

Increased Risk of Peripheral Arterial Disease After Hip Replacement: An 11-Year Retrospective Population-Based Cohort Study

Tzu-Yi Chou, Ta-Wei Su, Heng-Jeng Jou, Pei-Yu Yang, Hsuan-Ju Chen, Chih-Hsin Muo, and Chia-Hung Kao

Abstract: The correlation between hip replacement (Hip-Rep) and peripheral arterial disease (PAD) remains uncertain. Thus, we investigated the relationship between Hip-Rep and risk of developing PAD in a nationwide retrospective cohort study.

National Health Insurance data were used to assemble a cohort of patients who were diagnosed from 2000 to 2011. Patients with a history of PAD were excluded. A total of 5284 patients who received a Hip-Rep and 21,124 matched controls were enrolled. We used Cox proportional hazards regression model to analyze the adjusted risk of developing PAD.

The risk of developing PAD in the Hip-Rep group was 1.24-fold higher (95% CI = 1.05–1.48) than that in the control group. The adjusted risk of developing PAD increased with patient age; compared with patients aged 50 years or younger, the risk among those ages at least 80 years was 4.87-fold higher. Patients with diabetes exhibited the highest risk of developing PAD (HR = 1.58, 95% CI = 1.34–1.86). Compared with patients who had not received a Hip-Rep or reported any comorbidity, patients who received a Hip-Rep were 2.45-fold more likely to develop PAD (95% CI = 1.54–3.89); the risk increased with the number of comorbidities.

Hip-Reps might be independently linked with an increased risk of developing PAD. The impact of Hip-Reps on this risk was greater in women and patients ages 65 years and younger and within the first year of follow-up.

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From the Department of Physical Medicine and Rehabilitation, China Medical University Hospital, Taichung (T-YC, P-YY); Division of Thoracic and Cardiovascular Surgery, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan (T-WS); Department of Orthopedic Surgery, Kuang Tien General Hospital, Taichung (H-JJ); Department of Nursing, Hungkuang University, Taichung (H-JJ); School of Medicine, China Medical University, Taichung (P-YY, H-JC, C-HM); Management Office for Health Data, China Medical University Hospital, Taichung (H-JC, C-HM); Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung (C-HK); and Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan (C-HK).

Correspondence: Chia-Hung Kao, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yude Road, Taichung City 404, Taiwan (e-mail: d10040@mail.cmuh.org.tw).

Author contributions: Conception and design—T-YC, T-WS, H-JJ, P-YY, C-HK; administrative support—C-HK; collection and assembly of data—H-JC, C-HM, C-HK; data analysis and interpretation—H-JC, C-HM, C-HK; manuscript writing and final approval of manuscript—all authors.

T-YC and T-WS contributed equally to this work.

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Abbreviations: CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, Hip-Rep = hip replacement, HR = hazard ratio, HTN = hypertension, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IS = ischemic stroke, NHIRD = National Health Insurance Research Database, PAD = peripheral arterial disease.

INTRODUCTION

Hip replacement (Hip-Rep), also called total hip arthroplasty, is a common and efficacious surgical procedure.^{1,2} The number of Hip-Reps rapidly increased over the past decade.³ Kurtz et al reported a significant increase in the primary total Hip-Rep rate in the United States from 47/100,000 in 1990 to 69/100,000 in 2002 (an increase of 22/100,000 in 12 years).⁴ A Taiwan-based cohort study revealed that the rate of primary total Hip-Reps and primary partial Hip-Reps increased from 37/100,000 in 1996 to 55/100,000 in 2004 (an increase of 18/100,000 in 8 years).⁵

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and is highly related to the risk of ischemic stroke (IS), myocardial infarction, and fatal vascular events. Even without previous myocardial infarction or IS, patients with PAD exhibit an almost equal relative risk of death from cardiovascular causes as do patients with a history of coronary or cerebrovascular disease.^{6–8} The worldwide prevalence rate of PAD ranges from 3% to 12%.^{9,10} Regensteiner and Hiatt reported that nearly 20% of adults older than 70 years have PAD.¹¹ Claudication, atypical leg discomfort, and rest pain are common symptoms of PAD; however, most critically, as many as 50% of patients with PAD are asymptomatic.^{10,12} The reported risk factors for developing PAD include aging, diabetes mellitus (DM), smoking, hypertension (HTN), and hyperlipidemia.^{6,9} In this article, “PAD” denotes vascular diseases including atherosclerosis of the abdominal aorta, iliac, and extremity arteries; extremity artery bypass graft; arterial embolisms and thrombosis; and unspecified disorders of the arteries and arterioles.

Several studies have reported that Hip-Rep is associated with an increased risk of PAD;^{2,13–15} however, no research has investigated this association in an Asian context. Thus, we conducted a nationwide retrospective cohort study to examine the risk of developing PAD in patients who received a Hip-Rep, hypothesizing that the procedure might increase the risk of developing PAD.

METHODS

Data Source

This retrospective cohort study used data from the Longitudinal Health Insurance Database (LHID). The LHID is a

subset of the National Health Insurance Research Database (NHIRD) program, which was established by the Taiwan Bureau of NHI (BNHI). The NHI program, inaugurated in 1995, covers approximately 99% of the more than 23 million people in Taiwan.

By the end of 2010, the BNHI had contracts with all hospitals and 92% of clinics nationwide. Each person covered by the NHI receives a unique identification number. All NHI data sets can be interlinked using these anonymized identification numbers. Comprehensive information on insured patients, including demographic data, clinic visit dates, disease diagnoses, and prescription details, is included in the LHID. The diagnostic codes used were those in the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). This study was approved by the institutional review board of China Medical University and Hospital, Taiwan (CMU-REC-101-012).

Study Population

This national population-based cohort study included 2 groups. We identified 5284 patients who received a Hip-Rep (ICD-9-CM codes 815.1 and 815.2) but had no history of PAD (ICD-9-CM codes 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, and 447.9) from 2000 to 2011. The date of Hip-Rep was used as the index date. A control group was randomly selected from insured people with no Hip-Rep or history of PAD and was matched with the Hip-Rep group at a ratio of approximately 4:1 according to sex, age, and year of Hip-Rep. The index dates of the control cohort were assigned according to days and months randomly, and the index years were the same year as those of the matched cases. In total, 5284 patients were included in the Hip-Rep group and 21,124 patients comprised the control group.

Covariates and Main Outcome

Demographic factors included sex and age (in groups ages <50, 50–64, 65–79, and >80 years). Patients with HTN (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), DM (ICD-9-CM code 250), ischemic stroke (IS, ICD-9-CM codes 433–438), ischemic heart disease (IHD, ICD-9-CM codes 410–414), chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 490, 491, 495, and 496), or chronic kidney disease (CKD, ICD-9-CM code 585) diagnosed before the index date were considered to have a comorbidity.

We identified a significant outcome of PAD development (ICD-9-CM codes 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, and 447.9). Patients were followed from the index date until either December 2011, onset of PAD, death, or withdrawal from the NHI.

Statistical Analysis

The distribution of sex, age, and comorbidities (HTN, hyperlipidemia, DM, IS, IHD, COPD, and CKD) between the Hip-Rep and the control groups were compared. Differences were examined using the chi-square tests for categorical variables and the Student *t* test for continuous variables. Follow-up time in person-years was calculated for each person from the index date until PAD development. The incidence rate was calculated by dividing the number of PAD diagnoses by the number of person-years. The cumulative incidence of PAD was computed using the Kaplan–Meier method, and the difference in cumulative incidence between the groups was tested using a log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models to

assess the association between Hip-Rep and PAD, with sex, age, and comorbidities adjusted for. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC). The significance level was set at less than .05 for the 2-sided *P* value.

RESULTS

A total of 5284 patients who had received a Hip-Rep between 2000 and 2011 was frequency-matched according to sex, age, and year of Hip-Rep with 21,124 patients who had not received a Hip-Rep. The Hip-Rep group had a mean age of 67.2 years (standard deviation [SD] = 16.2 years) and a slight female predominance (52.5%). Compared with the control group, the Hip-Rep group exhibited a significantly higher prevalence of HTN (58.5% vs 51.1%), DM (22.1% vs 17.4%), IS (27.7% vs 19.9%), IHD (30.0% vs 26.9%), COPD (32.6% vs 28.1%), and CKD (5.2% vs 2.6%) (Table 1).

The results of Kaplan–Meier analysis revealed that the Hip-Rep group had a higher cumulative incidence rate of PAD than did the control group (log-rank test, *p* = 0.001) (Figure 1). During the follow-up period, the incidence rates of PAD for the Hip-Rep and control groups were 7.79 and 5.79 per 1000 person-years, respectively. After adjustments for sex, age, and comorbidities, patients who received a Hip-Rep exhibited an increased risk of PAD compared with those in the control group (adjusted HR = 1.24, 95% CI = 1.05–1.48) (Table 2). Compared with patients ages 50 years and younger, the adjusted HR of PAD was 3.46-fold higher among those ages 50–64 years, 4.61-fold higher among those ages 65–79 years, and 4.87-fold higher among those ages 80 years and older. Multivariate Cox proportional hazards analysis revealed that PAD was independently associated with HTN (adjusted HR = 1.35, 95% CI = 1.12–1.63), DM (adjusted HR = 1.58, 95% CI = 1.34–1.86), IHD (adjusted HR = 1.70, 95% CI = 1.44–1.99), and CKD (adjusted HR = 1.75, 95% CI = 1.29–2.37).

TABLE 1. Demographics Between Hip-Rep and Comparison Group

	Hip-Rep (N = 5284)		Comparison (N = 21,124)		P-Value
	N	%	n	%	
Men	2508	47.5	10,027	47.5	0.97
Age, year					0.99
<50	942	17.8	3768	17.8	
50–64	1053	19.9	4212	19.9	
65–79	2045	38.7	8180	38.7	
>80	1244	23.5	4964	23.5	
Mean (SD) [†]	67.2	(16.2)	66.5	(16.1)	
Comorbidity					
HTN	3093	58.5	10,801	51.1	<0.0001
Hyperlipidemia	1478	28.0	5646	26.7	0.07
DM	1165	22.1	3685	17.4	<0.0001
IS	1466	27.7	4209	19.9	<0.0001
IHD	1585	30.0	5687	26.9	<0.0001
COPD	1724	32.6	5936	28.1	<0.0001
CKD	276	5.22	558	2.64	<0.0001

CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, Hip-Rep = hip replacement, HTN = hypertension, IHD = ischemic heart disease, IS = ischemic stroke, SD = standard deviation. Chi-square test and [†]*t* test.

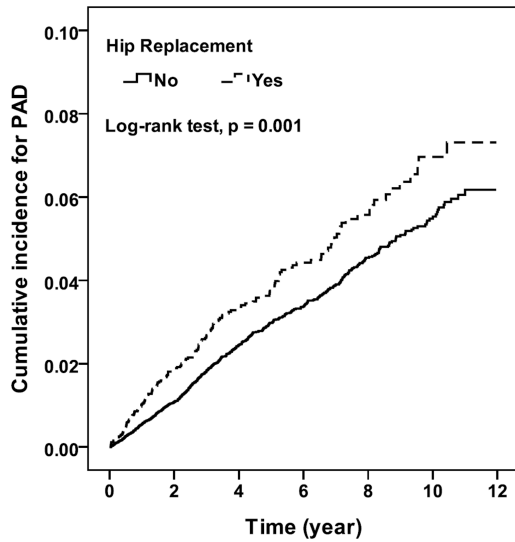


FIGURE 1. Cumulative incidence of peripheral arterial disease in hip replacement and control cohorts.

Stratified by sex, the incidence rates of PAD in women and men who received a Hip-Rep were 9.34 and 9.17 per 1000 person-years, respectively, both higher than those in women and men in the control cohort (6.54 and 5.01 per 1000 person-years, respectively). In addition, women who received a Hip-Rep exhibited a 1.29-fold (95% CI=1.03–1.61) higher risk of developing PAD than did women who did not receive a Hip-Rep. Among the age groups, a significantly higher HR of PAD was observed among patients who received a Hip-Rep while ages 65 years or younger (adjusted HR = 1.67, 95% CI = 1.18–2.36). Stratified by follow-up year, the Hip-Rep group exhibited a significantly higher risk than did the comparison group of developing PAD within 0.5 years and 0.5–1 years (adjusted HR = 1.69, 95% CI = 1.03–2.78 and adjusted HR = 1.63, 95% CI = 1.01–2.63, respectively) (Table 3).

Compared with patients without the examined diseases and Hip-Rep treatment, patients received Hip-Rep without any comorbidity had a 2.45-fold risk for PAD (95% CI = 1.54–3.89). Patients with only DM exhibited the highest risk of developing PAD (adjusted HR = 3.66, 95% CI = 1.67–7.99), followed by those with only IS (adjusted HR = 3.64, 95% CI = 1.80–7.35) and those with only IHD (adjusted HR = 3.44, 95% CI = 1.71–6.94) compared to people with

TABLE 2. Hazard Ratio and 95% Confidence Intervals for PAD and PAD-Associated Risk Factor

	Hip-Rep		HR (95% CI)	
	Case no.	IR	Crude	Adjusted
Replacement				
No	586	5.79	1.00	1.00
Yes	173	7.79	1.34 (1.13–1.59)***	1.24 (1.05–1.48)*
Gender				
Women	443	7.05	1.35 (1.16–1.55)***	1.08 (0.93–1.25)
Men	316	5.22	1.00	1.00
Age, year				
<50	30	1.11	1.00	1.00
50–64	129	4.90	4.40 (2.96–6.55)***	3.46 (2.31–5.18)***
65–79	410	8.27	7.42 (5.12–10.6)***	4.61 (3.11–6.83)***
>80	190	9.25	8.28 (5.63–12.2)***	4.87 (3.22–7.37)***
Comorbidity				
HTN				
No	213	3.31	1.00	1.00
Yes	546	9.54	2.78 (2.37–3.26)***	1.35 (1.12–1.63)**
DM				
No	532	5.10	1.00	1.00
Yes	227	11.94	2.33 (1.99–2.72)***	1.58 (1.34–1.86)***
IS				
No	511	5.05	1.00	1.00
Yes	248	11.14	2.19 (1.88–2.55)***	1.18 (0.99–1.39)
IHD				
No	393	4.23	1.00	1.00
Yes	366	12.02	2.83 (2.46–3.27)***	1.70 (1.44–1.99)***
COPD				
No	494	5.35	1.00	1.00
Yes	265	8.53	1.58 (1.36–1.84)***	0.98 (0.84–1.15)
CKD				
No	713	5.91	1.00	1.00
Yes	46	16.91	2.83 (2.10–3.81)***	1.75 (1.29–2.37)***

CI = confidence interval, CKD = chronic kidney disease. IR, incidence density rate, per thousand person-years, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, Hip-Rep = hip replacement, HR = hazard ratio, HTN = hypertension, IHD = ischemic heart disease, IS = ischemic stroke, SD = standard deviation. Manually adjusted for sex, age and comorbidity. *P < 0.05, **P < 0.01, ***P < 0.001

TABLE 3. Hazard Ratio and 95% Confidence Intervals for PAD Compared to Comparison Cohort Stratified by Gender, Age, and Follow-up Year

	Hip-Rep		Comparison		Hip-Rep vs. Comparison
	Case No.	IR	Case No.	IR	HR (95% CI)
Gender [†]					
Women	106	9.34	337	6.54	1.29 (1.03–1.61)*
Men	67	9.17	249	5.01	1.19 (0.91–1.56)
Age, year [†]					
<65	48	4.77	111	2.57	1.67 (1.18–2.36)**
65–79	86	9.97	324	7.91	1.13 (0.89–1.44)
>80	39	11.05	151	8.88	1.18 (0.83–1.68)
Follow-up year [‡]					
<0.5	23	9.29	51	5.03	1.69 (1.03–2.78)*
0.5–1.0	25	11.22	55	5.84	1.63 (1.01–2.63)*
>1.0	125	7.14	480	5.88	1.13 (0.93–1.38)

CI = confidence interval, Hip-Rep = hip replacement, HR = hazard ratio, IR = incidence density rate, per thousand person-years, PAD = peripheral arterial disease. **P* < 0.05, ***P* < 0.01.

[†] Manually adjusted for sex, age, and comorbidity.

[‡] Adjusted for sex, age, and comorbidity.

no comorbidity. Among patients who received a Hip-Rep, those with four or more comorbidities exhibited a significantly increased risk of PAD (adjusted HR = 6.00, 95% CI = 4.16–8.67), followed by those with any three comorbidities (adjusted HR = 4.32, 95% CI = 2.84–6.59), those with any two comorbidities (adjusted HR = 3.49, 95% CI = 2.25–5.43), and those with one comorbidity (adjusted HR = 2.80, 95% CI = 1.74–4.49) (Table 4).

DISCUSSION

We conducted this nationwide population-based retrospective cohort study to elucidate the relationship between Hip-Rep and the risk of developing PAD. After adjustments for sex, age, HTN, DM, IS, IHD, COPD, and CKD, patients who received a

Hip-Rep exhibited a 1.24-fold higher risk of developing PAD than did patients in the control group. Age, HTN, DM, IHD, COPD, and CKD were also significantly associated with PAD. Most notably, a significantly higher risk of developing PAD was noted among women who received a Hip-Rep, patients who received a Hip-Rep while ages 65 years or younger, and patients who received a Hip-Rep within the first follow-up year.

Our data revealed that advanced age, rather than sex, influenced the risk of developing PAD. This outcome was consistent with those in previous studies.^{6,10} However, this study did not demonstrate that patients with only hyperlipidemia were at increased risk of developing PAD (compared with patients without the examined diseases), as previous studies have shown. Using more cases or longer study periods might

TABLE 4. Joint Effect for PAD between Hip Replacement and PAD-Associated Risk Factor

Variable	N	Case No.	IR	HR (95% CI)
None	6895	63	1.65	1.00
Only Hip-Rep	1314	25	3.83	2.45 (1.54–3.89)***
Only HTN	1753	45	5.07	2.25 (1.52–3.32)***
Only Hyperlipidemia	520	8	2.99	1.66 (0.80–3.47)
Only DM	227	7	6.73	3.66 (1.67–7.99)**
Only IS	232	9	8.53	3.64 (1.80–7.35)***
Only IHD	226	9	7.53	3.44 (1.71–6.94)***
Only COPD	982	16	3.5	1.76 (1.01–3.05)*
Only CKD	23	0	0.00	–
Without Hip-Rep and with any two or more comorbidities	10,266	429	9.84	4.10 (3.10–5.42)***
Hip-Rep with any one comorbidity	976	24	5.54	2.80 (1.74–4.49)***
Hip-Rep with any two comorbidities	949	30	7.75	3.49 (2.25–5.43)***
Hip-Rep with any three comorbidities	902	35	10.14	4.32 (2.84–6.59)***
Hip-Rep with any four or more comorbidities	1143	59	14.65	6.00 (4.16–8.67)***

CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, Hip-rep = hip replacement, HTN = hypertension, IHD = ischemic heart disease, IS = ischemic stroke, SD = standard deviation. Adjusted for age and sex. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

reveal the positive association between hyperlipidemia and the risk of developing PAD.

This study revealed that patients who received a Hip-Rep had more comorbidities (HTN, DM, and CKD) than did patients in the control group. Moreover, HTN, DM, and CKD are associated with PAD.^{6,16,17} Accordingly, one possible reason for the increased risk of PAD in the Hip-Rep group is that the patients in the group had a significantly higher prevalence of comorbidities. We did not have sufficient data on the prevalence of comorbidities in Asian patients who received a Hip-Rep. However, a 1990–2004 National Hospital Discharge Survey-based statistical analysis in the United States reported that patients who received a Hip-Rep had an increased likelihood of developing DM, HTN, hypercholesterolemia, obesity, pulmonary disease, or CAD.¹⁸

Alternatively, the population of patients with PAD identified in this study might have been underestimated because PAD is frequently underdiagnosed.^{10,19} Thus, the number of patients with PAD was likely greater than that diagnosed and enrolled; therefore, the impact of Hip-Rep on the risk of developing PAD might have been underestimated.

Limitations were also caused by incomplete data. First, the diagnoses recorded in the National Health Insurance Research Database (NHIRD) are primarily for administrative billing purposes and were not validated for academic purposes. Second, data on symptoms of PAD, family medical history, lifestyle, smoking habit, BMI status, laboratory data, and imaging findings, which are all potentially relevant to this study, are not included in the NHIRD. Third, the evidence derived from a retrospective cohort study is generally of lower methodological quality than that of prospectively randomized trials because a retrospective cohort study design is subject to numerous biases related to adjustments for confounding factors. Despite our meticulous study design with the adequate control of confounding factors, a key limitation was that bias could have existed because of possible unmeasured or unknown confounders. Thus, a bias such as PAD patients with a mistaken diagnosis of arthrosis might occur. Fourth, causality could not be established beyond doubt in this observational study. We could not verify the exact temporal relationship between Hip-Rep and PAD by using the NHIRD data.

Our findings have clinical importance. First, the results indicated that Hip-Rep independently increases the risk of developing PAD. Because Hip-Rep has been reported as being associated with an increased risk of atherosclerosis and unspecified cardiovascular disease² and arterial thrombosis,¹³ few studies have examined the specific relationship between Hip-Rep and PAD or considered Hip-Rep an independent risk factor for developing PAD. Some reports suggested a positive association between Hip-Rep and risk of developing PAD. For example, Islam and Blake reported a total infrarenal aortic occlusion condition after primary Hip-Rep, and that an aorto-bifemoral bypass resolved the problem.²⁰ Hemodynamic change, or vascular compromise, was proposed as a potential factor or an aggravated factor for developing PAD.^{15,21} However, future prospective, large-scale research; systematic reviews; or meta-analyses might validate this finding. The second clinically notable aspect of this study is that the more comorbidities in the Hip-Rep group, the more risk of PAD and related morbidity and mortality; physicians should consider these conditions and treat patients accordingly.

This study has several strengths. First, this study is the first to examine the relationship between Hip-Rep and the risk of developing PAD in an Asian country. Second, we conducted

this retrospective cohort research using nationwide population data from the NHIRD, which covers a highly representative sample of the general population of Taiwan because the reimbursement policy is universal and operated only by the government. Moreover, all insurance claims are scrutinized by peer review and medical reimbursement specialists. PAD was accurately diagnosed and coded (ICD-9 codes) by the specialists according to the standard diagnosed criteria including typical symptoms/signs, laboratory data, and imaging findings. In addition, if the doctors or hospitals make the wrong codes or diagnoses, the National Health Insurance Administration will punish them with a lot of penalty. Therefore, the diagnoses of PAD in this study were highly reliable. Third, the joint effect of Hip-Rep and different numbers of comorbidities are discussed, possibly elucidating the risk of PAD among patients with multiple comorbidities.

In conclusion, patients who received a Hip-Rep might have an increased risk of developing PAD. Age, HTN, DM, IHD, and CKD are also crucial risk factors for developing PAD. Patients who receive a Hip-Rep and have the aforementioned comorbidities are at an even higher risk of developing PAD. An increased risk of developing PAD was present among women who received a Hip-Rep, patients who received a Hip-Rep while ages 65 years or younger, and patients who received a Hip-Rep within the first follow-up year in our study period. Although Hip-Rep is an orthopedic procedure, it might influence the vascular system profoundly. We suggest that further research involving larger samples and a more rigorous methodology be conducted.

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