Invasive Dental Treatment and Risk for Vascular Events

TO THE EDITOR: We read Minassian and colleagues’ article (1) with great interest. The authors’ use of a self-controlled case series (SCCS) to prove a causal relationship and their oversight of some important intraperson confounding factors have forced us to challenge their conclusion.

Self-controlled case series can involve intraperson biases, as Minassian and colleagues’ study (1) demonstrated. In addition, case series are useful only for generating hypotheses, not for demonstrating causal relationships (2). Several time-varying intraperson confounding factors that Minassian and colleagues ignored include acute upper respiratory infections that were reported to increase cardiovascular risk (3); illicit drug use that can cause severe arrhythmia, thrombosis, and cardiac arrest (3); and menopause, which can engender increased plasminogen activator inhibitor-1 levels and a decreased ability to cope with stress that may contribute to a surge in endogenous catecholamines and can lead to arrhythmia and subsequent cardiovascular events (4). Thus, because nearly two thirds of the events occurred in peri- and postmenopausal women, confounding by thrombogenic tendency and adrenergic dysregulation due to menopause might be directly responsible for some of the findings reported in this study.

Furthermore, all of the most prevalent dental procedures that the authors cited as invasive in their Appendix Table 1 suggest past oral infections and indicate potential dental neglect. Root remnants, which are the vestiges of serious past dental infections, strongly contributed to the asymptomatic dental score, which was associated with coronary artery disease in our data (5).

Cardiovascular disease is a chronic, multifactorial process, although its manifestations seem to be acute and sudden. Without knowing the molecular changes in cardiovascular pathology in patients in Minassian and colleagues’ study, we are reluctant to accept their results as unbiased or causal. It is unfortunate that this study, with its biases and inadequacies, might still provoke unsubstantiated fears in the general public and elicit further avoidance of needed dental treatments.

In addition, the bias-ridden results of this study could become a platform for baseless litigations or inappropriate health policy inclusions. The take-home message to the public is that it is better to prevent serious dental surgical procedures by taking care of dental disease when it is incipient and easily manageable. Thus, the need for a health policy that includes routine dental care as a part of overall health is evident.

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IN RESPONSE: We are pleased that our study on the risk for vascular events after invasive dental treatment has generated interest. However, it is clear that some readers poorly understood this study, and we would like to address some of the points that they raised.

Dr. Janket and colleagues may have misinterpreted the SCCS method that we used as a collection of case reports with no comparison group. We agree that such uncontrolled case series could be prone to confounding and are unsuitable for investigating causal relationships. Readers should not confuse this method with the SCCS method that we used, which provides an alternative to the more established cohort method for estimating the relative incidence of an event.

The SCCS method is derived from a Poisson cohort model and makes within-person comparisons; thus, each individual serves as his or her own control. We used this method to assess the risk for vascular events after invasive dental treatment by deriving incidence ratios of events that occurred during exposed periods after invasive dental treatment versus unexposed periods. This method has been extensively used in epidemiology to assess causal associations in various settings (1–3). The Appendix in our article explains the approach and its advantages in detail.

We used the SCCS design because it avoids much of the problems of confounding to which other observational study designs are prone. This goal is achieved because each comparison is within-person, which thus implicitly controls for fixed covariates. The only scope for confounding is by intraperson risk factors for vascular events that change with time and that also are associated with the timing of invasive dental treatment.

Dr. Janket and colleagues did not seem to consider that all analyses were adjusted for the time-varying effect of age; thus, any possible age-related confounding factors were controlled for implicitly. Because the other factors they mention, such as acute upper respiratory infections and illicit drug use, are unlikely to be associated with the timing of dental treatment, they also are not confounders.

Dr. Janket and colleagues rightly state that many of the procedures studied suggest past oral infections and dental neglect. However, such infections or neglect could not confound the association observed unless their onset coincided with the timing of dental treatment.

We further believe that Dr. Janket and colleagues’ assertion that our study results are “bias-ridden” reveals a misunderstanding of the study design, which we carefully chose over all of the available alternatives to minimize bias. We strongly disagree with their suggestion that our study “might still provoke unsubstantiated fears in the general public and elicit further avoidance of needed dental treatments.” Because we recognize the long-term benefits of such treatment and vascular events that could feasibly cause bacteremia and induce an inflammatory response; these procedures were not, in fact, confined to extractions nor did they necessarily follow acute infections. Even if acute infection at the time of dental treatment partially caused the effect that we observed, this actually would support an inflammatory mechanism for the association between dental treatment and vascular events.

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Internal Medicine Residency Redesign

TO THE EDITOR: We appreciate Dr. Whitcomb’s thoughtful comments in his editorial (1) on our article on competency-based education and training in internal medicine. We agree that the ultimate goal of competency-based evaluation is “to ensure that residents are prepared to provide high-quality care to the patients whom they are likely to encounter when they enter practice.” To meet this goal, medical educators need a reliable and valid process for evaluating residents; at the same time, they must understand what aspects of residents’ knowledge, skills, attitudes, and performance should form

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the substrate of the evaluation. We believe that it is important to distinguish "how to evaluate" (the evaluation process) from "what to evaluate" (the specific attributes of the resident that are evaluated).

We agree with Dr. Whitcomb that direct observation of residents caring for patients is critical to the valid assessment of resident competency ("how to evaluate"), and we stress this point in our article. Surrogate markers of competency, such as the use of standardized patients, may document that a resident can "show how" but do not demonstrate that he or she "does." This aspect can be shown only through direct observation of residents providing care to real patients. Unfortunately, both the quantity and the quality of direct observation of residents' care of patients are lacking (2). Providing resources for faculty to have the time and the skills to evaluate residents is an important challenge for medical educators, one that is critical to overcome in order to meet the goals of competency-based evaluation.

Dr. Whitcomb comments that "collective results of the assessment process that the ACGME [Accreditation Council for Graduate Medical Education] has adopted for accreditation purposes simply cannot indicate whether residents are actually competent clinicians when they complete residency training." However, we believe that the 6 general competencies identified by the ACGME and the more recent set of milestones developed by members of the internal medicine education community (3) provide a valuable roadmap for both faculty and trainees of "what to evaluate."

The work of ten Cate and Scheele (4) introducing the concept of "entrustable professional activities" is a reasonable strategy for ensuring that competency-based assessment includes the ACGME framework of 6 general competencies and ultimately addresses the ability of trainees to practice independently. The effectiveness of any set of criteria about what to evaluate, however, depends on how well we evaluate; this is where direct observation, supported by effective faculty development, is an important piece of the evaluation process.

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Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-1728.

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Observation

Epidemiologic Implications of the First Isolation and Cultivation of Tropheryma whippelii From a Saliva Sample

Background: Tropheryma whippelii causes acute diseases, such as gastroenteritis, bacteremia, and pneumonia (1), as well as chronic Whipple disease (2). It can be cultivated from stool samples, which are a potential source of infection (3). Detection of T. whippelii DNA in saliva also suggests an oral–oral method of transmission. However, cultivation of T. whippelii from saliva has been impossible because of heavy contamination by other bacteria.

Methods and Findings: Examination of a T. whippelii–positive sputum sample by immunofluorescence testing revealed that it is smaller than other bacteria (Figure, left). Saliva samples were filtered, and the filtrates were inoculated on axenic medium to isolate T. whippelii from saliva (4).

We obtained a 1-mL saliva sample from a patient presenting with diarrhea and blood culture–negative endocarditis. Polymerase chain reaction (PCR) detected T. whippelii DNA with a bacterial load of 10^6 colony-forming units/mL (5). The saliva was gently vortexed with 12 mL of axenic medium and then successively filtered the combined saliva and medium through 5-, 1.2-, 0.8-, and 0.45-μm pore-sized filters. We mixed 5 mL of filtrate with 5 mL of fresh medium for incubation at 37 °C with 5% carbon dioxide in flasks with ventilated caps.

On days 14, 28, and 42, we harvested 200 μL for cytocentrifugation and performed immunofluorescence testing. We replenished the culture with 10 mL of fresh medium. On day 28, we detected few fluorescent bacilli, whereas on day 42, we observed a statistically significant number (Figure, right). We used PCR amplification to confirm that the bacilli were T. whippelii (5). The strain of T. whippelii that we identified is currently established.

Discussion: After the T. whippelii 16S rRNA gene sequence was published, primers against this gene detected the bacterium in up to 35% of saliva samples from healthy individuals (5). However, these primers were later shown to amplify other bacteria present in saliva, such as Actinomyces species and Capnocytophaga gingivalis (5). By using a novel primer–probe set that is highly specific for T. whippelii, we demonstrated by PCR that this bacterium is present in only 0.2% of saliva samples from healthy persons (1). However, we could not culture T. whippelii from these samples.

Our laboratory has developed protocols for T. whippelii isolation by successively refining the culture procedures. After we successfully cultured a T. whippelii isolate obtained from a cardiac valve on human erythrocyte cells, we were able to culture the bacterium from a saliva sample.
from nonsterile and sterile samples by using the same system (2). Analysis of the *T. whipplei* genome and the development of an axenic medium allowed us also to culture isolates from sterile sites (4). This medium was then used to culture an isolate from a stool sample after pretreatment with glutaraldehyde, which was used to select for *T. whipplei* growth because this bacterium is highly resistant to this compound (3). However, glutaraldehyde, like all other antibiotics that were tested for pretreatment of nonsterile samples, also has deleterious effects on *T. whipplei*.

The presence of living *T. whipplei* in saliva suggests oral–oral transmission. In developed countries, contamination occurred through the indirect ingestion of contaminated water, as suggested by a high percentage of *T. whipplei* carriage by sewage workers (1). In addition, the prevalence of *T. whipplei* in 44% of stool samples obtained from healthy children from Senegal suggests that the fecal–oral route is the most common mode of transmission (1). Recently, we also observed that detection of *T. whipplei* in stool samples from children younger than 4 years with gastroenteritis was common in France (1).

**Conclusion:** The presence of live *T. whipplei* in saliva suggests that oral–oral contamination with this bacterium may exist. This finding is similar to that previously observed for such pathogens as *Helicobacter pylori* and rotavirus.

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**Potential Conflicts of Interest:** None disclosed.

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**Correction**

Correction: Comments on the Affordable Care Act and the Future of Clinical Medicine

In a recent letter (1), the author’s name was listed as John M. Goldman, MD. His correct name is John A. Goldman, MD. This has been corrected in the online version.

**Reference**

1. Goldman JA. Comments on the affordable care act and the future of clinical medicine [Letter]. Ann Intern Med. 2011;154:140-1.