Unfinished Root Canal Treatments and the Risk of Cardiovascular Disease

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Abstract

Introduction: Root canal treatments (RCTs) aim to eradicate pulpal diseases and save the infected teeth by eliminating microorganisms from the root canal system. Starting but not finishing an RCT can perpetuate a dead space for bacterial growth, which can spread to other sites in the body and develop systemic symptoms. The objective of the present study was to investigate the association between unfinished RCTs and the risk of cardiovascular disease (CVD) using a nationwide population-based database. **Methods:** A total of 283,590 participants who received at least 1 RCT and with no cardiovascular history before 2005 were recruited and followed until the end of 2011. An unfinished RCT was defined as a tooth on which an RCT was started but with no completion code. Cox proportional hazards models were used to estimate the effect of unfinished RCTs on the risk of CVD. **Results:** A total of 3626 participants underwent CVD hospitalization during an average observation period of 6.01 years, thus yielding an overall CVD hospitalization incidence rate of 0.21% per person year. Compared with the participants with no unfinished RCTs, the adjusted CVD hospitalization hazard ratio for the participants with 1 or 2 unfinished RCTs was 1.22 (95% confidence interval, 1.11–1.35) and for those with 3 or more unfinished RCTs, it was 3.61 (95% confidence interval, 2.36–5.51; test for trend, $P < .0001$). **Conclusions:** Participants with unfinished RCTs were associated with a higher risk of CVD hospitalization. *(J Endod 2015;■ :1–6)*

Key Words

Coronary disease, endodontics, myocardial infarction, stroke, survival analysis, Taiwan National Health Insurance Research Database

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Cardiovascular disease (CVD) is one of the leading causes of mortality worldwide, accounting for approximately 30% of all deaths (1). Atherosclerosis, the most common cause of CVD, is considered not only a cholesterol storage disorder but also a multifactorial disease because it is associated with several anatomic, physiological, and behavioral risk factors (2). In recent years, low-grade chronic inflammation and bacterial or viral organisms involved in chronic inflammatory processes have been proposed as strong factors associated with atherosclerosis and CVD events (3–5).

Periodontal and pulpal diseases are 2 major low-grade chronic inflammatory infectious diseases of the oral cavity. Several systematic reviews have shown that periodontal diseases may contribute to the genesis of CVD (6–8); however, the association of pulpal diseases and CVD has not been studied extensively. A modest association between root canal treatment (RCT) and CVD was hypothesized after patients with self-reported RCT were found to have an increased incidence of coronary heart disease (9, 10). This risk is attributed to cytokine production in inflamed pulp and periapical granulomatous tissues, and systemic levels of inflammatory mediators have been observed in patients undergoing RCT (11–14). A plausible mechanism is that infectious processes associated with the root canal system may not only cause local manifestations of oral cavities but also extend to both nearby and distant body compartments along anatomic pathways or systemic circulation.

The objective of RCTs is to disinfect pulpal diseases and save the infected teeth by eliminating microorganisms from the root canal system. Starting but not finishing an RCT can perpetuate a dead space for bacterial growth, which can opportunistically spread to other body sites and develop systemic symptoms such as maxillofacial cellulitis. Compared with the inadequate quality of completed RCT, unfinished RCT is the major risk factor for hospitalization of odontogenic maxillofacial abscesses (15); however, scant evidence is available for any association between unfinished RCTs and future cardiovascular events. The aim of the present study was to investigate, using a nationwide population-based database, the possible association between unfinished RCT and the risk of CVD hospitalization.

Materials and Methods

Study Database

The Taiwan National Health Insurance program was implemented in 1995; it provides health care through compulsory health insurance and covers nearly 99% of the 23.5 million residents of Taiwan. Our study used the records of the Longitudinal Health Insurance Database 2005, which includes the registration data and medical claims between 2001 and 2011 of 1,000,000 randomly sampled beneficiaries from the total number of national health insurance beneficiaries of 2005. No statistically significant differences were reported in the age or sex distribution between the sampled group and the entire set of enrollees. Many longitudinal epidemiologic endodontic studies have used this database (16–18).

Study Population

The present retrospective cohort study included all participants with at least 1 RCT during 2001–2011 and no CVD outpatient or inpatient diagnosis history during 2001–2004 (Fig. 1). The start of each endodontic therapy session was identified by a specific treatment code (90015C), and its end was identified by completion codes (90001C for

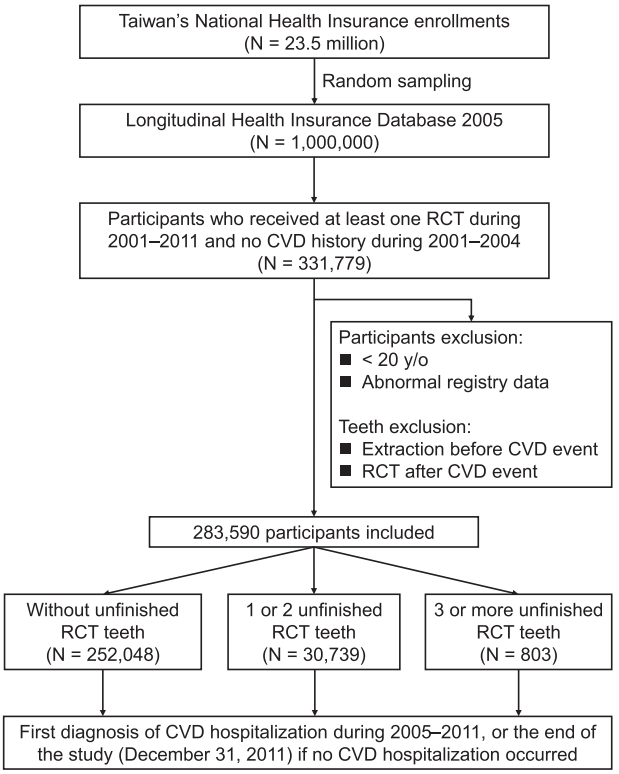

Figure 1. Flowchart of the selection of study participants from Taiwan's National Health Insurance Research Database.

a 1-canal system, 90002C for a 2-canal system, 90003C for a 3-canal system, 90019C for a 4-canal system, and 90020C for a 5-or-more-canal system), which require supporting evidence, such as periapical radiographic films for claims. Unfinished RCT in the present study was operationally defined as a tooth on which RCT was started but with no completion code. Teeth extracted before CVD hospitalization were excluded. In addition, participants with abnormal registry data, such as missing sex and inconsistent birth data, were excluded from the study. Moreover, participants younger than 20 years old were excluded because the incidence rate of CVD in children and adolescents is low. This study was approved by the Institutional Review Board of National Yang-Ming University, Taipei, Taiwan (approval number: YM102042 E).

The study participants were classified into 3 groups on the basis of the number of unfinished RCT teeth before CVD hospitalization: (1) without unfinished RCT teeth, (2) 1 or 2 unfinished RCT teeth, and (3) 3 or more unfinished RCT teeth (Fig. 1). The entry date for the first group was the start date of the first RCT; for participants with 1 unfinished RCT tooth, the entry date was the start date of the unfinished RCT; for participants with 2 unfinished RCTs, the entry date was the start date of the second unfinished RCT; and for participants with 3 or more unfinished RCTs, the entry date was the start date of the third unfinished RCT. The participants were followed until the first diagnosis of CVD hospitalization for acute myocardial infarction (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]: 410), ischemic stroke (*ICD-9-CM*: 433, 434, 436, and 437.1), or coronary heart disease (*ICD-9-CM*: 410–414) during 2005–2011 or the end of the study (December 31, 2011) if no CVD hospitalization occurred. This produced a mean observation period of 6.01 years.

The comorbidities considered were periodontal disease (*ICD-9-CM*: 523.3–523.5), diabetes mellitus (*ICD-9-CM*: 250, including types I and II), hypertension (*ICD-9-CM*: 401–405), subclinical atherosclerosis (*ICD-9-CM*: 440, 437.0), chronic kidney diseases (*ICD-9-CM*: 580–589), and hyperlipidemia (*ICD-9-CM*: 272) (17, 19, 20). To increase the validity of diagnoses in the administrative data set, we included only outpatients with 3 or more repeat diagnoses of the aforementioned comorbidities during 2005–2011.

Statistical Analysis

The differences among the 3 groups in CVD hospitalization incidence, demographic and clinical characteristics, and mean observed days were analyzed using variance tests and Mantel-Haenszel chi-square tests. Univariate and multivariate Cox proportional hazard models were used to estimate the effect of unfinished RCT on the risk of CVD during 2005–2011. Potential confounding factors such as sex, age, annual tooth scaling frequency after RCT, periodontal disease, and systemic diseases were adjusted in the Cox regression analyses. All statistical tests were performed using SAS 9.2 (SAS Institute Inc, Cary, NC), and the level of significance was $P < .05$ (2-tailed).

Results

Among the 283,590 participants with at least 1 RCT during 2001–2011 and with no CVD history before 2005, 3626 participants were hospitalized for CVD during 2005–2011, thus yielding an incidence rate of 0.21% per person year. The CVD hospitalization incidence rate for the participants with 3 or more unfinished RCTs was 0.58% per person year, which is significantly higher than those for participants without unfinished RCTs (0.21%) and with 1 or 2 unfinished RCTs (0.28%) (Table 1, $P < .0001$). Among the 3 types of CVD, participants with 3 or more unfinished RCTs had significantly higher incidence rates of ischemic stroke and coronary heart disease than those with 2 or fewer unfinished RCTs (Table 1, all $P < .05$).

Table 1 lists the demographic and clinical characteristics of the participants. Men and older patients tended to have 3 or more unfinished RCTs and a higher incidence rate of CVD hospitalization ($P < .0001$). Participants with 3 or more unfinished RCTs received an average of 5.17 RCTs during 2001–2011, which was significantly more than the RCTs received by those with 2 or fewer unfinished RCTs ($P < .0001$). Compared with the other groups, a larger percentage of participants with 3 or more unfinished RCTs exhibited comorbidities, including periodontal disease, diabetes mellitus, and hyperlipidemia (all $P < .0001$).

Figure 2 shows the cumulative hazard probabilities categorized by the number of unfinished RCTs for CVD hospitalization. The CVD hospitalization hazard probability for the participants with 3 or more unfinished RCTs after 11 years was 0.061, which was significantly higher than that for those with 1 or 2 unfinished RCTs (0.037) and with no unfinished RCTs (0.026) ($P < .0001$, log-rank test). The Cox proportional hazard regression analysis revealed that the crude hazard ratio (HR) for CVD hospitalization was 1.36- and 2.92-fold higher for the participants with 1 or 2 unfinished RCTs (95% confidence interval [CI], 1.23–1.50) and 3 or more unfinished RCTs (95% CI, 1.92–4.44), respectively, when compared with that for the participants with no unfinished RCTs (Table 2). After adjusting for potential confounding factors (age, sex, number of RCTs, annual scaling frequency after RCT, periodontal disease, and systemic diseases), the adjusted HR for CVD hospitalization for participants with 1 or 2 unfinished RCTs was 1.22 (95% CI, 1.11–1.35) compared with those who did not have any unfinished RCT teeth; the adjusted HR for CVD hospitalization for participants with 3 or more unfinished RCTs was 3.61 (95% CI, 2.36–5.51), which was

TABLE 1. Baseline Characteristics of the Study Participants

Variables	Without unfinished RCT teeth *n* = 252,048		1 or 2 unfinished RCT teeth *n* = 30,739		3 or more unfinished RCT teeth *n* = 803		*P* value
	n (%)	IR (%/PY)	*n* (%)	IR (%/PY)	*n* (%)	IR (%/PY)	
Sex							<.0001
Female	142,720 (56.62)	0.13	16,647 (54.16)	0.17	419 (52.18)	0.40	
Male	109,328 (43.38)	0.31	14,092 (45.84)	0.40	384 (47.82)	0.78	
Age (y)							
20–40	118,853 (47.15)	0.03	14,571 (47.40)	0.05	393 (48.94)	0	<.0001
40–60	103,518 (41.07)	0.24	11,594 (37.72)	0.33	275 (34.25)	1.25	
>60	29,677 (11.77)	0.83	4,574 (14.88)	0.89	135 (16.81)	0.90	
Mean number of RCTs during 2001–2011 (SD)	2.20 (1.76)		2.67 (2.10)		5.17 (2.40)		<.0001
Annual tooth scaling frequency after RCT (SD)	0.57 (0.45)		0.45 (0.48)		0.47 (0.55)		<.0001
Periodontal disease							<.0001
Yes	101,880 (40.42)	0.23	10,300 (33.51)	0.31	281 (34.99)	1.21	
No	150,168 (59.58)	0.19	20,439 (66.49)	0.26	522 (65.01)	0.33	
Diabetes mellitus							<.0001
Yes	20,604 (8.17)	0.87	2,913 (9.48)	1.04	88 (10.96)	2.65	
No	231,444 (91.83)	0.14	27,826 (90.52)	0.19	715 (89.04)	0.30	
Hypertension							.10
Yes	45,203 (17.93)	0.77	5,665 (18.43)	0.97	142 (17.68)	2.19	
No	206,845 (82.07)	0.07	25,074 (81.57)	0.10	661 (82.32)	0.22	
Subclinical atherosclerosis							.71
Yes	1,620 (0.64)	1.36	195 (0.63)	2.03	7 (0.87)	2.89	
No	250,428 (99.36)	0.20	30,544 (99.37)	0.26	796 (99.13)	0.56	
Chronic kidney disease							.053
Yes	4,868 (1.93)	1.09	656 (2.13)	1.35	16 (1.99)	2.15	
No	247,180 (98.07)	0.19	30,083 (97.87)	0.25	787 (98.01)	0.54	
Hyperlipidemia							<.0001
Yes	33,197 (13.17)	0.70	3,757 (12.22)	0.97	105 (13.08)	1.83	
No	218,851 (86.83)	0.12	26,982 (87.78)	0.17	698 (86.92)	0.39	
Mean observed years (SD)	6.09 (3.10)		5.39 (3.38)		4.74 (3.28)		<.0001
Total hospitalization events of cardiovascular diseases	3,147 (1.25)	0.21	457 (1.49)	0.28	22 (2.74)	0.58	<.0001
Acute myocardial infarction	473 (0.19)	0.03	71 (0.23)	0.04	2 (0.25)	0.05	.074
Ischemic stroke	1,290 (0.51)	0.08	195 (0.63)	0.12	10 (1.25)	0.26	<.0001
Coronary heart disease	1,384 (0.55)	0.09	191 (0.62)	0.11	10 (1.25)	0.26	.0006

IR, incidence rate; PY, person year; RCT, root canal treatment; SD, standard deviation.

significantly higher than that for participants with no unfinished RCTs (Table 2). The multivariate Cox proportional hazard regression model analysis revealed that the participants with a higher number of unfinished RCTs were independently associated with a higher risk of future CVD hospitalization.

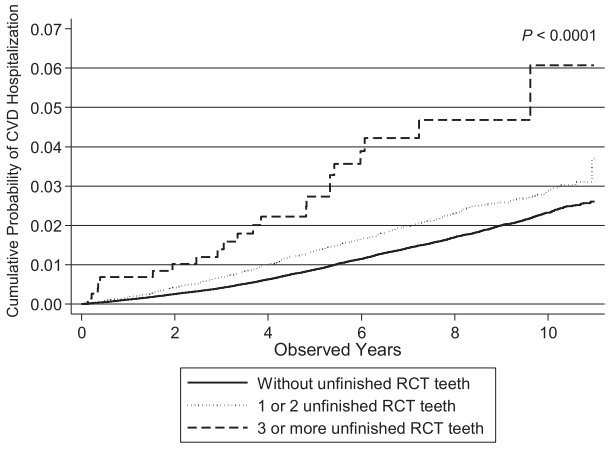

Figure 2. Cumulative hazard probabilities for CVD hospitalization categorized by the number of unfinished RCTs between 2005 and 2011.

Discussion

The present nationwide population-based study, which included participants with at least 1 RCT and with no CVD history, is the first population-based study to investigate the association between unfinished RCTs and the risk of CVD hospitalization. The results showed that participants with unfinished RCTs were independently associated with a higher risk of future CVD hospitalization.

The present study revealed a CVD hospitalization incidence rate of 0.21% per person year (0.03% for acute myocardial infarction, 0.09% for ischemic stroke, and 0.09% for coronary heart disease) among participants with at least 1 RCT. This result was lower than that obtained by Cheng et al (21), which was extracted from the same database for the period 1996–2001; they reported a coronary heart disease hospitalization rate of 0.24% per person year among men and 0.15% among women. The present study excluded participants with a history of CVD before 2005; therefore, the hospitalization rate may have been underestimated. Previous studies have shown high sensitivity (100%) and specificity (95%) in identifying CVD hospitalization events using *ICD-9-CM* codes from the same database (22–24).

The possible consequences pertaining to CVD after undergoing RCT remain controversial. Joshipura et al (9) evaluated the association between the number of self-reported RCTs and the incidence of CVDs from the Health Professionals Follow-Up Study and reported that patients who have undergone RCT may be at an increased risk of coronary

TABLE 2. Results of the Univariate and Multivariate Cox Regression Analyses Conducted to Identify Risk Factors of Cardiovascular Disease Hospitalization Based on Taiwan's National Health Insurance Research Database Entries from 2005–2011

	Univariate				Multivariate			
Variables	**Hazard ratio**	**95% CI lower**	**95% CI upper**	***P* value**	**Hazard ratio**	**95% CI lower**	**95% CI upper**	***P* value**
Numbers of unfinished RCT teeth								
1 or 2 vs 0	1.36	1.23	1.50	<.0001	1.22	1.11	1.35	<.0001
3 or more vs 0	2.92	1.92	4.44	<.0001	3.61	2.36	5.51	<.0001
Sex								
Male vs female	2.36	2.20	2.52	<.0001	2.18	2.04	2.34	<.0001
Age (y)								
40–60 vs 20–40	7.44	6.55	8.45	<.0001	4.07	3.57	4.65	<.0001
>60 vs 20–40	25.17	22.16	28.59	<.0001	8.19	7.14	9.40	<.0001
Mean number of RCTs during 2001–2011								
+1	0.89	0.88	0.91	<.0001	0.86	0.85	0.88	<.0001
Annual tooth scaling frequency after RCT								
+1	0.78	0.72	0.86	<.0001	0.84	0.76	0.94	.001
Periodontal disease								
Yes vs no	1.22	1.14	1.30	<.0001	1.12	1.04	1.22	.005
Diabetes mellitus								
Yes vs no	5.99	5.60	6.41	<.0001	1.61	1.49	1.74	<.0001
Hypertension								
Yes vs no	10.23	9.52	11.00	<.0001	3.46	3.18	3.75	<.0001
Subclinical atherosclerosis								
Yes vs no	6.86	5.89	8.00	<.0001	1.78	1.52	2.08	<.0001
Chronic kidney disease								
Yes vs no	5.72	5.16	6.35	<.0001	1.52	1.37	1.69	<.0001
Hyperlipidemia								
Yes vs no	5.55	5.20	5.92	<.0001	1.77	1.65	1.91	<.0001

CI, confidence interval; RCT, root canal treatment.

Test for trend for numbers of unfinished RCT teeth, $P < .0001$.

heart disease (relative risk = 1.21; 95% CI, 1.05–1.40). Caplan et al (10) reported that patients with 2 or more RCTs were 1.62 times (95% CI, 1.04–2.53) more likely to develop coronary heart disease compared with those who had not reported any RCT. However, these 2 studies used questionnaires to obtain the number of RCTs; therefore, misclassifications may have occurred. Although the present study was unable to explore the effect of RCT on CVD risk for only recruiting treatment after 2001, the results of the multivariate Cox regression analyses revealed that participants who underwent a higher number of RCTs between 2001 and 2011 were associated with a lower risk for CVD hospitalization (adjusted HR = 0.86; 95% CI, 0.85–0.88; Table 2), which indicated that RCT completion can effectively reduce coronal leakage and bacterial contamination, seal the apex from periapical tissue fluids, and entomb remaining irritants within the root canal system such that the amount of pulpal inflammation and future CVD hospitalization risk decrease (25).

The present study determined that participants with a higher number of unfinished RCTs were independently associated with a higher risk of future CVD hospitalization. An RCT can be left unfinished for several reasons, including symptomatic teeth infected with gram-negative anaerobic bacteria (26, 27). The root canal flora of teeth with clinically intact crowns and necrotic pulps is dominated by obligate anaerobes, including *Fusobacterium*, *Porphyromonas*, *Prevotella*, *Eubacterium*, and *Peptostreptococcus* (28). In the case of unfinished RCTs, these anaerobic microbiota can indirectly elevate inflammatory mediator levels and cytokine concentrations, such as those of interleukin (IL)-6 and IL-2 (29). This low-grade chronic inflammation may be a risk factor for the development of atherosclerosis and CVD because of its ability to induce endothelial dysfunction (12, 30).

A patient with 1 or 2 unfinished RCTs may have experienced unceasing symptoms. However, patients with 3 or more unfinished RCTs are more likely to have been noncompliant; in other words, the patient ignored subsequent appointments of the RCT procedure after the symptoms subsided. An unfinished RCT, typically one involving a temporary restoration, can increase the risk of contamination of the oral cavity over time, leading to bacterial infection of the root canal system and subsequent apical periodontitis when the inflammation progresses to the periapical tissues. Apical periodontitis is hypothesized to be an immune response to prevent the diffusion of the infection into the bone; it is supposed to confine and restrict the infectious elements. However, when unbalanced, apical periodontitis induces an acute phase spreading of the infection. Two studies have revealed that the number of endodontic lesions was significantly associated with coronary heart disease diagnosis (31, 32). In addition, Willershausen et al (33) reported that patients who have experienced myocardial infarction had a higher number of radiographic apical lesions compared with healthy patients. Although the underlying mechanisms remain unclear, Cotti et al (30) suggested that patients with apical periodontitis tend to have higher inflammation markers (IL-1, IL-2, and IL-6) and the systemic vascular function marker (asymmetrical dimethylarginine), which play independent roles in the pathogenesis and progression of CVD.

Another possible pathological mechanism is that unfinished RCTs more likely indicate poor oral health. Poor oral health has been considered as a risk factor for CVD because infectious agents collaborate in atherosclerosis formation and indirectly induce chronic inflammation (34, 35). Two studies that used the same health insurance database revealed that the frequency of tooth scaling was associated with a reduced risk of CVD incidence (19, 20). The present study showed that participants with a higher annual frequency of tooth scaling was associated with a significantly lower risk of future CVD hospitalization (adjusted HR = 0.84; 95% CI, 0.76–0.94; Table 2). After controlling for this factor, unfinished RCT was independently associated with a higher risk of future CVD hospitalization.

The present study had several limitations. First, some crucial risk factors of CVD hospitalization, such as smoking, body mass index, alcohol consumption, dietary status, and family history, are not available in the study database, which may have resulted in inadequate adjustment of the confounding factors, leading to uncertainty of the causal relationship. Second, we did not consider the latent period of CVD events. However, a Cox regression analysis after excluding participants observed for <2 years produced consistent results (243,271 participants; adjusted HR = 1.14 [95% CI, 1.02–1.28] for the participants with 1 or 2 unfinished RCTs; adjusted HR = 2.92 [95% CI, 1.75–4.86] for the participants with 3 or more unfinished RCTs). Finally, the database does not contain some clinical parameters of RCT, such as the irrigant used and the cleaning and shaping techniques; therefore, we cannot clearly distinguish the inflammatory status and reason for each unfinished RCT tooth. In addition, we cannot ensure the absence of bacterial or pulpal inflammation in the completed RCTs. Nevertheless, the results of the present study show a real-world pattern that provides dentists and patients with valuable information.

Conclusion

After adjusting for potential confounding factors (age, sex, number of RCTs, annual scaling frequency after RCT, periodontal disease, and systemic diseases), the participants with unfinished RCTs were associated with a higher risk of future CVD hospitalization. Additional studies are necessary to further evaluate a causal relationship between unfinished RCT and subsequent CVD events.

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The authors deny any conflicts of interest related to this study.

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