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# Association Between Vascular Access Dysfunction and Subsequent Major Adverse Cardiovascular Events in Patients on Hemodialysis

## *A Population-Based Nested Case–Control Study*

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**Abstract:** The association between dialysis vascular access dysfunction and the risk of developing major adverse cardiovascular events (MACE) in hemodialysis patients is unclear and has not yet been investigated. We analyzed data from the National Health Insurance Research Database of Taiwan to quantify this association. Adopting a case–control design nested within a cohort of patients who received hemodialysis from 2001 to 2010, we identified 9711 incident cases of MACE during the stage of stable maintenance dialysis and 19,422 randomly selected controls matched to cases on age, gender, and duration of dialysis. Events of vascular access dysfunction in the 6-month period before the date of MACE onset (ie, index date) for cases and before index dates for controls were evaluated retrospectively. The presence of vascular access dysfunction was associated with a 1.385-fold higher odds of developing MACE as estimated from the logistic regression analysis. This represents a significantly increased adjusted odds ratio (OR) at 1.268 (95% confidence interval [CI] = 1.186–1.355)

after adjustment for comorbidities and calendar years of initiating dialysis. We also noted a significant exposure–response trend ( $P < 0.001$ ) between the frequency of vascular access dysfunction and MACE, with the greatest risk (adjusted OR = 1.840, 95% CI = 1.549–2.186) noted in patients with  $\geq 3$  vascular access events. We concluded that dialysis vascular access dysfunction was significantly associated with an increased risk of MACE. Hence, vascular access failure can be an early sign for MACE in patients receiving maintenance hemodialysis. Active monitoring and treatment of cardiovascular risk factors and related diseases, not merely managing vascular access dysfunction, would be required to reduce the risk of MACE.

(*Medicine* 94(26):e1032)

**Abbreviations:** CDC = Centers for Disease Control and Prevention, CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, GEE = generalized estimating equation, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, MACE = major adverse cardiovascular events, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, OR = odds ratio, SD = standard deviation, USRDS = United States Renal Data System, WHO = World Health Organization.

Editor: Anastasios Lymperopoulos.

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This research is based on the National Health Insurance Research Database from the National Health Research Institutes, Miaoli, Taiwan and was supported by the NCKUH-10302005 grant from National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001032

## INTRODUCTION

According to the updated statistics reports by the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO), cardiovascular disease represents the first leading cause of death in the general population, both in the United States and worldwide.<sup>1</sup> The specific population of patients with end-stage renal disease (ESRD) is no exception for this trend. Patients with ESRD have an extraordinarily increased risk of mortality compared with the general population, with cardiovascular disease as the most common cause of death, too.<sup>2,3</sup> In addition to cardiovascular mortality, cardiovascular morbidity and major adverse cardiovascular events (MACE) are commonly observed in these patients. The prevalence of coronary artery disease, congestive heart failure, cerebrovascular disease, or peripheral artery disease in patients receiving dialysis each range from 20% to 30% in Japan and Europe to approximately 50% in the United States.<sup>4</sup> The widespread presence of diabetes, hypertension, dyslipidemia, increased presence of multiple comorbid conditions, inflammation, and ESRD itself, the last stage of chronic kidney disease (CKD) requiring dialysis, are to blame for the high prevalence of cardiovascular morbidity and mortality in the dialysis population.<sup>5,6</sup> In addition, repeated dialysis-related cardiovascular

insults could raise the probability of subsequent MACE, including volume overload before each dialysis session, subclinical myocardial ischemia during dialysis and disturbed calcium–phosphate metabolism.<sup>7–9</sup>

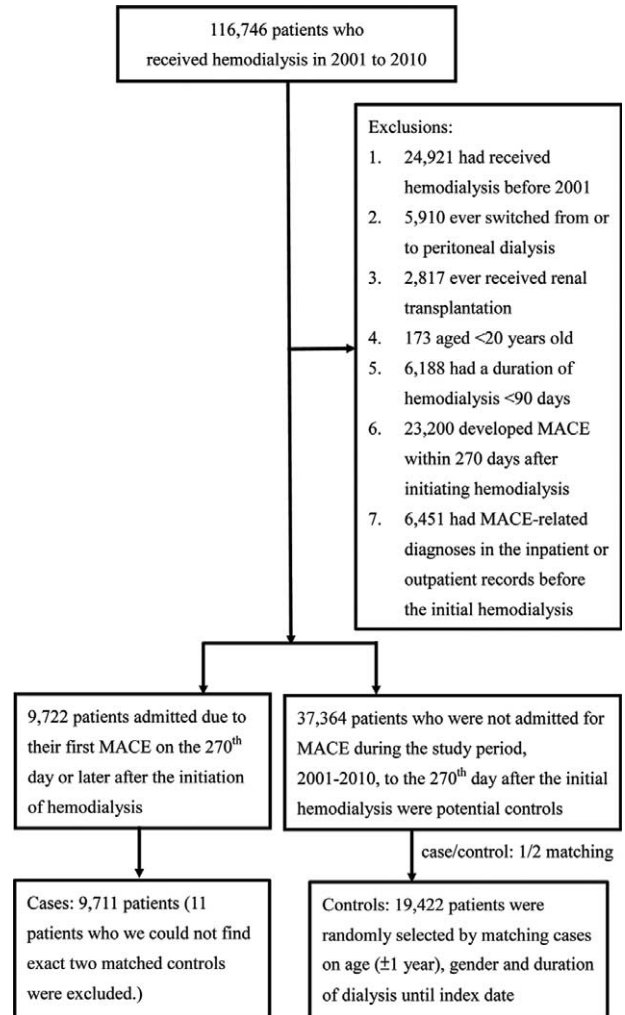
Among dialysis-related cardiovascular morbidities, thrombosis or dysfunction of the vascular access is usually regarded as a matter of course after a certain period of time on dialysis. Vascular access dysfunction is affected not only by the traditional cardiovascular risk factors commonly noted in other cardiovascular diseases<sup>10–13</sup> but also by the trauma of cannulation.<sup>14,15</sup> Vascular access dysfunction, ranging from 16% to 30% within 3 years after the creation of the access, is the leading cause of dialysis-related morbidity and is associated with 15% to 25% of hospital stays among prevalent patients with ESRD.<sup>3,13,16</sup>

It is possible that there is an association between vascular access dysfunction and MACE,<sup>17</sup> because both conditions are commonly observed in the dialysis population and the vessels involved in both are similar in every patient with ESRD. The present study tried to explore whether vascular access failure in dialysis patients could be an early sign of MACE by using the National Health Insurance Research Database (NHIRD), an administrative database for reimbursement claims in Taiwan, over the 10-year period from 2001 to 2010.

## METHODS

### Data Source

The setting of this study was based on the NHIRD, a longitudinal health insurance database that includes claim data for all of the health beneficiaries in Taiwan.<sup>18</sup> The National Health Insurance (NHI), a compulsory NHI program covering over 99% of the population in Taiwan, was initiated in 1995. The comprehensive insurance package consists of all the necessary medical services, including outpatient, inpatient, and dental services, as well as dialysis therapies for the patients with ESRD.<sup>19</sup> For research and administrative use, the National Research Institute of Taiwan set up the NHIRD, providing all administrative records of medical services for reimbursement purposes since 1996. The prevalence of ESRD on maintenance hemodialysis therapy was increasing and kept substantially high in Taiwan after the ubiquitous coverage of the NHI.<sup>3,20</sup> Patients with ESRD who receive dialysis therapy would be issued catastrophic illness certificates, which could help them waive co-payment of all of the ESRD-related inpatient and outpatient care. Because all of the inpatient and outpatient expenditures related to dialysis are fully reimbursed by the NHI system, the records of claim data can serve as a comprehensive source of information for these specific patients. The NHIRD created a catastrophic illness profile consisting of the registry data of all of the insurance beneficiaries with catastrophic illnesses, which include ESRD, cancer, congenital illness, and many other major illnesses. The present study obtained the information from all dialysis patients registered in the Catastrophic Illness Database, a subset database extracted from NHIRD by using this catastrophic illness profile. All of the relevant information about the inpatient/outpatient diagnosis, coded in the format of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), and treatment claims of all dialysis patients in Taiwan can be acquired from the Catastrophic Illness Database. This study was approved by the Institutional Review Board, National Cheng Kung University Hospital (A-ER-102-222).



**FIGURE 1.** Flowchart describing the selection of incident hemodialysis patients and matching case–control pairs. MACE, major adverse cardiovascular event.

### Study Design and Cohort

The study used a nested case–control design in which the selection of study subjects and matching method are presented in Figure 1. From the Catastrophic Illness Database, we identified all patients with ESRD (ICD-9-CM code: 585) who received hemodialysis therapy between January 1, 2001 and December 31, 2010 ( $n = 116,746$ ). Patients with any hemodialysis treatment codes in 2000 were excluded ( $n = 24,921$ ). Patients who had renal transplantation ( $n = 2817$ ) or received peritoneal dialysis ( $n = 5910$ ), either before or after hemodialysis, were also eliminated. In addition, we excluded patients younger than 20 years of age ( $n = 173$ ) and those receiving hemodialysis for  $<90$  days ( $n = 6188$ ), leading to a total of 76,737 patients who became the study cohort analyzed in this study.

### Selection of Cases and Controls

The United States Renal Data System (USRDS) Wave 2 study demonstrated increased risks of myocardial infarction,

congestive heart failure, peripheral vascular disease, and cerebrovascular disease in the incident dialysis patients with vascular access associated infection.<sup>21</sup> To explore the similar association between vascular access and cardiovascular events, we defined MACE in the present study accordingly. Cases were defined as those who developed MACE and were hospitalized on the 270th day or later after their initial dialysis. The period of 270 days selected as the washing period was mainly because the initial MACEs after hemodialysis are most likely to occur before the 8th to 9th month of hemodialysis.<sup>22</sup> Excluding those early onset MACEs ( $n = 23,200$ ) ensured that the cases were those hemodialysis patients who were in a clinically stable condition. The minimum 270-day washing period is also equal to 6 months plus 3 months: the 6-month period was utilized in our design of surveying vascular access dysfunction and the 3-month period would be the elapsed time of determining long-term maintenance dialysis. The washing period would eliminate the chances of erroneously taking necessary vascular access operations/interventions, which would be performed before hemodialysis initiation or in the 3-month observation period, as vascular access dysfunction.

The index date of each case was the date of his/her date of first ever hospitalization for MACE, including myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease (ICD-9-CM codes: 410, 412 for myocardial infarction; 402.01, 402.11, 402.91, 425, 428, 429.3 for congestive heart failure; 440, 441, 442, 443.1–443.9x, 447.1x, 785.4x for peripheral vascular disease; 362.34, 430–436, 437–437.1, 437.9, 438, 781.4, 784.3, 997.0 for cerebrovascular disease). Because the information about diagnosis retrieved from inpatient claims is considered more valid and reliable,<sup>23</sup> we limited cases to those patients hospitalized due to MACE. In addition, those who had MACE-related diagnoses in the inpatient or outpatient records before initiating hemodialysis were also excluded ( $n = 6451$ ) for their potential confounding. Finally, among the 47,086 patients enrolled in the study, there were 9722 patients who had experienced MACE after 270 days since their initial hemodialysis.

For each case, we randomly selected 2 controls using the following method. Each MACE case was matched to 2 controls with the same sex, birth year ( $\pm 1$  year), and duration of hemodialysis. By doing so, an individual could be selected as a control before he/she became an MACE case. Eleven patients did not have 1:2 matched controls and were excluded. The sampling finally resulted in a total of 19,422 controls. The index date for each control would be defined as the first day of hemodialysis, plus the matched duration of hemodialysis.

### Definition of Vascular Access Dysfunction

Vascular access malfunction or dysfunction is defined as vascular access failure that occurs beyond 3 months after the initial hemodialysis to exclude the early failure of vascular access, as the causes of early failure are somewhat different from those associated with late failures.<sup>24</sup> We retrospectively searched for vascular access-related procedure (arteriovenous fistula/graft operation, permanent/temporary double-lumen catheter placement, surgical thromboembolectomy or percutaneous intervention of access) codes which can be regarded as surrogates for vascular access failure events because hemodialysis patients in stable condition would receive these procedures only when their vascular accesses are dysfunctional.

Information about vascular access dysfunction during the 6-month period before the index dates was retrieved from both

inpatient and outpatient claims. The rationale for using a 6-month period to retrospectively search for vascular access dysfunction is not only based on the temporal nearness of easy connecting shunt dysfunction and MACE in clinical settings but also considers the washing period, the unstable hemodialysis period in the beginning, and the initial MACE mostly occurring in the beginning 9 months of hemodialysis, which are described in the aforementioned case selection method.

### Definitions of Comorbidities

The patients' comorbidities analyzed in this study included diabetes, hypertension, ischemic heart disease, dyslipidemia, myocardial infarction, heart failure, peripheral artery disease, stroke, dementia, chronic lung disease, peptic ulcer disease, liver disease, hemiplegia/paraplegia, and malignancy. Information on comorbidity was determined by the ICD-9-CM codes in the Romano Charlson comorbidity index, which was validated and showed high accuracy in the administrative data of the NHIRD.<sup>23</sup> The existing comorbidities are defined by the following criteria: In the inpatient database, the ICD-9-CM codes of the selected comorbidity appeared at least 1 time within 1 year before the initial hemodialysis and, in the outpatient database, the patient had at least 2 instances of the same diagnosis of the selected comorbidity, and the timestamps of the first diagnosis and the last 1 should be at least 30 days apart within 1 year before hemodialysis initiation.

### Statistical Analysis

Baseline demographic and comorbid characteristics were presented as means  $\pm$  standard deviation (SD) and proportion as appropriate and compared using Chi-squared statistics. Data regarding vascular access dysfunction were summarized in 2 formats: with or never with vascular access events and counts of events, which were further stratified into 4 categories: 0, 1, 2, and  $\geq 3$ . We conducted logistic regression analyses by clustering each case-control pair with the generalized estimating equation model to identify the association between MACE and vascular access dysfunction events. The association of interest was determined by odds ratios (OR) and 95% confidence intervals (CI). Multiple logistic regression models were applied by adjusting for various subsets of covariates, and the adjusted ORs and 95% CIs of MACE in relation to vascular access dysfunction were calculated. The data were analyzed using the SAS statistical software (version 9.3 for Windows; SAS Institute Inc., Cary, NC). Results were considered statistically significant when  $P < 0.05$ .

## RESULTS

### Patient Characteristics

The demographic data and comorbid states of cases and controls are presented in Table 1. The mean age of initiating dialysis was 63.4 years (SD = 12.2 years) in the case group and 63.2 years (SD = 11.9 years) in the control group. There were 72.1% patients in the case group who began their dialysis in the first half of the study period (2001–2005), while the distribution of initiating dialysis for the control group was similar between the first and second half of the study period. Compared with the control group, the case group was associated with a significantly higher prevalence of diabetes and coronary artery disease and a significantly lower prevalence of liver disease and malignancy.

**TABLE 1.** Clinical Characteristics of Patients

Characteristics	Case (n = 9711)	Control (n = 19,422)	P Value
Age (y)	63.4 ± 12.2	63.2 ± 11.9	0.439
Gender (male)	4889 (50.3)	9778 (50.3)	–
First MACE since dialysis (d)	1122 ± 715	–	–
Calendar year of dialysis initiation			<0.001
2001–2005	7001 (72.1)	9429 (48.6)	
2006–2010	2710 (27.9)	9993 (51.4)	
Calendar year of index date			<0.001
2001–2005	2748 (28.3)	3259 (16.8)	
2006–2010	6963 (71.7)	16163 (83.2)	
Baseline comorbidities			
Diabetes mellitus	5237 (53.9)	9564 (49.2)	<0.001
Hypertension	7522 (77.5)	14985 (77.2)	0.560
Coronary artery disease	1699 (17.5)	2936 (15.1)	<0.001
Dyslipidemia	1976 (20.4)	3866 (19.9)	0.374
Myocardial infarction	–	–	–
Congestive heart failure	–	–	–
Peripheral artery disease	–	–	–
Cerebrovascular disease	–	–	–
Dementia	76 (0.8)	180 (0.9)	0.214
Chronic pulmonary disease	774 (8.0)	1459 (7.5)	0.166
Peptic ulcer disease	1964 (20.2)	3758 (19.4)	0.076
Mild liver disease	375 (3.9)	986 (5.1)	<0.001
Moderate or severe liver disease	55 (0.6)	204 (1.1)	<0.001
Hemiplegia/paraplegia	67 (0.7)	107 (0.6)	0.147
Malignancy	585 (6.0)	1640 (8.4)	<0.001

Data are presented as the mean ± standard deviation or number (percentage). MACE, major adverse cardiovascular event.

### Associations of Vascular Access Dysfunction With MACE

Logistic regression analysis (Table 2) demonstrated that cases were more likely than controls to experience vascular access dysfunction within 6 months before the index dates (OR = 1.385, 95% CI = 1.300–1.475). After adjusting for potential confounders related to traditional risks for MACE (ie, diabetes, hypertension, coronary artery disease, and dyslipidemia), MACE was still significantly associated with a prior history of vascular access dysfunction (OR = 1.376, 95% CI = 1.292–1.466). The OR was slightly reduced, but still significant, at 1.270 (95% CI = 1.188–1.357) when the calendar year of initiating dialysis was further adjusted. This remained almost unchanged (OR = 1.268, 95% CI = 1.186–1.355) when both the calendar year of initiating dialysis and other underlying comorbid states of the patients were further considered. (see Table, Supplemental Digital Content 1, <http://links.lww.com/MD/A318>, which illustrates the models and their fittings for association between vascular access dysfunction and subsequent MACE.)

### Frequency of Vascular Access Dysfunction as a Risk Factor for MACE

When the event counts of vascular access dysfunction were taken into consideration, compared with those without events, the risk of MACE was significantly associated with an increased number of events, with a dose-gradient pattern ( $P < 0.001$ ; Table 3). The OR was highest for patients experiencing 3 or more access events within 6 months before the index date (crude

OR = 2.066, 95% CI = 1.761–2.423), followed by those with 2 events (crude OR = 1.672, 95% CI = 1.479–1.890), and 1 event (crude OR = 1.217, 95% CI = 1.130–1.311). After controlling for potential confounders, the ORs were slightly reduced, but continued to demonstrate a positive relationship between the number of vascular access dysfunction events and risk of MACE.

### DISCUSSION

The present study highlights the temporal nearness and exposure–response relationship between vascular access dysfunction and MACE, which could stem from some specific common factors for both. The factors associated with vascular access dysfunction, especially fistula failure, in dialysis patients can be divided into predisposing and precipitating factors. The predisposing factors include female gender, elderly age, smoking, greater body mass index, diabetes, coronary artery disease, peripheral vascular disease, surgical expertise levels, small vessel or anatomical anomaly, and hypercoagulable state.<sup>25–29</sup> On the other hand, hypovolemia, hypotension, excessive pressure to obtain hemostasis at the cannulation site, and repeated cannulation, can be the precipitating causes of access failure. Moreover, traditional cardiovascular disease risk factors seem to be intuitive causes of cardiovascular disease in hemodialysis patients. However, these traditional cardiovascular risk factors may neither well predict cardiovascular disease nor associate with vascular access thrombosis in hemodialysis patients.<sup>8,30</sup> CKD itself is regarded as an independent risk factor for adverse cardiovascular outcomes.<sup>6</sup>



**TABLE 2.** Logistic Regression Analyses\* for Association of Vascular Access Dysfunction Within 6 Months Before Index Date and Subsequent MACE

Models	Odds Ratio	95% CI for OR	P Value
Univariate analysis	1.385	1.300–1.475	<0.001
Multivariate analysis adjusted for covariate set 1 <sup>†</sup>	1.376	1.292–1.466	<0.001
Multivariate analysis adjusted for covariate set 2 <sup>‡</sup>	1.270	1.188–1.357	<0.001
Multivariate analysis adjusted for covariate set 3 <sup>§</sup>	1.268	1.186–1.355	<0.001

\* By clustering case–control pairs with the generalized estimating equation (GEE) model.

<sup>†</sup> Adjusted by patients’ baseline states of diabetes mellitus, hypertension, coronary artery disease, and dyslipidemia.

<sup>‡</sup> Adjusted by patients’ baseline states of diabetes mellitus, hypertension, coronary artery disease, dyslipidemia, and calendar year of initiating dialysis (2001–2005, 2006–2010).

<sup>§</sup> Adjusted by patients’ baseline states of diabetes mellitus, hypertension, coronary artery disease, dyslipidemia, calendar year of initiating dialysis (2001–2005, 2006–2010), dementia, chronic pulmonary disease, peptic ulcer disease, liver disease, paraplegia/hemiplegia, and malignancy. CI, confidence interval; MACE, major adverse cardiovascular event; OR, odds ratio.

Hence, some nontraditional risk factors, CKD/uremia, and the hemodialysis procedure itself for example, may play a role in the high incidence of cardiovascular events. The risk factors for vascular access dysfunction are likely interrelated with the risk factors for MACE through the uremia/dialysis bridge.

The resemblance of the small-to-medium vessels in the cardiovascular system and the artificially created vascular structures prompted us to consider the putative link between vascular access dysfunction and the risk of MACE. Several mechanisms that may possibly explain the relationship between vascular access dysfunction and MACE have been proposed: high flow causing hyperkinetic circulation, low flow causing under-dialysis, and access micro-inflammation.<sup>31</sup> High vascular access flow would contribute to a high cardiac output state and has been considered to lead to subsequent heart failure and cardiac death.<sup>32</sup> Hemodialysis relies on the patency of the vascular access to provide an adequate dialysis dose. Low access flow leads to under-dialysis which has been proven to be the cause of high morbidity and mortality in dialysis patients.<sup>33,34</sup> Chronic colonization by microbes on the synthetic accesses implants or biofilm inside may be the cause of higher cardiovascular risks and poorer survival due to sustained micro-inflammation.<sup>35,36</sup>

Additionally, there are some types of relationship between vascular access dysfunction and MACE, but they have not been well elucidated. Vascular calcification, a CKD/dialysis-related calcium–phosphate disturbance, is a recognized risk factor for cardiovascular mortality in patients with ESRD.<sup>37</sup> In the study by Schlieper et al,<sup>38</sup> calcification of the arteriovenous fistula or synthetic graft was identified as an independent risk factor for cardiovascular mortality. Another study demonstrated the connection between the dialysis vascular access and cardiac injury and showed that higher blood flow in the forearm fistula were associated with lower dialysis-induced cardiac injury.<sup>39</sup> However, results of some trials did not support such findings. The Normal Hematocrit Cardiac Trial was terminated before it was complete due to the higher rates of mortality from nonfatal myocardial infarction in the group with a high hematocrit.<sup>40</sup> The rate of adverse vascular access events was also significantly high in the high hematocrit group. The association may be linked by a high hematocrit. Nonetheless, the occurrence of vascular access thrombosis due to high hematocrit was not observed in other studies.<sup>41–43</sup> The benefits of antiplatelet therapy in decreasing the risk of cardiovascular events/hemodialysis vascular access dysfunction are supported by various clinical investigations and trials.<sup>44,45</sup> However, neutral and even

**TABLE 3.** Logistic Regression Analyses\* for Association Between Number of Vascular Access Events Within 6 Months Before Index Date and Subsequent MACE

No. of Vascular Access Events	Crude Odds Ratio			Adjusted Odds Ratio <sup>†</sup>		
	Estimate	95% CI	P Value	Estimate	95% CI	P Value
0	1 (Reference)			1 (Reference)		
1	1.217	1.130–1.311	<0.001	1.120	1.036–1.211	0.005
2	1.672	1.479–1.890	<0.001	1.528	1.341–1.741	<0.001
≥3	2.066	1.761–2.423	<0.001	1.840	1.549–2.186	<0.001
			<0.001 <sup>‡</sup>			<0.001 <sup>‡</sup>

CI, confidence interval; MACE, major adverse cardiovascular event.

\* By clustering case–control pairs with the generalized estimating equation (GEE) model.

<sup>†</sup> Adjusted by patients’ baseline states of diabetes mellitus, hypertension, coronary artery disease, dyslipidemia, calendar year of initiating dialysis (2001–2005, 2006–2010), dementia, chronic pulmonary disease, peptic ulcer disease, liver disease, paraplegia/hemiplegia, and malignancy.

<sup>‡</sup> P for trend.

conflicting results about antiplatelets/anticoagulation and dialysis vascular access patency have been demonstrated.<sup>45–47</sup>

The present study is a small step toward exploring the association between vascular access and MACE, which could be overlooked. Our results suggest that the more vascular access events hemodialysis patients experience, the more subsequent MACE they will have. Hence, we have demonstrated that there is an exposure–response relationship between access failure events and MACE.

Our study has several limitations. First, there was a lack of vascular access types in the analysis. According to the results of recent investigations, types of vascular access for dialysis can be related to inflammation, cardiovascular events, and mortalities.<sup>48</sup> Catheter or graft use for long-term dialysis is associated with increased risk of death, infection, and hospitalization. We did not identify and group patients for comparison according to their different vascular access types in this study due to a lack of clear access-type records in the NHIRD. For example, when some tunneled cuffed catheter placements and fistula/graft creations were performed at the same time at the beginning of hemodialysis, data in the NHIRD gave us limited information about which vascular access was used and how long it was used. Second, neither clinical parameters related to cardiovascular risks, including blood pressure, physical status, smoking, body mass index, residual renal function, dialysis dose, and anatomical location of vascular access, nor the laboratory data for lipid profile, hemoglobin/hematocrit, inflammation markers, and calcium–phosphate product were available from the NHIRD. Besides, polymorphisms of genes highly associated with cardiovascular complications,<sup>49–52</sup> which may play a role in these high-risk patients for cardiovascular events, were not taken into consideration. Failure to consider the above variables may have led to a certain degree of residual confounding. Third, the information on comorbidity was solely dependent on the ICD-9-CM codes claiming for reimbursement, which could lead to potential disease misclassification, and again, leading to residual confounding. Fourth, the prescribed medications in our hemodialysis bundle, including erythropoiesis-stimulating and phosphate-lowering agents, were not claimed and cannot be obtained from the NHIRD. As such, we were unable to assess the roles of some prescribed medications in explaining the relationship between vascular access dysfunction and MACE. Fifth, the results were acquired from those incident patients in a relatively stable stage of their maintenance hemodialysis treatment. Extrapolating our results to patients with other clinical characteristics, especially the initial unstable status of ESRD and dialysis vascular access, would be difficult. This study also has several strengths. First, the universal medical coverage in Taiwan allows for obtaining data from the whole population, and the claims data for hemodialysis patients are of a sufficient size for data processing and matching to document our study outcomes. Second, the nested case–control design helps us avoid selection bias in such an observational study.

In conclusion, we found that dialysis vascular dysfunction is significantly associated with an increased risk of subsequent MACE, especially after clusters of vascular access dysfunction. The outcome of our study shed light on the issue regarding another possible risk factor, which can be easily noted in the dialysis population, for MACE. Further research exploring the association between dysfunction of each specific type of vascular access and subsequent MACE will help us understand more about their interrelatedness and elucidate the mechanism. Nevertheless, vascular access failure can be an early sign of MACE for patients receiving maintenance hemodialysis. Active

monitoring and treatment of cardiovascular risk factors and the related diseases, not merely managing vascular access dysfunction, would be required to reduce the risk of MACE.

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