknown IE-risk, respectively (Table 3). Amoxicillin 2g accounted for 75% of AP prescriptions, followed by clindamycin 600mg (17%), clarithromycin 500mg (4%), azithromycin 500mg (3%) and cephalexin 2g (1%). AP cover for IDP in those at high IE-risk was associated with significant reduction in IE-risk (OR 0.38, 95% CI 0.22-0.62, p=0.002) compared to no AP. This reduction was most pronounced following extractions (OR 0.13, 95% CI 0.03-0.34, p<0.0001) and other oral surgical procedures (OR 0.09, 95% CI 0.01-0.35, p=0.002) (Table 4 and Central Illustration). AP cover was of no significant benefit following other IDP or in individuals at moderate or low/unknown IE-risk.

A similar pattern of associations between IDP (particularly extractions and surgical procedures) and IE, and of AP efficacy was observed over a 4-month exposure period, albeit with smaller effect size (Supplemental Tables S6 and S9).

Case-Crossover Study - *Dental Procedures Model*

Within the 3,774 IE-admissions cohort, the incidence of IDP, extractions and surgical-procedures peaked in the 30-days before IE-admission for those at high IE-risk (Figures 1 and S1). In this group, there was also a significant positive association between IDP (but not intermediate-dental procedures or non-IDP) and IE-related hospital admission (OR 2.00, 95% CI 1.59-2.52, p=0.002; Table 5) when comparing the 30-day case-period with the preceding 12-month control-period (months 2-13). Sub-analysis revealed a significant association with extractions (OR 11.08, 95% CI 7.34-16.74, p<0·0001) and surgical-procedures (OR 50.77, 95% CI 20.79-123.98, p<0.0001) in the 30-days before IE admission. There were no significant positive associations between IDP and IE for those at moderate IE-risk, but a small positive association between surgical-procedures (OR 3.50, 95% CI 1.66-7.36, p=0.02) and IE in those at low/unknown IE-risk. This anomaly may relate to misclassification of individuals whose only record of a predisposing high-risk procedure or condition occurred before January 2000 (see Limitations).

The high-risk group demonstrated a similar pattern of associations in the 4-month case-period analysis (Supplemental Table S10). In addition, there was a significant positive association between extractions and IE in those at moderate IE-risk (OR 2.05, 95% CI 1.42-2.95, p=0.003).

Case-Crossover - *Antibiotic Prophylaxis Model*

AP administration before IDP in individuals at high IE-risk was associated with significant reduction in the odds of developing IE within 30-days (OR 0.49, 95% CI 0.29-0.85, p=0.01; Table 5). Sub-analysis demonstrated that this reduction was most marked following extractions (OR 0.15, 95% CI 0.04-0.55, p=0.004) and surgical procedures (OR 0.08, 95% CI 0.01-1.13, p=0.06), although the latter did not reach statistical significance.

AP was also associated with significant reduction in IE risk following IDP in those at moderate IE-risk (OR 0.34, 95% CI 0.14-0.88, p=0.025), but this association did not encompass specific procedures.

Using a 4-month case-period, AP was associated with significant reduction in IE risk in high (but not moderate or low/unknown) IE-risk individuals undergoing IDP, particularly extractions (Supplemental Table S11).

Discussion

There has been longstanding debate concerning the association between IDP and IE, and the efficacy of AP, owing to a lack of robust data consequent upon the infrequency of IE and need for very large clinical trials to demonstrate any effect. Herein, we report cohort and case-crossover studies that demonstrate an association between IDP and IE, and between AP and reduced risk of IE, in a 7.95 million population.

Case-crossover studies were first proposed to assess the effect of transient events in triggering subsequent outcomes while eliminating selection bias and confounding by each individual (with constant characteristics, such as oral-hygiene) serving as their own control.[20] Using this methodology, we identified significant association between IE-related hospital admissions and extractions or other oral surgical procedures during the preceding 30-days in those at high IE-risk, and a similar (albeit weaker) association using a 4-month case-period.

However, we cannot exclude the possibility that the pathology necessitating the procedure (rather than the procedure itself) conferred this increased risk.

In the case-crossover study, we identified a non-significant reduction in scaling procedures in the month before IE-admission that may explain why IDP overall were not significantly associated with IE. This finding was unexpected, since scaling is invasive and causes equivalent bacteremia to extractions.[25] A possible explanation is that patients who regularly attend a dentist or hygienist for scaling are protected from IE as a result of less gingival inflammation and better oral hygiene.[6,26] Conversely, those requiring extractions or surgical-procedures are likely to be infrequent dental attenders, and more prone to IE.[27] A previous case-control study identified a similar association between IE and extractions or surgical procedures, but not scaling.[28] Although scaling in regular dental attenders with good oral hygiene might not be a threat, deep scaling in those with poor oral hygiene could still pose a risk. Without further research, our data on scaling and endodontic procedures (where procedure numbers were low) are insufficient to recommend that AP cover should cease for these procedures.

We also observed a small but significant increase in extractions in the month before IE-admission in those at moderate IE-risk (that persisted using a 4-month case-period). Time course data suggest that the association between IDP and IE persists over a longer period (3-4-months) before IE-related hospital admission in those at moderate IE-risk, potentially reflecting a lower index of suspicion and delayed diagnosis in this cohort or more rapid progression of IE in patients at high-IE-risk.

Data concerning the interval between a precipitating event and IE are sparse. In one study, the majority of patients with streptococcal-IE following an invasive procedure developed symptoms in ≤7 days (many within hours),[29] whilst another study found that 75% of IE

diagnoses occurred within 4 weeks of symptoms (70% in <7 days). Although early diagnosis is more likely in staphylococcal-IE (particularly in high IE-risk patients),[30] 64% of oral streptococcal-IE was diagnosed early. These observations are consistent with our data and suggest that studies using longer case-periods may underestimate associations between IDP and IE, particularly in those at high IE-risk.

Importantly, we demonstrate that AP use for IDP (particularly extractions or other oral surgical-procedures) was associated with significantly reduced IE incidence in high IE-risk individuals, providing the first clinical evidence supporting the AHA [8,15] and ESC [31] recommendations that high IE-risk individuals should receive AP before IDP.

Paradoxically, the low use of AP for IDP in those at high IE-risk (32.6%), even for dental extractions (34.6%), that we detected in this study suggests that compliance with the AHA recommendations is concerningly low. However, these findings are similar to those of other recent US studies. Another study using US national data from the same source, found only 27% of IDP dental visits in high IE-risk patients were likely to have had AP cover, 9% were possibly covered and 64% were unlikely to have had AP cover,[16] while, a US Veterans' Administration study found only 15% of AP prescriptions were compliant with AHA guidelines.[32] Similarly, a large study using French national data found low compliance with ESC AP guidelines, with only 52,280 (50.1%) of 103,463 IDP performed in high risk patients covered by AP.[24] Smaller and earlier case-control and cohort studies also found low levels of compliance, with only 26%,[28] 27%,[33] 42%[34] or 50%[35] of invasive dental procedures covered in patients recommended for AP cover. These observations are also reflected in the views expressed in a recent large survey of US dentists. A majority (63.3%) agreed that "the patient's cardiologist or physician should decide if a patient needs antibiotic prophylaxis when undergoing invasive dental procedures", rather than the dentist. It also identified

considerable uncertainty about the appropriate use of AP, with only 30.1% strongly agreeing that "the patient groups who should receive AP were well defined and clear" and 29.8% that "dental procedures that require AP are well defined and clear".[36]

Previous IE case-crossover studies have been small and lacked statistical power.[22-24] One study of 648 high-risk patients with prosthetic valves detected a statistically significant association between IDP and IE, but failed to demonstrate an association between AP and IE-risk reduction.[24] The authors speculated this was because too few patients had received AP. Two further studies enrolling 170 [23] and 739 IE-cases [22] failed to demonstrate an association between IDP and IE, most likely due to failure to specifically evaluate those at high IE-risk. In addition, there have been 6 case-control or cohort studies, [24,28,33,35,37,38] five of which investigated the association between IDP and IE [24,28,33,37,38] (three reporting a positive association [28,33,37] even though they were small, underpowered and performed in populations where AP use could have reduced any association). Three studies assessed AP efficacy [24,28,35] and two reported a protective effect, despite being small and underpowered.[28,35] The largest cohort study demonstrated that AP was associated with a non-significant 60% reduction in the incidence of oral streptococcal-IE amongst prosthetic-valve patients 3-months following IDP (77/million procedures vs.195/million procedures, p=0·08).[24] Although IE incidence after IDP in high-risk individuals who did not receive AP was higher in our study (1,009/million procedures), this is unsurprising since, (A) we examined all high-risk patients (not just those with prosthetic valves), and (B) we assessed the 30-days immediately before IE admission when time-course data demonstrate strongest associations between IDP and IE. Focussing on this shorter 30-day exposure period, we demonstrated a similar (65%), but statistically significant, reduction in IE incidence associated with AP (to 358/million, p<0.0001). This effect persisted when we used a longer exposure period (4-months), albeit at a reduced level of statistical significance (p<0·05).

Frequent bacteremias caused by daily-activities, such as toothbrushing, flossing and mastication, has been proposed as an alternative explanation for oral bacteria-related IE.[7,15] Although these activities, like IDP, can cause bacteremia, we are unaware of data definitively linking them with subsequent IE. Whilst it is likely that both IDP and daily activities play a role, it remains speculative to say which is more important or accounts for the greater number of IE cases without definitive data. Frequency of bacteremia is only one factor - the size and duration of bacterial load, and varying tolerance of bacteremia in individuals with different levels of IE-risk, are also likely to play a part in determining whether an individual develops IE or not. Nonetheless, the association we demonstrate between IDP and IE (particularly in those at high IE-risk), and the ability of AP to mitigate this association, support current AHA[15] and ESC[31] recommendations. Our data also identified an association between extractions and IE in those at moderate-IE-risk in both the cohort and case-crossover analyses. However, we only identified a significant effect of AP in those at moderate-IE-risk undergoing IDP (that didn't extend to extractions or other subtypes of IDP) in the case-crossover study. This association, and effect, warrant further attention and investigation but may not alone be sufficient to warrant a change to current recommendations. Indeed, as they stand, they support the decision of the AHA and ESC guideline committees to focus their recommendations on the use of AP to prevent IE, on those at highest risk. [8,15,31]

Although we have focused on IDP and IE, we also acknowledge the importance of daily activities as potential causes of IE, particularly in those with poor oral hygiene.[6] Maintenance of good oral hygiene in those at increased IE-risk reduces the size and frequency of bacteramia associated with both daily activities and IDP, and is likely to be more important than AP alone in reducing the risk of oral streptococcal-IE.

Limitations

Misclassification is possible in administrative databases, particularly for challenging diagnoses such as IE. Nonetheless, a recent study reported 0.95 sensitivity (95% CI 0.86-0.99), 1.0 specificity (95% CI 1-1) and 0.6 PPV (95% CI 0.49-0.69) for identifying modified Duke-criteria definite IE using ICD-10 codes (equivalent to ICD-9 used in this study).[39] Administrative databases also afford larger sample sizes than clinical trials and capture the entire spectrum of IE-related admissions, thereby reducing potential referral bias. Nonetheless, sparse data bias could affect some small sub-group comparisons.

The MarketScan databases encompass a large sample of US employer-provided health insurance enrollees, however, our study only included those with medical, dental and prescription benefits cover. It is unlikely therefore to be representative of the entire US population, particularly those on Medicaid, with no health insurance cover or those whose health insurance is paid for in other ways. Although we adjusted for differences in age, sex, and comorbidities in the cohort study, other unadjusted differences or unmeasured confounders could have influenced outcomes. Reassuringly, however, the results of our cohort and case-crossover studies were consistent.

To increase our chance of demonstrating an association between IDP and IE, we would have preferred to restrict our analysis to the 30-40% of IE cases caused by oral streptococci. However, this was not possible since the MarketScan databases do not record microbiological data. We are unable, therefore, to comment on the nature or cause of the bacteraemia associated with each case of IE. Nevertheless, we were able to demonstrate a significant temporal association between IDP and IE.

Our study used CPT and ICD-9 codes to identify those at moderate or high IE-risk. However, records of predisposing procedures or conditions were incomplete before January 2000, resulting in potential misclassification of some high or moderate risk individuals as

low/unknown risk. This could explain the small but significant association between extractions or surgical-procedures and IE in those at low/unknown IE-risk.

Low levels of AP use in those at high IE-risk, and its continued use in those for whom it is no longer recommended, enabled our analysis of AP effects. However, some AP use in those at moderate or low/unknown IE-risk may have been in individuals with prosthetic joints (as recommended by many orthopedic surgeons). Combined with misclassification, this effect could explain the apparent adverse effect of AP on IE incidence in some of those at moderate or low/unknown IE-risk.

Varying dental AP-prescribing strategies (particularly use of a single prescription for multiple courses) made it difficult to verify whether a particular dental-procedure was covered. Even when a single AP-dose was prescribed immediately before a dental-procedure, we could not verify that it had been taken or that it was taken at the correct time i.e., 30-60 minutes before the procedure.[8,15] Similarly, even when there was no evidence of AP-prescribing, it is possible that a patient was provided AP by some other means. However, we have previously validated our methodology and demonstrated 88% (95% CI 82-92%) sensitivity and 96% (95% CI 94-97%) specificity for identification of AP prescribing and distinction from antibiotic use to treat infections.[16] Since 75% of AP prescriptions were for amoxicillin, there were insufficient data to allow comparison of the efficacy of different antibiotic regimes.

Conclusions

Using cohort and case-crossover methodologies in a population of almost 8 million people, we demonstrate associations between IDP (particularly extractions and surgical-procedures) and IE in those at high-IE-risk, and between AP use and reduced IE incidence. These findings provide evidence to support the current AHA and ESC recommendation that those at highest IE-risk should receive AP before IDP.[15,31]

Clinical Perspectives:

Competency in Medical Knowledge 1: An association between invasive dental procedures (IDP) and subsequent infective endocarditis (IE) has been assumed in individuals at high-risk from IE due to predisposing cardiac conditions, but evidence to support an association is sparse. Using two different methods, this study provided confirmatory evidence to support an association between IDP and IE, particularly for those undergoing dental extractions or oral surgery procedures.

Competency in Medical Knowledge 2: Antibiotic prophylaxis (AP) cover of IDP has been recommended to reduce the risk of IE in those at high-IE-risk. However, evidence to support the benefit of using of AP is lacking. This study demonstrated a reduced incidence of IE following IDP, particularly extractions and oral surgery procedures, covered by AP.

Translational Outlook: This study provides evidence to support the current American Heart Association recommendation that individuals at high-IE-risk should receive AP before invasive dental procedures.[15]

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Figure Legends

Figure 1. IDP incidence over 16-months before IE-admission and effect of AP.

Case-crossover study evaluating dental procedure incidence over the 16-months before IE-related hospital admission and the effect on incidence of antibiotic prophylaxis (AP).

Upper panels: Incidence of (A) invasive-dental procedures (IDP) (B) intermediate-dental procedures or (C) non-invasive dental procedures (non-IDP), or (D-F) IDP subtypes (scaling, extractions or surgical-procedures) in those at high, moderate or low/unknown IE-risk.

Lower panels: Use of antibiotic prophylaxis (AP) or no-AP on IDP incidence in those at (A) high, (B) moderate or (C) low/unknown IE-risk, and in those at high IE-risk undergoing (D) scaling (E) extractions or (F) surgical-procedures.

Central Illustration. IE-incidence within 1-month of dental-procedures performed with or without AP

Cohort study data quantifying the incidence of infective endocarditis (IE) within 1-month of dental procedures performed with or without antibiotic prophylaxis (AP) in individuals at high, moderate, or low/unknown IE-risk. Odds ratios (OR) show the reduction in IE incidence following dental procedures covered by AP (compared to no AP cover) for those situations where the reduction was significant. # = OR 0·38, 95% CI 0·22-0·62, p=0·002. § = OR 0·13, 95% CI 0·03-0·34, p<0·0001. ¶ = OR 0·09, 95% CI 0·01-0·35, p=0·002.

Table 1. Cardiac conditions used to classify individuals as being at high- or moderate-IE-risk

High-IE-Risk
Previous history of Infective endocarditis
Presence of prosthetic cardiac valve (including transcatheter valves)
Prosthetic material used for valve repair (including annuloplasty and percutaneous valve procedures using prosthetic material)
Unrepaired cyanotic congenital heart disease
Congenital heart disease in which palliative shunts or conduits were used
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by transcatheter during the first 6 months after the procedure only.
Moderate-IE-Risk
Rheumatic heart disease
Non-rheumatic valve disease (including mitral valve prolapse)
Congenital valve anomalies (including aortic stenosis)
Hypertrophic cardiomyopathy

Notes: Based on American Heart Association guidelines.[8,15] More extensive details of all diagnoses and procedures (including the relevant ICD-9-CM diagnosis and procedure codes and CPT procedure codes) included in the definition of those at High- or moderate-IE-risk are provided in Supplemental Tables S1 and S2.

Table 2. Examples of invasive-dental procedures (IDP), intermediate-dental procedures and non-invasive dental procedures (non-IDP)

Invasive-Dental Procedures (IDP) – procedures that should be covered by AP
Dental extractions (including surgical removal of impacted teeth and residual tooth roots)
Oral surgery procedures (including biopsies, periodontal surgery, implant surgery and other oral surgery and maxillofacial procedures involving oral soft tissues or bone)
Scaling procedures (including dental prophylaxis, periodontal scaling and root planning, periodontal maintenance and gingival irrigation or delivery of antimicrobial agents into the diseased gingival crevice)
Endodontic treatment (including pulpal debridement, endodontic treatment and re-treatment, apexification/recalcification, apicectomy and peri-radicular procedures)
Intermediate-Dental Procedures – procedures that may or may not require AP cover
Restorative dental procedures (fillings, inlays, crowns and bridges) and oral examination procedures that may on occasion involve gingival manipulation (when AP cover should be provided), but on other occasions do not involve gingival manipulation (when AP should not be provided).
Non-Invasive-Dental Procedures (non-IDP)
Oral examinations not involving manipulation of the gingival or apical tissues
Dental radiographs
Placement of removable prosthodontic or orthodontic appliances
Adjustment of orthodontic appliances and placement of orthodontic brackets

Notes: Based on American Heart Association guidelines.[8,15] More extensive details of the dental procedures (including the relevant American Dental Association CDT and ICD-9 procedure codes) used to define invasive-dental procedures (IDP), intermediate-dental procedures and non-IDP, and each category of IDP (extractions, oral surgical procedures, scaling and endodontic treatments) are provided in Supplemental Tables S1 and S2.

Table 3. Demographic and Descriptive Data for the Commercial/Medicare-Supplemental Cohort and Case-Crossover Study Populations

Cohort Study Patients	High IE-Risk	Moderate IE-Risk	Low/Unknown IE-Risk	All
Cohort Data by Patient	Patients (%)	Patients (%)	Patients (%)	Patients (%)
All Patients	36,773 (0.46%)	563,689 (7.09%)	7,617,072 (95.79%)	7,951,972 (100%)
- Age 18-34	2,816 (7.7%)	40,889 (7.3%)	2,405,202 (31.6%)	2,435,930 (30.6%)
- Age 35-44	2,425 (6.6%)	56,001 (9.9%)	1,538,657 (20.2%)	1,573,862 (19.8%)
- Age 45-54	5,124 (13.9%)	109,218 (19.4%)	1,728,720 (22.7%)	1,794,556 (22.6%)
- Age 55-64	10,076 (27.4%)	159,936 (28.4%)	1,381,733 (18.1%)	1,473,689 (18.5%)
- Age 65+	16,332 (44.4%)	197,645 (35.1%)	562,760 (7.4%)	673,935 (8.5%)
Male	22,072 (60.0%)	243,140 (43.1%)	3,545,565 (46.5%)	3,691,739 (46.4%)
Northeast region	44,546 (16.1%)	826,160 (19.0%)	8,696,064 (16.3%)	9,566,770 (16.5%)
North Central region	117,778 (42.7%)	1,439,931 (33.2%)	17,018,525 (31.8%)	18,576,234 (32.0%)
South region	77,718 (28.2%)	1,625,371 (37.4%)	17,926,644 (33.5%)	19,629,733 (33.8%)
West region	35,448 (12.9%)	443,637 (10.2%)	9,659,980 (18.1%)	10,139,065 (17.5%)
CCI = 0	13,612 (37.0%)	293,789 (52.1%)	6,411,896 (84.2%)	6,592,951 (82.9%)
CCI = 1	8,842 (24.0%)	126,154 (22.4%)	779,515 (10.2%)	851,694 (10.7%)
CCI = 2	5,642 (15.3%)	66,536 (11.8%)	249,642 (3.3%)	287,476 (3.6%)
CCI = 3+	8,677 (23.6%)	77,210 (13.7%)	176,019 (2.3%)	219,851 (2.8%)
Medicare	16,705 (45.4%)	202,580 (35.9%)	578,812 (7.6%)	692,270 (8.7%)
Cohort Data by Dental Proc. Type	Procedures (%)	Procedures (%)	Procedures (%)	Procedures (%)
All Dental Proc.	275,853 (0.48%)	4,341,528 (7.48%)	53,440,767 (92.05%)	58,058,148 (100%)
- Invasive (IDP)	180,991 (65.6%	2,871,532 (66.1%)	36,416,168 (68.1%)	39,468,691 (68.0%)
- Intermediate	46,715 (16.9%)	730,199 (16.8%)	8,908,468 (16.7%)	9,685,382 (16.7%)
- Non-Invasive (non-IDP)	48,147 (17.5%)	739,797 (17.0%)	8,116,131 (15.2%)	8,904,075 (15.3%)
Types of IDP				
- Scaling	160,999 (89.0%)	2,567,587 (89.4%)	32,899,901 (90.3%)	35,629,327 (90.3%)
- Extractions	11,483 (6.4%)	168,278 (5.9%)	1,942,999 (5.3%)	2,122,760 (5.4%)

- Endodontic treatment	6,621 (3.7%)	113,780 (4.0%)	1,344,624 (3.7%)	1,465,025 (3.7%)
- Surgery (oral or periodontal)	2,696 (1.5%)	46,699 (1.6%)	480,468 (1.3%)	529,863 (1.3%)
IE within 4 months of procedure	431 (0.156%)	572 (0.013%)	1,054 (0.002%)	2,057 (0.004%)
All dental proc. covered with AP	90,208 (32.7%)	421,710 (9.7%)	1,605,013 (3.0%)	2,116,931 (3.7%)
IDP covered with AP	59,045 (32.6%)	272,133 (9.5%)	1,047,154 (2.9%)	1,378,332 (3.5%)
Intermediate covered with AP	16,673 (35.7%)	77,405 (10.6%)	289,421 (3.3%)	383,499 (4.0%)
Non-IDP covered with AP	14,490 (30.1%)	72,172 (9.8%)	268,438 (3.3%)	355,100 (4.0%)
Types of IDP covered with AP				
- Scaling	52,073 (32.3%)	235,079 (9.2%)	887,700 (2.7%)	1,174,852 (3.3%)
- Extractions	3,970 (34.6%)	20,424 (12.1%)	89,212 (4.6%)	113,606 (5.4%)
- Endodontic treatment	2,398 (36.2%)	12,864 (11.3%)	54,238 (4.0%)	69,500 (4.7%)
- Surgery (oral or periodontal)	863 (32.0%)	4,981 (10.7%)	20,269 (4.2%)	26,113 (4.9%)

Case-Crossover IE-Cases	**High IE-Risk**	**Moderate IE-Risk**	**Low/Unknown IE-Risk**	**All**
All IE-Case-Crossover Cases	1,292 (34.2%) 35,135/million	831 (22.0%) 1,474/million	1,651 (43.8%) 217/million	3,774 (100%) 475/million
- Age 18-34	121 (1.7%)	21 (2.5%)	137 (8.3%)	279 (7.4%) 115/million
- Age 35-44	110 (8.5%)	39 (4.7%)	120 (7.3%)	269 (7.1%) 171/million
- Age 45-54	196 (15.2%)	118 (14.2%)	340 (20.6%)	654 (17.3%) 364/million
- Age 55-64	414 (32.07%)	220 (26.5%)	546 (33.1%)	1,180 (31.3%) 801/million
- Age 65+	451 (35.0%)	433 (52.1%)	508 (30.8%)	1392 (36.9%) 2,066/million
Male	808 (62.5%)	527 (63.4%)	1,003 (60.8%)	2,338 (62.0%) 633/million
CCI = 0	786 (60.8%)	598 (72.0%)	1,148 (69.5%)	2,532 (67.1%) 3,837/million
CCI = 1	182 (14.1%)	65 (7.8%)	185 (11.2%)	432 (11.5%) 506/million
CCI = 2	116 (9.0%)	50 (6.0%)	108 (6.5%)	274 (7.3%) 953/million
CCI = 3+	208 (16.1%)	118 (14.2%)	210 (12.7%)	536 (14.2%) 2,438/million

Notes: CCI = Charlson Comorbidity Index score for previous 12 months. IDP = invasive dental procedure, non-IDP = non-invasive dental procedure, proc. = procedure

Table 4. Cohort Study (a) IE-incidence within 30-days of a dental procedure, (b) IE-incidence following procedures with or without AP cover

(a) Cohort Dental Procedures Model						
Prior IE Risk	**High IE-Risk Individuals**		**Moderate IE-Risk Individuals**		**Low/Unknown IE-Risk Individuals**	
Type of Dental Proc.	Adjusted IE/million proc	Odds Ratio (95%CI)	Adjusted IE/million proc	Odds Ratio (95%CI)	Adjusted IE/million proc	Odds Ratio (95%CI)
All	467.6		24.2		3.8	
Non-Invasive (Non-IDP) (control)	434.6	1	25.6	1	5.1	1
Intermediate	294.5	0.65 (0.32-1.29)	17.5	0.69 (0.33-1.41)	3.8	0.77 (0.49-1.22)
Invasive (IDP)	521.1	1.17 (0.74-1.94)	25.5	1.03 (0.63-1.77)	3.5	0.73 (0.52-1.05)
- Scaling	204.9	0.46 (0.26-0.81)	20.9	0.85 (0.51-1.48)	2.7	0.57 (0.40-0.84)
- Extractions	4,112.0	9.22 (5.54-15.88), p<0.0001	93.0	3.25 (1.61-6.46), p=0.03	13.1	2.41 (1.44-3.95), p=0.02
- Endodontic	416.5	0.82 (0.16-2.55)	43.8	1.74 (0.54-4.49)	6.6	1.27 (0.57-2.54)
- Surgical	9,943.5	20.18 (11.22-36.74), p<0.0001	85.4	2.90 (0.76-8.16)	23.0	3.74 (1.79-7.15), p=0.02
(b) Cohort Antibiotic Prophylaxis Model						
Prior IE Risk	**High IE-Risk Individuals**		**Moderate IE-Risk Individuals**		**Low/Unknown IE-Risk Individuals**	

Type of Dental Procedure	Adjusted IE/million proc	Odds Ratio (95%CI)	Adjusted IE/million proc	Odds Ratio (95%CI)	Adjusted IE/million proc	Odds Ratio (95%CI)
Non-IDP - AP	747.4	1.65 (0.62-4.51)	8.2	0.23 (0.00-1.76)	14.0	1.80 (0.49-4.81)
Non-IDP – No AP	534.1		31.1		5.2	
Intermediate - AP	528.4	1.10 (0.37-3.55)	38.9	1.62 (0.31-5.84)	20.7	3.86 (1.35-9.23)
Intermediate – No AP	448.3		24.0		3.6	
IDP - AP	358.3	0.38 (0.22-0.62), p=0.002	29.1	1.32 (0.55-2.73)	14.2	3.29 (1.80-5.59)
IDP – No AP	1,009.3		22.6		3.1	
- Scaling - AP	330.1	2.00 (0.83-5.41)	29.8	1.64 (0.63-3.66)	13.4	3.84 (1.93-7.03)
- Scaling – No AP	152.4		18.2		2.2	
- Extract - AP	939.3	0.13 (0.03-0.34), p<0.0001	90.0	0.93 (0.10-4.12)	18.9	1.18 (0.13-4.62)
- Extract - No AP	8,967.9		104.5		14.6	
- Endo - AP	1,119.7	1.10 (0.09-13.70)	69.4	0.91 (0.01-11.45)	61.7	7.50 (1.35-30.24)
- Endo – No AP	1,286.0		61.4		6.9	
- Surgical - AP	1,916.1	0.09 (0.01-0.35), p=0.002	202.4	1.98 (0.01-43.60)	30.4	0.87 (0.01-6.91)
- Surgical – No AP	24,042.7		108.8		30.6	

Notes: IE rates were adjusted for differences in the age, sex and Charlson Comorbidity Index (CCI) score between the groups compared in each estimation and therefore differ between the

Dental Procedures Model (Table 3a) and the Antibiotic Prophylaxis Model (Table 3b). Surgical Procedures includes both oral surgery and periodontal surgery procedures. AP = antibiotic prophylaxis, Extract = extractions, Endo = endodontic, IE = infective endocarditis, IDP = invasive-dental procedure, non-IDP = non-invasive dental procedure, proc = procedure. Odds ratio significantly higher than control non-IDP value (dental procedures model) or AP significantly reduced IE incidence compared to no AP (antibiotic prophylaxis model), Bonferroni corrected p values shown where $p<0.05$ (other p values not significant).

Table 5. Case-Crossover Study (a) dental-procedure incidence in case- compared to control-period, (b) AP covered procedures compared to not covered procedures.

(a) Case-Crossover Dental Procedures Model. (All IE admissions = 3,774)									
Prior IE Risk	**High IE-Risk Admissions** (1,292)			**Moderate IE-Risk Admissions** (831)			**Low/Unknown IE-Risk Admissions** (1,651)		
Type of Dental Procedure	Proc/m in 1m Case Period	Proc/m in 12m Control Period	OR (95% CI)	Proc/m in 1m Case Period	Proc/m in 12m Control Period	OR (95% CI)	Proc/m in 1m Case Period	Proc/m in 12m Control Period	OR (95% CI)
Non-Invasive (non-IDP) - all	48	45.8	1.32 (0.97-1.78)	48	76.8	0.77 (0.57-1.03)	95	133.8	0.87 (0.71-1.08)
Intermediate - all	15	18.3	1.00 (0.59-1.70)	14	29.8	0.57 (0.33-0.97)	37	52.2	0.86 (0.62-1.21)
Invasive (IDP) - all	87	55.2	2.00 (1.59-2.52), p=0.002	61	89.3	0.86 (0.66-1.12)	114	152.2	0.93 (0.77-1.13)
Type of invasive-dental procedure (IDP)									
Scaling	27	48.4	0.69 (0.47-1.02)	42	76.9	0.69 (0.51-0.95)	78	130.4	0.75 (0.59-0.94)
Extractions	44	5.2	11.08 (7.34-16.74), p<0.0001	13	9	1.66 (0.93-2.98)	23	14.7	1.79 (1.15-2.77)
Endodontic	2	1.9	1.20 (0.28-5.17)	4	3.2	1.60 (0.56-4.56)	8	5.9	1.82 (0.86-3.83)
Surgical	25	0.6	50.77 (20.79-123.98), p<0.0001	3	1.8	1.90 (0.56-6.47)	9	3.1	3.50 (1.66-7.36)

(b) Case-Crossover Antibiotic Prophylaxis Model. (All IE admissions = 3,774)									
Prior IE Risk	**High IE-Risk Admissions** (1,292)			**Moderate IE-Risk Admissions** (831)			**Low/Unknown IE-Risk Admissions** (1,651)		
Type of Dental Procedure	Proc/m in 1m Case Period	Proc/m in 12m Control Period	OR (95% CI)	Proc/m in 1m Case Period	Proc/m in 12m Control Period	OR (95% CI)	Proc/m in 1m Case Period	Proc/m in 12m Control Period	OR (95% CI)
Non-IDP - AP	22	16.2	1.83 (1.16-2.88)	2	14.7	0.16 (0.04-0.65)	9	8.6	1.32 (0.66-2.65)
Non-IDP - No AP	26	29.8	1.06 (0.71-1.59)	46	62.2	0.92 (0.68-1.24)	86	125.2	0.84 (0.67-1.05)
Non-IDP AP v No AP			1.71 (0.93-3.15)			0.18 (0.04-0.74)			1.57 (0.76-3.26)
Intermediate – AP	7	7.0	1.24 (0.57-2.71)	2	5.8	0.41 (0.10-1.69)	7	3.9	2.37 (1.04-5.36)
Intermediate - No AP	8	11.3	0.86 (0.42-1.76)	12	24.1	0.60 (0.34-1.08)	30	48.3	0.75 (0.52-1.09)
Intermediate AP v No AP			1.45 (0.50-4.19)			0.68 (0.15-3.14)			3.14 (1.28-7.70)
IDP – AP	19	20.4	1.20 (0.74-1.93)	5	18.1	0.34 (0.14-0.84)	12	10.3	1.45 (0.79-2.66)
IDP - No AP	68	34.8	2.44 (1.87-3.18), p=0.006	56	71.2	1.00 (0.76-1.31)	102	141.8	0.89 (0.73-1.10)
IDP AP v No AP			0.49 (0.29-0.85), p=0.01			0.34 (0.14-0.88), p=0.025			1.62 (0.86-3.07)
Type of Invasive-Dental Procedure (IDP)									
Scaling - AP	14	17.8	1.01 (0.59-1.75)	4	15.2	0.33 (0.12-0.89)	9	8.2	1.36 (0.68-2.71)
Scaling - No AP	13	30.7	0.52 (0.30-0.90)	38	61.8	0.79 (0.57-1.09)	69	122.2	0.71 (0.55-0.90)

Scaling AP v No AP			1.95 (0.89-4.25)			0.42 (0.15-1.20)			1.92 (0.92-4.00)
Extractions - AP	3	1.9	2.15 (0.62-7.47)	1	2.0	0.57 (0.08-4.25)	1	1.5	0.71 (0.09-5.31)
Extractions - No AP	41	3.2	15.26 (9.62-24.21), p<0.0001	12	7.0	1.98 (1.07-3.67)	22	13.2	1.92 (1.22-3.02)
Extractions AP v No AP			0.15 (0.04-0.55), p=0.004			0.29 (0.04-2.35)			0.37 (0.05-2.91)
Endodontic – AP	1	0.8	1.72 (0.21-14.09)	0	0.7	0 (0-Inf)	2	0.6	12.00 (1.69-85.19)
Endodontic - No AP	1	1.2	0.92 (0.12-7.11)	4	2.6	2.01 (0.69-5.81)	6	5.3	1.41 (0.61-3.30)
Endodontic AP v No AP			1.87 (0.10-34.97)			0 (0-Inf)			8.49 (1.00-71.81)
Surgical – AP	1	0.2	6.00 (0.54-66.17)	0	0.6	0 (0-Inf)	0	0.4	0 (0-Inf)
Surgical - No AP	24	0.4	73.34 (25.39-211.82), p<0.0001	3	1.2	2.78 (0.79-9.79)	9	2.7	4.02 (1.89-8.57)
Surgical AP v No AP			0.08 (0.01-1.13)			0 (0-Inf)			0 (0-Inf)

Notes: Case-Crossover Study (a) dental procedure incidence in the 1-month case period (months 0-1 before IE admission) and the 12-month control period (months 2-13 before IE admission), (b) Antibiotic Prophylaxis Model - comparing antibiotic prophylaxis (AP) cover with no AP-cover of dental procedures in the case and control periods. Surgical Procedures includes both oral surgery and periodontal surgery procedures. AP = Antibiotic Prophylaxis, IE = Infective Endocarditis, Inf = infinity, IDP = invasive dental procedure, m = month, non-IDP = non-invasive dental procedure, OR = Odds ratio, proc = procedures, v = versus (compared with). OR for case period significantly higher than for control period (dental procedures model) or

AP odds significantly reduced when compared with No AP odds (antibiotic prophylaxis model). Bonferroni corrected p values shown only where $p<0.05$. Other p values not significant.