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Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive-Dental Procedures

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Abbreviations:

ADA = American Dental Association
AHA = American Heart Association
AP = Antibiotic prophylaxis
CCI = Charlson Comorbidity Index
CPT = Current Procedural Terminology
CDT = Common Dental Terminology
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

Supplemental-Methods:

Data Source:

The IBM® MarketScan® databases integrate de-identified patient-level health-data across a series of healthcare related databases. We linked data, including prescription benefits data, from the MarketScan® Commercial (private health insurance cover provided mainly by employers as a benefit for their employees), Medicare-Supplemental (top up health insurance cover provided by employers for their retirees to improve the basic cover provided by Medicare) and Dental (insurance cover for private dental care) databases.[1,2] Because the MarketScan® data are deidentified in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and meet limited-use dataset criteria, studies using the data are exempt IRB review.[3] All enrollees over 18, with more than 16 months of linked medical, dental and prescribing data from January 2000 through August 2015 were included.

We only included data until August 215, because in October 2015 the US transitioned from using ICD-9 to ICD-10 diagnosis and procedure codes. This change caused major disruption to the recording of diagnoses and procedures because ICD-10 codes don't always translate directly into corresponding ICD-9 codes. Indeed, numerous studies using US coding data that spanned the changeover period have reported significant disruption to the recording of the incidence or prevalence of specific diagnoses.[4-6] Hence, to avoid this disruption and to ensure data integrity and continuity we confined our study to the period before October 2015. Changes to the recording of CPT (medical procedure codes) and CDT (dental procedure codes) after October 2015 caused further disruption that could have affected the data used in this study.

IE admissions and IE-risk stratification:

ICD-9 or CPT diagnosis/procedure codes were used to identify individuals as being at high-IE-risk (Supplemental Table S1) or moderate-IE-risk (Supplemental Table S2) as defined by the AHA guidelines.[7,8] Individuals not so identified were considered at low/unknown-IE-risk.

IE-hospital-admissions were identified using ICD-9 421.0, 421.1 or 421.9, primary or secondary discharge diagnosis codes. Previously described methods were used to ensure single continuous IE-episodes were only counted once.[9] After IE-admission, enrollees were considered at high-risk for future IE episodes. New episodes were distinguished from readmissions by only accepting IE-admissions >6 months apart.[10,11]

Invasive Dental-Procedures:

The American Dental Association (ADA) Code on Dental Procedures and Nomenclature (CDT codes)[12] and ICD-9 procedure codes[13] were used to classify 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 and endodontic procedures, i.e. those dental procedures that the AHA guidelines recommend 'should' be covered with AP,[8,14] (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 will 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).[8,14] 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 specific codes for dental

extractions, oral surgical procedures, scaling and endodontic procedures (Table 2 and Supplemental Table S3).

Prescription benefits data were used to identify whether each dental procedure was likely to have been AP-covered or not using methodology previously described[15] and briefly outlined here. For each patient in the cohort, that patient's prescription benefits data was searched for antibiotic prophylaxis (AP) prescriptions matching the 2007 AHA recommendations.[8] These were identified in the database using the following prescribing criteria (a) mode of antibiotic delivery – oral, (b) antibiotic – amoxicillin, clindamycin, cephalexin, azithromycin or clarithromycin, (c) dosage - 2g for amoxicillin, 600 mg for clindamycin, 2g for cephalexin, 500mg for azithromycin or 500mg for clarithromycin. Our earlier study identified that dentists often prescribed multiple courses of AP cover as a single prescription, in order to ensure that patients had sufficient supplies to cover several invasive dental procedure visits i.e. to avoid the patient having to fill a separate prescription for each invasive dental procedure visit. They also often prescribed at the end of a course of dental treatment so that the patient would have supplies available in advance for a future course of dental treatment. To address these eventualities, we evaluated several different algorithms against the gold standard of the actual prescribing and dental records of 80 patients at high IE-risk, 40 moderate-risk and 40 low-unknown risk patients. The algorithm that best identified when an invasive dental procedure was likely to have been covered by AP included the 3 elements above (a-c) where the number of day's supply of the antibiotic was ≤5 and the time between the prescription fill date and the invasive dental procedure date was ≤73 where the number of day's supply = 1, ≤146 where day's supply = 2, ≤219 where day's supply = 3, ≤292 where day's supply = 4 or ≤365 where day's supply = 5. Using this algorithm had 88% (95% CI 82-92%) sensitivity and 96% (95% CI 94-97%) specificity for identifying when a dental procedure was likely to have been covered by AP[15] and this was the algorithm employed in the current study to determine if a dental procedure was likely to have been covered by AP or not.

Cohort Study:

We studied the entire 7.95 million cohort of individuals, >18, with Commercial/Medicare-Supplemental health cover and linked medical/dental/prescription data. They were stratified by IE-risk and followed until study end, death or the end of linked data cover. Individuals could move from a lower- to higher-risk stratification depending on the occurrence of risk-related diagnoses or procedures.

We quantified IE-incidence in the 30-day exposure period following dental-procedures, and repeated the analysis using a 4-month exposure period. Crude incidence rates were adjusted for differences between cases and controls for age, sex or Charlson comorbidity index (CCI).[16] To model the IE-outcome we used Firth correction penalized logistic regression because the outcome of interest is rare.[17] 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.[17,18] The odds of IE following an IDP or intermediate-dental procedure, or a sub-type of IDP i.e. dental extraction, oral surgical procedure, scaling or endodontic procedure was estimated by comparing the IE-incidence with the IE-incidence following a 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 case-crossover design was first proposed by Maclure for studying the effect of transient events in triggering subsequent outcomes while eliminating control selection bias and confounding by constant within subject characteristics,[19] each individual acting as their own control. The case-crossover study was performed on the 3,774 hospital admissions for IE (identified from the cohort of 7,951,972 individuals with linked medical, dental and prescription benefits data). For each IE-related hospital-admission, we quantified monthly exposure to different dental-procedures in the 16-months prior to admission. This data was plotted (Figures 1 and S1) to identify the timing of any association between IDP and IE-admission. These revealed a higher incidence of IDP in the month before IE-admission than at any other time. We therefore performed a case-crossover analysis[19-22] comparing the 1-month (30 day) exposure or case-period immediately before IE-related hospital-admission with the 12-month (months 2-13) control-period before that, using conditional logistic regression (with fixed effects to control for time invariant patient characteristics over the duration of the study). Mittleman *et al* have shown that sampling the control frequency over a full-year prior to the case-period is twice as efficient as sampling control-periods of equal duration to the case-period, even when many such control-periods are sampled and the 12-month control period reduces any periodic time-dependent effects in the control period.[22] Because other case-crossover studies examining the association between IDP and IE have used a longer case-period, usually 3-4 months,[23-25] we repeated the analysis using a 4-month case-period and 12-month control-period (months 5-16). Bonferroni correction was also applied to p values where multiple comparisons were made.

Table S1. ICD-9-CM Diagnosis and Procedure Codes, and CPT Outpatient Procedure codes used to identify 'high-risk' cardiac conditions

Cardiac Condition	ICD-9-CM Codes (and CPT outpatient procedure codes)
Previous IE	**ICD-9 Diagnostic Code:** 4210 acute and subacute bacterial endocarditis 4211 acute and subacute infective endocarditis (in diseases classified elsewhere) 4219 acute endocarditis, unspecified
Prosthetic cardiac valve	**ICD-9 Procedure Codes:** 3505 endovascular replacement of aortic valve 3506 transapical replacement of aortic valve 3507 endovascular replacement of pulmonary valve 3508 transapical replacement of pulmonary valve 3509 endovascular replacement of unspecified heart valve 3520 open and other replacement of unspecified heart valve 3521 open and other replacement of aortic valve with tissue graft 3522 open and other replacement of aortic valve 3523 open and other replacement of mitral valve with tissue graft 3524 open and other replacement of mitral valve 3525 open and other replacement of pulmonary valve with tissue graft 3526 open and other replacement of pulmonary valve 3527 open and other replacement of tricuspid valve with tissue graft 3528 open and other replacement of tricuspid valve 3583 total repair of truncus arteriosus **CPT Procedure Codes:** 0256T Implantation of catheter-delivered prosthetic aortic heart valve; endovascular approach 0257T Implantation of catheter-delivered prosthetic aortic heart valve; open thoracic approach (eg, transapical, transventricular) 0258T Transthoracic cardiac exposure (eg, sternotomy, thoracotomy, subxiphoid) for catheter-delivered aortic valve replacement; without cardiopulmonary bypass 0268T Implantation of catheter-delivered prosthetic pulmonary valve, endovascular approach 0318T Implantation of catheter-delivered prosthetic aortic heart valve, open thoracic approach, (eg, transapical, other than transaortic) 33361 Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach 33362 Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach 33363 Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach 33364 Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach 33365 Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy) 33366 Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy) 33405 Replacement, aortic valve, with cardiopulmonary bypass; with prosthetic valve other than homograft or stentless valve 33406 Replacement, aortic valve, with cardiopulmonary bypass; with allograft valve (freehand) 33410 Replacement, aortic valve, with cardiopulmonary bypass; with stentless tissue valve 33411 Replacement, aortic valve; with aortic annulus enlargement, noncoronary sinus 33412 Replacement, aortic valve; with transventricular aortic annulus enlargement (Konno procedure) 33413 Replacement, aortic valve; by translocation of autologous pulmonary valve with allograft replacement of pulmonary valve (Ross procedure) 33430 Replacement, mitral valve, with cardiopulmonary bypass 33465 Replacement, tricuspid valve, with cardiopulmonary bypass 33475 Replacement, pulmonary valve 33477 Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed 33496 Repair of non-structural prosthetic valve dysfunction with cardiopulmonary bypass (separate procedure) **ICD-9 Diagnostic Codes:** 99602 mechanical complication due to heart valve prosthesis 99671 other complications due to heart valve prosthesis V433 heart valve replaced by other means

Prosthetic material used for valve repair	**ICD-9 Procedure Codes:** 3533 annuloplasty 3597 percutaneous mitral valve repair with implant **CPT Procedure Codes:** 0343T Transcatheter mitral valve repair percutaneous approach including transseptal puncture when performed; initial prosthesis 0344T Transcatheter mitral valve repair percutaneous approach including transseptal puncture when performed; additional prosthesis (es) during same session (List separately in addition to code for primary procedure) 33391 Valvuloplasty, aortic valve, open, with cardiopulmonary bypass; complex (eg, leaflet extension, leaflet resection, leaflet reconstruction, or annuloplasty) 33418 Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; initial prosthesis 33419 Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; additional prosthesis(es) during same session (List separately in addition to code for primary procedure) 33426 Valvuloplasty, mitral valve, with cardiopulmonary bypass; with prosthetic ring 33427 Valvuloplasty, mitral valve, with cardiopulmonary bypass; radical reconstruction, with or without ring 33464 Valvuloplasty, tricuspid valve; with ring insertion 33468 Tricuspid valve repositioning and plication for Ebstein anomaly 33478 Outflow tract augmentation (gusset), with or without commissurotomy or infundibular resection 33600 Closure of atrioventricular valve (mitral or tricuspid) by suture or patch 33602 Closure of semilunar valve (aortic or pulmonary) by suture or patch 33612 Repair of double outlet right ventricle with intraventricular tunnel repair; with repair of right ventricular outflow tract obstruction 33860 Ascending aorta graft, with cardiopulmonary bypass, includes valve suspension, when performed 33863 Ascending aorta graft, with cardiopulmonary bypass, with aortic root replacement using valved conduit and coronary reconstruction (eg, Bentall) 33864 Ascending aorta graft, with cardiopulmonary bypass with valve suspension, with coronary reconstruction and valve-sparing aortic root remodeling (eg, David Procedure, Yacoub Procedure)
<u>Unrepaired cyanotic congenital heart disease (CHD)</u>	**ICD-9 Diagnostic Codes:** 7450 common truncus 74510 complete transposition of great vessels 74511 double outlet right ventricle 74519 other transposition of great vessels 7452 tetralogy of Fallot 7453 common ventricle 74560 endocardial cushion defects 7457 cor biloculare 74741 total anomalous pulmonary venous connection
<u>CHD in whom a palliative shunt or conduit has been used</u>	**ICD-9 Procedure Codes:** 3541 enlargement of existing arterial septal defect 3542 creation of septal defect in heart 3591 interatrial transposition of venous return 3592 creation of conduit between right ventricle and pulmonary artery 3593 creation of conduit between left ventricle and aorta 3594 creation of conduit between atrium and pulmonary artery 390 systemic to pulmonary shunt 3921 caval-pulmonary artery anastomosis **CPT Procedure Codes:** 33404 Construction of apical-aortic conduit 33606 Anastomosis of pulmonary artery to aorta (Damus-Kaye-Stansel procedure) 33608 Repair of complex cardiac anomaly other than pulmonary atresia with ventricular septal defect by construction or replacement of conduit from right or left ventricle to pulmonary artery 33610 Repair of complex cardiac anomalies (eg, single ventricle with subaortic obstruction) by surgical enlargement of ventricular septal defect 33611 Repair of double outlet right ventricle with intraventricular tunnel repair; 33612 Repair of double outlet right ventricle with intraventricular tunnel repair; with repair of right ventricular outflow tract obstruction 33615 Repair of complex cardiac anomalies (eg, tricuspid atresia) by closure of atrial septal defect and anastomosis of atria or vena cava to pulmonary artery (simple Fontan procedure)

	33617	Repair of complex cardiac anomalies (eg, single ventricle) by modified Fontan procedure
	33619	Repair of single ventricle with aortic outflow obstruction and aortic arch hypoplasia (hypoplastic left heart syndrome) (eg, Norwood procedure)
	33697	Complete repair tetralogy of Fallot with pulmonary atresia including construction of conduit from right ventricle to pulmonary artery and closure of ventricular septal defect
	33735	Atrial septectomy or septostomy; closed heart (Blalock-Hanlon type operation)
	33736	Atrial septectomy or septostomy; open heart with cardiopulmonary bypass
	33737	Atrial septectomy or septostomy; open heart, with inflow occlusion
	33750	Shunt; subclavian to pulmonary artery (Blalock-Taussig type operation)
	33755	Shunt; ascending aorta to pulmonary artery (Waterston type operation)
	33762	Shunt; descending aorta to pulmonary artery (Potts-Smith type operation)
	33764	Shunt; central, with prosthetic graft
	33766	Shunt; superior vena cava to pulmonary artery for flow to 1 lung (classical Glenn procedure)
	33767	Shunt; superior vena cava to pulmonary artery for flow to both lungs (bidirectional Glenn procedure)
	33768	Anastomosis, cavopulmonary, second superior vena cava (List separately in addition to primary procedure)
	33774	Repair of transposition of the great arteries, atrial baffle procedure (eg, Mustard or Senning type) with cardiopulmonary bypass;
	33775	Repair of transposition of the great arteries, atrial baffle procedure (eg, Mustard or Senning type) with cardiopulmonary bypass; with removal of pulmonary band
	33776	Repair of transposition of the great arteries, atrial baffle procedure (eg, Mustard or Senning type) with cardiopulmonary bypass; with closure of ventricular septal defect
	33777	Repair of transposition of the great arteries, atrial baffle procedure (eg, Mustard or Senning type) with cardiopulmonary bypass; with repair of subpulmonic obstruction
	33782	Aortic root translocation with ventricular septal defect and pulmonary stenosis repair (ie, Nikaidoh procedure); without coronary ostium reimplantation
	33783	Aortic root translocation with ventricular septal defect and pulmonary stenosis repair (ie, Nikaidoh procedure); with reimplantation of 1 or both coronary ostia
	33786	Total repair, truncus arteriosus (Rastelli type operation)
	33918	Repair of pulmonary atresia with ventricular septal defect, by unifocalization of pulmonary arteries; without cardiopulmonary bypass
	33920	Repair of pulmonary atresia with ventricular septal defect, by construction or replacement of conduit from right or left ventricle to pulmonary artery
	92992	Atrial septectomy or septostomy; transvenous method, balloon (eg, Rashkind type) (includes cardiac catheterization)
	92993	Atrial septectomy or septostomy; blade method (Park septostomy) (includes cardiac catheterization)
<u>Completely</u> <u>repaired CHD</u> <u>defect with</u> <u>prosthetic</u> <u>material or</u> <u>device, whether</u> <u>placed by</u> <u>surgery or</u> <u>catheter</u> <u>intervention,</u> **<u>during first 6</u> <u>months after</u> <u>the procedure</u> <u>only.</u>**	**ICD-9 Procedure Codes:** 3550 repair of unspecified septal defect of heart with prosthesis 3551 repair of atrial septal defect with prosthesis, open technique 3552 repair of atrial septal defect with prosthesis, closed technique 3553 repair of ventricular septal defect with prosthesis, open technique 3554 repair of endocardial cushion defect with prosthesis 3555 repair of ventricular septal defect with prosthesis, closed technique 3560 repair of unspecified septal defect of heart with tissue graft 3561 repair of atrial septal defect with tissue graft 3562 repair of ventricular septal defect with tissue graft 3563 repair of endocardial cushion defect with tissue graft 3570 other and unspecified repair of unspecified septal defect of heart 3571 other and unspecified repair of atria septal defect 3572 other and unspecified repair of ventricular septal defect 3573 other and unspecified repair of endocardial cushion defect 3581 total repair of tetralogy of Fallot 3582 total repair of total anomalous pulmonary venous connection 3584 total correction of transposition of great vessels 3598 other operations on septa of heart **CPT Procedure Codes** 0166T Transmyocardial transcatheter closure of ventricular septal defect, with implant; without cardiopulmonary bypass 0167T Transmyocardial transcatheter closure of ventricular septal defect, with implant; with cardiopulmonary bypass 33545 Repair of postinfarction ventricular septal defect, with or without myocardial resection 33641 Repair atrial septal defect, secundum, with cardiopulmonary bypass, with or without patch 33645 Direct or patch closure, sinus venosus, with or without anomalous pulmonary venous drainage 33647 Repair of atrial septal defect and ventricular septal defect, with direct or patch closure 33660 Repair of incomplete or partial atrioventricular canal (ostium primum atrial septal defect), with or without atrioventricular valve repair	

	33665	Repair of intermediate or transitional atrioventricular canal, with or without atrioventricular valve repair
	33670	Repair of complete atrioventricular canal, with or without prosthetic valve
	33675	Closure of multiple ventricular septal defects;
	33676	Closure of multiple ventricular septal defects; with pulmonary valvotomy or infundibular resection (acyanotic)
	33677	Closure of multiple ventricular septal defects; with removal of pulmonary artery band, with or without gusset
	33681	Closure of single ventricular septal defect, with or without patch;
	33684	Closure of single ventricular septal defect, with or without patch; with pulmonary valvotomy or infundibular resection (acyanotic)
	33688	Closure of single ventricular septal defect, with or without patch; with removal of pulmonary artery band, with or without gusset
	33692	Complete repair tetralogy of Fallot without pulmonary atresia;
	33694	Complete repair tetralogy of Fallot without pulmonary atresia; with transannular patch
	33710	Repair sinus of Valsalva fistula, with cardiopulmonary bypass; with repair of ventricular septal defect
	33770	Repair of transposition of the great arteries with ventricular septal defect and subpulmonary stenosis; without surgical enlargement of ventricular septal defect
	33771	Repair of transposition of the great arteries with ventricular septal defect and subpulmonary stenosis; with surgical enlargement of ventricular septal defect
	33778	Repair of transposition of the great arteries, aortic pulmonary artery reconstruction (eg, Jatene type);
	33779	Repair of transposition of the great arteries, aortic pulmonary artery reconstruction (eg, Jatene type); with removal of pulmonary band
	33780	Repair of transposition of the great arteries, aortic pulmonary artery reconstruction (eg, Jatene type); with closure of ventricular septal defect
	33781	Repair of transposition of the great arteries, aortic pulmonary artery reconstruction (eg, Jatene type); with repair of subpulmonic obstruction
	93580	Percutaneous transcatheter closure of congenital interatrial communication (ie, Fontan fenestration, atrial septal defect) with implant
	93581	Percutaneous transcatheter closure of a congenital ventricular septal defect with implant

Notes:

1. Patients at "high-risk" of developing IE were identified by determining whether they had been diagnosed with a "high-risk" condition (ICD-9 codes) or undergone a "high-risk" procedure (ICD-9 or CPT procedure codes) at any time before they first developed IE or at any-time for those who did not develop IE during the study period (within the available healthcare records for that individual) using all available data back to January 2000.

2. Since the AHA guidelines consider patients with congenital heart disease repaired with prosthetic material to be high-risk only for the first 6 months after the procedure, they were treated as high-risk for the first 6 months after the procedure only.

Table S2. ICD-9-CM Diagnosis and Procedure Codes, and CPT Outpatient Procedure codes used to identify 'moderate-risk' cardiac conditions.

Cardiac Condition	ICD-9-CM Codes
Rheumatic heart disease	**ICD-9 Diagnostic Codes:** 390 rheumatic fever without heart involvement 3910 acute rheumatic pericarditis 3911 acute rheumatic endocarditis 3912 acute rheumatic myocarditis 3918 other acute rheumatic heart disease 3919 acute rheumatic heart disease, unspecified 3920 rheumatic chorea with heart involvement 3929 rheumatic chorea without heart involvement 3941 rheumatic mitral insufficiency 3940 mitral stenosis 3942 mitral stenosis with insufficiency 3949 other unspecified mitral disease 3950 rheumatic aortic stenosis 3951 rheumatic aortic insufficiency 3952 rheumatic aortic stenosis with insufficiency 3959 other and unspecified aortic rheumatic diseases 3960 mitral and aortic stenosis 3961 mitral stenosis and aortic insufficiency 3962 mitral insufficiency and aortic stenosis 3963 mitral insufficiency and aortic insufficiency 3968 multiple involvement of mitral and aortic valves 3969 mitral and aortic valve disease unspecified 3970 diseases of tricuspid valve 3971 rheumatic diseases of pulmonary valve 3979 rheumatic diseases of endocardium, valve unspecified 39890 rheumatic heart disease, unspecified 39899 other rheumatic heart diseases
Non-Rheumatic Valve Disease	**ICD-9 Diagnostic codes:** 4240 mitral valve disorders 4241 aortic valve disorders 4242 tricuspid valve disorders specified as non-rheumatic 4243 pulmonary valve disorders
Hypertrophic cardiomyopathy	**ICD-9 Diagnostic Codes:** 42511 hypertrophic obstructive cardiomyopathy 42518 other hypertrophic cardiomyopathy
Congenital valve anomalies	**ICD-9 Diagnostic codes:** 74600 congenital pulmonary valve anomaly, unspecified 74601 atresia of pulmonary valve, congenital 74602 stenosis of pulmonary valve, congenital 74609 other congenital anomalies of pulmonary valve 7461 tricuspid atresia and stenosis, congenital 7462 Ebstein's anomaly 7463 congenital stenosis of aortic valve 7464 congenital insufficiency of aortic valve 7465 congenital mitral stenosis 7466 congenital mitral insufficiency 7467 hyperplastic left heart syndrome 74681 sub-aortic stenosis 74683 infundibular pulmonic stenosis 74689 other specified congenital heart anomalies of heart

Notes: Patients at "moderate-risk" of developing IE were identified by determining whether they had been diagnosed with a "moderate-risk" condition (ICD-9 codes) at any time before they first developed IE or at any-time for those who did not develop IE during the study period (within the available healthcare records for that individual).

Table S3. Invasive-Dental Procedure (IDP), Intermediate-Dental Procedure and non-IDP CDT and ICD-9 Procedure Codes, and Codes for Specific Types of IDP

Analyses	CDT Codes	ICD-9 Codes
All Invasive-Dental Procedure (IDP) Codes i.e. those procedures that 'should' be covered by AP according to the 2007 AHA recommendations	D0180, D0472-4, D1110, D1120, D3221, D3310, D3320, D3330, D3332-3, D3346-8, D3351-3, D3410, D3421, D3425-32, D3450, D3460, D3470, D3910, D3920, D4210-2, D4230-1, D4240-1, D4245, D4249, D4260-1, D4263-8, D4270, D4273-8, D4283, D4341-2, D4346, D4355, D4381, D4910, D4921, D6010-3, D6040, D6050, D6080-1, D6100-4, D7111, D7140, D7210, D7220, D7230, D7240-1, D7250-1, D7260-1, D7270, D7272, D7280, D7282-3, D7285-6, D7290-5, D7310-1, D7320-1, D7340, D7350, D7410-5, D7465, D7440-1, D7450-1, D7460-1, D7471-3, D7485, D7490, D7510-1, D7520-1, D7530, D7540, D7550, D7560, D7610, D7630, D7671, D7710, D7730, D7770, D7941, D7943-50, D7952-3, D7955, D7960, D7963, D7970-2, D7981-3, D7991, D7996-8	2301, 2309, 2311, 2319, 235, 236, 2370-3, 240, 2411-2, 242, 2431-2, 2439, 244, 245, 246, 2491, 2499, 2502, 251, 252, 253, 254, 2551, 2559, 2591-4, 2599, 260, 2612, 2621, 2629-32, 2641-2, 2649, 270, 271, 2721-4, 2731-2, 2741-3, 2749, 2751-7, 2759, 2761-4, 2769, 2771-3, 2779, 2791-2, 2799, 9654
All Intermediate-Dental Procedure Codes i.e. those procedures that 'may' be covered by AP on some occasions, but not on others, according to the 2007 AHA recommendations	D0120, D0150, D2150, D21601, D2330-2, D2335, D2390, D2392-4, D2520, D2530, D2542-4, D2620, D2630, D2642-4, D2651-2, D2662-4, D2710, D2712, D2720-2, D2740, D2750-2, D2780-3, D2790-2, D2794, D2799, D2929-34, D2960-2, D4999, D6051-2, D6055-7, D6065-7, D6075-7, D6545, D6548-9, D6600-15, D6624, D6634, D6710, D6720-2, D6740, D6750-2, D6780-3, D6790-4, D7620, D7640, D7650, D7660, D7670, D7680, D7720, D7740, D7750, D7760, D7771, D7780	232, 233, 2341, 2342, 2343, 2349
Non-IDP i.e. those procedures for which there is no AP recommendation	All CPT dental procedure codes not listed as being and IDP or intermediate-dental procedure.	All ICD-9 dental procedure codes not listed as being an IDP or intermediate-dental procedure.
Codes For Specific Types of Invasive-Dental Procedure (IDP)		
Scaling	D1110, D1120, D4341-2, D4346, D4355, D4381, D4910, D4921,	9654
Extractions	D7111, D7140, D7210, D7220, D7230, D7240-1, D7250-1,	2301, 2309, 2311, 2319,
Endodontic Procedures	D3221, D3310, D3320, D3330, D3332-3, D3346-8, D3351-3, D3410, D3421, D3425-32, D3450, D3460, D3470, D3910, D3920,	2370-3,
Surgical Procedures (including oral surgical procedures, periodontal surgery procedures, implant procedures and biopsies)	D0472-4, D4210-2, D4230-1, D4240-1, D4245, D4249, D4260-1, D4263-8, D4270, D4273-8, D4283, D6010-3, D6040, D6050, D6080-1, D6100-4, D7260-1, D7270, D7272, D7280, D7282-3, D7285-6, D7290-5, D7310-1, D7320-1, D7340, D7350, D7410-5, D7465, D7440-1, D7450-1, D7460-1, D7471-3, D7485, D7490, D7510-1, D7520-1, D7530, D7540, D7550, D7560, D7610, D7630, D7671, D7710, D7730, D7770, D7941, D7943-50, D7952-3, D7955, D7960, D7963, D7970-2, D7981-3, D7991, D7996-8	240, 2411-2, 242, 2431-2, 2439, 244, 245, 246, 2491, 2499, 2502, 251, 252, 253, 254, 2551, 2559, 2591-4, 2599, 260, 2612, 2621, 2629-32, 2641-2, 2649, 270, 271, 2721-4, 2731-2, 2741-3, 2749, 2751-7, 2759, 2761-4, 2769, 2771-3, 2779, 2791-2, 2799,

Table S4. Cohort Study, Dental Procedures Model - Crude IE Incidence Within 1-Month (30 days) of a Dental Procedure.

Commercial/Medicare Supplemental Patients												
IE-Risk	**High IE-Risk Individuals**				**Moderate IE-Risk Individuals**				**Low/Unknown IE-Risk Individuals**			
Type of Dental Procedure	Procedures (n)	IE (n)	Crude IE/million proc	OR (95%CI)	Procedures (n)	IE (n)	Crude IE/million proc	OR (95%CI)	Procedures (n)	IE (n)	Crude IE/million proc	OR (95%CI)
All	275,853	125	453.1		4,341,528	101	23.3		53,440,767	199	3.7	
Non-Invasive (non-IDP) (control)	48,147	20	415.4	1	739,797	18	24.3	1	8,116,131	40	4.9	1
Intermediate-	46,715	13	278.3	0.67 (0.33-1.35)	730,199	12	16.4	0.68 (0.33-1.40)	8,908,468	33	3.7	0.75 (0.47-1.19)
Invasive- (IDP)	180,991	92	508.3	1.22 (0.75-1.98)	2,871,532	71	24.7	1.02 (0.61-1.70)	36,416,168	126	3.5	0.70 (0.49-1.00)
Type of Invasive-Dental Procedure (IDP)												
- Scaling	160,999	31	192.6	0.46 (0.26-0.81)	2,553.431	51	20.0	0.82 (0.48-1.40)	32,758,079	87	2.7	0.54 (0.37-0.78)
- Extractions	11,483	45	3,918.8	9.43 (5.59-16.13), p<0.0001	168,278	14	83.2	3.42 (1.70-6.90), p=0.03	1,942,999	24	12.4	2.51 (1.51-4.15), p=0.02
- Endodontic	6,621	2	302.1	0.73 (0.17-3.12)	113,780	4	35.2	1.45 (0.49-4.27)	1,344,624	8	5.9	1.21 (0.57-2.58)
- Surgical	2,696	25	9,273.0	22.73 (12.50-40.00), p<0.0001	46,699	3	64.2	2.64 (0.78-8.93)	480,468	10	20.8	4.22 (2.11-8.48), p=0.03

Notes: Crude data without adjustment for differences in the age, sex and Charlson Comorbidity Index (CCI) score between cases and controls. Surgical Procedures includes both oral surgery and periodontal surgery procedures. IDP = Invasive-Dental Procedures, IE = Infective Endocarditis, Proc = Procedure, OR = Odds Ratio, Non-IDP = Non-Invasive Dental Procedure. OR significantly higher than control non-IDP value, Bonferroni corrected p values shown where p<0.05 (other p values not significant).

Table S5. Cohort Study, Antibiotic Prophylaxis Model - Crude IE Incidence Within 1-Month (30 days) of Dental Procedures Covered or Not Covered by Antibiotic Prophylaxis.

Commercial/Medicare Supplemental Patients								
IE-Risk	**AP /**	**High IE-Risk Individuals**			**Moderate IE-Risk Individuals**		**Low/Unknown IE-Risk Individuals**	
Type of Dental Procedure	No AP	Crude IE/million proc	OR (95%CI) NNP		Crude IE/million proc	OR (95%CI)	Crude IE/million proc	OR (95%CI)
Non-Invasive (non-IDP)	AP	621.1	1.44 (0.54-3.87)		nc	nc	11.2	2.34 (0.72-7.63)
	No AP	431.6			nc	nc	4.8	
Intermediate-	AP	419.8	1.25 (0.40-3.95)		25.8	1.37 (0.30-6.36)	17.3	5.24 (2.01-13.64)
	No AP	335.2			18.8		3.3	
Invasive- (IDP)	AP	338.7	0.35 (0.21-0.59), p=0.02		25.7	1.21 (0.54-2.70)	13.4	4.47 (2.55-7.82)
	No AP	966.7			21.2		3.0	
Type of Invasive-Dental Procedure (IDP)								
Scaling	AP	288.1	2.30 (0.89-5.94)		25.5	1.53 (0.63-3.68)	12.4	5.74 (3.03-10.90)
	No AP	125.1			16.7		2.2	
Extractions	AP	755.7	0.09 (0.03-0.29), p<0.0001		49.0	0.61 (0.08-4.79)	11.2	0.87 (0.12-6.44)
	No AP	8,308.9			80.6		12.9	
Endodontic	AP	417.0	0.89 (0.06-14.30)		0	nc	36.9	7.23 (1.46-35.81)
	No AP	466.4			26.9		5.1	
Surgical	AP	1,158.7	0.05 (0.01-0.40), p=0.03		0	nc	0	nc
	No AP	21,363.2			32.1		23.8	

Notes: Surgical Procedures includes both oral surgery and periodontal surgery procedures. AP = Antibiotic Prophylaxis, IDP = Invasive-dental procedure, IE = Infective Endocarditis, OR = Odds Ratio, nc = not calculable, Non-IDP = Non-Invasive Dental Procedure, Proc. = Procedure. AP significantly reduced IE incidence compared to no AP, Bonferroni corrected p values shown where p<0.05 (other p values not significant).

Table S6. Cohort Study, Dental Procedures Model - Adjusted IE Incidence Within 4-Months of a Dental Procedure.

Commercial/Medicare Supplemental Patients											
IE-Risk	High IE-Risk Individuals				Moderate IE-Risk Individuals				Low/Unknown IE-Risk Individuals			
Type of Dental Procedure	Procedures (n)	IE (n)	Adjusted IE/million proc	OR (95%CI)	Procedures (n)	IE (n)	Adjusted IE/million proc	OR (95%CI)	Procedures (n)	IE (n)	Adjusted IE/million proc	OR (95%CI)
All	275,853	356	1,305.0		4,341,528	446	103.6		53,440,767	838	15.8	
Non-invasive (non-IDP) (control)	48,147	72	1,140.1	1	739,797	102	112.1	1	8,116,131	212	20.8	1
Intermediate-	46,715	66	1,217.7	1.06 (0.73-1.53)	730,199	94	101.2	0.91 (0.66-1.24)	8,908,468	187	16.3	0.80 (0.64-1.00)
Invasive- (IDP)	180,991	293	1,371.4	1.20 (0.90-1.63)	2,871,532	376	102.1	0.94 (0.74-1.20)	36,416,168	655	14.5	0.73 (0.62-0.87)
Type of Invasive-Dental Procedure (IDP)												
- Scaling	160,999	206	1,039.4	0.92 (0.68-1.26)	2,553,431	293	88.2	0.81 (0.63-1.05)	32,758,079	532	13.0	0.66 (0.55-0.79)
- Extractions	11,483	67	5,470.7	4.65 (3.23-6.73), p<0.0001	168,278	63	324.0	2.65 (1.87-3.73), p=0.02	1,942,999	76	33.6	1.56 (1.16-2.07)
- Endodontic	6,621	6	864.7	0.70 (0.26-1.55)	113,780	17	112.7	1.00 (0.53-1.75)	1,344,624	33	21.5	1.03 (0.68-1.51)
- Surgical	2,696	26	9,745.4	7.63 (4.67-12.16), p<0.0001	46,699	12	231.8	1.90 (0.94-3.45)	480,468	18	34.8	1.44 (0.83-2.31)

Notes: Adjusted data corrected for differences in the age, sex and Charlson Comorbidity Index (CCI) score between cases and controls. Surgical Procedures includes both oral surgery and periodontal surgery procedures. IDP = Invasive-Dental Procedure, IE = Infective Endocarditis, Proc = Procedure, OR = Odds Ratio, Non-IDP = Non-Invasive Dental Procedure. OR significantly higher than control non-IDP value, Bonferroni corrected p values shown where p<0.05 (other p values not significant).

Table S7. Cohort Study, Antibiotic Prophylaxis Model - Adjusted IE Incidence Within 4-Months of Dental Procedures Covered or Not Covered by Antibiotic Prophylaxis.

Commercial/Medicare Supplemental Patients								
IE-Risk	AP /	High IE-Risk Individuals		Moderate IE-Risk Individuals		Low/Unknown IE-Risk Individuals		
Type of Dental Procedure	No AP	Adjusted IE/million proc	OR (95%CI) NNP	Adjusted IE/million proc	OR (95%CI)	Adjusted IE/million proc	OR (95%CI	
Non-Invasive (non-IDP)	AP	1,503.9	1.48 (0.77-2.89)	180.3	1.75 (0.89-3.17)	39.8	1.34 (0.67-2.41)	
	No AP	1,090.7		107.5		20.3		
Intermediate-	AP	1,609.3	1.16 (0.63-2.15)	196.2	2.43 (1.27-4.40)	47.6	2.09 (1.13-3.57)	
	No AP	1,317.9		82.1		15.1		
Invasive- (IDP)	AP	1,312.9	0.73 (0.54-0.99)	225.0	2.75 (2.01-3.70)	39.9	2.06 (1.47-2.81)	
	No AP	1,823.1		81.9		13.2		
Type of Invasive-Dental Procedure (IDP)								
Scaling	AP	1,266.2	1.38 (0.94-2.06)	196.7	2.83 (1.97-3.98)	36.9	2.06 (1.40-2.92)	
	No AP	887.3		70.1		11.7		
Extractions	AP	2,238.6	0.23 (0.10-0.47), p<0.0001	648.5	2.27 (1.12-4.37)	76.2	1.95 (0.78-4.12)	
	No AP	11,123.9		270.9		33.3		
Endodontic	AP	1,546.4	0.93 (0.14-6.23)	245.5	2.09 (0.38-8.07)	70.8	2.25 (0.60-6.17)	
	No AP	1,752.3		125.5		23.5		
Surgical	AP	1,916.1	0.09 (0.01-0.35), p=0.002	938.5	5.43 (1.13-26.07)			
	No AP	24,042.7		0.1541				

Notes: Adjusted data corrected for differences in the age, sex and Charlson Comorbidity Index (CCI) score between cases and controls. Surgical Procedures includes both oral surgery and periodontal surgery procedures. AP = Antibiotic Prophylaxis, IDP = Invasive-Dental Procedures, IE = Infective Endocarditis, OR = Odds Ratio, Non-IDP = Non-Invasive Dental procedures, Proc. = Procedure. AP significantly reduced IE incidence compared to no AP, Bonferroni corrected p values shown where p<0.05 (other p values not significant).

Table S8. Cohort Study, Dental Procedures Model - Crude IE Incidence Within 4-Months of a Dental Procedure.

Commercial/Medicare Supplemental Patients												
IE-Risk	**High IE-Risk Individuals**				**Moderate IE-Risk Individuals**				**Low/Unknown IE-Risk Individuals**			
Type of Dental Procedure	Procedures (n)	IE (n)	Crude IE/million proc	OR (95%CI)	Procedures (n)	IE (n)	Crude IE/million proc	OR (95%CI)	Procedures (n)	IE (n)	Crude IE/million proc	OR (95%CI)
All	275,853	356	1,290.5		4,341,528	446	102.7		53,440,767	838	15.7	
Non-Invasive (non-IDP) (control)	48,147	72	1,495.4	1	739,797	102	137.9	1	8,116,131	212	26.1	1
Intermediate-	46,715	66	1,412.8	0.94 (0.68-1.32)	730,199	94	128.7	0.93 (0.71-1.24)	8,908,468	187	21.0	0.80 (0.66-0.98)
Invasive- (IDP)	180,991	293	1,618.9	1.08 (0.84-1.40)	2,871,532	376	130.9	0.95 (0.76-1.18)	36,416,168	655	18.0	0.69 (0.59-0.80)
Type of Invasive-Dental Procedure (IDP)												
- Scaling	160,999	206	1,279.5	0.86 (0.65-1.12)	2,553.431	293	114.7	0.83 (0.66-1.04)	32,758,079	532	16.2	0.62 (0.53-0.73)
- Extractions	11,483	67	5,834.7	3.92 (2.81-5.46), p<0.0001	168,278	63	374.4	2.72 (1.98-3.72), p=0.002	1,942,999	76	39.1	1.50 (1.15-1.95)
- Endodontic	6,621	6	906.2	0.61 (0.26-1.39)	113,780	17	149.4	1.08 (0.65-1.81)	1,344,624	33	24.5	0.94 (0.65-1.36)
- Surgical	2,696	26	9,643.9	6.49 (4.15-10.20), p<0.0001	46,699	12	257.0	1.87 (1.02-3.39)	480,468	18	37.5	1.43 (0.89-2.32)

Notes: Surgical Procedures includes both oral surgery and periodontal surgery procedures. IDP = Invasive-Dental Procedures, IE = Infective Endocarditis, OR = Odds Ratio, Non-IDP = Non-Invasive Dental procedures, Proc = Procedure. OR significantly higher than control non-IDP value, Bonferroni corrected p values shown where p<0.05 (other p values not significant).

Table S9. Cohort Study, Antibiotic Prophylaxis Model - Crude IE Incidence Within 4-Months of Dental Procedures Covered or Not Covered by Antibiotic Prophylaxis.

Commercial/Medicare Supplemental Patients						
IE-Risk	AP /	**High IE-Risk Individuals**		**Moderate IE-Risk Individuals**		**Low/Unknown IE-Risk Individuals**
Type of Dental Procedure	No AP	Crude IE/million proc	OR (95%CI) NNP	Crude IE/million proc	OR (95%CI)	Crude IE/million proc	OR (95%CI)
Non-Invasive (non-IDP)	AP	1,518.3	1.07 (0.60-1.92)	249.4	2.03 (1.20-3.43)	44.7	1.78 (0.99-3.19)
	No AP	1,418.3		123.2		25.1	
Intermediate-	AP	1,739.3	1.24 (0.70-2.17)	271.3	2.82 (1.68-4.73)	65.7	3.48 (2.16-5.60)
	No AP	1,408.0		96.2		18.9	
Invasive- (IDP)	AP	1,608.9	0.81 (0.61-1.07)	286.6	2.84 (2.18-3.70)	49.7	3.09 (2.32-4.11)
	No AP	1,988.0		100.9		16.1	
Type of Invasive-Dental Procedure (IDP)							
Scaling	AP	1,574.7	1.30 (0.95-1.78)	251.0	1.86 (1.34-2.59)	47.3	1.78 (1.22-2.61)
	No AP	1,213.7		134.8		26.5	
Extractions	AP	2,267.0	0.55 (0.24-1.28)	685.5	1.38 (0.69-2.78)	78.5	1.74 (0.16-19.14)
	No AP	4,092.4		496.4		26.8	
Endodontic	AP	834.0	1.74 (0.16-19.14)	233.2	1.55 (0.35-6.91)	55.3	1.92 (0.99-3.70)
	No AP	481.0		150.9		26.3	
Surgical	AP	1,158.8	0.33 (0.03-3.16)	803.1	1.71 (0.46-6.35)	0	
	No AP	3,529.4		471.2		50.7	

Notes: Surgical Procedures includes both oral surgery and periodontal surgery procedures. AP = Antibiotic Prophylaxis, IDP = Invasive-Dental Procedures, IE = Infective Endocarditis, OR = Odds Ratio, Non-IDP = Non-Invasive Dental Procedures, Proc. = Procedure. AP significantly reduced IE incidence compared to no AP, Bonferroni corrected p values shown where $p<0.05$ (other p values not significant). Note, there are no significant reductions in crude 4-month IE incidence comparing AP to no AP.

Table S10. Case-Crossover Analysis Using 4-Month Case Period and 12-Month Control Period (months 5-16) – Dental Procedures Model.

| Case-Crossover Analysis of Individuals Who Developed Infective Endocarditis (IE)									
Prior IE-Risk	High IE-Risk Individuals			Moderate IE-Risk Individuals			Low/Unknown IE-Risk Individuals		
Type of Dental Procedure	Proc/m in 4m Case Period	Proc/m in 12m Control Period	Odds Ratio (95% CI)	Proc/m in 4m Case Period	Proc/m in 12m Control Period	Odds Ratio (95% CI)	Proc/m in 4m Case Period	Proc/m in 12m Control Period	Odds Ratio (95% CI)
Non-Invasive (non-IDP) - all	40.5	36.3	1.12 (0.93-1.34)	56.2	62.0	0.91 (0.78-1.05)	108.5	105.5	1.03 (0.92-1.15)
Intermediate - all	16.2	14.2	1.15 (0.86-1.53)	20.5	24.2	0.85 (0.66-1.08)	41.5	41.5	1.00 (0.84-1.19)
Invasive (IDP) - all	57.2	43.3	1.33 (1.14-1.56), p=0.01	65.8	72.5	0.91 (0.79-1.04)	116.0	123.0	0.94 (0.85-1.05)
Type of Invasive-Dental Procedure (IDP)									
Scaling	37.8	38.1	0.99 (0.82-1.19)	50.8	63.5	0.80 (0.68-0.93)	94.8	105.3	0.90 (0.80-1.01)
Extractions	14.8	3.9	3.81 (2.59-5.60), p=0.001	12.2	6.0	2.05 (1.42-2.95), p=0.003	13.2	12.2	1.09 (0.80-1.49)
Endodontic	1.2	1.7	0.75 (0.28-2.00)	2.5	2.8	0.91 (0.45-1.85)	6.5	4.4	1.47 (0.92-2.36)
Surgical	6.2	0.6	10.75 (4.65-24.85), p<0.0001	2.2	1.3	1.69 (0.75-3.84)	3.5	2.7	1.31 (0.70-2.46)

Notes: AP = Antibiotic Prophylaxis, IDP = Invasive-Dental Procedure, IE = Infective Endocarditis, m = month, Non-IDP = Non-Invasive Dental Procedures, Proc = Procedures. Surgical Procedures includes both oral surgery and periodontal surgery procedures. OR for case period significantly higher than for control period, Bonferroni corrected p values shown where p<0.05 (other p values not significant).

Table S11. Case-Crossover Analysis Using 4-Month Case Period and 12-Month Control Period (months 5-16) – Antibiotic Prophylaxis Model.

Case-Crossover Analysis of Commercial/Medicare-Supplemental Patients Who Developed Infective Endocarditis (IE)								
Prior IE-Risk	High IE-Risk Individuals			Moderate IE-Risk Individuals			Low/Unknown IE-Risk Individuals		
Type of Dental Procedure	Proc/m in 4m Case Period	Proc/m in 12m Control Period	Odds Ratio (95% CI)	Proc/m in 4m Case Period	Proc/m in 12m Control Period	Odds Ratio (95% CI)	Proc/m in 4m Case Period	Proc/m in 12m Control Period	Odds Ratio (95% CI)
Non-Invasive (Non-IDP) - No AP	25.5	23.4	1.09 (0.87-1.37)	47.0	50.3	0.93 (0.79-1.10)	100.8	98.8	1.02 (0.91-1.15)
Non-IDP - AP	15.0	13.0	1.16 (0.86-1.57)	9.2	11.8	0.78 (0.54-1.13)	7.8	6.8	1.15 (0.76-1.75)
Non-IDP AP v No AP			1.06 (0.73-1.54)			0.84 (0.56-1.25)			1.13 (0.73-1.74)
Intermediate - No AP	10.5	8.5	1.24 (0.86-1.78)	16.8	19.5	0.86 (0.65-1.13)	38.2	38.1	1.00 (0.84-1.21)
Intermediate – AP	5.8	5.7	1.02 (0.63-1.63)	3.8	4.7	0.80 (0.45-1.42)	3.2	3.4	0.95 (0.51-1.78)
Intermediate AP v No AP			0.82 (0.45-1.49)			0.94 (0.50-1.76)			0.95 (0.49-1.82)
Invasive (IDP) - No AP	40.2	27.0	1.50 (1.24-1.82)	52.5	58.4	0.90 (0.77-1.05)	106.8	114.8	0.93 (0.83-1.04)
IDP – AP	17.0	16.3	1.04 (0.79-1.38)	13.2	14.1	0.94 (0.69-1.28)	9.2	8.2	1.12 (0.77-1.64)
IDP AP v No AP			0.70 (0.50-0.98), p=0.04			1.05 (0.74-1.48)			1.21 (0.81-1.80)
Type of Invasive-Dental Procedure (IDP)									
Scale - No AP	23.8	23.8	1.00 (0.79-1.26)	40.5	51.4	0.78 (0.66-0.93)	87.2	98.9	0.88 (0.78-0.99)
Scale - AP	14.0	14.2	0.98 (0.73-1.33)	10.2	12.1	0.85 (0.60-1.20)	7.5	6.4	1.17 (0.77-1.80)
Scale AP v No AP			0.99 (0.67-1.45)			1.08 (0.73-1.59)			1.33 (0.86-2.07)
Extract - No AP	12.8	2.4	5.31 (3.36-8.38)	9.8	4.8	2.06 (1.37-3.10)	12.0	11.0	1.09 (0.78-1.52)
Extract - AP	2.0	1.5	1.34 (0.58-3.09)	2.5	1.2	2.00 (0.90-4.46)	1.2	1.2	1.07 (0.39-2.98)
Extract AP v No AP			0.25 (0.10-0.66), p=0.01			0.97 (0.40-2.39)			0.98 (0.34-2.88)
Endo - No AP	0.8	1.0	0.75 (0.21-2.66)	2.2	2.2	1.04 (0.49-2.22)	5.8	3.9	1.47 (0.89-2.43)
Endo – AP	0.5	0.7	0.75 (0.16-3.54)	0.2	0.6	0.43 (0.05-3.48)	0.8	0.5	1.50 (0.38-6.00)
End AP v No AP			1 (0.14-7.43)			0.41 (0.04-3.83)			1.02 (0.23-4.45)
Surg - No AP	6.0	0.4	14.45 (5.51-37.89)	1.5	1.0	1.50 (0.56-4.00)	3.5	2.2	1.56 (0.82-2.97)
Surg – AP	0.2	0.2	1.5 (0.14-16.54)	0.8	0.3	2.25 (0.50-10.05)	0.0	0.4	0 (0-6.83e+198)
Surg AP v No AP			0.10 (0.01-1.38)			1.50 (0.25-8.95)			0 (0-4.39e+198)

Notes: AP = Antibiotic Prophylaxis, endo = endodontic procedures, extract = extractions, IE = Infective Endocarditis, inf = infinity, IDP = Invasive-Dental Procedure, m = month, NA = not available, Non-IDP = Non-Invasive Dental Procedure, proc = number of dental procedures, scale = scaling procedures, surg = surgical procedures (including both oral surgery and periodontal surgery procedures), v = versus (compared with). AP odds significantly reduced when compared with No AP odds, Bonferroni corrected p values shown where p<0.05 (other p values not significant).

Figure S1. Incidence of different types of dental procedure over the 16-months before IE-admission (0 = admission date) in those at high-, moderate- or low/unknown-IE-risk.
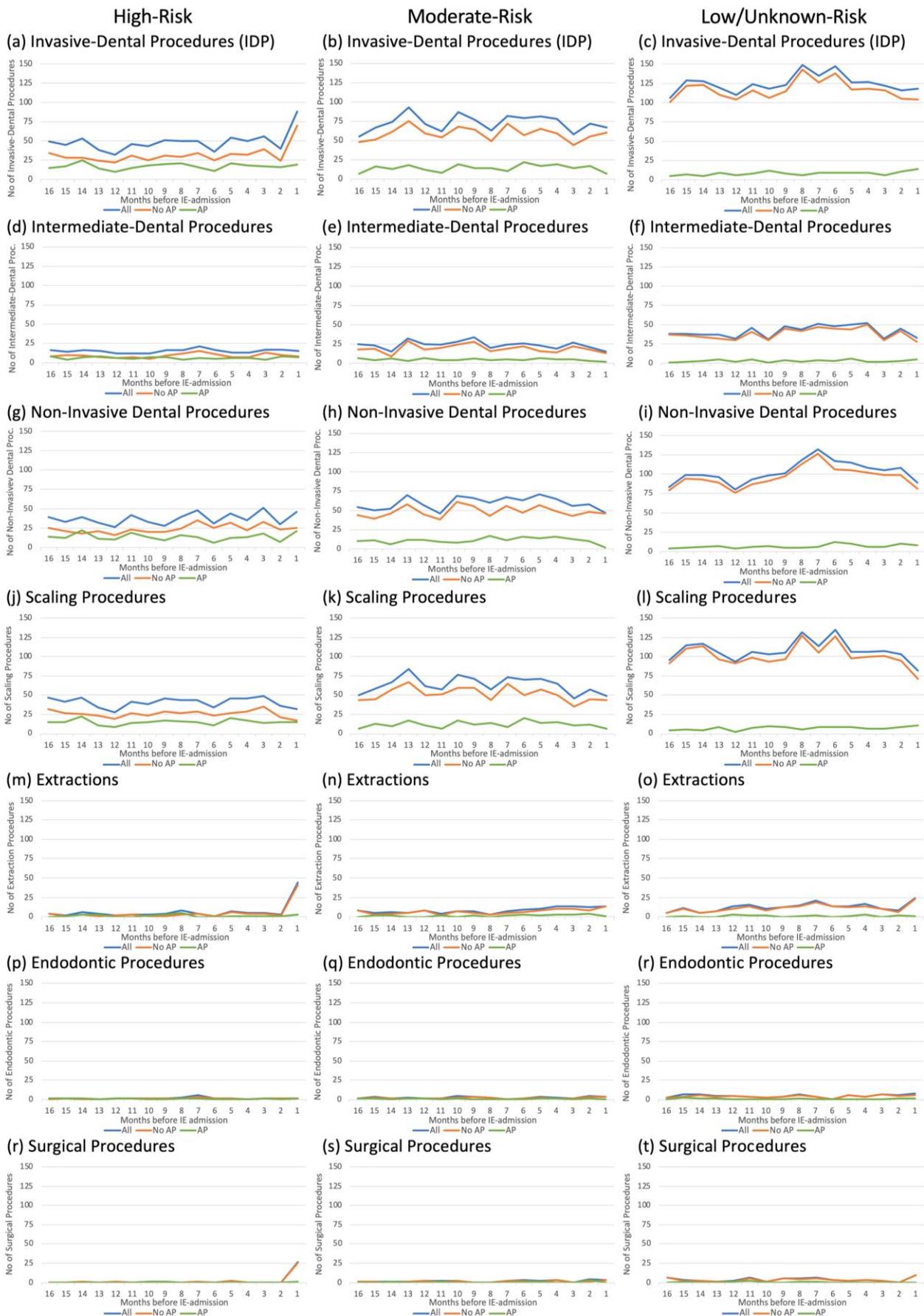
References:

1. IBM Watson Health. The IBM MarketScan Research Databases for Life Sciences Researchers - Data Brochure. Somers, NY: IBM Watson Health; 2019 April 2019.
2. IBM Watson Health. The Truven Health MarketScan Databases for health services researchers - White Paper. Somers, NY: IBM Watson Health; 2019 April 2019.
3. Health Insurance Portability and Accountability Act 1996. 1996. (Accessed April 6th 2022, 2022, at https://www.hhs.gov/hipaa/index.html.)
4. Hamedani AG, Blank L, Thibault DP, Willis AW. Impact of ICD-9 to ICD-10 Coding Transition on Prevalence Trends in Neurology. Neurol Clin Pract 2021;11:e612-e9.
5. Salemi JL, Tanner JP, Kirby RS, Cragan JD. The impact of the ICD-9-CM to ICD-10-CM transition on the prevalence of birth defects among infant hospitalizations in the United States. Birth Defects Res 2019;111:1365-79.
6. Sebastiao YV, Metzger GA, Chisolm DJ, Xiang H, Cooper JN. Impact of ICD-9-CM to ICD-10-CM coding transition on trauma hospitalization trends among young adults in 12 states. Inj Epidemiol 2021;8:4.
7. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. Circulation 1997;96:358-66.
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;116:1736-54.
9. 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.
10. Chu VH, Sexton DJ, Cabell CH, et al. Repeat infective endocarditis: differentiating relapse from reinfection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2005;41:406-9.
11. Thornhill MH, Jones S, Prendergast B, et al. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. European Heart Journal 2018;39:?-?
12. Code on Dental Procedures and Nomenclature (CDT Code). American Dental Association (ADA),, 2019. (Accessed Sept 8th, 2019, at https://www.ada.org/en/publications/cdt.)
13. International Classification of Diseases,Ninth Revision, Clinical Modification (ICD-9-CM). Centers for Disease Control and Prevention (CDC),, 2019. (Accessed Sept 8th, 2019, at https://www.cdc.gov/nchs/icd/icd9cm.htm.)
14. Wilson WR, Gewitz M, Lockhart PB, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. Circulation 2021;143:e963-e78.
15. Thornhill MH, Gibson TB, Durkin MJ, et al. Prescribing of antibiotic prophylaxis to prevent infective endocarditis. JADA 2020;151:835-45.
16. 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;40:373-83.
17. Doerken S, Avalos M, Lagarde E, Schumacher M. Penalized logistic regression with low prevalence exposures beyond high dimensional settings. PLoS One 2019;14:e0217057.
18. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1991;80:27-38.
19. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133:144-53.
20. Maclure M, Mittleman MA. Should we use a case-crossover design? Annu Rev Public Health 2000;21:193-221.
21. Smeeth L, Donnan PT, Cook DG. The use of primary care databases: case-control and case-only designs. Fam Pract 2006;23:597-604.

22. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. Am J Epidemiol 1995;142:91-8.

23. Chen PC, Tung YC, Wu PW, et al. Dental Procedures and the Risk of Infective Endocarditis. Medicine (Baltimore) 2015;94:e1826.

24. 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;28:269-73.

25. 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.