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Invasive Dental Treatment and Risk for Vascular Events

A Self-Controlled Case Series

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Background: Treatment of periodontal disease may reduce cardiovascular risk in the longer term, but studies have suggested a link among dental procedures, acute inflammation, and endothelial dysfunction. However, whether such acute inflammatory effects translate into a short-lived increased risk for vascular events is not known.

Objective: To investigate whether invasive dental treatment transiently increases the risk for vascular events.

Design: Self-controlled case series.

Setting: Data came from the U.S. Medicaid claims database.

Patients: All persons exposed to invasive dental treatment with a primary hospital discharge diagnosis of ischemic stroke ($n = 650$) or myocardial infarction ($n = 525$) from 2002 to 2006.

Measurements: The incidence of ischemic stroke and myocardial infarction in periods immediately after invasive dental treatment was compared with the incidence in all other observed time periods. Incidence ratios and 95% CIs were calculated.

Results: The rate of vascular events significantly increased in the first 4 weeks after invasive dental treatment (incidence ratio, 1.50 [95% CI, 1.09 to 2.06]) and gradually returned to the baseline rate within 6 months. The positive association remained after exclusion of persons with diabetes, hypertension, or coronary artery disease or persons with prescriptions for antiplatelet or salicylate drugs before treatment.

Limitations: Power to examine the effects of invasive dental treatment on stroke and myocardial infarction separately was limited because of the low frequency of invasive dental procedures. Lack of information about use of over-the-counter drugs limited the ability to assess confounding by possible withholding of antiplatelet or salicylate drugs before invasive dental treatment or by the use of nonsteroidal anti-inflammatory drugs after treatment.

Conclusion: Invasive dental treatment may be associated with a transient increase in the risk for vascular events. However, the absolute risks are minimal, and the long-term benefits on vascular health will probably outweigh the short-lived adverse effects.

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There is considerable interest in the role of inflammatory mechanisms in the occurrence of cardiovascular events. Local inflammation—the process by which the body responds to injury or infection—plays an important role in the pathogenesis of the atherosclerotic lesion (1). Moreover, long-term, low-grade chronic systemic inflammation has been linked to adverse cardiovascular outcomes (2). Acute inflammation after surgery (3), or bacterial infection (4), has also been associated with a short-term increase in the risk for vascular events, with endothelial dysfunction representing a possible common pathway through which several risk factors, including inflammation, may influence the atherogenic process (5, 6).

Epidemiologic data implicate exposure to low-grade dental infection—particularly periodontitis (a common chronic infection of the oral cavity caused by bacteria)—in the cause of cardiovascular disease. Such infections have been found to be associated with elevated levels of C-reactive protein and other inflammatory biomarkers (7), endothelial dysfunction (8), atherosclerosis, and an increased risk for stroke and myocardial infarction (9). Recent studies have shown that intensive periodontal treatment leads to transiently impaired, flow-mediated dilatation (a measure of endothelial function) and increased markers of inflammation and endothelial activation in the week after treatment followed by a longer-term improvement relative to baseline (10, 11). The more invasive the dental treatment (12), the more marked the changes.

Ischemic stroke and myocardial infarction share a common pathophysiologic process: arterial thrombosis occurring in a background of atherosclerosis. We have previously established that infections cause a transient increased risk for both myocardial infarction and stroke (6). If the likelihood of a vascular event is associated with variations in the underlying inflammatory state and endothelial function, then invasive dental treatment sufficient to produce an inflammatory response may transiently increase the risk for vascular events—namely myocardial infarction and stroke—despite providing longer term vascular benefits due to reducing the infectious burden. To test this hypothesis of a transient increased risk, we examined the incidence

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Context

Chronic inflammatory states, such as periodontal disease, are increasingly believed to play a role in the cause of cardiovascular disease.

Contribution

Using data from a large administrative database, researchers found that adults who underwent discrete invasive dental procedures have an increased risk for myocardial infarction or stroke in the 4 weeks immediately after the procedure, but not at later times.

Implication

Acute dental inflammation may transiently increase cardiovascular disease risk.

—The Editors

of ischemic stroke and myocardial infarction after invasive dental treatment by using Medicaid claims data from the United States and the self-controlled case series method.

METHODS

Medicaid Database

Medicaid is a federally funded, state-administered health care program for persons without private insurance coverage. It is used by approximately 13% of U.S. citizens and provides inpatient, outpatient, drug treatment, and long-term care. The Medicaid claims database contains pooled data from 9 geographically dispersed states, including medical and dental records and details of interventional treatment, prescription drug claims, and enrollment. The data have high levels of completeness and validity (13). Eligibility is income-related and evaluated monthly. All information obtained from the database is anonymous.

Case Series Method

We examined the risk for vascular events after exposure to invasive dental procedures. Persons who have had invasive dental treatment may differ from those who have not in ways that can be difficult to measure and control for. Some of these differences may also be associated with the future risk for vascular events, which makes a conventional cohort design a less reliable source of information on this association. Therefore, we used the self-controlled case series method (14), which relies on within-person comparisons in a sample of persons, all of whom had an outcome of interest. The main advantage of this method is that inference is within a person; hence, fixed confounders (those that do not vary with time during the observation period) are implicitly controlled for. We derived incidence ratios of events occurring during predefined risk periods after an exposure, relative to all other observed time periods for each person. Our null hypothesis was that rates of vascular events remain constant from day to day and are not affected by exposure to invasive dental treatment. The **Figure** illustrates this method and the time intervals used.

A key assumption underlying the case series method is that events are independent within a person. This does not hold for vascular events because the occurrence of an ischemic stroke or myocardial infarction increases the probability of subsequent events. In the case in which this assumption fails, a reasonable strategy is to restrict the analysis to first events, provided that these are not common (14, 15). We therefore chose not to look at recurrent events and instead used the first event in the study period to assess the effect of invasive dental treatment on vascular events. Our approach is reasonable because both ischemic stroke and myocardial infarction are relatively uncommon conditions.

Participants

Participants were derived from a population of 9 901 464 persons for whom data were available in the Medicaid database from January 2002 to December 2006. This comprised approximately 28 million person-years of observation. All incident cases of ischemic stroke or myocardial infarction occurring during this period were identified from primary discharge diagnoses that were coded by using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), classification system.

Candidates were those who had a first hospitalization record for ischemic stroke or myocardial infarction at least 24 weeks after their enrollment period began. This ensured a minimum of 24 weeks of observation before each outcome, thus allowing participants' exposure status to be ascertained throughout this period. Restricting to the first event record avoided the problem of repeated coding of a single event within the database. Because participants who were eligible had at least 24 weeks of continuous observation before their first event record, we could be confident that their first event record was not a repeated record for an earlier event. We excluded persons if they were younger than 20 years at the time of their first hospitalization record for stroke or myocardial infarction because the cause of the event could have differed from that of older persons. Because eligibility for Medicaid health care is ascertained on a monthly basis, gaps were often found in a person's enrollment. Events or procedures occurring during such gaps are unlikely to be recorded in the database. This could lead to misclassification of exposure status. To avoid this, we identified each person's maximum period of continuous enrollment and restricted the person's follow-up to this period. Persons whose stroke or myocardial infarction occurred outside this period were subsequently excluded from the relevant analyses.

All candidates not excluded for these reasons were eligible for the study. However, in a case series analysis, persons not exposed during their observation period do not contribute to the estimates of association between exposure and outcome. The primary analysis was therefore restricted

to eligible persons who had both an event and invasive dental treatment during their continuous enrollment period.

Exposure

Data were extracted on claims for invasive dental procedures. Dental procedures are recorded in Medicaid by using the Current Dental Terminology coding system (16). We defined invasive dental procedures as those that may feasibly result in bacteremia and induce an inflammatory response. These included periodontal therapy and other invasive dental surgery, such as simple or complicated tooth extractions, also known to be associated with bacteremia (17, 18) and raised markers of inflammation (19). Some persons had several records of procedures, sometimes within a few days of one another. We defined procedures recorded at least 1 week apart as repeated procedures, and we excluded, for each person, all procedure records occurring within 1 week of a previous record, assuming these to be repeated records of the same treatment program. When addressing repeated procedures, we assumed the risk to be the same after each procedure, thus not allowing for a dose effect. **Appendix Table 1** (available at www.annals.org) describes all of the invasive dental procedures found in the study participants' records.

Outcome Measures

The accuracy of hospital discharge diagnostic codes for stroke and myocardial infarction classifications in administrative claims databases has been examined and validated (20, 21). On the basis of the criteria by Tirschwell and Longstreth (20), we defined ischemic stroke as any one of the following ICD-9-CM primary discharge diagnostic codes on inpatient admission records: 433.x1 (in which "x" can vary to specify a specific arterial distribution), 434 (excluding 434.x0), and 436. If any traumatic brain injury (ICD-9-CM codes 800 to 804 or 850 to 854) was recorded for the same hospitalization, the stroke was excluded. We defined myocardial infarction, according to criteria used by Kiyota and coworkers (21), as an ICD-9-CM primary discharge diagnostic code of 410.x1 and a hospital length of stay lasting from 3 to 180 days. If the patient died during hospitalization, the length of stay could be less than 3 days.

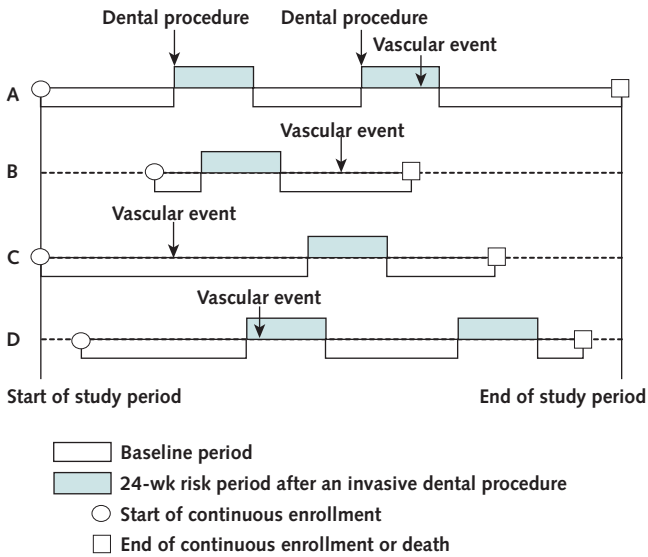
For descriptive purposes and sensitivity analyses, we identified persons with a diagnosis of diabetes, hypertension, coronary artery disease, or rheumatoid arthritis on inpatient admission or outpatient claim records before their invasive dental treatment. We defined each condition according to the following ICD-9-CM diagnostic codes: diabetes (code 250), hypertension (codes 401 to 405), coronary artery disease (codes 410 to 414 and 429.2), and rheumatoid arthritis (code 714).

Statistical Analysis

The exposed period started 1 day after an invasive dental procedure and extended up to 24 weeks later. It was subdivided into 1 to 4, 5 to 8, 9 to 12, 13 to 16, and 17 to 24 weeks because we assumed the risk to be similar during the last 8 weeks. All other observation time was considered the baseline (unexposed) period. Persons who were exposed to at least 1 invasive dental procedure were included in the primary analysis. For persons who had more than 1 procedure during the observation period, each procedure was followed by a 24-week exposed period. Our decision to start the exposed period 1 day after a procedure is based on current evidence that the host response and vascular function are affected at their maximum 24 hours after invasive dental treatment (10–12). We used a 24-week exposed period on the basis of previous work, which suggested any increased risk would have returned to baseline by 24 weeks (6, 22), and thus we would be able to fully describe the resolution of any increased risk. In the case of overlapping risk periods, we adopted a simple convention: later procedures take precedence over earlier ones (14).

Analyses were done for vascular events overall and separately by event type (ischemic stroke or myocardial infarction). We estimated incidence ratios and 95% CIs for events occurring within each stratum of the exposed period compared with baseline by using conditional Poisson re-

Figure. **Pictorial representation of the case series method.**



Four possible scenarios for the timing of vascular events and invasive dental procedures (each representing a single participant) are shown. **A.** Participant is followed for the duration of the study period, has two 24-week risk periods (each after an invasive dental procedure), and has a vascular event during the second risk period. **B.** Participant is followed for part of the study period and has 1 dental procedure followed by a vascular event at baseline. **C.** Participant is followed from the start of the study period, has a vascular event at baseline before a dental procedure, and dies before the end of the study period. **D.** Participant is followed for most of the study period, has 2 dental procedures, and has a vascular event during the first risk period. All participants included in a particular analysis had at least 1 exposure and at least 1 vascular event. Each risk period began the day after a procedure, lasted 24 weeks (not drawn to scale relative to length of baseline periods), and was divided into the following intervals: 1 to 4, 5 to 8, 9 to 12, 13 to 16, and 17 to 24 weeks.

gression. We adjusted for age in 5-year age groups (for example, 20 to 24 years, 25 to 29 years, and 30 to 34 years). Each person's observation was split into successive intervals determined by changes in age group and exposure status, thus allowing persons to contribute to different age groups over time. In a case series analysis, persons not exposed at any time during follow-up do not contribute to the estimates of the association between exposure and outcome. However, including these unexposed persons can help control for confounding by age because they contribute information on the age-specific incidence of the outcome of interest. We did a sensitivity analysis including unexposed cases to check that the estimates did not vary.

The validity of the case series method rests on the assumption that the probability of exposure is not affected by the occurrence of an outcome event. This may not hold true if the event of interest increases the mortality rate (as is the case for ischemic stroke or myocardial infarction); therefore, we conducted a sensitivity analysis excluding persons who died during their hospital stay for the vascular event or whose enrollment ended within 1 month of their event (possibly indicating death). Although fixed covariates are implicitly controlled for in a case series analysis, we recognized that there may be potential for confounding by possible withholding of antiplatelet or salicylate medications before invasive dental treatment among high-risk persons receiving such drug regimens. We therefore did a sensitivity analysis restricted to patients who had no recorded use of antiplatelet or salicylate agents before invasive dental treatment. The rationale for this is that among such patients, cessation of drug therapy at the time of dental treatment is unlikely to occur. Thus, any observed increased risk for a vascular event after the dental therapy is unlikely to be attributable to cessation of antiplatelet or salicylate therapy. To address the possibility that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) after invasive dental procedures for pain control may confound the association observed, we did an additional sensitivity analysis excluding persons with a recorded diagnosis of rheumatoid arthritis at any time before invasive dental treatment (who were probably taking NSAIDs) or with an NSAID prescription around the time of their dental treatment (4 weeks before to 4 weeks after treatment). Similarly, the potential for confounding by the development of diabetes, hypertension, or coronary artery disease in the period leading up to invasive dental treatment was addressed in sensitivity analyses excluding patients with these conditions newly diagnosed within the year before dental treatment.

To eliminate the possibility that our convention (allowing later procedures to take precedence over earlier ones if the risk periods overlapped) might contribute to an observed effect in earlier time frames, we did additional sensitivity analyses by excluding persons with overlapping risk periods and persons with repeated procedures. Finally, given that most dental procedures included in our analyses were extractions, we repeated our analyses, restricting to only these homogeneous exposures. Data were analyzed by using Stata software, version 10 (StataCorp, College Station, Texas). The **Appendix** (available at www.annals.org) provides further details of our analysis.

Role of the Funding Source

A Wellcome Trust Senior Fellowship grant and a senior fellowship from the British Heart Foundation funded this study. The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit this manuscript for publication.

RESULTS

A total of 32 060 persons were identified from the Medicaid database with a hospitalization for ischemic stroke (n = 17 741) or myocardial infarction (n = 14 783); 11 691 were excluded for 1 of the following reasons: Less than 24 weeks of observation had passed before their first event record (n = 10 822); they were younger than 20 years at the time of their first event (n = 104); or the first event occurred outside the continuous enrollment period (n = 765). Among the remaining 20 369 eligible persons, the median age at the time of diagnosis was 67.3 years (interquartile range [IQR], 56.5 to 79.6 years), 34.3% were men, the mean observation period was 3.4 years, and 7.7% died during their hospital stay. Among eligible persons with ischemic stroke (n = 11 284), the median age at the time of diagnosis was 68.8 years (IQR, 57.5 to 80.4 years), 31.4% were men, the mean observation period was 3.4 years, and 5.6% died during their hospital stay. Among eligible persons with myocardial infarction (n = 9484), the median age at the time of diagnosis was 65.2 years (IQR, 55.3 to 78.4 years), 37.7% were men, the mean observation period was 3.3 years, and 10.3% died during their hospital stay.

Only cases that had been exposed to an invasive dental procedure at least once during follow-up were included in the primary analysis of vascular events, overall and by event type. **Table 1** provides demographic details of these persons. The identification of the 1152 persons included in the primary analysis of vascular events is illustrated in **Appendix Figure 1** (available at www.annals.org). The mean duration of total observation for patients with vascular events was 4.2 years (4.2 years for patients with ischemic stroke and 4.1 years for patients with myocardial infarction). During the observation period, 1152 (5.7%) eligible persons with a vascular event (629 with ischemic stroke only, 504 with myocardial infarction only, and 19 with both) had 1 or more invasive dental procedures; 861 (74.7%) of whom had a single exposure period, 281 (24.4%) had 2 to 4 exposure periods, and 10 (0.9%) had 5 or more exposure periods. Of these 1152 exposed persons, 4.1% died during their hospital stay (2.6% of those first hospitalized for ischemic stroke and 5.7% of those first hospitalized for myocardial infarction). The median number of days between adjacent procedures was 56.5 days

(IQR, 21 to 245 days). A total of 89% of all invasive dental procedures included in the primary analysis were extractions, and more than 95% of persons had at least 1 extraction (**Appendix Table 1**). **Table 2** shows the number of exposed persons who had an ischemic stroke or myocardial infarction and the age-adjusted incidence ratios after invasive dental treatment.

The rate of vascular events ($n = 1152$) significantly increased in the first 4 weeks after invasive dental treatment compared with the baseline (unexposed) period (incidence ratio, 1.50 [95% CI, 1.09 to 2.06]) and decreased thereafter. No events occurred on the same day as an invasive dental procedure. Examining stroke and myocardial infarction separately yielded similar findings, although these were not statistically significant. The rate of myocardial infarction ($n = 525$) was higher in the first 4 weeks after an invasive dental treatment compared with baseline (incidence ratio, 1.56 [CI, 0.98 to 2.47]) and seemed to decrease over 24 weeks. For ischemic stroke ($n = 650$), a slightly elevated risk was seen during the first 4 weeks after an invasive dental treatment (incidence ratio, 1.39 [CI, 0.89 to 2.15]), although this was less marked and the pattern of resolution was less clear. Repeating the analyses to include unexposed cases did not materially alter the estimates of the effect of invasive dental procedures on ischemic stroke or myocardial infarction.

We conducted further sensitivity analyses: restricting to persons whose enrollment continued for at least 1 month after their vascular event and hence did not die immediately or shortly after stroke or myocardial infarction; excluding persons with overlapping risk periods; excluding persons with repeated procedures; excluding persons probably taking NSAIDs around the time of dental treatment (those with a rheumatoid arthritis diagnosis at any time before treatment or an NSAID prescription 4 weeks before or after treatment); restricting our exposure to extractions; and restricting to persons who were healthy, as defined by an absence of diabetes, hypertension, or coronary artery disease diagnoses at any time before invasive dental treatment. To assess whether any observed effect could be attributable to persons stopping antiplatelet or salicylate therapy before their dental treatment, we did an analysis restricted to persons with no antiplatelet or salicylate drug prescriptions at any time before their dental treatment. Among this group, stopping therapy was unlikely to be an issue. Finally, to assess whether the development of diabetes, hypertension, or coronary artery disease might confound the observed association between invasive dental treatment and vascular events, we excluded persons with these conditions newly diagnosed within 1 year before their dental treatment. These analyses made no material difference to our findings, and if anything, they yielded a marginally stronger effect 1 to 4 weeks after dental treatment. **Table 3** summarizes the results of the sensitivity analyses.

***Table 1.* Characteristics of Study Participants**

Characteristic	Patients With Vascular Events ($n = 1152$)*	Patients With Ischemic Stroke ($n = 650$)†	Patients With Myocardial Infarction ($n = 525$)†
Men, *n (%)*	458 (39.8)	233 (35.9)	236 (45.0)
Women, *n (%)*	694 (60.2)	417 (64.2)	289 (55.1)
Ethnicity, *n (%)*			
White	558 (48.4)	282 (43.4)	282 (53.7)
Black	463 (40.2)	303 (46.6)	171 (32.6)
Hispanic	17 (1.5)	9 (1.4)	8 (1.5)
Other	114 (9.9)	56 (8.6)	64 (12.2)
Age at first event, *n (%)*			
20–29 y	24 (2.1)	21 (3.2)	3 (0.6)
30–39 y	74 (6.4)	41 (6.3)	33 (6.3)
40–49 y	258 (22.4)	117 (18.0)	147 (28.0)
50–59 y	282 (24.5)	156 (24.0)	138 (26.3)
60–69 y	228 (19.8)	139 (21.4)	93 (17.7)
70–79 y	167 (14.5)	100 (15.4)	67 (12.8)
80–89 y	111 (9.6)	72 (11.1)	40 (7.6)
≥90 y	8 (0.7)	4 (0.6)	4 (0.8)
Diabetes diagnosis at any time before IDT, *n (%)*	474 (41.2)	269 (41.4)	214 (40.8)
Hypertension diagnosis at any time before IDT, *n (%)*	809 (70.2)	463 (71.2)	366 (69.7)
Coronary artery disease diagnosis at any time before IDT, *n (%)*	470 (40.8)	211 (32.5)	278 (53.0)

IDT = invasive dental treatment.
* Persons included in the primary analysis of vascular events.
† Twenty-three patients had both an ischemic stroke and a myocardial infarction during their observation period: 19 were included in each analysis (vascular events overall and by event type), and 4 (2 from each analysis, by event type) were excluded from the primary analysis of vascular events because their earlier event met the exclusion criteria.

DISCUSSION

Our study has shown that invasive dental procedures may be associated with a transient increase in the risk for stroke and myocardial infarction in the first 4 weeks after treatment. These findings provide further evidence to support the link between acute inflammation and the risk for vascular events.

In studies investigating the risk for vascular events after inflammatory exposures, the potential for confounding is great because persons who have invasive dental treatment may differ from those who do not in ways that are difficult to control for. The major strength of our study is the use of a case series analysis in which within-person comparisons are done, thereby overcoming the problem of potential confounding associated with the influence of risk factors, which may vary among persons. Confounding would occur only if intraperson risk factors for vascular events that change with time are also associated with the timing of invasive dental treatment. In addition, to produce the effect observed, any such factors would need to have a large

Table 2. **Age-Adjusted Incidence Ratios of a First Vascular Event in Risk Periods After Exposure to Invasive Dental Treatment**

Outcome and Risk Period	Cases, *n*	Age-Adjusted Incidence Ratio (95% CI)
Vascular event (*n* = 1152)*		
Risk period after procedure		
1–4 wk	40	1.50 (1.09–2.06)
5–8 wk	29	1.11 (0.77–1.61)
9–12 wk	30	1.16 (0.81–1.68)
13–16 wk	25	0.96 (0.64–1.43)
17–24 wk	53	1.08 (0.82–1.43)
Baseline period†	975	1.00
Ischemic stroke (*n* = 650)		
Risk period after procedure		
1–4 wk	21	1.39 (0.89–2.15)
5–8 wk	14	0.94 (0.55–1.60)
9–12 wk	18	1.21 (0.76–1.95)
13–16 wk	11	0.73 (0.40–1.32)
17–24 wk	33	1.18 (0.83–1.69)
Baseline period†	553	1.00
Myocardial infarction (*n* = 525)		
Risk period after procedure		
1–4 wk	19	1.56 (0.98–2.47)
5–8 wk	16	1.35 (0.82–2.23)
9–12 wk	13	1.12 (0.64–1.95)
13–16 wk	14	1.20 (0.70–2.05)
17–24 wk	20	0.90 (0.57–1.42)
Baseline period†	443	1.00

* Vascular events are 639 ischemic strokes (55.5%) and 513 myocardial infarctions (44.5%).
† Baseline period is all observation time except for the 24-wk period after an invasive dental procedure.

acute effect and their time-dependent effect would need to operate in a large proportion of included participants. Possible confounding by the development of diabetes, hypertension, or coronary artery disease; the cessation of antiplatelet or salicylate medications before invasive dental treatment; or the use of NSAIDs after treatment for pain control were addressed in sensitivity analyses that excluded persons with these newly diagnosed conditions, those with recorded use of antiplatelet or salicylate drugs before dental treatment, and those probably taking NSAIDs around the time of dental treatment. These exclusions made no material difference to our findings. Nevertheless, we recognize that our ascertainment of use of antiplatelet agents, salicylates, or NSAIDs may be incomplete because some patients probably received these agents both through prescription and over the counter. Because the database does not capture over-the-counter use, we cannot exclude the possibility of residual confounding by differential use of these agents around the time of invasive dental treatment. Further sensitivity analyses demonstrated that our results were robust with regard to assumptions underlying the within-person case series.

In our study, the exposed period starts 1 day after an invasive dental procedure; hence, the day of a dental procedure contributes to the baseline period. This avoids the problem of events occurring on the same day as a procedure, which are a consequence of some other factors unrelated to the dental treatment included in our risk estimates. Any bias occurring from this convention would lead to an underestimate of effect. However, this is of no concern in our study because no vascular events occurred on the same day as a procedure.

A further strength of the study is that the Medicaid database has high levels of completeness and validity (13). It contains records of all medical care provided to eligible persons, therefore eliminating the problems of recall or interviewer bias in both exposure and outcome. Neverthe-

Table 3. **Results of Sensitivity Analyses**

Analysis of Vascular Event Risk*	Cases Included in Analysis, *n*	Age-Adjusted Incidence Ratio (95% CI)†
Primary analysis		
Vascular events‡	1152	1.50 (1.09–2.06)
Sensitivity analyses, by exclusion criteria		
Overlapping risk periods (204 excluded)	948	1.65 (1.17–2.33)
Several invasive dental procedures (291 excluded)	861	1.53 (1.04–2.25)
Procedures that were not extractions (135 excluded)	1017	1.58 (1.13–2.21)
Enrollment ending or death within 1 mo after vascular event (83 excluded)	1069	1.62 (1.17–2.24)
Antiplatelet or salicylate drug prescription record at any time before IDT (486 excluded)	666	2.23 (1.56–3.18)
NSAID prescription 4 wk before to 4 wk after IDT or rheumatoid arthritis diagnosis at any time before IDT (687 excluded)	465	1.84 (1.17–2.89)
Earliest record of diabetes within 12 mo before IDT (224 excluded)	928	1.46 (1.02–2.10)
Earliest record of hypertension within 12 mo before IDT (398 excluded)	754	1.64 (1.12–2.40)
Earliest record of coronary artery disease within 12 mo before IDT (239 excluded)	913	1.70 (1.21–2.40)
Diagnosis of diabetes, hypertension, or coronary artery disease at any time before IDT (924 excluded)	228	1.76 (0.92–3.36)

IDT = invasive dental treatment; NSAID = nonsteroidal anti-inflammatory drug.
* 1–4 wk after procedure compared with baseline. Baseline period is all observation time except for the 24-wk risk period after an invasive dental procedure.
† 1–4 wk after an invasive dental procedure.
‡ Vascular events are 639 ischemic strokes (55.5%) and 513 myocardial infarctions (44.5%).

less, we cannot exclude the possibility of case ascertainment bias, whereby patients with events may be more likely to be designated as having an outcome in the first month after a dental procedure than later. There is also some scope for misclassification of exposure status. We cannot determine who had dental coverage—only who made dental claims. If some persons did not qualify for dental coverage yet had undergone an invasive dental treatment (either self-funded or covered by another insurer), this would not be captured in the database. These persons would be misclassified as unexposed, which could lead to an underestimate of effect. This is unlikely to be a major problem in our study because only those persons with an invasive dental procedure record (and thus with dental coverage) contributed to the analyses, and the chance of their dental coverage changing during enrollment is probably small.

Our study was based on claims data, and a potential weakness may relate to the skewed nature of the population eligible for Medicaid. Eligibility is income-related, which raises the question of generalizability of these findings to other populations. Eligible groups include low-income adults and their children and persons with certain disabilities. Patients with diseases that put them at greater risk for thrombotic events may be more likely to enter the Medicaid program to pay for needed care, including dental care. However, this is more of a problem in descriptive studies and less of a concern in an analytical study such as ours, particularly because each person serves as his or her own control. The relatively small study population is another limitation. In a case series design, only persons exposed at least once during follow-up contribute to the analyses. Given that invasive dental procedure claims were fairly uncommon, a relatively small proportion of our initial study sample contributed to the analyses. This resulted in a loss of power, which unfortunately limited our ability to examine the effects of invasive dental treatment on stroke and myocardial infarction separately. Nevertheless, the stringent criteria used to define our exposure and outcomes and the suitability of our statistical approach together make the case for the validity of our findings.

Increasing evidence implicates low-grade dental infections, such as periodontitis, in the cause of systemic diseases. Several epidemiologic studies have shown that periodontal disease is associated with elevated markers of inflammation (23–25) and increased cardiovascular disease risk in the long term (9, 26, 27). Treatment of periodontitis may yield a positive influence on longer term cardiovascular disease risk by reducing the infectious burden (28). Recent studies have found that intensive periodontal therapy produces an acute systemic inflammatory response 1 week in duration and a transient impairment of endothelial function followed by a subsequent improvement relative to baseline (10–12). Our findings of a small but statistically significant association between invasive dental treatment and vascular event risk over the short term are consistent with these earlier studies. Although we cannot exclude the possibility that other mechanisms may be involved, such as elevated stress due to pain arising from invasive dental treatment, possible discontinuation of antiplatelet or salicylate therapy before treatment, or the use of NSAIDs after treatment, our findings lend support to the hypothesis that inflammation may play an important role in the occurrence of vascular events.

Although the mechanisms are uncertain, we conclude that invasive dental treatment may be associated with a transient increase in the risk for stroke and myocardial infarction in adults. The short-lived adverse effects are nevertheless likely to be outweighed by long-term benefits of invasive dental treatment to vascular health.

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Appendix

The following provides a brief overview of the self-controlled case series (SCCS) method and further details of its application to our study on invasive dental treatment and risk for vascular events. For readers interested in using the SCCS method, the Web site run by the statistician who developed the method (http://statistics.open.ac.uk/sccs/) provides a tutorial (14) and files to download to implement the method in several statistical software packages: Stata (StataCorp); SAS (SAS Institute, Cary, North Carolina); R (R Foundation for Statistical Computing, Vienna, Austria); GLIM (Royal Statistical Society, London, United Kingdom); and GenStat (VSN International, Hemel Hempstead, United Kingdom).

Background and Description of SCCS Method

The SCCS method uses within-person comparisons in a population of persons who had the outcome of interest to investigate the association between time-varying exposures and outcome events. It is derived from a Poisson cohort model by conditioning on the number of events and exposure history that a person has during a predefined observation period: the time during which, if an event occurred, the person would be sampled. Although the method was originally developed to investigate associations between vaccination and acute adverse events (29, 30), it has subsequently been applied in other settings (for example, to investigate the risk for myocardial infarction and stroke [6] and deep venous thrombosis and pulmonary embolism [22] after acute infection) and has been extensively used in pharmacoepidemiology (31–34).

The SCCS method provides an alternative to the more established cohort method for estimating the relative incidence of an event (that is, the ratio of the rate of events in a defined period after exposure to the rate of events in the absence of exposure). **Appendix Figure 2** illustrates this method. Only cases are sampled—there is no comparison control group of persons. Comparisons are within person. To take this into account, the likelihood is conditional on an outcome event having occurred during the observation period. Thus, the likelihood is based on the probability density that a person's event occurred when it did in relation to exposure, given that the event occurred during the observation period.

Advantages

The main advantage of the SCCS method is that inference is within persons; hence, fixed or stable characteristics, such as genetic factors, sex, socioeconomic status, and underlying health status (individual characteristics that do not vary over the observation period) are implicitly controlled for. The method uses only case patients, which reduces the cost and effort involved in data collection and provides consistent estimates of the relative incidence of events. In addition, it allows age or temporal variation in baseline incidence to be controlled for. It also often has high statistical efficiency relative to the cohort method from which it is derived.

Limitations and Assumptions

The SCCS method produces only estimates of relative incidence and not absolute incidence. Hence, our study reports only incidence ratios. The method also requires some variability in the time or age at event: It would fail if all events occurred at the same age (an unlikely scenario and not an issue in our study). In addition, the validity of the method rests on some important assumptions (35). First, the occurrence of an event does not affect a person's subsequent exposure; second, the occurrence of an event does not alter the duration of the observation period; and third, events are independent within a person. In the context of our study, these assumptions are discussed in the section, Addressing the Assumptions Underlying the SCCS Method.

Application of the SCCS Method to Our Study

To examine the risk for vascular events after exposure to invasive dental procedures, we used the SCCS method because persons who have had invasive dental treatment may differ from those who have not in ways that can be difficult to measure and control for. Some of these differences may also be associated with the future risk for vascular events, which makes a conventional cohort design a less reliable approach for examining this association.

Persons who had a vascular event and at least 1 invasive dental procedure during their observation period were included in the primary analysis. The observation period for each person was the time during which, if a vascular event occurred, the person would be sampled (that is, the continuous enrollment period in Medicaid from January 2002 to December 2006). Thus, each person was followed from the start of his or her continuous enrollment period until he or she died or the continuous enrollment period ended (whichever occurred first), regardless of when the vascular event occurred. We took into account repeated invasive dental procedures during the observation period, assuming the same level of risk after each procedure. By using conditional Poisson regression, we derived incidence ratios of vascular events occurring during predefined risk periods extending up to 24 weeks after an invasive dental procedure, relative to all other observed time periods. Our null hypothesis was that rates of vascular events remain constant from day to day and are not affected by exposure to invasive dental treatment.

Although fixed covariates are implicitly controlled for in a case series analysis, there is still scope for confounding if intraperson risk factors for vascular events that change with time are also associated with the timing of invasive dental treatment. As the baseline risk for vascular events varies with age (that is, the risk in the absence of exposure to invasive dental treatment), we split each person's follow-up into successive intervals determined by changes in age (by using 5-year groupings) and exposure status. The time-varying effect of age was thus controlled for by including the age group factor as a covariate in each model.

We recognized that there may be potential for confounding by the development of diabetes, hypertension, or coronary artery disease; possible withholding of antiplatelet or salicylate medication before invasive dental treatment; or the use of NSAIDs after dental treatment for pain control. Therefore, we conducted sensitivity analyses excluding persons with these conditions newly diagnosed during the year before invasive dental treatment, those with recorded use of antiplatelet or salicylate drugs before dental treatment (who thus had the opportunity to withhold from their medication), or those with a recorded diagnosis of rheumatoid arthritis before dental treatment (who were probably taking NSAIDs) or with an NSAID prescription around the time of their dental treatment. These exclusions made no material difference to our findings or conclusions.

Addressing the Assumptions Underlying the SCCS Method

Assumption 1: The Occurrence of an Event Should Not Affect the Probability of Subsequent Exposure. This is perhaps the most restrictive assumption underlying the SCCS method (36). Other than the vascular outcome itself being fatal (thus curtailing the probability of exposure), we can think of no major factors likely to alter exposure to invasive dental treatment after a vascular event. To address the issue of fatal vascular events, we conducted a sensitivity analysis excluding persons who died during their hospital stay for their vascular event or whose enrollment ended within a month of their event, possibly indicating death. Excluding all such possible deaths did not materially alter our findings or conclusions. We found a marginally stronger effect in 1 to 4 weeks after invasive dental treatment.

Assumption 2: The Occurrence of the Event Should Not Censor or Alter the Duration of the Observation Period. In a case series study, each person's observation period is usually determined by using predefined calendar time boundaries, age limits, or both and must be independent of the timing of the event. This assumption may also be violated when the event of interest is likely to increase the short-term death rate. Thus, the sensitivity analyses described previously also addressed this assumption.

Assumption 3: Events Are Independent Within a Person. The case series method requires that the occurrence of an event should not affect the rate at which subsequent events may occur. If this assumption fails, a reasonable strategy is to restrict the analysis to first events, provided that these are not common (14, 15, 36). We restricted our analyses to the first event during the observation period (that is, the first occurring during baseline or a risk period). We did this because the recurrence times of events under study (ischemic stroke and myocardial infarction) cannot be assumed to be independent within persons. Occurrence of a first stroke or myocardial infarction is known to increase the risk for further strokes or myocardial infarctions. All events subsequent to the first in a person's observation period were not included in the analysis, yet each person was followed for the duration of his or her continuous enrollment period. Thus, his or her predefined observation period was preserved. Although excluding subsequent events could underestimate the absolute risk for events, this is unlikely to have any material effect on the relative risk (the outcome of our study). A similar approach was taken in a study exploring the risk for myocardial infarction and stroke after acute infection and vaccination (6). **Appendix Table 2** shows the number of subsequent events excluded from each of our analyses.

Overlapping Risk Periods

Some persons had several dental procedures during their observation period. When 2 or more procedures occur within 24 weeks of each other, the risk periods for these procedures overlap. A simple convention to address overlapping risk periods is that later exposures take precedence over earlier ones (14). We used this convention in our study; thus, when a person had 2 or more dental procedures and a later procedure occurred at some point during the risk period of an earlier procedure, a new 24-week risk period started from that point. This means that the later procedure takes precedence, although it does not replace the earlier procedure. The earlier procedure is not ignored. **Appendix Figure 3** illustrates our convention with 2 possible scenarios. First, if

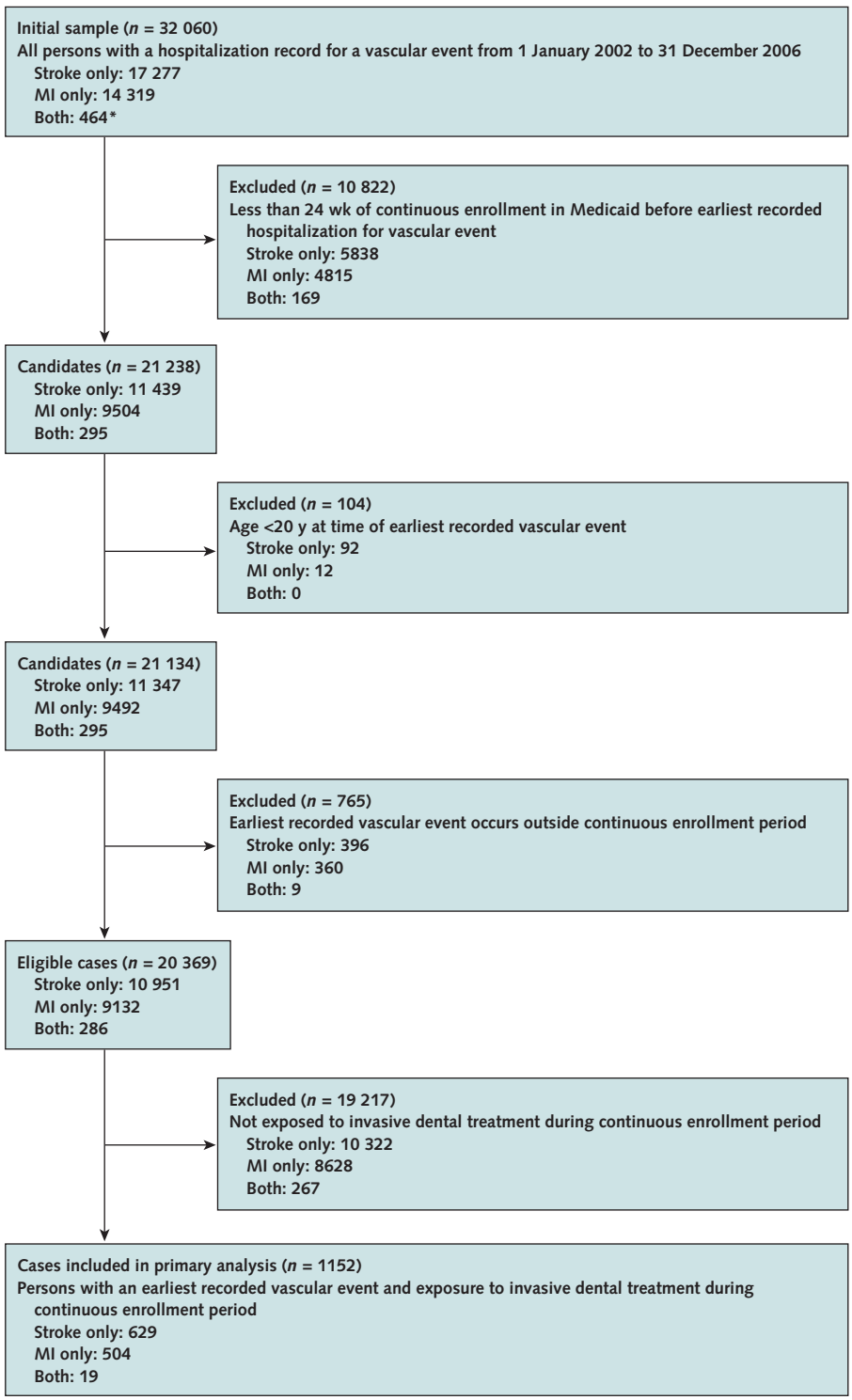
a person had a dental procedure followed by a vascular event 2 weeks later and then a second dental procedure 20 weeks after the first, the vascular event would not be classified as occurring during baseline; it would be classified as occurring in the risk period corresponding to the first procedure (**Appendix Figure 3,** *scenario A*). However, a vascular event occurring 2 weeks after the second dental procedure would be classified as occurring during the risk period of this second procedure rather than during the risk period of the first (**Appendix Figure 3,** *scenario B*). This convention reflects the actual exposure experience: In both scenarios, the event occurred 2 weeks after exposure.

Appendix Table 1. **Distribution of Invasive Dental Procedures Found in Study Participants' Records**

Dental Procedure Code*	Description	Persons With ≥1 Procedure Record, *n* (%)		
		Patients With Vascular Events (*n* = 1152)†	Patients With Ischemic Stroke (*n* = 650)	Patients With Myocardial Infarction (*n* = 525)
D7210	Surgical removal of erupted tooth requiring elevation of mucoperiosteal flap and removal of bone, section of tooth, or both	847 (73.5)	499 (76.8)	364 (69.3)
D7250	Surgical removal of residual tooth roots (cutting procedure)	151 (13.1)	90 (13.8)	67 (12.8)
D7310	Alveoloplasty in conjunction with extractions (≥4 teeth or tooth spaces per quadrant)	104 (9.0)	49 (7.5)	55 (10.5)
D7510	Incision and drainage of abscess (intraoral soft tissue)	25 (2.2)	15 (2.3)	11 (2.1)
D4341	Periodontal scaling and root planning (≥4 teeth per quadrant)	23 (2.0)	7 (1.1)	16 (3.0)
D7320	Alveoloplasty not in conjunction with extractions (≥4 tooth spaces per quadrant)	16 (1.4)	9 (1.4)	8 (1.5)
D7240	Removal of impacted tooth (completely bony)	15 (1.3)	10 (1.5)	5 (1.0)
D7230	Removal of impacted tooth (partially bony)	13 (1.1)	8 (1.2)	6 (1.1)
D4211	Gingivectomy or gingivoplasty (1–3 contiguous teeth or bounded teeth spaces per quadrant)	6 (0.5)	3 (0.5)	5 (1.0)
D7471	Removal of lateral exostosis (maxilla or mandible)	5 (0.4)	3 (0.5)	2 (0.4)
D4210	Gingivectomy or gingivoplasty (≥4 contiguous teeth or bounded teeth spaces per quadrant)	4 (0.3)	1 (0.2)	3 (0.6)
D7241	Removal of impacted tooth (completely bony, with unusual surgical complications)	4 (0.3)	3 (0.5)	1 (0.2)
D7999	Unspecified oral surgery procedure, by report	4 (0.3)	0 (0)	4 (0.8)
D7540	Removal of reaction-producing foreign bodies (musculoskeletal system)	3 (0.3)	3 (0.5)	0 (0)
D3410	Apicoectomy or periradicular surgery (anterior)	2 (0.2)	1 (0.2)	1 (0.2)
D7960	Frenulectomy (frenectomy or frenotomy) as a separate procedure	2 (0.2)	0 (0)	2 (0.4)
D7970	Excision of hyperplastic tissue (per arch)	2 (0.2)	0 (0)	2 (0.4)
D3421	Apicoectomy or periradicular surgery (bicuspid [first root])	1 (0.1)	1 (0.2)	0 (0)
D4342	Periodontal scaling and root planning (1–3 teeth per quadrant)	1 (0.1)	1 (0.2)	0 (0)
D7290	Surgical repositioning of teeth	1 (0.1)	0 (0)	1 (0.2)
D7321	Alveoloplasty not in conjunction with extractions (1–3 teeth or tooth spaces per quadrant)	1 (0.1)	0 (0)	1 (0.2)
D7410	Excision of benign lesion ≤1.25 cm	1 (0.1)	0 (0)	1 (0.2)
D7460	Removal of benign nonodontogenic cyst or tumor (lesion diameter ≤1.25 cm)	1 (0.1)	0 (0)	1 (0.2)
D7461	Removal of benign nonodontogenic cyst or tumor (lesion diameter >1.25 cm)	1 (0.1)	0 (0)	1 (0.2)
D7520	Incision and drainage of abscess (extraoral soft tissue)	1 (0.1)	1 (0.2)	0 (0)
D7550	Partial ostectomy or sequestrectomy for removal of nonvital bone	1 (0.1)	1 (0.2)	0 (0)

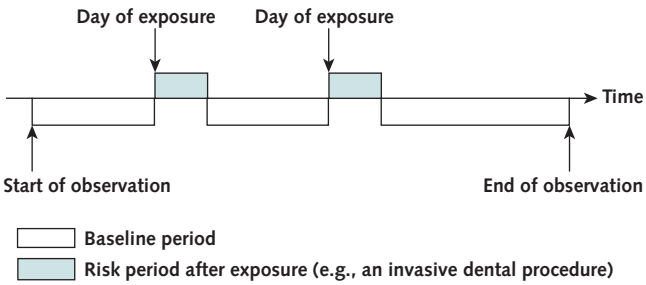
* From Current Dental Terminology (16).
† Persons included in the primary analysis of vascular events.

Appendix Figure 1. **Study flow diagram.**



MI = myocardial infarction.
* Individuals who had both an ischemic stroke and an MI during the study period.

Appendix Figure 2. **Pictorial representation of the self-controlled case series method.**



A single participant who had 2 exposures during the observation period is shown. The outcome event could occur at any time during the observation period.

Appendix Table 2. **Cases With a Subsequent Event and Number of Subsequent Events Excluded From Analysis**

Outcome	Cases Included, *n*	Cases With a Subsequent Event, *n* (%)	Subsequent Events Excluded (Range), *n*
Vascular event*	1152	126 (10.9)	158 (2–5)
Ischemic stroke	650	73 (11.2)	93 (2–5)
Myocardial infarction	525	38 (7.2)	46 (2–3)

* Ischemic stroke or myocardial infarction.

Appendix Figure 3. **Pictorial representation of overlapping risk periods.**