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ORIGINAL INVESTIGATIONS

Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive Dental Procedures

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ABSTRACT

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

OBJECTIVES The purpose of this study was to investigate any association between IDPs and IE, and the effectiveness of AP in reducing this.

METHODS We performed a case-crossover analysis and cohort study of the association between IDPs and IE, and AP efficacy, in 7,951,972 U.S. subjects with employer-provided Commercial/Medicare-Supplemental coverage.

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 IDPs 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 IDPs (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 the American Heart Association, and other, recommendations that those at high IE risk should receive AP before IDP. (J Am Coll Cardiol 2022;80:1029-1041)

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 (IDPs) has long been postulated to explain the 30% to 40% of IE cases caused by oral streptococci.[4] Consequently, the American Heart Association (AHA) has issued guidelines on

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ABBREVIATIONS AND ACRONYMS

ADA = American Dental Association

AHA = American Heart Association

AP = antibiotic prophylaxis

ESC = European Society of Cardiology

ICD = International Classification of Diseases

IDP = invasive dental procedure

IE = infective endocarditis

antibiotic prophylaxis (AP) to prevent IE in patients undergoing IDPs 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 IDPs and IE has been questioned, and routine daily activities (eg, 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 IDPs. In the UK, it was recommended that AP cease completely.[10] The aim of this study, therefore, was to identify any temporal association between IDPs and IE, and any effect of AP on IE incidence.

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METHODS

DATA SOURCE. The study was conducted in a U.S. health care population and reported following STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) 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 the Supplemental Appendix for more details on these). Because MarketScan databases are statistically deidentified in compliance with the Health Insurance Portability and Accountability Act of 1996 and meet its limited-use data set criteria, they are not subject to Institutional Review Board review.[12] All enrollees ≥18 years of age with >16 months linked data (January 2000 to August 2015) were included. Data after 2015 was not included because of changes in the way diagnosis and procedure codes were recorded in the United States after this date (see the Supplemental Appendix for more details)

IE ADMISSIONS AND IE RISK STRATIFICATION. IE-related hospital admissions were identified using primary or secondary International Classification of Diseases-9th Revision (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 readmissions by excluding IE admissions <6 months apart.[14] ICD-9 or Current Procedural Terminology diagnosis/procedural codes were used to identify individuals as previously being at high or moderate IE risk (**Table 1**, Supplemental Tables 1 and 2), 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 Common Dental Terminology or ICD-9 procedure codes were used to classify dental procedures into the following: 1) IDPs—those dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa (eg, dental extractions, oral surgical procedures, scaling [supragingival or subgingival]), and endodontic procedures, ie, those dental procedures that the AHA guidelines recommend "should" be covered by AP[8,15]; 2) intermediate dental procedures, eg, 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; and 3) non-IDPs, eg, routine dental examination, dental radiographs, or placement of removable prosthodontic or orthodontic appliances, for which AP is not recommended (**Table 2**, Supplemental Table 3).[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. IDPs were also subanalyzed using codes specific for dental extractions, oral surgical procedures, scaling, and endodontic procedures (**Table 2**, Supplemental Table 3).

Prescription benefits data were used to identify if AP was prescribed for each dental visit using previously validated methodology[16] (see also the 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 before 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 procedures, and procedures with or without AP

cover. Crude incidence (Supplemental Tables 4 and 5) was adjusted for differences in age, sex, and Charlson comorbidity index 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 subanalyses) when using traditional maximum likelihood logistic regression that can lead to the nonconvergence of regression estimates.[18,19] The odds of IE following an IDP (including subtypes) 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 IDPs was quantified over the 16 months before admission and plotted to identify the timing of any association with IE. Accordingly, incidence of IDPs, extractions, and surgical procedures peaked in the 30 days before IE admission in those at high IE risk (**Figure 1**, Supplemental Figure 1). 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**).

TABLE 1 Cardiac Conditions Used to Classify Individuals as Being at High or Moderate IE Risk

High IE risk
Previous history of IE
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 mo after the procedure only.
Moderate IE risk
Rheumatic heart disease
Nonrheumatic valve disease (including mitral valve prolapse)
Congenital valve anomalies (including aortic stenosis)
Hypertrophic cardiomyopathy

Based on American Heart Association guidelines.[8,15] More extensive details of all diagnoses and procedures (including the relevant International Classification of Diseases-Ninth Revision-Clinical Modification diagnosis and procedure codes and Current Procedural Terminology procedure codes) included in the definition of those at high or moderate infective endocarditis (IE) risk are provided in Supplemental Tables 1 and 2.

The odds of developing IE were nonsignificantly higher following IDPs compared with non-IDP procedures in high-IE-risk patients (**Table 4**). However, subanalysis of IDPs 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.

AP model. AP was prescribed to cover 32.6%, 9.5%, and 2.9% of IDPs in those at high, moderate, and low/unknown IE risk, respectively (**Table 3**). Amoxicillin 2 g accounted for 75% of AP prescriptions, followed by clindamycin 600 mg (17%), clarithromycin 500 mg (4%), azithromycin 500 mg (3%), and cephalexin 2 g (1%). AP cover for IDPs 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 with 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, Central Illustration**). AP cover was of no significant benefit following other IDPs or in individuals at moderate or low/unknown IE risk.

TABLE 2 Examples of IDP, Intermediate Dental Procedures, and Non-IDP

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 retreatment, 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-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

Based on American Heart Association guidelines.[8,15] More extensive details of the dental procedures (including the relevant American Dental Association Common Dental Terminology 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 1 and 2.

A similar pattern of associations between IDPs (particularly extractions and surgical procedures) and IE, and of AP efficacy was observed over a 4-month exposure period, albeit with a smaller effect size (Supplemental Tables 6 to 9).

CASE-CROSSOVER STUDY. Dental procedures model. Within the 3,774 IE admissions cohort, the incidence of IDPs, extractions, and surgical procedures peaked in the 30 days before IE admission for those at high IE risk (**Figure 1**, Supplemental Figure 1). In this group, there was also a significant positive association between IDPs (but not intermediate-dental procedures or non-IDPs) 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). Subanalysis 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 IDPs and IE for those at moderate IE risk, but there was 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 Study Limitations section).

The high-risk group demonstrated a similar pattern of associations in the 4-month case-period analysis (Supplemental Table 10). 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; $P = 0.003$).

AP model. AP administration before IDPs 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**). Subanalysis 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 IDPs 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 IDPs, particularly extractions (Supplemental Table 11).

DISCUSSION

There has been longstanding debate concerning the association between IDPs and IE, and the efficacy of AP, because of 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 IDPs 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 nonsignificant reduction in scaling procedures in the month before IE admission that may explain why IDPs overall were not significantly associated with IE. This finding was unexpected, because 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 IDPs 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.

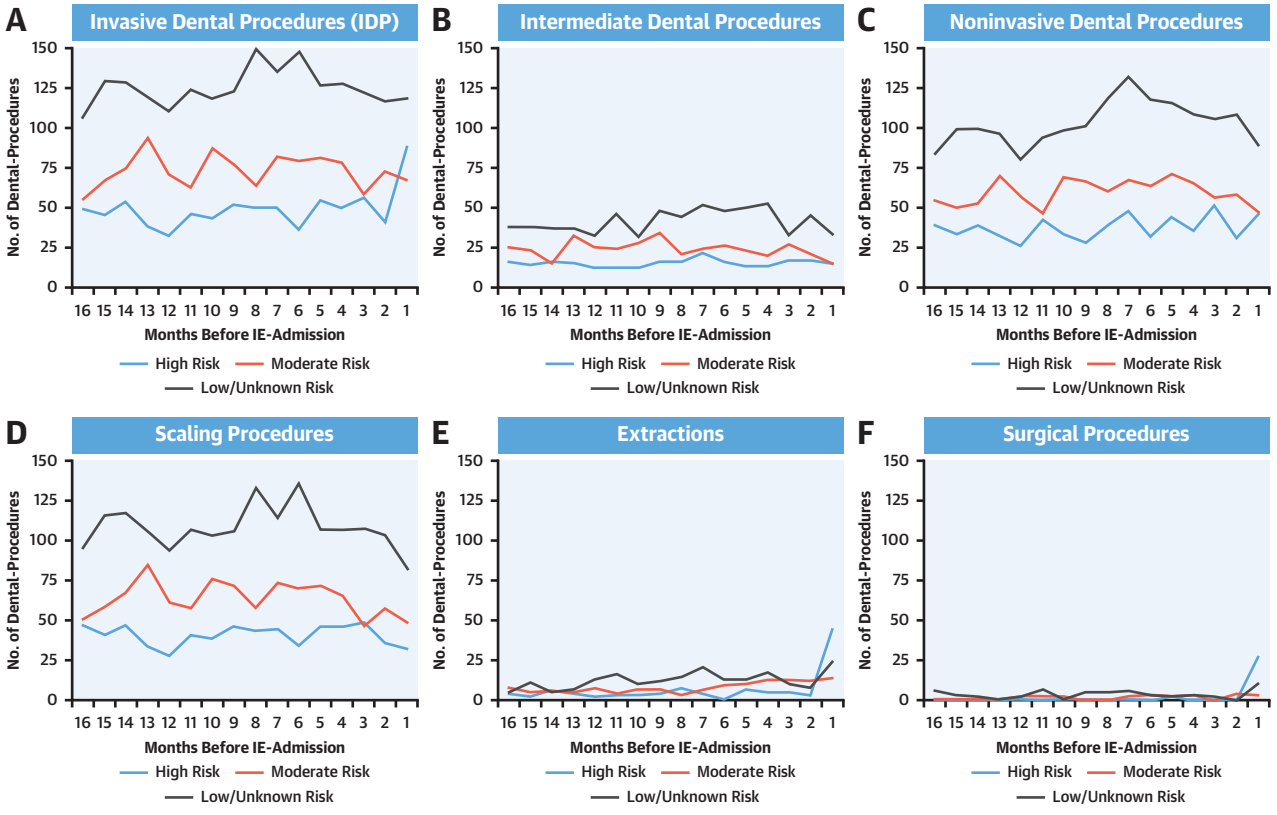
Data concerning the interval between a precipitating event and IE are sparse. In 1 study, the majority of patients with streptococcal IE following an invasive procedure developed symptoms in ≤7 days (many within hours),[29] and another study found that 75% of IE diagnoses occurred within 4 weeks of symptoms (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 IDPs and IE, particularly in those at high IE risk.

Importantly, we demonstrate that AP use for IDPs (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 IDPs.

Paradoxically, the low use of AP for IDPs 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 U.S. studies. Another study using U.S. 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] and a U.S. Veterans' Administration study found that 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 IDPs 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 U.S. 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 IDPs and IE, but failed to demonstrate an association between AP and IE risk reduction.[24] The authors speculated that 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 IDPs and IE, most likely because of 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] 5 of which investigated the association between IDPs and IE[24,28,33,37,38] (3 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 2 reported a protective effect, despite being small and underpowered.[28,35] The largest cohort study demonstrated that AP was associated with a nonsignificant 60% reduction in the incidence of oral streptococcal IE among prosthetic-valve patients 3 months following IDPs (77/million procedures vs 195/million procedures; $P = 0.08$).[24] Although IE incidence after IDPs in high-risk individuals who did not receive AP was higher in our study (1,009/million procedures), this is unsurprising because of the following: 1) we examined all high-risk patients (not just those with prosthetic valves); and 2) we assessed the 30 days immediately before IE admission when time-course

FIGURE 1 **IDP Incidence Over 16 Months Before IE Admission and Effect of AP**



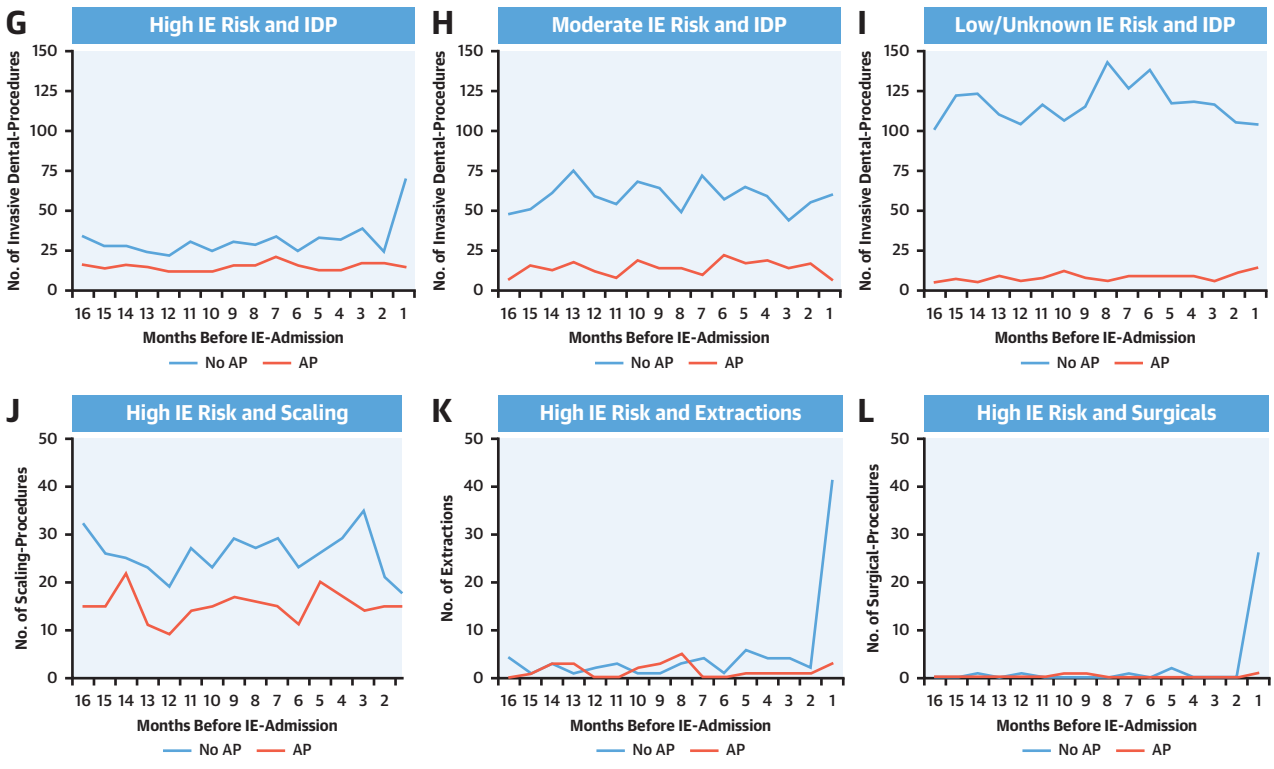
Case-crossover study evaluating dental procedure incidence over the 16 months before IE-related hospital admission and the effect on incidence of antibiotic prophylaxis (AP). Incidence of **(A)** invasive dental procedures (IDPs), **(B)** intermediate dental procedures, or **(C)** noninvasive dental procedures (non-IDPs), or **(D to F)** IDP subtypes (scaling, extractions, or surgical procedures) in those at high, moderate, or low/unknown IE risk. Use of antibiotic prophylaxis (AP) or no-AP on IDP incidence in those at **(G)** high, **(H)** moderate, or **(I)** low/unknown IE risk, and in those at high IE risk undergoing **(J)** scaling, **(K)** extractions, or **(L)** surgical procedures.

Continued on the next page

data demonstrate the strongest associations between IDPs and IE. Focusing 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 IDPs, can cause bacteremia, we are unaware of data definitively linking them with subsequent IE. Although it is likely that both IDPs 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 1 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 IDPs 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 IDPs (that did not extend to extractions or other subtypes of IDPs) in the case-crossover study. This association, and effect, warrant further attention

FIGURE 1 Continued



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 IDPs 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 bacteremia associated with both daily activities and IDPs, and is likely to be more important than AP alone in reducing the risk of oral streptococcal IE.

STUDY 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 positive predictive value (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 subgroup comparisons.

The MarketScan databases encompass a large sample of U.S. employer-provided health insurance enrollees; however, our study only included those with medical, dental, and prescription benefits coverage. It is unlikely, therefore, to be representative of the entire U.S. population, particularly those on Medicaid, with no health insurance coverage 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 IDPs and IE, we would have preferred to restrict our analysis to the 30% to 40% of IE cases caused by oral streptococci. However, this was not possible because the MarketScan databases do not record microbiological data. We are unable, therefore, to comment on the nature or cause of the bacteremia associated with each case of IE. Nevertheless, we

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				
All patients	36,773 (0.46)	563,689 (7.09)	7,617,072 (95.79)	7,951,972 (100.0)
Age, y				
18-34	2,816 (7.7)	40,889 (7.3)	2,405,202 (31.6)	2,435,930 (30.6)
35-44	2,425 (6.6)	56,001 (9.9)	1,538,657 (20.2)	1,573,862 (19.8)
45-54	5,124 (13.9)	109,218 (19.4)	1,728,720 (22.7)	1,794,556 (22.6)
55-64	10,076 (27.4)	159,936 (28.4)	1,381,733 (18.1)	1,473,689 (18.5)
≥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)
1	8,842 (24.0)	126,154 (22.4)	779,515 (10.2)	851,694 (10.7)
2	5,642 (15.3)	66,536 (11.8)	249,642 (3.3)	287,476 (3.6)
≥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 procedure type				
All dental procedures	275,853 (0.48)	4,341,528 (7.48)	53,440,767 (92.05)	58,058,148 (100.0)
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)
Noninvasive (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 procedures 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				
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 (100.0) 475/million
Age, y				
18-34	121 (1.7)	21 (2.5)	137 (8.3)	279 (7.4) 115/million
35-44	110 (8.5)	39 (4.7)	120 (7.3)	269 (7.1) 171/million
45-54	196 (15.2)	118 (14.2)	340 (20.6)	654 (17.3) 364/million
55-64	414 (32.07)	220 (26.5)	546 (33.1)	1,180 (31.3) 801/million
≥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
1	182 (14.1)	65 (7.8)	185 (11.2)	432 (11.5) 506/million
2	116 (9.0)	50 (6.0)	108 (6.5)	274 (7.3) 953/million
≥3	208 (16.1)	118 (14.2)	210 (12.7)	536 (14.2) 2,438/million

Values are n of patients or procedures (%) or n (%) n/million.
CCI = Charlson Comorbidity Index score for previous 12 months; IDP = invasive dental procedure.

TABLE 4 Cohort Study IE Incidence Within 30 Days of a Dental Procedure and Following Procedures With or Without AP Cover

	Prior IE Risk					
	High-IE-Risk Individuals		Moderate-IE-Risk Individuals		Low/Unknown-IE-Risk Individuals	
Type of Dental Procedure	Adjusted IE/Million Procedures	OR (95% CI)	Adjusted IE/Million Procedures	OR (95% CI)	Adjusted IE/Million Procedures	OR (95% CI)
Cohort dental procedures model						
All	467.6		24.2		3.8	
Noninvasive (non-IDP) (control)	434.6	1.00	25.6	1.00	5.1	1.00
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); $P = 0.02$
Cohort antibiotic prophylaxis model						
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)
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)
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)
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)
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)
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)
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)
No AP	24,042.7		108.8		30.6	

Infective endocarditis (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 and the antibiotic prophylaxis (AP) model (Table 3). Surgical procedures includes both oral surgery and periodontal surgery procedures. ORs significantly higher than control non- invasive dental procedure (IDP) value (dental procedures model) or AP significantly reduced IE incidence compared with no AP (antibiotic prophylaxis model), Bonferroni corrected *P* values shown where $P < 0.05$ (other p values not significant).

Extract = extractions; Endo = endodontic.

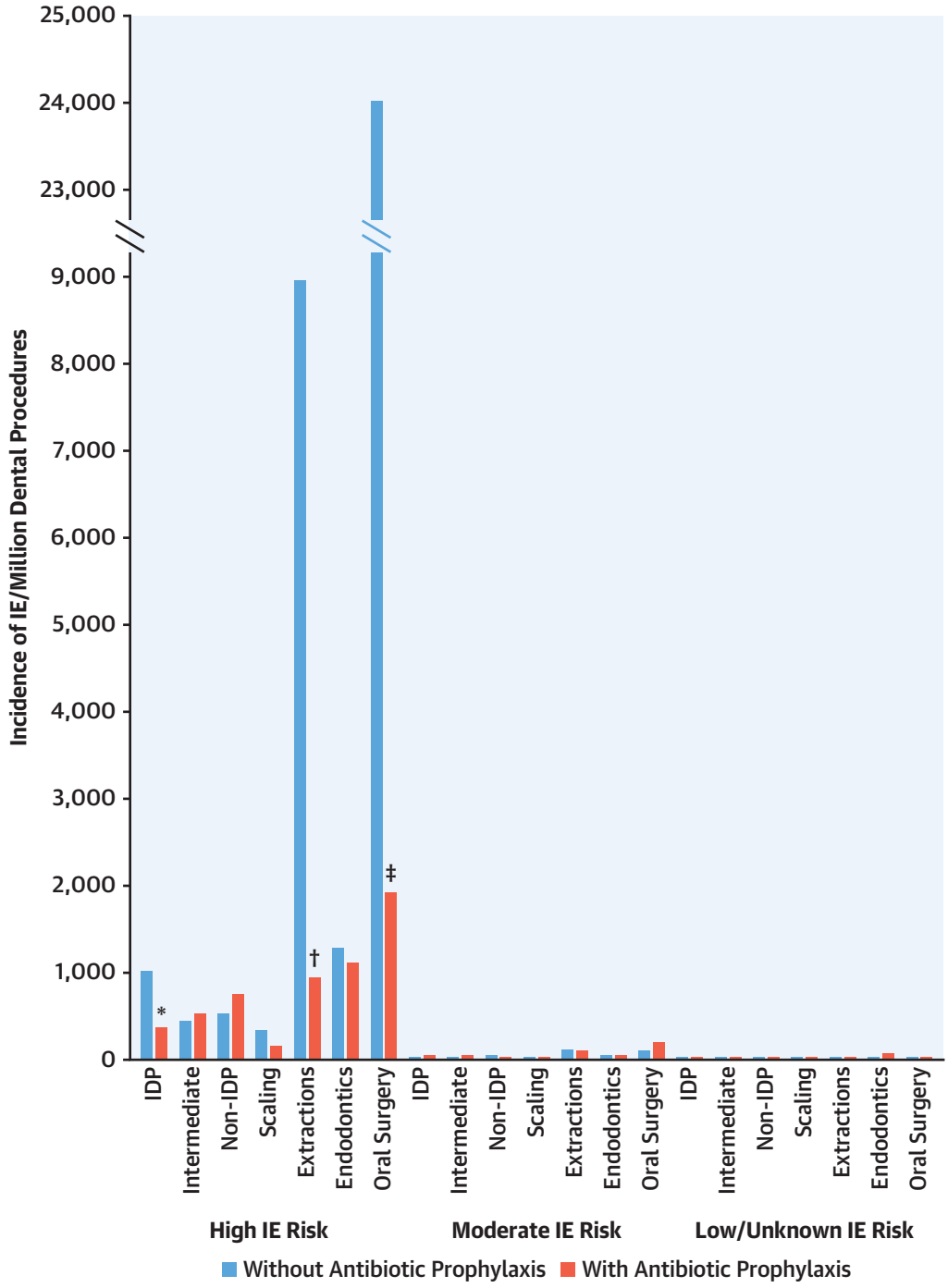
were able to demonstrate a significant temporal association between IDPs and IE.

Our study used Current Procedural Terminology 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-risk 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)

CENTRAL ILLUSTRATION **Infective Endocarditis Incidence Within 1 Month of Dental Procedures Performed With or Without Antibiotic Prophylaxis**



Thornhill MH, et al. J Am Coll Cardiol. 2022;80(11):1029-1041.

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. ORs 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; $P = 0.002$. IDP = invasive dental procedure.

TABLE 5 Case-Crossover Study Dental Procedure Incidence in Case Compared With Control Period, and AP Covered Procedures Compared With Not Covered Procedures

	Prior IE Risk								
	High-IE-Risk Admissions (n = 1,292)			Moderate-IE-Risk Admissions (n = 831)			Low/Unknown-IE-Risk Admissions (n = 1,651)		
Type of Dental Procedure	Procedures/ Month in 1-mo Case Period	Procedures/ Month in 12-mo Case Period	OR (95% CI)	Procedures/ Month in 1-mo Case Period	Procedures/ Month in 12-mo Case Period	OR (95% CI)	Procedures/ Month in 1-mo Case Period	Procedures/ Month in 12-mo Control Period	OR (95% CI)
Case-crossover dental procedures model (all IE admissions = 3,774)									
Noninvasive (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 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)
Case-crossover antibiotic prophylaxis model (all IE admissions = 3,774)									
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)
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)
AP vs 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)
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)
AP vs 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)
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)
AP vs 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 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)
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)
AP vs 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)
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)
AP vs 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)
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)
AP vs 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)
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)
AP vs No AP			0.08 (0.01-1.13)			0 (0-Inf)			0 (0-Inf)

Case-crossover study 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), and AP model comparing 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. OR for case period significantly higher than for control period (dental procedures model) or AP odds significantly reduced when compared with no AP odds (AP model). Bonferroni corrected *P* values shown only where $P < 0.05$. Other *P* values not significant.

Inf = infinity; other abbreviations as in Table 4.

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, ie, 30 to 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] Because 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 IDPs (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 IDPs.[15,31]

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In both a case-crossover analysis and a cohort study, there was a temporal association between IDPs (particularly extractions and oral surgical procedures) and subsequent IE in patients at high risk for developing IE, and AP was associated with a lower incidence of postprocedural IE. These data support recommendations that patients at high risk for IE receive AP before IDPs.

TRANSLATIONAL OUTLOOK: Having demonstrated an association between invasive dental procedures and IE, studies are now needed to investigate the risk of oral bacterial IE posed by daily oral activities, eg, toothbrushing, flossing, and chewing, particularly in those with poor oral hygiene.

REFERENCES

1. Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet*. 2015;387:882–893.

2. Jensen AD, Ostergaard L, Petersen JK, et al. Temporal trends of mortality in patients with infective endocarditis: a nationwide study. *Eur Heart J Qual Care Clin Outcomes*. Published online March 8, 2022. https://doi.org/10.1093/ehjqcco/qcac011.

3. Thornhill MH, Jones S, Prendergast B, et al. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. *Eur Heart J*. 2018;39:586–595.

4. Lewis T, Grant R. Observations relating to subacute infective endocarditis. *Heart*. 1923;10:21–77.

5. Jones TD, Baumgartner L, Bellows MT, et al. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. *Circulation*. 1955;11:317–320.

6. Lockhart PB, Brennan MT, Thornhill M, et al. Poor oral hygiene as a risk factor for infective endocarditis-related bacteremia. *J Am Dent Assoc*. 2009;140:1238–1244.

7. Roberts GJ. Dentists are innocent! "Everyday" bacteremia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. *Pediatr Cardiol*. 1999;20:317–325.

8. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736–1754.

9. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J*. 2009;30:2369–2413.

10. National Institute for Health and Care Excellence (NICE). Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. Clinical guideline [CG64]. Accessed March 2008. http://www.nice.org.uk/guidance/cg64

11. STROBE. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. Accessed May 6, 2022. https://www.strobe-statement.org

12. U.S. Department for Health and Human Services. Health Insurance Portability and Accountability Act 1996. Accessed April 6, 2022. https://www.hhs.gov/hipaa/index.html

13. Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. *BMJ*. 2011;342:d2392.

14. Chu VH, Sexton DJ, Cabell CH, et al. Repeat infective endocarditis: differentiating relapse from reinfection. *Clin Infect Dis*. 2005;41:406–409.

15. Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of viridians group streptococcal infective endocarditis: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e963–e978.

16. Thornhill MH, Gibson TB, Durkin MJ, et al. Prescribing of antibiotic prophylaxis to prevent infective endocarditis. *J Am Dent Assoc*. 2020;151:835–845.

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.

18. Doerken S, Avalos M, Lagarde E, Schumacher M. Penalized logistic regression with low prevalence exposures beyond high dimensional settings. *PLoS One*. 2019;14:e0217057.

19. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1991;80:27–38.

20. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.

21. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol*. 1995;142:91–98.

22. Chen PC, Tung YC, Wu PW, et al. Dental procedures and the risk of infective endocarditis. *Medicine (Baltimore)*. 2015;94:e1826.

23. Porat Ben-Amy D, Littner M, Siegman-Igra Y. Are dental procedures an important risk factor for infective endocarditis? A case-crossover study. *Eur J Clin Microbiol Infect Dis*. 2009;28:269–273.

24. Tubiana S, Blotiere PO, Hoen B, et al. Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and a case crossover study. *BMJ*. 2017;358:j3776.

25. Reis LC, Rocas IN, Siqueira JF Jr, et al. Bacteremia after supragingival scaling and dental extraction: Culture and molecular analyses. *Oral Diseases*. 2018;24:657–663.

26. Smiley CJ, Tracy SL, Abt E, et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. *J Am Dent Assoc*. 2015;146:525–535.

27. Talakey AA, Bernabe E. Long-term regular dental attendance and tooth retention among British adults: a cross-sectional analysis of national survey data. *Int J Dent Hyg*. 2019;17:64–70.

28. Van der Meer JT, Van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. *Lancet*. 1992;339:135–139.

29. Starkebaum M, Durack D, Beeson P. The "incubation period" of subacute bacterial endocarditis. *Yale J Biol Med*. 1977;50:49–58.

30. N'Guyen Y, Duval X, Revest M, et al. Time interval between infective endocarditis first symptoms and diagnosis: relationship to infective endocarditis characteristics, microorganisms and prognosis. *Ann Med*. 2017;49:117–125.

31. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128.

32. Suda KJ, Fitzpatrick MA, Gibson G, et al. Antibiotic prophylaxis prescriptions prior to dental visits in the Veterans' Health Administration (VHA), 2015-2019. *Infect Control Hosp Epidemiol*. 2022:1–10.

33. Lacassin F, Hoen B, Leport C, et al. Procedures associated with infective endocarditis in adults. A case control study. *Eur Heart J*. 1995;16:1968–1974.

34. Horstkotte D, Rosin H, Friedrichs W, Loogen F. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. *Eur Heart J*. 1987;8:379–381.

35. Imperiale TF, Horwitz RI. Does prophylaxis prevent postdental infective endocarditis? A controlled evaluation of protective efficacy. *Am J Med*. 1990;88:131–136.

36. Lockhart PB, Thornhill MH, Zhao J, et al. Prophylactic antibiotic prescribing in dental practice: findings from a National Dental Practice-Based Research Network questionnaire. *J Am Dent Assoc*. 2020;151:770–781.e6.

37. Duval X, Millot S, Chirouze C, et al. Oral streptococcal endocarditis, oral hygiene habits, and recent dental procedures: a case-control study. *Clin Infect Dis*. 2017;64:1678–1685.

38. Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. *Ann Intern Med*. 1998;129:761–769.

39. Tan C, Hansen M, Cohen G, Boyle K, Daneman N, Adhikari NK. Accuracy of administrative data for identification of patients with infective endocarditis. *Int J Cardiol*. 2016;224:162–164.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.