Estimated Risk of Endocarditis in Adults with Predisposing Cardiac Conditions Undergoing Dental Procedures With or Without Antibiotic Prophylaxis

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Background. Although antibiotic prophylaxis for infective endocarditis (IE) has been recommended for persons with predisposing cardiac conditions (PCCs) for many years, its efficacy, which has not been demonstrated, has been recently challenged. To assess its usefulness, we estimated the risk of developing IE after undergoing a dental procedure for which subjects would be eligible for prophylaxis, both in subjects having (protected procedure) or not having (unprotected procedure) received antibiotic prophylaxis.

Methods. The number of French persons with PCCs, the annual number of dental procedures in which subjects would be eligible for antibiotic prophylaxis, and the number of procedures that were unprotected were estimated on the basis of a survey performed on a sample of 2805 subjects aged 25–84 years. The annual number of IE cases possibly due to an unprotected procedure was estimated on the basis of a 1-year epidemiological study of IE conducted in an area inhabited by 16 million people.

Results. After standardization, extrapolation of results to the age-equivalent general population (39 millions subjects) indicated the following: first, 3.3% (95% confidence interval [CI], 2.6%–4%) of the subjects had PCC, 2.7 million (95% CI, 2.3–3.2 million) of whom had undergone at least 1 at-risk dental procedures within the survey year, and the procedures were unprotected in 62% of cases; second, 37 (95% CI, 18–68; 2.7%) of the 1370 annual IE cases in France were possibly related to unprotected procedures. Thus, the risks of developing IE were estimated to be 1 in 46,000 for unprotected procedures (1 in 10,700 and 1 in 54,300 for subjects with prosthetic and native valve PCC, respectively) and 1 in 150,000 for protected procedures.

Conclusions. A huge number of prophylaxis doses would be necessary to prevent a very low number of IE cases.
tients to the risk of anaphylactic reaction (1.5–4 cases per 10,000 patients treated), which is potentially fatal (mortality rate, 0.15 deaths per 10,000 uses) [11, 12].

The lack of any comparative study and firm conclusion leads to interpretations of data that differ between recent recommendations and guidelines [2, 13–16]. The French recommendations issued in 2002 advocate reducing the use of systematic prophylaxis to only high-risk persons [13]; the 2004 British recommendations dramatically increased the number of persons and procedures to be covered [15, 17], the modification of which has been diversely appreciated [18]. The recent review of the Cochrane Database concluded that “there is lack of evidence to support published guidelines in this area” [19]. These contradictions in approaches are partly the result of the absence of a real estimation of the risk of developing IE after dental procedures. To contribute to the debate, we estimated the risk in adults with known PCC of developing IE after an invasive procedure on the basis of whether dental procedures were performed with or without antibiotic prophylaxis.

METHODS

The analysis was restricted to the 25–84-year-old persons from the French population, hereafter referred to as “the adults.” To assess the risk of developing IE after an at-risk dental procedure, we estimated (1) the annual number of at-risk dental procedures performed in adults with known PCCs in France (i.e., the “denominator”), and (2) the estimated annual number of IE cases that occur after at-risk dental procedures in adults with known PCCs in France (i.e., the “numerator”).

The risk of IE after an at-risk dental procedure was estimated by combining these estimations in the following formula: risk = annual number of IE cases after at-risk dental procedures in adults with known PCCs/annual number of at-risk dental procedures in adults with known PCCs. Two risk estimates were calculated, according to whether at-risk dental procedures were “protected” or “unprotected.” Dental procedures at risk for IE were those defined by the French recommendations for IE prophylaxis, which are very close to the American ones [2, 20]. At-risk procedures were considered to be “unprotected” if antibiotic prophylaxis recommendations were not applied and were considered to be “protected” if they were applied. For protected and unprotected dental procedures, risk estimates were calculated for all patients with known PCCs, and estimates were calculated separately on the basis of whether the patients had native valve PCCs or prosthetic valve PCCs.

Estimation of the annual number of at-risk dental procedures in adults with known PCCs (denominator). The prevalence of known PCCs was estimated from a sample of 2805 adults drawn from 2 studies ongoing in 1998: (1) 1829 subjects, including all 25–74-year-old subjects from the CANEVAS study, a cross-sectional epidemiological survey of a randomly selected sample of inhabitants of a French area of 2.3 million inhabitants [21]; and (2) all 976 subjects (age, 75–84 years) seen at the 10-year follow-up visit of the PAQUID research program, a prospective cohort study of normal and pathological cerebral aging, composed of a representative sample of randomly selected subjects (age, ≥65 years) living in the communities of 2 French areas (1.7 million inhabitants) [22]. A structured and previously validated questionnaire was administered by phone interview to classify subjects as having a PCC or not [23]. PCCs were defined according to the French recommendations for IE prophylaxis.

Subjects who declared that they had a PCC were also asked whether they had undergone any dental procedures within the previous month and, if so, what type of procedure (with use of a standardized questionnaire) and whether antibiotic prophylaxis had been given. Dental procedures were subsequently classified as being at risk or not at risk for IE on the basis of French recommendations for IE prophylaxis. The annual number of dental procedures in adults with known PCCs in France was estimated from the previous number, using standardization for sex and for age, on the basis of the distribution of the 1999 French population [24].

Estimation of the annual number of IE cases after at-risk dental procedure in adults with known PCC (numerator). The annual number of IE cases in French adults with PCCs was derived after standardization for sex and age from results of the 1999 one-year French epidemiological survey on IE, which was conducted in an area with 16 million inhabitants—a sample that represents 25% of the French population and that was comparable in terms of sex and age to the global population on the basis of a comparison to the national census results [25]. Of the 390 definite IE cases in this survey, 352 occurred in adults, 182 of whom had a known PCC.

The annual number of IE cases possibly related to dental procedures was also obtained from the 1999 French survey. An IE possibly related to dental procedures was defined as an IE due to a microorganism belonging to the oral flora that developed within 1 month after an at-risk dental procedure. Each case was validated by 2 independent specialists.

IE prophylaxis strategies impact assessment. On the basis of our estimates of (1) the risk of IE after an at-risk dental procedure in a patient having or not having received antibiotic prophylaxis and (2) the number of at-risk dental procedures performed yearly in France, we were able to estimate the number of IE cases that would have been prevented during 1 year if antibiotic prophylaxis had been administered in 100% of cases of at-risk dental procedures.

Estimated incidence of IE. To verify the validity of the estimates established by the present study, we also calculated the annual incidence of IE in adults with known PCCs; we
then compared this incidence rate to published estimates. The annual incidence of IE in adults with known PCCs was calculated by dividing the estimated annual French number of IE cases in patients with known PCCs by the estimated number of French adults with known PCCs derived from the CANEVAS and the PAQUID studies.

**Statistical analysis: estimation method of total number of cases in French adult population.** The number of PCCs in the adult French population, the number of dental procedures performed yearly in France, and the annual number of IE cases in France, as well as their 95% CIs, were calculated with a method based on the γ distribution [26]. The 95% CI of the risk of IE after a dental procedure was estimated by Monte Carlo simulation technique [27]. This method consists of randomly generating a high number (i.e., 10,000) of ratios (the number of cases/the number of expositions) and calculating the median and 5th–95th percentile intervals of the distribution of obtained ratios. The numerators and the denominators of ratios were generated from Poisson distributions with the observed number of cases and the number of exposed persons, respectively, as mean values. SAS software, version 8.05 (SAS Institute), was used for statistical analysis.

**Ethics.** The study was approved by the Commission Nationale Informatique et Libertés (National Committee for the Protection of Privacy and Civil Liberties), and subjects were informed of the study but did not need to give consent.

**RESULTS**

**Prevalence of PCC and the annual number of at-risk dental procedures in adults with known PCC (denominator).** Of the 2805 interviewed adults, 104 reported having a native valve PCC, 15 of whom had undergone an at-risk dental procedure within the previous month; the procedure had been unprotected in 12 cases. Twenty-four other adults had a prosthetic valve PCC, 4 of whom had undergone an at-risk dental procedure; the procedure had been unprotected in 2 cases. Applying these figures to the adult French population (39 million) resulted in the following estimations: in 1999, a total of 1,287,296 adults (95% CI, 999,196–1,575,396) had a known PCC, corresponding to 3.3% (95% CI, 2.6%–4%) of the 39 million French adults, 1,058,726 native valve PCCs, and 228,570 prosthetic valve PCCs. Figure 1 shows the percentage of the 39 million French adults with a predisposing cardiac condition, according to age group.

In 1999, a total of 2,746,384 at-risk dental procedures (95% CI, 2,304,094–3,188,384) were performed in these adults, accounting for a rate of 2.1 procedures per subject per year; 1,704,195 (62%) of these procedures were performed without antibiotic prophylaxis (i.e., there were 75,409 unprotected procedures), whereas, in subjects with known native valve diseases, 73% of the at-risk dental procedures were performed without antibiotic prophylaxis (i.e., there were 1,628,787 unprotected procedures) (table 1).

**Annual number of IE cases after at-risk dental procedures in adults with known PCCs (numerator).** Among the 182 cases of IE that occurred in adults with PCC in the 1999 survey, 12 occurred after an at-risk dental procedure and were due to an oral microorganism. This dental procedure was unprotected in 10 cases. When considering the estimated 1370 annual cases of IE in France, 714 cases would have occurred in adults with PCC, of which 44 were attributable to dental procedures (37 [2.7%] without and 7 [0.5%] with antibiotic prophylaxis) (table 2).

**Risk of IE after at-risk dental procedures in adults with known PCC.** If applied to the number of at-risk procedures performed in adults with known PCC, the estimated risk of IE was 1 case per 46,000 (95% CI, 36,236–63,103) unprotected at-risk dental procedures. It was 1 case per 54,300 (95% CI, 41,717–77,725) unprotected at-risk dental procedures in adults with native valve PCC and 1 case per 10,700 (95% CI, 6000–25,149) unprotected at-risk dental procedures in adults with prosthetic valve PCCs. This risk was 1 case per 149,000 (95% CI 86,988–347,509) protected dental procedures; thus, there was a 70% reduction in the risk, compared with unprotected procedures.

**Assessment of IE prophylaxis strategies impact.** According to the estimated annual number of procedures (table 1) and the risk estimates above, if antibiotics have been administered in 100% of at-risk dental procedures (i.e., 2.7 million administered antibiotic courses, corresponding to 2,228,545 courses for patients with native valve PCCs and 517,829 courses for patients with prosthetic valve PCCs), 41 cases (95% CI, 29–53 cases) of IE would have been prevented in patients with native valve PCCs, and 39 cases (95% CI, 11–72 cases) would have been prevented in patients with prosthetic valve PCCs in France in 1999.
Table 1. Estimated number of known predisposing cardiac conditions (PCCs) among French adults (age, 25–84 years) and of annual at-risk dental procedures among subjects with PCCs.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adults</th>
<th>Total</th>
<th>Protected procedures</th>
<th>Unprotected procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native valve PCCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (% of patients or yearly procedures)</td>
<td>1,058,726</td>
<td>2,228,545</td>
<td>599,758 (27)</td>
<td>1,628,787 (73)</td>
</tr>
<tr>
<td>95% CI</td>
<td>798,276–1,319,176</td>
<td>1,824,926–2,632,164</td>
<td>367,012–832,504</td>
<td>1,299,033–1,968,540</td>
</tr>
<tr>
<td>No. of procedures/patient/year</td>
<td>…</td>
<td>…</td>
<td>0.57</td>
<td>1.54</td>
</tr>
<tr>
<td>Prosthetic valve PCCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (% of patients or yearly procedures)</td>
<td>228,570</td>
<td>517,839</td>
<td>442,430 (85.4)</td>
<td>75,409 (14.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>105,413–351,726</td>
<td>336,973–698,705</td>
<td>264,100–620,760</td>
<td>45,229–105,588</td>
</tr>
<tr>
<td>No. of procedures/patient/year</td>
<td>…</td>
<td>…</td>
<td>1.93</td>
<td>0.33</td>
</tr>
<tr>
<td>Total</td>
<td>1,287,296</td>
<td>2,746,384</td>
<td>1,042,189 (38)</td>
<td>1,704,195 (62)</td>
</tr>
<tr>
<td>95% CI</td>
<td>999,196–1,575,396</td>
<td>2,304,094–3,188,674</td>
<td>748,978–1,335,399</td>
<td>1,373,064–2,035,327</td>
</tr>
</tbody>
</table>

* Protected procedures were defined as invasive procedures in which antibiotic prophylaxis was administered.
* Unprotected procedures were defined as invasive procedure in which antibiotic prophylaxis was not administered.

Estimated incidence of IE. The annual incidence of IE was 35 cases per million inhabitants (95% CI, 32–39 cases per million inhabitants) in the entire 25–84-year-old French population. This incidence was 555 cases (95% CI, 520–588 cases) per million 25–84-year-old subjects with known PCC, 980 cases (95% CI, 875–1090 cases) for patients with prosthetic valve PCCs, and 460 cases (95% CI, 415–500 cases) for patients with native valve PCCs. The incidence was 18 cases (95% CI, 16–21 cases) per million 25–84-year-old subjects without known PCCs.

DISCUSSION

This study provides results that contribute to the debate on what should be the optimal policy for antibiotic prophylaxis of IE [4]. The present findings give credence to a protective effect of antibiotic prophylaxis for at-risk dental procedures in patients with known PCCs. However, given the low risk of IE after at-risk dental procedures, a considerable number of patients would need to receive antibiotic prophylaxis to avoid 1 case of IE.

The validity of our estimation of the number of PCCs in adults in France in 1999 is difficult to assess, because no similar information is available from other countries. The prevalence of 6% in the 55–65-year-old population is comparable to the 6.2% prevalence reported by Strom et al. [9]. The validity of the estimation used in the present study can be indirectly supported, as it made possible the estimation of the annual incidence of IE in adults with known PCC; this incidence rate could then be compared with information that does exist in the literature. These annual incidences (~500 cases of IE per million adults with native valve PCCs and 1000 cases of IE per million adults with prosthetic valve PCCs) are, in fact, found to be comparable to those determined by observing cohorts of such at-risk subjects over a long period of time (annual incidence, 400–800 cases of IE per million subjects with native valve PCCs).

Table 2. Estimation of the annual number of infective endocarditis (IE) cases, according to the nature of the involved valve and to the performance of a protected or unprotected dental procedure in France.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects with native valve PCCs</th>
<th>Subjects with prosthetic valve PCCs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual no. of IE cases in adults with known</td>
<td></td>
<td></td>
<td>714 (663–768)</td>
</tr>
<tr>
<td>PCCs in France (95% CI)</td>
<td>490 (448–535)</td>
<td>224 (195–255)</td>
<td></td>
</tr>
<tr>
<td>IE cases possibly related to a dental procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (% of procedures)</td>
<td>30 (6)</td>
<td>15 (7)</td>
<td>44</td>
</tr>
<tr>
<td>95% CI</td>
<td>13–58</td>
<td>4–38</td>
<td>23–77</td>
</tr>
<tr>
<td>No. of protected procedures (95% CI)*</td>
<td>0</td>
<td>7 (1–27)</td>
<td>7 (1–27)</td>
</tr>
<tr>
<td>No. of unprotected procedures (95% CI)*</td>
<td>30 (13–58)</td>
<td>7 (1–27)</td>
<td>37 (18–68)</td>
</tr>
</tbody>
</table>

* Protected procedures were defined as invasive procedures in which antibiotic prophylaxis was administered.
* Unprotected procedures were defined as invasive procedure in which antibiotic prophylaxis was not administered.

NOTE. At-risk dental procedures were performed within the previous month, and the microorganism responsible for IE originated from the oral cavity. PCC, predisposing cardiac condition.
valve PCCs and 2000 cases of IE per million subjects with prosthetic valve PCCs) [28, 29]. Our annual incidence in subjects with known PCCs is 30 times higher than the incidence in subjects without known PCCs—a risk increase in concordance with the nearly 20-fold (95% CI, 7.4–37.4-fold) higher risk reported by Strom et al. [9] in their case-control study.

The huge number (∼1,700,000) of unprotected procedures performed per year in this population was estimated using an adherence rate to antibiotic prophylaxis recommendations of 38%, which is comparable to the rate from other countries [30–32]. In such individuals, we were not able to establish whether prophylaxis (antibiotic choice, route, dose, and timing of administration) was correctly given. However, in a semidirective telephone survey that we conducted in 2001, among a randomly chosen representative sample of 200 French dental practitioners, only 40% of those having prescribed prophylaxis had correctly applied the French prophylaxis recommendations [33]. Thus, the number of unprotected procedures is likely higher than our reported figure of ∼1,700,000.

In contrast to this huge number of unprotected procedures in adults with PCCs, the corresponding annual number of IE cases possibly related to these procedures was extremely low (2.7% of all IE cases, which is similar to other reported percentages, such as the 3% rate reported by Strom et al. [9] and the 5% rate reported by van der Meer et al. [31]). This 2.7% figure corresponds to a very limited risk of developing IE after unprotected dental procedures, even in adults with prosthetic valve PCCs who have a 5-fold higher risk of developing IE after dental procedures, compared with adults who have native valve PCCs. These very low risk rates probably explain why case-control studies have failed to prove a statistically significant link between procedures and IE [8–10]. The lower risk of developing IE after invasive procedures observed in our study in adults receiving prophylaxis supports the occasional (but real) responsibility of dental procedures in IE genesis on the one hand, and the effectiveness of antibiotic prophylaxis with an estimated protective efficacy of 70% on the other.

We acknowledge that the results generated in this study are based on extrapolations to the general French population of data extracted from smaller—but representative—samples. It explains why the 95% CIs were rather large. However, even if we consider the lower values of the intervals, the risk of IE after an unprotected dental procedure remains considerably low.

We conclude that antibiotic prophylaxis reduces the risk of IE after a dental procedure. However, because of the very limited risk of “spontaneous” IE after unprotected dental procedures in adults with known PCCs, a huge number of doses of prophylaxis must be prescribed to prevent a very low number of IE cases. Thus, considering this risk, the better prognosis of IE due to microorganisms originating from the oral flora (compared with other organisms), and the possible fatal adverse reactions to antibiotics, use of prophylaxis should probably target the procedures and populations with the highest risk, and energy should be focused on such populations to improve the rate of adherence to prophylaxis recommendations. The information obtained from this study could be useful for future updating of IE prophylaxis recommendations.

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Potential conflicts of interest. All authors: no conflicts.

References


