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# Infective Endocarditis Hospitalizations and Antibiotic Prophylaxis Rates Before and After the 2007 American Heart Association Guideline Revision

Editorial, see p 181

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**BACKGROUND:** In 2007, the American Heart Association recommended antibiotic prophylaxis for the prevention of infective endocarditis (IE) for only the highest-risk patients. Whether this change affected the use of antibiotic prophylaxis and the incidence of IE is unclear.

**METHODS:** IE-related hospitalizations were identified from 2002 to 2014 among all adults and those at high and moderate risk for IE, stratified by age. Prescriptions for antibiotic prophylaxis were obtained from the Ontario Drug Benefit database for adults ≥65 years of age. Outcomes were antibiotic prophylaxis prescription rates and incidence of IE-related hospitalization. Trends in patient and pathogen characteristics were analyzed. Time series analyses were performed with segmented regression and change-point analyses.

**RESULTS:** Prescriptions for antibiotic prophylaxis decreased substantially in the moderate-risk cohort after the guideline revision (mean quarterly prescriptions, 30 680 versus 17 954 [level change, −6,481; *P*=0.0004] per 1 million population) with a minimal, yet significant, decrease followed by a slow increase in the high-risk group. There were 7551 IE-related hospitalizations among 6884 adults ≥18 years of age. Among adults ≥65 years of age, the mean IE rate increased from 872 to 1385 and 229 to 283 per 1 million population at risk per quarter in the high- and moderate-risk groups, respectively. Change-point analyses indicated that this increase occurred in the second half of 2010 in adults ≥65 years of age, 3 years after the American Heart Association guideline revision. *Staphylococcus aureus* and streptococcal species accounted for 30.3% and 26.4% of all IE, with a decrease in streptococcal infections over time.

**CONCLUSIONS:** Antibiotic prophylaxis decreased significantly in the moderate-risk group with minimal change in the high-risk group after the American Heart Association guideline revision in 2007. However, IE-related hospitalizations increased among both high- and moderate-risk patients 3 years after the revision. Our study provides support for the cessation of antibiotic prophylaxis in the moderate-risk population.

**Key Words:** antibiotic prophylaxis ■ endocarditis

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## Clinical Perspective

### What Is New?

- The 2007 American Heart Association guideline revision recommended limiting antibiotic prophylaxis for dental procedures for patients with cardiac conditions associated with the highest risk of adverse outcomes from endocarditis.
- Antibiotic prophylaxis decreased significantly in the moderate-risk group with minimal change in the high-risk group after publication of the American Heart Association guidelines in 2007.
- Infective endocarditis–related hospitalizations have increased since 2010, 3 years after the guideline revision, among both high- and moderate-risk patients and are unlikely to be related to change in antibiotic prophylaxis.

### What Are the Clinical Implications?

- Our study provides support for the 2007 American Heart Association guideline revision of the cessation of antibiotic prophylaxis for the moderate-risk population and limiting its use to those with the highest risk.

Infective endocarditis (IE) is an uncommon but life-threatening condition that is associated with significant morbidity and mortality.[1] For more than half a century, antibiotics have been administered prophylactically before invasive dental procedures with the aim of reducing or eliminating bacteremia to prevent IE in at-risk individuals. Despite the lack of randomized clinical trial evidence and the inadequate data to support the effectiveness of antibiotic prophylaxis for the prevention of IE, this practice persists as standard of care in many parts of the world.[1,2]

Given the lack of proven efficacy and concerns about perceived risks of antibiotic prophylaxis (eg, development of antibiotic resistance), the American Heart Association (AHA) in 2007 and the European Society of Cardiology in 2009 published revised guidelines recommending cessation of antibiotic prophylaxis before dental procedures for patients at moderate risk of IE while continuing the practice in highest-risk patients.[3] In the same year, the Canadian Cardiovascular Society and the Canadian Dental Association endorsed and adopted these AHA revised guidelines.[4–6] In contrast, in 2008, the UK National Institute for Health and Clinical Excellence modified its guidelines recommending the complete cessation of antibiotic prophylaxis in the United Kingdom.[7]

Recent studies examining the effect of restricting oral antibiotic prophylaxis have found conflicting results. A UK study (data from 2004–2013) demonstrated an increase in the incidence of IE corresponding to a significant decrease in antibiotic prophylaxis after the policy change.[8] However, various North American studies have not shown a similar increase in IE incidence.[9–12] Unlike the UK study, North American studies have not specifically assessed or correlated actual antibiotic prescription data to IE incidence. Because of the differing evaluation periods and methodologies used, it is unclear whether the conflicting findings are associated with the differences in practice recommendations between the regions (National Institute for Health and Excellence versus AHA guidelines).[2,13] Furthermore, these previous studies have focused their evaluations on the overall population rate of IE rather than explicitly examining the specific at-risk populations targeted by the guidelines for the prevention of IE.

The AHA has defined individuals with underlying cardiac conditions that predispose them to having high (or moderate) risk for adverse outcomes from IE.[3,14] The AHA also recognizes that these same individuals are those with the highest lifetime risk of acquiring IE.[3] The intent of the AHA guidelines is to identify patients in whom antibiotic prophylaxis should be used to reduce the risk of acquisition of IE.[3]

The first aim of our study was to examine the impact of the revised AHA guidelines on the use of antibiotic prophylaxis among individuals in high- or moderate-risk cohorts based on the AHA guidelines. Second, we sought to determine whether there has been a discernable change in the incidence of IE and, if so, whether this timing corresponds to the release of the 2007 AHA guidelines.

## METHODS

### Study Design and Setting

We conducted a population-based, cross-sectional time series analysis in cohorts of individuals 18 to 105 years of age at high and moderate risk of IE between January 1, 2002, and December 31, 2014, in Ontario, Canada (≈14 million population). All residents of Ontario obtain healthcare services from a government-administered single-payer system. The study was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, ON, Canada). Participant informed consent was not required. This report follows the RECORD (Reporting of studies Conducted by Using the Observational Routinely-Collected Health Data) statement. The data, analytical methods, and study materials will not be made publicly available to other researchers for purposes of reproducing the results or replicating the procedure. However, with review and approval, the information is available from the Institute for Clinical Evaluative Sciences (ICES) under established data-sharing procedures.

### Data Sources

The study obtained data from multiple population-based administrative healthcare databases from the province of Ontario that are housed at ICES. We obtained cohorts at high

and moderate risk of IE and data pertaining to comorbidities and hospitalizations for IE using hospital and emergency department visits from the Canadian Institute for Health Information Discharge Abstract Database (inpatient hospitalizations), Canadian Institute for Health Information National Ambulatory Reporting Care System (emergency department visits and day surgeries), and the Ontario Health Insurance Plan databases (physician service claims). We ascertained prescription claims using the Ontario Drug Benefit program database, which provides provincially funded universal drug coverage to residents ≥65 years of age. The practice specialty of the prescribers was identified with the Corporate Provider Database. Finally, the Registered Persons Database and the Canadian Census database were used to obtain basic demographic and vital statistics. All databases were linked through the use of unique encoded identifiers and analyzed at ICES. These databases have previously been used to evaluate the impact of policy changes and other healthcare evaluations.[15–17] Detailed database definitions, variable definitions, and administrative codes are given in (Tables I through V in the online-only Data Supplement).

## Identification of Cohorts at High and Moderate Risk for IE

We divided the 13-year study period into quarterly (3-month) intervals for a total of 52 periods. In each quarter, we identified all Ontario residents ≥18 years of age who were alive on the first day of each quarter (and therefore eligible to receive health services in Ontario) and stratified them into 2 mutually exclusive IE risk groups of high and moderate risk. Data were prepared for 2 distinct interventional time series analysis focused only on the populations defined by the 1997 and 2007 AHA guidelines: high-risk and moderate-risk cohorts.[3,14] Using a look-back period of 10 years, we reviewed all recorded diagnostic and procedural codes, and individuals were categorized into either the high- or the moderate-risk cohort. Residents meeting the definition for both high and moderate risk were preferentially categorized into the high-risk cohort. The high-risk cohort was defined as those individuals with cardiac conditions that included previous IE, prosthetic cardiac valve replacement or prosthetic material used in cardiac valve repair, and certain forms of congenital heart disease (eg, cyanotic congenital heart disease or surgical or percutaneous procedures in patients with congenital heart disease).[3,18] The moderate-risk cohort had cardiac conditions that included acquired valvular heart disease, hypertrophic cardiomyopathy, and other congenital cardiac malformations not included in the high-risk category[14] (Tables II and III in the online-only Data Supplement). Each of the risk cohorts was further stratified by age into 2 groups: 18 to 64 and ≥65 years of age.

## Outcome Definitions

### *Antibiotic Prophylaxis*

In accordance with the AHA guidelines, we identified antibiotic prophylaxis for IE as a 1-day supply of amoxicillin, cephalexin, clindamycin, clarithromycin, or azithromycin using the Ontario Drug Benefit database.[3] Prescriptions for antibiotic prophylaxis were restricted to residents ≥65 years of age and were presented as quarterly rates for residents at high or moderate risk for IE. As a sensitivity analysis and to confirm that observable differences over time were unrelated to changes in the availability or coverage of the candidate antibiotics, we also collected the quarterly rates for the 5- to 10-day course of the same medications, which are often used for other indications. We also documented the specialty of the prescribers.

### *Hospitalizations for IE*

Within each study quarter, we identified new episodes of IE, defined as an admission for IE with no previous hospital discharge for IE in the previous 90 days. IE hospitalizations were ascertained with discharge diagnoses codes (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 4210 or 4219 for January 1, 2002–March 31, 2002, and *International Classification of Diseases, 10th Revision* [*ICD-10*] code I-330 or I-339 for the subsequent period, April 1, 2002–December 31, 2014).

## Patient and Pathogen Characteristics

We collected a number of characteristics of patients experiencing a new episode of IE over the study period, including baseline demographic and clinical characteristics. For baseline characteristics, we focused on the first episode to avoid comparing the same patient at different ages and risk over time and collapsed reporting into 3 time periods (2002–2006, 2007–2010, and 2011–2014) for ease of presentation.

For each episode of IE, we also identified the causal microorganisms associated with the hospital encounter using primary and secondary diagnostic codes based on *ICD-9*/*ICD-10* classification as follows: *Staphylococcus aureus*, other staphylococcal species, streptococcal species, Gram-negative bacilli, candida, enterococcal, and unknown.

## Statistical Analysis

We conducted time series analyses to examine the impact of the April 2007 release of the revised AHA guidelines on the prescribing of antibiotic prophylaxis in residents ≥65 years of age and new episodes of IE in residents 18 to 64 and ≥65 years of age. All results were analyzed separately for residents meeting the definitions for high and moderate risk for IE. To enable comparisons with previously conducted studies, we also evaluated the population rate of antibiotic prophylaxis (calculated at a monthly rate) and new IE episodes over time. We presented all results at a rate of per 1 million population at risk.

All analyses were conducted with the segmented regression analysis of interrupted time series data, a method that quantifies the immediate impact of the 2007 guideline change as measured by a change in the level (ie, rate) and the trend (ie, slope) after the release of the revised guidelines. Segmented linear regression is an appropriate method to evaluate the impact of a health policy change and has been used in numerous studies.[8,17,19,20]

We further conducted change-point analyses using the R package changepoint to determine whether a discernable change in the pattern of new episodes of IE occurred over the study period and to ascertain the timing of any such change.[21] Model appropriateness was assessed by reviewing the autocorrelation, partial autocorrelation, and inverse

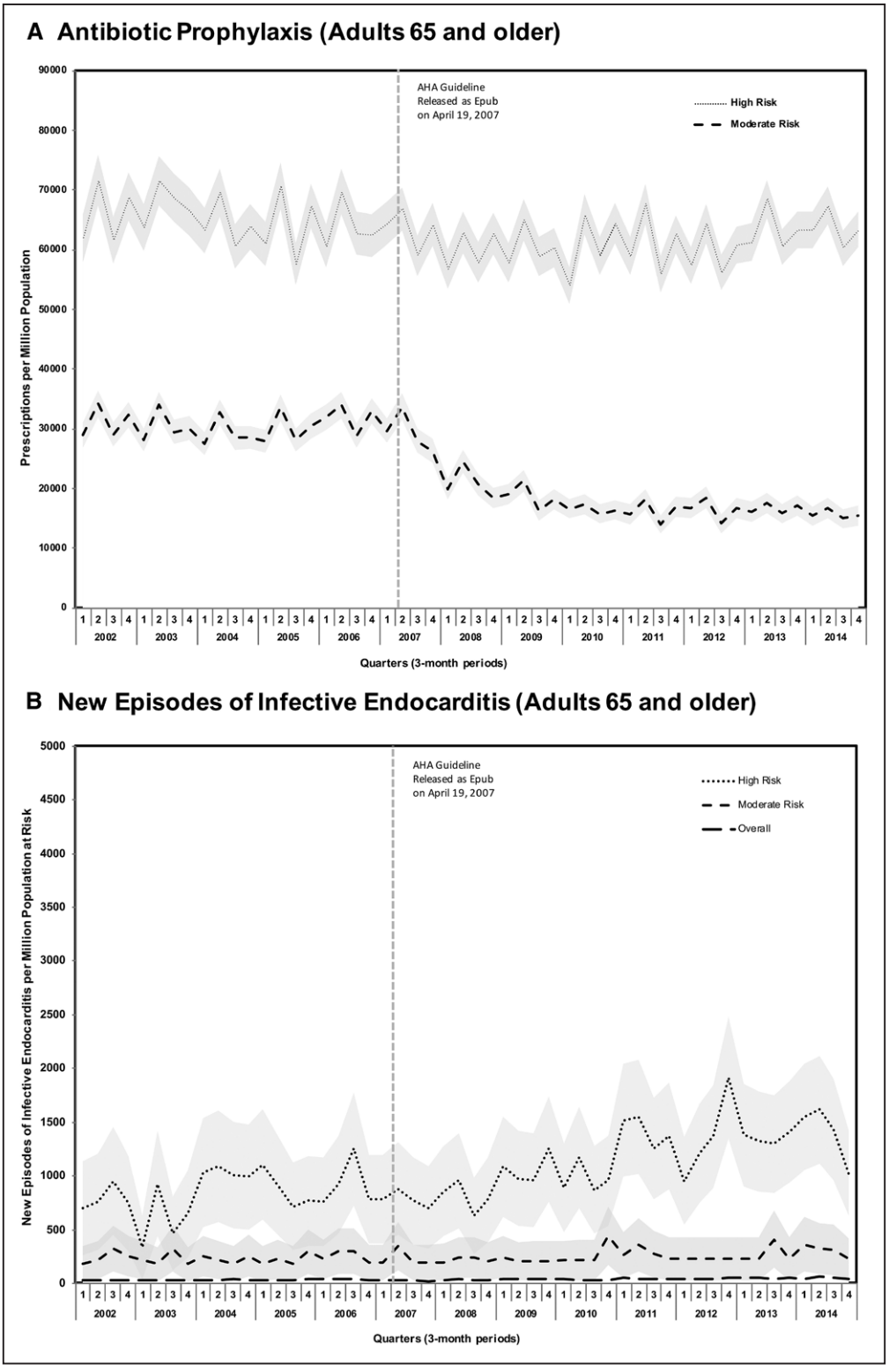


**Figure 1. Antibiotic prophylaxis and infective endocarditis hospitalizations (adults 65 and older).**
**A**, Quarterly rate (per 1 million population) of prescriptions dispensed for antibiotic prophylaxis among residents at high and moderate risk for infective endocarditis (IE; ≥65 years of age) from 2002 to 2014. Denominator is the number of residents who met the criteria for high or moderate risk of IE. Numerator is the number of antibiotics dispensed for the respective risk populations within the quarter. **B**, Quarterly rate (per 1 million population) of new episodes of IE hospitalizations among residents at high risk, moderate risk, and all risk combined (overall) for IE among those ≥65 years of age from 2002 to 2014. Denominator for the high- and moderate-risk groups is the number of residents who met the criteria for high or moderate risk of IE, respectively. Denominator for overall group is the population estimate of Ontario residents ≥65 years of age. Numerator is the number of individuals who experienced a new episode of IE for the respective risk populations within the quarter. Shaded regions indicate 95% CIs. Dashed vertical line indicates the release of the updated American Heart Association (AHA) guidelines as published electronically ahead of print in PubMed. Numerator counts of ≤5 recoded as 5 to adhere to Institute for Clinical Evaluative Sciences privacy requirements.

autocorrelation functions, whereas the order of autocorrelations was assessed with the Durbin-Watson test.

When a change point was detected, the average slope before and after the change point was calculated with the ordinary least squares method, and the mean quarterly incidence rate was calculated for the period before and after.

We compared the characteristics of patients who experienced a new episode of IE during the 3 study time periods: 2002 to 2006, 2007 to 2010, and 2011 to 2014. Categorical variables were reported as proportions and continuous variables as means (SD) and medians (interquartile range). Differences between the time periods were assessed using the $\chi^2$ test for categorical data and 1-way ANOVA for continuous data. The 90-day crude mortality rate was calculated for each year of the study across risk strata and age groups. The annual percentage change was calculated with a Poisson regression model and is presented as annual percentage change with its 95% CI. All analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC) and R 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). All *P* values are 2 sided, and a value of $P<0.05$ was considered statistically significant.

# RESULTS

## Antibiotic Prophylaxis Prescriptions

Among older adults (≥65 years of age) at high risk for IE, antibiotic prophylaxis was prescribed at an average quarterly rate of 62 996 (SD, 4262) prescriptions per 1 million population (Figure 1A and Table VI in the online-only Data Supplement). The release of the revised AHA guidelines resulted in a minimal yet statistically significant immediate decrease in prescriptions (level change, −3889 prescriptions per 1 million population; $P=0.006$), followed by a slow increase in the rate thereafter ($P=0.01$). In contrast, there was a rapid and significant decrease in rate of antibiotic prophylaxis in the moderate-risk cohort after the release of the revised AHA guidelines, with the mean quarterly rate of prescriptions dropping from 30 680 (SD=2311) to 17 954 (SD=3280) per 1 million population in the periods before and after the guideline release (level change, −6481 prescriptions per 1 million population; $P=0.0004$). A similar significant decrease in prophylaxis was also observed at the population level (Figure I in the online-only Data Supplement). The majority of the prescriptions (78%) were issued by dentists or dental surgeons, followed by general practitioners (17%).

Sensitivity analyses did not identify a change in prescriptions from a 5-day to a 10-day course of the same antibiotics during the same period ($P=0.649$ for level change; Figure II in the online-only Data Supplement). This extended course of antibiotics was prescribed mostly by general practitioners (68%); 23% were prescribed by dentists or dental surgeons.

## Incidence of IE

Between January 1, 2002, and December 31, 2014, there were a total of 7551 new hospitalizations for IE among 6884 adult patients ≥18 years of age in Ontario. Although most patients were hospitalized for 1 episode of endocarditis (6352, 92.3%), 430 (6.3%) experienced 2 episodes, and 102 (1.4%) had ≥3 episodes of IE over the 13-year study period.

Among adults ≥65 years of age, both the high-risk and moderate-risk groups exhibited an increase in the quarterly rate of new IE episodes over the study period, whereas the magnitude of the event rates differed substantially (Figure 1B). The rate of new IE episodes ranged from 336 to 1915 per 1 million population for patients at the highest risk of IE, 180 to 440 per 1 million population for patients at moderate risk of IE, and 23 to 60 per 1 million population among all adults ≥65 years of age. Change-point analysis identified a significant change in the quarterly rate of new episodes of IE within the latter half of 2010 (third and fourth quarters) for all risk groups (high-risk cohort: mean IE rate increased from 872 [SD, 195] to 1385 [SD, 221] per 1 million population before and after the identified change point; moderate-risk cohort: mean rate increased from 229 [SD, 45] to 283 [SD, 70] per 1 million population; all adults ≥65 years of age: mean rate increased from 32 [SD, 4] to 47 [SD, 5] per 1 million population; Figure III in the online-only Data Supplement).

The pattern of new episodes of IE was similar in the younger adult group (18–64 years of age) among the high- and moderate-risk groups (Figure 2). Change-point analysis detected a significant change in rates of IE in the second quarter (April–June) of 2010 among the high- and moderate-risk groups (high-risk cohort: mean IE rate increased from 1061 [SD, 25] per 1 million population to 1754 [SD, 30] per 1 million population before and after the identified change point; moderate-risk cohort: rate increased from 308 [SD, 37] to 423 [SD, 66] per 1 million population). However, no significant change point was detected for the overall 18- to 64-year-old group (mean rate, 9 [SD, 2.7] per 1 million population throughout the study period; Figure III in the online-only Data Supplement). Using of the 2014 estimate, we found that the rates of new episodes of IE were 1.41-fold, 1.42-fold, and 3.55-fold higher among adults ≥65 years of age compared with the 18- to 64-year-old group in the high-risk, moderate-risk, and overall populations, respectively.

## Patient Characteristics

The mean age of all the patients experiencing a new episode of IE was 60.7 years, and 63.7% were male (Table). High-risk and moderate-risk features for risk of IE were present in 19.2% and 6.6% of cases, respectively.

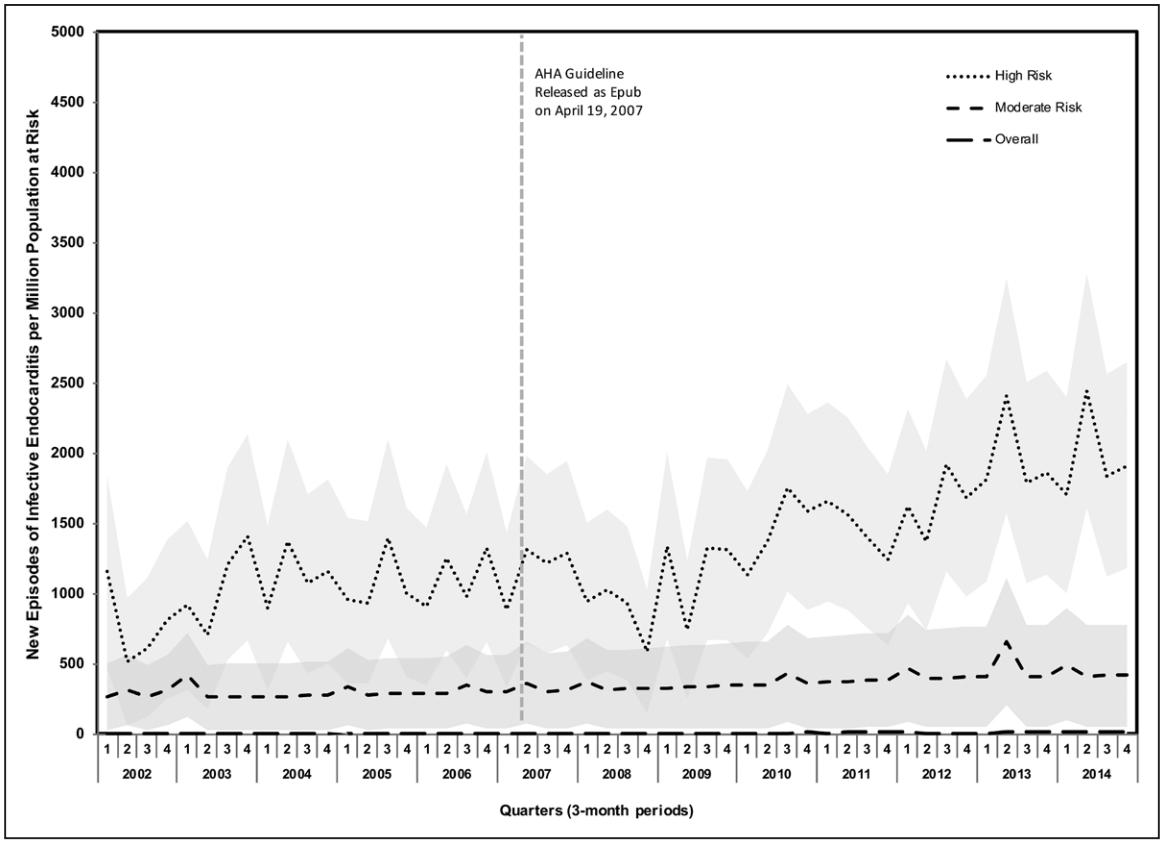


**Figure 2. Infective endocarditis hospitalizations (adults 18–64).**
Quarterly rate (per 1 million population) of new episodes of infective endocarditis (IE) hospitalizations among residents at high risk, moderate risk, and all risk combined (overall) for IE in individuals 18 to 64 years of age from 2002 to 2014. Denominator for high- and moderate-risk groups is the number of residents who met the criteria for high or moderate risk of IE, respectively. Denominator for the overall group is population estimate of Ontario residents 18 to 64 years of age. Numerator is the number of individuals who experienced a new episode of IE (no previous hospitalization for IE in the previous 90 days) for the respective risk populations within the quarter. The shaded regions indicate 95% CIs. Dashed vertical line indicates the release of the updated American Health Association (AHA) guidelines as published electronically ahead of print in PubMed. Numerator counts of ≤5 recoded as 5 to adhere to ICES privacy requirements.



Preexisting acquired valve disease, both rheumatic and nonrheumatic, was recorded in 25.1% of all patients and was twice as likely to be present in the older age group compared with those 18 to 64 years of age. Previous valve replacement and repair was present in 18.6% and 2.9%, respectively. Although there was an increase in rates of valve replacement and repair with time in patients ≥65 years of age (23.4% and 2.2% in the 2002–2006 period to 30.7% and 5.0% in the 2011–2014 period, respectively; $P<0.001$ for both), rates of valve replacement and repair were unchanged in the 18- to 64-year-old group during the study period ($P=0.400$ and $P=0.599$, respectively). Other comorbidities (diabetes mellitus, chronic kidney disease, hypertension, dialysis) also increased over time. Although the fraction of patients with a history of drug abuse, mental disorder, or hepatitis C increased over time in the 18- to 64-year-old group, these rates declined or remained steady in the older adult group and were more commonly present in the younger age group. Average length of stay for IE was 30.7 days and did not change over the period. The crude 90-day mortality rate was unchanged from 2002 through 2014 (18- to 64-year-old group: from 18.0% to 18.0%, respectively; annual percentage change, 0.66% [95% CI, −1.26 to 2.61]; $P=0.50$; ≥65-year-old group: from 38.0% to 36.0%, respectively; annual percentage change, −0.80% [95% CI, −2.31 to 0.74]; $P=0.31$). The 90-day mortality annual percentage change was not significant for any of the risk groups (Table VII in the online-only Data Supplement).

## Pathogens

An associated microorganism was reported as a coexisting diagnosis in 5573 (73.8%) episodes of IE. *Staphylococcus aureus* and streptococcal species were the most commonly reported pathogens, recorded in 30.3% and 26.4% of the episodes, respectively. Other staphylococcal species were recorded for 10.5% of the cases, whereas Gram-negative or candida species were present in 6.5% of cases. Multiple organisms (≥2) were reported in 8.7% of hospitalizations. Among adults ≥65 years of age, *S aureus* and streptococcal species accounted for the majority of episodes (21.5% and 29.0%, respectively), with no significant change over

**Table. Baseline Characteristics**

| | 2002–2006 | | 2007–2010 | | 2011–2014 | | All Years |
|---|---|---|---|---|---|---|---|
| | Ages 18–64 y | Age ≥65 y | Ages 18–64 y | Age ≥65 y | Ages 18–64 y | Age ≥65 y | Age ≥18 y |
| No. | 1074 | 997 | 1075 | 857 | 1479 | 1402 | 6884 |
| IE hospitalization | | | | | | | |
| Year | | | | | | | |
| 2002 | 215 (20.0) | 180 (18.1) | … | … | … | … | 395 (5.7) |
| 2003 | 198 (18.4) | 187 (18.8) | … | … | … | … | 385 (5.6) |
| 2004 | 224 (20.9) | 213 (21.4) | … | … | … | … | 437 (6.3) |
| 2005 | 215 (20.0) | 191 (19.2) | … | … | … | … | 406 (5.9) |
| 2006 | 222 (20.7) | 226 (22.7) | … | … | … | … | 448 (6.5) |
| 2007 | … | … | 256 (23.8) | 173 (20.2) | … | … | 429 (6.2) |
| 2008 | … | … | 244 (22.7) | 203 (23.7) | … | … | 447 (6.5) |
| 2009 | … | … | 252 (23.4) | 251 (29.3) | … | … | 503 (7.3) |
| 2010 | … | … | 323 (30.0) | 230 (26.8) | … | … | 553 (8.0) |
| 2011 | … | … | … | … | 362 (24.5) | 320 (22.8) | 682 (9.9) |
| 2012 | … | … | … | … | 318 (21.5) | 323 (23.0) | 641 (9.3) |
| 2013 | … | … | … | … | 389 (26.3) | 356 (25.4) | 745 (10.8) |
| 2014 | … | … | … | … | 410 (27.7) | 403 (28.7) | 813 (11.8) |
| Demographics | | | | | | | |
| Age, median (IQR), y | 49 (38–57) | 76 (70–80) | 49 (39–58) | 76 (70–81) | 49 (35–57) | 76 (70–82) | 63 (48–75) |
| Male, n (%) | 718 (66.9) | 594 (59.6) | 683 (63.5) | 550 (64.2) | 920 (62.2) | 917 (65.4) | 4382 (63.7) |
| Rural residence, n (%) | 159 (14.8) | 129 (12.9) | 129 (12.0) | 104 (12.1) | 197 (13.3) | 176 (12.6) | 894 (13.0) |
| Neighborhood income quintile, n (%) | | | | | | | |
| 1 | 254 (23.6) | 182 (18.3) | 303 (28.2) | 160 (18.7) | 477 (32.3) | 258 (18.4) | 1634 (23.7) |
| 2 | 227 (21.1) | 195 (19.6) | 218 (20.3) | 152 (17.7) | 290 (19.6) | 286 (20.4) | 1368 (19.9) |
| 3 | 204 (19.0) | 216 (21.7) | 205 (19.1) | 174 (20.3) | 266 (18.0) | 270 (19.3) | 1335 (19.4) |
| 4 | 199 (18.5) | 188 (18.9) | 169 (15.7) | 189 (22.1) | 219 (14.8) | 296 (21.1) | 1260 (18.3) |
| 5 | 190 (17.7) | 216 (21.7) | 180 (16.7) | 182 (21.2) | 227 (15.3) | 292 (20.8) | 1287 (18.7) |
| Comorbidities, n (%) | | | | | | | |
| Charlson Comorbidity Index score, median (IQR) | 0 (0–2) | 2 (0–3) | 1 (0–2) | 2 (0–4) | 1 (0–3) | 2 (1–4) | 1 (0–3) |
| Diabetes mellitus, n (%) | 198 (18.4) | 345 (34.6) | 267 (24.8) | 356 (41.5) | 371 (25.1) | 632 (45.1) | 2169 (31.5) |
| Chronic kidney disease, n (%) | 127 (11.8) | 215 (21.6) | 153 (14.2) | 212 (24.7) | 226 (15.3) | 366 (26.1) | 1299 (18.9) |
| Dialysis, n (%) | 81 (7.5) | 67 (6.7) | 88 (8.2) | 74 (8.6) | 140 (9.5) | 121 (8.6) | 571 (8.3) |
| History of drug abuse, mental disorder, n (%) | 252 (23.5) | 76 (7.6) | 299 (27.8) | 33 (3.9) | 460 (31.1) | 23 (1.6) | 1143 (16.6) |
| Hepatitis C, n (%) | 119 (11.1) | 9 (0.9) | 171 (15.9) | 6 (0.7) | 274 (18.5) | 12 (0.9) | 591 (8.6) |
| Predisposing conditions, n (%) | | | | | | | |
| Previous IE | 59 (5.5) | 39 (3.9) | 24 (2.2) | 13 (1.5) | 37 (2.5) | 14 (1.0) | 186 (2.7) |
| Previous valve replacement | 108 (10.1) | 233 (23.4) | 120 (11.2) | 245 (28.6) | 141 (9.5) | 431 (30.7) | 1278 (18.6) |
| Previous valve repair | 24 (2.2) | 22 (2.2) | 22 (2.0) | 36 (4.2) | 25 (1.7) | 70 (5.0) | 199 (2.9) |
| Previous CHD (high risk) | 19 (1.8) | 7 (0.7) | 18 (1.7) | 15 (1.8) | 21 (1.4) | 21 (1.5) | 101 (1.5) |
| Previous CHD (moderate risk) | 47 (4.4) | 17 (1.7) | 47 (4.4) | 27 (3.2) | 50 (3.4) | 32 (2.3) | 220 (3.2) |
| Acquired valvular disease | 176 (16.4) | 340 (34.1) | 181 (16.8) | 300 (35.0) | 224 (15.1) | 505 (36.0) | 1726 (25.1) |
| Risk category, n (%) | | | | | | | |
| High | 143 (13.3) | 242 (24.3) | 125 (11.6) | 236 (27.5) | 144 (9.7) | 434 (31.0) | 1324 (19.2) |
| Moderate | 64 (6.0) | 117 (11.7) | 53 (4.9) | 71 (8.3) | 64 (4.3) | 86 (6.1) | 455 (6.6) |

CHD indicates congenital heart disease; IE, infective endocarditis; and IQR, interquartile range.

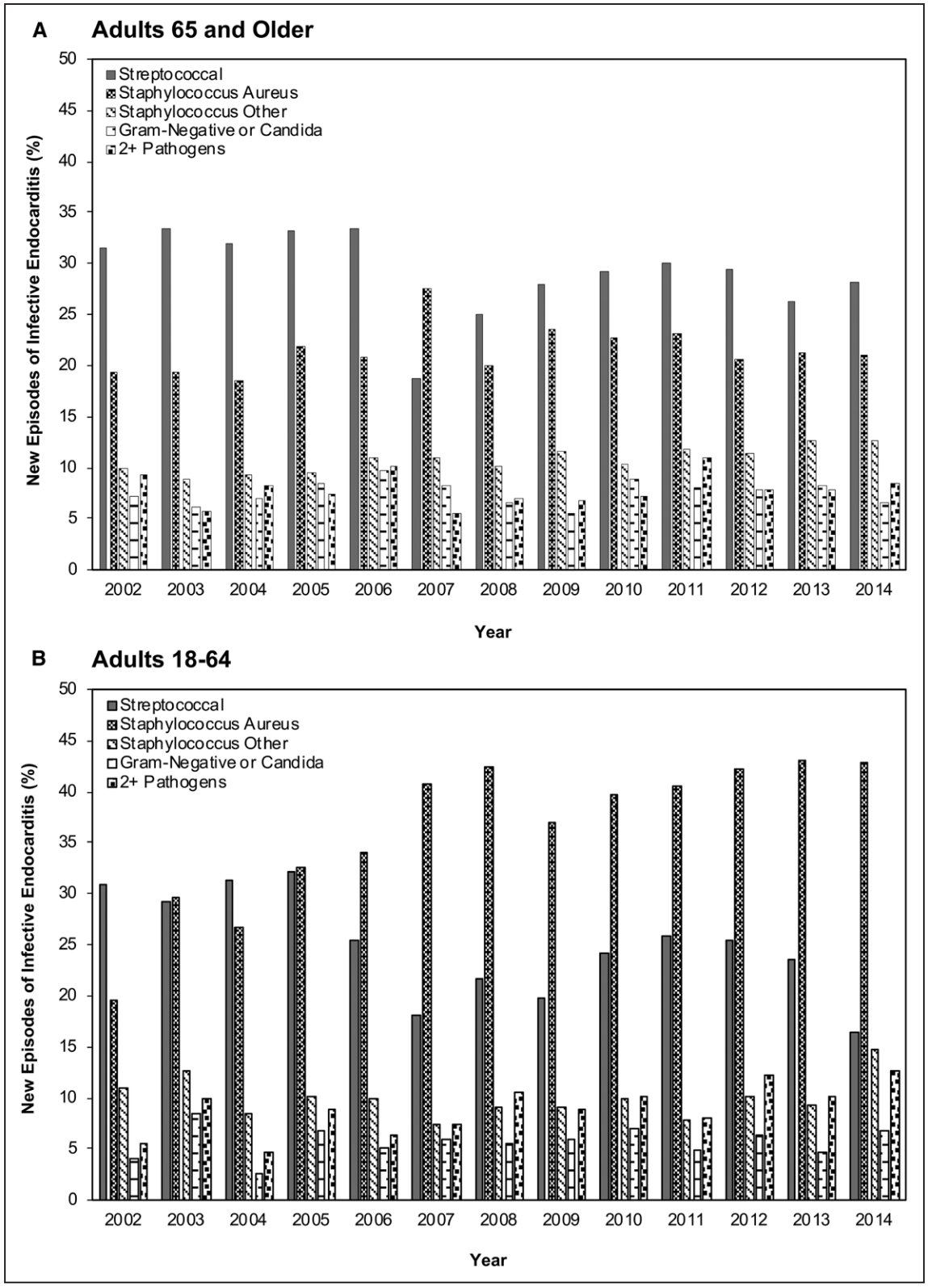


**Figure 3. Pathogens associated with infective endocarditis.**
**A**, Percent of recorded pathogens associated with new episodes of infective endocarditis (IE) among adults ≥65 years of age. **B**, Percent of recorded pathogens associated with new episodes of IE among adults 18 to 64 years of age from 2002 to 2014.

time (proportion change per year for *S aureus*: slope, 0.18, *P*=0.31; for streptococcal species: slope, –0.40, *P*=0.19; Figure 3A). Among the 18- to 64-year-old group, *S aureus* was recorded most often (37.7%), with the proportion of *S aureus* increasing substantially from 2002 through 2014 (from 20% to 43%; slope, 1.65;

*P*<0.0001), whereas the proportion of streptococcal species decreased (from 31% to 20%; slope, −0.87; *P*=0.007; Figure 3B).

## DISCUSSION

This study examined the impact of the revised AHA guidelines published in April 2007 among individuals at high and moderate risk for IE. We found a sustained reduction in antibiotic prophylaxis prescriptions among individuals at moderate risk for IE that coincided with the change in guidelines. In contrast, although there was a decreasing trend in antibiotic prophylaxis among individuals at high risk of IE and a minimal drop was noted after the guideline release, the overall rates of prophylaxis prescribing in this group have continued to climb since early 2007. Collectively, these findings suggest appropriate uptake of the revised AHA guidelines. Furthermore, over the 13-year study period, we identified a significant increase in hospitalizations for new episodes of IE ≈3 years after the AHA guidelines were revised. This time lag, along with the rise in IE incidence in both the high- and moderate-risk groups, suggests that this observed increase in endocarditis is likely unrelated to the change in the prescribing practice of antibiotic prophylaxis. This conclusion is further supported by the overall decrease in endocarditis cases attributable to streptococcal infections over time, a finding contrary to what might be expected as a result of the reduction in antibiotic prophylaxis.

Ours is the first and among the most comprehensive studies to evaluate the uptake and impact of the revised AHA guidelines by describing both the change in antibiotic prescription rates and the incidence of IE in various groups at risk for IE. Only 1 other study has described both antibiotic prophylaxis rates and IE incidence: In the United Kingdom, where the National Institute for Health and Excellence advised against antibiotic prophylaxis entirely in 2008, Dayer et al[8] demonstrated a significant (79%) reduction in antibiotic prophylaxis prescribing after the introduction of the National Institute for Health and Excellence guidelines, and this was temporally associated with a significant increase in the population rate of IE of 0.11 cases per 10 million people per month. As with the overall increase in IE incidence in the UK study, we found an increase in IE incidence in both the high- and moderate-risk groups, although this change occurred 3 years after the AHA guideline revision. However, as targeted by the AHA revision, antibiotic prophylaxis rates were significantly lower in the moderate-risk group with minimal change in the high-risk group. Thus, in contrast to the UK study, our study suggests that antibiotic prophylaxis may make little difference to IE incidence and supports the AHA position of cessation of antibiotic prophylaxis in the moderate-risk group.

Similar efforts to examine the effects of the AHA 2007 guidelines on the incidence of IE in North America have yielded conflicting results. Analysis of the Nationwide Inpatient Sample database in the United States showed that the population-wide incidence of IE rose steadily from 2000 to 2011, with an increased incidence of IE attributable to streptococcal IE (but not of staphylococcal) after the publication of the revised AHA guidelines.[22] Unlike the UK study, however, the authors did not perform a formal change-point analysis and were therefore unable to conclude a change in hospitalizations for IE after the guideline release.[22] In a smaller community-based study from the United States, DeSimone et al[23] explored the incidence of IE resulting from streptococcal species and found no increased incidence after the AHA guideline revision. Other North American population-based studies have also found no evidence for an increase in endocarditis incidence coinciding with the AHA guideline amendment.[9,11,12] However, in contrast to our study, none of these other studies examined antibiotic prophylaxis rates to evaluate any association between changes in antibiotic prophylaxis and the magnitude and timing of change in IE incidence, and none focused on at-risk populations targeted by the guideline revision.

We found that the rates of IE increased in all risk groups over the study period, with the magnitude of increase greatest in the high-risk group, followed by the moderate-risk group and overall population among older adults. A few other population-based studies have also reported an increase in IE incidence over time.[22,24–27] Olmos et al[26] showed an increase in IE incidence in Spain from 2003 to 2014, with the rise being significantly higher among older adults. However, in our study, change-point analysis identified a significant change in the second half of 2010, 3 years after the AHA guideline revision. The cause of such a change in 2010 is unclear, and we were unable to identify a sudden change in predisposing condition that could explain the increased incidence. Among patients ≥65 years of age, there was an increase in rates of previous valve replacements and repair over time with increasing comorbidities such as diabetes mellitus, whereas the rates of hepatitis C and history of drug abuse or mental disorder, a surrogate for intravenous drug use, were steady. A similar increase in comorbidities and predisposing conditions has been shown in other studies[26,28] and may explain the increase in IE incidence in older adults. In contrast, although we were unable to ascertain intravenous drug use rates specifically, among the 18- to 64-year-old group, rates of history of hepatitis C and drug abuse or mental disorder increased over time. It is possible that an increase in intravenous drug use in the younger age group may be responsible for at least part of the increase in IE and is consistent with the increase in *S aureus* infections seen in this age group.

Antibiotic administered prophylactically before invasive dental procedures to prevent IE in at-risk individuals

is targeted to prevent streptococcal infections. With the reduction in antibiotic prophylaxis seen in our study, we did not find a concomitant increase in proportion of IE caused by streptococcal infections. Among adults ≥65 years of age, although streptococcal species accounted for the majority of episodes (29.0%), there was no significant change over time. In the 18- to 64-year-old group, *S aureus* accounted for the majority of episodes (38%), with increasing proportion over time and a decrease in streptococcal infections. Our findings are in contrast to data from the US Nationwide Inpatient Sample database,[22] which suggested increasing rates of streptococcal endocarditis, but are consistent with findings from more recent analysis of data from larger population-based studies from California, New York, and Spain.[12,26]

Our study has several limitations. The data are derived from administrative databases, which are prone to misclassification. However, previous validation studies in Canada (using *ICD-10*) and the United States (using *ICD-9*) have shown that cases of IE can be accurately identified from administrative data using ICD codes with positive predictive value ranging from 78% to 94%.[12,29–32] Furthermore, coding is performed by trained coders and is based on discharge diagnoses rather than admission codes, according to standardized protocols defined and validated by the Canadian Institutes of Health Information. Moreover, we defined endocarditis on the basis of primary and secondary diagnoses to avoid underestimation of IE in discharge diagnoses. In addition, we used more specific *ICD-10* codes from 2002 onward to increase diagnostic specificity and validity. However, endocarditis may not universally result in hospital admission, and we may have underestimated the true incidence of endocarditis. The organisms identified were assumed to be causative if they were coded during the hospitalization, but this could not be validated, and microbiological data were missing in 26% of cases. There are limited data on the validity of organism-specific ICD codes. Although a recent New York study suggested a positive predictive value of 88% for causal microorganisms identified by *ICD-9* codes, there are no similar validation studies with *ICD-10* codes.[12] Furthermore, we did not have data on resistant microorganisms. Antibiotic prophylaxis prescription data were available only for oral prescriptions; in-hospital intravenous use of prophylaxis was not captured. Lastly, the data are observational and are subject to confounding. However, a randomized trial to evaluate causal association between antibiotic prophylaxis and IE prevention is highly unlikely because of cost and logistics.[33]

## Conclusions

Antibiotic prophylaxis decreased significantly in the moderate-risk group with minimal change in high-risk group after publication of the AHA guidelines in 2007. IE-related hospitalizations have increased since 2010 among both high- and moderate-risk patients and are unlikely to be related to change in antibiotic prophylaxis. Our study provides support for the AHA guideline revision of the cessation of antibiotic prophylaxis for the moderate-risk population. Further studies are needed to explore potential reasons for the recent increase in the incidence of IE.

## ARTICLE INFORMATION

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